25 January 2018
EMA/205473/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lamzede

International non-proprietary name: velmanase alfa

Procedure No. EMEA/H/C/003922/0000

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	Three-minute stair climb test
6MWT	Six-minute walk test
ADA	Anti-drug antibody
ADC	Apparent diffusion coefficient
AE	Adverse event
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ATC	anatomical therapeutic code
ATS	American Thoracic Society
AUC	The area under the plasma concentration curve from zero to infinity calculated as AUC (0 last) plus Cz/λz
BBB	blood-brain barrier
BLOQ	Below limit of quantification
BLQ	below limit of quantification
BMI	Body Mass Index
BMT	bone marrow transplantation
BOT2	Bruininks-Oseretsky test of motor proficiency
CEV	Comprehensive Evaluation Visit
CHAQ	childhood health assessment questionnaire
CHO	Chinese hamster ovary
CI	Confidence interval
Cmax	The maximum observed plasma concentration
CNS	Central nervous system
CRF	case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTR	clinical trial report
CV	curriculum vitae
ECG	Electrocardiogram
ECHO	echocardiogram
EIA	Enzyme immuno assay

ELISA	Enzyme-linked immunosorbent assay
EOW	every other week
ERT	Enzyme replacement therapy
FAS	Full analysis set
FEV1	forced expiratory volume in one second
FVC	Forced vital capacity
GCP	good clinical practice
GFAp	Glial fibrillary acidic protein
GLP	good laboratory practice
GM2	GM2 ganglioside
GMP	Good Manufacturing Practice
HPLC	High-performance liquid chromatography
IC	informed consent
IMP	investigational medicinal product
INR	International normalized ratio
IRR	Infusion-related reaction
IV	Intravenous
LAMAN	Lysosomal acid alpha-mannosidase
LLOQ	Lower limit of quantification
LNR	Lower normal range
LOQ	Limit of quantification
LSD	Lysosomal storage disorders
M-6-P	Mannose 6 phosphate
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MVOF	Minimum value of the objective function
NAB	Neutralizing antibodies
NCA	Non-compartmental analysis
NFLp	Neurofilament protein
PFT	pulmonary function test
PT	preferred term
PTA	pure tone audiometry

SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SOC	system organ class
TEAE	Treatment emergent adverse event
Tmax	time to maximum concentration
TPP-1	Reference lysosomal protein
VAS	visual analogue scale
Vd	apparent volume of distribution
Vz	The apparent volume of distribution during the terminal phase
WT	Wild type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Chiesi Farmaceutici S.p.A. submitted on 30 August 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Lamzede, 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 23 January 2014.

Lamzede, was designated as an orphan medicinal product EU/3/04/260 on 26 January 2005 in the following condition: Treatment of alpha-Mannosidosis

The applicant applied for the following indication:

Lamzede is indicated for long-term enzyme replacement therapy in patients with alpha-mannosidosis. Lamzede is indicated in adults, adolescents and children aged 6 years and older.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that velmanase alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical 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 P/0122/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0122/2014 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 requests for consideration

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation.

New active Substance status

The applicant requested the active substance velmanase 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 on 27 May 2010, 30 November 2011 and 20 March 2014. The Protocol Assistance pertained to non-clinical and clinical 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: Martina Weise

- The application was received by the EMA on 30 August 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on
  28 December 2016.
- During the meeting on 12 January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2017.
- During a meeting of an Expert group on 4 December 2017, experts were convened to address questions raised by the CHMP. The CHMP considered the views of the Expert group as presented in the minutes of this meeting.
- During the meeting on 14 December 2017, the CHMP agreed on a second List of Outstanding Issues to be sent to the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 10 January 2018.
- During the meeting on 21-25 January 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 under exceptional circumstances to Lamzede on 25 January 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Lamzede is intended as long-term enzyme replacement therapy in adults, adolescents and children aged 6 years and older with alpha-mannosidosis.

2.1.2. Epidemiology

The prevalence of alpha-mannosidosis reported in the literature ranges from 1:500 000-1:1 000 000 worldwide. A study from Norway reported six (later eight) patients in a population of 4.5 million (Malm D, *et al.* 1995).

Alpha-mannosidosis has been described in most parts of the world, and is not specific to any ethnic group or sex.

2.1.3. Aetiology and pathogenesis

Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder caused by mutations in the MAN2B1 gene on chromosome 19 which codes for the enzyme alpha-mannosidase. The alpha-mannosidosis Mutation Database maintained by the University of Tromsø, the Arctic University of Norway, and the University Hospital of North Norway currently reports 155 mutations identified in 190 patients. No mutation is predominant, most are private mutations, and 3 mutations are present in more than 30% of European alpha-mannosidosis patients.

The effect of the enzyme deficiency is blockage of the degradation of glycoproteins, which results in the accumulation of mannose rich oligosaccharides in all tissues. Progressive lysosomal accumulation of non-degradable metabolites results in generalized cell and tissue dysfunction and multi-systemic pathologies.

2.1.4. Clinical presentation, diagnosis and prognosis

Clinical presentation

The disorder is generally classified into three separate subtypes: mild (type 1), moderate (type 2) and severe (type 3). Most affected individuals diagnosed fall into the moderate subtype. It is important to note, because of the highly variable nature of the disorder, that affected individuals will not have all of the symptoms discussed below.

The mild form may not be evident until the teen years and progresses slowly. Symptoms typically include muscle weakness. Skeletal abnormalities are usually not present. Most patients have normal cognitive and physical development, although some present with mild to moderate intellectual disability.

In the moderate form of the disorder signs of skeletal abnormalities and muscle weakness may appear before ten years of age and progress slowly. Ataxia (an impaired ability to coordinate voluntary movements) may develop by the age of 20-30.

The severe form begins within the first year of life. In most cases, infants appear normal at birth, but the condition grows progressively worse. Type 3 alfa-mannosidosis is characterized by rapid progression of intellectual disability, hydrocephalus, progressive impairment of the ability to coordinate voluntary movements (ataxia), enlargement of the liver and spleen (hepatosplenomegaly), skeletal abnormalities, and coarse facial features. Intellectual disabilities associated with alfa-mannosidosis can range from mild cognitive impairment to profound mental deficiency. A diminished or abnormal immune system response can make affected individuals more susceptible to bacterial infections, particularly of the respiratory system. Infections affecting the middle ear and gastrointestinal tract are also common.

The wide range of disease severity may reflect allelic forms of the disease. The variability in the clinical course of the disease even in patients with the same mutations suggests the existence of epigenetic effects (Govender *et al.*2014*)*.

Some experts have recognized that the disease encompasses “a continuum of clinical findings from a perinatal-lethal form to one that is not diagnosed until adulthood”. In general, phenotypes of patients with alpha-mannosidosis are not considered “clearly distinguishable” and the prediction of the clinical course for an individual patient is very challenging.

There is no clear relationship between the degree of alpha-mannosidase activity loss and the clinical phenotype or a defined genotype-phenotype relationship.

Diagnosis

A diagnosis is made by measuring the enzymatic activity of alpha-D-mannosidase in white blood cells. If there is a decreased level of the enzyme in comparison to standard levels, a diagnosis can be made. It is thought that this disorder might be under-diagnosed for a few different reasons—the diagnosis is often made late in the disease's progression, symptoms are often mild, or the biochemical diagnosis does not yield conclusive results.

Prognosis

The life expectancy in alpha-mannosidosis is highly variable. Individuals with early onset severe and rapid progressive disease often do not survive beyond childhood, whereas those with milder disorders may survive well into adult life.

2.1.5. Management

Given the clinical severity and the typical age of diagnosis, most severe patients are potential candidates for haematopoietic stem cell transplantation (HSCT) or bone marrow transplantation (BMT).

Currently, no licensed therapy is available, and the older less severe patients are managed with supportive care including symptom management, medical and surgical treatment of complications (e.g. infections, skeletal deformities), and physical therapy.

About the product

Lamzede is a recombinant human alpha mannosidase developed as an intravenous enzyme replacement therapy (ERT) for the treatment of alpha-mannosidosis. The objective of treatment with velmanase alfa is to administer the deficient enzyme into the blood stream, from where it will be

internalised by the cells and transported to the lysosomes. Here it will act as the endogenous enzyme, which these patients are known to be deficient in. The ERT is given life long and aims to normalise oligosaccharide levels in the body, to prevent progression of the disease thereby preventing abnormalities from being developed and to improve the patient's condition.

The claimed indication for Lamzede was for the long-term enzyme replacement therapy in patients with alfa-mannosidosis. Lamzede is indicated in adults, adolescents and children aged 6 years and older.

The indication approved by the CHMP was "Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis."

The recommended dose regimen of Lamzede is 1 mg/kg of body weight administered once every week by intravenous infusion at a controlled speed.

Type of Application and aspects on development

The applicant sought scientific advice in 2010, 2011 and 2014. The initial advice was in relation to pre-clinical development and the proposed target population and age of patients, as well as dose selection and design of the phase III placebo controlled study, and selection of endpoints.

The follow up advice related to the phase-3 trial choice of endpoints, the placebo/control ratio and the possibility for an application under exceptional circumstances. The final advice related to quality and pre-clinical issues.

The application was submitted as a full application according to Article 8(3) of Directive 2001/83/EC,

- Exceptional circumstances

The Applicant considered that the grounds for marketing authorisation under exceptional circumstances apply to Lamzede according to the Article 14 (8) of Regulation (EC) 276/2004 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.

Alpha-mannosidosis is an orphan condition, with an estimated prevalence of approximately 1:1,000,000 people, and received orphan medicinal product designation in 2005 for the treatment of alpha-Mannosidosis (EU/3/04/260).

At present, there are no orphan medicinal products marketed in the EU for the treatment of alpha-mannosidosis.

The applicant also noted that:

- the availability of subjects for conduct of trials is very limited;
- the clinical development programme has been conducted taking into account limitations due to the extremely low incidence of the disease and the limited availability of patients;
- due to the rarity and extreme variability in clinical symptomatology there is no disease-specific validated clinically relevant endpoint.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for solution for infusion containing 10 mg of velmanase alfa as active substance. The powder is to be reconstituted with 5 mL sterile water for injections (WFI) prior to use. The reconstituted finished product is a colourless liquid of pH 7.5 ± 0.5. The strength of the reconstituted finished product is 2 mg/mL.

Other ingredients are disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine.

The product is available in a 10 ml vial (Type I glass) with a bromobutyl rubber stopper, an aluminium seal and a polypropylene flip off cap.

2.2.2. Active Substance

2.2.2.1. General Information

Genetic deficiency of lysosomal alpha-mannosidase leads to the accumulation of non-degraded oligosaccharides in the lysosome and symptoms consistent with the lysosomal storage disease, alpha-mannosidosis. Lysosomal alpha-mannosidases are members of the glycoside hydrolase family 38 (GH38 Class II). They are involved in the catabolism of Asn-linked glycans of glycoproteins and play a vital role in maintaining cellular homeostasis. These enzymes catalyse the hydrolysis of α-1,2-, α-1,3- and α-1,6-glycosidic bonds with retention of confirmation of the anomeric carbon of the released mannose residue.

Velmanase alfa is an active form of the human lysosomal enzyme alpha-mannosidase which is expressed in genetically modified Chinese Hamster Ovary (CHO) cells as a 1011 amino acid precursor including a 49 residue N-terminal signal sequence. The molecular mass of mature velmanase alfa (monomer) including glycosylation is 130 kDa. The velmanase alfa glycoprotein was identified to have 11 potential N-glycosylation sites and 10 of them were found to be fully or partially glycosylated.

After internalisation into the lysosome the enzyme is further processed/maturated to 5 peptides that are held together with disulfide bridges, ionic or hydrophobic forces maintaining the 3D structure. Once in the lysosome, the active enzyme then sequentially starts to degrade stored oligomannoses releasing mannoses which can then be reused by the body. The uptake at lower concentrations is mediated via the mannose-6-phosphate receptor (M6PR) but at higher enzymatic concentrations other receptors or mechanisms also seem to be involved.

2.2.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacturing site for the active substance is Rentschler Biopharma SE, Germany.

A cell culture fed-batch process is used as upstream process. The seed train includes cell expansion from the WCB via shake flasks followed by a bioreactor. The production of velmanase alfa is performed in a fed-batch bioreactor system. At the end of the production stage, the supernatant is harvested by centrifugation and clarified by depth filtration and finally filtered through a bioburden reduction filter.

The purification process starting from clarified culture supernatant contains four chromatographic steps. The active substance bulk is formulated in a sodium phosphate/glycine/ D-Mannitol buffer.

The container closure consists of a sterile bag. Sufficient information on the container closure system has been provided.

Control of Materials

The parental cell line used for the transfection was derived from the Chinese hamster cell line CHO DG44 that was originally obtained as an adherent cell line, and was routinely sub-cultured in fetal bovine serum (FBS). The cell line was adapted to serum free suspension culture for production in larger scale. The history of the parenteral cell line and the generation of the velmanase alfa cDNA and expression vector have been described in sufficient detail.

A two-tier cell bank system, consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB) has been established. In addition, 'end of production' (EOP) cell banks have also been generated. The MCB, WCB and EOP cell banks have been characterized and tested for identity, purity, stability and adventitious agents as per ICH guidelines.

Extensive information has been provided on raw materials, including overviews of all compendial and non-compendial raw materials (the latter with specifications). In addition, the composition of all buffers used during purification has been specified in detail.

Control of critical steps and intermediates

There are no intermediates isolated within the active substance manufacturing process.

Due to the fact that the protein is quite large (2 x 130 kDa) and cannot be fully and conclusively characterised and controlled, the control of the process is of utmost importance to ensure a consistent quality of the desired product. The Applicant provided an appropriate overview of the control strategy for the manufacturing process.

In process controls (IPCs) and performance indicators have been provided. Upon request, the applicant has provided a list of identified critical quality attributes (CQAs) including a justification for the assignment. The CQAs are reflected in the specification. The information provided on the classification of CQAs is considered acceptable.

Process verification studies and small scale studies of selected steps and parameters generally support the identified IPCs.

Classification of critical process parameters (CPPs) is relatively conservative. Full linkage studies between CQAs and CPPs have not been performed, but are also not expected, taking into consideration that the process is not developed by a full Quality by Design approach.

Ranges and/or operational set points have been established for the CPPs. The implication of the classification of process parameter and performance indicators, including handling of deviations and changes, is sufficiently transparent.

Process validation

The applicant has provided an overview of small scale evaluation studies for the upstream and downstream process (USP and DSP). These process evaluation studies were based on criticality evaluation by FMEA (Failure Mode and Effect Analysis) assessment. Small scale models were used to support process characterisation. Suitability of the models was demonstrated by running them in parallel to full scale GMP lots. The results of individual unit operations of the small scale runs were

compared to the results of the full scale runs. The evaluation studies were used to adapt and optimise the manufacturing process and to establish a control strategy.

The results from the process verification were satisfactory. The hold times have been appropriately justified. Impurity removal evaluation has been performed for some impurities in small scale models.

Removal of impurities throughout the process has been validated at full scale for host cell DNA and HCP.

Aggregates were tested as high molecular weight (HMW) species. The proposed commercial life time of the chromatography resins is set in accordance with results from small scale studies. A verification program will be implemented at full scale when the number of lifetimes exceeds the number currently verified by production scale runs.

A satisfactory risk assessment and information on extractables/leachables has been provided for container closure systems such as Bioprocess containers used to store/hold process buffers and product containing process solutions, the primary packaging material for active substance, the tubing used for transfer of product containing process solution (aliquotation) and process and sterile filters.

Manufacturing process development

The process history has been described in detail. The active substance manufacturing process has undergone minor process optimisations during non-clinical and clinical development. The manufacturing process principles in terms of the USP and DSP steps have not changed, but some steps were optimised to reduce product loss, to simplify the subsequent finished product manufacturing process, and to ensure process robustness and reproducibility.

Retrospective review of IPC data for each affected process step and active substance batch analysis data have been provided. In order to support the claim that the USP and DSP process optimizations have not impacted on product quality, the results of performance parameters for each process batch and batch analysis result ranges for each process iteration have been retrospectively reviewed and are presented. A change history of the specification has also been provided. Based on the data provided the comparability of the GMP batches is considered demonstrated.

Characterisation

In the active native state the enzyme forms a homodimer of 2 x 130 kDa. In the lysosome, the enzyme is maturated by proteolytic cleavage into five peptides linked together with disulphide bridges and/or hydrophobic and electrostatic forces, maintaining the 3D structure. The enzyme coordinates one Zn^{2+} ion in the active site and has 4 disulphide bridges and one free thiol. The enzyme is heavily glycosylated and has a wide variety of isoforms. Eleven potential glycosylation sites have been identified and 10 of them are fully or partially glycosylated.

The applicant has employed a range of techniques in order to elucidate the primary structure of velmanase alfa, including intact mass analysis by MALDI-TOF (matrix assisted laser desorption ionization-time of flight), determination of amino acid composition by acid hydrolysis and RP-HPLC (reversed phase high performance liquid chromatography), peptide mapping, N and C-terminal sequencing by MALDI-ISD (matrix assisted laser desorption ionization – in source decay) and SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis). 100% amino acid sequence coverage was achieved by peptide mapping. All other results also confirm the primary structure of the active substance. Disulphide bridges have been investigated by LC/MS-MS (Liquid chromatography-tandem mass spectrometry) and also circular dichroism studies have been performed for the

determination of the secondary structure. The 3D structure of the enzyme has been characterised by X-ray crystallography.

N-glycan characterisation has been performed and the structures have also been confirmed using mass spectrometry. N-glycan profiling and mannose-6-phosphate analysis of digested N-glycans has been performed. The content of sialylated glycans has been determined. HILIC (hydrophilic interaction liquid chromatography) chromatograms of three active substance batches and two finished product batches have been presented.

Size variants have been analysed by PAGE and SEC (size exclusion chromatography). The results of the SEC analysis confirmed the qualitative data of the Native-PAGE analysis, in that the most abundant form of the protein was dimer. Monomer was present, while low amounts of the multimer form was detected. Aggregation properties have been intensively investigated with UV-Vis absorbance, 90° light-scattering, intrinsic fluorescence spectroscopy, Nile Red fluorescence spectroscopy, 1,8-ANS fluorescence spectroscopy, Nile Red fluorescence microscopy, SEC-MALS, mFF-MALS and FFF-MALS. Low levels of aggregates have been observed.

Purity has also been studied with RP-HPLC. Co-elution of peaks has been observed and fraction analysis of shoulders by SDS-PAGE has been performed. Characterisation data for the peaks observed in the RP-HPLC chromatograms have been provided. Fractionation of the peaks followed by peptide mapping has been performed. Deamidation and oxidation have been studied.

Due to glycosylation several isoforms of the velmanase alfa protein exist. Further characterisation by chromatographic methods yielded a complex pattern of heterogeneity, which is mainly due to sialylation.

Deamidation and oxidation has been studied by peptide mapping.

In vitro studies have demonstrated that a small proportion of added velmanase alfa can enter cells via the M6P receptor which is considered as the main uptake mechanism at therapeutic doses of velmanase alfa. A biological assay for measuring enzymatic activity against accumulated natural substrate has been performed. All batches were found to be equally effective in removal of the storage products.

A synthetic substrate was used for the quantitative determination of the enzymatic activity for all active substance and finished product batches. The results were similar, indicating that the catalytic efficiency between velmanase alfa batches can be considered equivalent.

Forced degradation studies investigating effects of temperature, agitation, pH and light have been performed.

2.2.2.3. Specification

The active substance specification consists of the following attributes: appearance and description (colour, clarity, and pH), microbiology (bioburden and bacterial endotoxins), identity (peptide map and SDS-PAGE, reduced), content (protein concentration), potency (enzymatic activity), purity (HCP, size, related substances, charge) and carbohydrate structure.

For each attribute of the specification a justification of the respective acceptance criteria has been provided. Process capability and manufacturing history have been taken into account for the setting of specifications.

The uptake of velmanase alfa into the target cells is necessary for the clinical efficacy. In vitro experiments have indicated that at therapeutic doses of velmanase alfa the cellular uptake is mediated

by mannose-6-phosphate (M6P) receptors. As cellular uptake is crucial for clinical efficacy suitable tests addressing the cellular uptake should be included into the active substance specification. A major objection was raised during the procedure regarding the specification for M6P (mol/mol) and the absence of a validated cellular uptake assay.

A cell-based method is being developed to analyse the ability of velmanase alfa to be internalized by target cells (cellular uptake), with the read-out of the method being velmanase alfa intracellular enzymatic activity.

Upon request, the acceptance criteria for the M6P specification were tightened during the procedure. The limits should also be reviewed when further experience has been gained, with a view to further tightening the limits.

With regard to the oligosaccharide profile, quantitative criteria have been introduced. The approach is considered acceptable in general to control consistency of glycosylation.

Analytical methods

The analytical methods have been satisfactorily described and validated according to ICH Q2. A surrogate enzyme assay using a synthetic substrate is used to determine the potency of velmanase alfa. The relative activity of an unknown sample is defined in comparison to the reference material.

Batch analysis

Batch analysis data for active substance batches manufactured at the 250L scale, including batches manufactured using the intended commercial process, have been provided. All results comply with the specifications in force at the time of testing. Development of the specifications has been adequately described.

Reference materials

Sufficient information on the history of the active substance reference standards has been provided as well as a description of the generation of future reference standards.

2.2.2.4. Stability

The stability studies were performed in accordance with ICH Q5C.

All quality attributes tested demonstrated no change when active substance was stored at -70 °C and no significant trends could be observed. Data is available for up to 24 months for three batches and up to 12 months for one batch. Data for up to 6 months at -70 °C is available for the batches filled in Celsius bags.

Data has also been presented for all pivotal batches stored under accelerated conditions for 6 months and stressed conditions for 4 weeks.

A 24 month shelf life at -70 ± 10 °C is considered sufficiently justified based on the provided data.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and Pharmaceutical Development

The finished product (10 mg) is supplied in a 10 mL Type I glass vial as a powder for solution for infusion (white to off-white powder) which is to be reconstituted with 5 mL water for injections (not supplied) prior to use. The reconstituted finished product is a colourless liquid with pH 7.5 ± 0.5. The strength of the reconstituted finished product is 2 mg/mL, formulated in glycine, mannitol and Na_2HPO_4/NaH_2PO_4. The finished product includes a 6% overfill.

The excipients are commonly used and comply with compendial requirements (Ph.Eur).

The container closure for the finished product consists of a sterile, clear 10 mL Type I glass vial sealed with 20 mm Bromobutyl stopper with an aluminium seal and green polypropylene flip off cap.

The formulation development studies were based on an initial formulation, which had previously been successful for other similar products and then challenging its performance against modified formulations by testing a number of Critical Quality Attributes (CQAs). Formulation variables such as pH, ionic strength, buffer system were tested as well as addition of detergents, sucrose, albumin, EDTA and protease inhibitor cocktail. Ultimately the original formulation buffer using the conservative lyophilisation cycle was considered to be fit for purpose.

Three distinct manufacturing processes (process 1-3) were used for manufacturing finished product for clinical studies.

The strategy to confirm the change from Process 2 to Process 3 is based on comparison of release testing and additional characterisation on one batch of old versus new. The batch analysis results of five Process 3 batches are well in line with those of process 2 batches. Furthermore, the additional characterisation data indicate similar quality attributes and it is concluded that Process 2 and Process 3 product are highly similar.

2.2.3.2. Manufacture of the product and process controls

One batch of finished product comprises aliquots of one or more active substance batch, pooled, aseptically filtered, filled, lyophilized and capped. There are no additional formulation steps in the manufacture of finished product following receipt of the active substance bulk.

The finished product manufacturing process has been appropriately described.

Process parameters are presented as set points and, if applicable, ranges. Relevant lyophilisation parameters are provided as set points for each lyophilisation step. Critical process parameters have been satisfactorily identified and the process is adequately controlled.

Process verification studies consist of three velmanase alfa finished product batches that were produced in accordance with the process validation protocol using two active substance batches. All process parameters were operated within their predefined operating ranges. Performance indicator testing results were within the predefined acceptance criteria. Homogeneity of fill was demonstrated at the start, beginning and end of fill by monitoring multiple quality attributes of the product. The lyophilisation process was validated at minimum and maximum loads according to a pre-defined sampling plan. The process verification studies were adequately designed and the yielded results are considered satisfactory.

2.2.3.3. Product specification

The finished product specification includes tests for appearance and description for the lyocake and reconstituted product, microbiology (sterility and bacterial endotoxins), identity (isoelectric focusing and SDS-PAGE, reduced), content (protein concentration), potency (enzymatic activity) and purity (size, related substances). The approach for setting the acceptance criteria for each specification has been described and analytical results from batches have been provided. Upon request, the acceptance criteria of a number of specifications were tightened in order to ensure that the quality of future batches will be comparable to those used in clinical trials.

Analytical methods

With the exception of appearance, residual moisture and reconstitution time of the freeze-dried product, the non-compendial methods are the same as those used for the active substance. As the matrix of the active substance and the reconstituted finished product are identical, the active substance validation data are also applicable to the finished product.

Batch analysis

Batch analysis data were provided. All batches complied with the specifications in place at the time of manufacture.

Reference materials

Please refer to the active substance section. The same reference standards are used for testing both the active substance and finished product.

2.2.3.4. Stability of the product

The proposed shelf life for the finished product is 2 years when stored at 2-8 °C.

The stability studies are based on the principles outlined in ICH Q5C. The primary packaging material used is representative of the proposed commercial primary packaging (type I glass vial).

Long term stability data are available up to 24 months for four batches. No clear trends were observed and the studies indicate that the product is stable for 24 months at 2-8 °C.

The applicant has presented compatibility/in-use stability data covering storage at 5°C for 24 hours, storage at 25°C for 10 hours and infusion time bracketing the worst case scenarios for body weight. These in-use studies adequately support the information in the SmPC, i.e. chemical and physical in-use stability has been demonstrated for 24 hours at 2-8 °C.

Based on results from a photostability study it was concluded that the finished product should be stored protected from light. This is appropriately reflected in the SmPC.

In conclusion, the proposed shelf life of 2 years when stored at 2-8 °C is acceptable.

2.2.3.5. Adventitious agents

The velmanase alfa manufacturing process contains 4 orthogonal viral clearance steps, including virus inactivation and removal steps. These manufacturing steps have been validated using suitable model viruses in accordance with ICH Q5A (R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.

The unfiltered harvest (unprocessed bulk) is tested for the presence of adventitious viruses and mycoplasma in accordance with the European Pharmacopoeia.

Two virus assays are routinely performed.

An acceptable retroviral risk assessment has been presented; the risk of a retrovirus-like particle contamination in the finished product is considered to be negligible.

In summary, the data on adventitious agents and virus validation data suggest that viral safety of velmanase alfa is sufficiently assured.

2.2.3.6. Post Approval Change Management Protocol for the Finished Product

The Applicant included a Post Approval Change Management Protocol (PACMP) to add a second finished product manufacturing and batch release as well as stability testing site. Consequential changes are adaption of the finished product manufacturing process to the new site and introduction of primary packaging materials of the same quality but with slightly different dimensions.

To demonstrate the suitability of the newly defined manufacturing parameters, process validation runs with commercial scale batches will be performed following a pre-defined validation protocol. Specifications for process controls and testing of samples taken at each step of the manufacturing process have been provided.

A comparability assessment following the principles outlined in ICH Q5E will be initiated.

The PACMP was considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

Due to the fact that the protein is quite large (2 x 130 kDa) and cannot be fully and conclusively characterised and controlled by analytical methods, especially as regards monomer/dimer formation, charge heterogeneity, biological activity and glycosylation, the control of the process is of utmost importance to ensure a consistent quality of the desired product.

During the procedure a major objection was raised on the control strategy of the active substance. In response the Applicant amended the control strategy as regards CQAs and CPP and the process is now considered sufficiently under control.

In vitro experiments indicate that at therapeutic doses of velmanase alfa the cellular uptake is mediated by M6P receptors. As cellular uptake is essential for clinical efficacy suitable tests addressing the cellular uptake should be included into the active substance specification. A major objection was raised during the procedure regarding the specification for M6P and the absence of a validated cellular uptake assay. In response, the Applicant tightened the limit for M6P which provides additional reassurance with respect to consistent quality of the product. In addition, the limits should be reviewed when further experience has been gained. Further control is however needed by implementation of a cellular uptake assay, which is currently being developed. The Applicant committed to finalise the development and validation of the cellular uptake assay and to include it in the release specifications.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

Lamzede (velmanase alfa) is a form of human alpha-mannosidase produced in mammalian Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

The non-clinical testing strategy followed for the development of velmanase alfa took into account the ICH S6 (R1) guidance on Preclinical Safety Evaluation of Biotechnology- Derived Pharmaceuticals and guidance obtained in the Scientific Advice Procedure with the EMA in 2010 and 2014.

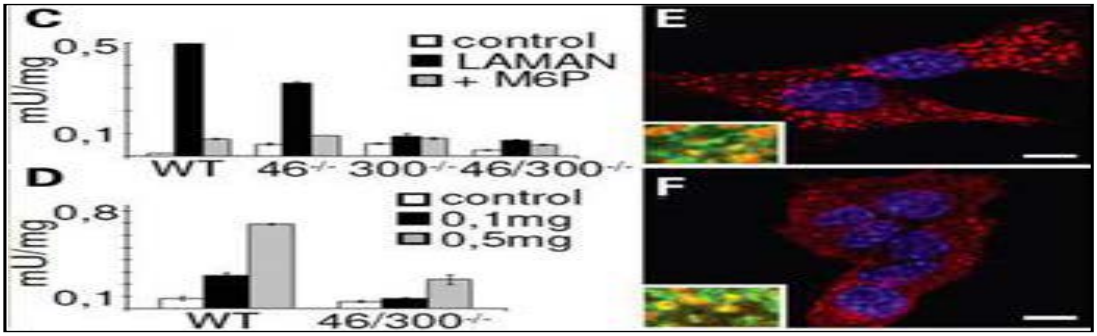
2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro experiments were conducted to establish the cellular uptake mechanisms and stability of velmanase alfa. These studies demonstrated that fibroblasts from alpha-mannosidosis patients were as efficient as HeLa (human cervical cancer cells) and J774 cells (mouse monocytic/macrophage cell line) in internalizing velmanase alfa whereas MPR 46/300 cells (Mannose-6-Phosphate (M6P) receptor deficient mouse fibroblasts) did not take up any appreciable amounts of velmanase alfa (data not shown).

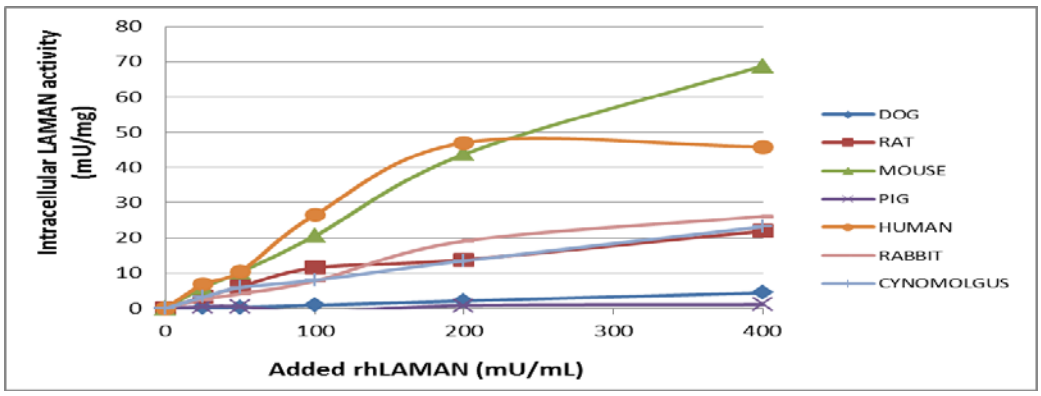
In order to further establish the contribution of the M6P receptor to the cellular uptake of velmanase alfa, cell cultures from alpha-mannosidosis patients were fortified with M6P concomitantly with velmanase alfa
(**Figure 1)**.

Figure 1. Cellular uptake of velmanase alfa (LAMAN) in control (WT) fibroblasts and MPR46 and/or MPR300 cells in the absence and presence of M6P (C) and in relation to dose (D) Immunofluorescence staining of WT fibroblasts (E) and M6P receptor deficient cells (F) demonstrating localization of velmanase alfa (red) in LAMP1 (green, inset) positive vesicles



Experiments were also conducted to assess the uptake of velmanase alfa into fibroblast from different species (**Figure 2**). The cells were grown confluent before addition of velmanase alfa (rhLAMAN in figure) in different concentrations. After 2 days incubation, the cells were harvested and intracellular LAMAN activity was measured and correlated to total protein content.

Figure 2. Cellular uptake of velmanase alfa (26U/mg) by fibroblasts from different species



A number of different *in vivo* ERT studies in mice models of α-mannosidosis were conducted and are summarised in **Table 1**.

Six investigations were conducted in α-mannosidosis KO mice. Since repeated dosing in α-m KO mice resulted in a progressive immune response, a different α-mannosidosis mouse model (Tg+/α-mKO mice) was developed to circumvent the immunogenicity of velmanase alfa (4.2.1.1.5; 4.2.1.1.6; 4.2.1.1.9). The immune tolerance was achieved by inserting a gene that expresses an inactive form of the human LAMAN enzyme (MutH72L) into blastocysts which were then implanted into pseudopregnant mice (4.2.1.1.5). The litters that expressed the transgene were then used for backcrossing into α-mKO mice. Prior to investigating the dose response relationship of velmanase alfa in these Tg+/α-mKO

mice, the tissue expression of the transgene was demonstrated and there was also demonstration of deficient α-mannosidase activity

Table 1. Overview of ERT studies conducted with velmanase alfa (LAMAN) in mouse models of α-mannosidosis.

Model	Dose regimen	Main endpoints	Main findings	Reference
LAMAN gene KO mice (α-mKO)	Single iv dose, 100 mU mouse LAMAN; Single and two iv doses of 50 mU rhLAMAN	LAMAN tissue activity, amount of neutral oligo-saccharides in tissues	Short-lasting ↑ in LAMAN tissue activity longer lasting ↓ in tissue oligosaccharides	4.2.1.1.2 Roces *et al*. 2004
LAMAN gene KO mice (α-mKO)	Two to four iv injections of 25-500 U/kg	LAMAN tissue activity, amount of neutral oligo-saccharides in tissues	Wide distribution of ↑ in LAMAN tissue activity, effect on storage of oligosaccharides in different brain regions	4.2.1.1.3 Blantz *et al*. 2008 4.2.1.1.4 Damme *et al*. 2011
LAMAN gene KO mice (α-mKO)	Three iv injections of 25 or 500 U/kg (comparison of lab scale and clinical scale product)	Amount of neutral oligosaccharides in spleen and brain	Similar activity of both products	4.2.1.1.8
LAMAN gene KO mice (α-mKO)	A singe iv injection of PBS or 1000 U/kg (clinical scale product)	Tissue enzyme activity at 1 and 24 hrs post dose	Highest activity at 1 hr post dose except brain. Highest activity in liver, heart, lung, and spleen	4.2.1.1.7
Immune-tolerant LAMAN gene KO mice (Tg+/α-mKO)	Biweekly or weekly inj of 125 up to 750 U/kg for 12 weeks	LAMAN tissue activity, amount of neutral oligosacch. in tissues, microglia activation	Long term efficacy noted on brain LAMAN activity, clearance of oligo-sacch. and inhibition of microglia activation	4.2.1.1.5 4.2.1.1.6 Damme *et al.* 2015
Immune-tolerant LAMAN gene KO mice (Tg+/α-mKO)	Weekly inj of 500 U/kg for 9 months	Tissue levels of oligosaccharides, microglia activation, LAMP-1, spatial-cognitive abilities, electrophysiology in Hippocampus	Clearance of oligosaccharides and inhibition of microglia activation with weekly dosing, positive effects on spatial-cognitive abilities	4.2.1.1.9 Stroobants *et al.* 2016

Tissue LAMAN activity and impact on tissue oligosaccharides in α-mKO mice (study 4.2.1.1.2)

This study examined the effect of single iv dose of bovine LAMAN and recombinant mouse and human LAMAN (rhLAMAN) on tissue LAMAN activity and impact on tissue neutral oligosaccharides. The effect of two iv injections of rhLAMAN given 3 days apart was also studied.

The clearance decreased from bovine to human to mouse LAMAN with plasma half-times of 4, 8 and 12 min, respectively. The apparent half-life of the internalized enzyme was dependent on the enzyme source as well as tissue type and varied between 3 and 16 h.

Injections of 100 mU of mouse LAMAN to α-mKO mice, showed a maximum LAMAN activity in investigated organs at 2–4 h after injection. Between 4 and 10 hrs after injection the enzyme activity decreased rapidly in liver, spleen and kidney with an apparent half-life of about 3 hrs.

The corrective effect on the tissue storage of neutral oligosaccharides was transient but also time-, tissue- and dose-dependent (for time- and tissue dependency, After a single dose of rhLAMAN the maximum corrective effect was observed between 3 and 6 days after injection. In general the corrective effect of the rhLAMAN was higher than that of the mouse LAMAN. Injection of 250 mU rhLAMAN/g body weight followed by a subsequent injection 3.5 days later was sufficient to clear liver, kidney and heart from neutral oligosaccharides. A decrease in mannose containing oligosaccharides was also observed in the brain, with levels lower than 30% of those found in control animals.

Tissue rhLAMAN activity and impact on tissue oligosaccharides in α-mKO mice – extended study 4.2.1.1.3

Another study in α-mKO mice, was conducted to further assess the cellular/tissue uptake of velmanase alfa and investigate the dose-response (**Figure 3**), effects on behavioural deficits (**Figure 4**) and impact on tissue oligosaccharides (**Figure 5**).

Figure 3. LAMAN activity in selected number of tissues from α-mKO mice treated with 2-4 iv injections of 25-500 U velmanase alfa/kg (2.1-42 mg/kg).

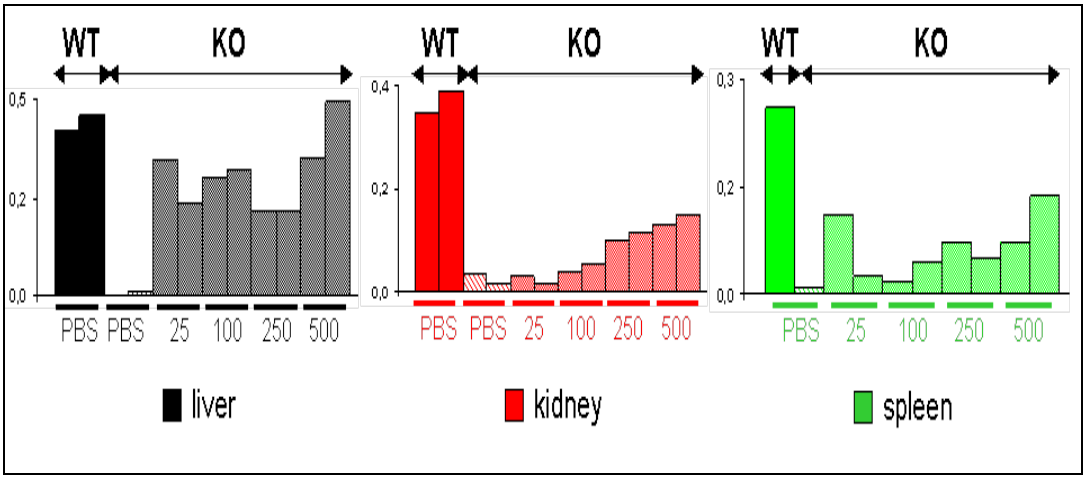


Figure 4. Analyses of neuromotor performance (treadmill) in mock- and ERT-treated α-mKO mice. WT- and ERT-treated α-mKO mice always performed better than mock-treated KO mice, as exemplified by increased error latencies during the training phase (N) and a decrease in the number of errors (O) during the challenge phase of the experiment.

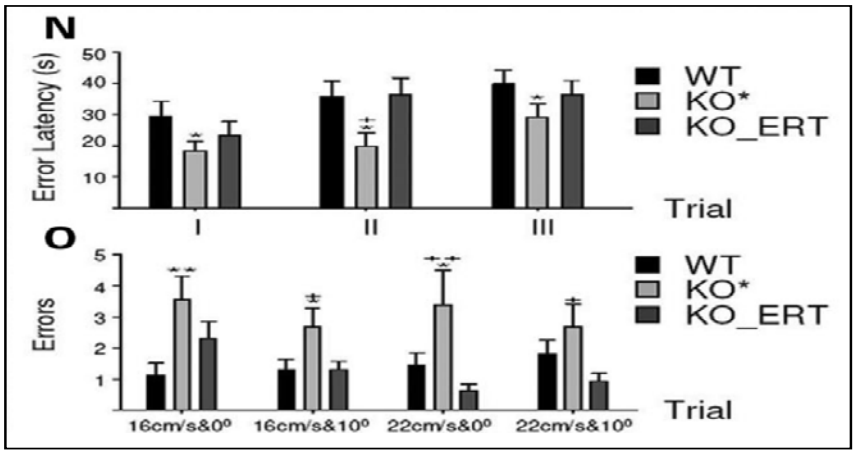
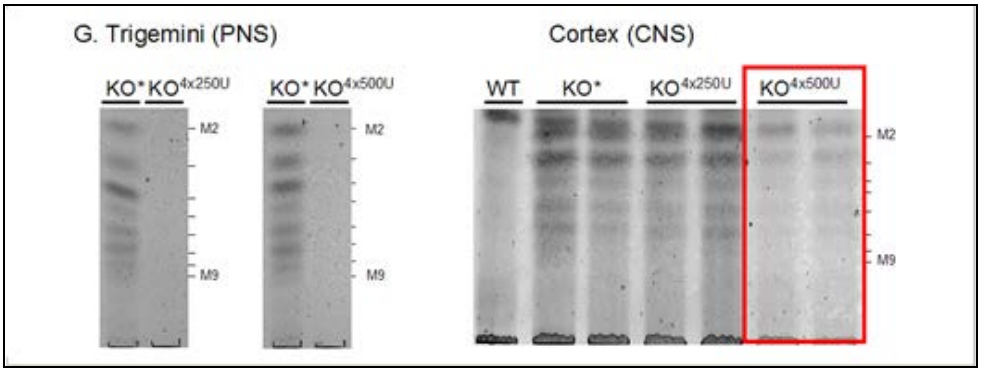


Figure 5. Thin layer chromatograms showing reductions of mannosyl-linked oligosaccharides in the CNS and PNS of α-mKO mice treated with rhLAMAN



Tissue distribution of large scale rhLAMAN material in α-mKO mice – study 4.2.1.17

A separate tissue distribution study in α-mKO mice was conducted to verify the tissue enzyme activity of clinical scale velmanase alfa . A single iv dose of 1000 U/kg showed highest LAMAN activity at 1 hr post dose in liver. The order of activity in other investigated tissues was heart > lung > spleen > thymus > kidney > brain. At 24 hrs post injection, the alpha-mannosidase activity was reduced by more than 50% except for the brain which showed higher enzyme activity at 24 hours compared to at one hour suggesting a slow transport of enzyme across the BBB and/or the blood-CSF barrier.

Tissue LAMAN activity and impact on tissue oligosaccharides in 12 weeks study in younger LAMAN Tg+/KO mice (study 4.2.1.1.5)

Two 12-week efficacy studies were conducted with Tg+/α-mKO mice. One study assessed the dose response of bi-weekly injections with 125, 250, 375 and 500 U/kg (corresponding to 4.8, 9.7, 15 and 19 mg/kg) velmanase alfa and the other assessed the effect of weekly injections with 125 – 750 U/kg (corresponding to 4.7-28 mg/kg) velmanase alfa. In the dose-response study, the dose levels were 125, 250, 375 and 500 U/kg (corresponding to 4.8, 9.7, 15 and 19 mg/kg) and WT mice and Tg+/α-mKO mice injected with PBS served as controls. Activity assessment was based on tissue LAMAN

activity, measurement of β-hexosaminidase (lysosomal enzyme upregulated due to primary sugar storage), oligosaccharide storage in brain and spleen and measurement of free cholesterol in brain and microglia activation.

Velmanase alfa treated Tg+/α-mKO mice showed a dose dependent increase of brain lysate LAMAN activity (5-14% of WT activity) while the β-hexosaminidase activity was reduced/normalized (75-82 % of WT levels) in all treated mice (Figure 2.1.2.6).

A dose-dependent effect on the content of oligosaccharides in brains was also demonstrated with the highest dose (500 U/kg) being most effective. Also the lowest dose of 125 U/kg showed a brain storage reduction of oligosaccharides of > 50%. At this dose, a complete reduction of stored sugars was observed in the spleen.

The staining of brain tissue of WT mice and PBS and velmanase alfa treated Tg+/α-KO mice for free cholesterol and activated microglia (CD68 positive cells), showed no change in free cholesterol in velmanase alfa treated Tg+/α-KO mice whereas microglia activation was reduced in both the lowest and highest velmanase alfa dose, 125 and 500 U/kg, respectively.

In the 12-week study in Tg+/α-mKO mice where the injection frequency was reduced to once weekly (4.2.1.1.5), the highest increase in brain lysate LAMAN activity was observed in brains of mice treated with 750 U/kg, the highest dose investigated, whereas use of lower doses did not demonstrate a dose dependent uptake of velmanase alfa. Measurements of β-hexosaminidase activity revealed reduced enzyme levels in all ERT treated mice when compared to non-treated mice independent of the used dosage but this effect was less pronounced compared to that observed in bi-weekly treated mice. The high dose of 750 U/kg were needed to significantly reduce storage of mannosyl-linked oligosaccharides in the brain and decrease microglia activation thus demonstrating the importance of dosing frequency (continuous exposure) for pharmacological response.

Tissue LAMAN activity and impact on tissue oligosaccharides in 12 weeks study in older LAMAN Tg+/KO mice (study 4.2.1.1.6)

To extend the information obtained in the dose-response study, a separate experiment was conducted in "older" Tg+/α-KO mice (4 months old at start of treatment) where velmanase alfa was administered as biweekly injections of 500 U/kg (15.6 mg/kg) for 14 weeks (4.2.1.1.6). Similar to previous studies, 500 U/kg was effective in reducing oligosaccharide tissue storage and LAMP-1 levels and in normalizing lysosomal enzyme levels. CD68 staining showed clear attenuation of microglia activation in the hippocampus, cerebral cortex and thalamus but not in the cerebellum. Improved neuromotor function was observed when assessed in the treadmill and there were indications of improvement in short-term working memory but not in "long-term reference memory"; the latter assessment were from water maze experiments.

Tissue LAMAN activity and impact on tissue oligosaccharides in 39 weeks study in LAMAN Tg+/KO mice (study 4.2.1.1.9)

The effect of once weekly dosing of velmanase alfa was examined also in a longer study (9 months)) than the above referenced 12-week study (4.2.1.1.6). The dose administered was 500 U/kg (15.6 mg/kg), a dose also used in the 12-week study. Compared to the 12-week study, a more extensive battery of endpoints was investigated. Velmanase alfa reduced oligosaccharide storage and neuro-inflammation in hippocampus. Treatment of 30 weeks or longer improved spatial-cognitive abilities of α-mannosidosis mice to a significant degree whereas the shorter treatment period (10 weeks+)

resulted in a more modest effect. Long-term ERT was, however, unable to restore higher cognitive abilities (measured in the Morris-type water maze with hidden escape platform) to the level observed in healthy mice.

Secondary pharmacodynamic studies

Due to the specific activity of velmanase alfa no secondary pharmacodynamic effects are anticipated and therefore secondary pharmacodynamic studies were not conducted.

Safety pharmacology programme

The potential adverse effect of velmanase alfa on vital organs system was investigated in the repeat dose toxicity studies which are presented in Section 2.2.4 of this Report.

Pharmacodynamic drug interactions

No pharmacodynamic interaction studies were submitted as the applicant considered that unless patients are treated other ERT's which utilizes the M6P receptor for cellular uptake of the enzyme, no pharmacodynamic interactions are expected when using the velmanase alfa.

2.3.3. Pharmacokinetics

Absorption

The plasma disposition of iv administered velmanase alfa was similar in the species used for repeat dose toxicity testing (**Table 2**).

Table 2. Mean pharmacokinetic parameters after iv administration in mice, rats, rabbits and monkeys; data presented are from the lowest dose investigated**.**

Species/ Study ID	Dose (mg/kg)	Dose (IU/kg)	main PK parameters[a]				Single/ Repeated dose
			C_{max} [a,b)] (µg/ml)	AUC [a,b,c)] (min·mg/ml)	$t_{½}$ (min)	CL (ml/min/kg)	
Mice/ 4.2.3.2.2	5.4	144	90.9/94.5	42.9/52.7	510/550	0.126/0.102	Single
			57.1/42.1	57.9/35.0	1709/1023	0.093/0.154	Rep. 26W
Rats/ 4.2.2.7.1	5.0	141	113/109.5	97.1/103.1	762/953	0.052/0.048	Single
Juvenile Rats/ 4.2.3.5.4.2	5.5	142	96.5/164.7	131.7/180.1	1226/861	0.042/0.031	Rep. 10W
Pregnant Rats/ 4.2.3.5.2.2	3.3	ND	79.1	31.1	516	0.123	Day 1 of EFD study
Pregnant Rabbits/ 4.2.3.5.2.5	3.3	85	122	38.1	ND	0.087	Day 1 of EFD study
Monkeys/4.2.3.2.1	5.1	131	98.3/98.3	75.6/70.7	819/715	0.070/0.079	Single
			55.1/58.9	6.9/11.3	53/109	1.258/0.673	Rep. 4W
			90.9/68.2	17.7/13.5	128/119	0.383/0.664	Rep. 13W

a) *Female/male values are given;*

b) *b) The weight unit for Cmax was chosen to be "µg" and "mg" was chosen for AUC in order to obtain smaller and more readable numbers*

c) *c) AUCinf is given except for in rabbits where AUC0-24 is reported ND = Not determined*

Distribution

The PK data obtained from samples collected on the first day of dosing in the conducted repeat dose toxicity study in monkeys (4.2.3.2.1), the pharmacokinetic study in rats (4.2.2.7.1) and the 26-week toxicity study in Tg+/α-mKO mice (4.2.3.2.2), gave volume of distribution (Vd_{area}) figures in low dose females/males of 80/77, 57/66 and 92/81 mL/kg, respectively. The calculated Vd_{area} in mice was much higher (approximately 2.5-fold) when calculated from the 26-week data than one calculated from the Day 1 data.

Metabolism and Excretion

There are no data that specifically address the metabolism or degradation of velmanase alfa. It is expected that velmanase alfa, just like the endogenous LAMAN and other proteins, will undergo proteolytic digestion to its amino acid constituents and subsequently to CO_2 and H_2O when fully metabolised.

Pharmacokinetic drug interactions

There are no non-clinical studies addressing pharmacokinetic drug interactions. Such interactions affecting either the safety or efficacy of the product are not expected owing to the nature of the product (endogenous enzyme) and the method of administration (intravenous injection).

2.3.4. Toxicology

The non-clinical toxicity of velmanase alfa has been investigated in a set of repeat dose toxicity studies as well as in a full program of reproduction toxicity studies including a 10-week study in the juvenile rat. These studies were all GLP compliant.

Single dose toxicity

No specific single dose toxicity studies was performed in accordance with GLP but data on the acute toxicity of velmanase alfa can be extracted from investigative/pilot studies in the juvenile rat, in the monkey and in the rabbit.

<u>Acute toxicity in rat</u>

In a preliminary juvenile toxicity study in rats (Study 4.2.3.5.4.1), groups of 11 and 28 day old rats were administered velmanase alfa iv at dose levels of 466 and 1400 U/kg twice weekly (~19 mg/kg and 58 mg/kg, respectively). After the first dose and thereafter, swollen feet/limbs, swollen muzzles and/or piloerection, which lasted up to 4 hours after dosing, were observed. In high dose animals, excessive grooming was also noted. When rats, who had been treated twice weekly for three weeks at

1400 U/kg (~58 mg/kg) were dosed twice daily for 3 consecutive days no clinical observation was observed from the morning of the second consecutive dosing day and throughout the rest of the dosing period.

Acute toxicity in monkey

In a dose escalation study in monkeys where velmanase alfa was administered biweekly as a slow iv bolus for 8 weeks, 1400 U/kg was shown to cause a marked reduction in food consumption whereas 466 U/kg was associated with increased salivation (Study 4.2.3.1.1).

Acute toxicity in rabbit

In a small study in rabbits (n=2), a slow iv bolus dose of approximately 485 U/kg (20 mg/kg) was found to be well tolerated (Study 4.2.3.5.2.3).

Repeat dose toxicity

The repeat-dose toxicity studies are summarised in **Table 3.**

Table 3. Major findings in repeated dose toxicology studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
26 weeks Tg+/α-mKO mice 4.2.3.2.2 GLP	10/sex/group + 3 or 9 satellite Tg+/α-mKO mice	0, 144,433,1300 U/kg IV – twice weekly Corresponding to 5.4, 16 and 49 mg/kg biweekly	26 weeks	1300 U/kg/biweekly	No treatment related findings
MTD study cyn. monkey 4.2.3.2.3 Non-GLP	1m, 1f cynomolgous monkey – escalating dose	Dose esc. 155, 466, 1400 U/kg IV twice weekly	8 weeks		
Feeding study 4.2.3.2.4 Non-GLP	3f cynomolgous monkey	1310 U/kg IV twice weekly	4 weeks		
13-weeks study in Cynomolgous monkey 4.2.3.2.1 GLP PWM0002	4/sex/group cynomolgous monkey	0, 131, 414, 1310 U/kg IV twice weekly Corresponding to 5.1, 16 and 51 mg/kg biweekly	13 weeks	NOAEL = 1310 U/kg/biweekly	In treated animals ↑ inc & sev. hyperplasia of lymph nodes or lymphoid tissue. dose response and /or sex dependency was Difficult to establish

Genotoxicity and carcinogenicity

Since velmanse alfa is a recombinant human enzyme, no genotoxicity or carcinogenicity studies were conducted, in accordance with the ICHS6 (R1) guidance on Preclinical Safety Evaluation of Biotechnology- Derived Pharmaceuticals (EMA/CHMP/ICH/731268/1998).

Reproduction Toxicity

Investigations of the toxicity of velmanase alfa on reproduction consisted of a standard package of reproduction toxicity studies i.e. a fertility and early embryonic development study in the rat, two embryo-fetal development studies, one in the rat and one in the rabbit (both supported by preliminary

or dose-finding studies) and a prenatal and postnatal development study in the rat. In addition, a 10-week juvenile rat toxicity study was conducted and supported by a pilot study in juvenile animals.

Table 4. Observations in reproductive and developmental toxicity studies

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Male fertility 4.2.3.5.1.1	20 Crl:WI (Han) rats 20/group	0, 3.3, 10 or 30 mg/kg IV biweekly	Throughout the study Necropsy 2 wk post mating	**≤10** swollen muzzles (after 2nd dose), **=30** minor effects on BW and FC 31/103 antibody titers (f & m together)	NOAEL for fertility 30 mg/kg biweekly
Female fertility 4.2.3.5.1.1	Crl:WI (Han) rats 20/group	0, 3.3, 10 or 30 mg/kg IV biweekly	During pre-paring and on GD1 and GD6 - Necropsy GD13	**≤3,3** **≤10** swollen muzzles (after 2nd dose), 3f piloerection (after 6th dose) **=30** minor effects on BW and FC , 1 f piloerection (after 6th dose) 31/103 antibody titers (f & m together)	NOAEL for fertility 30 mg/kg biweekly
EFD RAT – preliminary 4.2.3.5.2.1	7 f Crl:WI(Han) rats	0,20 mg/kg daily	GD6-GD17	**=20** swollen muzzles (6/7) enduring for >4 hr in 2 animals only at first day	nd
EFD-RAT-main 4.2.3.5.2.2	Crl:WI (Han) rats 20/group	0, 3.3, 10, 20 mg/kg **daily**	GD6-GD17	**F0** **= 20** swollen mouth @GD6 and 7, laboured breathing GD13 (1f), piloerection (GD13, 1f and GD14 1f) piloerection was, ↓ BW @GD20, ↓ food intake GD12-GD15 and overall mean food intake **F1** **=20** Dam# 67 Foetus R2 Duplicated 1st to 6th sternebrae Dam# 68 Foetus L6 Cleft palate and palatine Dam# 75 Foetus L1 Severely bent scapula Foetus R4 Severely bent scapulae Thus: 4/223 fetuses in 3/20 litters of high dose group had major abnormalities	F0= 20 mg/kg daily F1= ?
EFD Rabbit-preliminary	New Zeeland White Rabbits, 5/group	0, 20 mg/kg daily	GD6-GD18	**=20** slight ↓ in BW gain	F0 F1
EFD Rabbit - Main *4.2.3.5.2.5*	New Zeeland White Rabbits, 22/group	0, 3.3, 10, 30 mg/kg **daily**	GD6-GD18	**F0** **≤3,3** ↓ Food intake from GD12 **≤10** ↓ Food intake remained until GD24 **=30** ↓ in BW gain from GD12, **F1** **=30** ↓ Group mean foetal and placental weights	F0 = 30 mg/kg/day F1 = 30 mg/kg/day
PPND rat 4.2.3.5.3.1	Crl:WI (Han) rats 22/group	0, 3.3, 10, 30 mg/kg every three days.	GD6 to Lactation D20	**F0** **≤3,3** 2f (1/2 was euthanized) with clonic convulsions on D1 and D8 of lactation without macroscopic abnormalities, **≤10** GD15 piloerection, decreased activity, slow breathing (4f) and 2/4 also prostrate ¼ found dead on GD16 **=30** swollen muzzles GD6-GD9, on GD16 2f euthanized due to	F0 = not determined F1 = 30 mg/kg every 3 days

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
				piloerection, decreased activity, slow breathing, 1 had reddened caecum, ileum and a Gelatinous & had pale liver and kidneys, ↓ food intake & BW after first dose	
DRF juvenile rat study 495110	Group 1-3: 4/sex/group Group 4-5: 2/sex/group	Gr. 1-3: 0, 466,1400 U/kg (=0, 19, 58 mg/kg) BW IV Gr 4: 466 – 1400 esc. dose Gr 5: 1400 U/kg + 3 daily @ end	Group 1-3 From PND 11 (day1) 10 weeks Group 4-5 PND 28 on.	**= 1400** swollen feet limbs, swollen muzzles and piloerection up to 4 hr after last dose, excessive grooming symptoms decreased upon daily dosing	
10 weeks juvenile rat 495126	Sprague-Dawley Rat, 12/sex/group	0, 142, 426, 1290 U/kg/biweekly (= 0, 5.5, 17 and 50 mg /kg/ **bi weekly**), IV	From PND 11 (day1) 10 weeks	≤142 swollen tail (1f) ≤ 426 swollen feet/limbs, muzzles and swollen tail Bases (2m, 2f) =1290 swollen feet/limbs (all, from 5th day of dosing), muzzles (4m, 3f) and tail Bases (1f)	NOAEL= 1290 U/kg

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

In the conducted 10-week juvenile toxicity study in rats, which used bi-weekly iv dosing with up to 1290 U/kg (50 mg/kg), the assessment of "development parameters" included monitoring of vaginal opening and preputial separation, performance on rota-rod, open field, water maze and a functional observation battery. Except from the common observation in rats exposed to velmanase alfa of swollen feet/limbs, swollen muzzles or swollen tail bases that were transient, no treatment-related findings were observed. The main findings from these studies are summarised in **Table 5.**

Table 5. Major findings from studies in which the offspring (juvenile animals) were dosed and/or further evaluated

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL SM (AUC)*	Major findings
495110 / (4.2.3.5.4.1) preliminary	rat Crl:CD®(SD) 4 (♀/♂) group + rat Crl:CD®(SD) 2 (♀/♂) group	iv, (0, 466, 1400) U/kg/2 x w ~ (0, 19, 58) mg/kg/2 x w	10w	NOEL 164 U/kg ~ 6.7 mg/kg	**(466, 1400) U/kg** (swollen feet/limbs, swollen muzzles, piloerection), transient (♀/♂) **1400 U/kg** (excessive grooming, subdued behavior) transient (♀/♂), liver weight ↑ slight ♂
495126 / (4.2.3.5.4.2) pivotal GLP	rat Crl:CD®(SD) 12 (♀/♂) group	iv, (0, 142, 426, 1290) U/kg ~ (0, 5.5, 17, 50) mg/kg	2 x w / 10w	NOAEL 1290 U/kg ~ 50 mg/kg 57 x (♂, w10) 48 x (♀, w10)	**1290 U/kg** swollen muzzle ♂ transient **(426, 1290) U/kg** (swollen feet/limbs, swollen tail bases) transient **142 U/kg** swollen tail base transient **(0, 142, 426, 1290) U/kg** liver weight ↑ ♂ slight, time to vaginal opening ↑ slight, phosphate ↑ ♂ slight AB present in 1 animal

GLP (good laboratory practice), w (week), d (day), on day), ♂ (male,), ♀ (female), iv (intravenous), AB (antibody), ↓ (decrease), ↑ (increase), NOEL (non-observed effect level), NOAEL (non-observed adverse effect level), SM (safety margin), AUC (area under the curve)

rat** *(♀/♂, w10)* C_{max} *1430/1337 µg/ml, AUC 1517/1273 mg min/ml,* ***human *clinical exposure (1g, rhLAMAN 03)* C_{max} *17.3 µg/ml, AUC 26.64 mg min/ml*

Toxicokinetic data

Investigations on potential untoward effects on vital organ system (the respiratory, CNS and cardiovascular system), the repeat dose toxicity programme and the reproduction toxicity studies were used to estimate safety margins for velmanase alfa (**Table 6**).

Table 6. Safety Margins in toxicity studies conducted with velmanase alfa

Study type	NOAEL[1]	Safety Margins[2]		
Safety Pharmacology		**mg/kg**	**mg/m²**	**AUC (h*µg/mL) Male/Female**
CNS, respiration (in conjunction with 10+-week rat Juvenile study)	1290 U/kg (50 mg/kg)	100	16	353/296
Cardiovascular (in conjunction with 13-week monkey study)	1310 U/kg (51 mg/kg)	102	32	229
Repeat Dose Toxicity				
TG+/KO Mouse (4.2.3.2.2)	1300 U/kg (49 mg/kg)	98	6	121
Monkey (4.2.3.2.1)	1310 U/kg (51 mg/kg)	102	32	229
Rat Juvenile (4.2.3.5.4.2)	1290 U/kg (50 mg/kg)	100	16	353/296
Reproduction Toxicity Studies				
Fertility and Early Embryonic Development	30 mg/kg	60	8	ND
Embryo-foetal Development - Rat	20 mg/kg	40	6	48
Embryo-foetal Development - Rabbits	30 mg/kg	60	18	32
Pre- postnatal Development	30 mg/kg	60	8	ND

*[1]The NOAEL's related to bi-weekly dosing in all studies except for the EFD studies in rats and rabbits where daily dosing during organogenesis was used.[2] The safety margins calculations have adjusted for the different dose regimens in the repeat dose toxicity studies compared to the clinical use which is once weekly. For the reproduction studies, there has been no adjustment for the different regimens used when calculating safety margins on a mg/kg and mg/m² basis. [3]The steady-state mean clinical Cmax was 7.5 µg/mL and AUC_{0-168} 143.1 µg*h/mL, n=12; from Study rhLAMN-10. ND = not determined; Animal AUC values are taken from the last sampling time during the study*

Local Tolerance

Local Tolerance was investigated by a thorough macroscopic and histopathological examination of the injection/infusion sites from the repeated dose toxicity studies and the juvenile rat developmental study. There were no findings in the 26-week TG+KO mouse study or in the 10 week juvenile rat study. In the 13 week monkey study, which in contrast to the rodent studies used a 1 hour infusion, a number of histological changes were observed at the infusion site primarily involving the tail vein. However, these changes were also observed in control animals and were attributed to the mechanical trauma associated with the repeated catheterization of the infusion site vein.

Other toxicity studies

Antigenicity

The presence of antibodies against the product has been assessed in rat and monkey in four studies.

Monkey PMW001

Sera from rh-LAMAN injected monkeys taken six weeks after study start from three individual cynomolgus monkeys were analysed for inhibitory antibodies. The inhibition was calculated by comparing each immune serum to a pool of cynomolgus monkey pre-sera. The average inhibition for each serum was significantly below 8 % and was not considered to be inhibitory. LAMAN activity was also measured in the samples. The results for all three sera were below the linear range of the assay.

Monkey- CRL 515896

Sera from two rh-LAMAN injected monkeys (taken 18, 39 and 54 days from study start) were analysed. The sera were compared to a pool of cynomolgus monkey non immune sera. No sample was found to be inhibitory.

Monkey PWM002

Sera from six rhLAMAN injected monkeys (two per dose group, 4 and 13 weeks from study start) were analyzed. The inhibition was calculated by comparing each immune serum to a pool of cynomolgus monkey pre-sera 1010047180, 1010047181, 1010047182 and 1010047183 (from study CRL 515896). None of the sera gave inhibition and there was no detectable rhLAMAN activity in any samples.

Rat - CRL495110

In the rat study all samples contained high concentrations of rhLAMAN and it could not be excluded that these samples contain inhibitory antibodies. Sera collected at week 5 and 10 from 1 male and one female from each of the two dose groups investigated in the preliminary juvenile rat toxicity study was also assayed for inhibitory antibodies. Since high velmanase alfa concentrations were present in the samples assayed, the inhibitory activity of the antibodies could not be determined.

Other studies

Velmanase alfa is a human enzyme and the protein is produced in CHO cells. The protein will be broken down into amino acids, which are naturally occurring in the human body and the environment. Given the nature of the product and its mechanism of action, no dedicated studies were submitted to address immunotoxicity, dependence, metabolism, and impurities.

2.3.5. Ecotoxicity / environmental risk assessment

No ERA specific studies were submitted, as velmanase alfa is a therapeutic enzyme which is classified as a protein and in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), it is considered unlikely that Lamzede will pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

In vitro experiments showed a low uptake (0.5 to 2%) of velmanase alfa in cells of different tissues and species, among them fibroblasts of an alpha-mannosidosis patient.

When single fibroblast cell lines of several species were investigated for velmanase alfa uptake, mouse and human fibroblasts showed the highest uptake, rat, rabbit and cynomolgous monkey intermediate uptake and dog and pig fibroblasts the lowest uptake. This observation was used for the selection of mice, rats, rabbits, monkeys as the species in non-clinical safety studies.

Addition of M6P to the incubation medium containing velmanase alfa led in wild-type (WT)-cells and cells expressing at least one type of M6P receptor led to a decrease of the amount of enzymatic activity taken up into cells. This result and the observation that velmanase alfa is taken up to a much smaller extent in M6P receptor deficient cell lines compared to M6P receptor non-deficient cell lines indicates M6P receptor dependent uptake into cells. As uptake of enzymatic activity was also demonstrated using high velmanase alfa concentrations in fibroblasts lacking M6P receptors, M6P receptor independent uptake also contributes to the uptake of velmanase alfa into cells. These results indicate that there are at least two mechanisms involved in the uptake of velmanase into cells.

Intracellullar distribution to lysosomes was indicated using immunohistochemistry after *in vitro* incubation of WT fibroblasts in medium containing a high velmanase alfa concentration.

Relative high doses were needed to demonstrate a clear reduction of mannosyl-linked oligosaccharides in central and peripheral nervous tissues; four injections of 500 U/kg (~42 mg/kg) were needed for reduction in the cortex while 250 U/kg was needed for a reduction in the neurones of the trigeminal ganglion. The four injections of 500 U/kg in α-mKO mice resulted in 14.8% of the measured LAMAN activity in brain lysates of WT mice suggesting that not complete restoration of LAMAN activity is needed for significant reduction of CNS oligosaccharides.

Examination of neuromotor (treadmill), total exploratory (open-field, elevated plus maze) and neurocognitive (water maze) abilities 4 days after the last injection in velmanase alfa-treated α-mKO mice (biweekly injections for two weeks of 500 U/kg) showed a complete or nearly complete reversal of ataxic symptoms but no or only marginally improvement in neurocognitive and exploratory defects. A possible explanation for this is that two weeks of treatment may be too short for reversing neurobehavioral deficits.

Although proof of concept was shown in the mouse model, extrapolation of the efficacy of the product in mice to the human situation was hampered, as mice were dosed higher than humans. In addition, the *in vitro* assay showed that uptake in human cells reached a plateau at 200 mU/mL (which is likely reached as Cmax, with the recommended once weekly dose of 1 mg/kg). However, uptake in mice cells was more efficient than in human cells and did not reach a plateau at the highest concentration used in the assay of 400 mU/mL. C_{max} in animals used for *in vivo* PD studies reaches levels of 12 fold (low dose) and 50 fold (high dose) the highest tested concentration in the *in vitro* PD studies 400 mU/mL. Thus, it is assumed that more velmanase alfa is taken up in mice cells. As a reduction of oligosaccharides was observed in mouse brains, it was concluded that velmanase alfa can cross the BBB. However, in humans, velmanase alfa activity was not detected in the CSF, indicating that most likely it does not cross the BBB in humans.

Single dose toxicity studies were not conducted. Acute toxicity symptoms, retrieved from preliminary studies or dose escalation studies, revealed swollen feet/limbs, swollen muzzles and piloerection in rats. Monkeys showed marked reduction in food consumption and in rabbits velmanase alfa was well tolerated.

A 26 week repeated dose toxicity study has been conducted in immune tolerant transgenic Tg+/α-mKO mice. In this study, antibodies against velmanase alfa were developed as well as in the 13 weeks monkey repeated dose study. Antibodies seem to affect T ½ of and exposure to velmanase alfa. In the juvenile study in rat, one high dose animal developed antibodies without effect on exposure and T ½. In the EFD studies, both rat and rabbits developed antibodies against velmanase alfa, which seems to decrease exposure levels. As exposure in animals was sufficiently in excess compared to exposure in humans, antibody formation does not compromise the safety assessment of velmanase alfa in animals.

Velmanase alfa is a recombinant human enzyme and genotoxicity studies are not warranted (ICH S6). The absence of genotoxicity and carcinogenicity studies is thus agreed.

The applicant did not submit a complete tissue distribution study. However, the distribution and efficacy pharmacology study present in the PD section suffices as a tissue distribution study for this product.

Fertility, embryonic foetal development, pre and post-natal development were conducted in Han Wistar rats and the juvenile toxicity studies have been conducted in Sprague Dawley rats. As a second species for EFD study, New Zeeland White rabbits were used.

In the fertility studies in male and female Han Wistar rats at doses of 3.3, 10 and 30 mg/kg biweekly, swollen muzzles and piloerection (females) were observed starting at mid dose treated animals, which is not regarded as a serious adverse event.

In the rat EFD study, the F1 generation showed major abnormalities in 4/223 foetuses present in 3/20 litters of high dose group. Effects were seen at a ± 50 fold higher C_{max} and exposure, compared to humans. Data from historical controls are not provided, but considering the nature of the product and the indication of enzyme replacement, it is unlikely that these effects are related to treatment nor relevant for humans.

In the main juvenile toxicity study Sprague Dawley rat were dosed with 5.5, 17 or 50 mg/kg biweekly (corresponding to 142, 426 and 1290 U/kg, respectively). Swelling was observed in the feet/limbs, muzzles and tail bases in all groups and as the rats did not appear to be in any pain, and the NOAEL was considered to be the high dose, i.e. 1290 U/kg administered twice weekly.

Antibodies against velmanase alfa develop in nearly all animal studies including the 26 weeks study with velmanase alfa in Tg+/α-mKO mouse, expected to be immune tolerant, as well as in the 13 weeks monkey repeated dose study. Antibodies affect T½ of and exposure to velmanase alfa. In the juvenile study in rat, one high dose animal developed antibodies without effect on exposure and T½. In the EFD studies, both rat and rabbits developed antibodies against velmanase alfa, which decrease exposure levels.

The analysis of presence of velmanase alfa inhibitory antibodies is only possible when no velmanase alfa stimulatory activity is present in the sample. For the rat, inhibitory antibodies could not be detected due to presence of velmanase alfa activity. In the monkey, it seemed that antibodies were not inhibitory. However as exposure in mice is considerably higher than human exposure, the assay may also be of limited relevance.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of velmanase-alfa have been adequately characterised from a non-clinical perspective.

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 ID	Number of patients	Design	Treatments	Number of Patients per Group Enrolled / Completed	Duration	Primary efficacy endpoints
rhLAMAN-01	45	Natural history	None	45/43	2.5 years	N/A
rhLAMAN-02	10	Dose escalation	Weekly IV dosing of velmanase alfa: 6.25 U/kg 12.5 U/kg 25 U/kg 50 U/kg 100 U/kg	 2/2 2/2 2/2 2/2 2/2	 5 weeks 4 weeks 3 weeks 2 weeks 1 week	N/A
rhLAMAN-03	10	Open-label, randomised, controlled, parallel group study	Weekly IV dosing of velmanase alfa: 25 U/kg 50 U/kg	 5/4 5/5	12 months	N/A
rhLAMAN-04	9	Open-label study	Weekly IV dosing: 1 mg/kg velmanase alfa	9/9	Up to 20 months	Change from Baseline in serum oligosaccharides, CSF oligosaccharides 3MSCT, 6MWT, PFTs
rhLAMAN-05	25	Double-blind, randomised, placebo-controlled, parallel-group study (Pivotal study)	Weekly IV dosing: 1 mg/kg velmanase alfa Placebo	15/15 10/10	12 months	Change from Baseline to Month 12 in serum oligosac-charides, 3MSCT (primary analysis also performed on the prioritized secondary endpoints 6MWT and FVC % predicted)
rhLAMAN-07[a]	7	Open-label study	Weekly IV dosing: 1 mg/kg velmanase alfa	7/NA	Ongoing	N/A (Efficacy endpoints were secondary in this study.)
rhLAMAN-09[a]	8	Open-label study	Weekly IV dosing: 1 mg/kg velmanase alfa	8/NA	Ongoing	N/A (Efficacy endpoints were secondary in this study)

rhLAMAN-10	18	Open-label study Pivotal study	Weekly IV dosing: 1 mg/kg velmanase alfa As part of ongoing compassionate use programme	18/18	1 week of treatment /assess-ments and then return to ongoing compassionate use programme	Change from Baseline in serum oligosaccharides, 3MSCT

[a] *Studies rhLAMAN-07 and rhLAMAN-09 are long-term follow-up studies of identical design. Study -07 is for patients in France, and Study -09 is for patients in Poland and Norway. The data collected in these studies have not been summarised separately but are included in the dataset for the rhLAMAN-10 integrated analysis.*
Abbreviations: IV=intravenous; NA=not applicable

2.4.2. Pharmacokinetics

The PK profile of velmanase alfa was investigated following a single IV infusion at escalating doses (6.25 to 100 U/kg, approximately 0.2 to 3.2 mg/kg) and after multiple infusions following weekly doses of 25 or 50 U/kg (0.8 or 1.6 mg/kg) up to approximately 4 years. These data has been generated from 34 patients diagnosed with alpha-mannosidosis from 6 clinical studies.

The PK Analysis Set was defined as all patients from the safety analysis set excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK.

Dose Conversion

The dose selected for clinical development was rounded up to 1 mg/kg for dose convenience. Although the 1 mg/kg dose is actually equivalent to a dose of approximately 30 U/kg, for the purposes of the integrated PK analyses, the 25 U/kg (0.8 mg/kg) dose was considered to be equivalent to 1 mg/kg. This was considered acceptable as all 16 patients received 1 mg/kg at first and last PK assessment (Day 1 and steady state, respectively) except for one patient who received 25 U/kg at Day 1.

Absorption

After single-dose administration, Cmax appeared to increase proportionally with the dose up to 100 U/kg, except from the lowest 6.25 U/kg, where dose-normalized Cmax was up to 50% lower as compared to other doses. At steady-state Cmax was proportional at both 25 and 50 U/kg. AUC increased in a more than dose-proportional manner after both a single dose and at steady-state. At steady state after weekly infusion of 1 mg/kg, mean Cmax was approximately 8000 µg/L and was reached at 1.8 hours after the start of the infusion. The mean AUC accumulation ratio at steady state versus Day 1 was 1.6 (range 1.0 to 1.9; CV 16%). Mean t1/2 was approximately 2-fold higher (15 vs 30 hrs), mean total body clearance was lower (10.7 vs 6.7 ml/h/kg), and the volume of distribution was slightly higher (2.2 vs 2.7 L/kg).

Distribution

The steady state volume of distribution was low (0.27 L/kg), indicating distribution confined to plasma.

Elimination

Velmanase alfa is a recombinant version of the naturally occurring human enzyme, and the metabolic pathway is, therefore, predicted to be similar to other natural occurring proteins that degrade into small peptides and finally into amino acids. Mean clearance (normalised by body weight) was 6.7 mL/h/kg after repeated weekly dosing of 1 mg/kg CHF-LMZYMAA1. At steady state, velmanase alfa clearance normalised by body weight in paediatric patients (<18 years, N=4) was higher than clearance in adult patients (≥18 years, N=8): 86 mL/h/kg versus 57 mL/h/kg, respectively. Mean elimination half-life was 30 hours after repeated dosing.

Dose proportionality and time dependencies

Dose proportionality was evaluated based on the data from studies rhLAMAN-02 and rhLAMAN-03.

The mean velmanase alfa serum concentrations over 7 days of a single dose of 6.25, 12, 25, 50 or 100 U/kg from Study rhLAMAN-02 is presented in **Figure 6**. The PK profile for all patients which received the proposed therapeutic dose of 1 mg/kg is presented in **Table 7**.

Figure 6. Superimposed Mean Velmanase Alfa Serum Concentrations in Patients Following IV Administration of velmanase alfa at the Doses of 6.25, 12.5, 25, 50, 100 U/kg body weight (Studies rhLAMAN-02 and rhLAMAN-03)

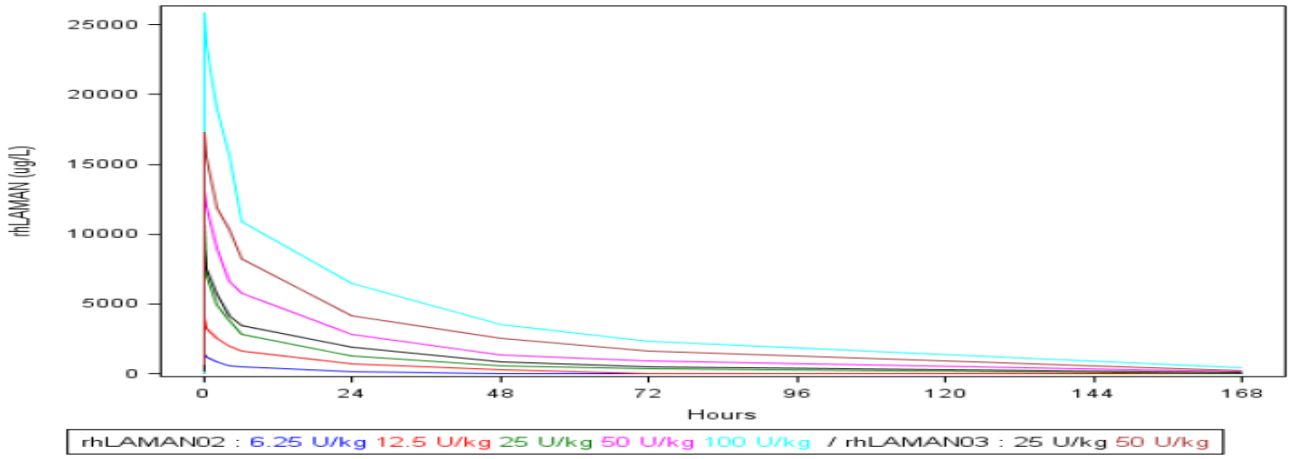


Table 7. PK Parameters for Patients who Received 1 mg/kg velmanase alfa (PK Analysis Set)

		Day 1[a]	Steady state
AUC_{0-t} (h*µg/L)	n	16	12
	Mean (SD)	87052.51 (27110.75)	143128.85 (32730.06)
	Median (min, max)	84924.41 (40480.54, 134454.42)	141186.35 (91882.00, 202998.52)
	CV%	31.14	22.87
	Geometric mean	82771.20	139614.45
AUC_{inf} (h*µg/L)	n	15	12
	Mean (SD)	99913.60 (27792.01)	158877.64 (38824.62)
	Median (min, max)	97966.78 (46911.37, 145172.35)	155211.96 (98340.26, 228700.71)
	CV%	27.82	24.44
	Geometric mean	95956.32	154395.38
$\%AUC_{extr}$ (%)	n	15	12
	Mean (SD)	10.42 (2.89)	9.54 (2.48)
	Median (min, max)	10.28 (6.98,18.50)	8.91 (6.57 16.00)
	CV%	27.77	26.04
	Geometric mean	10.10	9.29
C_{max} (µg/L)	n	16	12
	Mean (SD)	8488.75 (4463.84)	7485.00 (1100.33)
	Median (min, max)	7775.00 (4000.00, 23200.00)	7555.00 (5570.00, 9650.00)
	CV%	52.59	14.70
	Geometric mean	7729.78	7409.39
t_{max} (h)		16	12
	Mean (SD)	1.851 (0.931)	1.781 (0.317)
	Median (min, max)	1.750 (0.667, 3.500)	1.658 (1.483, 2.483)
	CV%	50.294	17.777
	Geometric mean[b]	1.714	1.765
CL (L/h/kg)	n	15	12
	Mean (SD)	0.0107 (0.0038)	0.0067 (0.0018)
	Median (min, max)	0.0091 (0.0069, 0.0213)	0.0065 (0.0044, 0.0103)
	CV%	35.4021	26.4465
	Geometric mean	0.0102	0.0065
V (L/kg)	n	15	12
	Mean (SD)	0.217 (0.037)	0.274 (0.037)
	Median (min, max)	0.216 (0.137,0.280)	0.267 (0.209, 0.339)
	CV%	17.130	13.479
	Geometric mean	0.213	0.272
$t_{1/2}$ (h)	n	15	12
	Mean (SD)	15.13 (4.21)	29.88 (6.88)
	Median (min, max)	14.58 (7.91, 21.08)	31.53 (18.35, 40.93)
	CV%	27.85	23.01
	Geometric mean	14.53	29.06
λ (/h)	n	15	12
	Mean (SD)	0.0500 (0.0172)	0.0246 (0.0069)
	Median (min, max)	0.0475 (0.0329, 0.0876)	0.0220 (0.0169, 0.0378)
	CV%	34.3303	27.9022
	Geometric mean	0.0477	0.0239

The mean AUC accumulation ratio at steady state versus Day 1 was 1.6 (range 1.0 to 1.9; CV 16%).

Mean t1/2 was approximately 2-fold higher (15 vs 30 hrs), mean total body clearance was lower (10.7 vs 6.7 ml/h/kg), and the volume of distribution was slightly higher (2.2 vs 2.7 L/kg).

Intra- and Inter-Individual Variability in AUC_{inf} and C_{max}

Mean intra-individual variability in AUC_{inf} and C_{max} (the mean of all individual CV%) was 30% and 24%, respectively.

The inter-individual variability in AUC_{inf} and C_{max} (CV%) was 33% and 20%, respectively.

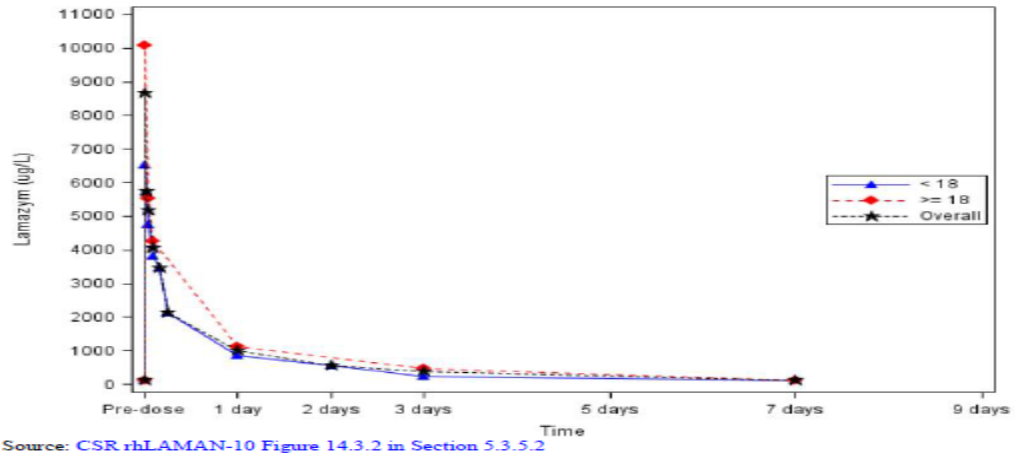
Special populations

No studies were submitted using velmanase alfa to investigate PK in special populations. Velmanase alfa is predicted to be degraded into small peptides and finally into amino acids.

The influence of age (<18 years and ≥18 years) on the PK of velmanase alfa was investigated in the rhLAMAN-10 integrated analysis in patients who received the 1 mg/kg dose.

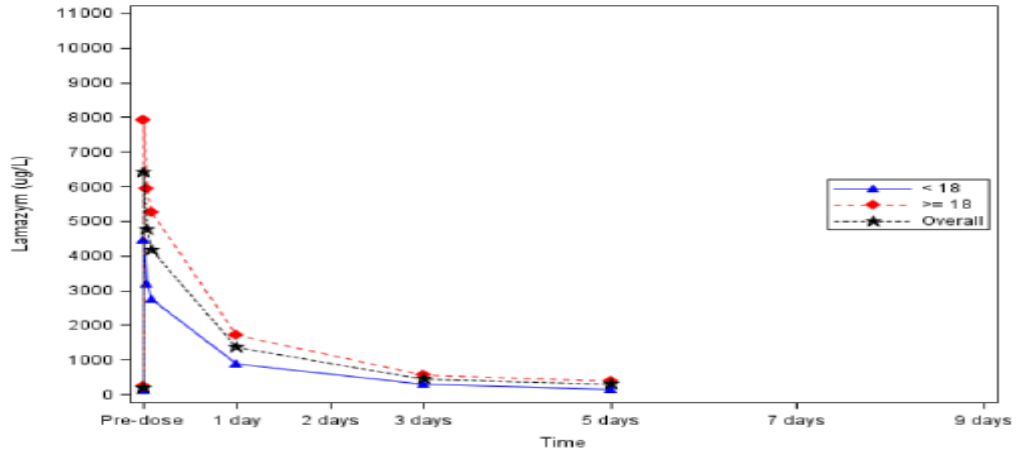
The PK profiles at Day 1 and the last PK assessment are plotted for patients below 18 years and for patients 18 years and above in **Figure 7** and **Figure 8**.

Figure 7. Mean Velmanase Alfa Plasma Concentration after First Infusion (Day 1) of 1 mg/kg velmanase alfa by Age Group (PK Analysis Set)



Source: CSR rhLAMAN-10 Figure 14.3.2 in Section 5.3.5.2

Figure 8. Mean Velmanase Alfa Plasma Concentration after the Last Infusion (Steady State) of 1mg/kg velmanase alfa by Age Group (PK Analysis Set)



Source: CSR rhLAMAN-10 Figure 14.3.3 in Section 5.3.5.2

Pharmacokinetic interaction studies

Due to nature of the product, no interactions at CYP450 level or other drug-drug interactions are expected.

Population PK analysis

The objective of this population analysis was to develop a model to describe the pharmacokinetics of velmanase alfa in patients with alpha-mannosidosis, and to identify sources of interindividual variability in the PK of velmanase alfa.

Population PK models were developed using nonlinear mixed-effects modeling which had 2 components:

(1) a structural model (one- or two-compartment model) that characterised the concentration-time relationship after velmanase alfa administration;

(2) a random effects model containing inter-individual variability (IIV) in the PK parameters, and a residual-error component that accounted for intra-individual variability and measurement errors.

Both one- and two-compartment models were fitted to the plasma concentration data. The structural parameters for a two-compartment model included clearance (CL), volume of distribution of the central compartment (V1), inter-compartmental clearance (Q), and volume of distribution of the peripheral compartment (V2).

The predictability of the final model was evaluated using the visual predictive check (VPC) method (Yano 2001).

Results

Data set

The final dataset for analysis contained 420 plasma concentration-time records from 34 subjects (20 males and 14 females). The subjects contributed a total of 64 plasma concentration-time profiles. Subjects received single or repeated administrations of velmanase alfa administered as IV infusion at doses ranging from 6.25 to 100 U/kg. Subjects in the active treatment groups ranged in age between 6 and 35 years (median = 17 years), in body weight (WT) between 18.7 and 105 kg (median = 62.6 kg), in height (HT) between 112 and 191 cm (median = 159 cm), and in body mass index (BMI) between 14.6 and 35.4 kg/m^2 (median = 24.5 kg/m^2).

Covariate Model

Demographic variables such as weight, BMI, age, and height were highly correlated. Unexpected correlations were also observed between Study and Dose (higher doses in early studies) and demographics likely due to the unique design of the clinical development program (lower age and body weight (WT) in early studies). Diagnostic plots from the base model revealed a strong correlation between IIV of all four PK parameters and WT. Once WT was added to the model, age and sex were tested as covariates of CL and V1. The results indicate that neither age nor sex were significant covariates of CL and V1 (data not shown).

Final Model

The final model is summarised in **Table 8**.

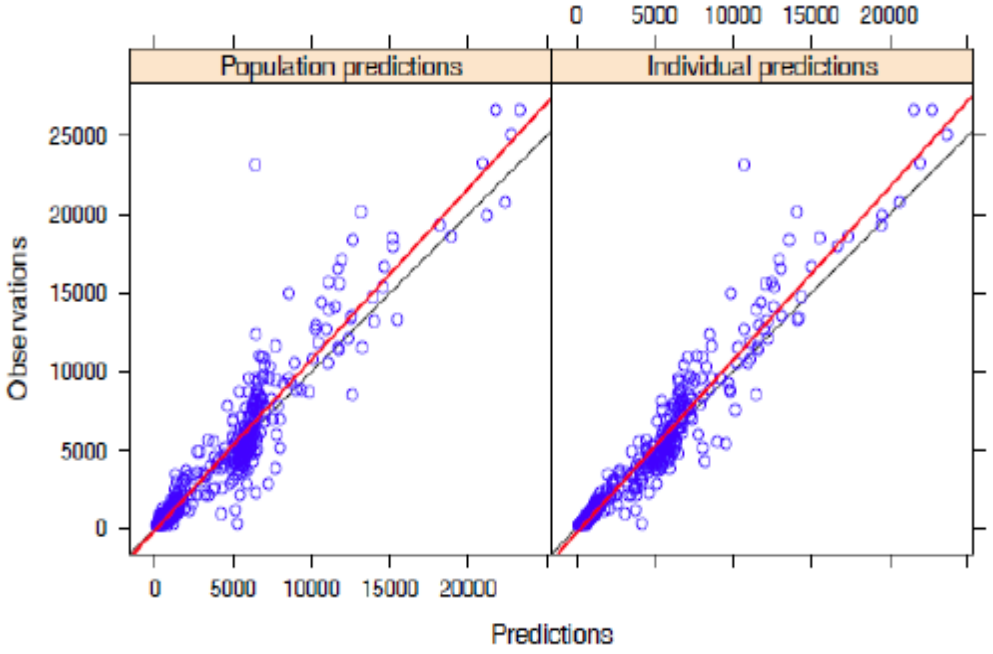
Table 8. Estimated Velmanase Alfa Pharmacokinetic Parameters in Final Model

Parameter	Study	Population Value (%RSE)	95% CI	Interindividual CV% (%RSE)	% ETA Shrinkage
CL (L/h)	2, 3	0.279 (7.06)	(0.240, 0.318)	27.9 (46.5)	3.56
	Others	0.485 (6.76)	(0.419, 0.551)		
V1 (L)	2, 3	5.41 (10.5)	(4.27, 6.55)	17.3 (55.0)	17.5
	Others	9.25 (4.24)	(8.47, 10.0)		
V2 (L)	All	15.5 (29.0)	(6.50, 24.5)	33.0 (97.2)	37.3
Q (L/h)	All	0.378 (18.5)	(0.238, 0.518)	14.1 (FIX)	76.4
Exponent for (WT/63) in CL	All	0.436 (36.7)	(0.116, 0.756)	NA	NA
Exponent for (WT/63) in V1	All	0.776 (9.05)	(0.636, 0.916)	NA	NA
Exponent for (WT/63) in V2	All	1.33 (21.1)	(0.770, 1.89)	NA	NA
Exponent for (WT/63) in Q	All	0.428 (29.7)	(0.174, 0.682)	NA	NA
Residual Error Parameters	**Estimate (%RSE)**				
Additive	39.4 (259)				
Proportional (%)	49.2 (12.9)				

Note: %RSE = Relative Standard Error (SE*100/Point Estimate). Scaling for weight on CL, V1, V2, and Q was based on (WT/63 kg)^a, where *a* is an exponent. NA = not applicable.

The correlation between predicted and observed concentrations is shown in **Figure 9**. No significant (P<0.01) correlations were observed between the interindividual estimates across the primary PK parameters. The results of the Visual Predictive Check demonstrated that most of the observed data fell within the range of the 5th and 95th percentiles of the predicted steady-state data (data not shown).

Figure 9. Predicted and Observed Plasma Concentration (µg/L) of Velmanase Alfa – Final Model



The population model was used for the simulation of the steady-state plasma concentration-time data in children and adolescents between 0 and 17 years of age after weekly doses of 25 U/kg (~1 mg/kg).

Simulated steady state PK parameters of velmanase alfa by age groups are summarised in **Table 9**.

Table 9. Simulated steady state PK parameters of velmanase alfa (mean ± sd) after weekly doses of 25 U/kg (~1 mg/kg)**.**

Age group	**0-2 years**	**2 - 5 years**	**5 - 11 years**	**11 - 17 years**
females				
C_{max} (µg/l)	8887 ± 676	8860 ± 723	8733 ± 770	8597 ± 854
AUC_{0-144h} (µg.h/l)	141871 ± 88678	151458 ± 96913	154929 ± 102572	171352 ± 112757
males				
C_{max} (µg/l)	8914 ± 702	8842 ± 690	8877 ± 704	8573 ± 754
AUC_{0-144h} (µg.h/l)	147970 ± 92596	150589 ± 92722	161725 ± 96721	159098 ± 95497

Comparable pharmacokinetics were observed in children below the age of 6 years and above the age of 6 years, after 1 mg/kg weekly administrations, when doses were normalised by body weight. The simulation data obtained for children above 6 years of age was comparable to the data obtained from a PK study in children above 6 years of age.

2.4.3. Pharmacodynamics

Mechanism of action

The primary PD action of velmanase alfa is reduction of serum oligosaccharides, which has been evaluated in patients across the clinical programme as a primary efficacy marker. The velmanase alfa enzyme is only active at acid pH in alpha-mannosidosis patients and so does not directly degrade oligosaccharides present in the serum.

A reduction in serum oligosaccharides is representative of the intracellular lysosomal activity of CHF-LMZYMAA1, which is lacking in alpha-mannosidosis patients.

Primary and Secondary pharmacology

Serum oligosaccharides were measured in all studies and are presented in detail in the clinical efficacy section of this report.

Based on studies in in the murine LAMAN knockout model and confirmed by human PD markers (CSF oligosaccharides, neurodegenerative biomarkers and brain magnetic resonance spectroscopy (MRS) of white matter, grey matter and centrum semiovale) it can be concluded that velmanase alfa does not enter the CNS.

No secondary pharmacologic effects were reported in the documentation submitted by the applicant.

No PD drug interaction studies were performed as these are not anticipated based on the structure of the drug substance (recombinant human glycoprotein).

2.4.4. Discussion on clinical pharmacology

Velmanase alfa is a recombinant version of the naturally occurring human enzyme, and the metabolic pathway is, therefore, predicted to be similar to other natural occurring proteins that degrade into small peptides and finally into amino acids.

Velmanase alfa exhibited an approximately linear (i.e. first-order) pharmacokinetic profile, and Cmax and AUC increased approximately proportionally to the dose with doses ranging from 0.8 to 1.6 mg/Kg (corresponding to 25 and 50 U/Kg). The steady state volume of distribution was low (0.27 L/Kg), indicating distribution confined to plasma. Cmax appeared to increase proportionally with the dose up to 100 U/kg, except from the lowest 6.25 U/kg, where dose-normalized Cmax was up to 50% lower as compared to other doses. This partly could be explained by the fact that subjects in this dose group received only 80% of the planned dose.

The clearance from plasma (mean 6.7 mL/h/Kg) is consistent with a rapid cellular uptake of the velmanase alfa via mannose receptors. At steady state, velmanase alfa clearance normalised by body weight in paediatric patients was higher than clearance in adult patients. However, the observed difference could be due to a small number of subjects, since in popPK analysis age was not a significant covariate.

After the end of the infusion, velmanase alfa plasma concentrations fell in a biphasic fashion with a mean terminal elimination half-life of about 30 hours.

The mean intra-individual variability in AUC_{inf} and C_{max} (the mean of all individual CV%) was 30% and 24%, respectively. The inter-individual variability in AUC_{inf} and C_{max} (CV%) was 33% and 20%, respectively.

Due to the expected degradation of velmanase alfa into small peptides and amino acids, studies in hepatic impairment are not considered necessary. In addition, proteins larger than 50.000 Da, as velmanase alfa, are not eliminated renally. The lack of studies in patients with renal impairment is thus justified. Pharmacokinetic data in elderly is not considered necessary as no patients older than 41 years are described across Europe. Furthermore, due to nature of the product, no interactions at CYP450 level or other drug-drug interactions are expected.

The PK properties of velmanase alfa after intravenous administration were described by an allometrically scaled two-compartment model with first-order elimination. Due to the scarcity of data, only a limited number of covariates (body weight, height, age, dose and study) were available for investigation.

The predicted concentrations were highly correlated to the observed concentrations, with a slope of approximately 1, demonstrating the adequacy of the population fit. Likewise, residuals were uniformly distributed with time and concentrations with no obvious bias.

Neither age nor sex, were statistically significant covariates of CL and V1in the final model, once body weight was added to the model.

Velmanase alfa is an ERT aiming to replace the deficient alpha-mannosidase enzyme in patients with alpha-mannosidosis. A reduction in serum oligosaccharides (discussed in detail in the clinical efficacy section of this report) is indicative of intracellular lysosomal activity of velmanase alfa, which is reduced/lacking in alpha-mannosidosis patients.

No secondary pharmacologic effects were investigated by the applicant. As no potential off-target or unintentional effects of velmanase alfa are foreseen the lack of secondary pharmacology studies is acceptable.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of velmanase alfa is considered to have been adequately characterised from the submitted data and no additional measures are considered necessary.

2.5. Clinical efficacy

2.5.1. Dose response studies

Two dose response studies were conducted in the same population (rhLAMAN-02 and RhLAMAN-03 (patients from study 2 rolled over into study 3).

Study rhLAMAN-02, was a single center, open-label, dose escalation study of the safety and pharmacokinetics (PK) of velmanase alfa for the treatment of patients with alpha-mannosidosis.

Study, rhLAMAN-03, was a single center, randomized, open-label, multiple-dose study of the efficacy and long-term safety of velmanase alfa for the treatment of patients with alpha-mannosidosis.

Participants were included in these studies after a diagnosis of alpha-mannosidosis, which was confirmed by alpha-mannosidase activity < 10% of normal activity in blood leukocytes. Patients were between ≥ 5 year and ≤ 20 years of age at screening.

In Study rhLAMAN-02, two patients were allocated to each of the following groups: Group 1: 6.25 U/kg, Group 2: 12.5 U/kg and group 3: 25 U/kg, group 4: 50 U/kg and group 5: 100 U/kg body weight. Treatment was assigned by stratification. Following evaluation of baseline assessments, all 10 patients were stratified based on what was considered of primary importance; sex and age, to obtain homogenous pairs in each group. The pairs of patients were to be randomized to dose with the restriction that both the youngest and the oldest should be represented in one of the high dose groups.

After a single infusion in study rhLAMAN-02, Cmax was proportional to dose with an estimated proportionality factor for Cmax versus dose of 1.03 (CI: 0.86 to 1.21). For AUC, the estimate of exposure-dose proportionality was a factor of 1.42 (CI: 1.19 to 1.64).

In study rhLAMAN-03, the dose levels randomised were in blocks in the rhLAMAN-03 randomization, i.e. one patient from each dose level in study rhLAMAN-02 was randomized to 25 U/kg and 50 U/kg respectively. The demographic and baseline characteristics of the patients included in study rhLAMAN-03 are summarised in **Table 10.**

Table 10. Demographic and baseline characteristics of patients- Study rhLAMAN-03

	25 U/kg	50 U/kg	Total
	(N=5)	(N=5)	(N=10)
Age (years) n	5	5	10
Mean (SD) Median	12.7 (3.6)12.0	12.5 (4.4)15.2	12.6 (3.8)13.6
Min;Max	8.5;17.5	7.7;16.0	7.7;17.5
Race, E (%) n	5	5	10
White	5 (100.0)	5 (100.0)	10 (100.0)
Height (m) n	5	5	10
Mean (SD)	1.47 (0.16)	1.41 (0.24)	1.44 (0.19)
Median	1.46	1.53	1.50
Min;Max	1.26;1.70	1.13;1.62	1.13;1.70
Weight (kg) n	5	5	10
Mean (SD)	51.9 (12.2)	44.1 (21.9)	48.0 (17.2)
Median	48.6	52.5	50.8
Min;Max	34.4;68.2	18.7;71.7	18.7;71.7
BMI (kg/m*m) n	5	5	10
Mean (SD) Median	23.7 (1.3)23.8	20.6 (4.7)20.8	22.2 (3.6)22.8
Min;Max	21.7;25.0	14.6;27.3	14.6;27.3
Sex, E (%) n	5	5	10
Female Male	1 (20.0)4 (80.0)	2 (40.0)3 (60.0)	3 (30.0) 7 (70.0)

The effect of velmanase treatment to baseline values of serum and urine oligosaccharide levels in Study rhLAMAN-03 are summarised **Table 11** and **Table 12** respectively.

Table 11. Serum Oligosaccharides levels (umol/l) of patients in Study rhLAMAN-03

VISIT	**25 U/kg**		**50 U/kg**		**50 U/kg - 25 U/kg**		
	N	**mean (min, max)**	**N**	**mean (min, max)**	**mean**	**Min, max**	**P value**
Baseline	5	9.800 (7,11)	5	9.200 (6,11)			
3 Months	5	4.000 (1,11)	5	2.000 (1,3)			
Change	5	-5.800	5	-7.200	-1.74	(-6.29, 2.81)	0.396
Change (%)	5	-59.307	5	-78.990	-33.76	(-78.68, 105.81)	0.419
6 Months	4	3.500 (3,5)	5	2.400(2,3)			
Change	4	-6.000	5	-6.800	-1.13	(-2.47, 0.21)	0.085
Change (%)	4	-60.173	5	-73.434	-31.16	(-54.81, 4.86)	0.073

Table 12. Urine Oligosaccharides levels (umol/l) of patients in Study rhLAMAN-03

VISIT	25 U/kg		50 U/kg		50 U/kg - 25 U/kg	
	N	Mean (min, max)	N	Mean (min, max)	Mean (Min, max)	P value
Baseline	5	771.400 (599, 949)	5	682.200 (468, 1185)		
3 Months	4	357.250 (278,407)	5	199.600 (160,275)		
Change	4	-369.75	5	-482.60	-152.29 (-227.83, -76.76)	0.003
Change (%)	4	-49.767	5	-68.650	--42.31 (-57.06, -22.49)	0.004
6 Months	4	402.250 (245,716)	5	297.600 (185,427)		
Change	4	-324.75	5	-34.60	-103.27 (-399.41, 192.87)	0.426
Change (%)	4	-51.967	5	-73.434	-22.80 (-64.58, 68.29)	0.448

2.5.2. Main studies

Study rhLAMAN-05: A multi-centre, double-blind, randomized, placebo controlled, parallel group trial, investigating the efficacy and safety of repeated velmanase alfa treatment of subjects with alpha-mannosidosis.

Methods

The trial consisted of a screening visit (visit -1), a baseline visit (visit 0, prior to first dose) in order to evaluate inclusion/exclusion criteria and to perform the baseline procedures, a first dose visit (visit 1), up to 55 dose visits, a midterm evaluation after 26 weeks (visit 26a) and an end evaluation after 52 weeks (visit 52a). An additional last EOT visit was performed at week 56 (visit 56).

A midterm evaluation was done at week 26 for demonstration on efficacy evaluation of the 3MSCT and serum oligosaccharide values. A statistical significant improvement for 3MSCT of $p \leq 0.05$ (two-sided) and $p \leq 0.025$ (two-sided) for serum oligosaccharide reduction was considered for the midterm analyses.

In case of statistical improvement the Placebo group would be shifted to active treatment and the remainder of the trial would be for safety evaluation only, otherwise the blinded trial continued until end evaluation after 52 weeks (visit 52a), where positive effect was defined as a trend in the efficacy endpoints and statistical significant ($p \leq 0.025$) serum oligosaccharide reduction. The trend was defined as an improvement in the mean value of 3MSCT for active compound compared to Placebo. Since no a statistical significant change emerged at the midterm evaluation (week 26), the trial continued as blinded until the final evaluation after 52 weeks (visit 52a).

Study Participants

Inclusion criteria

- Subject or subjects legally authorized guardian(s) must provide signed, informed consent prior to performing any trial-related activities.
- The subject and his/her guardian(s) must have the ability to comply with the protocol.
- The subject must have a confirmed diagnosis of alpha-Mannosidosis as defined by alpha-Mannosidase activity <10% of normal activity (historical data).
- The subject must have an age at the time of screening ≥ 5 years and ≤ 35 years.
- The subject must have the ability to physically and mentally cooperate in the tests.
- The subject must have an ECHO without abnormalities that, in the opinion of the Investigator, would preclude participation in the trial.

Exclusion criteria

- The subjects diagnosis cannot be confirmed by alpha-mannosidase activity < 10% of normal activity.
- The subject cannot walk without support
- Presence of known chromosomal abnormality and syndromes affecting psychomotor development, other than alpha-mannosidosis.
- History of BMT
- Presence of known clinically significant cardiovascular, hepatic, pulmonary, or renal disease or other medical conditions that, in the opinion of the Investigator, would preclude participation in the trial.
- Any other medical condition or serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the trial.
- Pregnancy: pregnant women are excluded. Before start of the treatment the Investigators will for women of childbearing potential perform a pregnancy test and decide whether or not there is a need for contraception.
- Psychosis; any psychotic disease, also in remission, is an exclusion criteria.
- Planned major surgery that, in the opinion of the Investigator, would preclude participation in the trial.
- Participation in other interventional trials testing IMP (including velmanase alfa) within the last 3 months.
- Adult patients who, in the opinion of the Investigator, would be unable to give consent, and who does not have any legal protection or guardianship.
- Total IgE >800 IU/ml.
- Known allergy to the IMP or any excipients (Sodium-Phosphate, Glycine, Mannitol)

Treatments

Weekly i.v. dosing of velmanase alfa at 1 mg/ml or placebo through 12 months; a minimum of 49 infusions and a maximum of 55 infusions were administered to each patient.

Objectives

The primary objective of this study was:

- to demonstrate the efficacy of velmanase alfa over placebo in terms of 3MSCT improvement and serum oligosaccharide reduction over 52 weeks of treatment.

The key secondary objectives of this study were:

- to demonstrate a positive trend of velmanase alfa over placebo in terms of improvement of 6MWT and FVC percent of predicted normal value over 52 weeks of treatment. The secondary objectives of this study were:
- to evaluate the effect velmanase alfa on other secondary efficacy parameters, functional capacity, pulmonary function testing, hearing and mental development;
- to assess the safety and the tolerability of the study treatments;
- to perform a PK analysis

Outcomes/endpoints

Efficacy

- Change from baseline to week 52 in serum oligosaccharides
- Change from baseline to week 52 in the 3-minute stair climb test (3MSCT)

The prioritized secondary efficacy endpoints of this study are:

- Change from baseline to week 52 in 6 minute walk test (6MWT)
- Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)

The other secondary efficacy variables of this study are:

- Change from baseline to other visits in the Questionnaires (CHAQ and EQ-5D) (total score and domain scores)
- Change from baseline to other visits in the Bruininks-Oseretsky test of motor proficiency (BOT2) (total score and domain scores)
- Change from baseline to other visits in the Leiter R (total score and domain scores)
- Change from baseline to other visits in CSF oligosaccharides and Cerebrospinal fluid biomarkers (Tau, NFL and GFAp)
- Change from baseline to other visits in Pulmonary function tests [FEV1 (l), FEV1 (%), FVC (l) and PEF (l/s)]
- Change from baseline to other visits in Pure tone audiometry (PTA) (air conduction left and right ear and bone conduction for the best ear)

Safety

- Adverse events (AEs)
- Vital signs and change in physical examination
- Clinical laboratory parameters (haematology, biochemistry and urinalysis)
- Development of velmanase alfa antibodies and neutralizing/inhibitory antibodies

Pharmacokinetics:

- The serum concentrations of velmanase alfa after the first administration

Sample size

A total of 26 patients were screened in the rhLAMAN-05 trial. There was one screening failure due to level of IgE not compatible with exclusion criteria. Twenty five (25) patients were enrolled in the study. No formal estimation of sample size was performed for the trial.

Randomisation

Randomization, in a 3:2 ratio, into active or placebo group was stratified on age and was used to allocate the patients into blocks. Within the blocks, a standard randomization into active and placebo was performed.

Blinding (masking)

This was a double-blind study. Placebo and active drug infusions were visually and physiological indistinguishable.

Statistical methods

Primary and prioritized secondary efficacy variables

The primary analysis on the two primary endpoints (serum oligosaccharides and 3MSCT) and two prioritized secondary endpoints (6MWT and FVC [in %]) was performed on the relative change from baseline to week 52. Data were log-transformed and then submitted to an analysis of covariance (ANCOVA) with treatment as fixed factor, corresponding baseline values and age as continuous covariates. The adjusted means in each treatment group, the adjusted mean difference between velmanase alfa and placebo, their 95% CIs and associated p-values were estimated by the model.

The following sensitivity analyses were performed to check the robustness of the results:

- The primary model with absolute change from baseline to week 52
- The primary model with the relative change from baseline to week 26 using log-transformation.
- The primary with model the absolute change from baseline to week 26.

A responder analysis was also undertaken, where a responder was defined as follows:

- for serum oligosaccharides a percentage reduction ≥70%.
- for 3MSCT, 6MWT and FVC (%) a percentage increase ≥ 10%.

Demonstration of efficacy was defined as:

- a statistically significant improvement in the two primary endpoints (under significance levels of 0.025 and 0.05, respectively) at the interim analysis;

or

- a statistically significant reduction in serum oligosaccharides (under a significance level of 0.025) and a trend for improvement in the 3MSCT and one of the prioritized secondary endpoints at the 52 week analysis.

Results

Participant flow

A total of 26 patients were screened in the rhLAMAN-05 trial. There was one screening failure due to level of IgE not compatible with exclusion criteria. Twenty-five (25) patients were randomized to velmanase alfa (n=15) or placebo (n=10). No patients withdrew from the rhLAMAN-05 trial.

Recruitment

Study Start Date: 10-Sept-2012 ((First Patient First Visit)
Study Completion Date: 02-May-2014 (Last Patient Last Visit)

Conduct of the study

No major protocol deviations were reported. Most minor deviations related to missed collection of PK samples or the performance of an ECG.

Baseline data

Demographic and other baseline characteristics of the trial population are presented in **Table 13**.

Table 13. Demographic and other baseline characteristics in Study rhLAMAN-05

Demographic parameter	**Lamzede N=15**	**Placebo N=10**	**All N=25**
Age, years Mean (SD) Range	18.5 (9.0) 6;35	19.7 (8.9) 6;35	19.0 (8.8) 6;35
Age, (n,%)			
< 12 years	4 (26.7)	2 (20.0)	6 (24.0)
12 -18 years	3 (20.0)	3 (30.0)	6 (24.0)
≥ 18 years	8 (53.3)	5 (50.0)	13 (52.0)
Race, (n,%) White	15 (100.0)	10 (100.0)	25 (100.0)
Height, m			
Mean (SD)	1.51 (0.19)	1.61 (0.14)	1.55 (0.17)
Range	1.12;1.75	1.31;1.80	1.12;1.80
Weight, kg			
Mean (SD)	60.2 (21.5)	64.2 (12.2)	61.8 (18.1)
Range	20.5;95.2	36.1;75.0	20.5;95.2
BMI, kg/m^2			
Mean (SD)	25.1 (4.9)	24.7 (2.7)	24.9 (4.1)
Range	16.3;31.6	21.0;28.5	16.3;31.6
Sex, (n,%)			
Female	6 (40.0)	5 (50.0)	11 (44.0)
Male	9 (60.0)	5 (50.0)	14 (56.0)
3MSCT, steps/min			
Mean (SD)	52.9 (11.2)	55.5 (16.0)	54.0 (13.1)
Range	37.7;83.3	32.0;78.0	32.0;83.3
6MWT, metres			
Mean (SD)	460 (72.3)	466 (140)	462 (102)

Range	335;627	219;696	219;696
FVC, (% of predicted)			
Mean (SD)	81.7 (20.7)	90.4 (10.4)	85.4 (17.3)
Range	50.0; 119	72.0;109	50.0; 119
FVC, (L)			
Mean (SD)	2.5 (1.1)	3.3 (0.9)	2.8 (1.1)
Range	0.9;4.6	2.6;5.3	0.9;5.3
FEV1, (% of predicted)			
Mean (SD)	80.3 (19.6)	85.9 (18.2)	82.7 (18.8)
Range	50.0;119	45.0;107	45.0;119
FEV1, (L)			
Mean (SD)	2.3 (1.0)	2.9 (0.9)	2.6 (1.0)
Range	0.9;4.3	1.5;4.9	0.9;4.9
PEF, (L/s)			
Mean (SD)	4.6 (2.2)	5.7 (1.6)	5.1 (2.0)
Range	1.8;8.4	3.1;8.8	1.8;8.8
Total Equivalence Age-AM, years			
Mean (SD)	6.3 (2.6)	6.6 (1.8)	6.4 (2.2)
Range	2.3;10.2	4.2;9.1	2.3;10.2
Total Equivalence Age-VR, years			
Mean (SD)	5.7 (1.7)	6.1 (1.6)	5.9 (1.7)
Range	3.3;8.7	3.4;9.0	3.3;9.0
Serum Oligosaccharides, µmol/l			**-**
Mean (SD)	6.8 (1.2)	6.6 (1.9)	
Range	4.9;8.7	4.4;10.2	
CSF Oligosaccharides, µmol/l			**-**
Mean (SD)	11.4 (3.0)	10.3 (2.9)	
Range	6.4;17.9	5.0;14.0	
BOT2 Total Score, points			-
Mean (SD)	94.93 (41.68)	109.2 (51.84)	
Range	26.0;156.0	14.0;167.0	
CHAQ Disability Index, score			-
Mean (SD)	1.37 (0.82)	1.59 (0.64)	
Range	0.00;2.63	0.38;2.75	
EQ-5D-5L Index, score			-
Mean (SD)	0.61 (0.19)	0.61 (0.18)	
Range	0.27;1.00	0.42;1.00	

Numbers analysed

The following analysis populations were defined:

• The Randomised population: all randomised patients.

• The Safety Analysis Set: all randomised patients who received at least one dose of the study treatment (i.e. all subjects having received at least one injection with IMP) and analysed according to the actual treatment received.

• The Full Analysis Set (FAS): all randomized subjects who receive at least one dose of the study treatment with at least one post baseline efficacy measurement and analysed according to their planned treatment regimen.

• Per Protocol Analysis Set (PP): all patients from the FAS who did not have substantial deviations to the protocol.

• PK Analysis Set (PK): all patients from the Safety population and treated with Lamzede excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK.

Table 14. Analysis populations in study rhLAMAN-05

	Lamzede (N=15) (n,%)	**Placebo (N=10) (n,%)**	**All (N=25) (n,%)**
Analysis Sets			
Randomized	15 (100.0)	10 (100.0)	25 (100.0)
Full Analysis Set (FAS)	15 (100.0)	10 (100.0)	25 (100.0)
Safety	15 (100.0)	10 (100.0)	25 (100.0)
Per Protocol	15 (100.0)	10 (100.0)	25 (100.0)
PK Set	15 (100.0)	10 (100.0)	25 (100.0)
Patient Status			
Completed the study	15 (100.0)	10 (100.0)	25 (100.0)
Discontinued from the study	0 (0.0)	0 (0.0)	0 (0.0)

Outcomes and estimation

Co-primary endpoint: Serum Oligosaccharides

Results of ANCOVA analysis on relative and absolute changes of serum oligosaccharides from baseline to week 52 and week 26 are shown in **Table 15.**

Table 15. Serum oligosaccharides: Relative (%) and Absolute ((µmol/L) changes form baseline in study rhLAMAN-05

	Lamazym (N=15)	Placebo (N=10)
Change from baseline to week 52		
Relative change (%)		
Adjusted mean (95% CI)	-77.60 (-81.58, -72.76)	24.14 (-40.31, -3.59)
Adjusted mean difference vs Placebo (95% CI) (p-value)	-70.47 (-78.35, -59.72) p<0.001	
Absolute change (µmol/L)		
Adjusted mean (95% CI)	-5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)
Adjusted mean difference vs Placebo (95% CI) (p-value)	-3.50 (-4.37, -2.62) p<0.001	
Change from baseline to week 26		
Relative change (%)		
Adjusted mean (95% CI)	-65.85 (-72.05, -58.28)	-7.88 (-27.94, 17.77)
Adjusted mean difference vs Placebo (95% CI) (p-value)	-62.93 (-73.03, -49.06) p<0.001	
Absolute change (µmol/L)		
Adjusted mean (95% CI)	-4.30 (-5.04, -3.55)	-0.47 (-1.38, 0.45)
Adjusted mean difference vs Placebo (95% CI) (p-value)	-3.83 (-5.01, -2.65) p<0.001	

A post-hoc analysis was conducted to stratify results by age group which is summarised in **Table 16.**

Table 16. Serum oligosaccharides: Relative (%) and Absolute ((µmol/L) changes form baseline in study rhLAMAN-05 by age group

			Lamazym			Placebo		
		Statistic	Value	Absolute Change	% Change	Value	Absolute Change	% Change
<18 years	**Baseline**	n	7			5		
		Mean	7.3			6.0		
		SD	1.1			2.4		
	Week 26	n	7	7	7	5	5	5
		Mean	2.7	-4.6	-61.2	6.2	0.2	10.3
		SD	1.3	1.9	20.0	1.6	2.4	33.2
	Week 52	n	7	7	7	5	5	5
		Mean	2.1	-5.2	-70.6	5.3	-0.8	-7.2
		SD	1.0	1.5	14.6	0.9	1.7	19.3
>=18 years	**Baseline**	n	8			5		
		Mean	6.3			7.2		
		SD	1.1			1.0		
	Week 26	n	8	8	8	5	5	5
		Mean	2.2	-4.1	-65.6	6.3	-1.0	-13.5
		SD	0.6	0.9	8.3	2.2	2.1	29.7

Week 52	n	8	8	8	5	5	5
	Mean	1.2	-5.1	-80.3	4.9	-2.4	-33.4
	SD	0.3	1.0	4.4	1.9	1.4	22.2

Co-primary endpoint: *Three minute stair climb test (3MSCT)*

Results of ANCOVA analysis on relative and absolute changes of 3MSCT from baseline to week 52 and week 26 are shown in **Table 17.**

Table 17. 3MSCT**:** Relative (%) and Absolute ((steps/min) changes form baseline in study rhLAMAN-05

	Lamazym (N=15)	**Placebo (N=10)**
Change from baseline to week 52		
Relative change (%)		
Adjusted mean (95% CI)	-1.07 (-9.05, 7.61)	-3.97 (-13.38, 6.47)
Adjusted mean difference vs Placebo (95% CI)	3.01 (-9.86, 17.72)	
(p-value)	0.648	
Absolute change (steps/min)		
Adjusted mean (95% CI)	0.46 (-3.58, 4.50)	-2.16 (-7.12, 2.80)
Adjusted mean difference vs Placebo (95% CI)	2.62 (-3.81, 9.05)	
(p-value)	0.406	
Change from baseline to week 26		
Relative change (%)		
Adjusted mean (95% CI)	0.93 (-7.17, 5.72)	-3.78 (-11.15, 4.19)
Adjusted mean difference vs Placebo (95% CI)	2.96 (-7.12, 14.14)	
(p-value)	0.562	
Absolute change (steps/min)		
Adjusted mean (95% CI)	0.11 (-2.79, 3.01)	-1.86 (-5.42, 1.70)
Adjusted mean difference vs Placebo (95% CI)	1.97 (-2.64, 6.59)	
(p-value)	0.384	

Table 18 shows a summary of a post-hoc analysis by age subgroups.

Table 18. 3MSCT**:** Relative (%) and Absolute ((steps/min) changes form baseline in study rhLAMAN-05 by age group

				Lamazym			Placebo	
		Statistic	Value	Absolute Change	% Change	Value	Absolute Change	% Change
<18 years	**Baseline**	n	7			5		
		Mean	56.2			57.8		
		SD	12.5			12.6		
	Week 26	n	7	7	7	5	5	5
		Mean	55.3	-1.0	-2.3	55.7	-2.1	-3.6
		SD	16.5	7.0	12.2	13.2	3.5	7.2
	Week 52	n	7	7	7	5	5	5
		Mean	59.7	3.5	5.8	55.5	-2.3	-4.4
		SD	18.0	10.0	18.0	14.8	5.4	10.8
>=18 years	**Baseline**	n	8			5		
		Mean	50.0			53.2		
		SD	9.8			20.1		
	Week 26	n	8	8	8	5	5	5
		Mean	50.8	0.8	1.0	51.9	-1.3	-2.1
		SD	11.6	3.4	7.4	21.9	7.1	17.9
	Week 52	n	8	8	8	5	5	5
		Mean	48.1	-1.9	-4.1	50.7	-2.5	-2.8
		SD	11.8	6.7	13.7	17.6	6.2	16.4

Prioritised secondary endpoint: Six Minute Walk Test (6MWT)

The adjusted mean relative change (%) from baseline to week 52 in the 6MWT was 0.64 (95% CI: -4.74, 6.32) in the velmanase-alpha group and -1.20 (95% CI: -7.63, 5.68) in the Placebo group. The adjusted mean difference for velmanase-alpha vs Placebo was 1.86 (95% CI: -6.63, 11.12), and was not statistically significant (p=0.664). See table 11.11.

The adjusted mean absolute change (metres) from baseline to week 52 in the 6MWT was 3.74 (95% CI: - 20.32, 27.80) in the velmanase-alpha group and -3.61 (95% CI: -33.10, 25.87) in the Placebo group. The adjusted mean difference for velmanase-alpha vs Placebo was 7.35 (95% CI: -30.76; 45.46), and was not statistically significant (p=0.692).

A post-hoc analysis by age sub-groups is shown in **Table 19**.

Table 19. 6MWT**:** Relative (%) and Absolute (metres) changes form baseline in study rhLAMAN-05

				Lamazym			Placebo	
		Statistic	Value	Absolute Change	% Change	Value	Absolute Change	% Change
<18 years	Baseline	n	7			5		
		Mean	452.4			468.8		
		SD	63.9			79.5		
	Week 26	n	7	7	7	5	5	5
		Mean	466.3	13.9	3.2	480.0	11.2	3.3
		SD	69.8	37.8	8.6	65.0	40.5	10.0
	Week 52	n	7	7	7	5	5	5
		Mean	464.7	12.3	2.0	472.4	3.6	1.2
		SD	102.2	43.2	7.8	82.5	43.0	9.4
>=18 years	Baseline	n	8			5		
		Mean	465.9			462.6		
		SD	82.7			195.1		
	Week 26	n	8	8	8	5	5	5
		Mean	462.5	-3.4	-0.8	452.8	-9.8	-0.0
		SD	97.4	47.8	10.7	176.5	35.5	9.1
	Week 52	n	8	8	8	5	5	5
		Mean	463.4	-2.5	0.4	449.8	-12.8	-2.8
		SD	68.3	50.4	11.7	190.1	41.6	12.8

Prioritised secondary endpoint: Forced Vital Capacity (FVC) (% of predicted)

The adjusted mean relative change (%) from baseline of FVC (% of predicted) to week 52 was 10.11 (95% CI: 1.31,19.67) in the velmanase-alpha group and 1.58 (95% CI: -9.48, 13.99) in the Placebo group. The adjusted mean difference for velmanase-alpha vs Placebo was 8.40 (95% CI: -6.06, 25.08), and was not statistically significant (p=0.269). See Table 11-5.

The adjusted mean absolute change (% of predicted) from baseline to week 52 was 8.21 (95% CI: 1.79, 14.63) in the velmanase-alpha group and 2.30 (95% CI: -6.19, 10.79) in the Placebo group. The adjusted mean difference for velmanase-alpha vs Placebo was 5.91 (95% CI: -4.78; 16.60), and was not statistically significant (p=0.278)

Table 20. FVC (%of predicted)**:** Relative and Absolute changes form baseline in study rhLAMAN-05

				Lamazym			Placebo	
		Statistic	Value	Absolute Change	% Change	Value	Absolute Change	% Change
<18 years	Baseline	n	6			4		
		Mean	69.7			88.0		
		SD	16.8			10.9		
	Week 26	n	6	6	6	4	4	4
		Mean	81.5	11.8	17.8	85.8	-2.3	-3.1
		SD	19.0	6.9	12.3	15.9	7.1	8.4
	Week 52	n	6	6	6	4	4	4
		Mean	83.8	14.2	20.5	96.0	8.0	9.5
		SD	21.5	8.7	11.2	9.3	4.2	5.6
>=18 years	Baseline	n	6			5		
		Mean	93.7			92.4		
		SD	17.7			10.8		
	Week 26	n	7	5	5	4	4	4
		Mean	98.0	-1.4	-1.2	96.3	1.0	1.0
		SD	15.2	7.1	7.1	11.8	3.6	3.7
	Week 52	n	8	6	6	5	5	5
		Mean	97.0	2.2	2.3	89.6	-2.8	-4.1
		SD	21.6	7.2	7.5	23.9	15.5	18.7

Other endpoints: Childhood health assessment questionnaire (CHAQ)

Disability Index (DI)

The mean (SD) Disability Index (score) at baseline, week 26 and week 52 was 1.37 (0.82), 1.31 (0.72) and 1.36 (0.76) in the velmanase alfa group and 1.59 (0.64), 1.75 (0.53) and 1.76 (0.50) in the placebo group, respectively.

Visual Analogue Scale (VAS) Pain

The mean (SD) VAS Pain (score) at baseline, week 26 and week 52 was 0.84 (0.86), 1.00 (0.91) and 0.97 (1.02) in the velmanase alfa group and 0.40 (0.56), 0.63 (0.76) and 0.50 (0.62) in the placebo group, respectively.

VAS General

The mean (SD) VAS General (score) at baseline, week 26 and week 52 was 1.00 (0.83), 0.99 (0.80) and 1.46 (0.62) in the velmanase alfa group and 1.02 (0.80), 1.43 (0.67) and 1.46 (0.61) in the placebo group, respectively.

Study rhLAMAN-10: A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-mannosidosis who previously participated in Lamazym trials.

Methods

Patients included had all previously been treated with Lamazym in the phase 1, 2a, 2b or phase 3 trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04 and rhLAMAN-05). All patients were receiving weekly intravenous infusions of Lamazym according to the AfterCare Program.

Patients attended a Screening visit (Visit 0) on Day 1, at which eligibility was checked and informed consent was signed. After consent was obtained, patients attended an evaluation visit (also on Day 1), at which they underwent pre-infusion evaluations, and then received their infusion of investigational medicinal product (IMP). This infusion was the weekly infusion for that week as part of the AfterCare program in which they were already enrolled, and was the same dose in mg/kg body weight as usually administered according to the local treatment in the AfterCare Program. Further evaluations were then carried out over Days 1-6. An End of Trial (EOT) visit was held on Day 6 after the evaluations had been completed and before the patient left the trial site.

Study Participants

Inclusion criteria

- The patient must have had participated in the previously conducted phase 1, 2a, 2b or 3 trials with recombinant human alpha-mannosidase;
- The patient had to still be receiving weekly intravenous infusions of velmanase alfa according to the AfterCare Program;
- The patient or patients legally authorized guardian (s) had to provide signed, informed consent prior to performing any trial-related activities;
- The patient and his/her guardian (s) had to have the ability to comply with the protocol.

Inclusion Criterion number 2 was evaluated according to a patient-specific clinical report produced by the local site of treatment.

Exclusion criteria

- History of BMT
- Presence of known clinically significant cardiovascular, hepatic, pulmonary or renal disease or other medical conditions that, in the opinion of the Investigator, would have precluded participation in the trial. Patients unable to perform the motor tests independently from support were permitted to participate in the trial and were to be evaluated for the remnant non motor endpoints;
- Any other medical condition or serious intercurrent illness, or extenuating circumstance that, in the opinion of the investigator, would have precluded participation in the trial;
- Pregnant and/or lactating women could not participate in the trial. Concerning women of child bearing potential, the investigators decided whether or not there was a need for contraception. This assessment was done through interviews with the patient and parents;
- Participation in other interventional trials testing IMP, including rhLAMAN-07 and rhLAMAN-09 trials with velmanase alfa;
- Pause of the IMP for 2 consecutive weeks during the last month. Patients were allowed to be re-screened.

Exclusion Criterion number 6 was evaluated according to a patient-specific clinical report produced by the local site of treatment.

Treatments

Each patient was to receive weekly a single dose of velmanase alfa at a dose of 1mg/kg body weight intravenously. The infusion duration was calculated individually from the maximum infusion rate of 45 mL/hour to control the protein load, though infusion duration was to be a minimum of 50 minutes.

Objectives

The primary objective of the trial was to evaluate the impact of the long-term treatment with velmanase alfa in patients with alpha-mannosidosis upon the level of biomarker oligosaccharides in serum and upon the endurance as measured by the change from Baseline in the number of steps climbed in 3 minutes.

As secondary objectives, the long term efficacy of velmanase alfa was investigated upon endurance as measured by the change from Baseline in the number of meters walked in six minutes (6MWT), upon pulmonary function, motor proficiency by BOT-2 and hearing capability by audiometry.

Outcomes/endpoints

Efficacy
The primary efficacy endpoints of this trial were:

- Change from Baseline in serum oligosaccharides
- Change from Baseline in the 3MSCT

The main secondary efficacy endpoints were:

- The 6MWT

- PFT endpoints: FVC (%), FVC (L), FEV1 (%), FEV1 (L) and PEF (L/s);
- BOT-2: total subtest point score (sum of the 7 administered subtests) and motor-area composites (FMC, MC, BC, and the subtest RSA);
- CSF-Oligosaccharides (µmol/L), GFA-p (ng/L), NFL (ng/L) Tau (ng/L) and serum immunoglobulin (g/L);
- The Leiter-R test composite variables Total Equivalence Age-VR and Total Equivalence Age-AM ;
- PTA (air conduction in left and right ear and bone conduction for the best ear);
- CHAQ endpoints: Disability Index, VAS pain and VAS general
- EQ-5D-5L Health Index value and VAS for best health values

Safety

- Adverse events (AEs)
- Vital signs and physical examination
- Electrocardiogram and echocardiography
- Safety laboratory parameters (haematology, biochemistry and urinalysis)
- Development of velmanase alfa antibodies

Sample size

No formal calculation of sample size was performed for this trial. The total number of patients represents the available patients from the previous AfterCare program. Up to 20 patients were expected to be enrolled in this trial. Patients enrolled in this trial were pooled with those currently enrolled in the rhLAMAN-07 protocol (n=7) and the rhLAMAN-09 protocol (n=8). Thus up to 34 patients were expected to be included in the analysis.

Randomisation

Not applicable.

Blinding (masking)

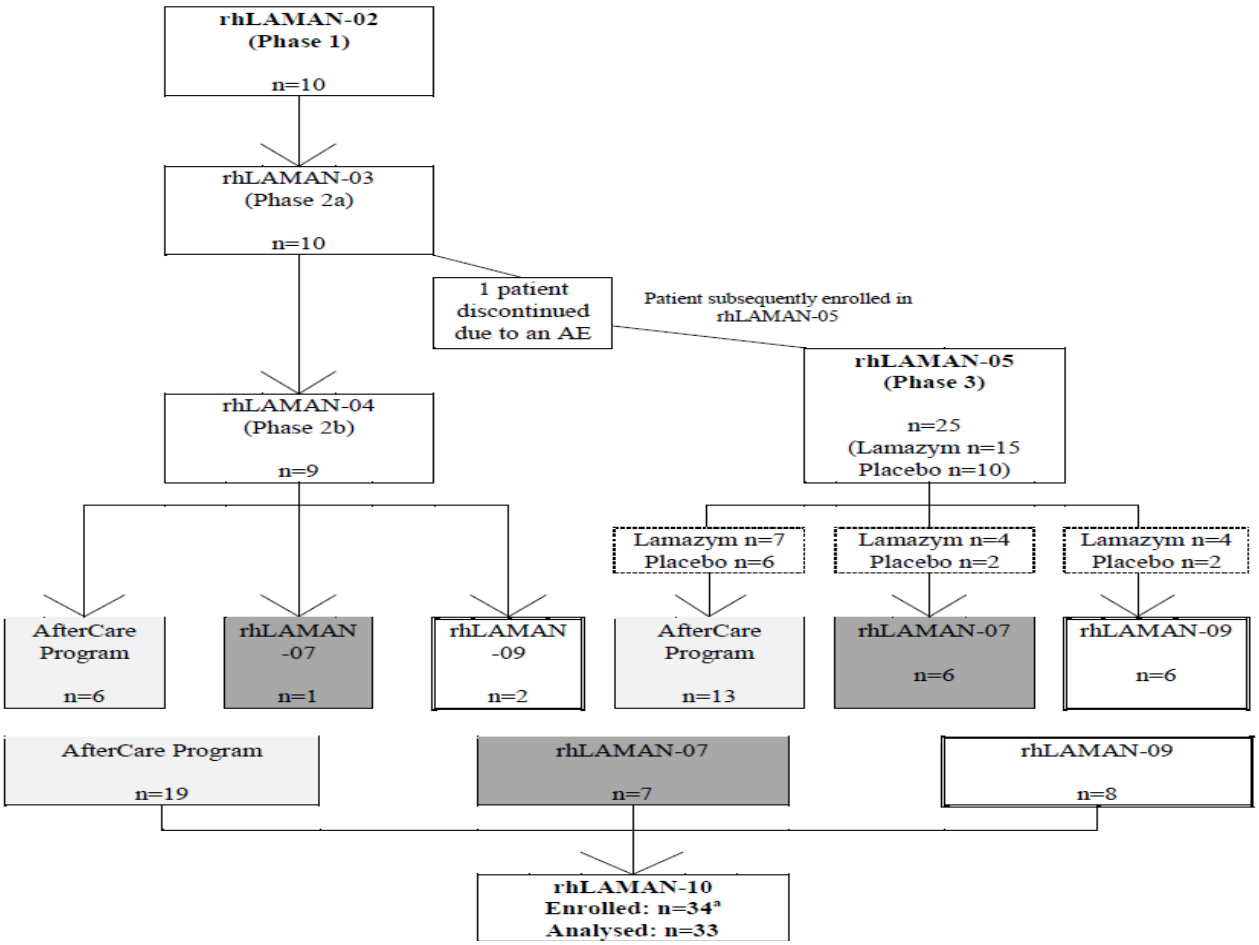
This was an open label study.

Statistical methods

Results

Participant flow

Figure 10. Patient Disposition by Parental Study and by Current Trial at Time of Enrolment in rhLAMAN-10



One patient discontinued the treatment shortly after starting the AfterCare program. As this patient had no data collected during the active treatment the patients was excluded from all analyses.

Recruitment

Study Start Date: 16-Feb-2015 ((First Patient First Visit)

Study Completion Date: 13-June-2015 (Last Patient Last Visit)

Conduct of the study

There were no major protocol deviations. Most commonly reported minor deviation was in relation to a missed visit for some of the patients initially enrolled in studies rhLAMAN-07 and rhLAMAN-09.

Baseline data

Demographic and other baseline characteristics of the trial population are presented in **Table 21.**

Table 21. Demographic characteristics of the trial population in in rhLAMAN-10

		Parental Study				Overall (N=33)		
		rhLAMAN-02 (N=9)	rhLAMAN-05 (N=24)					
		<18 years	<18 years	≥18 years	Total	<18 years	≥18 years	Total
		N=9	N=10	N=14	N=24	N=19	N=14	N=33
Age (years)	Mean (SD)	12.4 (3.8)	10.9 (3.7)	24.6 (5.3)	18.9 (8.3)	11.6 (3.7)	24.6 (5.3)	17.1 (7.8)
	Median (min, max)	15.0 (7.0;17.0)	11.0 (6.0;17.0)	22.5 (18.0;35.0)	19.0 (6.0;35.0)	12.0 (6.0;17.0)	22.5 (18.0;35.0)	15.0 (6.0;35.0)
Sex (n%)	Male	7 (77.8)	6 (60.0)	7 (50.0)	13 (54.2)	13 (68.4)	7 (50.0)	20 (60.6)
	Female	2 (22.2)	4 (40.0)	7 (50.0)	11 (45.8)	6 (31.6)	7 (50.0)	13 (39.4)
Race, n (%)	White	9 (100.0)	10 (100.0)	14 (100.0)	24 (100.0)	19 (100.0)	14 (100.0)	33 (100.0)
Height (m)	Mean (SD)	1.46 (0.19)	1.45 (0.21)	1.63 (0.08)	1.55 (0.17)	1.46 (0.20)	1.63 (0.08)	1.53 (0.18)
	Median (min, max)	1.53 (1.13;1.70)	1.45 (1.12;1.75)	1.59 (1.53;1.81)	1.59 (1.12;1.81)	1.48 (1.12;1.75)	1.59 (1.53;1.81)	1.57 (1.12;1.81)
Weight (kg)	Mean (SD)	49.5 (17.5)	50.1 (22.5)	70.9 (6.2)	62.3 (18.1)	49.8 (19.7)	70.9 (6.2)	58.8 (18.6)
	Median (min, max)	52.5 (18.7;71.7)	42.9 (20.5;95.2)	71.6 (60.0;84.5)	67.5 (20.5;95.2)	49.0 (18.7;95.2)	71.6 (60.0;84.5)	65.0 (18.7;95.2)

Numbers analysed

The population sets analysed in this trial are summarised in

Table 22.

Table 22. Data sets analysed in study rhLAMAN-10

		Enrolled N=34 n (%)
Analysis Set	Enrolled	34 (100.0)[a]
	Safety Analysis Set (SAS)	33 (97.1)
	Full Analysis Set (FAS)	33 (97.1)
	Per-Protocol (PP)	33 (97.1)
	Pharmacokinetics Set (PK)	33 (97.1)

Outcomes and estimation

Primary Efficacy Endpoints

Serum oligosaccharides

Changes in serum oligosaccharides from baseline to last observation overall, by age and by parental study are presented in **Table 23**.

Table 23: Serum Oligosaccharides (µmol/l) at Baseline and Last Observation Overall, by Age and by Parental Study in rhLAMAN-10

			Baseline	Last observation		
				Actual value	Change from Baseline	
					Absolute	%
Overall		**n**	33			
		Mean (SD)	6.90 (2.30)	2.31 (2.19)	-4.59 (3.23)	-62.76 (33.61)
		Median (min, max)	7.00 (2.3; 15.0)	1.70 (0.5; 12.5)	-5.00 (-13.3; 4.40)	-75.00 (-91.8;54.3)
		P (95% CI)			(-5.74, -3.45) <.001	(-74.68,-50.85) <.001
By Age	**<18 years**	**n**	19			
		Mean (SD)	7.63 (2.52)	2.37 (2.71)	-5.26 (3.74)	-66.6 (36.09)
		Median (min, max)	7.70 (4.6; 15.0)	1.60 (0.5; 12.5)	-5.50 (-13.3; 4.4)	-80.0 (-91.8; 54.3)
	≥18 years	**n**	14			
		Mean (SD)	5.91 (1.54)	2.23 (1.30)	-3.68 (2.20)	-57.6 (30.46)
		Median (min, max)	6.25 (2.3;7.8)	1.90 (0.7; 5.8)	-4.40 (-6.1; 0.7)	-71.3 (-85.9; 13.7)
By parental study	**rhLAMAN-02**	**n**	9			
		Mean (SD)	9.00 (2.74)	1.57 (0.90)	-7.43 (2.81)	-81.8 (11.65)
		Median (min, max)	8.00 (6.0; 15.0)	1.60 (0.5;3.6)	-6.90 (-13.3; -4.4)	-85.7 (-91.8;-55.0)
	rhLAMAN-05	**n**	24			
		Mean (SD)	6.11 (1.53)	2.59 (2.47)	-3.53 (2.73)	-55.6 (36.46)
		Median (min, max)	6.05 (2.3;8.7)	1.80 (0.7; 12.5)	-3.90 (-7.2;4.4)	-71.7 (-85.9; 54.3)

3MSCT

Change in 3MSCT from Baseline to last observation overall, by age and by parental study are presented in **Table 24**.

Table 24: 3MSCT (steps/min) at Baseline and Last Observation Overall, by Age and by Parental Study in rhLAMAN-10

			Baseline	Last observation		
				Actual value	Change from Baseline	
					Absolute	%
Overall		**n**	33			
		Mean (SD)	53.60 (12.53)	59.98 (16.29)	6.384 (10.54)	13.77 (25.83)
		Median (min, max)	55.00 (16.67;83.33)	60.67 (31.33;99.67)	5.667 (-14.00;36.67)	12.14 (-30.88; 100.00)
		P (95% CI)			0.001 (2.645,10.12)	0.004 (4.609, 22.92)
By Age	**<18 years**	**n**	19			
		Mean (SD)	54.04 (13.34)	64.68 (16.24)	10.65 (10.32)-	23.11 (27.27)
		Median (min, max)	55.00 (16.67;83.33)	66.33 (33.33;99.67)	8.000 (-7.67;36.67)	15.43 (-13.9;100.0)
	≥18 years	**n**	14			
		Mean (SD)	53.00 (11.82)	53.60 (14.55)	0.595 (7.972)	1.083 (17.65)
		Median (min, max)	48.00 (37.67;71.33)	55.17 (31.33;76.00)	-0.833 (-14.0;15.00)	-1.11 (-30.9;37.82)
By parental study	**rhLAMAN-02**	**n**	9			
		Mean (SD)	52.63 (14.25)	69.70 (15.14)	17.07 (9.929)	39.11 (31.31)
		Median (min, max)	57.67 (16.67;62.67)	72.00 (33.33;83.67)	14.67 (7.00;36.67)	26.67 (12.14;100.0)
	rhLAMAN-05	**n**	24			
		Mean (SD)	53.96 (12.14)	56.33 (15.45)	2.375 (7.673)	4.260 (15.53)
		Median (min, max)	51.67 (37.67;83.33)	55.17 (31.33;99.67)	3.500 (-14.0;16.33)	6.676 (-30.9;37.82)

Secondary Efficacy Endpoints

6MWT

Table 25: 6MWT (m) by Time point (FAS) in study in rhLAMAN-10

Time point			n	Mean (SD)	Median (Min; Max)	T test	
						p	95% CI
Baseline	Actual value		33	466.6 (90.1)	454.0 (180; 690)		
Month 6	Actual value		24	474.6 (84.1)	468.5 (332; 620)		
	Change from baseline	Absolute		17.6 (62.7)	13.0 (-90; 158)	0.183	-8.9,44.0
		%		6.1 (21.1)	2.8 (-21;88)	0.169	-2.8,15.0
Month 12	Actual value		31	492.4 (83.7)	480.0 (375; 690)		
	Change from baseline	Absolute		21.9 (65.2)	20.0 (-106; 209)	0.071	-2.0,45.8
		%		7.3 (23.3)	3.6 (-20; 116)	0.090	-1.2,15.9
Month 18	Actual value		11	499.9 (95.6)	519.0 (330; 615)		
	Change from baseline	Absolute		55.5 (66.3)	41.0 (-26; 155)	0.020	11.0, 100.0
		%		16.4 (25.7)	8.6 (-7;83)	0.061	-0.9; 33.6
Month 24	Actual value		10	486.6 (90.7)	465.0 (335; 659)		
	Change from baseline	Absolute		5.0 (58.5)	37.0 (-87;73)	0.793	-36.9,46.9
		%		1.2 (12.3)	8.8 (-21;12)	0.766	-7.6,10.0
Month 36	Actual value		6	471.2 (83.5)	442.0 (390; 616)		
	Change from baseline	Absolute		59.3 (85.9)	43.5 (-18; 210)	0.151	-30.8, 149.5
		%		24.4 (46.1)	9.7 (-4; 117)	0.252	-24.0,72.7
Month 48	Actual value		9	522.6 (77.1)	528.0 (378; 625)		
	Change from baseline	Absolute		69.7 (81.1)	64.0 (-33; 198)	0.033	7.4, 132.0
		%		22.5 (35.8)	14.1 (-7; 110)	0.096	-5.0,50.0

Last observation	Actual value		33	489.0 (85.7)	468.0 (335; 659)		
	Change from baseline	Absolute		22.4 (63.2)	24.0 (-87; 198)	0.050	-0.0,44.8
		%		7.1 (22.0)	5.9 (-21; 110)	0.071	-0.7,14.9

Predicted Forced vital capacity

Table 26 presents the percentage of predicted FVC at Baseline and the absolute and percentage changes from Baseline to last observation overall, by age and by parental study and age.

Table 26: FVC (%) at Baseline and Last Observation Overall, by Age and by Parental Study (FAS) in study rhLAMAN-10

				Baseline	**Last observation**		
					Actual value	**Change from Baseline**	
						Absolute	**%**
Overall			**N**	29	31	29	29
			Mean (SD)	84.9 (18.6)	93.1 (21.7)	8.1 (14.8)	10.5 (20.9)
			Median (min, max)	91.0 (50;119)	95.0 (35;130)	7.0 (-17;43)	7.2 (-31;62)
			p (95% CI)	-	-	0.007 (2.4, 13.7)	0.011 (2.6, 18.5)
By Age	**<18 years**		**N**	17	17	17	17
			Mean (SD)	79.6 (16.4)	91.2 (19.5)	11.6 (15.7)	16.4 (22.0)
			Median (min, max)	83.0 (50;99)	93.0 (56; 130)	13.0 (-17;43)	13.4 (-18;62)
	≥18 years		**N**	12	14	12	12
			Mean (SD)	92.5 (19.4)	95.4 (24.7)	3.0 (12.4)	2.1 (16.7)
			Median (min, max)	97.5 (51; 119)	102.0 (35; 125)	1.0 (-16;33)	1.0 (-31;41)
By parental study and age	**rhLAMAN-02**	**<18 years**	**N**	9	9	9	9
			Mean (SD)	81.7 (14.1)	93.0 (17.6)	11.3 (18.4)	15.9 (26.8)
			Median (min, max)	84.9 (61;99)	94.0 (56; 112)	12.0 (-17;43)	12.1 (-18;62)
	rhLAMAN-05	**Overall**	**N**	20	22	20	20
			Mean (SD)	86.4 (20.4)	93.1 (23.6)	6.6 (13.1)	8.1 (17.9)
			Median (min, max)	95.0 (50; 119)	97.0 (35; 130)	4.5 (-16;36)	5.2 (-31;4)
		<18 years	**N**	8	8	8	8
			Mean (SD)	77.1 (19.4)	89.1 (22.5)	12.0 (13.1)	17.0 (16.9)
			Median (min, max)	79.5 (50;99)	86.0 (64; 130)	13.5 (-4;36)	17.2 (-4;38)
		≥18 years	**N**	12	14	12	12

			Mean (SD)	92.5 (19.4)	95.4 (24.7)	3.0 (12.4)	2.1 (16.7)
			Median (min, max)	97.5 (51; 119)	102.0 (35; 125)	1.0 (-16;33)	1.0 (-31;41)

Other endpoints: Childhood health assessment questionnaire (CHAQ)
Disability Index (DI)

The mean (SD) Disability Index (score) at baseline was 1.36 (0.77). There was a decrease in the CHAQ Disability Index from Baseline to the last observation, but this change was not statistically significant: the mean (SD) CHAQ Disability Index score at the last observation was 1.23 (0.66), representing a mean (SD) absolute change from Baseline of -0.13 (0.44) and a mean (SD) percentage change of -2.41% (45.03%).

Visual Analogue Scale (VAS) Pain

At Baseline the mean (SD) CHAQ pain VAS score was 0.618 (0.731). There was no statistically significant absolute or percentage change from Baseline at any time point or at last observation. At last observation the mean (SD) CHAQ Pain VAS score was 0.431 (0.616), representing a mean (SD) change from Baseline of -0.173 (0.647) and a mean (SD percentage change from Baseline of -17.0% (109.8%).

CHAQ general VAS

At Baseline the mean (SD) CHAQ general VAS score was 1.049 (0.770). There were no statistically significant absolute or percentage changes from Baseline at any time point or at last observation. At last observation the mean (SD) CHAQ general VAS score was 0.952 (0.723), representing a mean (SD) change from Baseline of -0.068 (0.621).

Subgroups by ADA Immune Response

A conservative approach was taken to classify patients as ADA positive (i.e. including patients who were ADA positive at any time, including pre-treatment, and setting a relatively low threshold of 1.4 U/mL to determine ADA status). With this definition, 8/33 patients were considered to be ADA positive for at least one time point on-treatment and at least one further confirmatory positive result was present in 6 of these patients. In 2 patients the titre level of ADAs was >80 U/mL (with a maximum value of 1012 U/mL in one patient and remaining very low (<30 U/mL) in the remnant patients. No clear differences were seen between patients who were ADA negative throughout the study, and those who became ADA positive at some point during the study in any of the efficacy endpoints evaluated by ADA status (serum oligosaccharides, 3MSCT and 6MWT [m and % predicted].

Ancillary analyses

To address the evaluation of the clinical relevance of the observed changes, the Applicant defined a Minimal Clinically Important Difference (MID) threshold for each efficacy variable and organized the overall set of variables into clusters based on their similarity (i.e. their belonging to homogeneous functional domains).

The MIDs for the clinical endpoints tested in the velmanase alfa development trial have not been previously defined for alpha-mannosidosis. As a consequence, the Applicant decided to import MIDs used in diseases with similar characteristics.

In order to address this issue, the Applicant conducted an extensive review of the literature and consulted with experts in the field. The key guiding element in the definition of proxies was the similarity with other rare diseases, and in particular lysosomal storage disorders with limitation in mobility, as well as the age range during which these diseases manifest.

Table 27 summarises the MID threshold identified for the key efficacy variables serum oligosaccharide, 6MWT, 3MSCT, FCV, CHAQ-DI, and CHAQ-VAS.

Table 27. Responder Criteria Definitions based on Minimal Clinically Important Differences in the various endpoints investigated in the velmanase alfa development programme

Domain	Criterion	Description
Pharmacodynamic	Oligosaccharides	Last Serum Oligosaccharides Value ≤ 4umol/l
Functional	3MSCT	3MSCT Absolute change ≥ 7 steps/min
	6MWT	6MWT Absolute change ≥ 30 m
	FVC (%)	FVC (%) Absolute change ≥ 10%
Quality of Life	CHAQ-DI	CHAQ-DI Absolute change ≤ -0.130
	CHAQ-VAS	CHAQ-VAS Absolute change ≤ -0.246*

Responder Analysis Using the Minimum Clinically Important Difference by Endpoint and Domain

The response rates were calculated for each endpoint and domain, both for the placebo-controlled study rhLAMAN-05 at 12 months and the Last observation (LO) from rhLAMAN-10 integrated analysis at 29.3 (15.2) months **(Table 28**).

Table 28: MCID Responders Rates by Endpoints and Domains in studies rhLAMAN-05 and rhLAMAN-10

			Responders at month 12 rhLAMAN-05 (n=25)		**Responders at last observation rhLAMAN-10 (n=33)**
Domain	**Parameter**	**Responder criteria definition**	**Placebo Responders, n (%) n=10**	**Velmanase alfa Responders, n (%) n=15**	**All patients treated with velmanase alfa Responders, n (%) n=33**
Pharmacodynamic	Oligosaccharides	Serum oligosaccharides Value ≤4 µmol/L	2 (20.0)	15 (100.0)	30 (90.9)
	Domain response (MCID reached)		**2 (20.0)**	**15 (100.0)**	**30 (90.9)**
Functional	3MWSCT (steps/min)	3MSCT absolute change ≥7 steps/min	1 (10.0)	3 (20.0)	16 (48.5)
	6MWT (m)	6MWT absolute change ≥30 m	1 (10.0)	3 (20.0)	16 (48.5)
	FVC (% of predicted)	FVC (%) absolute change ≥10%	2 (20.0)	5 (33.3)	13 (39.4)

			Responders at month 12 rhLAMAN-05 (n=25)		Responders at last observation rhLAMAN-10 (n=33)
Domain	**Parameter**	**Responder criteria definition**	**Placebo Responders, n (%) n=10**	**Velmanase alfa Responders, n (%) n=15**	**All patients treated with velmanase alfa Responders, n (%) n=33**
	Domain response (MCID[1] reached in at least one parameter)		**3 (30.0)**	**9 (60.0)**	**24 (72.7)**
Quality of life	CHAQ DI	CHAQ DI Absolute change ≤-0.130	2 (20.0)	3 (20.0)	14 (42.2)
	CHAQ VAS	CHAQ VAS Absolute change ≤-0.246	4 (40.0)	5 (33.3)	15 (45.5)
	Domain response (MCID reached in at least one parameter)		**4 (40.0)**	**6 (40.0)**	**22 (66.7)**
Overall response	**Three domains**		**0**	**2 (13.3)**	**15 (45.5)**
	Two domains		**3 (30.0)**	**11 (73.3)**	**14 (42.4)**
	One domain		**3 (30.0)**	**2 (13.3)**	**3 (9.1)**
	No domains		**4 (40.0)**	**0**	**1 (3.0)**

Summary of main studies

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 29. Summary of Efficacy for trial rhLAMAN-O5

Title: A multi-center, double-blind, randomized, Placebo controlled, parallel group trial, investigating the efficacy and safety of repeated velmanase alfa treatment of subjects with alfa-Mannosidosis			
Study identifier	rhLAMAN-05		
Design	a parallel group, randomized, double-blind, placebo-controlled phase 3 study to evaluate efficacy and safety of CHF-LMZYMAA1 at the intended clinical dose		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year 9 months not applicable not applicable
Hypothesis	Exploratory		
Treatments groups	Velmanase alfa group		Velmanase alfa 1 mg/kg weekly. 52 weeks, n=15
	Placebo group		placebo. 52 weeks, n=10
Endpoints and definitions	Co-Primary endpoint	Serum oligosaccharides	serum oligosaccharide reduction over 52 weeks of treatment as a measure of the biological activity
	Co-Primary endpoint	3MSCT	3MSCT improvement as an indication of the clinical relevance.
	Prioritized secondary endpoint	6MWT	Change from baseline to week 52 in 6 minute walk test (6MWT)
	Prioritized secondary endpoint	FVC	Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)
	Secondary endpoint	BOT2	Change from baseline to other visits in the Bruininks-Oseretsky test of motor proficiency (BOT2) (total score and domain scores)
	Secondary endpoint	Leiter R	Change from baseline to other visits in the Leiter R (total score and domain scores)
	Secondary endpoint	CSF oligosaccharides and Tau, NFL and GFAp	Change from baseline to other visits in CSF oligosaccharides and Cerebrospinal fluid biomarkers (Tau, NFL and GFAp)
	Secondary endpoint	FEV1 (l), FEV1 (%), FVC (l) and PEF (l/s)	Change from baseline to other visits in pulmonary function tests [FEV1 (l), FEV1 (%), FVC (l) and PEF (l/s)]
	Secondary endpoint	PTA	Change from baseline to other visits in pure tone audiometry (PTA) (air conduction left and right ear and bone conduction for the best ear)
	Secondary endpoint	CHAQ and EQ-5D	Change from baseline to other visits in the Questionnaires (CHAQ and EQ-5D) (total score and domain scores)
Database lock	02-May-2014		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat is in this case also Per protocol after 52 weeks treatment		
Descriptive statistics and estimate variability	Treatment group	Velmanase alfa	placebo
	Number of subject	15	10
	Absolute change Serum Oligosaccharide Concentration (µmol/l); Mean (95% CI)	- 5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)
	Absolute change 3MSCT (steps/min); Mean (95% CI)	0.46 (-3.58, 4.50)	-2.16 (-7.12, 2.80)
	Absolute change 6MWT (metres) Mean (95% CI)	3.74 (-20.32, 27.80)	-3.61 (-33.10, 25.87)
	Absolute change FVC (% of Predicted); Mean (95% CI)	8.20 (1.79, 14.63)	2.30 (-6.19, 10.79)
	Absolute change FVC (l) Mean (95% CI)	0.40 (95% CI: 0.16, 0.64)	0.13 (95% CI: -0.19, 0.45)
	FEV1 (% of predicted) Mean (95% CI)	6.31 (95% CI: 1.67, 10.96)	4.54 (95% CI: -0.69, 9.77)
	FEV1 (l) Mean (95% CI)	0.29 (95% CI: 0.13, 0.46)	0.23 (95% CI: 0.05, 0.42)
	PEF (l/s) Mean (95% CI)	0.85 (95% CI: 0.33,1.37)	0.76 (95% CI: 0.13, 1.40)
	BOT2 Total Score (points) Mean (95% CI)	5.83 (95% CI: 0.00, 11.67)	1.30 (95% CI: -6.00, 8.59)
	BOT-2 Running Speed and Agility (points) Mean (95% CI)	-0.27 (95% CI: -1.58, 1.03)	-0.27 (95% CI: -1.93, 1.39)
	BOT-2 Body Coordination (points) Mean (95% CI)	0.71 (95% CI: -2.05, 3.46)	-1.88 (95% CI: -5.54, 1.77)
	BOT-2 Fine Manual Control (points) Mean (95% CI)	2.49 (95% CI: -0.51, 5.49)	0.18 (95% CI: -4.02, 4.38)
	BOT-2 Manual Coordination (points) Mean (95% CI)	2.60 (95% CI: -0.31, 5.51)	3.25 (95% CI: -0.41, 6.90)
	Leiter R Total Equivalence Age for the Visualization and Reasoning (years) Mean (95% CI)	0.15 (95% CI: -0.18, 0.48)	0.19 (95% CI: -0.21, 0.60)
	Leiter R Total Equivalence Age for Attention and Memory (years) Mean (95% CI)	-0.02 (95% CI: -0.59, 0.55)	0.16 (95% CI: -0.54, 0.87)
	CSF Oligosaccharides (µmol/l) Mean (95% CI)	-0.43 (95% CI: -0.98, 0.12)	-0.48 (95% CI: -1.16, 0.19)
	CSF Tau Protein (ng/l) Mean (95% CI)	-47.65 (95% CI: -91.97, -3.33)	-80.13 (95% CI: -134.77, -25.48)

	CSF Neurofilament Protein (NFLp) (ng/l)) Mean (95% CI)	-4.64 (95% CI: -18.56, 11.65)	-32.95 (95% CI: -150.58, 84.68)
	Glial Fibrillary Acidic Protein (GFAp) (ng/l) Mean (95% CI)	102.06 (95% CI: -5.76, 209.88)	148.91 (95% CI: 16.66, 281.16)
	Audiometry in Best Ear Using Bone Conduction (dB) Mean (95% CI)	6.31 (95% CI: 0.16, 12.83)	-1.94 (95% CI: -8.62, 5.24)
	Audiometry in Left Ear Using Air Conduction (dB) Mean (95% CI)	1.45 (95% CI: -2.35, 5.26)	0.01 (95% CI: -4.66, 4.68)
	Audiometry in Right Ear Using Air Conduction (dB) Mean (95% CI)	2.24 (95% CI: -3.54, 8.02)	-2.34 (95% CI: -9.44, 4.76)
	CHAQ Disability Index Mean (SD)	-0.01 (0.32)	0.18 (0.36)
	CHAQ Pain From VAS Mean (SD)	0.19 (0.69)	0.15 (0.71)
	CHAQ General Evaluation from VAS Mean (SD)	0.51 (0.93)	0.44 (0.62)
	EQ-5D-5L Index Mean (SD)	0.04 (0.09)	0.03 (0.16)
	EQ-5D-5L VAS Mean (SD)	2.00 (17.95)	3.70 (15.71)
Effect estimate per comparison	Co-Primary endpoint Serum Oligosaccharides	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	-3.50 (-4.37, -2.62)
		P-value	p<0.001
	Co-Primary endpoint 3MSCT	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	2.62 (-3.81, 9.05)
		P-value	0.406
	Secondary endpoint 6MWT	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	7.35 (-30.76, 45.46)
		P-value	0.692
	Secondary endpoint FVC (% of Predicted)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	5.91 (-4.78, 16.60)
		P-value	0.278
	Secondary endpoint FVC (l)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.27 (95% CI: -0.14; 0.68)

		P-value	p=0.202
	Secondary endpoint FEV1 (% of predicted)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.29 (95% CI: -0.06; 0.64
		P-value	p=0.101
	Secondary endpoint FEV1 (l)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.26 (95% CI: -0.01, 0.52),
		P-value	p=0.057
	Secondary endpoint PEF (l/s)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.95 (95% CI: 0.24; 1.66),
		P-value	p=0.009
	Secondary endpoint BOT2 Total Score (points)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	4.54 (95% CI: -4.86, 13.94),
		P-value	p=0.344
	Secondary endpoint BOT2 Running Speed and Agility (points)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.0 (95% CI: -2.17; 2.16)
		P-value	p=0.998
	Secondary endpoint BOT2 Fine Manual Control (points)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	2.31 (95% CI: -2.86, 7.48)
		P-value	p=0.381
	Secondary endpoint BOT2 Manual Coordination (points)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	-0.65 (95% CI: -5.33; 4.04)
		P-value	p=0.787
	Secondary endpoint Leiter R Total Equivalence Age for the Visualization and Reasoning (years)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	0.28 (95% CI: -7.43, 8.62)
		P-value	p=0.943
	Secondary endpoint Leiter Total Equivalence Age for Attention and Memory (years)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	-0.18 (95% CI: -1.09, 0.73),
		P-value	p=0.681
	Secondary endpoint	Comparison groups	Velmanase alfa - placebo

	CSF Oligosaccharides (µmol/l)	Adjusted mean difference vs Placebo (95% CI)	0.06 (95% CI: -0.82, 0.93)
		P-value	p=0.897
	Secondary endpoint CSF Tau Protein (ng/l)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	32.48 (95% CI: -39.01, 103.96)
		P-value	p=0.356
	Secondary endpoint CSF Neurofilament Protein (NFLp) (ng/l)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	-35.09 (95% CI: -188.3, 118.09)
		P-value	p=0.639
	Secondary endpoint CSF Glial Fibrillary Acidic Protein (GFAp) (ng/l)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	-46.85 (95% CI: -218.1, 124.38)
		P-value	p=0.575
	Secondary endpoint Audiometry in Best Ear Using Bone Conduction (dB)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	2.87 (95% CI: -1.68; 7.42)
		P-value	p=0.217
	Secondary endpoint Audiometry in Left Ear Using Air Conduction (dB)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	1.44 (95% CI: -4.62; 7.50)
		P-value	p=0.626
	Secondary endpoint Audiometry in Left Ear Using Air Conduction (dB)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	1.44 (95% CI: -4.62; 7.50)
		P-value	p=0.626
	Secondary endpoint Audiometry in Right Ear Using Air Conduction (dB)	Comparison groups	Velmanase alfa - placebo
		Adjusted mean difference vs Placebo (95% CI)	4.58 (95% CI: -4.64; 13.81),
		P-value	p=0.313
Notes	For the CHAQ and EQ-5D-5L no comparative analysis was submitted		

Table 30: Summary of efficacy for trial rhLAMAN-10

Title: A single centre, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alfa-mannosidase or Velmanase alfa) treatment in subjects with alfa-mannosidosis who previously participated in velmanase alfa trials.			
Study identifier	rhLAMAN-10		
Design	single centre, open label clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		5 month not applicable not applicable
Hypothesis	Exploratory		
Treatments groups	Velmanase alfa group		Velmanase alfa 1mg/kg weekly, 34 patients randomised, duration of follow-up is variable varying from 3 to 52 months
Endpoints and definitions	Co-Primary endpoint	Serum oligosaccharides	serum oligosaccharide reduction over 52 weeks of treatment as a measure of the biological activity
	Co-Primary endpoint	3MSCT	3MSCT improvement as an indication of the clinical relevance
	Prioritized secondary endpoint	6MWT	Change from baseline to week 52 in 6 minute walk test (6MWT)
	Prioritized secondary endpoint	FVC	Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)
	Secondary endpoint	BOT2	Change from baseline to other visits in the Bruininks-Oseretsky test of motor proficiency (BOT2) (total score and domain scores)
	Secondary endpoint	Leiter R	Change from baseline to other visits in the Leiter R (total score and domain scores)
	Secondary endpoint	CSF oligosaccharides and Tau, NFL and GFAp	Change from baseline to other visits in CSF oligosaccharides and Cerebrospinal fluid biomarkers (Tau, NFL and GFAp)
	Secondary endpoint	FEV1 (l), FEV1 (%), FVC (l) and PEF (l/s)	Change from baseline to other visits in pulmonary function tests [FEV1 (l), FEV1 (%), FVC (l) and PEF (l/s)]
	Secondary endpoint	PTA	Change from baseline to other visits in pure tone audiometry (PTA) (air conduction left and right ear and bone conduction for the best ear)
	Secondary endpoint	CHAQ and EQ-5D	Change from baseline to other visits in the Questionnaires (CHAQ and EQ-5D) (total score and domain scores)
Database lock	13 June 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol using LOCF		

Descriptive statistics and estimate variability	Treatment group	Velmanase alfa 1 mg/kg weekly	
Analysis population and time point description	Number of subjects	33	
	endpoint	Point estimate	p-value
Descriptive statistics and estimate variability Effect estimate per comparison	change from baseline Serum Oligosaccharide Concentration (µmol/L); Mean (95% CI)	-4.59 (-5.74,-3.45)	<0.001
	change from baseline 3MSCT (steps/min); Mean (95% CI)	6.384 (2.645,10.12)	0.004
	change from baseline 6MWT (metres) Mean (95% CI)	22.4 (-0.0,44.8)	0.050
	change from baseline FVC (% of Predicted); Mean (95% CI)	8.1 (2.4, 13.7)	0.007
	change from baseline FVC (l) Mean (95% CI)	0.578 (0.310, 0.845)	<.001
	change from baseline FEV1 (% of predicted) Mean (95% CI)	4.0 (-2.4,9.9)	0.226
	change from baseline FEV1 (l) Mean (95% CI)	0.399 (0.165, 0.633)	0.002
	change from baseline PEF (l/s) Mean (95% CI)	1.160 (0.501, 1.819)	0.001
	BOT2 Total Score (points) Mean (95% CI)	5.1 (1.0,25.0)	0.035
	BOT-2 Running Speed and Agility (Age equivalent score) Mean (SD)	0.0 (0.5)	--
	BOT-2 FMP (Age equivalent score) Mean (SD)	0.4 (1.6)	--
	BOT-2 FMI (Age equivalent score) Mean (SD)	0.2 (2.0)	--
	BOT-2 MD (Age equivalent score) Mean (SD)	0.3 (0.8)	--
	BOT-2 ULC (Age equivalent score) Mean (SD)	0.2 (1.3)	--
	BOT-2 BLC (Age equivalent score) Mean (SD)	0.3 (0.7)	--
	BOT-2 Balance (Age equivalent score) Mean (SD)	0.0 (0.4)	--
	Leiter R Total Equivalence Age for the Visualization and Reasoning (years) Mean (95% CI)	0.265 (0.637)	--
	Leiter R Total Equivalence Age for Attention and Memory (years) Mean (95% CI)	0.156 (1.519)	--
	CSF Oligosaccharides (µmol/l) Mean (SD)	-0.59 (1.97)	--
	CSF Tau Protein (ng/l) Mean (95% CI)	20.8 (162.6)	--

	CSF Neurofilament Protein (NFLp) (ng/L) Mean (95% CI)	-26.2 (209.4)	--
	Glial Fibrillary Acidic Protein (GFAp) (ng/L) Mean (95% CI)	174.8 (498.8)	--
	Audiometry in Best Ear Using Bone Conduction (dB) Mean (SD)	-0.49 (6.58)	--
	Audiometry in Left Ear Using Air Conduction (dB) Mean (95% CI)	-2.83 (7.14)	--
	Audiometry in Right Ear Using Air Conduction (dB) Mean (95% CI)	-1.41 (10.31)	--
	CHAQ Disability Index Mean (SD)	0.00 (-0.29, 0.02)	0.095
	CHAQ Pain From VAS Mean (SD)	-0.173 (0.647)	--
	CHAQ General Evaluation from VAS Mean (SD)	0.000 (-0.291,0.156)	0.543
	EQ-5D-5L Index Mean (SD)	0.050 (0.135)	--

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

See section on Study rhLAMAN-10.

Clinical studies in special populations

No studies in special populations were submitted.

Supportive studies

Studies rhLAMAN-02, -03, -05, -07 and -09 were part of the integrated analysis (rhLAMAN-10) described above.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In all submitted velmanase alfa clinical studies, alpha-mannosidosis was defined for study eligibility as alpha-mannosidase activity <10% of normal activity in blood leukocytes. Patients were all over the age of 5 at screening. Furthermore patients should have been able to physically and mentally cooperate in the tests. In all clinical studies, patients with a history of BMT were excluded as were patients who could not walk without aids or who had psychosis.

Therefore only patients with mild to moderate disease burden were evaluated. The most severely affected young patients were not included in the submitted studies. The mean age at the first dose of active treatment of the 33 patients included in the rhLAMAN-10 integrated analysis was 17.1 years, and the median was 15 years (range: 6 to 35 years).

In the dose-escalation study (Study rhLAMAN-02), pairs of patients were randomized to 6.25, 12.5, 25, 50, or 100 U/kg iv velmanase alfa. All 10 patients included in rhLAMAN-02 were enrolled in study

rhLAMAN-03 and randomised in a 1:1 ratio to receive weekly iv infusions of 25 U/kg or 50 U/kg velmanase alfa. The 9 patients who completed the study were then enrolled in Study rhLAMAN-04 to evaluate 1 mg/kg iv velmanase alfa, the intended clinical dose.

In study rhLAMAN-05, 25 naïve patients were randomized to treatment or placebo in a 3:2 ratio and were randomly allocated to active treatment of 1 mg/kg iv or placebo. Using this design and sequence of studies the applicant efficiently used the very limited number of patients available to gain some information on dose finding. Combining these limited data with those obtained from the non-clinical studies the choice of 1 mg/kg (25 IU/kg) given as a weekly infusion is well justified.

Study rhLAMAN-05 was a placebo controlled study which provides information on the efficacy compared to a placebo. For this is a double blind randomised design this study is the only source of information between treated and untreated patients with a comparable burden of disease. The integrated analysis (rhLAMAN-10) lacks the direct comparison but provides efficacy data for over 4 years.

The applicant used many endpoints ranging from pharmacodynamic (oligosaccharides in serum, urine and CSF), endurance (6MWT and 3MSCT), lung function (FVC, FEV1 and PEF), hearing, motor development (BOT-2), psychological development (Leiter-R) and quality of live (CHAQ and EQ-5D-5L). All endpoint are relevant for the disease and changes compared to placebo could be assessed in the rhLAMAN-05 study.

At the request of the CHMP and to support the assessment of the overall effect, the applicant performed a post-hoc responder analysis. Endpoints were grouped into three domains, identified as pharmacodynamic (serum oligosaccharide response), functional (3MSCT, 6MWT and FVC% predicted) and quality of life (CHAQ disability index and CHAQ VAS pain).

The Minimal Important Differences (MIDs) for the functional domain have not been previously defined for alpha-mannosidosis. To define MIDs the applicant conducted an extensive literature review and consulted with experts.

For the FVC% predicted the proposed MID by the applicant was accepted. A MID for the 6MWT is more difficult to define as major differences in MID for various conditions using this endpoint have been reported. For the CHAQ disability index and CHAQ VAS pain scores the only available information is from one publication. For the 3MSCT no publications evaluating the MID were submitted as the applicant failed to identify relevant publications.

Given the limited information available on the matter, the CHMP considered the definitions of MID proposed by the applicant in this very rare condition acceptable.

Efficacy data and additional analyses

The biological activity of velmanase alfa was confirmed in study rhLAMAN-5, by the significant difference between groups in clearing serum oligosaccharides. The adjusted mean relative change (%) in serum oligosaccharides from baseline to week 52 was -77.60 (95% CI: -81.58, -72.76) in the velmanase alfa group and -24.14 (95% CI: -40.31, -3.59) in the placebo group. The adjusted mean difference for velmanase alfa vs placebo was -70.47 (95% CI: -78.35, -59.72) showing a statistically significant difference between the two groups ($p<0.001$) in favour of the velmanase alfa group.

With respect to the 3MSCT as primary endpoint, the treatment with velmanase alfa 1 mg/kg i.v. once weekly resulted in a modest improvement in the 3MSCT in the overall population of alpha-mannosidosis patients. The adjusted mean relative change (%) from baseline to week 52 was -1.07

(95% CI: -9.05, -7.61) in the velmanase alfa group and –3.97 (95% CI: -13.38, 6.47) in the placebo group. The adjusted mean difference in the 3MSCT for velmanase alfa vs placebo was 3.01 (95% CI: -9.86, 17.72). Although a numerical improvement was observed the comparison between the two groups was not statistically significant (p=0.648).

Numerical improvement of endurance was also captured in the 6MWT. The adjusted mean relative change (%) from baseline to week 52 was 0.64 (95% CI: -4.74, 6.32) in the velmanase alfa group and -1.20 (95% CI: -7.63, 5.68) in the placebo group. The adjusted mean difference for velmanase alfa vs placebo was 1.86 (95% CI: -6.63, 11.12). The comparison between the two groups was not statistically significant (p=0.664).

For the FVC (% of predicted) the adjusted mean relative change (%) from baseline to week 52 was 10.11 (95% CI: 1.31, 19.67) in the velmanase alfa group and 1.58 (95% CI: -9.48, 13.99) in the placebo group. The adjusted mean difference for velmanase alfa vs placebo was 8.40 (95% CI: -6.06, 25.08). The comparison between the two groups was not statistically significant (p=0.269).

Overall, the endpoints with the highest clinical relevance did not show a statistical significant change compared to placebo but only a numerical improvement over placebo (2 to 8%) in the year of observation. The small but consistent improvement observed suggests that velmanase alfa may slow down the existing disease progression. This is further supported by the fact that patients included in the study did not deteriorate as would have been expected given the natural history of the disease. It is therefore likely that a one year observation is too limited to expect differences between treated and untreated patients for the endpoints investigated. The Expert Advisory Group which was consulted for this application (see below, Additional expert consultation) also considered that trials of longer duration than the timeframe of the placebo-controlled study would be required to establish the true magnitude of effect of velmanase alfa, especially in adult patients. However, the CHMP acknowledged that such trials could not realistically be expected in this very rare condition.

In a post-hoc analysis conducted by the applicant, age appeared as the most critical prognostic parameter for a response in motor function (3MSCT) results. Numerical improved responses were also observed in the youngest treated patients across multiple domains (Peripheral Nervous System by BOT2, respiratory tests with pronounced improvement in FVC as % of predicted, data not shown) which suggest that the clinical benefits of velmanase alfa might be more clinically pronounced if administered to younger patients under 6 years old which were not included in the clinical trial.

The Expert Group which was convened to discuss this application also stressed that clinical benefits of velmanase treatment could be expected, regardless of the age of the patient. The Group however, acknowledged that the available data does not allow for the use of the product in the most severely affected patients with skeletal abnormalities, and obvious progression, leading to an early death from primary CNS involvement or myopathy.

Based on the definition of the MCID, the applicant submitted responder analyses for the various endpoints as well as a multi-parametric responder analysis. The responder analysis of rhLAMAN-05 showed a discernible treatment difference between the two groups, with a clinical response in at least two domains at 12 months observed in 87% of patients treated with velmanase alfa compared to 30% treated with placebo. Moreover, 13% of the velmanase alpha treated patients but none of the placebo patients reported a clinically significant response in all three domains.

In the integrated overview study (rh-LAMAN-10), results demonstrated an acute effect on the serum oligosaccharides which was maintained for the duration of the trial. At baseline, mean (SD) serum oligosaccharides were 6.90 (2.30) µmol/L. There was a statistically significant decrease in serum oligosaccharides from Baseline to the last observation: mean (SD) serum oligosaccharide levels at the

last observation were 2.31 (2.19) µmol/L, representing a mean (SD) absolute change from Baseline of -4.59 (3.23) µmol/L, and a mean (SD) percentage change from baseline of -62.8% (33.61%) ($p<0.001$ for both absolute and percentage changes from Baseline).

In addition there was a statistically significant improvement in both the 3MSCT (6.4 steps/minute), the 6MWT (22.4 metres) as well as in predicted FVC. This supports the notion that to observe clinical meaningful effects, exposure to velmanase alfa, longer than the study period of rhLAMAN-05 would be required.

In the post-hoc responder analysis at 12 months, 79% of patients showed a significant response in at least two domains, and 24% in all three. The proportion increases at Last Observation with a important response in at least two domains achieved in 88% patients (100% of paediatric patients and 71% of adult patients) and in all three domains in 45% patients (53% of paediatric patients and 36% of adult patients).

There were no statistically significant changes in any CHAQ endpoint (CHAQ Disability Index, CHAQ pain VAS and CHAQ general VAS) from Baseline to any time point or to the last observation. The mean changes from Baseline in the CHAQ Disability Index did not reach the minimal clinically important improvement of 0.13 at the last observation in the patients.

In both rhLAMAN-05 and rhLAMAN-10 velmanase alfa treatment had limited or no impact on CSF oligosaccharides, CSF proteins or cognitive function. These results are not unexpected as velmanase alfa does not appear to cross the BBB in humans. This is of significant clinical importance as a high proportion of patients with Alpha-mannosidosis have intellectual impairment (approximately 85% of those participating in rhLAMAN-05 had diagnosis of mental retardation at baseline). As a result the CHMP considered that the lack of an effect on the neurological manifestations of the diseases should be explicitly stated in the approved indication for Lamzede.

The CHMP considering the totality of the data and the comments raised by the Expert Group concluded that it would not be appropriate to restrict the population that could be treated with velmanase alfa to patients above 6 years old as was initially proposed by the applicant. The CHMP noted that all available data indicate that patients most likely to benefit the most are younger patients. Therefore, it is important that treatment is to be initiated as early as possible in patients with the mild to moderate form after manifestation of the symptoms of the disease 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:

1. How do you judge the clinical relevance of the observed effects of velmanase alfa on the pharmacodynamic and functional outcomes in patients with alpha-mannosidosis?

The expert group noted the significant effect of velmanase-alpha on the serum concentration of oligosaccharides and highlighted that a pharmacodynamic effect in the context of an enzyme replacement therapy was an absolute requirement to demonstrate efficacy. However, the expert group noted that such a response would not be sufficient to predict any clinical benefit of treatment with velmanase alfa.

The expert group also noted that the results for the functional outcomes did not reach statistical significance but suggested some effect of the active treatment compared to placebo. Interpretation of

the true clinical relevance of these results is difficult, due to both the rarity, the heterogeneity of the disease as well as the variability of the chosen outcome parameters.

The expert group considered that based on the results from rhLAMAN-05, only a sub-population of patients with alpha-mannosidosis would probably benefit from treatment with velmanase alfa. Identifying these patients however would be challenging, and is discussed further in the responses to Questions 2 and 3 below.

The expert group finally noted the absence of any meaningful effect on the endpoints used to determine the impact of velmanase treatment on the Central Nervous System, which is expected since velmanase alfa does not cross the Blood Brain Barrier.

2. Can the expected clinical benefits of velmanase alfa be extrapolated to patients with alpha-mannosidosis, not included in the clinical trial programme? For instance, can the experts give their views on the role of velmanase alfa in the very young patients with the most severe manifestations, asymptomatic patients or those with very mild symptoms or late onset of disease?

As noted above, it is difficult to ascertain which patients are the ones most likely to benefit the most from velmanase alfa treatment. The expert group noted that younger patients, under the age of 18 that were included in the trial seemed to benefit the most. Nevertheless, the expert group by majority considered that based on the observed results, it would be reasonable to expect clinical benefits in very young patients (i.e. below 6 years of age) with mild or moderate manifestations of the disease. Some concerns were raised about extrapolating to such patients, mainly as safety in that population has not been investigated. The expert group agreed that further data would be required, for the very young patients with severe (type 1) phenotype.

For adult patients, the expert group considered that velmanase treatment could be of benefit only for some of them, but in the absence of data on the natural disease course in adults, caution should be taken with initiation of therapy. Studies of longer duration (2-3 years) in larger groups of patients would probably be required to determine the magnitude of effect in those patients. The group suggested to initiate treatment in adults only in those with potentially reversible signs or symptoms, i.e. excluding skeletal or neurological/psychiatric disease as a sole criterion to start therapy. They also noted that they were not aware of any adult patients where central nervous system involvement was not a prominent feature and this would limit any potential benefits of velmanase treatment in this population.

3. Within the different sub-types of alpha-mannosidosis, are there patients you would expect to benefit more than others from velmanase alfa treatment? Are there any disease related or prognostics factors that can be helpful to decide which patients should be treated or not treated?

Available data do not allow for clear identification of patients that would benefit the most. The expert group considered that, according to the mechanism of action of the medicine and the pathophysiology of the disease, the earlier treatment starts the higher the benefit to be expected. However it was also noted that there are no prognostic factors which could help determine which patients would respond better to treatment.

The expert group also recommended that the effects of treatment with velmanase should be periodically evaluated and discontinuation of treatment considered in cases where no clear benefits could be observed.

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 velmanase alfa?

The expert group highlighted the importance of establishing a disease registry to collect further data in this rare disease setting. The expert group considered that preferably such a registry should be directly under the governance of the clinicians treating the patients that would be included in the registry.

In terms of data collection, emphasis should be given Patient Reported Outcomes as well as Mental Health Scales, as for example those relevant for psychosis, which is a known complication in patients with alpha mannosidosis. Additional data on infections and antibiotic use would be relevant as well. It would also be important to collect information on antibodies in treated patients to characterise any potential effect they may have on effectiveness over long term treatment.

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 Lamzede under normal conditions of use could not be considered comprehensive as for a number of clinical endpoints only a numerical improvement was shown for Lamzede over placebo but this was not confirmed from a statistical view point.

The CHMP noted that it is not feasible to generate a comprehensive data set due to the rarity of the disease which reduces dramatically the availability of the subjects for the conduct of the trials but also the variability in clinical symptoms of the condition which means that there is no disease specific validated clinically relevant endpoint. In addition, due to the 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 number of obligations, including a disease registry in order to evaluate the long-term effectiveness of treatment with Lamzede under conditions of routine clinical care. Data collection from this registry will also enable further characterisation of the alpha mannosidosis population with regards to the variability of clinical manifestation and disease progression.

In addition, the results of an ongoing open label 24 month study will be submitted in order to provide further confirmation of efficacy in children ≤ 6 years which were not included in the Lamzede clinical trial programme.

2.5.4. Conclusions on the clinical efficacy

A clear pharmacodynamic effect (decrease of serum oligosaccharides), has been demonstrated for velmanase alfa from the data submitted in patients with alpha-mannosidosis. For most of the clinical endpoints consistent numerical differences were also shown in the randomised clinical trial, however the observation period of 1 year is not considered sufficient to fully characterise the magnitude of change in the various endpoints in this condition and in which disease progression can be slow.

Additional evidence of efficacy was provided from the integrated analysis of all the clinical studies conducted with velmanase alfa. In a post-hoc, multi-parametric responder analysis a large majority of

patients showed a significant response in two of the three investigated domains (pharmacodynamic, functional and Quality of Life). Additional analyses revealed that the youngest patients were the ones most likely to benefit from treatment.

Therefore, it was concluded that velmanase alfa is an effective treatment option for patients with alpha mannosidosis.

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

- An alpha-mannosidosis disease registry, to evaluate long tem effectiveness of treatment with velmanase alfa
- An open label study to further characterise the efficacy in patients from birth to < 6 years of age.

2.6. Clinical safety

The safety data submitted in support of the use of velmanase alfa in patients with alpha mannosidosis is combined from a number of different sources as outlined below:

1) Patients treated with CHF-LMZYMAA1 who completed the dose-ranging studies (rhLAMAN-02, 03 and 04) and who were:

a) exposed for ~4 years and were monitored in the follow-up studies (rhLAMAN-07 or 09) giving ~4 years of exposure with continuous safety data records or

b) treated in the compassionate use programme with only standard expedited reporting giving ~4 years of exposure with ~2 years of continuous safety data records and a follow-up visit in rhLAMAN-10.

2) Patients initially treated with CHF-LMZYMAA1 in the placebo-controlled study (rhLAMAN-05) and who were:

a) monitored in the follow-up studies (rhLAMAN-07 or 09) giving ~2 years of continuous safety data records or

b) treated in the compassionate use programme with only standard expedited reporting giving ~2 years of exposure with ~1 year of continuous safety data records and a follow-up visit in rhLAMAN-10.

3) Patients initially treated with Placebo in rhLAMAN-05 study who then received CHFLMZYMAA1 and who were:

a) monitored in the follow-up studies (rhLAMAN-07 or 09) giving ~1 year of continuous safety data records or

b) treated in the compassionate use programme with only standard expedited reporting giving ~1 year of exposure with Baseline data pre-treatment and a single follow-up visit in rhLAMAN-10.

Patient exposure

Overall, thirty-three (33) patients have received treatment with velmanase alfa during clinical studies. Exposure data from patients who were treated with velmanase alfa in the compassionate use programme (18 patients) were also included in the SAS. Therefore, approximately one third of patients (9 patients (27.3%) had been exposed to velmanase alfa up to 48 months. However, during the compassionate use programme only spontaneous reports were collected.

Duration of exposure periods for all patients included in the SAS are detailed in

Table 31.

Table 31: Duration of Exposure to velmanase alfa by age group of patients included in the integrated safety analysis

		<18 years N=19, n (%)	**>=18 years N=14, n (%)**	**Overall N=33, n (%)**
Integrated Analysis Exposure Intervals	0 -| 6 months	19 (57.6)	14 (42.4)	33 (100.0)
	6 -| 12 months	19 (57.6)	14 (42.4)	33 (100.0)
	12 -| 18 months	17 (51.5)	11 (33.3)	28 (84.8)
	18 -| 24 months	15 (45.5)	10 (30.3)	25 (75.8)
	24 -| 30 months	14 (42.4)	5 (15.2)	19 (57.6)
	30 -| 36 months	12 (36.4)	1 (3.0)	13 (39.4)
	36 -| 42 months	9 (27.3)		9 (27.3)
	42 -| 48 months	9 (27.3)		9 (27.3)

Adverse events

An overall summary of Treatment Emergent Adverse Events (TEAEs), by age group is presented in **Table 32**.

Table 32. Overall summary of TEAEs by age in patients exposed to velmanase alpfa in the safety analysis set

	Aged <18 years[1] (N=19)		Aged ≥18 years (N=14)		Overall (N=33)	
	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	17 (89.5)	423	12 (85.7)	123	29 (87.9)	546
Serious TEAE	7 (36.8)	9	5 (35.7)	5	12 (36.4)	14
Serious Treatment related TEAEs	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Severe TEAEs	2 (10.5)	3	1 (7.1)	1	3 (9.1)	4
TEAE with fatal outcome	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE leading to discontinuation	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Serious treatment related TEAEs (related events: Defintely, possible or probable according to investigator

Dose finding studies

In the dose-ranging studies a total of 239 TEAEs were reported by the 10 patients during the rhLAMAN-02 and -03 trials and by the remaining 9 patients in the rhLAMAN-04 trial. The most frequently reported TEAEs were nasopharyngitis (35 events in 10 patients), excoriation (14 events in 4 patients), headache (13 events in 6 patients), pyrexia (9 events in 6 patients), arthralgia (9 events in 4 patients), contusion (8 events in 5 patients) and weight increased (7 events in 6 patients). The majority of TEAEs were mild (207 events in 10 patients) or moderate (31 events in 8 patients). One (1) patient reported 1 severe AE (loss of consciousness), which was also an SAE.

rhLAMAN -05 study

In the placebo controlled rhLAMAN-05 study, a total of 270 TEAEs were reported by 24 patients: 157 events in the velmanase alfa group and 113 events in the placebo group. The most frequently reported TEAEs were nasopharyngitis (30 events in 10/15 patients of the velmanase alfa group and 16 events in 7/10 patients of the placebo group), pyrexia (11 events in 6/15 patients of the velmanase alfa group and 11 events in 5/10 patients of the placebo group) and headache (7 events in 5/15 patients of the velmanase alfa group and 9 events in 3/10 patients of the placebo group). All related TEAEs were of mild and moderate intensity: 27 events were mild (20 in 5/15 patients of the velmanase alfa group and 7 in 4/10 patients of the placebo group) while 12 events were moderate (10 in 4/15 patients of the velmanase alfa group and 2 in 1/10 patient of the placebo group).

rhLAMAN-010 study

In the pooled safety analysis set (SAS), 546 TEAEs were reported in 29 (87.9%) patients (**Table 33**).

Table 33. Summary of All TEAEs by Age Group and System Organ Class and by Preferred Terms for Events Reported in >1 Patient Overall (SAS)

	Aged <18 years (N=19)		Aged ≥18 years (N=14)		Overall (N=33)	
System Organ Class Preferred Term	**N (%)**	**E**	**N (%)**	**E**	**N (%)**	**E**
Any Adverse Event	**17 (89.5)**	**423**	**12 (85.7)**	**123**	**29 (87.9)**	**546**
Blood And Lymphatic System Disorders	**2 (10.5)**	**2**			**2 (6.1)**	**2**
Lymphadenopathy	2 (10.5)	2			2 (6.1)	2
Cardiac Disorders	**1 (5.3)**	**1**			**1 (3.0)**	**1**
Congenital, Familial And Genetic Disorders	**1 (5.3)**	**1**			**1 (3.0)**	**1**
Ear And Labyrinth Disorders	**3 (15.8)**	**7**	**1 (7.1)**	**1**	**4 (12.1)**	**8**
Eye Disorders	**5 (26.3)**	**10**	**3 (21.4)**	**8**	**8 (24.2)**	**18**
Conjunctival Hyperaemia	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Eye Infection	2 (10.5)	2			2 (6.1)	2
Eye Pruritus	2 (10.5)	4	1 (7.1)	1	3 (9.1)	5
Gastrointestinal Disorders	**13 (68.4)**	**36**	**8 (57.1)**	**15**	**21 (63.6)**	**51**
Abdominal Pain	3 (15.8)	3			3 (9.1)	3
Abdominal Pain Upper	4 (21.1)	4			4 (12.1)	4
Diarrhoea	6 (31.6)	7	3 (21.4)	4	9 (27.3)	11
Nausea	3 (15.8)	3			3 (9.1)	3
Reflux Gastritis	2 (10.5)	2			2 (6.1)	2
Toothache	2 (14.3)	3			2 (6.1)	3
Vomiting	8 (42.1)	12	2 (14.3)	2	10 (30.3)	14
General Disorders And Administration Site Conditions	**11 (57.9)**	**46**	**6 (42.9)**	**13**	**17 (51.5)**	**59**
Chills	2 (10.5)	9			2 (6.1)	9
Fatigue	2 (10.5)	3	1 (7.1)	1	3 (9.1)	4
Malaise	2 (10.5)	3			2 (6.1)	3
Oedema Peripheral	1 (5.3)	1	2 (14.3)	2	3 (9.1)	3
Pyrexia	9 (47.4)	23	2 (14.3)	3	11 (33.3)	26
Immune System Disorders	**2 (10.5)**	**5**	**2 (14.3)**	**5**	**4 (12.1)**	**10**
Hypersensitivity	2 (10.5)	4	2 (14.3)	5	4 (12.1)	9
Infections And Infestations	**15 (78.9)**	**112**	**9 (64.3)**	**29**	**24 (72.7)**	**141**
Acute Tonsillitis	2 (10.5)	2			2 (6.1)	2
Ear Infection	4 (21.1)	5	2 (14.3)	2	6 (18.2)	7
Gastroenteritis	5 (26.3)	6	1 (7.1)	1	6 (18.2)	7
Influenza	2 (10.5)	2	1 (7.1)	1	3 (9.1)	3
Laryngitis	2 (10.5)	2			2 (6.1)	2
Nasopharyngitis	14 (73.7)	71	9 (64.3)	18	23 (69.7)	89
Urinary Tract Infection	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Otitis Media	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Injury, Poisoning And Procedural Complications	**13 (68.4)**	**63**	**2 (14.3)**	**2**	**15 (45.5)**	**65**
Arthropod Bite	3 (15.8)	4			3 (9.1)	4
Contusion	6 (31.6)	10			6 (18.2)	10

Excoriation	5 (26.3)	18			5 (15.2)	18
Ligament Sprain	2 (10.5)	2			2 (6.1)	2
Post Lumbar Puncture Syndrome	3 (15.8)	3	1 (7.1)	1	4 (12.1)	4
Wound	6 (31.6)	9	1 (7.1)	1	7 (21.2)	10
Investigations	**10 (52.6)**	**13**	**1 (7.1)**	**1**	**11 (33.3)**	**14**
Weight Increased	6 (31.6)	7			6 (18.2)	7
Metabolism And Nutrition Disorders	**2 (10.5)**	**2**	**2 (14.3)**	**2**	**4 (12.1)**	**4**
Increased Appetite	2 (10.5)	2			2 (6.1)	2
Musculoskeletal And Connective Tissue Disorders	**11 (57.9)**	**38**	**7 (50.0)**	**9**	**18 (54.5)**	**47**
Arthralgia	5 (26.3)	10	2 (14.3)	4	7 (21.2)	14
Back Pain	3 (15.8)	3	2 (14.3)	2	5 (15.2)	5
Myalgia	2 (10.5)	3			2 (6.1)	3
Pain In Extremity	5 (26.3)	13	1 (7.1)	1	6 (18.2)	14
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**2 (10.5)**	**2**			**2 (6.1)**	**2**
Skin Papilloma	2 (10.5)	2			2 (6.1)	2
Nervous System Disorders	**10 (52.6)**	**34**	**6 (42.9)**	**9**	**16 (48.5)**	**43**
Dizziness	3 (15.8)	4			3 (9.1)	4
Headache	9 (47.4)	22	4 (28.6)	5	13 (39.4)	27
Loss Of Consciousness	2 (10.5)	2			2 (6.1)	2
Syncope	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Psychiatric Disorders	**3 (15.8)**	**4**	**2 (14.3)**	**6**	**5 (15.2)**	**10**
Renal And Urinary Disorders	**1 (5.3)**	**1**	**3 (21.4)**	**4**	**4 (12.1)**	**5**
Pollakiuria			2 (14.3)	2	2 (6.1)	2
Respiratory, Thoracic And Mediastinal Disorders	**11 (57.9)**	**20**	**4 (28.6)**	**8**	**15 (45.5)**	**28**
Bronchitis	2 (10.5)	2			2 (6.1)	2
Cough	8 (42.1)	11	1 (7.1)	1	9 (27.3)	12
Rhinorrhoea	2 (10.5)	3	1 (7.1)	1	3 (9.1)	4
Skin And Subcutaneous Tissue Disorders	**9 (47.4)**	**13**	**5 (35.7)**	**10**	**14 (42.4)**	**23**
Acne			2 (14.3)	2	2 (6.1)	2
Erythema	3 (15.8)	4	1 (7.1)	1	4 (12.1)	5
Rash	2 (10.5)	2	3 (21.4)	3	5 (15.2)	5
Scar Pain	1 (5.3)	1	1 (7.1)	1	2 (6.1)	2
Surgical And Medical Procedures	**8 (42.1)**	**11**			**8 (24.2)**	**11**
Catheter Removal	2 (10.5)	2			2 (6.1)	2
Ear Tube Insertion	2 (10.5)	2			2 (6.1)	2
Tooth Extraction	4 (21.1)	4			4 (12.1)	4
Vascular Disorders	**2 (10.5)**	**2**	**1 (7.1)**	**1**	**3 (9.1)**	**3**

E=number of events, n=number of patients, PT=preferred term, SOC=system organ class, SAS=safety analysis set, TEAE=treatment emergent adverse event

Serious adverse event/deaths/other significant events

No deaths were reported during the clinical development program.

No serious TEAEs were reported in rhLAMAN-02 or rhLAMAN-10. 5 TEAEs were reported from the placebo controlled rhLAMAN-05.

The integrated database contains reports of 14 serious TEAEs (**Table 34**) reported in 12 patients (36.4%). Serious TEAEs were reported in a similar proportion of patients aged <18 years (7 patients, 36.8%) and aged ≥18 years (5 patients, 35.7%).

Table 34. Summary of Serious TEAE by Age Group, SOC and PT (SAS)

	Aged <18 years (N=19)		**Aged ≥18 years (N=14)**		**Overall (N=33)**	
System Organ Class Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any Adverse Event	**7 (36.8)**	**9**	**5 (35.7)**	**5**	**12 (36.4)**	**14**
General Disorders And Administration Site Conditions			**1 (7.1)**	**1**	**1 (3.0)**	**1**
Malabsorption From Injection Site			1 (7.1)	1	1 (3.0)	1
Infections And Infestations	**2 (10.5)**	**3**	**1 (7.1)**	**1**	**3 (9.1)**	**4**
Device Related Infection	1 (5.3)	2			1 (3.0)	2
Ear Infection	1 (5.3)	1			1 (3.0)	1
Sepsis			1 (7.1)	1	1 (3.0)	1
Injury, Poisoning And Procedural Complications	**1 (5.3)**	**1**			**1 (3.0)**	**1**
Craniocerebral Injury	1 (5.3)	1			1 (3.0)	1
Musculoskeletal And Connective Tissue Disorders	**3 (15.8)**	**3**	**1 (7.1)**	**1**	**4 (12.1)**	**4**
Arthritis	1 (5.3)	1			1 (3.0)	1
Joint Swelling			1 (7.1)	1	1 (3.0)	1
Knee Deformity	1 (5.3)	1			1 (3.0)	1
Sjogren`s Syndrome	1 (5.3)	1			1 (3.0)	1
Nervous System Disorders	**1 (5.3)**	**1**	**1 (7.1)**	**1**	**2 (6.1)**	**2**
Loss Of Consciousness	1 (5.3)	1			1 (3.0)	1
Somnolence			1 (7.1)	1	1 (3.0)	1
Renal And Urinary Disorders			**1 (7.1)**	**1**	**1 (3.0)**	**1**
Renal Failure Acute			1 (7.1)	1	1 (3.0)	1
Vascular Disorders	**1 (5.3)**	**1**			**1 (3.0)**	**1**
Syncope	1 (5.3)	1			1 (3.0)	1

E=number of events, n=number of patients, SOC=system organ class, PT=preferred term, SAS=safety analysis set, TEAE=treatment emergent adverse event

In the Compassionate use programme only one serious event of infection was spontaneously reported.

Serious TEAEs were considered to be related to treatment in 2 patients:

One case of Loss of Consciousness (severe, possibly related, resolved)

A patient allocated to 6.25 U/kg, 50 U/kg and 1 mg/kg of velmanase alfa in the rhLAMAN- 02, -03 and -04 trials, respectively. 14 months after start of treatment and 7.8 days after last dose administration had difficulties in breathing, and his mother found the patient unconscious in his bed with stiffness of the body (tonic seizure).

The patient gained consciousness within 2-3 minutes and was brought to the hospital by ambulance, where he was treated with i.v. saline and glucose infusions. All examinations were normal, and he recovered completely after 6.5 hours and was discharged from the hospital with no further follow-up. The patient was subsequently examined by the local doctor/hospital and no clinically significant observations were made. The patient continued in the trial with no change in dose level. The investigator assessed this severe and serious loss of consciousness to be possibly related to trial drug.

One case of Acute renal failure (moderate, possibly related, resolved)

The patients experienced a serious ADR of acute renal failure 291 days after start of treatment.

The event, which occurred in the context of long-term therapy with Ibuprofen, 600mg BID, was moderate in intensity, led to an interruption of study treatment for 4 weeks, and subsequently resolved after a duration of 92 days.

Immunological events

Serum samples for antidrug antibody (ADA) testing were collected at baseline and every 2 weeks (Study rhLAMAN-02), every 4 weeks (Studies rhLAMAN-03, -04, and 05), or every 12 weeks (studies rhLAMAN-07 and -09); a single sample was also collected for patients in the compassionate use programme enrolled in rhLAMAN-10 at the CEV. Although antibody data were collected through the ongoing Studies rhLAMAN-07 and 09, data were only extracted for the CEV used in the integrated analysis in rhLAMAN-10. Anti-velmanase alfa IgG was measured by enzyme-linked immunosorbent assay, and samples from the seropositive patients were then tested for the presence of inhibitory antibodies.

Overall, 11 of the 34 patients included in the development program had positive titres for anti-drug antibodies (ADA) (≥1.4U/mL) at any time during the study, however 5 of these were detected during placebo treatment and a further 3 were present at baseline before treatment with velmanase alfa. No on-treatment data is available for one of these patients.

Of the remaining ten, 6 patients were confirmed as ADA+ under treatment, but only 4 patients were ADA+ at the last on-treatment assessment, and in one of these the titre at endpoint was lower than the titre at baseline.

There were only 2 ADA+ patients with titres recorded above 80 U/mL and these were also the only ADA+ patients to report IRR. Narratives for these patients are provided in subparagraph *Infusion Related Reactions* . The remaining patients had titres <30 U/mL.

A summary of ADA status by time point and age group is presented in **Table 35**.

Serum oligosacharride levels increased above baseline in three patients, but in each patient this was at a single visit. For the first patient, serum oligosacharides were 8.2 µmol/L at screening, 5.6 µmol/L during placebo treatment and 5.1 µmol/L at baseline for the integrated analysis. This patient was assessed on-treatment only at the CEV. At the CEV the patient was ADA-, serum oligosacharides were 5.8 µmol/L pre-infusion dropping to 1.2 µmol/L at 5 days.

The second patient was ADA- at baseline, recorded a single low positive titre of 1.7U/L during placebo treatment, but was ADA- again at the baseline for the integrated analysis. Serum oligosacharides were 4.5 µmol/L at screening 4.5 µmol/L during placebo treatment and 4.8 µmol/L at baseline. This patient

assessed on-treatment only at the CEV. At the CEV the patient was ADA+ (24U/L), Serum oligosacharides were 5.5 µmol/L pre-infusion dropping to 1.3 µmol/L at 72 hours.

Table 35: Summary of Anti-Drug Antibodies by Time point and Age Group (SAS).

		rhLAMAN-02	rhLAMAN-05			Overall		
	ADA	<18 years	<18 years	≥18 years	Total	<18 years	≥18 years	Total
Baseline	n	9	10	14	24	19	14	33
	+		5 (50.0)	1 (7.1)	6 (25.0)	5 (26.3)	1 (7.1)	6 (18.2)
	-	9 (100.0)	5 (50.0)	13 (92.9)	18 (75.0)	14 (73.7)	13 (92.9)	27 (81.8)
0-6 months	n	9	7	12	19	16	12	28
	+	1 (11.1)	5 (71.4)	1 (8.3)	6 (31.6)	6 (37.5)	1 (8.3)	7 (25.0)
	-	8 (88.9)	2 (28.6)	11 (91.7)	13 (68.4)	10 (62.5)	11 (91.7)	21 (75.0)
6-12 months	n	9	8	11	19	17	11	28
	+	1 (11.1)	4 (50.0)	1 (9.1)	5 (26.3)	5 (29.4)	1 (9.1)	6 (21.4)
	-	8 (88.9)	4 (50.0)	10 (90.9)	14 (73.7)	12 (70.6)	10 (90.9)	22 (78.6)
12-18 months	n	9	8	8	16	17	8	25
	+	1 (11.1)	4 (50.0)	-	4 (25.0)	5 (29.4)	-	5 (20.0)
	-	8 (88.9)	4 (50.0)	8 (100.0)	12 (75.0)	12 (70.6)	8 (100.0)	20 (80.0)
18-24 months	n	8	5	3	8	13	3	16
	+	1 (12.5)	2 (40.0)	-	2 (25.0)	3 (23.1)	-	3 (18.8)
	-	7 (87.5)	3 (60.0)	3 (100.0)	6 (75.0)	10 (76.9)	3 (100.0)	13 (81.3)
24-30 months	n	-	4	6	10	4	6	10
	+	-	2 (50.0)	-	2 (20.0)	2 (50.0)		2 (20.0)
	-	-	2 (50.0)	6 (100.0)	8 (80.0)	2 (50.0)	6 (100.0)	8 (80.0)
30-36 months	n	3	-	-	-	3	-	3
	+	-	-	-	-	-	-	-
	-	3 (100.0)	-	-	-	3 (100.0)	-	3 (100.0)
36-42 months	n	3	-	-	-	3	-	3
	+	-	-	-	-	-	-	-
	-	3 (100.0)	-	-	-	3 (100.0)	-	3 (100.0)
42-48 months	n	9	-	-	-	9	-	9
	+	1 (11.1)	-	-	-	1 (11.1)	-	1 (11.1)
	-	8 (88.9)	-	-	-	8 (88.9)	-	8 (88.9)
Overall [a]	n	9	10	14	24	19	14	33
	+	1 (11.1)	6 (60.0)	2 (14.3)	8 (33.3)	7 (36.8)	2 (14.3)	9 (27.3)[a]
	-	8 (88.9)	4 (40.0)	12 (85.7)	16 (66.7)	12 (63.2)	12 (85.7)	24 (72.7)

ADA+: Value ≥1.4, ADA-: Value <1.4

ADA=anti-drug antibody, SAS=full analysis set, n=number of patients

a "overall" includes Baseline. One patient was ADA positive at Baseline, but not on-treatment. Another patient had ADA measurements ≥1.4 U/mL during placebo treatment and the patient was therefore considered as ADA+ in the Listings. However, after the first dose of velmanase alfa the patient only had ADA measurements <1.4 and therefore is considered ADA negative in this table. One patient who was excluded from the FAS due to no on-treatment data, was also ADA+ at baseline.

1. Data from Study rhLAMAN 03 are not summarised for one patient who was also positive for ADA in this earlier study, and therefore overall during a longer treatment exposure than reported in the pooled data.

Serum oligosacharides levels increased above baseline in three patients, but in each patient this was at a single visit. For the first patient, serum oligosacharides were 8.2 µmol/L at screening, 5.6 µmol/L during placebo treatment and 5.1 µmol/L at baseline for the integrated analysis. This patient was assessed on-treatment only at the CEV. At the CEV the patient was ADA-, serum oligosacharides were 5.8 µmol/L pre-infusion dropping to 1.2 µmol/L at 5 days.

The second patient was ADA- at baseline, recorded a single low positive titre of 1.7U/L during placebo treatment, but was ADA- again at the baseline for the integrated analysis. Serum oligosacharides were 4.5 µmol/L at screening 4.5 µmol/L during placebo treatment and 4.8 µmol/L at baseline. This patient assessed on-treatment only at the CEV. At the CEV the patient was ADA+ (24U/L), Serum oligosacharides were were 5.5 µmol/L pre-infusion dropping to 1.3 µmol/L at 72 hours.

The third patient also experienced an infusion related reaction and showed no quantifiable velmanase alfa plasma levels during the CEV. At the previous assessment, ADA was below 250 U/mL, while at the CEV, ADA increased to 1012 U/mL.

Infusion Related Reactions

Infusion related reactions (IRRs) were defined as those ADRs which occurred during or up to two hours after the infusion of velmanase alfa and that were assessed by the investigator as being infusion related.

The IRR encountered during clinical development concern 3 paediatric patients with the majority of events experienced by one patient. Most of the IRR (11/19 events) involved disturbances of temperature homeostasis. The IRR did not involve any of the body systems leading to concerns regarding anaphylaxis. There were no respiratory symptoms, and no rashes associated with IRR.

Amongst the 3 patients who had IRR reported, one was ADA negative throughout the study, and experienced an IRR of mild pyrexia during the first infusion (100 U/kg) only. The other two patients had IRR with a consistent pattern of onset - more than 1 month after initiation of treatment; seroconversion - neither were ADA+ prior to first infusion; increased ADA titres (above 80 U/mL); management by premedication and reductions in infusion speed and with appropriate premedication, ADA titres reduced with time and, in the longer term, management measures could be reduced or stopped.

The 3 patients with IRR were all paediatric patients initially treated in the dose-ranging studies and occurred in 3/10 of those patients. In the 14 treatment-naïve patients who received velmanase alfa during Study rhLAMAN-05 no IRRs were observed during the course of the study. No IRR were reported in any of the 10 patients originally under placebo treatment who received their first infusion of velmanase alfa during Studies rhLAMAN-07, or -09, or during the Compassionate use programme.

Hypersensitivity

In the clinical development programme of velmanase alfa, there were 9 reports of hypersensitivity (Preferred term) in 4 patients out of 33 patients. These were considered non-serious ADRs.

Medication Errors

Medication errors (human-error or device-related) have been identified as an Important Potential Risk for this product in common with other enzyme replacement therapies. During the clinical development programme, errors in administration of volume of investigational product were reported as minor

protocol deviations. These medication errors consisted of a lower or higher dose administered compared to the dose as planned in the protocol. No medication errors were recorded as having clinical sequelae and none were considered overdoses.

Laboratory findings

Haematology

In the pooled safety population, severe abnormalities in haematological parameters occurred in only 2 patients (6.1%, all neutropenia). Both patients were aged <18 years old, and neither abnormality was reported as a TEAE. Mild to moderate abnormalities in haematological parameters were reported (in order of descending frequency) for leukocytes in 14 patients (42.4%), neutrophils in 11 patients (33.3%), haemoglobin in 10 patients (30.3%), platelets in 8 patients (24.2%) and lymphocytes in 6 patients (18.2%).

Abnormalities in haemoglobin were reported in a similar frequency of patients aged <18 years and ≥18 years old. All other parameters had a higher proportion of abnormalities reported in patients <18 years old; abnormalities in lymphocytes and leukocytes were only reported in patients <18 years old.

Biochemistry

In the pooled safety population, severe abnormalities in biochemistry parameters occurred in 3 patients (9.1%) who had hyperphosphatemia in the context of polyarthritis. None of these abnormalities were reported as TEAEs by the investigators. Mild to moderate decreases in biochemistry parameters were reported (in order of descending frequency) for albumin in 10 patients (30.3%), phosphate and sodium both in 6 patients (18.2%) and potassium in 3 patients (9.1%). Mild to moderate increases in biochemistry parameters were reported (in order of descending frequency) for alkaline phosphatase in 13 patients (39.4%), sodium in 12 patients (36.4%), potassium in 9 patients (27.3%), creatinine and bilirubin both in 6 patients (18.2%), ALT in 5 patients (15.2%), amylase in 4 patients (12.1%) and creatinine kinase in 1 patient (3.0%).

Abnormalities in biochemistry parameters tended to be reported in a higher proportion of patients aged <18 years than aged ≥18 years, with the exception of ALT and potassium, where the incidence was similar for both age groups.

Coagulation

Coagulation CTC abnormalities reported in the pooled safety population were all mild to moderate increases in prothrombin INR, which occurred in one third of patients (11 patients, 33.3%), with a similar incidence in patients aged <18 years and those aged ≥18 years.

Cerebrospinal Fluid
In placebo-controlled study rhLAMAN-05, CSF by time (and shifts in CSF from baseline to week 26 and 52 did not show any clinically relevant changes Parameters reported were: albumin, protein, eosinophils, glucose, IgG, lymphocytes, monocytes, neutrophils, erythrocytes and leukocytes.

Urinalysis
In the dose-ranging studies, 1 patient reported positive leukocytes in urine. Another patient reported positive leukocytes, protein and nitrite in urine. Neither event was considered related to treatment. Otherwise, no clinically significant abnormal laboratory values were seen during the trials.

Safety in special populations

Safety in patients with renal or hepatic impairment has not been evaluated, due to the rarity of the disease. Safety has not been evaluated in patients with cardiac impairment.

No data are available and no relevant use in elderly is described, due to the rarity of the disease. No patients older than 41 years have been described across Europe (rhLAMAN-01: The natural history of alpha-Mannosidosis).

Safety related to drug-drug interactions and other interactions

No PD drug interaction studies were performed as these are not anticipated based on the structure of the drug substance (recombinant human glycoprotein).

Discontinuation due to adverse events

One patient in rhLAMAN-03 was reported as having a mild anaphylactoid reaction but this period was excluded from the pooled analysis.

This patient was only included in the pooled analyses from the Baseline of Study rhLAMAN-05. This patient dosed at 25 U/kg was withdrawn from Study rhLAMAN-03 following a long term interruption of treatment due to repeated IRR (mild, treatment-related, anaphylactoid reaction) and the patient's desire not to receive premedication. The patient was later enrolled in Study rhLAMAN-05, dosed at 1 mg/kg, and tolerated further IRR managed by reduction in infusion rates and pre-medications. No other TEAEs led to discontinuation.

Post marketing experience

No Marketing Authorisation is currently available for velmanase alfa. However, a Compassionate use programme is ongoing. As of May 2016, 18 patients in the compassionate use programme are still under treatment.

2.6.1. Discussion on clinical safety

In the integrated study rhLAMAN-10, patients from study rhLAMAN-07 protocol (n=7), rhLAMAN-09 protocol (n=8), and the compassionate use program (n=19) were included. The parental studies, for patients and data included in the FAS, was rhLAMAN-02 for 9 (all paediatric) patients (27.3%) and rhLAMAN-05 for 24 patients (72.7%).

In study rhLAMAN-02 the 9 paediatric patients received short term velmanase alfa as result of dose finding. In rhLAMAN-05, 15 patients (45.5%) received the proposed dose of 1 mg/kg and 9 patients (27.3%) first received placebo treatment for 12 months.

In the pooled studies reported in rhLAMAN-10, all 33 patients were exposed to velmanase alfa for at least 12 months. It should also be noted that data during this period were not recorded systematically for patients in the compassionate use program. Over half the subjects (19/33 subjects 57.6%) were exposed for 24 months or more.

In the pooled safety analysis set (integrated study rhLAMAN-010), 546 TEAEs were reported in 29/33 (87.9%) patients. In patients <18 years 423 events were reported compared to patients aged ≥18 years for whom 123 events were reported. This might be contributed the longer exposure in the patients <18 years, especially those (n=9) of study rhLAMAN-02. It should be noted that overall similar frequencies for TEAEs are reported between both age-groups, 89.5% versus 85.7%.

The most frequently affected SOCs were Infections and Infestations (in 24 patients, 72.7%), Gastrointestinal Disorders (21 patients, 63.6%), Musculoskeletal and Connective Tissue Disorders (18 patients, 54.5%) and General Disorders and Administration Site Conditions (17 patients, 51.5%).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

In study rhLAMAN-10, serious TEAEs were reported in a similar proportion of patients aged <18 years (7 patients, 36.8%) and aged ≥18 years (5 patients, 35.7%) and no preferred term was reported as serious in more than one patient. Serious TEAEs were considered to be ADRs in 2 patients: loss of consciousness and acute renal failure. Both of these adverse events are included in the RMP as important potential risks and in Section 4.8 of the SmPC.

Three of 33 patients (9.1%) reported IRR's and it was concluded that these events were related to velmanase alfa administration. Overall, there were approximately 2800 velmanase alfa infusions in the clinical trials included in the integrated analyses, with approximately 2000 of these in paediatric patients. Thus only 1 in 147 infusions overall, or 1 in 105 infusions in children, led to an IRR.

IRRs are included in the RMP as an important identified risk and information is provided in the product information regarding the management of IRRs, which should be based on the severity of the reaction. In addition the patient is recommended to remain under observation for IRRs for one hour or longer after the infusion, according to the treating physician's judgement.

Overall, 11 of the 34 patients included in the development program had positive titres for anti-drug antibodies (ADA) (≥1.4U/mL) at any time during the study. Three of these patients were detected positive at baseline before treatment with velmanase alfa. The CHMP noted the relatively low threshold of 1.4 U/mL was established to determine ADA positive status to ensure that all positive immunogenicity samples would be identified, although it also increased the possibility of identifying false positives. However, the applicant has developed a new analytical method for detecting ADAs, which has been shown to be more accurate and allows for more precise results and less intra- and inter variability between samples. The new bioanalytical method will be used for new patient assessments.

No clear correlation was found between antibody titres (velmanase alfa IgG antibody level) and reduction in efficacy or occurrence of anaphylaxis or other hypersensitivity reactions. Nevertheless, immunogenicity is included in the RMP as an important identified risks and the product information states that, in instances of development of severe IRRs or lack or loss of treatment effect, patients

should be tested for the presence of anti velmanase alfa antibodies. In case the patient's condition deteriorates during ERT, cessation of treatment should be considered.

There were 9 report of hypersensitivity reactions reported. All were considered as non-serious ADRs, however, as with any intravenous protein product, allergic-type hypersensitivity reactions are possible. Therefore, hypersensitivity is included in the RMP as an important identified risk, and the product information stipulates that appropriate medical support should be readily available when velmanase alfa is administered. If a severe allergic or anaphylactic-type reaction occurs, immediate discontinuation of velmanase alfa is recommended and current medical standards for emergency treatment should be followed.

Safety in patients with renal, hepatic or cardiac impairment were not evaluated, due to the rarity of the disease. Therefore, use of velmanase alfa in those patients is included in the RMP as missing information.

No data are available in elderly and no relevant use is described, due to the rarity of the disease. Although currently no patients older than 41 years are described across Europe it is to be expected that with the advancement in the understanding and management of the disease older patients can be anticipated in the future. Therefore this population is also included in the RMP as missing information.

As children aged 0 to 6 years were not included in the clinical trials submitted, safety information in this population is lacking, even though it is expected that the safety profile in these patients would be in line with that of the older patients. Additional safety information in these patients will be collected through the disease registry but also through Study rhLAMAN-8, which will exclusively enrol patients within that age range.

No interaction studies were performed. Velmanase alfa is a recombinant protein product and is unlikely to affect cytochrome P450 related metabolism.

There are no data from the use of velmanase alfa in pregnant women. This has been added as missing information in the RMP.

No overdose was reported during the clinical studies. Some medication errors were reported, though these were not associated with any clinically important effects. However, further rinformation will be collected on medication erros through the activities described in the RMP in which it has been classified as an important potential risk.

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 Lamzede 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 of longer duration controlled trials.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to specific obligations, including the implementation of the alpha mannosidosis disease registry to evaluate the long term safety profile of Lamzede and in particular with regards to the important identified an potential risks associated with velmanase alfa use.

Additional safety information for patients below 6 years of age will also be collected through an ongoing open label study.

2.6.2. Conclusions on the clinical safety

Despite the limited size of the safety database, due to the rarity of alpha-mannosidosis, the overall safety profile of velmanase alfa is considered acceptable. The main safety concerns identified are of infusion related reactions, immunogenicity and hypersensitivity which are addressed adequately through appropriate routine risk minimisation measures.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- The Alpha-Mannosidosis disease registry to evaluate the long-term safety profile of Lamzede, especially in relation to IRR, immunogenicity hypersensitivity, loss of consciousness, acute renal failure and medication errors
- rhLAMAN-8 (2) an open label, 24 month study to characterise the pharmacokinetics and safety of Lamzede in patients from birth to < 6 years

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions Immunogenicity Hypersensitivity
Important potential risks	Acute renal failure Loss of consciousness Medication errors
Missing information	Safety in patients < 6 years of age Long term safety Safety in non-Caucasian patients Safety in pregnant or lactating women Safety in patients with hepatic or renal insufficiency Safety in patients not capable of performing endurance test. Administration of home infusion

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
rhLAMAN-7 **(3)** Ongoing open label study	Long-term safety and efficacy including QoL in patients previously enrolled in rhLAMAN-02 or rhlAMAN-05 Safety: AEs, vital signs, PE, anti-LAMAN/inhibitory antibody Efficacy: 3MSCT, 6MWT, FVC, Leiter R, PTA, QoL	Long-term safety and efficacy	Started	Final CSR August 2020
rhLAMAN-9 **(3)** Ongoing open label study	Long-term safety and efficacy including QoL in patients previously enrolled in rhLAMAN-02 or rhlAMAN-05 Safety: AEs, vital signs, anti-LAMAN/inhibitory antibody Efficacy: 3MSCT, 6MWT, FVC, Leiter R, PTA, QoL	Long-term safety and efficacy	Started	Final CSR August 2020
rhLAMAN-8 **(2)** Planned open label, 24 month study	Pharmacokinetics, safety and efficacy in patients from birth to < 6 years	Safety and efficacy in children age ≤ 6 years	Started	Final CSR November 2020
The Alpha-Mannosidosis Registry: (**2)** Long term effectiveness and safetyof Lamzede therapy in European patients with	To further characterize the long-term safety profile of Lamzede in the treatment of alpha-mannosidosis patients, under conditions of routine clinical care	Collect (long-term) safety data in particular relating to important identified risks (IRR, immunogenicity	Planned	To be defined

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
alpha-mannosidosis.	To further evaluate the long-term effectiveness of Lamzede in the treatment of alpha-mannosidosis patients, under conditions of routine clinical care	hypersensitivity), potential risks (loss of consciousness, acute renal failure, medication errors,e , and missing information in subgroups		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Infusion-related reactions	Posology and administration instructions in section 4.2 of SmPC Special warnings and precautions related to IRRs in section 4.4 of SmPC Listed in section 4.8 of SmPC Instructions for administration of infusion in section 6.6 of SmPC Warnings and precautions in section 2 of PIL Administration in section 3 of PIL Listed as possible side effects in section 4 of PIL	None
Immunogenicity	Special warnings and precautions related to immunogenicity in section 4.4 of SmPC Listed in section 4.8 of SmPC Warnings and precautions in section 2 of PIL	None
Hypersensitivity	Special warnings and precautions related to hypersensitivity in section 4.4 of SmPC Listed in section 4.8 of SmPC Warnings and precautions in section 2 of	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	PIL Possible side effects in section 4 of PIL	
Important potential risks		
Acute renal failure	Listed in section 4.8 of SmPC Possible side effects in section 4 of PIL	None
Loss of consciousness	Listed in section 4.8 of SmPC Possible side effects in section 4 of PIL	None
Medication errors	Posology and administration instructions in section 4.2 of SmPC Pharmaceutical particulars, incompatibilities, storage, disposal, reconstitution and administration instructions in section 6 of SmPC. How to use in section 3 of PIL How to store in section 5 of PIL	None
Missing information		
Safety in patients < 6 years of age	Statement in section 4.2 of SmPC regarding the lack of data on safety and efficacy in patiens < 6 years of age	None
Long term safety	N/A	None
Safety in non-Caucasian patients	N/A	None
Safety in pregnancy/lactation	Warnings and precautions with regards to use in pregnancy, lactation and impact on fertility in section 4.6 of SmPC Preclinical data on reproduction and development in section 5.3 of SmPC Pregnancy and breast feeding listed in warnings and precaution section, section 2 of PIL.	None
Safety in hepatic or renal insufficiency	Statement regarding no dose recommendations for use in hepatic or renal insufficiency in section 4.2 of SmPC Description of pharmacokinetic properties in section 5.2 of SmPC.	None
Safety in patients not capable of performing endurance test	N/A	None
Administration of home infusions	N/A	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 05.1 is acceptable.

2.8. Pharmacovigilance

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.

2.9. New Active Substance

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

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

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lamzede (velmanase 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

Alpha-mannosidosis is a rare monogenic autosomal recessive disorder, consisting of a deficiency of lysosomal alpha-mannosidase. The effect of the enzyme deficiency is blockage of the degradation of glycoproteins, which results in the accumulation of mannose rich oligosaccharides in all tissues. Progressive lysosomal accumulation of non-degradable metabolites results in generalized cell and tissue dysfunction and multi-systemic pathologies.

Based on the clinical presentation 3 sub-types for alpha-mannosidosis have been described (Malm *et al.*, 2008):

- a severe form with early death from central nervous system involvement or infection (type 3).
- a moderate form, clinically recognized at childhood (prior the age of 10 years), with myopathy, slow progression, and skeletal abnormalities (type 2).
- a mild form clinically recognized during adolescence or late in life (after the age of 10 years), with myopathy, slow progression, and absence of skeletal abnormalities. In Europe, no patients over the age of 50 years are known (type 1).

3.1.1. Disease or condition

3.1.2. Available therapies and unmet medical need

Currently there is no available treatment for alpha-mannosidosis. The most severe patients are potential candidates for haematopoietic stem cell transplantation (HSCT) or bone marrow transplantation.

The less severe alpha-mannosidosis patients are managed with supportive care including symptom management, medical and surgical treatment of complications (e.g. infections, skeletal deformities), and physical therapy.

3.1.3. Main clinical studies

The patients included in the pivotal studies represent a subpopulation of alpha-mannosidosis patients with a mild to moderate disease burden (type 1 and type 2 alpha mannosidosis). The younger patients with a higher disease burden, fast progression and the highest medical need are not included, neither are the older patients with a very mild disease burden.

At baseline the patients included showed a 20% reduction of endurance and lung function as compared to their healthy peers. The cognitive development for the children (<18 years) is about 6 years behind compared to the healthy peers.

In Study rhLAMAN-05, 25 treatment naïve patients were randomized to active treatment or placebo in a 3:2 ratio.

The integrated analysis (rhLAMAN-10) includes all patients (N=33) from previous finalised studies (rhLAMAN-02, -03, -05, -05, 07 and -09) and the patients included in the compassionated use

program. This is an open label analysis with no comparator. The integrated analysis provides efficacy data for over 4.5 years for some patients.

3.2. Favourable effects

Comparison with placebo (rhLAMAN-05)

The adjusted mean absolute change in serum oligosaccharides (µmol/l) from baseline to week 52 was -5.11 (95% CI: - 5.66, -4.56) in the velmanase alfa group and -1.61 (95% CI: -2.28, -0.94) in the placebo group. The adjusted mean difference for velmanase alfa vs placebo was -3.50 (95% CI: -4.37; -2.62) showing a statistically significant difference between the two groups (p< 0.001).

The adjusted mean absolute change in the 3MSCT (steps/min) from baseline to week 52 was 0.46 (95% CI: - 3.58, 4.50) in the velmanase alfa group and -2.16 (95% CI: -7.12, 2.80) in the placebo group. The adjusted mean difference for velmanase alfa vs placebo was 2.62 (95% CI: -3.81, 9.05, p=0.406) indicating a numerical improvement for the active treated patients.

Some numerical improvement of endurance was captured in the 6MWT. The adjusted mean difference for velmanase alfa vs placebo was 7.35 m (95% CI: -30.76; 45.46, p=0.692).

For the mean absolute change in FVC (% of predicted) the adjusted mean difference for velmanase alfa vs Placebo was 8.21 (95% CI: 1.79, 14.63) indicating an improvement in the actively treated population. The comparison between the two groups was not statistically significant (p=0.269).

A post-hoc analysis was performed on serum IgG (g/l). The adjusted mean difference for active arm vs Placebo arm was 3.47 (95%CI: 2.12, 4.81) showing a statistically significant difference between the two groups (p<0.001) in favour of velmanase alfa.

Based on the definition of the MCID as proposed by the applicant, the responder analysis of rhLAMAN-05 showed a discernible treatment difference between the two groups, with a clinical response in at least two domains at 12 months observed in 87% of patients treated with velmanase alfa compared to 30% treated with placebo. Moreover, 13% of the velmanase alpha treated patients but none of the placebo patients reported a clinically significant response in all three domains.

Integrated analysis (rhLAMAN-10)

There was an absolute decrease of -4.59 µmol/l in serum oligosaccharides from Baseline to the last observation (p<0.001).

There was an improvement in 3MSCT from Baseline to the last observation (absolute change of 6.4 steps/ min, p≤0.004).

There was an absolute increase in 6MWT from Baseline to the last observation of 22.4 (63.2) m (p=0.050). There was an increase in the percentage of predicted FVC from Baseline to the last observation of 8.1% (14.8%) (p=0.007).

For absolute FVC, FEV1 (percentage of predicted and absolute), PEF, BOT-2 total point, score Leiter-R total equivalent age, and hearing, a non-significant increase to last observation was demonstrated.

No clear changes were reported for CHAQ and EQ-5D-5L Health Index and VAS.

3.3. Uncertainties and limitations about favourable effects

Although the inclusion of 33 patients in the clinical development programme is acceptable given the rarity of the condition, the number is still limited especially when considering the wide range of phenotypes that patients can have.

Even though the results of the placebo controlled study show a consistent numerical improvement for most of the clinical endpoints, statistical significance was not established. There are a number of potential explanations for this, including the relatively short duration of the trial which is probably not sufficient to demonstrate a statistically compelling effect.

With regard to effects on CNS, in the clinical studies CSF oligosaccharides, tau proteins, NFL and GFAp and any of the MRI or MRS endpoints included both increases and decreases with no clear trend for a change over time in any parameter. Moreover, the clinical data suggests that velmanase does not pass the blood brain barrier and thus no direct effect on the neurological manifestations of the disease are to be expected and this is explicitly stated in the indication of the product.

3.4. Unfavourable effects

Patients treated with velmanase alfa showed similar frequencies in AEs as those in the placebo-group. All related TEAEs were of mild and moderate intensity. The most frequently reported TEAEs were pyrexia and headache. For the nervous system disorders, despite similar reported frequencies for headache and dizziness, syncope was reported in two patients in the velmanase alfa arm and not reported in the placebo arm.

Two cases of serious TEAEs were reported, e.g. syncope and acute renal failure. One case of the reported of loss of consciousness was actually part of a tonic seizure episode. Acute renal failure was considered treatment related.

In the integrated study rhLAMAN-010, TEAEs were reported in a similar proportion of patients aged <18 years and aged ≥ 18 years. No preferred term was reported in more than one patient.

Three of 33 patients (9.1%) reported infusion related reactions (IRR's). All three were paediatric patients. Eleven of 34 patients were anti-drug antibody positive (ADA positive) sometime during treatment.

3.5. Uncertainties and limitations about unfavourable effects

The safety data presented in the dossier were based upon the last data lock point 27 September 2015. Only 9 patients had follow-up data of 4 years or more. Twenty-three patients had follow-up data of two years or more.

The safety in children aged 0 to 6 years is not known, as such patients were not included in the clinical studies. The safety profile of velmanase alfa in these patients with mild or moderate disease burden however is expected to be in line with the population included in the studies however additional information will be collected through the ongoing and planned open label studies and the disease registry as described in the RMP. The safety in patients diagnosed with a severe form is not known and cannot be extrapolated form the information from patients with mild to moderate disease forms.

The safety in patients with renal, hepatic or cardiac impairment and pregnant women has not been evaluated. Use of velmanase alfa in these sub-populations is included in the RMP as missing information.

Three patients were ADA positive pre-treatment and 5 patients in the placebo group were ADA positive. Immunogenicity is included in the RMP as an important identified risk, and further information on the impact of ADAs on the effectiveness and safety of velmanase alfa is expected to be collected through the disease registry.

3.6. Effects Table

Table 36. Effects Table for velmanase alfa for the treatment of non-neurological manifestations in patients with mild to moderate alpha mannosidosis. (data cut-off: 27 September 2015)

Effect	Short description	Unit	Lamzede	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Serum oligosaccharides	Change from baseline Mean (95% CI)	µmol/l	-5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)	Strong pharmacodynamic effect	rhLAMAN-05
3MSCT		Steps/min	0.46 (-3.58, 4.50)	-2.16 (-7.12,2.80)	Numerical improvement but not statistical significant effects Consistent results with integrated efficacy analysis (rhLAMAN-10)	
FVC		% of predicted	8.21 (1.79, 14.63)	2.30 (-6.19, 10.79)		
Unfavourable Effects						
IRR	ADA +	N	3	Not applicable	Small number of events, but limited size of safety database	rhLAMAN-10
Immunogenicity			11			
Acute renal failure			1			
Syncope	SAE		1			

Abbreviations: 3MSCT: 3 Minute Stair Climb test, FVC: Forced Vital capacity, IRR: Infusion Related Reactions, ADA: Anti-Drug Antibody, SAE: Serious Adverse Event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clear pharmacodynamic effect was demonstrated**,** which indicates uptake of the enzyme in the lysosome and also enzyme activity. It can therefore be expected that velmanase alfa has the potential to arrest disease. Given the results of the natural history study some clinically relevant effects can only be expected after more than 2 years of treatment.

Compared to placebo a small numerical improvement in the most important clinical endpoints (3MSCT, 6MWT, predicted FVC, predicted FEV1, absolute FVC, absolute FEV1 and PEF) could be demonstrated., however, given the results of the natural history study some clinically relevant effects can only be expected after more than 2 years of treatment.

In the overall analysis the results of the endurance tests (3MSCT and 6MWT) and the lung function tests (predicted FVC, predicted FEV1, absolute FVC, absolute FEV1 and PEF) also showed some numerical improvement compared to baseline. Further clinical benefit is suggested by the post-hoc responder analysis based on MCID.

Although statistically compelling evidence is lacking for the clinical endpoints, the data suggests some further improvement or stabilisation of disease progression under continued treatment with velmanase alfa. The proposed long-term disease registry study (including untreated patients and patients treated with velmanase alfa or other treatments) will collect additional efficacy and safety data which to further confirm the positive trend in beneficial effects as observed in the studies.

Most adverse events reported during the clinical development programme of velmanase alfa appear to be mild and transient in nature. As expected, infusion related reactions were observed in patients receiving treatment. Adequate safety warnings to minimise this risk are included in the product information, and further data to better characterise the magnitude and the frequency of this risk can be expected through the alpha-mannosidosis registry.

3.7.2. Balance of benefits and risks

In the placebo controlled study a pharmacodynamic effect in terms of a decrease of serum oligosaccharides, has been demonstrated. Despite the slow disease progression in the placebo-treated patients and the natural history study and the short observation period most of the differences in endpoints compared to placebo showed a numerical improvement in favour of the velmanase alfa treated patients and therefore support efficacy of velmanase alfa.

In the placebo-controlled study, the younger group of patients showed a more pronounced improvement after 12 months of treatment when compared to the group of patients above 18 years. This finding is confirmed by the post-hoc responder analysis. Therefore, the lower age-limit of 6 years in the indication as initially proposed by the applicant has been replaced by a restriction to patients with mild to moderate disease. It is expected that the benefits of velmanase alfa can be fully extrapolated to patients below age 6 years as long as they do not suffer from the most severe type of alfa-mannosidosis that progresses rapidly, also with regard to neurological deterioration that is unlikely to be treatable by the drug.

The observed marginal improvement in older patients is thought to be related to irreversible damage resulting from prolonged disease activity that cannot be reversed by the drug. Nevertheless, disease stabilisation is considered beneficial in these older patients.

Velmanase alfa does not appear to cross the blood-brain-barrier, as illustrated by the lack of effect reported for the pharmacodynamic CNS related endpoints and the lack of effect on hearing loss and ataxia. Therefore, a direct effect on the neurological manifestations of alpha-mannosidosis deficiency is not expected. Hence, the indication is restricted to “Long-term enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis”.

From the integrated analyses, there was also a numerically improvement for most endpoints compared to baseline. Some clinical effect is also suggested by the post-hoc responder analysis based on MCID. The proposed long-term disease registry study will collect more efficacy and safety data to further confirm the positive trend in beneficial effects as observed in the studies.

The overall safety profile of velmanase alfa does not raise any particular concerns. In common with other enzyme replacement therapies, infusion related reactions were reported but it is expected that in clinical practice these can be easily managed.

Only two serious TEAEs were observed (acute renal failure, syncope (loss of consciousness)). Both are included in the RMP, as important potential risks, and further information to confirm a causal association with velmanase alfa treatment will be collected through the disease registry.

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 agreed that due to the very rare nature of the disease but also the rather slow disease progression in mild to moderate alpha mannosidosis which does not allow for more data to be generated within a reasonable time frame. 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 indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate subject to the following specific obligations:

- In order to collect additional information on the long term effectiveness and safety of treatment with velmanase alfa and to further characterise the entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history, the applicant is required to set up an alpha-mannosidosis disease registry;
- In order to investigate the safety and efficacy of velmanase alfa treatment in paediatric patients <6 years of age with alpha-mannosidosis the applicant is required to submit the results of a 24-month open label study.

Data from the disease registry should be generated on a regular basis for review in the context of the annual re-assessments

3.8. Conclusions

The overall B/R of Lamzede 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 Lamzede is favourable in the following indication:

treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

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 an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to obtain long term data on effectiveness and safety of treatment with Lamzede and to characterize the entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history, the MAH is requested to submit the results of a study based on adequate source of data deriving from a registry of patients with alpha-mannosidosis.	Annual reports to be submitted as part of the annual re-assessment
Paediatric Study rhLAMAN-08. A 24 month multi-center, open label phase II trial investigating the safety and efficacy of repeated velmanase alfa (recombinant human alpha mannosidase) treatment in paediatric patients <6 years of age with	Final Study report: November 2020

Description	Due date
Alpha-Mannosidosis.	

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 velmanase alfa is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.