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EMA/357933/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimizim

International non-proprietary name: elosulfase alfa

Procedure No. EMEA/H/C/002779/0000

Note

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

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List of abbreviations

°C	degrees Celsius
%CV	Coefficient of Variation
%RSD	Percent Relative Standard Deviation
%T	Percent Light Transmittance
µg	microgram
µL	microliter
µM	micromolar
µm	micrometre
µS	microSiemens
3MSCT	3-minute stair-climb test
6MWT	6-minute walk test
ADR	adverse drug reaction
AE	adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ALS	Amyotrophic lateral sclerosis
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APPT	Adolescent Paediatric Pain Tool
ARRB	Allergic Reaction Review Board
AST	Aspartate Aminotransferase
AQL	Acceptable Quality Level
$AUC_{0-\infty}$ or AUC_{0-inf}	Area under the Plasma Concentration-Time Curve from Time Zero to Infinity
AUC_{0-t}	Area under the Plasma Concentration-Time Curve from Time Zero to the Time of Last Measurable Concentration
avg	Average
BGLAP	Bone Gamma-Carboxyglutamate Protein
Bis-P-Man7	Bis mannose-6-phosphate oligomannose7
BLOQ or BLQ	Below Limit of Quantitation
Elosulfase Alfa	recombinant human N-acetylgalactosamine-6-sulfatase
BMP2	Bone Morphogenetic Protein 2
BMT	Bone Marrow Transplant
BSA	Bovine Serum Albumin
BSAP	Bone specific alkaline phosphatase
C6S or CS	Chondroitin-6-sulfatase
Cat Z	Cathepsin Z
cc	Cubic Centimetre
CC	Cutpoint control
CDF	cumulative distribution function
C_{eof}	End of Infusion Concentration
CGI	Clinical Global Impression instruments
CI	confidence interval
CI-M6PR	Cation-independent mannose-6-phospate receptor
CI_{95}	95% confidence interval
CL	Total Clearance of Drug
cm	Centimetre
C_{max}	Maximum Plasma Concentration
CNS	central nervous system
Col10A1	Type X Collagen
Col11a1	Type XI Collagen
Col15A1	Type 15 Collagen
Col1A1	Type I Collagen

Col2a1	Type II Collagen
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTX1	type I collagen C-terminal cross-linked C-telopeptide
CTx	type I collagen fragments
CV	cardiovascular
Da	Dalton
DF	Dilution Factor
DHFR	Dihydrofolate Reductase
DLS	Dynamic Light Scattering
DMC	Data Monitoring Committee
DS	Dermatan Sulphate
DXA	Dual-emission x-ray absorptiometry
ECG	electrocardiogram
ECHO	echocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
ERT	enzyme replacement therapy
FET	Forced Expiratory Time
FEV1	Forced Expiratory Volume in 1 Second
FIVC	Forced Inspiratory Vital Capacity
FVC	Forced Vital Capacity
g	Gram
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HAQ	Health Assessment Questionnaire
HR	heart rate
hr	hour
IAR	infusion associated reaction
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INN	International Non-Proprietary Name
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
kb	Kilobase
kDa	Kilodalton
kg	Kilogram
Km	Michaelis constant: concentration of substrate giving 50% of maximal reaction rate
KS	Keratan Sulphate
KSII	Skeletal Keratan Sulphate
K_{uptake}	Concentration of substance yielding 50% of maximal uptake into cells
kW	Kilowatt
L	Litre
LC/MS	Liquid Chromatography/Mass Spectrometry
LC/MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LD	lactation day
LDH	lactate dehydrogenase

LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carried Forward
LOD	Limit of detection
LOQ	Limit of quantitation
LS	Least squares
LSD	lysosomal storage disease
m	meter
M	Molar
M6P	mannose-6-phosphate
M6PR	mannose-6-phosphate receptor
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minutes
mL	millilitre
mm	millimetre
mM	millimolar
mOsm	milliosmole
MPS	mucopolysaccharidosis
MPS HAQ	MPS Health Assessment Questionnaire
MPS I	Hurler, Hurler-Scheie, Scheie syndrome
MPS II	Hunter Syndrome
MPS IVA	MPS IV type A; Morquio A Syndrome
MPS VI	Maroteaux-Lamy syndrome
MQCH	Morquio chondrocytes
MRI	Magnetic resonance imaging
MST	Muscle strength tests
MVV	Maximum Voluntary Ventilation
N	Normal
N/A or NA	Not Applicable
NAb	ELOSULFASE ALFA-specific neutralizing antibodies (that inhibit cellular receptor binding)
ng	nanogram
nM	nanomolar
nmol	nanomole
OSA	Obstructive sleep apnoea
PBO	Placebo
PD	pharmacodynamics
PedsQL	Paediatric Quality of Life Inventory
pg	picogram
PIIANP	Type IIA collagen N-propeptide
PIQ	Patient Impression Questionnaire
PK	pharmacokinetics
pM	picomolar
PO	per os; oral
PP	Per-Protocol
ppm	Parts Per Million
PR	interval measured from the beginning of the P wave to the beginning of the QRS complex
PT	Preferred Term
qow	every other week
QRS	Complex Consisting of the Q, R, and S Waves
QT	interval measured from the beginning of the Q wave to the end of the T wave
QTc	corrected QT
qw	once a week
RFT	Respiratory Function Test

rhASB	recombinant human arylsulfatase B
rhGALNS	recombinant human N-acetylgalactosamine-6-sulfatase
rhGNS	recombinant human Glucosamine (N-acetyl)-6-sulfatase
rhIDS	recombinant human Iduronate 2-sulfatase
ROQ	Range of quantitation
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
sCIMPR	soluble cation independent mannose-6-phosphate receptor
SD	standard deviation
SEM	Standard Error of Mean
SOC	System Organ Class
SOP	Standard Operating Procedures
$t_{1/2}$	elimination half-life
TAb	total antibody
T_{max}	time to reach C_{max}
TNFα	Tumour necrosis factor-alpha
U	Units
ULOQ	Upper Limit of Quantitation
urine KS or uKS	urine KS
V_{dz} or V_z	volume of distribution based upon the terminal phase
V_{dss} or V_{ss}	volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioMarin Europe Ltd submitted on 23 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vimizim, 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 19 July 2012

Vimizim, was designated as an orphan medicinal product EU/3/09/657 on 24 July 2009 in the following indication: for the treatment of mucopolysaccharidosis, type IV A (Morquio A syndrome).

The applicant applied for the following indication:

"Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) (see section 5.1)"

ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS, elosulfase 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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0240/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0240/2012 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.

New active Substance status

The applicant requested the active substance recombinant human N-acetylgalactosamine-6-sulfatase (elosulfase alfa) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 21 June 2012. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA, Brazil, Australia, Canada and Mexico.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

BioMarin Pharmaceutical, Inc.
Galli Drive Facility
46 Galli Drive
Novato, CA 94949
USA

Manufacturer of the finished product

Vetter Pharma-Fertigung GmbH & Co. KG
Mooswiesen 2
88214 Ravensburg, Germany

Manufacturer responsible for batch release

BioMarin Manufacturing Ireland Limited
Shanbally, Ringaskiddy, Co. Cork
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 23 April 2013.
- Accelerated Assessment procedure was agreed-upon by CHMP on 21 February 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 October 2013. Due to Major Objections identified by the CHMP, the accelerated assessment was not supported and the timetable was reverted to standard.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 November 2013.
- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2014.
- During the meeting on 17-20 February 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Vimizim.

2. Scientific discussion

2.1. Introduction

Mucopolysaccharidosis type IV, Morquio A syndrome (MPS IVA) is a rare, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine-

6-sulfatase (GALNS), which is an enzyme that degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate. With insufficient GALNS, GAGs progressively accumulate in multiple body organs and tissues.

The most common features of patients with MPS IVA are progressive skeletal dysplasia, frequent surgical procedures mostly related to musculoskeletal or respiratory dysfunction and a significant limitation in mobility, endurance, and respiratory function. Many patients end up using scooters, wheelchairs or other devices by their teen years. All patients have a profound skeletal dysplasia, which commonly results in severe short stature and malformations of knees, chest, and spine. The skeletal dysplasia, short stature, and joint abnormalities contribute to patient's restricted mobility. Patients may also experience both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and tracheal and bronchial abnormalities. These mechanical impediments often result in dyspnoea and recurrent respiratory infections, and potentially progress to respiratory failure. Additional symptoms include hearing loss, cataracts, corneal clouding, and heart valve disease, among others. Survival in patients with rapidly progressing phenotypes is limited to the second or third decade of life. Rarely, patients with slowly progressing forms of the disorder have been reported to survive beyond 60 years. Mortality commonly occurs due to cardio-respiratory or central nervous system complications (i.e. spinal/cervical cord compression [SCC]). Obstructive and restrictive lung disease predisposes patients to developing fatal pneumonia and respiratory failure. Regardless of rate of disease progression, all patients have serious and debilitating morbidities.

MPS IVA is a rare disorder, with incidence estimated to range from 1 in 76,000 to 1 in 640,000 live births in different populations. For the purposes of European Union (EU) Orphan Designation, the mean prevalence was estimated to be 0.06 in 10,000 live births, which leads to an approximation of 1300 MPS IVA patients in the EU. There is currently no standard accepted or otherwise authorised treatment for MPS IVA in the EU or in any other country other than supportive care. Limited experience indicates that bone marrow transplantation (BMT) has not resulted in improvement in biochemical or clinical disease manifestation. Supportive care has included both medications and surgical interventions. Nonsteroidal anti-inflammatory drugs have been administered for joint pain, antibiotics for pulmonary infection, and oxygen supplementation for pulmonary compromise and obstructive sleep apnoea. Surgical interventions include cervical spine fusion or decompression, femoral osteotomies for straightening of the legs, and corrective knee surgery for severe genu valgum deformity.

Enzyme replacement therapy (ERT) with recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS, elosulfase alfa) is a potential new treatment option for patients with MPS IVA. Elosulfase alfa is administered by intravenous infusion, allowing cellular uptake by the mannose 6 phosphate receptor and translocation to lysosomes. Elosulfase alfa is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS), and is identical to the naturally occurring human lysosomal enzyme in terms of the amino acid sequence and N-linked glycosylation sites. The uptake of acetylgalactosamine into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of N-acetylgalactosamine-6-sulfatase to the cation-independent mannose-6-phosphate receptor (CI-M6PR). The rationale for elosulfase alfa therapy is to increase the catabolism of KS in MPS IVA affected tissues by providing exogenous enzyme. No elosulfase alfa degradative effects on

other GAGs or on KS outside of the lysosomal compartment are anticipated due to the lack of elosulfase alfa activity at physiological pH, its CI-M6PR-targeted delivery to the lysosomal compartment.

The indication for Vimizim, as applied for by the applicant is:

Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA).

The indication for Vimizim, as adopted by the CHMP is:

Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

2.2. Quality aspects

2.2.1. Introduction

The active substance recombinant human N–acetylgalactosamine 6–sulfatase (rhGALNS, elosulfase alfa) is a single-chain glycosylated enzyme involved in the lysosomal degradation of the glycosaminoglycans (GAGs) keratan sulfate (primary natural substrate), chondroitin sulfate and dermatan sulfate. As elosulfase alfa is an exohydrolase, it does not hydrolyse sulfate groups internal to GAG chains. Complete degradation of keratan sulfate in the lysosome requires other lysosomal enzymes. An absence of these hydrolytic enzymes results in the abnormal lysosomal accumulation of unhydrolysable GAGs. Elosulfase alfa is taken up and translocated to the lysosomes by target cells through the cation-independent mannose-6-phosphate receptor.

Elosulfase alfa contains eight cysteine residues, six of which are involved in intramolecular disulfide bridges. One cysteine residue is unpaired. The last cysteine residue (C53) resides in the active site; it is post-translationally modified to formylglycine iin the endoplasmic reticulum of the production cell. The presence of formylglycine is a necessary condition for the sulfatase activity of elosulfase alfa.

Elosulfase alfa contains two consensus N-glycosylation sites (N178 and N397). The predominant glycans are mannose structures with or without phosphorylation.

Elosulfase alfa is produced in a Chinese Hamster Ovary (CHO) cell line transfected with rhGALNS cDNA and secreted as the mature monomer (496-amino acid protein, 55.4 kDa), which spontaneously forms a non-covalent dimer in solution.

2.2.2. Active Substance

Manufacture

The active substance is manufactured at BioMarin Pharmaceutical, Inc., Galli Drive Facility, 46 Galli Drive, Novato, CA 94949, USA.

Development genetics

The elosulfase alfa- cell bank used in the manufacture was derived from a CHO-K1 cell line.

The expression plasmid was constructed using the cDNA of rhGALNS and fused with the human cytomegalovirus promoter and selection was provided with a resistance marker.

Following transfection in the host cell line, a stable pool was generated by selection and the pool was limited-dilution cloned for single cell clones producing elosulfase alfa. One clone was selected

from the stable clones based upon titer and viability, and was selected to use in creation of the master cell bank (MCB). The resistance marker was removed from the culture process prior to preparation of the development bank, and was not utilised during generation of the MCB.

Cell banking system

A two-tiered cell banking system of MCB and Working Cell Bank (WCB) was developed and maintained in compliance with current Good Manufacturing Practices (cGMP) and ICH guidelines. The MCB was prepared from a single vial of the research bank stored in liquid nitrogen. WCB-1 was prepared using the same methodology as the MCB. Procedures followed for the preparation of the MCB, WCB were described. An extensive range of tests was performed for their characterisation, in accordance to ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation process

Frozen cells from the MCB or WCB are thawed and inoculated into cell culture flasks containing growth media.

When the target density is reached, a series of expansion steps is initiated. Bioreactors are inoculated according to a parallel or sequential seeding procedure. When the target density is reached, the harvested cell culture fluid (HCCF) is collected, sampled for analysis, and stored until the first step of the purification process is initiated.

Purification process

RhGALNS is purified in a sequence of chromatography, viral inactivation and filtration, and ultrafiltration/diafiltration steps.

Formulation to 3 mg/mL for frozen storage (≤-25 ºC) of the bulk active substance (BDS) can be used as an optional hold step. The BDS is thawed when needed for further processing and adjusted to a concentration of 1 mg/mL, producing the formulated bulk active substance (FBDS). Alternatively, the process fluid may be formulated directly to FBDS.

The FBDS is stored at 2–8 °C. The FBDS containers are shipped to the fill site under cold chain conditions using a validated shipping configuration.

Although this dossier is not considered as a Quality by Design application, certain elements of an enhanced approach were applied. Controls of critical steps and intermediates are achieved through process monitoring and in process testing. The control strategy is traditional and was developed around the critical quality attributes (CQAs) which were defined for elosulfase alfa and roughly comprise all test parameters of the FBDS specification. A systematic process characterisation risk assessment (PCRA) approach was used to evaluate the risk for each particular step in the process, linking process variables with their failure mode if operated outside the normal operating ranges (NORs) or proven acceptable ranges (PARs), their current control and the inherent control capability, classification as critical process parameter/key process parameter (CPP/KPP) or process parameter, potential impact on CQAs, the resulting risk prioritisation, justification, and if applicable, any additional process characterisation studies required.

The Applicant has identified KPPs and CPPs as follows:
- KPPs are defined as process parameters for which operating outside of the proven acceptable range will have an impact on the manufacturing process (i.e. yield, process time, throughput) but will not directly impact product quality.
- CPPs are parameters for which operating outside of the proven acceptable range will have a direct impact to product quality attributes (e.g. bioreactor temperature, intermediate hold times).
Other parameters are also considered for monitoring of the manufacturing process.

The process experience leading to establishing the PARs of S.2.2 and S.2.4 originates from various levels such as in-depth process characterisation studies, manufacturing experience from the clinical and commercial scale phase, parallel small scale validation studies representative of the process, and process experience from a similar BioMarin-process where applicable. For particular process variables the PARs were directly derived from the manufacturing campaigns in 2010 and 2011, while PARs may have additionally been enlarged based on further process characterisation studies/range-finding studies, small scale validation studies and experience taken over from the similar process.

Process validation

Satisfactory validation data have been provided for three qualification lots manufactured at the Galli site with the current commercial process. Validation studies were designed to demonstrate the acceptability, robustness and reproducibility of the defined manufacturing process.

Manufacturing process development

The active substance is manufactured using a standard fermentation and purification process. A number of changes were made during product development, which can be grouped in four categories:

- Cell culture: the cell culture process was scaled up prior to Phase 3, and adapted to the planned commercial process. A WCB was introduced.

- Purification: modifications were made to the purification process, including optimisation of chromatography steps, increasing the diameters of the chromatography columns, and optimisation of storage conditions for 3 mg/mL BDS.

Formulation: the formulation was optimised after Phase 1/2 to enhance product stability.

Facility: the process was moved to the commercial facility during Phase 3 manufacture.

Characterisation

The protein and carbohydrate structure, potency, strength and purity of clinical and commercial lots of elosulfase alfa have been characterised, and these data have been presented.

1. Elucidation of structure and other characteristics:

The protein and carbohydrate structure, potency, strength and purity of clinical and commercial lots of elosulfase alfa have been characterised, and these data have been presented.

1.1. Physicochemical characterisation:

Protein structure

Molecular mass of the glycosylated protein was determined by electrospray ionisation time of flight mass spectrometry (ESI-TOF MS).
SEC-HPLC and multi-angle laser light scattering (MALLS) further supported the findings that elosulfase alfa is in a dimeric form in solution.

The primary structure of elosulfase alfa was confirmed by peptide mapping. Peptide maps were also prepared without prior reduction and alkylation in order to confirm the three disulphide bridges in the elosulfase alfa molecule.

The N-terminal amino acid sequence of elosulfase alfa has been identified by Edman degradation. The observed major sequence is consistent with the expected primary structure. One truncated N-terminal variant was identified. On the basis of the arguments provided by the Applicant, it was considered unlikely that the observed degree of truncation would affect clinical safety or efficacy of the product.

The evaluation of charge heterogeneity, primarily determined by the glycosylation of elosulfase alfa, was performed.

Determination of disulphide linkages demonstrated the presence of three disulphide bridges and one free sulphydryl per polypeptide chain. The results are consistent with the crystal structure of elosulfase alfa.

Structural characterisation also included peptide mapping, C-terminal sequence identification, circular dichrosim spectroscopy, and analytical ultracentrifugation.

Glycosylation
The consistency of occupancy of the two consensus N-glycosylation sites (N178 and N397) was assessed by both peptide mapping (testing for unmodified peptides containing the glycosylation site) and using ESI-TOF MS.

Phosphorylation and mannose content of the glycans was assessed. The dominant glycans attached to elosulfase alfa are BisP-Man7 and BisP-Man6 and non-phosphorylated mannose-9 (Man9) and Man8. It has been demonstrated that the phosphorylated mannose glycans are attached to N178, while the neutral mannose glycans are attached to N397.

Monosaccharide composition analysis using hydrolysis was also used to determine if any monosaccharide other than mannose and N-acetylglucosamine can be detected. This confirmed that predominantly high mannose structures are attached to elosulfase alfa.

The oligosaccharide profile analysis did not detect any complex or hybrid glycans or other sialic acid containing glycans in elosulfase alfa lots. Results show the same dominant glycans for both the Phase 1/2 and Phase 3 lots tested.

Other data were used to characterise the elosulfase alfa molecule.

1.2. Biological characterisation:

Activity of elosulfase alfa is measured using an HPLC method using D-galactose-6-sulfate (Gal-6S) as the substrate. The assay was also utilized to characterise the kinetic parameters of the enzymatic activity.
Activity is also measured by monitoring the level of formylglycine conversion.

Cellular uptake of elosulfase alfa was measured.
2. Impurities

Detection and quantification of host cell proteins (HCPs) was performed.

DNA was measured in the eluate of the chromatography step known to remove DNA. DNA levels were below the limit of detection for all samples demonstrating consistency of DNA clearance.

Other potential process-related impurities were investigated.

Specification

Specifications were provided for the formulated active substance and pooled FBDS. FBDS lots may be pooled or processed as individual lots. Each FBDS lot must meet release specifications, prior to pooling. After pooling the pooled lot must meet all FBDS pooled release specifications.

Qualification data for the reference material used to date including release as well as characterisation data were submitted. Preparation and qualification of established and future reference materials is sufficiently described.

Stability

The Applicant has performed real-time and accelerated stability studies designed in accordance with ICH guidelines to monitor the time–temperature stability of cGMP lots. The characteristics included in stability testing were chosen based on method validation results and characterisation

studies. The appropriateness of the methods for indicating the stability of elosulfase alfa FBDS has been further supported by forced-degradation studies. The active substance is stored either as FBDS (1 mg/ml) or BDS (3 mg/ml).

For FBDS, the Applicant claims shelf life of 12 months when stored at long-term (5±3°C) conditions. For the stability batches the storage conditions included are 5±3°C, 25°C/ 60% RH and 40 °C/ 75% RH for study durations of up to 24 months.

For FBDS, 12 months stability when stored at long-term (5±3°C) conditions are currently concluded.

Based on the studies provided, the proposed storage time of the BDS intermediate of 36 months at ≤ -25° C can be accepted.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The finished product, referred to as elosulfase alfa, is a sterile solution for infusion, packaged in a container closure system consisting of a Type 1 borosilicate glass tubing vial, butyl rubber stopper and aluminium seal with flip off cap. Each vial is filled to a target volume of 5.3 mL of solution, which allows the withdrawal of 5.0 mL deliverable volume. Elosulfase alfais formulated with a target pH of 5.4. The visual appearance of the finished product is clear to slightly opalescent, and colorless to pale yellow.

The active substance is formulated with sodium acetate trihydrate, sodium phosphate monobasic monohydrate, L-arginine hydrochloride, sorbitol, polysorbate 20 and water for injections. All the excipients meet Ph. Eur. requirements.

For administration to patients, elosulfase alfa is diluted with 9 mg/mL (0.9%) sodium chloride solution.

The commercial formulation was selected based on the results of pre-formulation characterisation studies conducted to enhance elosulfase alfa stability by optimising pH and buffer composition. The commercial formulation was initially implemented in the pivotal Phase 3 and extension studies.

The container closure system was selected based on demonstrated compatibility with the liquid formulation. The vials and stoppers meet Ph. Eur. requirements.

Adventitious agents

Potential adventitious agent contamination in elosulfase alfa finished product is controlled through appropriate sourcing and screening of raw materials, testing of the cell banks, appropriate cleaning, and a robust system of inactivation, removal, and in-process testing during the manufacturing process. The controls, precautions, testing, and demonstrated clearance of multiple virus types in the manufacturing process collectively demonstrate that the elosulfase alfa manufacturing process is robust and reproducible, and provides adequate protection of elosulfase alfa FBDS against contamination by adventitious agents.

Elosulfase alfa finished product does not contain any animal-derived ingredients. Polysorbate 20 is used as a stabiliser, and is vegetable derived.

Virus removal studies were performed for the elosulfase alfa manufacturing process. The combination of steps evaluated for each model virus demonstrates that the manufacturing process provides separate methods and mechanisms for viral clearance. The column chromatography, membrane chromatography and filtration steps evaluated provide clearance by removal of virus, while the low pH step provides clearance by inactivation.

Manufacture of the product

The finished product is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Germany.

The solution is sterile filtered as the FBDS is filled into the vials. Satisfactory validation data has been provided to give assurance regarding the sterile filtration, filling, and capping procedures. Media fill data support the aseptic process, and media fills are performed routinely. The fill facility is operated under cGMP.

Product specification

Most of the analytical methods are identical to those used for the active substance.

All tests described by the Ph. Eur. for parenteral solutions are included in the specification. Specifications monitor quality attributes including identity, potency protein concentration, purity, and safety.
A number of finished product release limits were calculated based on a combination of BDS, FBDS, and finished product results.

Stability of the product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of elosulfase alfa drug product. For finished product manufactured at the originally qualified site, long term storage (5 ± 3°C) of commercial scale batch data (for three batches) up to 30 months and pilot scale batch data up to 36 months (one batch) are provided. For finished product manufactured at the more recently qualified fill site, long term storage (5 ± 3°C) of commercial scale batch data (three batches) and pilot scale batch (one batch) data up to 12 months are provided.

At long term storage all batch data remain within the pre-defined acceptance limits of the finished product shelf life specification.

Based on the data provided, finished product stability is concluded to be 36 months when stored at 5 ± 3°C.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

Origin, source, and history of the cells, characterisation and testing
The generation of the host cell line and the cell banking system is described in satisfactory detail. Comprehensive information on the cloning and establishment of the master cell bank (MCB) and working cell bank (WCB) has been provided. The Applicant has adequately tested the MCB, WCB and end-of-production cells for identity and the absence of infectious extraneous agents.

Manufacturing process
The single steps of the active substance manufacturing process are adequately described.
The set of process parameters defined throughout the manufacturing process covers various levels and input control points and as such adequately addresses the process performance at the operational level and consequently ensures process consistency.

Process validation
The process validation data show, overall, that the process is running consistently regarding the parameters/attributes investigated resulting in FBDS meeting pre-defined product quality specifications and active substance comparability to reference and historical material.

Validation data provided also support the pooling concept.

The Applicant has provided adequate data from small scale and commercial scale to support the hold times. Validation studies were performed at small scale to confirm the chromatography resin use-life for each of the three chromatography resins with satisfactory results.

Removal of impurities has adequately been demonstrated and is ensured through in process qualification studies, small-scale spiking studies and/or routine in process and release testing.

Manufacturing process development
All changes implemented to the manufacturing process were described with sufficient detail and supported by product comparability studies that ensured that the changes had no impact on the product characteristics.

Characterisation
A comprehensive characterisation has been performed by analytical evaluation of elosulfase alfa lots representative for phase 1/2, phase 3 and commercial manufacturing process at the BDS and the FBDS manufacturing stage. The selection of elosulfase alfa lots used for characterisation studies is considered appropriate.

Control of active substance – specifications
The choice of the test methods is adequate to verify the identity, heterogeneity, protein content, biological activity, purity, and formulation (including microbial control) of the active substance. A formal specification for the identity has been added for pooled FBDS. A number of limits were tightened and brought in line with the phase 3 clinical studies and commercial batches.

The enzymatic conversion of the cysteine residue in the active site (C53) into formylglycine (FGly 53) is required for sulfatase activity of elosulfase alfa. The variability of the amount of rhGALNS with a retained cysteine residue, measured in the active substance and finished product, was initially raised as a Major Objection. The additional information and justification provided by the Applicant during the evaluation procedure were satisfactory and this issue was considered resolved. However, the Applicant is recommended to continue their efforts to understand and improve the consistency of FGly conversion in elosulfase alfa where possible.

On request, the Applicant has included adequate acceptance criteria for degradation products and product-related impurities detectable using certain tests, and modified the specifications for other characteristics. The revised specifications are considered acceptable and adequately confirm the quality of the active substance. As the current number of batches manufactured at commercial scale is limited, the Applicant is recommended to re-evaluating the active substance specifications when results for 50 commercial lots are available.

Analytical procedures and validation of analytical procedures
Analytical methods used for the control of the active substance have been adequately described and validated. However, the Applicant is recommended to further evaluate certain factors of FGly measurements allowing for determination of the true process variability.

Furthermore, the current cellular uptake assay is variable and the CHMP recommends further efforts to reduce the variability and to replace it by an improved cell based bioassay using a variation procedure.

Stability
The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance to current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

On the basis of the stability data provided, the acceptable shelf life for the bulk active substance (BDS) is 36 months when stored at less than -25°C and 12 months for the formulated bulk active substance (FBDS) when stored at 5±3°C.

The Applicant is recommended to put an additional lot of BDS on stability per ICH Q5C.

In accordance to EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Finished product

Development
Comprehensive pre-formulation physicochemical characterisation studies as well as excipient selection and optimisation studies were conducted to identify the optimum formulation.

Manufacture
The manufacturing process of the finished product is adequately described with appropriate controls in place. Process validation of the finished product manufacturing process was performed in accordance with applicable international regulatory guidelines to demonstrate the acceptability, robustness, and reproducibility of the manufacturing process.

Control of finished product – specifications
The list of test parameters presented in the finished product release specification is considered adequate to control finished product quality.

However, the CHMP recommends to further re-evaluate certain finished product specifications when 50 commercial lots are available. It should be noted that the re-evaluation should be based on finished product release data only, unless it is demonstrated that the results of active substance, FBDS and finished are comparable for all parameters tested.

Stability
Real-time and accelerated stability studies were initiated in accordance to ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. On the basis of the data provided, the acceptable shelf-life for the finished product is 36 months at 5 ± 3°C.

In accordance to EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Vimizim is considered to be in line with the quality of other approved therapeutic enzymes manufactured by recombinant DNA technology. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Vimizim is considered acceptable.

2.2.6. Recommendations for future quality development

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

2.3. Non-clinical aspects

2.3.1. Introduction

The recombinant human N-acetylgalactosamin-6-sulfatase (rhGALNS, elosulfase alfa) is intended for treatment of patients suffering from mucopolysaccharidosis type IV A (MPS IV A) also known as Morquio disease. Morquio A disease is an inherited autosomal recessive lysosomal storage disorder caused by GALNS deficiency. GALNS is a lysosomal enzyme hydrolysing glycosaminoglycans (GAGs) such as keratan sulfate (KS) and chondroitine sulfate (CS). Reduced GALNS activity results in accumulation of KS in several tissues including growth plate, articular cartilage and cornea. Patients are suffering on skeletal dysplasia and corneal cloudiness, as well as frequently heart valve disease, restrictive lung disease, and hepatomegaly. Vimizim is intended as chronic enzyme replacement therapy. It is assumed, that the intravenously administered enzyme will be taken up by the Cation Independent Mannose 6-phosphate [CI-M6PR] transporter into cells and subsequently into the lysosomal compartment.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In primary pharmacology experiments in a human Morquio fibroblast cell line GM593, it was shown that elosulfase alfa is taken up by cells via the CI-M6PR receptor. Intracellular half-life in this cell line was estimated at 5-7 days.

The applicant has performed *in vitro* experiments to characterise the intended properties of elosulfase alfa. Primary human Morquio chondrocyte cell lines were established using cells from two Morquio patients. These cells showed signs of abnormal skeletal matrix development and/or remodelling, as gene expression of chondrocyte markers (including sox9 and MMP3) was altered compared to normal chondrocytes. Morquio cells also showed no detectable GALNS activity and accumulation of KS in the cells, and therefore thought to be an appropriate *in vitro* model to evaluate the pharmacological activity of elosulfase alfa. A reduced rate of proliferation compared to normal cells was also observed.

Most *in vitro* experiments were performed with up to 10 nM (555 ng/ml) elosulfase alfa, which is considered to be a clinically relevant concentration, since the Cmax in patients at the intended dose of 2 mg/kg is around 2000 ng/ml. Internalization of elosulfase alfa and some localization into the lysosome was shown by immunofluorescent detection, both in fresh cells and cultured cells containing accumulated KS. Although the localization seems rather limited, treatment of Morquio chondrocytes with 10 nM elosulfase alfa restored GALNS activity and reduced stored KS to levels comparable to normal chondrocytes, which is considered to be the most important parameter for proof of concept. Further analyses were conducted on gene expression to examine whether there is an effect of elosulfase alfa treatment on Morquio chondrocyte phenotype. As stated by the applicant, elosulfase alfa treatment led to partial normalization of the chondrogenic gene expression profile in Morquio chondrocytes. However, of the five markers, only sox 9 and Collagen I showed an expression similar to normal cells

after treatment, and this only applies to cells from patient 2. These data show that the gene expression in Morquio chondrocytes is variable among patients, which is also evident from the variable patient phenotypes. To restore gene expression to normal levels in cell culture, longer duration of treatment of the cells might be necessary, and other external factors which could influence the physiology of the cell are likely to be important.

These *in vitro* experiments show that elosulfase alfa is taken up into the cells, and restores enzyme activity in human Morquio chondrocytes. This is a clinically relevant model and thus the principle of this treatment has been sufficiently shown.

No *in vivo* studies have been performed with elosulfase alfa to show the pharmacodynamic activity, due to the lack of an appropriate animal model. Since relevant morphological effects are not anticipated by the treatment with GALNS in small laboratory animals, further studies would not provide relevant information at this stage of development.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted as elosulfase alfa is a large molecular protein drug that targets specific receptor. Consequently, no effect of elosulfase alfa unrelated to its desired therapeutic target is expected. This was acceptable to the CHMP.

Safety pharmacology programme

In safety pharmacology studies, single dose treatment of rats with up 20 mg/kg did not have any effect on central nervous system parameters as measured in the modified Irwin neurological assessment, or on respiratory system parameters. Single dose treatment of cynomolgus monkeys with up 20 mg/kg did not have any effect on cardiovascular system parameters.

Pharmacodynamic drug interactions

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

2.3.3. Pharmacokinetics

Analytical methods: The electrochemiluminescence assays to measure elosulfase alfa in rat, monkey and rabbit plasma and in rat breast milk were sufficiently validated with accuracy and precision at the LOQ of <25% in plasma and <30% in milk. An immunoassay was used to determine the total anti-elosulfase alfa antibody in rat, rabbit and monkey serum. The presence of low concentrations of elosulfase alfa (10 ng/ml) interfered with antibody detection and therefore samples were drawn prior to the new dose. The signal from quality controls was reproducible across multiple plates and analysts, indicating acceptable intermediate precision. The assay was robust and stability was demonstrated. Furthermore, an ELISA was developed to detect antibodies in rat and monkey serum inhibiting binding of elosulfase alfa to CI-M6PR and thus preventing uptake. The assay was specific for elosulfase alfa and was sufficiently validated. The presence of low concentrations of elosulfase alfa (10 ng/ml) interfered with antibody detection and therefore samples were drawn prior to the new dose. The CrossLaps ELISA was used for the quantitation of degradation products from the C-terminal telopeptide region of type I

collagen. The ELISA was sufficiently validated with accuracy and precision ≤ 25%. An LC-MS/MS assay was developed for the analysis of keratansulfate in rat and monkey plasma by measuring the two degradation products of keratansulfate Galβ1-4GlcNAc(6S) and Gal(6S)β1-4GlcNAc(6S). Accuracy and precision are ≤25%. The LOQ for Galβ1-4GlcNAc(6S) was 0.038 µg/mL in rat plasma and 0.011 µg/mL in monkey plasma. The LOQ for Gal(6S)β1-4GlcNAc(6S) was 0.237 µg/mL in rat plasma and 0.114 µg/mL in monkey plasma.

No separate pharmacokinetics studies were performed. Pharmacokinetics was investigated as toxicokinetics in single and repeated dose toxicity studies. In all these studies elosulfase alfa was administered once weekly *via* the clinically intended IV route. The dose levels chosen were 0, 1, 6 and 20 mg/kg b.w. In general, in rats and monkeys mean $t_{1/2}$ increases with dose and repeated doses. In the rat the smallest $t_{1/2}$ value was seen after the lowest dose of 1 mg/kg b.w.in the first week ($t_{1/2}$ = 2 min) and the largest $t_{1/2}$ value was observed at the highest dose of 20 mg/kg b.w. at week 26 ($t_{1/2}$ = 26 min). Half-life values of elosulfase alfa increased in the cynomolgus monkey from around 10 minutes at Dose 1 for all dose levels (1 – 20 mg/kg b.w.) to 30 to 40 minutes for 1 mg/kg and 6 mg/kg, and to 96 minutes for 20 mg/kg b.w. In general, with increasing dose increases in C_{max} and AUC in rats and monkeys were greater than proportional. These more than dose proportional increases were even more pronounced after repeated dosing (in the monkey up to about 17 times above dose proportionality between 1 and 20 mg/kg b.w. doses). No clear gender differences were observed.

Calculated volume of distribution is small in rats and increases with time. This indicates that the distribution to organs is slow. Distribution studies indicated that elosulfase alfa migrates from the blood stream to the target organs. Overall these data indicate that elosulfase alfa is mainly present in blood and the target organs. Volume of distribution and therefore also the half-life increased with increasing dose and number of doses.

An *in vivo* study was performed to evaluate the tissue distribution of elosulfase alfa in mice. It was shown that the enzyme distributes to the heart (mitral valves, atrium and septum), growth plate, articular cartilage, bone, bone marrow, and sinusoidal and Kupffer cells of the liver. Further analyses revealed localization into the lysosomal compartment of heart cells. An *in vivo* study in rabbit showed that elosulfase alfa is able to pass the placenta and into milk . Elosulfase alfa is a recombinant form of human N-acetylgalactosamine-6-sulfatase and is identical to the naturally occurring human enzyme in terms of the amino acid sequence and N-linked glycosylation sites. Elosulfase alfa will therefore be metabolised like the natural occurring enzyme. Thus, no metabolism studies are warranted. Based on the structure and molecular size of elosulfase alfa, no transporter studies are warranted. Elosulfase alfa is most likely excreted in the same way as the natural enzyme and thus, the absence of excretion studies to urine, bile, and faeces is justified. Elosulfase alfa is excreted into milk of rat after IV administration. Because of its molecular structure and size, elosulfase alfa is not likely to be a substrate for or inhibitor of drug transporters and CYP and conjugation enzymes involved in the transport and metabolism of drugs.

The CHMP noted that due to the mechanism of action of elosulfase alfa, which requires an appropriate lysosomal pH, drugs affecting lysosomal pH are expected to impair proper functioning of elosulfase alfa. The applicant acknowledged that the physiologic effects of potential drug interaction in the lysosome are not well documented *in vivo*. In regards to elosulfase alfa activity in the lysosome, changes in lysosomal pH could potentially decrease maximal activity

depending on the degree of lysosomal pH increase. However, elosulfase alfa intracellular half-life in the lysosome is 5 to 7 days enabling sulfate cleavage of the endogenous substrates at less than optimal enzyme activity as long as the pH stays below neutral pH. Elosulfase alfa is active in the acidic lysosomal compartment as pH ranges of 4.8 – 5.3. In addition, drugs known to change lysosomal pH under *in vitro* experimental conditions would not reasonably achieve concentrations high enough under approved, prescribed conditions to alter the lysosomal pH outside of the pH range in which GALNS is active. Therefore, no pharmacokinetic drug interaction studies were conducted and this is agreed by the CHMP.

2.3.4. Toxicology

The following toxicology studies were conducted: single dose toxicity study in rats, repeated dose toxicity studies of 26 weeks duration in rats and of 52 weeks duration in monkeys, with a 4 week recovery phase, each, a 4 week toxicity study in monkeys in which 3 different lots of elosulfase alfa were compared and DART studies. The general toxicity studies were designed as combined toxicology/pharmaco-(toxico-)kinetics studies. The single dose toxicity study in rats was in addition a combined CNS-safety study. The studies are summarised in the following table.

Single dose toxicity study with elosulfase alfa**:**

Study ID	Species / Sex / Number / Group	Dose / Route	Approx. lethal dose / observed max non-lethal dose	Major findings
0110-08-021	Rat 6/sex/dose	0, 1, 6, 20 mg/kg IV bolus	>20 mg/kg	No treatment related findings

Repeated dose toxicity studies with elosulfase alfa**:**

Study ID	Species / Sex / Number / Group	Dose / Route	Duration	NOEL / NOAEL (mg/kg/day)	Major findings
0110-08-020 GLP*	Rat 10/sex/dose 6/sex/dose for recovery	0, 1, 6, 20 mg/kg/week IV bolus	26 weeks 4 wks recovery	20 mg/kg/week	**≥1**: anaphylactoid-typ reactions, ↑ ALP (M), ↑ urine vol and pH (M), ↓ specific gravity (M) **=20**: ↓ spleen weight (F)
elosulfase alfa-10-100 GLP	Cynomolgus monkey 4/sex/dose	0, 20 mg/kg/week IV infusion	28 days	20 mg/kg/week	No treatment-related findings
0110-08-018 GLP	Cynomolgus monkey 4/sex/dose 3/sex for recovery	0, 1, 6, 20 mg/kg/week IV infusion	39-52 weeks	20 mg/kg/week	No treatment-related findings

** DPH-coadministration*

Single dose toxicity

A study was conducted to evaluate the toxicity and determine the TK parameters of elosulfase alfa when administered as a single dose *via* slow push bolus IV injection to SD rats. This was followed by a two-week recovery period to assess the reversibility, persistence, or delayed occurrence of any effects. Blood and urine samples were taken for haematology, coagulation, clinical chemistry, and urinalysis from fasted animals prior to scheduled euthanasia on day 15, when a full necropsy was performed and a subset of organs (adrenals, brain, epididymides,

heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, mandibular salivary gland, seminal vesicle, spleen, testes, thymus, thyroid with parathyroid, and uterus) were weighed. Brain, heart, injection sites, kidneys, lesions (if present), liver, lungs, and spleen were examined by histopathology. There were no elosulfase alfa -related changes in the clinical signs and body weight. No injection site reactions or elosulfase alfa -related changes in clinical pathology parameters, absolute or relative organ weight, or macroscopic or microscopic pathology were observed.

Repeat dose toxicity

Repeated dose toxicity of elosulfase alfa was evaluated in rats after 26 weekly doses, and in cynomolgus monkeys up to 52 weeks of dosing. In rats, expected anaphylactoid-type reactions were observed across all doses, which were attenuated by pre-treatment with diphenhydramine (DPH). Other findings were limited to urinary changes, e.g. increased urine volume and pH and decreased specific gravity; decreased ALP in males at all doses, and decreased spleen weight in high dose females. As these changes are only minor, and not seen in the monkeys, their toxicological relevance is questionable. The NOAEL in the rat was established as 20 mg/kg/week after 26 weeks of dosing.

In the 28-day repeated dose study with cynomolgus monkeys, 4 weekly 20 mg/kg infusions of three different batches were compared. Two batches represented a formulation used in the phase 3 studies, and one represented a batch used in phase 1 and 2 trials. No significant toxicological findings were observed in this study, and the difference between the batches was not apparent.

Elosulfase alfa was further evaluated in monkeys with 39 to 52 weekly infusion up to 20 mg/kg. The material used in this study was a formulation used in phase 1 and 2 trials. The monkeys were 2-3 years old at study initiation and represented the juvenile population intended to be treated. Special attention was paid to the bones of the animals, since this is the target organ of the elosulfase alfa pharmacodynamic effect. No anaphylactoid-type reactions or any other treatment-related effects were observed in these monkeys. Exposure in terms of AUC was above the human exposure at the intended clinical dose.

Genotoxicity

No genotoxicity studies were performed and the conduct of such studies is not considered necessary due to the protein structure and the enzymatic activity of the drug substance, which is acceptable to the CHMP.

Carcinogenicity

No carcinogenicity studies were conducted since the risk for carcinogenic potential is not anticipated for a biological molecule that lacks immunomodulatory or cellular proliferation activity. The enzymatic activity of elosulfase alfa is restricted to the lysosomal compartment where it specifically degrades KS and this mode of action does not raise concern of a potential for neoplasm induction or tumor promotion. No proliferative or neoplastic lesions were observed in repeat-dose elosulfase alfa toxicology studies. In addition, no carcinogenic potential in clinical studies has been observed in other marketed enzyme replacement therapies. This justification is adequate.

Reproduction Toxicity

Four developmental and reproductive toxicity studies were conducted to characterise the effects of elosulfase alfa on fertility, embryo-foetal and peri/postnatal development after daily administration. These studies included a combined fertility/embryo-foetal development rat study, a developmental and peri/postnatal reproduction rat study, and dose range-finding and definitive embryo-foetal development rabbit studies (see table below).

Reproduction toxicity studies with elosulfase alfa

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
elosulfase alfa-10-007 M/F fertility + Embryo-fœtal development GLP	SD rat 25/sex/dose	IV bolus 0, 0[a], 1, 6, 20 mg/kg/day	M: -D15 – D29 F: -D15 - GD20	**M,F0: ≥6**: ↓ motor activity, dehydration, ptosis, ↓ BW gain and food consumption up to D15 of dosing **F,F0: ≥6**: prostrate **DPH related**: injection site scab and ulceration, ↑ resorptions, ↑ post-implantation loss, short limbs (F1), incompletely ossified cervical vertebrae and hindlimb phalanx (F1)	Fertility: 20 mg/kg/day F1: 20 mg/kg/day
elosulfase alfa-10-008 Embryo-fœtal development DRF, non-GLP	NZW rabbit 8F/dose	IV infusion 0, 1, 6, 20 mg/kg/day	GD7-GD20	**F0: ≥6**: pitted areas in liver **=20**: ↓ BW gain and food consumption **F1: =20**: ↓ BW	F0: 1 mg/kg/day F1: 6 mg/kg/day
elosulfase alfa-10-061 Embryo-fœtal development GLP	NZW rabbit 20F/dose	IV infusion 0, 1, 3, 10 mg/kg/day	GD7-GD20	**F0: ≥10**: pitted areas in liver **F1:** no treatment-related findings	F0: 3 mg/kg/day F1: 10 mg/kg/day
elosulfase alfa-12-013 Peri & postnatal GLP	SD rat 25F/dose	IV bolus 0, 0[a], 1, 6, 20 mg/kg/day	GD7-LD20	**F0: ≥6**: dehydration, ↑ stillborn pups **=20**: ↓ BW gain and food consumption **DPH related**: scabs, ulceration, ↑ gestation duration **F1:≥20**: ↓ BW up to LD 4 **F2:** no treatment-related findings	F0: 1 mg/kg/day F1: 20 mg/kg/day F2: 20 mg/kg/day

[a] ELOSULFASE ALFA-treated animals received 10 mg/kg DPH, IP, 10 to 20 min prior to elosulfase alfa administration from the first dose onward to mitigate an expected anaphylactoid-type reaction. An additional vehicle-treated group was given 10 mg/kg DPH, IP, 10 to 20 min prior to elosulfase alfa administration to control for DPH administration.

Elosulfase alfa was evaluated in rats up to 20 mg/kg/day for effects on fertility and embryo/foetal development. Due to anaphylactoid-type reactions in the rats seen in the repeated dose study, animals were treated with DPH prior to dosing and a DPH control group was added. Some effects still remained in male and female F0 rats, but these are probably due to the daily dosing regimen. There was no major effect on the fertility parameters in males or females. A non-significant reduction in sperm motility was seen at the 6 mg/kg/day dose, and was therefore not considered treatment-related. Effects on reproduction, namely increased resorption, post-

implantation loss and incomplete ossification, were likely to occur due to DPH treatment, since they were also seen in the DPH control group. Thus, no elosulfase alfa related effects on embryo-fetal development in rats up to 20 mg/kg/day were observed.

In the dose rage finding (DRF) rabbit embryo/foetal development study, dams had pitted areas in the liver at doses from 6 mg/kg/day. This is likely due to a non-specific reaction to the protein in these animals. Body weight gain was reduced at the high dose, which coincided with reduced foetal body weight at this dose. The main study used doses up to 10 mg/kg/day. The high dose caused pitted areas in the liver of the dams, as seen in the DRF study. No other effects were observed, and therefore the NOAEL of BMN for embryo/foetal development in rabbits is 10 mg/kg/day in this study. Since no anaphylactoid-type reactions were observed in this species, DPH was not administered to any of the animals.

Pre- and postnatal development was evaluated in rats, which were dosed up to 20 mg/kg/day, up to lactation day 20. All animals were also dosed with DPH to counteract anaphylactoid-type reactions, and a DPH control group was added. Effects related to the DPH treatment included scabs, ulcerations and an increased duration of gestation. Effects related to elosulfase alfa treatment were limited to a reduction in body weight during the gestation period in high dose dams, corresponding to a decreased foetal weight up to lactation day 4. An increase in stillborn pups was also observed at the mid and high dose ranges. This effect was not seen in any other reproduction toxicity study. There were no other effects on any of the reproduction or development parameters in the F1 and F2 generations. Elosulfase alfa is secreted in rat milk at a dose of 6 mg/kg/day or higher, but not at 1 mg/kg/day.

Nevertheless, it is difficult to interpret these toxicological findings due to the simultaneously administration of DPH and evidence of any effects on pre– and postnatal development at doses up to 20 mg/kg cannot be excluded. Thus, the CHMP requested to include and appropriate statement in the SmPC informing the prescriber that animal studies are of limited relevance. As a precautionary measure, it is preferable to avoid the use of Vimizim during pregnancy, unless clearly necessary.

Toxicokinetic data

The toxicokinetics of elosulfase alfa was studied after single and repeated IV administration to male and female Sprague Dawley rats in general toxicity studies as discussed above.

Local Tolerance

The intended clinical route of administration is IV infusion. Repeated dose and safety pharmacology studies have been performed with IV administration, therefore no additional local tolerance studies are considered necessary. No local tolerance studies have been performed.

Other toxicity studies

Due to the nature of the compound elosulfase alfa and its mechanism of action, no additional studies on antigenicity, immunotoxicity, dependence, metabolites or impurities were performed. This is considered acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

Elosulfase alfa is a recombinantly generated glycosylated protein being administered parenterally. It is expected that elosulfase alfa is easily biologically degradable and that an increase in the concentration of intact elosulfase alfa in the environment is highly unlikely. An environmental risk assessment is not considered necessary. Elosulfase alfa is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The *in vitro* pharmacology experiments were performed in clinically relevant models, and this supports the use of elosulfase alfa in Morquio patients. Based on FDA advice, rat was chosen as additional toxicology species next to the monkey. It is to be noted that at least three types of KS, termed KSI, KSII and KSIII exist in the human body. Apart from small differences between the subtypes, it is the way in which the KS proteoglycan chain is attached to its core proteins that distinguishes the subtypes from each other. KSII seems to be the most important subtype, as humans affected with Morquio syndrome are most affected by abnormalities in cartilage and bones, the sites which predominantly express KSII. As is stated by the applicant, rodents do not express KSII, which further complicates the matter on species relevancy. However, in view of data acceptance across multiple regions, studies in rats have been performed. Although the rat studies are considered of limited relevance and the non-clinical programme could have been reduced, the rationale of the applicant with regard to their global product development program is acceptable to the CHMP.

No secondary pharmacodynamic and pharmacodynamics drug interaction studies were performed. The possibility that drugs affecting lysosomal pH could impair proper functioning of elosulfase alfa has been discussed and it was concluded that substances able to change lysosomal pH would not achieve concentrations reasonably high to alter and elevate the lysosomal pH to levels when the elosulfase alfa activity would be hampered.

The investigations of elosulfase alfa kinetic parameters show that its half-life is short in the animal species, but the interpretation of these data in relation to the distribution to the target cells is limited. The short half-life could indicate the enzyme is eliminated or distributed, or a combination of the two. The volume of distribution in rats is small. Overall, there is a high inter-individual variability. The distribution study in mice was exploratory. It was shown that fluorophore-labelled elosulfase alfa distributed in mice to well vascularized severely affected tissues, such as liver, and the heart valve and growth plate of long bones, representing the poorly vascularized severely affected target tissue. As a similar cellular uptake was shown of fluorophore-labelled and unlabelled-elosulfase alfa in rabbit synoviocytes, it is likely that the labelling will not have affected tissue distribution. Overall, the non-clinical pharmacokinetic results do not significantly contribute to the overall profile of elosulfase alfa. The clinical studies are considered of greater relevance.

The single dose toxicity study in rats did not reveal any toxicological findings with elosulfase alfa doses up to 20 mg/kg. Repeated dose toxicity was evaluated in rats after 26 weekly doses, and in cynomolgous monkeys up to 52 weeks of dosing. In rats, expected anaphylactoid-type reactions were observed across all doses and were attenuated by pre-treatment with DPH. Other

findings were limited to urinary changes and decreased ALP in males at all doses, and decreased spleen weight in high dose females. These changes were not seen in monkey and their toxicological relevance is questionable. Similarly, no toxicological findings were observed in repeated dose studies in monkeys.

No genotoxicity or carcinogenicity studies have been performed. The CHMP considered this acceptable, since due to the nature of the product, carcinogenic or genotoxic effects are not expected.

Elosulfase alfa was evaluated in rats for effects on fertility and embryo-foetal development. There was no significant effect on fertility parameters in males or females. A non-significant, treatment-nonrelated reduction in sperm motility was only seen at the 6 mg/kg/day dose. In rabbits, pitted areas in the liver of dams were observed at doses from 6 mg/kg/day, which were linked to a non-specific reaction to the protein in these animals. No anaphylactoid-type reactions were observed. Pre- and postnatal development was evaluated in rats, which were dosed up to 20 mg/kg/day, up to lactation day 20. Effects related to elosulfase alfa treatment were limited to a reduction in body weight during the gestation period in high dose dams, corresponding to a decreased foetal weight up to lactation day 4. An increase in stillborn pups was also observed at the mid and high dose. This effect was not seen in any other reproduction toxicity study. There were no other effects on any of the reproduction or development parameters in the F1 and F2 generations. At the dose of 20 mg/kg/day, the exposure was 27-fold higher than the human exposure at the intended clinical dose.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, elosulfase alfa is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

There are no major objections to the granting of a marketing authorization for Vimizim, from a non-clinical point of view. The applicant has clarified issues regarding the relevance of the non-clinical species and the rationale behind the non-clinical programme, as well as the unlikely appearance of the effects on lysosomal pH due to other drugs. The SmPC adequately describes the non-clinical profile of Vimizim and important observations were included in the information for prescribers and patients.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for marketing authorisation for Vimizim through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. Vimizim was designated an orphan medicinal product EU/3/09/657 on 24 July 2009 in the following indication: treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome). The applicant applied for the following indication: *"Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) (see section 5.1)"*

At the time of MAA submission, the applicant provided data from 6 clinical studies. These included 2 studies that were completed (MOR-002; MOR-004), and 4 studies that were ongoing (MOR-100; MOR-005; MOR-007; MOR-008). For MOR-008, only safety results were presented, due to limited exposure at the time of data cut-off. A further ongoing phase 2 study, MOR-006, was not included since enrollment was ongoing and exposure at data cut-off was very limited.

The pivotal trial for this application is considered to be the phase 3 study MOR-004. Thus study was initiated in January 2011 and was completed in August 2012. Furthermore, patients who completed this trial were given the opportunity to enroll in extension study MOR-005, which was initiated July 2011.

The applicant also initiated a natural history study MOR-001 (MorCAP) and data from the first visit of 325 patients have been included in the MAA.

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

The following table describes the clinical studies as submitted by the applicant at the time of applying for the MAA for Vimizim.

Study No	Primary Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Study Population	Duration	Trial Initiation	Status at time of submission; Anticipated Date of Last Patient Visit	Report/data included in marketing application
MOR-001 (MorCAP)[a]	Quantify endurance and respiratory function in patients with MPS IVA; better characterize spectrum of symptoms and biochemical abnormalities in MPS IVA over time.	Natural History Study	N/A	325	MPS IVA	up to 10 years	Oct 2008	Ongoing; Oct 2018	Publication containing Visit 1 data from 325 patients
MOR-002	Primary objective: evaluate safety of weekly infusions of elosulfase alfa in escalating doses to patients with MPS IVA.	Phase 1/2, Multicentre, Open-Label, Dose-Escalation Study	elosulfase alfa; Dose-Escalation Period: Weeks 1-12: 0.1 mg/kg/qw Weeks 13-24: 1.0 mg/kg/qw Weeks 25-36: 2.0 mg/kg/qw Optional continuation period: 1.0 mg/kg/qw for additional 36-48	20 (actual)	MPS IVA; age 5-18 years	Dose-escalation: 36 weeks Optional continuation: 36-48 weeks Total duration: 72-84 weeks	Apr 2009	Complete; Feb 2011 (actual)	Final CSR

Study No	Primary Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Study Population	Duration	Trial Initiation	Status at time of submission; Anticipated Date of Last Patient Visit	Report/data included in marketing application
			weeks; Weekly 4 to 5 hour i.v. infusions						
MOR-100	Primary objective: long-term safety and efficacy of weekly infusions 2.0 mg/kg elosulfase alfa in patients who participated in MOR-002	Multicentre, Open-Label, Extension Study	elosulfase alfa; 2.0 mg/kg/qw; 4 hour i.v. infusions	17 (actual)	MPS IVA; completed MOR-002	Up to 240 weeks	Nov 2010	Ongoing; Nov 2015	CSR containing complete safety data and efficacy data available from all patients collected up to data cut-off date 19 Jul 2012
MOR-004	Primary objective: evaluate ability of 2.0 mg/kg/qw and 2.0 mg/kg/qow elosulfase alfa compared to placebo to enhance endurance in MPS IVA measured by increase in number of meters walked in the 6 minute walk test (6MWT) from Baseline to Week 24.	Phase 3, Multinational, Multicentre, Double-blind, Placebo-controlled Study	elosulfase alfa or Placebo; 2.0 mg/kg/qw and 2.0 mg/kg/qow; 4 hour i.v. infusions	177 randomized 176 dosed (actual)	MPS IVA; age ≥ 5 years and able to walk ≥ 30 and ≤ 325 m in 6MWT	24 weeks	Jan 2011	Complete; Aug 2012 (actual)	Final CSR
MOR-005	Primary objective: • To evaluate the long- term safety and efficacy of elosulfase alfa administration at 2.0 mg/kg/qw and 2.0 mg/kg/qow in patients with MPS IVA.	Phase 3 Extension, Multinational, Multicentre, Double-Blind followed by Open-Label Study	elosulfase alfa; Double Blind: 2.0 mg/kg/qw and 2.0 mg/kg/qow; Open-Label: 2.0 mg/kg/qw as determined after analysis of final primary efficacy and safety results in MOR-004; 4 hour i.v. infusions	173 (actual)	MPS IVA; completed MOR-004	Up to 240 weeks	Jul 2011	Ongoing; Mar 2017	CSR containing complete safety data and efficacy data available from all patients collected up to data cut-off date 04 Jan 2013
MOR-006	Primary objective: evaluate efficacy and safety of weekly 2.0 mg/kg elosulfase alfa in MPS IVA patient population with limited ambulation (defined by domains of upper extremity function and dexterity, mobility, pain	Phase 2, Multinational, Open-Label Study	elosulfase alfa; 2.0 mg/kg/qw; 4 hour i.v. infusions	Approx. 20 (planned) 2 enrolled 14 Sep 2012	MPS IVA; age ≥ 5 years and severely limited ambulation (inability to walk ≥ 30 m in 6MWT	48 weeks	Aug 2012	Ongoing; May 2014	No report included due to limited data available; data cut-off 14 Sep 2012

Study No	Primary Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Study Population	Duration	Trial Initiation	Status at time of submission; Anticipated Date of Last Patient Visit	Report/data included in marketing application
	and self-care functional abilities).								
MOR-007	Primary objective of the primary treatment phase: • To evaluate safety and tolerability of infusions of elosulfase alfa at a dose of 2.0 mg/kg/qw over a 52-week period in MPS IVA patients less than 5 years of age Primary objective of the extension phase: • To evaluate the long- term safety of elosulfase alfa at a dose of 2.0 mg/kg/qw in patients with MPS IVA less than 5 years of age at enrolment	Phase 2, Multinational, Open-Label Study	elosulfase alfa; 2.0 mg/kg/qw 4 hour i.v. infusions	15 8 patients ≥ 3 and < 5 years (actual)	MPS IVA; < 5 years	Primary treatment: 52 weeks Total study duration including extension: Up to 209 weeks	Oct 2011	Ongoing; Jun 2016	CSR containing complete safety data and efficacy data available from all 15 patients collected up to data cut-off 28 Sep 2012
MOR-008	Primary objective of primary treatment phase: evaluate safety of 2.0 and 4.0 mg/kg/qw elosulfase alfa for 27 weeks. Primary objective of extension phase: evaluate long-term safety of 2.0 and 4.0 mg/kg/qw elosulfase alfa in MPS IVA	Phase 2, Randomized, Double-Blind, Multicentre study	elosulfase alfa; 2.0 mg/kg/qw and 4.0 mg/kg/qw; 4 hour i.v. infusions	25 (actual)	MPS IVA; age ≥ 7 years and able to walk at least 200 m in 6MWT	Primary treatment: 27 weeks Extension phase: up to 130 weeks Total study duration: up to 157 weeks	Apr 2012	Ongoing; Sep 2015	CSR containing complete safety data from all patients collected up to data cut-off 14 Sep 2012

2.4.2. Pharmacokinetics

Pharmacokinetics of elosulfase alfa was assessed in 3 *in vitro* non-clinical studies and in the 2 completed clinical trials MOR-002 and MOR-004. Additional assessments are planned for the ongoing clinical studies MOR-005 and MOR-008. Immunogenicity was or will be assessed in all 6 clinical trials (MOR-002, MOR-004, MOR-005, MOR-100, MOR-007, MOR-008).

Stability has been proven for the storage conditions of the majority part of the subject samples. Excluding the study samples for which stability has not yet been proven from the pharmacokinetic analysis, it was shown that this had not a major effect on the pharmacokinetics. As indicated by the applicant, long term stability evaluation is on-going to address the storage integrity of the remaining fifty samples stored at -35 to -45°C for approximately 105 days and -60 to -80°C for approximately 82 days and ninety-five samples at -60 to -80°C for longer periods. The results are expected to be available in Q3 2014. The CHMP requested the applicant to provide the data when available, as stated in section 2.4.5.

Absorption

Studies on absorption are not applicable since elosulfase alfa is administered intravenously.

Distribution

The mean Vdss for elosulfase alfa in patients receiving 2 mg/kg/qw was about 650 ml/kg. Organ distribution studies were not performed. Uptake into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to the cation-independent mannose-6-phosphate receptor (CI-M6PR). Its distribution to and subsequent uptake by tissues/target cells is receptor-driven. Plasma protein binding studies are considered not applicable for elosulfase alfa, as it is a protein and thus, does not expect to significantly interact with plasma proteins.

Elimination

The elosulfase alfa plasma concentrations fell rapidly with a short mean $t_{1/2}$ of about 7.5 min at the end of infusion after the recommended dose of 2 mg/kg/qw at week 0 and of about 36 min at week 22. The clearance value was about 7.1 ml/min/kg. The rapid clearance of elosulfase alfa from plasma is consistent with the uptake of elosulfase alfa into lysosomes via CI-M6PR. Elosulfase alfa is a protein, which is considered to be degraded into small proteins and single amino acids by well-known mechanisms. As such, metabolite studies were not performed. The lack of further evaluation of the elimination of elosulfase alfa is acceptable, since this is a protein expected to be degraded similarly as any endogenous enzymes to smaller proteins and amino acids.

Dose proportionality and time dependencies

Pharmacokinetics increased more than dose proportional over the 0.1 to 2 mg/kg/qw dose range. Clearance decreased from about 10.2 ml/min/kg to 7.5 ml/min/kg, as observed in study MOR-002. Patient data indicate that at higher doses exposure increases more than dose proportional. At steady state, AUCt increased by a factor of about 3.5. This reflects saturation of uptake in lysosomes and in addition saturation in metabolism.

Considering the rapid decline in plasma levels, no accumulation is expected in case of weekly dosing. Elosulfase alfa shows time dependent pharmacokinetics, i.e. pharmacokinetics at steady state increased more than expected based upon single dose data. This is likely to be explained by saturation of uptake into lysosomes resulting in a higher systemic plasma exposure.

Special populations

With respect to the patients with impaired renal function, no data were submitted by the applicant regarding the evaluation of pharmacokinetics in patients with impaired renal function. Considering that elosulfase alfa is a protein, no clinically relevant effect of an impaired renal function is expected. Furthermore, no data were submitted regarding evaluation of pharmacokinetics in patients with impaired hepatic function. Elosulfase alfa is a protein and thus, no clinically relevant effect of an impaired hepatic function is expected.

In study MOR-004, the effect of gender on the clearance of elosulfase alfa was evaluated. Although some difference were observed at week 0 and at week 22, the differences are considered not clinically relevant. The CHMP noted that no clear gender effect on the clearance of elosulfase alfa is observed.

In study MOR-004, the effect of race on the clearance of elosulfase alfa was evaluated. Due to a limited number of subjects, only two categories of races were used in the analysis: white and non-white. At week 0, clearance appeared to be higher in white subjects than non-white subjects, but this was not observed at week 22. Thus, the CHMP concluded that after multiple dosing at week 22 at qow and qw dose, no effect of race on the clearance of elosulfase alfa is observed. The effect of body weight on the clearance of elosulfase alfa was also evaluated. At week 0, clearance appeared to decrease with increase in body weight, but this was not observed at week 22. Thus, the CHMP concluded that after multiple dosing, no effect of body weight on the clearance of elosulfase alfa can be observed. This accounts for the week 22 qow and qw dose.

The CHMP noted that no elderly patients were included in the main clinical trials. However, this is expected, since most patients diagnosed with Morquio disease may not reach the age above 60 years. Nevertheless, study MOR-004 evaluated the effect of age on the clearance of elosulfase alfa. At week 0, clearance appeared to decrease with age increase, but this was not observed at week 22. Importantly, after multiple dosing, no effect of age on the clearance of elosulfase alfa is observed. This accounts at week 22 for the qow and qw dose.

Overall, after multiple dosing, at week 22 for the qow and qw dose, no effect of gender, age, body weight and race (white *vs* non-white) on the clearance of elosulfase alfa is observed.

Pharmacokinetic interaction studies

No PK interaction studies have been conducted. The lack of *in-vitro* and *in-vivo* interaction studies would usually be acceptable for a compound similar to an endogenous protein, but the mechanism of action for elosulfase alfa requires an appropriate lysosomal pH, as already discussed in the chapter on Non-clinical aspects. However, as stated by the applicant, the development of an assay in primary human chondrocytes for *in vitro* characterization of elosulfase alfa activity was not successful. In addition, *in vitro* assessments may not be reflective of *in vivo* changes involving tissue and cellular distribution.

Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been conducted.

2.4.3. Pharmacodynamics

Elosulfase alfa is taken up to the cells by cation-independent mannose-6-phosphate receptors, and hydrolyses the sulphate ester bonds from N-acetyl-galactosamine-6-sulphate or galactose-6-sulphate on the non-reducing ends of KS. Elosulfase alfa does not cleave sulphate groups internal to GAG chains and thus, cannot further degrade GAGs without the participation of all enzymes in the degradation pathway. Elosulfase alfa has a narrow pH optimum between pH 4.8 and 5.3 for enzyme activity and shows no enzymatic activity at neutral pH. Elosulfase alfa is not anticipated to degrade other GAGs or KS outside of the lysosomal compartment due to its lack of activity at neutral pH, its targeted delivery to the lysosomal compartment, and its substrate specificity.

Mechanism of action

In the absence of a relevant disease model for MPS IVA, the pharmacological activity of elosulfase alfa was evaluated *in vitro* in primary human Morquio chondrocytes and a Morquio fibroblast cell line. Elosulfase alfa cellular uptake, trafficking to the lysosomal compartment, and pharmacological activity were confirmed in primary human Morquio chondrocytes. Internalisation of elosulfase alfa was confirmed within *in vitro* studies in human Morquio fibroblasts. In human Morquio fibroblasts, the intracellular t½ was estimated to be 5 to 7 days in these same cells and support the every other week and weekly dosing regimens used in the Phase 3 studies. The distribution of elosulfase alfa to MPS IVA target tissues (growth plate, liver, and heart valves) and its subsequent trafficking to the lysosomal compartment was demonstrated in BALB/c wild-type mice after single or repeat dose bolus IV injections of elosulfase alfa *via* the tail vein.

Overall, the *in vitro* studies in patient chondrocytes demonstrated that elosulfase alfa is transported from outside the cell into the lysosome. In the lysosome, the accumulation of keratan sulfate was cleared. At a higher dose, elosulfase alfa was able to restore the expression of at least some of the chondrogenic genes. The mechanism of action of elosulfase alfa is considered adequately established.

Primary and Secondary pharmacology

Pharmacodynamic effects of elosulfase alfa in humans were estimated by measuring urine KS as a marker of biologic effect. Urine KS levels decreased rapidly in all 5 studies (MOR-002/MOR-100, MOR-004/MOR-005, MOR-007) following treatment with elosulfase alfa, and these decreases were sustained throughout the duration of each study or at data cut-off in on-going trials. The data indicate that elosulfase alfa is capable of breaking down accumulated KS. In study MOR-004, treatment with elosulfase alfa led to a rapid and sustained reduction of urine KS in both treatment arms at week 24. In the extension study MOR-005, an additional 24 weeks of treatment sustained the reduction in urine KS. Sensitivity analyses performed on the PP population up to week 48 yielded results consistent with those described for the ITT population. In study MOR-002, elosulfase alfa for 72 to 84 weeks resulted in decreases in urine KS levels, which were generally sustained through the extension MOR-100 in which all participants are receiving 2.0 mg/kg/qw. In study MOR-007 in children < 5 years of age mean normalised urine

KS values showed a comparable decline as observed in older children and adults. No dedicated secondary pharmacology studies were conducted, which is acceptable for an endogenous protein-like compound.

2.4.4. Discussion on clinical pharmacology

With respect to the pharmacokinetic profile of elosulfase alfa, the pharmacokinetic data are adequate for this application given that pharmacokinetic data are of limited value to predict efficacy and safety of this product.

The mechanism of action of elosulfase alfa is adequately established. Enzyme replacement therapy has been used successfully to treat lysosomal storage disorders by administering the enzyme systemically and by promoting the uptake into appropriate cells and tissues through specific targeting mechanisms. Elosulfase alfa is intended to provide exogenous N-acetylgalactosamine-6-sulphatase.

Pharmacodynamic effects of elosulfase alfa in humans were estimated by measuring urine KS as a marker of biologic effect; the glycosaminoglycan KS is normally degraded by N-acetylgalactosamine-6-sulphatase. Urine KS decreased rapidly in all 5 studies and these decreases were sustained throughout studies. The data indicate that elosulfase alfa is capable of breaking down accumulated KS. However, the relationship of urinary KS to other measures of clinical response remains to be established in clinical practice. The data support the use of elosulfase alfa at 2.0 mg/kg/qw.

No data on secondary pharmacology, drug-drug or drug-disease interaction, or on genetic differences in pharmacodynamic response have been provided, which is acceptable for a compound alike to an endogenous protein.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered the provided non-clinical and clinical data adequate to support the marketing authorisation application for Vimizim. Pharmacodynamic studies in patient chondrocytes demonstrated that elosulfase afa is transported from outside the cell into the lysosome. In the lysosome the accumulation of keratan sulfate was cleared. In patients suffering from MPS IVA elosulfase alfa is able to decrease the urine keratan sulfate, suggesting the clearance of the accumulated keratan sulfate from the lysosomes. This can be considered a proof of concept. The clinical relevance of this effect remains to be demonstrated in clinical practice.

The CHMP considers the following measures necessary to address issues related to clinical pharmacokinetics:

Area	Number	Description	Classification	Due date
Clinical pharmacokinetics	001	Long term stability evaluation of N-acetylgalactosamine-6-sulfatase in plasma is on-going to address the storage integrity of the remaining fifty samples stored at -35 to -45°C for approximately 105 days and -60 to -80°C for approximately 82 days and ninety-five samples at -60 to -80°C for longer	REC	30 September 2014

		periods. The applicant should submit these results if available.		

2.5. Clinical efficacy

The applicant provided data from six clinical studies, as listed in section 2.4.1: two studies have been completed (MOR-002; MOR-004) and four are on-going (MOR-100; MOR-005; MOR-007; MOR-008). For MOR-008 only safety results have been included due to limited exposure at time of data cut-off. Another on-going phase 2 study, MOR-006, has not been included as enrollment was on-going at the time of submission and exposure at data cut-off was very limited.

The pivotal trial for this application is the phase 3 study MOR-004, initiated January 2011 and completed August 2012; patients who completed this trial were given the opportunity to enroll in extension study MOR-005 initiated July 2011.

The applicant has also initiated a natural history study MOR-001 or MorCAP and data from the first visit of 325 patients have been included in the application at the time of submission. The population is estimated to include approximately 10% of the global MPS IVA patient population.

2.5.1. Dose response study

Doses of elosulfase alfa for the pivotal trial were selected based on the results of study MOR-002, a dose-escalation study conducted in 20 patients aged 5 to 18 years, as well as on the results of the non-clinical and *in vitro* studies with elosulfase alfa. Clinical and non-clinical data reported for other ERTs were also considered.

In study MOR-002, endurance as measured by 6MWT declined at weeks 6, 12, and 18 (0.1 mg/kg/qw), while the 6MWT distance increased at weeks 24 (1.0 mg/kg/qw) and 36 (2.0 mg/kg/qw) with mean changes from baseline (± SD) of about 16 m (72) and 14 m (63), respectively. After decreasing the dose to 1.0 mg/kg/qw in the continuation period, the mean changes from baseline (± SD) at weeks 48 and 72 were -5 m (65) and 4 m (87), respectively. The median changes from baseline in 6MWT at weeks 12, 24, 36, 48 and 72 were -1 m, 34 m, 18 m, 0 m, and 0.5 m, respectively. Mean changes from baseline (± SD) in the 3MSCT were 0 stairs/min (14) at week 12, 6 stairs/min (9) at week 24, 8 stairs/min (14) at week 36, and 10 stairs/min (14) at week 72. The median changes from baseline in 3MSCT at weeks 12, 24, 36, 48 and 72 were 1 stairs/min, 2 stairs/min, 6 stairs/min, 6 stairs/min, and 2 stairs/min, respectively. The mean percent changes from baseline (± SD) in FVC were 3% (11) at week 12, 0% (17) at week 24, 11% (21) at week 36, and 13% (15) at week 72. The median percent changes from baseline in FVC at weeks 12, 24, 36, and 72 were 3%, 0%, 11%, and 14%, respectively. Mean changes from baseline (± SD) in normalised urine KS were -7 µg/mg (7) at week 12, -9 µg/mg (8) at week 24, -13 µg/mg (9) at week 36, and -10 µg/mg (7) at week 72. The median changes from baseline in normalised urine KS at weeks 12, 24, 36, and 72 were -7 µg/mg, -9 µg/mg, -13 µg/mg, and -8 µg/mg, respectively. Mean and median changes from baseline in urine KS increased again in patients continuing treatment in the extension trial MOR-100 at a dose of 2.0 mg/kg/qw instead of 1.0 mg/kg/qw used from week 36 onwards in the base

study MOR-002. Mean and median changes from baseline in normalised urine KS were -14 µg/mg at weeks 24 and 60 with standard deviations of the mean of 8 and 11 µg/mg, respectively, supporting the hypothesis that urine KS reduction is more closely related to dose than to time on treatment.

Overall, although many efficacy measures showed improvements in median values from baseline at the end of the 1.0 mg/kg/qw dose interval (week 24), the data appear to be in favour of the 2.0 mg/kg/qw dose.

Although the CHMP acknowledged that the results of study MOR-002 are heterogeneous and interpretation is limited by the dose-escalating design, it is agreed that overall, the available data appear to be in favour of the 2.0 mg/kg/qw dose and the rational for including an alternative dose of 2.0 mg/kg/qow into the pivotal trial MOR-004 is agreed.

2.5.2. Main study

The main clinical efficacy and safety data are derived from the pivotal trial, MOR-004, titled *"A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/qw and 2.0 mg/kg/every other* week elosulfase alfa *in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).*" The trial was conducted between January 2011 and August 2012 by 34 principal investigators at 33 study centres in Argentina, Brazil, Canada, Colombia, Denmark, France, Germany, Italy, Japan, Portugal, Qatar, Saudi Arabia, South Korea, Taiwan, Netherlands, the United Kingdom, and the United States of America. Participants who completed this trial were eligible to continue treatment in the currently ongoing extension study MOR-005. Thus, the following sections of this report will discuss the conduct and results of this clinical trial.

Title of Study

MOR-004: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/qw and 2.0 mg/kg/every other week elosulfase alfa in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).

Methods

Study Participants

The study included participants $\geq$ 5 years of age, with documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte N-acetylgalactosamine 6 sulfatase enzyme activity or genetic testing confirming diagnosis of MPS IVA; had an average Screening 6MWT distance ≥ 30 and ≤ 325 meters; were willing to use an acceptable method of contraception during the study (if sexually active); were expected to be able to comply with the treatment schedule; and had never received hematopoietic stem cell transplant or had major surgery within 3 months of study entry. The CHMP was of the opinion that the included patient population is characteristic for a population of patients suffering from Morquio disease.

Treatments

Subjects randomised to the active drug treatment arms in study MOR-004 received intravenous (IV) infusions of elosulfase alfa at a dose of either 2.0 mg/kg/week or 2.0 mg/kg/qow. Subjects randomised to the 2.0 mg/kg/qow arm received infusions of placebo on alternating weeks, to mask active drug weeks. The CHMP noted that the treatment duration is relatively short and thus, only acute effects can be expected to be observed. Long-term efficacy and maintenance of effect cannot be assessed using this pivotal study.

Objectives

The primary objective of MOR-004 study was to evaluate the ability of 2.0 mg/kg/week and 2.0 mg/kg/ every other week (qow) elosulfase alfa, compared with placebo, to enhance endurance in subjects with mucopolysaccharidosis IVA, as measured by increase in meters walked in the 6-minute walk test (6MWT) from Baseline to Week 24.

The secondary objectives of the study were the following:

- to evaluate the ability of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, to enhance endurance in subjects with MPS IVA, as measured by increase in stairs climbed per minute in the 3-minute stair climb test (3MSCT) from Baseline to Week 24.
- to evaluate the ability of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, to reduce normalized urine keratan sulfate levels in subjects with MPS IVA, as measured by decrease in urine keratan sulfate levels from Baseline to Week 24.

The tertiary objectives of the study were:

- to determine the PK parameters of 2.0 mg/kg/week elosulfase alfa and 2.0 mg/kg/qow elosulfase alfa administered IV in a subset of subjects with MPS IVA.
- to evaluate the ability of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, to improve respiratory function as measured by percentage increase in pulmonary function tests from Baseline to Week 24.
- to evaluate the effect of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, on biochemical markers of inflammation and bone and cartilage metabolism.
- to evaluate the effect of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, on quality of life as assessed by the MPS HAQ.
- to evaluate the effect of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, on hearing as measured by audiometry.
- to evaluate the effect of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, on cardiac valve function as measured by echocardiogram (ECHO).
- to evaluate the effect of 2.0 mg/kg/week and 2.0 mg/kg/qow elosulfase alfa, compared with placebo, on corneal clouding as assessed by physical examination.

The safety objective of the study was to evaluate the safety and tolerability of elosulfase alfa infusions, at doses of 2.0 mg/kg/week and 2.0 mg/kg/qow, over a 24-week period.

The CHMP considered that the whole set of the objectives is acceptable to aim for determining a reasonable impression of the short-term effects of elosulfase alfa in the indicated patient group.

Outcomes/endpoints

The evaluation criteria for efficacy, safety, and pharmacokinetics in MOR-004 were as follows:

Efficacy:

- endurance tests (6MWT, 3MSCT)
- urine keratan sulfate concentration (normalized to creatinine)
- various respiratory function tests
- MPS Health Assessment Questionnaire
- blood inflammatory biomarkers
- blood biochemical markers of bone and cartilage metabolism
- anthropometric measurements (standing height, length, sitting height, and weight)
- skeletal radiographs of lumbar spine and lower extremity (lower extremity radiographs only in subjects ≤ 20 years of age)
- audiometry examinations
- echocardiogram
- corneal clouding

Pharmacokinetics:

- area under the plasma concentration time curve from time 0 to infinity (AUC0-∞)
- area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC0-t)
- maximum observed plasma concentration (Cmax)
- time to reach Cmax (Tmax)
- elimination half life (t1/2)
- total clearance of drug after intravenous administration (CL)
- apparent volume of distribution based upon the terminal phase (Vdz)
- apparent volume of distribution at steady state (Vdss)

Safety:

- AEs
- standard clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- pregnancy tests
- vital signs
- ECGs
- routine physical examinations (including standard neurologic examinations)
- concomitant medications
- immunogenicity tests: elosulfase alfa -specific total antibody (TAb), elosulfase alfa -specific neutralizing antibodies that inhibit cellular receptor binding (NAb), drug-specific immunoglobulin E (IgE).
- demographic data (for comparison with on-study safety data)
- medical history (for comparison with on-study safety data
- other lab assessments for subjects who experienced a serious adverse event

Sample size

It was calculated that in study MOR-004, approximately 162 patients were to be enrolled, 54 per treatment group, to have over 90% power for the primary analysis to detect a difference of 40 meters in mean change in the 6MWT distance between the active treatment groups and the placebo group, assuming that the common standard deviation was 65 meters with an overall 0.05 two-sided significance level with Hochberg method for multiplicity adjustment. The standard deviation of 65 meters was considered conservative compared to the standard deviation associated with the similar population subset found in the MOR-002 study (45 to 61 meters at weeks 24 through 48).

Randomisation

In study MOR-004, subjects were randomized (1:1:1) for 24 consecutive weeks to one of three treatment groups:

- elosulfase alfa 2.0 mg/kg/week, or
- elosulfase alfa 2.0 mg/kg/qow and placebo infusions on alternate weeks, or
- placebo

Blinding (masking)

Patients, investigators, and site personnel were blinded to treatment assignment throughout the study and until the final analysis was complete. The randomisation schedule was developed by an independent third party to ensure blinding. Elosulfase alfa and placebo were identical in appearance and the placebo solution consisted of the same excipients included in the elosulfase alfa formulation. Study drugs were labelled with the study number and a unique identification number. For unblinding in cases of serious or life-threatening AEs formal written approval of the applicant's medical monitor was required.

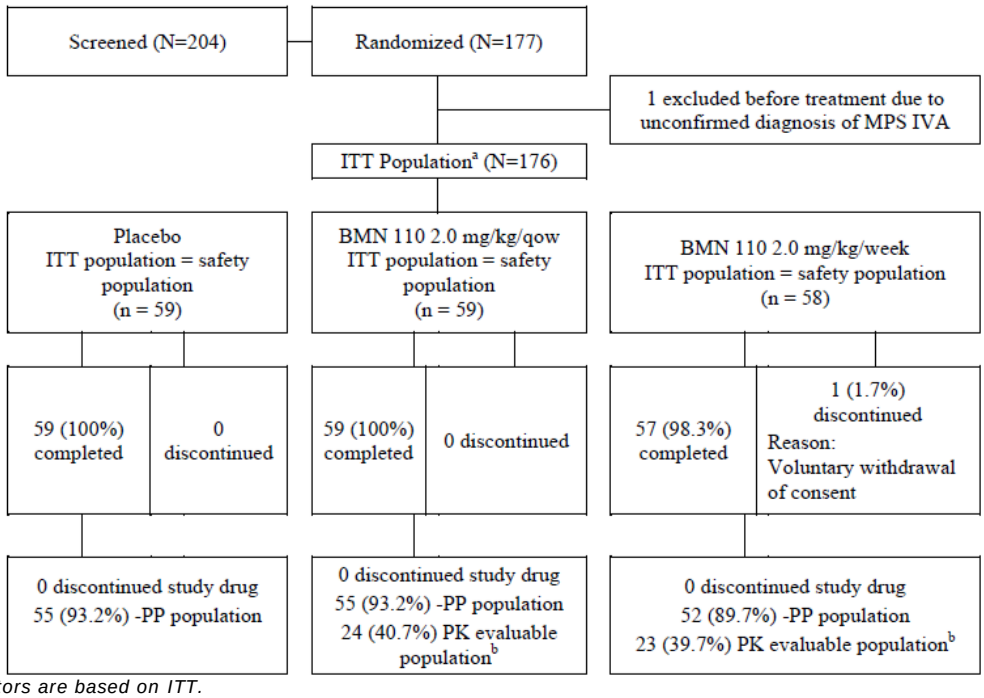
Statistical methods

The primary analysis change in 6MWT between active treatment and placebo was compared using an analysis of covariance model with baseline 6MWT distance and age group as covariates; the Hochberg method was be used for multiplicity adjustment to maintain the overall type I error rate of 0.05. In addition, a repeated measure model and a responder analysis were used as supportive analyses methods together with several sensitivity analyses. The secondary endpoints (number of stairs climbed per minute in the 3MSCT and normalized urine KS were analysed similarly. The averages of duplicate 6MW test and 3MSCT results at screening were used as the baseline values. The statistical analyses for tertiary endpoints were descriptive. The PK parameters were evaluated by non-compartmental methods using nominal dose levels, actual infusion duration, and blood sampling times for all calculations.

The statistical methods were considered adequate and in line with the CHMP protocol assistance.

Results

Participant flow



Denominators are based on ITT.
PK samples were drawn from a subset of 65 patients from selected sites.
Qow: every other week; PP: per-protocol; ITT: intent-to-treat
[a] *ITT population with no important protocol deviations.*
[b] *All placebo patients PK parameters were not estimable. An elosulfase alfa 2.0 mg/kg/qw patient (1024-4033) had only one PK sample, a predose sample at week 0, hence had no estimable PK parameters.*

Recruitment

The trial was conducted between 01 February 2011 (first patient enrolled) and 16 August 2012 (last dose given). Patients who completed the trial were eligible to enroll into extension study MOR-005 initiated July 2011.

The study protocol was originally approved on 10 June 2010 and amended once on 04 October 2010 prior to the start of the trial; all patients were enrolled after this amendment. The amendment concerned the incorporation of a third treatment arm of 2.0 mg/kg/qow in order to evaluate a dose level and regimen with a lower cumulative exposure and more convenience for patients, possibly leading to improved patient compliance.

Based on scientific advice received from CHMP on 31 May 2012 and Type C meeting feedback received from FDA on 09 July 2012 regarding the proposed statistical analyses, the applicant modified several of the analysis methods, and documented the final analysis methods in the Statistical Analysis Plan prior to data unblinding on 19 October 2012. No unscheduled unblindings occurred during the study. The proportion of patients with at least one major deviation and the categories of deviations seen were similar across treatment groups. The most common deviation category pertained to “out of window” infusion times, which was almost exclusively infusion rate escalations of less than 13 minutes’ duration (27.1% placebo, 25.4% elosulfase alfa 2.0 mg/kg/qow, 25.9% elosulfase alfa 2.0 mg/kg/qw). Upon clinical review, it was concluded that these protocol deviations did not impact the rights, safety, or welfare of the patients or the integrity of the data.

Baseline data

There were no relevant differences between groups in demographic baseline characteristics; patients in the elosulfase alfa 2.0 mg/kg/qw group were slightly younger than in the other groups with a higher percentage in the 5 to 11 years age group. Baseline disease characteristics were similarly distributed across treatment groups, but the 6MWT distance at baseline was higher in the placebo group compared to both elosulfase alfa groups. The proportion of patients with the stratification factor 6MWT ≤ 200 m and > 200 m was balanced. The number of stairs climbed per minute in the 3MSCT at baseline was lower in the elosulfase alfa qow group than in the placebo or elosulfase alfa qw group, while it was comparable between placebo and elosulfase alfa qw groups. Also the proportion of patients who used walking aids at baseline was higher in the elosulfase alfa qow group compared to placebo or elosulfase alfa qw. Medical history findings were similarly distributed across groups. Prior medication use of glucocorticoids was higher in the placebo group compared to both elosulfase alfa groups. Compliance was high throughout the trial, with similar mean number of infusions and mean number of incomplete infusions.

Numbers analysed

The ITT population consisted of all patients randomised and who received at least one dose of study drug. The primary efficacy analyses for all efficacy endpoints were based on the ITT population and data were analysed according to the treatment assigned at randomisation. The PP population was used to perform sensitivity analyses for the primary, secondary, composite, and MVV endpoints. The PP population was defined as the subset of the ITT population who were compliant with the protocol. The PP populations (% of ITT) were 55 (93.2%) in the placebo, 55 (93.2%) in the elosulfase alfa 2.0 mg/kg/qow, and 52 (89.7%) in the elosulfase alfa 2.0 mg/kg/qw group. Please see figure above. The number of patients excluded from the PP analysis was comparable between treatment groups.

Outcomes and estimation

Primary endpoint

In the elosulfase alfa 2.0 mg/kg/qw dosing group, a statistically significant mean change from baseline to week 24 in the 6MWT distance compared with placebo occurred; the change from baseline was not statistically different from placebo in the 2.0 mg/kg/qow group. The model based estimated treatment effect at week 24 compared with placebo was 22.5 m (95%CI: 4.0, 40.9; p = 0.0174) for the 2.0 mg/kg/qw regimen and 0.5 m (95%CI: -17.8, 18.9; p = 0.9542) for the 2.0 mg/kg/qow regimen. The effect was already evident at week 12 in the elosulfase alfa 2.0 mg/kg/qw dosing group; the mean changes from baseline (±SD) at week 12 were 23.7 m (42.2), 13.5 m (38.4), and 12.7 m (35.8) for the elosulfase alfa 2.0 mg qw, elosulfase alfa 2.0 mg qow, and placebo group, respectively. Results for the PP population were similar to those for the ITT population.

Primary Efficacy Analysis Mean Absolute Change from Baseline in 6MWT at Week 24 (ITT Population)

	BMN 110 2.0 mg/kg/qow[a] vs Placebo	BMN 110 2.0 mg/kg/week vs Placebo
Observed Treatment Effect[b] (Observed Case)		
n	58	57
Mean Difference (meters)	1.4	23.0
95% CI	(-15.5,18.3)	(2.9,43.1)
Observed Treatment Effect[b]		
n	59	58
Mean Difference (meters)	0.7	22.5
95% CI	(-16.1,17.5)	(2.6,42.5)
Modeled[c] Treatment Effect[b]		
n	59	58
LS Mean Difference (meters)	0.5	22.5
95% CI	(-17.8, 18.9)	(4.0, 40.9)
p-value[d]	0.9542	0.0174

[a] qow, every other week

[b] Treatment effect defined as: (change from Baseline to week 24, BMN 110) - (change from Baseline to Week 24, Placebo)

[c] ANCOVA model (primary end point analysis), adjusted for baseline covariates: age group and 6MWT category

[d] P-value determined by t-test from ANCOVA model

LS Mean, least squares mean

Number and proportion of patients who did not complete 1 of the duplicate tests at baseline or week 24 were low and comparable across groups. The proportion of patients who used walking aids during the 6MWT at any measurement was highest in the elosulfase alfa 2.0 mg/kg qow group (≈27%), compared with weekly dosing (≈16%), and placebo (≈19%).

A repeated-measures ANCOVA analysis supported the week 24 findings of the primary analysis. An improvement in walking distance was seen at week 12 in all groups, at which time point improvement in the placebo and elosulfase alfa 2.0 mg/kg/qow groups stabilised at a similar level. Results for the PP population were similar to those for the ITT population. A responder analysis of the estimated cumulative distribution function showed a clear separation of the weekly treatment group from the placebo group across various response thresholds, while the results for the elosulfase alfa every other week group were similar to placebo. In addition results of pre-specified supportive analyses, sensitivity analyses, and subgroup analyses were consistent with the primary analysis.

Part of the difference in treatment response between the two elosulfase alfa dosing groups as measured by the 6MWT might be attributable to the difference in the proportion of patients using walking aids during the 6MWT at any measurement; this was about 27% in the elosulfase alfa every other week group, compared to about 16% with weekly dosing, and about 19% in the placebo group. This does not question the effect of elosulfase alfa 2.0 mg/kg every week in patients with MPS IVA compared to placebo but might have led to a false negative effect in the every other week group. On the other hand the responder analysis showed a clear separation of the elosulfase alfa weekly treatment group from the placebo group across various response thresholds, while for the elosulfase alfa every other week group results were comparable to placebo.

Overall, the available data show a statistically significant and clinically relevant effect of elosulfase alfa once a week on the distance walked in the 6MWT compared to placebo, while the effects of elosulfase alfa every other week on the primary endpoint are more difficult to interpret.

Secondary endpoints

3-Minute Stair-Climb Test

The 3MSCT at week 24 compared to baseline was only slightly and not statistically significantly improved in the elosulfase alfa 2.0 mg/kg/qw group (4.8 stairs/min [25.7%]); the difference to placebo was 3.6 stairs/min (11.4%). No difference compared to placebo at week 24 was observed in the elosulfase alfa 2.0 mg/kg/qow group. At week 12 improvement in the 3MSCT was higher in both elosulfase alfa groups compared to placebo [placebo 2.9 stairs/min (10.1%), elosulfase alfa qow 3.6 stairs/min (22.7%), elosulfase alfa qw 3.6 stairs/min (16.6%)] with further improvement at week 24 for the elosulfase alfa once a week group. The number and proportion of patients who did not perform one or both of the duplicate tests at baseline or week 24 were low and similar across groups. In the placebo group, the same 3 patients (5.1%) did not perform both baseline and both week 24 tests, in the elosulfase alfa every other week group 1 patient (1.7%) did not perform both baseline tests and a different patient did not perform both week 24 tests, and in the elosulfase alfa once a week group 3 patients (5.2%) did not perform both baseline tests, and 2 of these (3.4%) did not perform both week 24 tests while the third patient did not perform the early termination test. In all cases the reported reason was that the patients were physically unable to perform. The model based estimated treatment effects at week 24 compared with placebo were 1.1 stairs/min (95%CI: -2.1, 4.4; p = 0.4935) for the 2.0 mg/kg/qw regimen and -0.5 stairs/min (95%CI: -3.7, 2.8; p = 0.7783) for the 2.0 mg/kg/qow regimen. Results for the per protocol population were similar.

Urine keratan sulfate

The mean change and mean percent change in the reduction of urine KS from Baseline to Week 24 were both greater in the elosulfase alfa treatment groups compared with placebo. Mean changes (±SD) in the ITT population from Baseline at Week 24 were -2.8 µg/mg (±8.0) for placebo, -12.2 µg/mg (±16.3) for elosulfase alfa 2.0 mg/kg/qow, and -12.6 µg/mg (±9.5) for elosulfase alfa 2.0 mg/kg/week. Treatment with elosulfase alfa led to a rapid, sustained, and dose-dependent reduction of urine KS with both elosulfase alfa treatment regimes.

Tertiary endpoints

As regards the tertiary endpoints, treatment with elosulfase alfa led to a not statistically significant improvement in the Maximum Voluntary Ventilation (MVV) percent change from baseline compared with placebo at week 24 of about 10% in the elosulfase alfa once a week and about 3% in the every other week group; these results were supported by responder analyses. A z-score of a composite measure comprising 6MWT, 3MSCT, and MVV showed a positive treatment effect compared with placebo at week 24 for the elosulfase alfa once a week group and none in the every other week group, thus supporting the efficacy of elosulfase alfa once a week in patients with MPS IVA. The proportions of patients with improvement in 2 or more measures were about 16%, 30%, and 42% and the proportions of patients with improvement in 3 measures were about 0%, 2%, and 10% in the placebo and elosulfase alfa every other week and once a week groups, respectively. Treatment with elosulfase alfa led to a small numerical improvement in the Forced Vital Capacity (FVC) per cent change from baseline compared to placebo at week 24, while the effect on Forced Expiratory Volume in 1 Second (FEV_1), Forced

Inspiratory Vital Capacity (FIVC), and Forced Expiratory Time (FET) are considered negligible. Treatment with elosulfase alfa did not lead to statistically significant changes from baseline in the Self Care Domain, the Caregiver Assistance Domain, or the Mobility Domain score compared with placebo at week 24. In post-hoc analyses of the MPS HAQ to assess questions about wheelchair or walking aid use yes or no, 6, 3, and 2, patients in the placebo, elosulfase alfa every other week, and once a week groups, respectively, subsequently required a wheelchair at week 24, while of those requiring a wheelchair at baseline 1, 3, and 2 patients, respectively, no longer required it at week 24; thus the number of patients using a wheelchair at week 24 increased by 5 in the placebo and 0 in both elosulfase alfa groups as compared to baseline. These differences were not seen for effects on walking aid use. Both dosing regimens had a positive treatment effect on normalised standing height and growth rate z-scores in male patients ≤ 18 years and female patients ≤ 15 years of age. No meaningful treatment effects were observed in audiometry, echocardiogram, corneal clouding, or lower extremity long bone length. elosulfase alfa treatment was not associated with reduction of TNFα or change in PIIANP or CTX1 levels.

Ancillary analyses

Safety analyses

None of the 176 subjects who initiated dosing in this trial withdrew or discontinued treatment due to an AE and >99% of subjects completed the study. The mean (±SD) total duration of elosulfase alfa exposure was 24.00 (±0.188) weeks for the 2.0 mg/kg/qow regimen and 23.57 (±3.029) weeks for the 2.0 mg/kg/week regimen and few infusions were missed (<2%). Nearly all subjects reported at least one treatment-emergent AE while on study. The most common System Organ Classes (SOCs) for AEs in elosulfase alfa -treated subjects were infections and infestations (66.1% placebo, 71.2% elosulfase alfa 2.0 mg/kg/qow, and 67.2% elosulfase alfa 2.0 mg/kg/week), general disorders and administration site conditions (62.7%, 67.8%, 65.5%), and gastrointestinal disorders (69.5%, 67.8%, 63.8%). Most AEs were mild to moderate in severity. Study drug-related AEs occurred in 61.0% placebo, 71.2% elosulfase alfa 2.0 mg/kg/qow, and 72.4% elosulfase alfa 2.0 mg/kg/week-treated subjects. The most common drug-related AEs in the placebo, elosulfase alfa 2.0 mg/kg/qow, and elosulfase alfa 2.0 mg/kg/week treated subjects, respectively, included pyrexia, vomiting, headache and nausea, and were mild to moderate. Most subjects experienced at least one infusion associated reaction (IAR), (91.5% placebo, 94.9% elosulfase alfa 2.0 mg/kg/qow, 89.7% elosulfase alfa 2.0 mg/kg/week). Most IARs were mild to moderate in severity. Further safety analyses are discussed in section 2.6.

Summary of main study

The following table summarises the efficacy results from the main study MOR-004 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial MOR-004

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0 mg/kg/every other week elosulfase alfa in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

Study identifier	MOR-004		
Design	Phase 3, randomised, double-blind, placebo-controlled, two dose, multinational trial in patients with MPS IVA		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable Extension was conducted as a separate clinical trial (MOR-005)
Hypothesis	Superiority of elosulfase alfa over placebo at week 24		
Treatments groups	elosulfase alfa 2.0 mg/kg/qw		58 randomized, 57 treated, 1 discontinuation
	elosulfase alfa 2.0 mg/kg/qow		59 randomized, 59 treated, 0 discontinuation
	Placebo		59 randomized, 59 treated, 0 discontinuation
Endpoints and definitions	Primary endpoint	6MWT	change in 6MWT distance from baseline to week 24 compared to placebo
	Secondary:	3MSCT	change from baseline to week 24 in numbers of stairs climbed in the 3MSCT compared to placebo
	Secondary:	urine KS	change in normalised urine KS (KS) concentration from baseline to week 24 compared to placebo
	Tertiary:	RFT	change in respiratory function tests (FET, FEV1, FIVC, FVC, MVV) from baseline to week 24 compared to placebo
	Tertiary:	MPS HAQ	change in MPS Health Assessment Questionnaire (MPS HAQ) from baseline to week24 compared to placebo
	Tertiary:		change in blood inflammatory biomarkers from baseline to week24 compared to placebo
	Tertiary:		change in blood biochemical markers of bone and cartilage metabolism from baseline to week24 compared to placebo
	Tertiary:		change in anthropometrics measurements (standing height, length, sitting height, and weight), from baseline to week24 compared to placebo
	Tertiary:		change in audiometry examinations from baseline to week24 compared to placebo
	Tertiary:		change in echocardiograms from baseline to week24 compared to placebo
	Tertiary:		change in corneal clouding from baseline to week24 compared to placebo
	Tertiary:		change in skeletal radiographs of lumbar spine and lower extremity (lower extremity radiographs only ≤ 20 years of age) from baseline to week24 compared to placebo
	Tertiary:	PK substudy	change in pharmacokinetic parameters from baseline to week24, subset of patients, selected sites

Database lock	Not identified in CSR, last dose given 16 August 2012, date of study report 11 March 2013			
Results and Analysis				
Analysis description	**Primary Analysis 6MWT**			
Analysis population and time point description	Intent to treat, week 24			
Descriptive statistics and estimate variability	**Treatment group**	**elosulfase alfa 2.0 mg/kg/qw**	**elosulfase alfa 2.0 mg/kg/qow**	**Placebo**
	Number of patient	57	58	59
	Mean change from baseline 6MWT (meter)	36.5	14.9	13.5
	± SD	58.5	40.8	50.6
	Median change from baseline 6MWT (meter)	20.0	16.1	9.9
	Min, Max 6MWT (meter)	-57.8, 228.7	-105.9, 114.2	-99.2, 220.5
Effect estimate per comparison	**Primary endpoint**	**elosulfase alfa 2.0 mg/kg/qw**	**elosulfase alfa 2.0 mg/kg/qow**	
	Observed Treatment Effect (Observed Case)			
	n	57	58	
	Mean Difference 6MWT (meter)	23.0	1.4	
	95% CI	2.9, 43.1	-15.5, 18.3	
	Observed Treatment Effect			
	n	58	59	
	Mean Difference 6MWT (meter)	22.5	0.7	
	95% CI	2.6, 42.5	-16.1, 17.5	
	Modelled Treatment Effect (ANCOVA model (primary end point analysis), adjusted for baseline covariates: age group and 6MWT category)			
	n	58	59	
	Least Squares Mean Difference 6MWT (meter)	22.5	0.5	
	95% CI	4.0, 40.9	-17.8, 18.9	
	p-value	0.0174	0.9542	
Analysis description	**Secondary analysis 3MSCT**			
Descriptive statistics and estimate variability	**Treatment group**	**elosulfase alfa 2.0 mg/kg/qw**	**elosulfase alfa 2.0 mg/kg/qow**	**Placebo**
	Number of patient	57	58	59

	Mean change from baseline 3MSCT (stairs/min)	4.8	3.4	3.6
	± SD	8.1	10.2	8.5
	Median change from baseline 3MSCT (stairs/min)	4.3	1.6	0.9
	Min, Max 3MSCT (stairs/min)	-12.4, 20.5	-19.3, 45.8	-13.0, 32.4

Effect estimate per comparison	**Secondary endpoint**	**elosulfase alfa 2.0 mg/kg/qw**	**elosulfase alfa 2.0 mg/kg/qow**
	Observed Treatment Effect (Observed Case)		
	n	57	58
	Mean Difference 3MSCT (stairs/min)	1.1	-0.2
	95% CI	-1.9, 4.2	-3.7, 3.2
	Observed Treatment Effect		
	n	58	59
	Mean Difference 3MSCT (stairs/min)	1.1	-0.4
	95% CI	-1.9, 4.1	-3.9, 3.0
	Modelled Treatment Effect (ANCOVA model (primary end point analysis), adjusted for baseline covariates: age group and 6MWT category)		
	n	58	59
	Least Squares Mean Difference 3MSCT (stairs/min)	1.1	-0.5
	95% CI	-2.1, 4.4	-3.7, 2.8
	p-value	0.4935	0.7783

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

At the time of application for marketing authorisation, only the phase 1/2 trial MOR-002 and the pivotal trial MOR-004 were finalised and thus, a comparison of efficacy results across trials is limited. Data were summarised for the phase 1/2 study MOR-002 and its extension MOR-100, as well as the phase 3 study MOR-004 and its extension MOR-005. Because of the differences in trial design, patient populations, study drug dosage, and exposure between the phase 1/2 programme and the phase 3 programme, efficacy data from studies MOR-002 and MOR-100 was not integrated with data from trials MOR-004 and MOR-005. The integrated analyses for the pairs of parent and extension studies have been reported in the CSR's of the relevant extension studies MOR-005 and MOR-100, as discussed below in section on Supportive studies.

Clinical studies in special populations

Initially, it was reported that the number of subjects using a wheelchair at Week 24 increased by 5 (8.8%) in the placebo group, and 0 (0%) in both elosulfase alfa treatment groups. In response

to the CHMP's major objection posed during the assessment, additional data on QoL and clinical improvements were submitted, which discuss the lack of evidence for actual clinical benefit for a patient. There also appears to be a benefit in the incidence of orthopaedic surgery in favour of the elosulfase alfa treated patients. After 72 weeks treatment, about 8% of the patients on elosulfase alfa treatment and about 18% on placebo had undergone orthopaedic surgery. A further analysis of the ADL items from the Health Assessment Questionnaire (HAQ) showed some improvement after 24 weeks treatment with most notably the improved ability to dress, go to the toilet, independent eating and drinking and the ability to get on and off furniture.

Supportive studies

Study MOR-005: In this ongoing extension of study MOR-004, the proportion of patients who used walking aids at baseline was higher, about twice, in the elosulfase alfa qow group. There were also imbalances between the placebo-switch cohorts in endurance measures and age at baseline; the re-randomisation was not stratified by age or 6MWT categories. Patients switched from placebo to elosulfase alfa qow had a higher 6MWT and 3MSCT and a lower baseline urine KS level, than those switched to elosulfase alfa qw. This indicates that patients switched from placebo to the elosulfase alfa every week group had more progressed or more severe disease than those switched from placebo to the every other week group. Continued treatment with elosulfase alfa showed a further increase in 6MWT distance in the QW-QW cohort at week 36 from baseline of MOR-004, but this improvement was not maintained in the ITT population at week 48, where 6MWT distance was comparable to that of week 24. Confidence intervals were widely overlapping and only about half of the patients per treatment group reached the week 48 assessment during part 1 of study MOR-005.

In both elosulfase alfa groups, the effects on the reduction of urine KS from study MOR-004 were sustained at weeks 36 and 48 and the reduction was higher in the qw group. Evaluation of effects on respiratory function tests is limited, but the available data appear to indicate sustained effects on respiratory function. The results of anthropometric measurements suggest that the treatment effects on normalized standing height and growth rate z-scores in males ≤ 18 years and females ≤ 15 years are maintained with longer term treatment in the once a week group, but standard errors were large. Antibody development occurred in all treated patients but clinical efficacy appeared not to have been influenced by total antibody titres. In patients switched from placebo, the effect of elosulfase alfa on the 6MWT distance and on the 3MSCT was significantly more pronounced in the qow group, but this might be attributable to the differences in baseline characteristics.

In summary the available data from the ongoing extension trial MOR-005 indicate a sustained effect of elosulfase alfa 2.0 mg/kg/qw in patients with MPS IVA.

Study MOR-002: Efficacy data from study MOR-002 indicate a dose related response of elosulfase alfa. As regards the distance walked in the 6MWT, after initially declining with the lower doses of elosulfase alfa at weeks 6, 12, and 18, it increased with the elosulfase alfa 2.0 mg/kg/qw dose, but after decreasing the dose to 1.0 mg/kg/qw in the continuation period, the mean change from baseline decreased again. Similarly, in the 3MSCT, the mean stair climb rate only increased significantly with a dose of elosulfase alfa 2.0 mg/kg/qw. The mean values for most of the respiratory function tests increased from baseline during the 36-week dose-escalation period, with continued increase through the continuation period. There was a minimal change of unclear significance in the mean HAQ category scores during the course of the study.

The bone biomarker procollagen type IIA N-propeptide, a marker reflecting synthesis of type IIA collagen, increased throughout the trial, while bone specific alkaline phosphatase, osteocalcin, and PTH remained within normal limits.

Study MOR-100: In the ongoing extension of study MOR-002, study MOR-100, patients receive elosulfase alfa 2.0 mg/kg/qw. Additional 84 weeks of treatment led to sustained improvements in the 6MWT distances during the first 36 weeks, but were more heterogeneous thereafter; confidence intervals were wide at all time-points. The reduction in normalised urine KS was comparable to the effect seen with elosulfase alfa 2.0 mg/kg/qw during study MOR-002. The effects on respiratory function tests were generally maintained during study MOR-100.

Study MOR-007: In the ongoing trial MOR-007, no patient completed the 52-week primary treatment phase at the time of application. In the 8 patients who completed week 26, elosulfase alfa 2.0 mg/kg/qw led to sustained reductions in normalised urine KS.

Study MOR-001/MorCAP: A natural history study in the MPS IVA population, MorCAP / MOR-001, was ongoing at the time of submission of this MAA. The trial started in 2008. Only 325 patients were enrolled. These 325 patients were recruited from 10 countries, ranging in age from 1 to 66 years with 79% being 18 years and younger; the median age at baseline was 14.5 years. The MorCAP population is estimated to include approximately 10% of the global MPS IVA patient population, enabling characterization of symptoms and disease progression that are generalizable to all patients. The mean urine KS was higher in patients ≤ 18 years when compared to patients >18 years, which may reflect the expected decrease in cartilage formation as patients reach puberty and bone growth plates fuse.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on one pivotal trial, study MOR-004. The doses used in this trial were based on results of study MOR-002 together with non-clinical data and experiences with other medicinal products for ERTs. The results of study MOR-002 are heterogeneous and interpretation is limited by the dose-escalating design; patients receiving doses of 1.0 mg/kg or 2.0 mg/kg were not naïve to treatment. The available data are overall in favour of the 2.0 mg/kg every week dose. The rational for including an alternative dose group of 2.0 mg/kg every other week into the pivotal trial MOR-004 based on experiences with other ERTs is endorsed by the CHMP. Since there is currently no causal treatment available for patients with MPS IVA the chosen placebo comparator is adequate. The design of study MOR-004 and the inclusion and exclusion criteria to select study participants are acceptable. The chosen objectives are considered adequate to investigate efficacy and safety of elosulfase alfa in patients with MPS IVA and the selected endpoints are considered suitable for the objectives of this trial. The primary endpoint was discussed during the CHMP protocol assistance in 2012 (EMA/CHMP/SAWP/381641/2012). The discriminatory ability of the 6MWT for this patient population and whether clinically relevant differences in this parameter can be expected in a 24 weeks' time frame for this condition were questioned, but it is agreed that no other single endpoint that would be more sensitive could be identified at the present time. The proposed secondary and tertiary analyses are considered helpful in order to support the clinical relevance of elosulfase alfa efficacy.

The sample size calculation is adequate and the study population is large relative to other phase 3 studies for ERTs. The randomisation strategy and blinding were appropriate. The statistical methods are acceptable and in line with the CHMP protocol assistance in 2012 (EMA/CHMP/SAWP/381641/2012). The protocol amendments are not considered to affect the outcome of this trial in a negative way. Protocol deviations appear to be equally distributed across study groups and no critical protocol deviations have been identified. No unscheduled unblindings occurred during the trial and only 1 patient in the elosulfase alfa 2.0 mg/kg every week group discontinued the study. No patient discontinued the study drug permanently while in the trial.

The combination of study populations in the elosulfase alfa clinical development programme appears to encompass the spectrum of age and disease severity of the overall patient population diagnosed with Morquio A syndrome. More specifically, the inclusion of patients based on genetic typing as conducted in MOR-004 trial, results in an attenuated population which is more comparable with the population expected to be treated. Disease characteristics appear representative of the range of disease symptoms reported in the literature and are similar to characteristics of MPS IVA subjects in the natural history study MorCAP (MOR-001). Since study MorCAP represented approximately 10% of the overall patient population, results from the elosulfase alfa clinical studies are anticipated to be generalizable to the overall MPS IVA population. The results of the natural history study, including clinical milestones like time to wheelchair dependency or respiratory assist or corrective surgery or death, might be used as a reference population; however, this information is currently not available. The long term efficacy and safety of elosulfase alfa could not be established within the current clinical programme and remains to be confirmed in clinical practise. The CHMP was in agreement with the set-up of a disease specific registry for patients diagnosed with Morquio disease, who are treated with Vimizim.

Efficacy data and additional analyses

The results of the dose escalating study MOR-002 including PK data, urinary KS data, preliminary efficacy indicators (6MWT, 3MSCT), and various respiratory function tests suggest that the highest clinical activity lies with 2.0 mg/kg/qw elosulfase alfa. In general, the results were sustained through the extension period (study MOR-100).

Within the pivotal study MOR-004, baseline and disease characteristics were comparable between the treatment groups. A large variation was seen in the baseline levels of 6MWT, varying between 36 meters and 321 meters. This can however be expected, given the heterogeneity of the disease. Treatment with elosulfase alfa at 2 mg/kg/qw dose led to improvements in 6MWT, whereas no effect was observed at dose 2 mg/kg/qow. The mean difference with placebo in the primary endpoint 6-MWT was 22.5 meters at week 24 and this was statistically significant. The clinical relevance of this difference can be derived from the secondary parameters and additional information on clinically important events. Given the improvement in 3MSCT, MVV, wheelchair dependency, orthopaedic surgery and ADL function, the observed effect of the 6MWT can be considered clinical relevant. The reduction in urine KS observed for both dosing regimens suggests a reduction in overall accumulated body and tissue storage of KS, and indicates an activity of the enzyme on a lysosomal level.

As the disease impacts different organs, multiple clinically relevant endpoints are of importance in terms of providing further support for clinical efficacy. Overall, secondary endpoints show a trend for improvement. The results of the 3MSCT support the efficacy of weekly injections in contrast to the every other week injections. Other endpoints like respiratory function and anthropometric measures also showed an improvement with 2.0 mg/kg/qw elosulfase alfa, supporting the primary outcome. This was further supported by results of the MPS Health assessment questionnaire, although not all domains showed an improvement.

Additional analyses showed an increase in wheelchair use observed in the placebo group (n=5) that was not seen in the treated arms (n=0) at week 24. Additional data on QoL and clinical improvements indicate a benefit. Further the incidence of orthopaedic surgery is in favour of the elosulfase alfa treated patients. After 72 weeks treatment about 8% of the patients on elosulfase alfa treatment and about 18% had undergone orthopaedic surgery. A further analysis of the ADL items from the HAQ showed some improvement after 24 weeks treatment with most notably the improved ability to dress, go to the toilet, independent eating and drinking and the ability to get on and off furniture.

The long-term effects have not been demonstrated yet. Although most data suggest that the treatment-effect is sustained in the long-term, overall interpretation is hampered by the limited number of patients in the clinical trials. Given the heterogeneity of the disease severity and progression of disease, clinically relevant efficacy should be supported by sufficient data obtained over a longer period before robust conclusions on patient benefit can be drawn. Thus, the CHMP imposed a disease-specific registry to be set up and followed in the post-authorisation phase to collect such clinical results.

2.5.4. Conclusions on the clinical efficacy

Treatment of Morquio A patients with elosulfase alfa in the proposed dose regimen (2.0 mg/kg/weekly) results in a statistically significant improvement of the 6MWT, which was agreed to be the primary endpoint. This effect is supported by a trend for improvement in various secondary endpoints. A benefit appears to be present in the incidence of orthopaedic surgery in favour of the elosulfase alfa treated patients. A further analysis of the ADL items from the HAQ showed some improvement after 24 weeks treatment with most notably the improved ability to dress, go to the toilet, independent eating and drinking, and the ability to get on and off furniture. Furthermore, a reasonable number of patients should be treated over the various years given the chronic condition and the time necessary to observe differences in the clinical relevant endpoints (e.g. wheelchair dependency, respiratory assist, corrective surgery and death). Moreover, the treated patients will be followed up for up to 5 years via enrolment into a registry, not only for efficacy but also for safety reasons. As formal commitment it is part of the CHMP imposed post-authorisation measures.

The CHMP considers the following measures necessary to address issues related to efficacy and safety:

The Applicant should set up an MPS IVA disease registry to assess the long term safety and efficacy of elosulfase alfa*:* The number of subjects enrolled in the clinical studies is small and adverse reactions with a frequency of uncommon or less may not have been detected. To overcome some of the limitations of the safety database including detection of adverse reactions

(ARs) due to prolonged exposure, ARs with a long latency or AEs due to cumulative effects, the applicant is requested to set up a disease registry. Furthermore, in light of the potentially life long treatment with elosulfase alfa, additional long term efficacy data are considered key for continued benefit risk assessment.

The applicant committed to setting up this registry within an agreed timeline.

2.6. Clinical safety

Patient exposure

The clinical safety database of elosulfase alfa includes results from six clinical trials in 235 subjects with MPS IVA between the ages of 0.8 and 57.4 years, who were exposed to elosulfase alfa. The combination of study populations encompasses the spectrum of age and disease severity of the overall patient population. Subjects were exposed for up to 169.7 weeks of continuous treatment. Exposure to study drug has been nearly maximal in the 6 studies with ≥98% of the infusions performed on schedule.

In the Proposed Dose Population, a total of 222 subjects were treated with elosulfase alfa at the dose of 2.0 mg/kg/week for periods ranging from 1 week to 100.1 weeks. The mean (± SD) total elosulfase alfa dose per subject was 56.8 (± 54.89) mg/kg. In the Proposed Dose Population with Long Term Exposure, a total of 52 subjects were treated with elosulfase alfa at the dose of 2.0 mg/kg/week for periods ranging from 49.0 weeks to 100.1 weeks. Total elosulfase alfa dose per subject ranged from 84.6 mg/kg to 193.5 mg/kg.

Adverse events

The most common AEs observed during the treatment with elosulfase alfa were associated with infusions and included vomiting, pyrexia, and headache, as summarised in the table below.

Incidence (≥ 10%) and Frequency of Adverse Events by Preferred Term: Proposed Dose Population

Incidence: n (%) Annualized Frequency: mean events/subject year	**Duration of elosulfase alfa Dosing, Weeks**					
Preferred Term	1-12 (n=222)	13-24 (n=121)	25-36 (n=98)	37-48 (n=82)	>48 (n=52)	Total (n=222)
Subjects with at least 1 reported AE	170 (76.6%) 27.50	97 (80.2%) 22.10	73 (74.5%) 17.27	66 (80.5%) 19.74	42 (80.8%) 11.68	171 (77.0%) 23.03
Vomiting	55 (24.8%) 2.22	23 (19.0%) 1.31	13 (13.3%) 0.96	14 (17.1%) 1.35	15 (28.8%) 0.98	77 (34.7%) 1.64
Pyrexia	46 (20.7%) 1.41	28 (23.1%) 1.64	20 (20.4%) 1.16	13 (15.9%) 1.12	14 (26.9%) 0.82	76 (34.2%) 1.14
Headache	52 (23.4%) 2.92	24 (19.8%) 2.10	14 (14.3%) 1.11	14 (17.1%) 1.60	13 (25.0%) 0.96	75 (33.8%) 2.56
Cough	29 (13.1%) 0.85	14 (11.6%) 0.62	7 (7.1%) 0.45	5 (6.1%) 0.35	9 (17.3%) 0.22	52 (23.4%) 0.68
Nausea	32 (14.4%) 1.16	12 (9.9%) 0.90	6 (6.1%) 0.35	10 (12.2%) 0.65	4 (7.7%) 0.21	43 (19.4%) 0.98
Diarrhoea	22 (9.9%) 0.65	7 (5.8%) 0.26	4 (4.1%) 0.22	4 (4.9%) 0.25	9 (17.3%) 0.43	37 (16.7%) 0.47

Pain in extremity	19 (8.6%) 0.62	5 (4.1%) 0.25	8 (8.2%) 0.49	9 (11.0%) 0.77	5 (9.6%) 0.23	36 (16.2%) 0.59
Arthralgia	18 (8.1%) 0.72	11 (9.1%) 0.45	9 (9.2%) 0.49	5 (6.1%) 0.28	5 (9.6%) 0.28	35 (15.8%) 0.71
Abdominal pain	21 (9.5%) 0.72	7 (5.8%) 0.43	5 (5.1%) 0.23	4 (4.9%) 0.30	2 (3.8%) 0.06	33 (14.9%) 0.46
Nasopharyngitis	11 (5.0%) 0.29	13 (10.7%) 0.53	6 (6.1%) 0.30	5 (6.1%) 0.34	7 (13.5%) 0.27	33 (14.9%) 0.34
Fatigue	15 (6.8%) 0.44	8 (6.6%) 0.45	5 (5.1%) 0.48	8 (9.8%) 0.58	5 (9.6%) 0.33	31 (14.0%) 0.41
Oropharyngeal pain	17 (7.7%) 0.51	9 (7.4%) 0.34	6 (6.1%) 0.33	7 (8.5%) 0.55	3 (5.8%) 0.16	31 (14.0%) 0.44
Upper respiratory tract infection	11 (5.0%) 0.26	13 (10.7%) 0.54	11 (11.2%) 0.62	6 (7.3%) 0.50	3 (5.8%) 0.14	30 (13.5%) 0.32
Abdominal pain upper	15 (6.8%) 0.59	5 (4.1%) 0.29	6 (6.1%) 0.49	3 (3.7%) 0.37	6 (11.5%) 0.31	25 (11.3%) 0.32
Rash	7 (3.2%) 0.22	10 (8.3%) 0.40	5 (5.1%) 0.24	5 (6.1%) 0.27	6 (11.5%) 0.22	23 (10.4%) 0.27

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 100.
Mapping was based on MedDRA version 15.0.

Most subjects experienced at least 1 infusion associated reactions (IAR). Although some AEs during infusion required slowing or stopping of the infusion and, medical intervention, all subjects received and tolerated subsequent infusions. IARs tended to occur less frequently with duration of treatment. In general, safety data are available from 86 subjects who have been exposed to elosulfase alfa for more than 48 weeks, including 52 subjects who have been exposed at the proposed dose of 2.0 mg/kg/week for more than 48 weeks. Analyses of these data show that elosulfase alfa continues to be well tolerated with longer-term exposure. When examining AE profiles over time on an annualized basis, the majority of events decreased over time or remained stable. The mean annualized frequencies of AEs including related AEs and IARs decreased over time. In addition, the mean annualized frequencies of SAEs and Hypersensitivity AEs did not increase over time.

Serious adverse event / deaths / other significant events

Serious adverse events (SAEs) and hypersensitivity AEs occurred infrequently. Most SAEs were related to the underlying disease or to intravenous administration of the investigational product. No deaths occurred until the data cut-off dates of the relevant trials. In the pivotal study MOR-004, the incidence of SAE was highest elosulfase alfa 2.0 mg/kg/qw group and lowest in the placebo group. Comparisons of individual SAEs between placebo and elosulfase alfa is not possible since most SAEs occurred only once except for pneumonia with 2 events.

Incidence and Frequency of Serious Adverse Events by Preferred Term All Exposed Population by Treatment Duration Interval (only those with a total of ≥ 2 reports)

Incidence: n (%) Annualized Frequency: mean events/subject year Preferred Term	**Duration of elosulfase alfa Dosing, Weeks**					
	1-12 (n=235)	13-24 (n=211)	25-3 (n=174)	37-48 (n=150)	>48 (n=86)	Total (n=235)
Subjects with at least 1 reported SAE	24 (10.2%) 0.54	15 (7.1%) 0.38	18 (10.3%) 0.52	9 (6.0%) 0.53	21 (24.4%) 0.52	69 (29.4%) 0.45
Knee deformity	4 (1.7%) 0.07	3 (1.4%) 0.06	2 (1.1%) 0.05	2 (1.3%) 0.08	5 (5.8%) 0.11	16 (6.8%) 0.07

Poor venous access	3 (1.3%) 0.06	0 (0.0%) 0.00	2 (1.1%) 0.05	1 (0.7%) 0.03	1 (1.2%) 0.02	6 (2.6%) 0.01
Otitis media	4 (1.7%) 0.07	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	(1.2%) 0.01	5 (2.1%) 0.01
Lower respiratory tract infection	2 (0.9%) 0.04	0 (0.0%) 0.00	1 (0.6%) 0.02	1 (0.7%) 0.03	0 (0.0%) 0.00	4 (1.7%) 0.02
Catheterisation venous	0 (0.0%) 0.00	1 (0.5%) 0.02	2 (1.1%) 0.05	0 (0.0%) 0.00	0 (0.0%) 0.00	3 (1.3%) 0.00
Central venous catheterization	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (1.3%) 0.07	1 (1.2%) 0.01	3 (1.3%) 0.01
Medical device implantation	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	2 (2.3%) 0.01	3 (1.3%) 0.01
Pneumonia	1 (0.4%) 0.02	2 (0.9%) 0.04	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	3 (1.3%) 0.01
Anaphylactic reaction	1 (0.4%) 0.02	1 (0.5%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (0.9%) 0.01
Hypersensitivity	1 (0.4%) 0.02	1 (0.5%) 0.03	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (0.9%) 0.02
Infusion site reaction	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (2.3%) 0.02	2 (0.9%) 0.00
Joint dislocation	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (1.2%) 0.03	2 (0.9%) 0.01
Knee operation	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (2.3%) 0.01	2 (0.9%) 0.00
Medical device removal	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (2.3%) 0.05	2 (0.9%) 0.01
Pyrexia	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (2.3%) 0.01	2 (0.9%) 0.00

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 170

Immunological events

Hypersensitivity reactions were reported for about 20% of the patients in the elosulfase alfa 2.0 mg/kg/week. Due to hypersensitivity reactions, two 2 infusions had to be interrupted and one infusion could not be completed. The hypersensitivity reactions appear not dose dependent. The incidence of the hypersensitivity reactions does not change over time. In the Proposed Dose Population, infusion associated reactions (IARs) were reported for 71.2% subjects. There were decreases with duration of treatment in the mean subject-year frequencies of IARs and IARs during infusion. The most common infusion associated reactions (IARs) by incidences (and annualized frequencies) were pyrexia, 26.1% (0.77 IAR events/subject year), vomiting 23.0% (1.06), and headache, 22.5% (1.37). The frequencies of IARs were generally higher during the first 12 weeks of treatment than during subsequent treatment duration intervals, and the IARs tended to occur less frequently with time. In the Proposed Dose Population, 13.96% of subjects had AEs during infusion that required infusion interruption or discontinuation as well as medical intervention to treat the event. Infusions interrupted due to an AE which also required medical intervention were reported for 11.26% of total subjects; infusions discontinued due to an AE which also required medical intervention were reported for 4.50% of total subjects. Across studies, IARs related to elosulfase alfa infusion were generally mild to moderate in severity and manageable with symptomatic treatment and/or infusion rate modification. A minority (<0.8%) of infusions in the All Exposed Population were interrupted or discontinued and also required medical intervention.

Laboratory findings

No clinically relevant changes in laboratory findings (haematology, blood chemistry, liver or kidney function, urinalysis) have been noted. No clinically significant abnormal ECG findings have been noted. In study MOR-004, no clear effect of elosulfase alfa on cardiac function was seen in echocardiogram (ECHO) data, but the trial was limited to 24 weeks and from the extension study MOR-005 no ECHO data are available. However, in study MOR-002, where relevant long-term ECHO data are available, no patient had clinically significant abnormal ECHO findings. The incidence of both mitral and aortic regurgitation increased from baseline over the study, but the applicant explained that this effect is consistent with the progression of MPS.

Safety in special populations

Information on safety in special populations, e.g. in children below 5 years of age, are limited; the relevant paediatric study MOR-007 is on-going in line with the agreed PIP. The limited data from this trial indicate that the incidence of vomiting and pyrexia is higher in this population than in previous elosulfase alfa studies in patients older than 5 years of age. Incidences of SAEs decreased in the age groups over 11 years of age, while mean annualized frequencies of hypersensitivity AEs and IARs were similar between age groups.

There was no relevant effect of gender or ethnicity on AEs.

Safety related to drug-drug interactions and other interactions

No drug-drug or drug-disease interaction studies were performed and no data on safety related to drug-drug or other interactions have been provided.

Discontinuation due to adverse events

After initiation of mandatory premedication for patients in order to manage IARs, no patient experienced an AE that resulted in permanent discontinuation of study drug or withdrawal from study as of the respective data cut-off.

Post marketing experience

Vimizim has not been marketed in any country at the time of application and thus, data from post-marketing use are not available.

2.6.1. Discussion on clinical safety

The applicant has provided safety data from 6 clinical studies in 235 patients with MPS IVA exposed to elosulfase alfa including the finalised pivotal trial MOR-004, the only study providing placebo-controlled safety data. Although this safety database is limited due to the size of the clinical studies, it is considered adequate for a rare disease MAA. In the placebo controlled study MOR-004 most AEs were graded mild to moderate in severity. The most commonly reported AEs were vomiting, pyrexia, and headache. These were also the most common AEs considered study-drug related. No deaths occurred until the data cut-off dates of the relevant trials.

In study MOR-004 the incidence of SAE was highest elosulfase alfa 2.0 mg/kg/qw group and lowest in the placebo group. SAEs appear to be either infusion or procedure related, or are not distinguishable from complications of the underlying disease including knee deformity, poor venous access, otitis media, and lower respiratory tract infection.

The risk of hypersensitivity reactions is adequately described in the SmPC together with recommendations on how to treat reactions. After initiation of mandatory premedication for patients to manage IARs no patient experienced an AE that resulted in permanent discontinuation of study drug or withdrawal from study as of the respective data cut-off. Most patients had at least one infusion associated reaction (IAR) and the most common IARs were headache, vomiting, and pyrexia. IARs led more than twice as often to infusion interruption in the elosulfase alfa groups as in the placebo group. The SmPC includes an adequate warning to the physicians as well as advice on how to deal with cases of IAR. All patients in the clinical trials became anti-elosulfase alfa total antibody (TAb) positive; about 80% showed anti-elosulfase alfa specific neutralizing antibodies (NAb) and about 10% developed anti-elosulfase alfa IgE. For neither TAb nor NAb a clear association with loss of efficacy was observed. Higher TAb or NAb titres have not been associated with increased incidence or severity of hypersensitivity AEs and IgE positivity has not consistently been associated with hypersensitivity AEs or drug interruption or discontinuation. No clinically relevant changes in laboratory findings have been noted.

Information on safety in children below 5 years of age is limited, as the relevant paediatric study MOR-007 is on-going, in line with the agreed PIP. The SmPC reflects the currently available information in paediatric patients. The majority of patients who received Vimizim during clinical studies were in the paediatric and adolescent age range (5 to 17 years). The treatment of young children < age 5 years might be started, although this population was not included in the pivotal study, but further data are expect to become available with the progress of study MOR-007. It is also important to start the treatment of these patients as soon as possible. The CHMP considered it reassuring that the safety results to date in 15 patients less than 5 years of age are consistent with results observed in patients 5 to 57 years old and no unexpected events were noted. The CHMP requested an amendment of the proposed indication in order to emphasize that Vimizim is indicated for treatment of patients of all ages.

The indication for Vimizim, as adopted by the CHMP is:

Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

Overall, the number of subjects enrolled in the clinical studies is small and adverse reactions with a frequency of uncommon or less may not have been detected. To overcome some of the limitations of the safety database including detection of adverse reactions (ARs) due to prolonged exposure, ARs with a long latency or AEs due to cumulative effects, the CHMP requested the applicant to set up a disease-specific registry. Furthermore, in light of the potentially life long treatment with elosulfase alfa, additional long term efficacy data are considered key for continued benefit risk assessment.

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

2.6.2. Conclusions on the clinical safety

The most common side effects observed with Vimizim treatment are infusion reactions, including anaphylaxis, hypersensitivity and vomiting. These and other safety issues have generally been adequately addressed in the PI. The safety database is too limited to draw robust conclusions,

with 52 subjects being exposed to the proposed dose for more than 48 weeks. However, the applicant has committed to set up a registry and to follow Morquio A patients up to 10 years and for safety as well as for efficacy reasons. Furthermore, a reasonable number of patients should be treated over various years given the chronic condition.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4.1, the PRAC considers by consensus that the risk management system for elosulfase alfa (Vimizim) in the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Infusion reactions (including anaphylaxis and severe allergic reactions)
Important potential risks	Immunogenicity Spinal/Cervical Cord Compression (including laxity and unmasking myelopathic symptoms) Medication Errors
Missing Information	Limitations of the safety database Safety in patients with hepatic impairments, safety in patients with renal impairments, safety in patients with cardiac impairments, and safety in pregnancy and lactation

- **Pharmacovigilance plans**

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
MPS IVA Clinical Registry Program	To characterize and describe the MPS IVA population as a whole, including the heterogeneity, progression, and natural history of MPS IVA. To evaluate the long-term effectiveness and safety of elosulfase alfa To help the MPS IVA medical community with the development of recommendations for monitoring subjects and reports on subject outcomes to optimize subject care To collect data on other treatment paradigms, evaluate the prevalence of their use and their effectiveness To characterize the effects of 5 years of elosulfase alfa treatment in subjects under 5 years of age.	Additional data collected will help broaden knowledge of identified and potential risks of elosulfase alfa, as well as increase the size of the safety database and possibly provide new information on use in identified subgroups (pregnancy, hepatic and renal impairment, cardiac impairment)	Planned to start Q3 2014	Annual interim reports. Final report due in 2025.

- **Risk minimisation measures**

Safety Concern	Additional risk minimisation measures	Routine risk minimisation measures
Infusion reactions (including anaphylaxis and severe allergic reactions)	Healthcare provider educational materials	SmPC language Section 4.4 and 4.8
Immunogenicity	None	SmPC language Section 4.8
Spinal/Cervical Cord Compression (including laxity and unmasking myelopathic symptoms)	None	SmPC language Section 4.4
Medication Errors	Healthcare provider educational materials	N/A
Limitations of the safety database	None	N/A
Safety in patients with hepatic impairments, safety in patients with renal impairments, safety in patients with cardiac impairments, and safety in pregnancy and lactation	None	N/A for hepatic, renal or cardiac impairments SmPC language Section 4.6 – Pregnancy and lactation

The CHMP endorsed this advice without changes.

2.9. 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.*

3. Benefit-Risk Balance

MPS IVA is a rare, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetyl-galactosamine 6-sulfatase (GALNS). The most common features of patients with MPS IVA are progressive skeletal dysplasia, frequent surgical procedures mostly related to musculoskeletal or respiratory dysfunction and a significant limitation in mobility, endurance, and respiratory function. Currently treatment options are limited to treatment alleviation of the signs and symptoms (treatment of infections, corrective surgery, wheelchair etc.). Vimizim (elosulfase alfa) is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS), and is identical to the naturally occurring human lysosomal enzyme. The enzyme reaches the lysosome and exerts its function there.

Benefits

Beneficial effects

For the primary endpoint 6 minute walk test (6MWT) statistical significance was shown in the pivotal study for the every week regimen with a mean difference with placebo in the primary endpoint 6-MWT of 22.5 meters at week 24. For most secondary endpoints improvement was seen although none of the differences reached statistical significance. Treatment with the every other week regimen resulted in walking distances comparable to placebo.

Data from MOR-002 and on-going studies (MOR-005, MOR-100, MOR-007, and MOR-008) further supported the efficacy of elosulfase alfa when administered intravenously at 2.0 mg/kg/week in subjects with MPS IVA. Treatment with elosulfase alfa was shown to be effective, albeit not always statistically significant, in improving performance in endurance tests (6MWT and 3MSCT), respiratory function tests (FVC, MVV, forced expiratory volume in 1 second [FEV1], forced inspiratory vital capacity [FIVC]), anthropometric measurements (standing height, length, sitting height, and weight), and in reducing urinary KS. Further, additional data show that the number of subjects using a wheelchair at Week 24 increased by 5 (8.8%) in the placebo group, and 0 (0%) in both elosulfase alfa treatment groups.

Additional data on QoL and a reduction in the incidence of orthopaedic surgery in favor of the elosulfase alfa treated patients further indicate clinical improvement. After 72 weeks treatment about 8% of the patients on elosulfase alfa treatment and about 18% in the placebo group had undergone orthopaedic surgery. A further analysis of the ADL items from the HAQ showed some improvement after 24 weeks treatment with most notably the improved ability to dress, go to the toilet, independent eating and drinking and the ability to get on and off furniture. Improvements in efficacy measures and decreases in urine KS were maintained in the presence of sustained positive anti- elosulfase alfa antibody results, and there was no apparent relationship between TAb titer, or the presence of neutralizing receptor binding antibody, and efficacy outcomes.

Uncertainty in the knowledge about the beneficial effects

Assessment of the clinical relevance of the observed effects for the overall population is hampered by the large variability seen in the mean change in 6MWT from baseline. This probably relates to the heterogeneity of the patient population included which varied considerably with patients being able to walk between 36 and 322 meter in the 6MWT. A reasonable number of patients should be treated over various years given the chronic condition and the time necessary to observe differences in the clinically relevant endpoints (among others wheelchair dependency, respiratory assist, corrective surgery and death). It is unclear whether an increase in the dose could enhance the efficacy. The applicant has committed to follow up on the patients up to 5 years, not only for efficacy but also for safety reasons. A disease-specific registry will thus be set up in the post-authorisation phase.

Risks

Unfavourable effects

The clinical safety database includes safety results from 6 clinical trials in 235 subjects with MPS IVA exposed to elosulfase alfa, and includes subjects between the ages of 0.8 and 57.4 years.

The combination of study populations in the elosulfase alfa clinical development program encompasses the spectrum of age and disease severity of the overall patient population. Subjects were exposed for up to 169.7 weeks of continuous treatment (overall mean [SD]) duration of exposure was 50.2 [±37.03] weeks), with 52 subjects being exposed to the proposed dose for more than 48 weeks. Most adverse events (including SAE) were infusion associated reactions (IARs) or could be considered disease related. Limited long-term safety data suggest that the frequency of IARs decreases over time. There were no clinically meaningful changes in laboratory values, ECGs, or ECHOs. Across studies, IARs related to elosulfase alfa infusion were generally mild to moderate in severity and manageable with symptomatic treatment and/or infusion rate modification.

Hypersensitivity reactions were reported for about 20% of the patients in the elosulfase alfa 2.0 mg/kg/week. In the Proposed Dose Population, IARs were reported for 71.2% subjects. 13.96% of subjects had AEs during infusion that required infusion interruption or discontinuation as well as medical intervention to treat the event. Infusions interrupted due to an AE which also required medical intervention were reported for 11.26% of total subjects; infusions discontinued due to an AE which also required medical intervention were reported for 4.50% of total subjects. From the total of infusions, <0.8% in the All Exposed Population were interrupted or discontinued and also required medical intervention

There was no apparent increase in incidence of AEs, study drug related AEs, or SAEs with increasing dose or increasing treatment duration. The majority of SAEs were consistent with events expected in untreated patients with MPS IVA disease.

All subjects treated with elosulfase alfa developed a persistent anti- elosulfase alfa antibody response. TAb titer levels were sustained in all subjects over the course of treatment and Nab antibodies were commonly detected. Despite the high incidence of anti- elosulfase alfa antibodies, decreases in urinary KS and improvements in efficacy measures were sustained in treated subjects. No correlations were found between higher TAb titers or higher NAb positivity and hypersensitivity AEs in elosulfase alfa treated subjects. Hypersensitivity AEs did not increase in incidence or severity with time of treatment or with development of anti-drug antibodies. Anti-elosulfase alfa IgE was detected in 6.8% and 8.6% of the 2.0 mg/kg/qow and 2.0 mg/kg/qw subjects in MOR-004, respectively. Anti- elosulfase alfa IgE positivity has not been associated with hypersensitivity AEs or treatment withdrawal, with the exception of one subject in MOR-002. The reason for increased clinical relevance of IgE positivity in the early study may have been related to the unique dose escalation treatment schedule in MOR-002 and/or the lack of pre-treatment with anti-histamines in this early subject.

Uncertainty in the knowledge about the unfavourable effects

The safety database is too limited to draw robust conclusions. Further a reasonable number of patients should be treated over various years. The applicant has committed to follow up on the patients up to 10 years, not only for efficacy but also for safety reasons. A disease-specific registry will thus be set up in the post-authorisation phase.

Benefit-risk balance

The observed statistically significant increase in 6-MWT translates into a clinical benefit for the patient population. Maintenance of effect and long-term clinical important improvements need to be demonstrated in a long-term follow-up study. Further the short-term safety profile appears manageable. The safety database, however, is limited both in duration and in actual numbers.

Importance of favourable and unfavourable effects

An effects table summarising the benefits and risks is provided below.

There is a clear rationale for the product in the proposed disease, where treatment options are limited. The shown effectiveness indicates benefit to the patient with a clear clinically relevant effect. Effect size might also differ based on baseline disease status. Effects on more functional endpoints, including MPS HAQ appear small but consistent. Again, this may be due to the heterogeneity of the population. Clinically important milestones (for example start of wheelchair dependency or start of respiratory aids), could provide additional support for efficacy taking into account the baseline disease characteristics of the patients, but it is recognised that this might be difficult before licensing.

Although the limited safety database is of concern, preliminary data appear promising due the lack of frequent serious adverse events. Further data will be collected during the post-authorisation phase through the spontaneous notification and the disease specific registry.

Benefit-risk balance

Available information strongly suggests that the increase in 6-MWT results obtained with once-weekly dosing of Vimizim is accompanied by other clinically relevant endpoints and therefore translates into a benefit for the patient population with an acceptable AE profile. Therefore, the benefit-risk balance is positive.

Discussion on the benefit-risk balance

The clinical efficacy of Vimizim will be further supported by additional long term clinically relevant milestones such as delay of wheelchair dependence, delay in time to respiratory assistance, fewer and more simple corrective operations or improvement of other events that has a serious impact on the QoL of the patient. The applicant has committed to assess through the set-up of a registry which is imposed as a condition to the marketing authorisation. Currently, the safety information is limited, nevertheless, data so far available do not indicate a major safety issue. The enzyme as such does introduce surprisingly little agent specific adverse events except for infusion related reactions. All infusion associated reactions can be treated with interruption of the infusion, or medical intervention or both, as reflected in the SmPC.

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 Vimizim in the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages,

is favourable and therefore recommends the granting of the marketing authorisation 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Vimizim are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a step by step dosing and administration guide that includes information on the following key elements:

- the calculation of the dose and of the volume of infusion
- the calculation of the infusion rate
- the risk of anaphylaxis and of severe allergic reactions and the measures necessary to minimise it:
    - all patients should receive antihistamines with or without antipyretics 30–60 minutes
    - prior to the start of infusion
    - appropriate medical support should be readily available when VIMIZIM® is administered
    - the need to immediately stop the infusion and initiate appropriate medical
    - treatment if these reactions occurred

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Set up a MPS IVA disease Registry to assess the long term safety and efficacy of elosulfase alfa.	Submission of final study report: March 2025

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that elosulfase alfa is qualified as a new active substance.

Paediatric Data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0240/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.