SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Aldurazyme. For information on changes after approval please refer to module 8.

1. Introduction

Aldurazyme contains a new active substance, laronidase (recombinant human α-L-iduronidase or rhIDU). Laronidase is isolated from cell culture supernatant following growth of a Chinese Hamster Ovary (CHO) cell line transfected with a recombinant expression vector containing the cDNA coding region for human α-L-iduronidase. Purified laronidase is a glycoprotein with a molecular weight of approximately 83 kD. Laronidase consists of 628 amino acids after cleavage of the N-terminus containing 6 potential N-linked oligosaccharide modification sites, all of which are used.

Aldurazyme is intended for the treatment of Mucopolysaccharidosis I (MPS I), a Lysosomal Storage Disorder (LSD). MPS I is an inherited metabolic disease characterised by the inability to process certain glycosaminoglycans, which accumulate in lysosomes in cells throughout the body. As the amount of stored material in the lysosomes increases over time, normal cellular functioning becomes increasingly impaired, leading to the emergence of clinical symptoms. In MPS I there is an α-L-iduronidase (IDU) deficiency in leukocytes. Deficiency of IDU results in the accumulation of glycosaminoglycans (GAG) in a variety of tissues and accumulation depends on the location of the affected substrates and their rate of turnover. The storage process can affect appearance, development and the function of various organs of the body.
The prevalence in the European Union is estimated to approximately 0.025 in 10,000 persons.

Patients with MPS I are usually classified into three clinical syndromes – Hurler, Hurler-Scheie and Scheie. However, these three phenotypes are arbitrary classifications as they cannot be distinguished by routine diagnostic procedures. All patients lack α-L-iduronidase activity and excrete excessive amounts of heparan sulphate and dermatan sulphate in urine. Patients have therefore been classified into a phenotype based on their symptoms and the severity of their symptoms. There is, however, considerable heterogeneity in the severity and symptomatology within each clinical phenotype, with substantial overlap of the symptomatology of the three syndromes. In MPS I patients the signs and symptoms are ubiquitous and most patients die between late childhood and early adulthood from pulmonary or cardiac causes.

The treatment options for the majority of MPS I patients are limited to symptomatic care. Bone marrow transplantation (BMT) has been applied to patients with the most severe phenotype (Hurler type, which encompasses primary CNS involvement). In those patients with adequate engraftment, there are improvements in liver and spleen storage, urinary GAG excretion and various clinical problems, with the exception of bone disease, which remains progressive. It is recognised that the evolution after BMT is especially favourable when BMT occurred in a child <2 year-old and with IQ>80 (early BMT prior to cognitive decline). BMT has been shown to slow or prevent the mental degeneration of Hurler patients. Late BMT is not effective in preventing the decline in cognitive functioning, presumably because changes that precede and cause the decline have already occurred. In Hurler-Scheie and Scheie MPS I disease, patients rarely undergo BMT because the risk/benefit ratio of BMT is unfavourable.

Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis MPS I to treat the non-neurological manifestations of the disease (see sections 5.1 of the SPC). Enzyme replacement therapy is intended to restore a level of enzymatic activity sufficient to hydrolyse the accumulated glycosaminoglycans and prevent further accumulation.

The proposed dosage regimen of Aldurazyme is 100 Units/kg body weight administered once a week as an intravenous infusion.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The finished product is presented as a sterile concentrate for solution for infusion. Each vial contains 5.3 ml Laronidase (Recombinant human α-L-iduronidase, rhIDU) 100 U/ml (0.58 mg/ml). The concentrate is diluted with 0.9% sodium chloride prior to intravenous administration. A 0.3 ml overage permits the withdrawal of 5.0 ml (500 U) of rhIDU. Each vial is intended for single use.

The container is a vial made of Type I borosilicate glass and is sulphur-treated to strengthen glass and reduce potential protein adsorption. Chlorobutyl rubber stopper selected for as suitable for a formulation with a high phosphate content. Stoppers are siliconised (Dimethicon) prior to sterilisation.

Active substance

Characterisation

Recombinant human α-L-iduronidase (rhIDU) is a monomer of 628 amino acid residues. It contains six asparagine-linked glycosylation sites, two of which carry the mannose-6-phosphate oligomannose$_7$ oligosaccharide, which binds to target cell surface receptor. It also contains 6 cysteine residues, two of which forming a single disulphide bond. The molecular mass derived from the translated cDNA sequence is 70.1 kDa. Based on SDS-PAGE the apparent molecular mass is 83 kDa, the additional 13 kDa is attributed to post-translational modification. Tryptic peptide mapping was used to identify the primary structure of rhIDU and is used as an identity test for lot release. Overall the primary and glycosylation structures have been sufficiently elucidated.

Three formulated bulk active substance process qualification lots and the Reference Standard were examined using a battery of standard physico-chemical and biochemical analytical methods. These methods are also used either for lot release or for additional characterisation.

Results provided evidence that the recombinant protein (active substance) from all samples is identical and is the same as predicted from the rhIDU cDNA and has the expected molecular mass. Adequately sensitive test methods are used to demonstrate and control the purity of laronidase in the bulk active substance and in the finished product.

Isoelectric focusing revealed multiple isoforms, which were due to glycosylation microheterogeneity resulting from post translational modifications of the protein. The occurrence of this heterogeneity is not a cause for concern and the Company has committed to provide the results from an ongoing study to demonstrate the consistency in the glycosylation site occupancy.

Development genetics and cell bank system

The production process of laronidase uses a transformed Chinese hamster ovary host cell line containing an expression plasmid from which rhIDU is expressed. One subclone of this cell line was selected as having the highest level of secreted rhIDU and was used to establish the Master Cell Bank (MCB) from which subsequent Working Cell Banks (WCB) were derived. Information on the methods and the raw materials used to establish the cell banks was provided.

The adequate genetic stability of the cell banks was demonstrated by comparing cells from the MCB with cells at the end of a representative production.

The MCB, current WCB, and EPC (End of production cells) were evaluated for cell line identity, sterility and adventitious agent contamination, and results indicate that the host cell bank system is suitable for the manufacture of a medicinal product.

The company committed to repeat the Southern Blot to determine the copy number and structure of the MCB, EPC and non-rDNA parent line in parallel. The company will also investigate a reliable viable count method to measure specific productivity.

Production process

The production process of the formulated bulk active substance (rhIDU) takes place at BioMarin Pharmaceutical Inc, Novato, CA. The facility contains clean room suites where cell culture, purification, and formulation operations are performed. The fermentation process, from the cell culture inoculum expansion to the final cell harvest, has been adequately described in the application.

Purification of rhIDU from pH adjusted harvest cell culture fluid (HCCF) involves six major steps: including 3 column chromatography steps, utilising several modes of separation, a viral inactivation step, DNA removal, and Viral filtration.

Process validation, routine tests and specifications of the active substance
Three consecutive process qualification (PQ) lots of rhIDU formulated bulk active substance were manufactured at the BioMarin facility. The results of the routine in-process testing through cell culture, purification and formulation, together with the results of EPC validation and bioreactor operating parameters, demonstrate that the proposed commercial process consistently produces rhIDU that meets the release specifications. The company will evaluate the limit for the acceptable criteria for oligosaccharide profiling on an annual basis.

Additional studies were performed using validated scaled-down versions of the commercial process for validation of the purification process. The critical parameters maintained were retention times and matrix-solution interactions. This was achieved by replicating the commercial-scale buffers, linear flow rates and column heights but adjusting the column diameter.
The validation of the column use life was performed for each of the three chromatography columns used for the purification of rhIDU. The maximum number of cycles was established
Cleaning of the three chromatography column resins was performed and showed that the procedures were effective in removing potential residues, including DNA, protein and other process-related impurities.
Other validation studies covered step yields in the purification process, cleaning ultrafiltration / diafiltration system and microbial control during the process steps. The results indicate that the manufacturing processes are well controlled and yield a consistent product.

Impurities
The manufacturing process has been adequately validated for the removal of the relevant process related impurities: In addition the process was validated for the removal of various adventitious viruses.

Batch Analysis
Batch analyses from twelve lots of formulated bulk active substance have demonstrated that rhIDU is consistently manufactured to meet the release specifications.

Stability of active substance
Based on both small-scale stability studies and intermediates taken from production-scale lots the holding times and storage conditions were proposed for various process intermediates. The results of real time stability studies support the proposed holding time at the conditions specified.

Formulated Bulk Active Substance
Real time and accelerated stability data for the three qualification lots packed in ethylene vinyl acetate bags and stored at 2-8°C and 25°C was provided. The results to date support the proposed storage period.

Conclusion on the active substance
Based on the physico-chemical and biological characterisation data provided, it can be concluded that sensitive and quantitative tests have been developed and validated for identity, purity, and potency of the active substance.

Other ingredients
The following pharmacopoeial grade materials or equivalent are used in the final formulation: sodium chloride, sodium phosphate monobasic, monohydrate, sodium phosphate dibasic, heptahydrate, polysorbate 80, and water for injections.

Product development and finished product
The phosphate buffer was selected to maintain enzyme activity. Polysorbate 80, a hydrophilic nonionic surfactant, was added to minimise precipitate formation. Polysorbate is known to be effective

against agitation-induced aggregation of proteins. The original Phase 1/2 clinical study formulation did not include polysorbate 80. The proposed commercial formulation was used from August 2000 in clinical studies BIO7500-001 and ALID-003-99. During development the potency was re-defined and the protein content adjusted. The rhIDU enzyme activity unitage was redefined based on two factors: (1) changes in the activity assay procedure to improve assay performance and (2) changes in the definition of an activity unit to be consistent with International Unit nomenclature. The change was not a change in either the actual dose or the formulation of the product, merely a change in assay conditions and unit definition.
Laronidase cannot withstand terminal sterilisation so the product is aseptically manufactured and sterilised by filtration. Container closure integrity has been validated through bacteriological challenge and dye leak testing.

Method of preparation
The manufacturing process of the finished product has been described in sufficient detail and consists of final sterile filtration, filling into vials, packaging and labelling. Environmental monitoring is performed during the manufacturing process. Stability data for formulated bulk active substance indicate the total allowable time from removal from the refrigerated holding area (2-8°C) to initiate the filtration, filling and packaging is 24 hours. Several different products are processed at both sites: procedures and the appropriate facility designs are in place to prevent cross contamination.

The manufacturing process has been adequately validated. Data for the validation of the sterile filtration, and aseptic filling and capping have been provided and are adequate. The data showed that the finished product consistently met the proposed specifications and demonstrated that the manufacturing process is consistently reproducible.

Specifications of the finished product
The proposed finished product specifications, based on analysis of thirteen lots, are acceptable. Control tests on the finished product have been validated and will sufficiently guarantee the consistency of the manufacturing process of the finished product.

Stability of the finished product
Stability studies have been initiated on nine lots of finished product. Six lots were packaged in the proposed commercial container/closure system. Three lots used a different closure system (bromobutyl lyophilizer stoppers). The vials were stored either upright or inverted at 2–8°C, 25°C or 37°C for the duration of the study. The parameters studied are based on characterisation and forced degradation studies and analytical validation results. The study protocol is consistent with ICH recommendations. The real time data and the data from the accelerated storage studies support the shelf life as indicated in the SPC.

For administration to patients, Aldurazyme is diluted with 0.9% sodium chloride solution in an infusion bag. Enzyme activity was followed to examine the stability of the infusion preparation when stored at room temperature (15–25°C) for up to 24 hours, and refrigerated (2–8°C) for up to 48 hours. These stability studies were performed to bracket the possible clinical range of dilutions of Aldurazyme. The results support the proposed in-use storage for diluted Aldurazyme for 24 hours at 2-8 °C followed by up to 12 hours at 15-25 °C. In view of the absence of preservative in the reconstituted and diluted solutions, the SPC recommends an immediate use of the product; if not used immediately, the dilution should have taken place under controlled and validated aseptic conditions.

Production Process History
The application documented the history of lots manufactured during development using the different production processes and the purpose of each lot. The Phase 1/2 clinical studies and preclinical studies in MPS I dogs were performed with product manufactured by the earlier production processes. The Phase 3 clinical study and the pre-clinical toxicology studies (acute and repeat dose) were performed with product manufactured by the commercial production process at the proposed manufacturing site.
The application documented the testing performed on rhIDU manufactured for clinical use by the different processes used during development. Comparative data for the pilot process and the commercial process are also reported.

Data from purity tests demonstrate that rhIDU manufactured by the commercial process is higher in purity when compared to rhIDU manufactured by the previous processes. Data from physico-chemical and biochemical characterisation tests demonstrate comparability between rhIDU manufactured by these processes. This provides confidence that all pre-clinical and clinical studies performed with rhIDU are relevant to assessing the license application. However, it remains significant that the most important studies performed to confirm the safety and efficacy of rhIDU, the acute and repeat dose toxicology studies and the Phase 3 clinical study, were completed with material manufactured by the commercial production process.

Viral safety

Process validation

Cell banks
The Master Cell Bank, Working Cell Bank and End of Production Cell material have been examined by standard procedures and found to be free of detectable viral contamination. Reverse Transcriptase (RT) activity has been detected in the EPC; this RT activity is associated with C-type retroviral particles, which are often present in CHO cell lines. The company committed to test one lot of the bulk harvest to confirm that these particles are not infectious using a more sensitive test such as the Mus Dunni test.

Viral validation
The steps in the manufacture of rhIDU were evaluated for their capacity to reduce adventitious viral contamination. Small scale studies based on commercial-scale manufacturing processes were performed using materials from actual full-scale production. Chromatographic studies used both new and used column resins. Four model viruses were used: xenotropic leukaemia virus (XmuLV) as a model murine retrovirus, murine minute virus (MMV), pseudorabies virus (PRV), and Reo virus 3 (Reo-3).
The results of these viral clearance studies show that the combination of the columns steps, viral inactivation step and the viral filtration provides a potential for virus removal.
In common with other recombinant derived products the manufacturing process has only a limited capacity to remove and inactivate small (<25 nm) non-enveloped, acid resistant viruses. The Company has committed to investigate additional steps to clear such viruses. The company will also repeat a viral clearance study of those steps contributing to the viral removal and inactivation. A small non-enveloped virus will be included as one of the model viruses.

Lot testing
Each production lot is tested by an *in vitro* assay for the presence of viral contaminants. The last sample removed prior to the termination of cell culture harvest stage must be negative.

TSE compliance
Bovine foetal serum (FBS) and porcine trypsin were used in the establishment of the both the MCB and the WCB. Both animal derived reagents are also used during the cell culture phase of the manufacturing process.

The FBS used for the MCB was collected from Mexican cattle and tested for bovine virus diarrhoea, parainfluenza virus 3 and infectious bovine rhinotracheitis. Although the geographical BSE risk (GBR) of Mexico is pending and although only limited data on the sourcing and preparation of the FBS could be gathered from the supplier, the overall benefit/risk balance is favourable with respect to FBS used in the preparation of the MCB. The FBS used for the WCB and current production has an EDQM Certificate of Suitability. The FBS is irradiated to minimise viral contamination. This material is considered TSE compliant.

Porcine trypsin is not a TSE risk material.
In the past animal derived glycerin (bovine and porcine) was used as a buffer ingredient, since 2000/01 a synthetic glycerin has been used. The animal glycerin was derived from rendered tallow,

which had been obtained from North American animals and subjected to rigorous processing (~250°C/~700 psi). TSE risk is minimal.

The excipient polysorbate 80 is of plant origin and the cytopore micro-carriers are manufactured from plant derived materials.

Conclusion
The starting materials and the product are screened for viral contamination and overall the viral safety of the product has been adequately demonstrated.

Discussion on the chemical, pharmaceutical and biological aspects

A comprehensive pharmaceutical dossier supported this application. In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated consistent production of laronidase, achieving a well-defined quality for the active substance and the finished product. The fermentation, down-stream processes, and purification of the active substance are adequately controlled. The manufacturing process of the finished product has been described in sufficient detail and product specifications are adequate. In general, methods to control the quality of the product are adequate.
Stability data support a shelf life for the finished product as indicated in the SPC.
Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Aldurazyme is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications. The starting materials and the product are screened for viral contamination. There are no outstanding TSE issues.

3. Part III: Toxico-pharmacological aspects

GLP

The pharmacodynamic studies conducted during early development in university laboratories were not conducted in compliance with GLP but did conform to current good scientific practices. The acute and repeat dose toxicology studies and the safety pharmacology study were conducted in compliance with GLP Regulations. Two exploratory toxicity studies, one examining the hemodynamic effects of rhIDU in dogs, and the other studying the effects of diluent on toxicity and immunogenicity in dogs were not conducted in compliance with GLP but were conducted in compliance with the facility standard operating procedures and conformed to good scientific practices. Overall, compliance with GLP is therefore satisfactory.

Pharmacodynamics

In vitro studies
The mechanism of action of laronidase (recombinant human alfa-L-iduronidase or rhIDU) is to substitute the naturally occurring enzyme, α-L-iduronidase, which is deficient or absent in MPS I patients and to hydrolyse the accumulated glycosaminoglycans (GAG) in cells and tissues that cause the symptoms of the disease.
In vitro studies have demonstrated that rhIDU is efficiently endocytosed into lysosomes of fibroblasts from severely affected MPS I patients via a mannose-6-phosphate dependent receptor. After uptake into lysosomes, rhIDU has been shown to hydrolyse GAG substrates thereby reducing GAG storage in fibroblasts even at very low (pM) concentrations. Uptake was inhibited by mannose-6-phosphate as the result of competitive receptor binding. The half-life of rhIDU in MPS I fibroblasts was estimated to be approximately five days. These results demonstrate that, once intracellular, the enzyme is relatively stable and pharmacologically active.

In vivo studies
The animal models chosen for pharmacodynamic efficacy studies included the MPS I dog and the MPS I cat. These animals provide a biochemical and clinical model for disease with lack of detectable α-L-iduronidase activity in all tissues, an abnormal GAG storage in all tissues and clinical symptoms comparable with these of the human disease.
The MPS I dog has many characteristics of the human disease and is genetically similar to the more severe forms of MPS I in humans. However, the dogs differ from human patients in that the bone disease is not as severe as in humans and is usually characterised by osteopenia only with very mild changes suggestive of dysostosis multiplex. Despite the large amount of GAG storage, the liver and spleen are not as enlarged as in humans. Further, mental and behavioural degeneration has not been observed in the dogs.
The MPS I cat shows a clinical and pathologic syndrome comparable to human MPS I.

Six studies were conducted in the MPS I dog and one in the MPS I cat, to evaluate the effects of administration of 3 different intravenous doses of rhIDU (0.1 mg/kg 1-3 times per week, 0.5 mg/kg/week and 2.0 mg/kg/week (bolus or continous infusion)), short term (5-12 days) to long term duration (up to 74 weeks), on disease symptoms, tissue α-L-iduronidase activity (liver, spleen, lung and kidney), tissue glycosaminoglycan (GAG) content and urinary GAG excretion.

Overall, the results from the studies in MPS I dogs indicated that a dose of 0.5 mg/kg/week of rhIDU, similar to the doses used clinically, was necessary to obtain measurable levels of enzyme activity in all tissues examined. The tissue levels in liver, spleen and lung were greater than those of normal animals and approaching such levels for most other tissues except cornea, brain and cartilage. However, no histopathological evidence of improvement was found in the CNS in any study. The presence of rhIDU in brain homogenates was attributed to uptake by brain capillary endothelial cells since there were no changes in GAG storage in neurons or perithelial cells.
The elevated enzyme levels led to significant decreases in GAG levels and also produced a rapid decline in urinary GAG excretion. Use of higher doses led to higher tissue α-L-iduronidase activities, but did not result in greater decreases in tissue GAG levels. After treatment at 0.1 mg/kg/week for 13 months or 0.5 mg/kg/week for 74 weeks, there was evidence of clinical improvement of the MPS I symptoms. Further, bolus infusion was shown to be more effective than continuous infusion.

Treatment was well tolerated with no adverse clinical, clinical pathology or histopathological findings. However, anaphylactoid reactions occurred in dogs and cats and were shown to be due to IgG-mediated activation of complement. These reactions were alleviated by pre-treating the dogs with antihistamine drugs, slowing the rate of infusion and adding serum albumin to the infusate. In dogs, the peak levels and the times at which they occurred differed greatly between the animals and did not appear to be dose-related. In some dogs, the levels declined despite continued treatment. Five of 6 cats produced IgG antibodies to rhIDU and the levels were dose-related. Mild complement activation occurred in three cats. The immune response was greater in cats receiving the higher dose of rhIDU.
The anaphylactoid reactions were thought to be caused by immunoreactive aggregates formed as the result of the presence of impurities and the absence of the detergent polysorbate 80 in the preparation.
However, the anaphylactoid reactions observed in these early preclinical studies were not observed with the current clinical drug product in either monkeys or dogs, even without pre-treatment with antihistamine drugs or in the absence of serum albumin in the infusate. The risk of hypersensitivity reactions in patients being treated with rhIDU is discussed in the clinical section.

Pharmacodynamic drug interactions
rhIDU is a recombinant version of a naturally occurring human enzyme. Laronidase is a protein and is expected to be metabolically degraded through peptide hydrolysis. No metabolic interactions are expected. Therefore, no formal drug interaction studies have been conducted. The SPC states that Aldurazyme should not be administered simultaneously with chloroquine or procaine due to a potential risk of interference with the intracellular uptake of laronidase. Any evidence of product interactions will be reported post-authorisation.

General and safety pharmacology programme
Cardiovascular and respiratory effects were examined in two studies in beagle dogs. It was concluded that, during intravenous infusion of rhIDU over 4 hours at doses up to 4.1 mg/kg and 24-hour follow-up post-infusion, there were no effects on peripheral circulation in beagle dogs. Further, during intravenous infusion of doses up to 11.6 mg/kg of rhIDU over 4 hours and 24-hour follow-up post-infusion, heart rate, mean arterial pressure, rectal temperature, respiratory rate and electrocardiographic examinations were within normal ranges in all of the dogs.

No additional safety pharmacology studies were conducted with rhIDU, the argument being that rhIDU is a protein normally produced by humans and is unlikely to cross the blood brain barrier. Neurological toxicity is therefore not expected. However, to patients with MPS I active rhIDU is a foreign protein, possibly immunogenic, and the administration route causes abnormal exposure of the enzyme to various tissues. Overall the relative lack of safety pharmacology studies is acceptable in the light of the results of the repeat dose toxicity tests and the preclinical pharmacodynamic studies.

Pharmacokinetics

Pharmacokinetic studies were conducted in MPS I dogs and toxicokinetic studies in the normal beagle dog and cynomolgus monkey. α-L-iduronidase activity was monitored in blood/plasma and tissues.

The pharmacokinetic profile of laronidase was investigated in two MPS I dogs (1 female and 1 male) after a single bolus dose (0,1 mg/kg) and repeated infusions (2 mg/kg/week) during 10 weeks.

Following a single injection, α-L-iduronidase enzyme activity in plasma decreased biphasically and rapidly ($t_{½}$ α< 1 min and $t_{½}$ β = 20 min). 24 hours post-injection, the highest enzyme activity was located in the liver and significant activity was also observed in the lung and kidney. No significant enzyme activity was observed in other tissues such as the brain, cartilage and cornea.
Following repeated infusions for 9 hours weekly, laronidase was cleared rapidly and biphasically at week 2 ($t_{½}$ α < 1 min and $t_{½}$ β ~ 1h). After 10 weeks of treatment, laronidase clearance became monophasic in MPS I dogs and AUC increased by 1-2 orders of magnitude ($t_{½}$ ~0,5 to 1h).

Toxicokinetic data were collected in normal beagle dogs after single dose administration and in cynomolgus monkeys after single and repeated dose (13 weeks) administration. Doses up to 20- and 30 times the intended dose for clinical use were tested.

Non-linear pharmacokinetics of laronidase was observed in both dogs and monkeys. In the monkey model, pharmacokinetic parameters (AUC and T1/2) appeared to be time- and dose dependent. In the dog model only single dose administration was carried out and therefore only dose dependency was observed. The lack of linearity might be explained theoretically by the presence of a high affinity mannose-6-dependant receptor on peripheral white blood cells that remove laronidase from the blood circulation. The saturation of this receptor at high doses is proposed as a possible explanation for the non-linearity of laronidase.

Toxicology

Single dose toxicity
Single dose studies were carried out in rats and dogs. In rats, rhIDU did not induce toxicity at the highest dose tested, 5.8 mg/kg, which is equivalent to approximately 1 mg/kg in humans on a surface area basis. In dogs, the no-observable-effect level (NOAEL) for the described treatment regimen is > 11.6 mg/kg, which is equivalent to > 5.8 mg/kg in humans on a surface area basis. These doses are 10- and 20-fold the dose administered to humans in the phase I/II and phase III clinical studies. Furthermore, an investigation of the cardiac function was performed in the dog and did not reveal any particular concern.

Repeat-dose toxicity
In the case of rhIDU, a well-characterised recombinant form of a native human protein, repeat dose studies were not carried out in a rodent because administration of rhIDU would be expected to

produce an immune response in animals that would obscure any potential toxicity. In analogy, formal toxicology studies in dogs were also not conducted. However, a limited 8-week study in dogs was undertaken. Cynomolgus monkeys were chosen for the non-rodent species because they are phylogenetically closer to humans than non-primates and, therefore, less likely to demonstrate a strong immune response.

In the repeated dose study, monkeys were administered weekly IV infusions of up to 16.6 mg/kg rhIDU for 26 weeks. The highest dose tested in these studies (16.6 mg/kg) was limited by the maximum volume that could be safely administered to the animals, which was 28.6 ml/kg, a volume feasible because of the length of the 8-hour infusion. At the 13-week interim analysis there were no adverse signs of toxicity, apart from a case of oedema in one animal. The no-observable-adverse-effect level (NOAEL) for rhIDU was 16.6 mg/kg through 13 weeks, which is 29-fold (10-fold on a surface area basis) the human dose of 0.58 mg/kg administered in phase I/II and phase III clinical studies.

The formation of antibodies was monitored in the acute dog and repeat dose monkey studies. In contrast to many of the pharmacodynamic studies, no pre-treatment with antihistamines was given and the infusate did not contain serum albumin. All of the monkeys that had been treated weekly with rhIDU developed antibodies when monitored at week 13. The antibody response was dose-dependent; no differences in antibody levels were noted comparing male and female animals.

Genotoxicity
Studies to assess the mutagenic potential of rhIDU have not been conducted. This approach is acceptable, considering the nature of the product. No mutagenic potential would be anticipated with rhIDU based on its structure (a recombinant human glycoprotein), its impurity profile and the excipients in the final product.

Carcinogenicity
No carcinogenicity studies have been conducted with rhIDU, although the compound is intended for long-term treatment. However, no carcinogenic potential would be anticipated with rhIDU based on its structure (a recombinant human glycoprotein) and its impurity profile. The biochemical properties of α-L-iduronidase are well characterised, and there are no known interactions with DNA.

Reproductive and developmental toxicity
No fertility, general reproduction or development toxicities were observed in rats at doses up to 3.6 mg/kg/day, a weekly dose 7x greater than the proposed human dose. However, the potential risk for humans is unknown, which is adequately reflected in the SPC. No studies of perinatal toxicity have been conducted with rhIDU.

Local tolerance
Preclinical local tolerance studies for rhIDU have not been performed. In non-clinical toxicity studies, there were no serious adverse findings related to the injection/infusion of rhIDU. In humans, there has been no sequel related to rhIDU administration that necessitates further investigation in animal studies. RhIDU is administered by intravenous infusion following dilution and does not include concentrations of irritant or corrosive components that are likely to lead to serious reactions at the injection site.

Ecotoxicity/environmental risk assessment
Considering the protein nature of the laronidase and the frequency of MPS I, exposure to the environment is considered very limited and therefore no risk of concern would be expected.

Discussion on toxico-pharmacological aspects

Overall, the limited programme of pharmacodynamic and pharmacokinetic studies, some in animal models of MPS I, provided adequate evidence for efficacy of rhIDU and sufficiently characterised its pharmaco-/toxicokinetics and distribution. Although the number of animals included in some studies was low, this is understandable in view of the requirement for MPS I strains.

Single-dose intravenous toxicity studies in rats and dogs at 10-20x the proposed clinical dose showed no signs of toxicity. A NOAEL of 29x the clinical dose was established. In a 6-month repeated-dose study in monkeys the only finding of potential clinical significance was one case of oedema consistent with a mild hypersensitivity reaction. Since rhIDU is a human protein and therefore foreign to the species of animals used in both the pharmacodynamic and toxicity studies, the immune reaction observed might have been expected. All animals treated repeatedly with rhIDU produced antibodies, the levels of which were dose-related in MPS I cats and in monkeys, but not in MPS I dogs. The levels decreased in some MPS I dogs with continued treatment.
Production of antibodies also resulted in IgG-mediated activation of complement that led to anaphylactoid reactions in some of the pharmacodynamic studies, in MPS I dogs and cats, conducted with less pure and differently formulated preparations of rhIDU than the current clinical product. These reactions were alleviated in subsequent pharmacodynamic studies through the use of antihistamine pre-treatment, a two-stage infusion regimen and inclusion of CSA in the infusate. Anaphylactoid reactions were not observed in repeat dose studies with the commercial formulation through 13 weeks in the 26-week study in monkeys or an 8-week study in dogs. Importantly, no study included antihistamine pre-treatment or use of albumin in the infusate.

No genotoxicity and carcinogenicity studies were performed, which is considered acceptable on the basis of the nature of the product.
Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown.
Aldurazyme should not be used during pregnancy unless clearly necessary. It is also recommended to stop breast-feeding during Aldurazyme treatment.

It can be concluded that the package of toxicity data as a whole suffices for this compound, provided that careful clinical observations are made and undertakings fulfilled post-marketing. The preclinical findings of potential serious clinical concern relate to immune reactions, anaphylaxis, hypersensitivity and the development of antibodies, which is further discussed in the clinical section.

4. Part IV: Clinical aspects

Aldurazyme (laronidase) is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease (see section 5.1 of the SPC). MPS I is caused by an inherited deficiency in the activity of the lysosomal enzyme α-L-iduronidase. It is an extremely rare disorder, with an estimated prevalence in the European Union of approximately 0.025 in 10,000 persons. Due to lack of functioning α-L-iduronidase, there is an abnormal accumulation and tissue deposition of certain glycosaminoglycans (GAG). At present, there is no treatment available for the disease, other than palliative.

The recommended dosage regimen of Aldurazyme is 100 U/kg body weight administered once every week as an intravenous infusion. The total volume of the administration should be delivered in approximately 3-4 hours. Since MPS I is a genetic disorder, the replacement therapy is foreseen to be a lifelong therapy.

Overview of Clinical Trials Programme

The clinical trials were performed according to Good Clinical Practise (GCP) standards and agreed international ethical principles.

Two clinical trials were performed as part of the development programme of rhIDU in the proposed indication. These studies enrolled a total of 55 patients with a confirmed diagnosis of MPS I based on IDU levels; 32 of these patients received rhIDU, the remaining patients received placebo.
The supportive study (BIO7500-001), a phase I/II open-label study enrolled 10 patients, 6 males and 4 females ranging in age from 5 to 22 years old with a mean age of 12.3 years. The objective of the phase I/II study was to evaluate the safety and efficacy of rhIDU in the treatment of patients with MPS I. A protocol amendment allows an extension of the treatment period to 152 weeks.

The pivotal study (ALID-003-99), a phase III, multicentre, double blind, randomised, placebo-controlled study enrolled 45 patients. The objective of the phase III study was to confirm the clinical safety and efficacy of treatment of MPS I patients with rhIDU during a 26-week treatment period. 45 patients were randomised, 23 in the placebo group (ranging in age from 6 to 39 years old with a mean age of 15.4 years) and 22 in the rhIDU group (ranging in age from 7 to 43 years old with a mean age of 15.6 years). Furthermore, the phase III pivotal trial (ALID-003-99) was extended as a phase III open-label extension study (ALID-006-001) evaluating the long-term safety and efficacy of rhIDU. Patients completing the phase III double-blind study were given the option to continue treatment with rhIDU in the open-label study. All patients chose to continue receiving rhIDU for up to 18 months. However, only summary details were provided with this application and the results from this extension phase will be submitted for review post-marketing.

The dose administered was the same in both studies; 100 U/kg body weight administered once weekly. The pre-clinical data suggested that this was the effective dose to guarantee adequate delivery of the enzyme to all tissues in order to demonstrate biochemical and clinical improvement in the disease. The choice of dosing interval (once per week) was based on a pre-clinical *in vitro* study using fibroblasts that demonstrated uptake into the lysosome, degradation of GAG, and suggested that the half-life of the enzyme was 5 days after uptake into the lysosome. The time of day of dosing was not specified, nor was the relation of dosing to meals. However, given the route of administration and nature of action of rhIDU, there are no anticipated effects of food and drink on efficacy.
The dosing regimen used in both of these studies, 100 U/kg (0.58 mg/kg) as a slow intravenous infusion once weekly, is that proposed for commercial use in humans (see section 4.2 of the SPC).

Clinical pharmacology

Human pharmacokinetic and pharmacodynamic data are derived from both the phase I/II and phase III clinical studies (see above).

Pharmacodynamics

A reduction of urinary GAG excretion due to removal of excess dermatan and heparan sulphate was selected as a pharmacodynamic endpoint (and one of the efficacy parameters) in both the phase III study and the phase I/II study. The scientific assumption was proposed that a 50% reduction in urinary GAG would be an appropriate surrogate marker for clinical improvement. Furthermore, rhIDU treatment was considered effective if at least two-thirds of the patients completing the study showed a 50% reduction in urinary GAG at week 52 (one of the primary endpoints in the phase I/II study).

Phase I/II study (BIO7500-001)
Pre-treatment GAG levels correlated with the severity of disease in all patients. After 1 to 2 weekly infusions of rhIDU, there was a decline in urinary GAG levels. After 5 to 6 doses, urinary GAG levels appeared to reach a plateau that was equivalent to a reduction of 30% of the pre-treatment level. A sustained gradual decline was reported at the end of the study period in all patients. The mean urinary GAG level had declined to 31.3% at week 26, 37.2% at week 52, and 26.4% at week 104. Seven patients with values at week 152 showed a mean reduction to 21.5%. Statistical analysis demonstrated that at weeks 6, 12, 26, and 52, the reduction in urinary GAG was statistically significant ($p<0.001$).
The primary endpoint of a ≥50% reduction in urinary GAG levels in two-thirds of the patients was met at weeks 26 and 52 and 10/10 patients showed a ≥ 50% reduction of urinary GAG at week 26, 8/10 patients showed a ≥ 50% reduction at week 52, 9/9 patients showed a ≥ 50% reduction at week 104 and 7/7 patients showed a ≥ 50% reduction at week 152.
This reduction confirmed the mechanism of action demonstrated *in vitro* of IDU replacement therapy, the hydrolyse of the accumulated GAG substrates (dermatan and heparan sulphate). Variations in pharmacokinetic parameters did not significantly affect rhIDU efficacy in terms of urinary GAG excretion. There was little correlation ($r^2 = 0.034$) between peak plasma IDU activity versus urinary GAG concentration.

Phase III study (ALID-003-99)
The difference between treatment groups in mean change from baseline to week 26 was evaluated for urinary GAG levels**.** For the placebo group, urinary GAG levels showed a mean increase of 47.3% over the 26 weeks, while the rhIDU group demonstrated a mean decrease of 54.1% ($p<0.001$). The mean urinary GAG levels for the rhIDU group differed from the placebo group by 101% at the end of the 26 weeks treatment period, which was statistically significant ($p<0.001$) and considered clinically relevant. The decrease in urinary GAG levels observed in the rhIDU group was evident by week 4 of the study period and was maintained through week 26. Overall, all patients in the active treatment group had a reduction in urinary GAG level although no patient achieved a normal level by week 26 of treatment.
All patients included in the study were evaluated for the development of IgG antibodies (ELISA). 20 of 22 patients who received rhIDU treatment tested positive for enzyme specific antibodies. The mean time to a positive ELISA result was 53 days after initiation of treatment (range 20 to 106 days). Despite the IgG formation, the decrease of urinary GAG was maintained over time with a magnitude similar to that observed in the phase I/II study.

Pharmacokinetics

A total of 22 patients were included in pharmacokinetic determination, all 10 patients from the phase I/II study and a subset of 12 patients on treatment from the phase III study. Due to the nature of enzyme replacement therapy, it was inappropriate to investigate rhIDU in studies in healthy volunteers. Hence, both studies were performed in MPS I patients.
The phase I/II study examined the pharmacokinetic profile of IDU in plasma following once weekly intravenous infusions of rhIDU (over approximately 3-4 hours) at a dose of 125,000 U/kg (0.50 mg/kg) (equivalent to 100 U/kg (0.58 mg/kg)) for 152 weeks. Plasma pharmacokinetic samples were taken at infusions 1, 2, 6 (two patients only), 12 and 26. Tissue enzyme activity was also assessed in the phase I/II study by evaluation of IDU enzyme levels in buccal brushings and leukocytes. No other patient tissue samples were collected in either clinical study.
The phase III study examined the pharmacokinetic profile of IDU following once weekly intravenous infusions of rhIDU (over approximately 4 hours) at a dose of 100 U/kg (0.58 mg/kg) for 26 weeks in a sub-group of patients. Pharmacokinetic samples were taken at infusions 1, 12 and 26.

Phase I/II study (BIO7500-001)
Plasma activity rose slowly over the first hour of slow infusion. During the increased infusion rate period (the following 2-3 hours), the plasma IDU activity level continued to rise and generally reached a peak activity level of 100-200 U/ml just at the end of the infusion (C_{max} range: 52 - 225 U/ml). After the infusion ended, the enzyme activity fell rapidly, reaching low but still detectable levels 4 hours after the end of the infusion. The peak activity levels achieved were about 10 times the half-maximal uptake *in vitro*.

Variations in C_{max}, $t_{½}$ and CL occurred within and between patients as treatment progressed. These variations appeared primarily related to changes in individual patient physiology rather than to immune response (4 patients developed IDU-specific antibodies).
The mean circulating $t_{½}$ of IDU was approximately 1.8 to 1.9 hours at weeks 1 and 2 and decreased to 1.2 to 1.4 hours at weeks 12 and 26. There was no evidence of accumulation of IDU over time. The $t_{½}$ early in rhIDU treatment was consistent among patients receiving different batches of enzyme, with an SD of 0.280 and 0.214 hours for weeks 1 and 2, respectively. During treatment the variation increased such that by weeks 12 and 26 the $t_{½}$ SD was 0.442 and 0.574 hours. Plasma CL was relatively consistent at weeks 1, 2, 6, and 26, with mean values between 270 and 350 ml/h/kg, but increased at week 12 to 506.3 ml/h/kg. No relationship was found between urinary GAG levels and enzyme pharmacokinetic parameters.

Tissue enzymatic activity was assessed by the evaluation of IDU enzyme levels in buccal brushings and leukocytes. Prior to treatment, all patients had very little or no detectable IDU in their buccal mucosa. By the week 2 pre-infusion assessment, enzyme was detectable in the buccal mucosa. When compared to the mean level of IDU in normal buccal mucosa IDU levels in MPS I patients reached an average of about 1% of normal in all patients, a level expected to reduce GAG storage. The presence

of IDU in the buccal mucosa provides a measure of the adequacy of the enzyme replacement process by showing that the enzyme is being delivered to distal tissue.
Leukocyte IDU levels were very low or undetectable at pre-treatment. When compared to the mean level of IDU in normal leukocytes, the mean trough plasma levels reached an average 18% of normal at week 26, 12% of normal at week 52, and 35% of normal at week 104. Leukocyte IDU levels provide further support that enzyme is being delivered to different cell types and demonstrates that, as expected, a higher level of enzyme uptake is achieved in cells that are in direct contact with the circulation.

Phase III study (ALID-003-99)
Due to the short $t_{½}$ observed in this study (2 to 4 hours) relative to the dosing frequency of once every week, each infusion was treated as a single dose for pharmacokinetic analysis. At infusion, the mean C_{max} was 0.197 U/ml, and was reached at a median of 3.93 hours, consistent with the median infusion time of 3.98 hours. Following the infusion, the plasma IDU concentration remained above concentration for half-maximal saturation of uptake into cells (0.7 nM; 0.01 U/ml) for approximately 3-4 hours.
Mean CL was 1.96 ml/min/kg, mean V_z was 0.604 L/kg, mean V_{ss} was 0.440 L/kg, mean $t_{½}$ was 3.61 hours and mean MRT was 3.83 hours. There were statistically significant differences ($p \leq 0.050$) among the infusions over time for C_{max}, V_z and V_{ss}, both normalised and not normalised for body weight. There was an increase in C_{max} over the 26-week dosing period, with a mean 7% increase between infusions 1 and 12, and a further mean 44% increase between infusions 12 and 26. This increase was probably due to a reduction in V_z by approximately 50% between infusions 1 and 12. The reduction in V_z may also account for the trend towards a reduction in $t_{½}$ over time. There was an inverse relationship between V_z and antibody level at weeks 12 and 26, which might suggests that the decrease in V_z could be related to formation of anti-rhIDU antibodies during treatment. However, CL did not appear to be affected by the duration of the treatment period (26 weeks), indicating that the irreversible transport of rhIDU out of the plasma was not affected. Antibody bound enzyme may have different distribution characteristics than unbound enzyme, thus increasing the fraction of the total body load of enzyme in the plasma and reducing the volume of distribution. Alternatively the V_z and V_{ss} decreases could be explained with the reduction of liver impairment i.e. an increased number of functional hepatocytes capable to better capture rhIDU.

Interaction studies

Since laronidase is a protein, it is not expected to bind to other proteins and metabolic degradation is expected to follow the pathways of other proteins, i.e. peptide hydrolysis. Laronidase is unlikely to be a candidate for drug-drug interactions and neither *in vitro* interaction studies nor specific *in vivo* clinical drug interaction studies were therefore carried out. However, there is a theoretical risk of inhibition of intracellular α-L-iduronidase activity by chloroquine and some other amines and this is appropriately reflected in section 4.5 of the SPC. Any evidence of product interactions will be reported post-authorisation. Analgesics and antibiotics that are often used in MPS I patients have in clinical studies been administered concurrently with rhIDU to a large number of patients without any reports of adverse events from potential interactions.

Special groups

The influence of renal function on the pharmacokinetics of α-L-iduronidase was not studied. Renal elimination of α-L-iduronidase is considered to be a minor pathway for clearance.
The influence of hepatic function on the pharmacokinetics of α-L-iduronidase was not studied. As metabolism is expected to occur by peptide hydrolysis, an impaired liver function is not expected to affect the pharmacokinetics of α-L-iduronidase in a clinically significant way.
There are no pharmacokinetic data in children below the age of 5 years and in patients older than 65 years and no dosage regimen can be recommended in these patients. However, the applicant is currently undertaking a study in patients < 5 years of age with MPS I and these data will be provided post-marketing. The lack of data has been clearly reflected in the SPC.

Bioequivalence studies

No bioequivalence studies were conducted.

Clinical efficacy

Supportive study

Description of the study
Study BIO7500-001 was an open-label phase I/II clinical study of the safety and efficacy of rhIDU in patients with MPS I when treated for 26 weeks. The protocol was later extended to allow for treatment and assessments out to 152 weeks. Up to 10 patients aged 5 years and over with a diagnosis of mucopolysaccharidosis I (MPS I) confirmed by clinical and enzymatic assessments were enrolled. The patient population comprised 6 males and 4 females ranging in age from 5 to 22 years of age (mean: 12.3 years). rhIDU in doses of 125,000 units per kg (0.58 mg/kg) was administered by slow intravenous infusion (over approximately 4 hours) once per week for 152 weeks. All patients were pre-treated with antihistamines and/or corticosteroids to help manage potential hypersensitivity reactions. The reasons for missed infusions in the phase I/II study were mainly due to unavailability of laronidase. However, the overall compliance rate was over 90%.

RESULTS

Primary efficacy variables
The primary endpoints studied included hepatosplenomegaly (through week 104) and urinary Glycosaminoglycans (GAG) (through week 152).

Hepatosplenomegaly: The mean decrease in liver volume from baseline to week 26 was 23%. At week 26, 8 of 10 patients had ≥ 20% reduction in liver volume and 5 of 10 patients had a ≥ 20% reduction in spleen size. At week 26, 8 of 10 patients had normalised liver sizes. At week 52, 7 of 10 patients had ≥ 20% reduction in liver volume and 6 of 10 patients had a ≥ 20% reduction in spleen size. The mean decrease in liver volume was 23% at week 26 and 26% at week 52. At week 52, 9 of 10 patients had normalized liver sizes and 2 of 10 patients had normalized spleen sizes when expressed as a percentage of body weight. At week 104, 7 of 9 patients had a ≥ 20% reduction in liver volume and 4 of 9 patients had a ≥ 20% reduction in spleen volume. At week 104, 9 of 9 patients had normalized liver sizes and 1 of 9 patients had normalized spleen sizes when expressed as a percentage of body weight.

Urinary Glycosaminoglycans (GAG): Initiation of weekly enzyme infusions induced a sharp decline in urinary GAG excretion within 2 to 3 weeks. 10 of 10 patients showed a ≥ 50% reduction of urinary GAG at week 26, 8 of 10 patients at week 52, 9 of 9 patients at week 104, and 7 of 7 patients at week 152. When compared to GAG excretion in a normal population, the excess GAG excretion was reduced to within 20% of the normal range at week 52, to 18% at week 104 and was within the normal range (101% reduction) at week 152. In 9 of the 10 patients, the urinary GAG excretion approached or was within the normal range.

Secondary efficacy variables
The secondary efficacy variables studied included airway obstruction (measured through week 26; week 52 for those with an abnormal baseline), Joint Range of Motion (ROM) (measured through week 104), Cardiac function (measured through week 104), and Eye Disease (measured through week 104).

Airway Obstruction: Total apnea and hypopnea events per night decreased from a mean of 6.6 to 1.1 (83% decrease) and 8.9 to 4.9 (45% decrease), respectively, at week 26. Seven patients with apneic or hypopneic events at baseline had a decreased number of events after starting treatment, 1 patient had no change, and 2 patients had an increased number of events. Minutes of hypoxia, defined as minutes below 90% oxygen saturation, decreased in the 2 patients with hypoxic events at baseline pre-treatment.

Joint Range of Motion (ROM): Shoulder flexion increased from baseline in 7 of 8 patients with a statistically significant increase in mean ROM of 28.13°(right) and 26.12°(left) at week 52 and 30.37°(right) and 23.89°(left) at week 104. Shoulder extension increased by 15.91°(right) and 14.66°(left) at week 104. The mean ROM of knee extension increased at week 52, with a statistically significant linear trend in right knee extension. The change in right knee extension was sustained at week 104, and left knee extension increased. Elbow extension ROM showed a statistically significant increase at week 52, with increases of approximately 7° in the right and left elbows. While mean ROM was still increased compared to pre-treatment at week 104, mean ROM had decreased from week 52.

Cardiac function: New York Heart Association (NYHA) Scores of functional capacity improved by one class or more in all 10 patients. The number of patients with Class I NYHA scores increased from 0 at pre-treatment to 5 at week 52 and 6 at week 104. All patients showed a decrease of at least one class by week 52. The results very likely reflect improvements in factors such as cardiac function, joint function, and pulmonary function.

Eye disease: All three patients with the worst visual acuity at pre-treatment showed improvement in one eye. Corneal clouding did not change appreciably in any patient.

Furthermore, MRI Studies of the Brain and the Cervical Cord was undertaken, as well as measurements of Lumbar Puncture Opening Pressure and GAG Levels of CSF. No substantial or consistent results were observed and the results were not statistically significant. However, although conducted in a smaller number of individuals (N=6) lumbar puncture for the evaluation of cerebrospinal fluid detected a reduction in the GAG concentration, which was not accompanied by any change in higher functions.
Evaluation of the bone, investigation of increases in height and weight as well evaluation in accordance with Wechsler Intelligence Scales, but without consistent or statistically significant results.

Main clinical study

Description of the study
Phase III study (ALID-003-99) was a multicenter, double-blind, randomised, placebo-controlled study of the safety and efficacy of rhIDU in patients with MPS I when treated for 26 weeks. The study was conducted at five sites; two in Europe, two in the US, and one in Canada.

To be eligible for the study a patient must have had an enzyme activity level of less than 10% of the lower limit of the normal range, must have been capable of standing independently for a minimum of six minutes and walking a minimum of five meters within six minutes, must have been able to perform a reproducible FVC manoeuvre, and must have had a baseline FVC value that is less than or equal to 80% of the patient's predicted normal FVC value.
Within 2 weeks of completing the baseline phase, patients were randomised into the treatment phase and received either rhIDU treatment or a placebo. During the treatment phase, patients received a 4-hour intravenous infusion of the study medication on a weekly basis (7± 3 days) at the investigative study centre for 26 consecutive weeks. Patients randomised to the rhIDU treatment group received 100 units/kg rhIDU. All patients received pre-treatment with both antihistamines and antipyretics. A minimum of 4 days was required between consecutive infusions.

A total of 45 patients were randomised into the study; 23 to the placebo group and 22 were randomised to receive rhIDU. All 45 randomised patients completed the study. The mean ages at baseline in the two treatment groups were comparable, with a mean age of 15.4 years in the placebo group and a mean age of 15.6 years in the rhIDU treatment group. The age range for this study was from 6 to 43 years of age. In addition, 49% of patients in the study were ≤ 12 years of age, 24% of patients were 13 to ≤ 18 years of age, and 27% of patients were 19 to ≤ 65 years of age. The distribution of male and female patients between the two treatment groups was comparable, as was the number of males and females entered into the study. 37 (82 %) patients in this study were classified as Hurler-Scheie patients, with 7 (16 %) patients being classified as Scheie patients, and 1 (2 %) patient

being classified as a Hurler patient. Both treatment groups had a low mean enzyme activity level (1.9 % and 1.2 % of lower normal range in the placebo and rhIDU groups, respectively).
In this study, personal reasons were responsible for missed infusions; patient or parent willing to received infusions less frequently than once a week. However, the overall compliance rate was over 90%.

RESULTS

Primary Efficacy Variables

The protocol defined two primary efficacy objectives for this study; each comparing the mean and median changes from baseline to week 26 between the laronidase treated group and the placebo-control group. First, the study sought to show a statistically significant increase in percent predicted normal forced vital capacity (FVC). Second, the study sought to show a statistically significant increase in the absolute distance travelled (in metres) during the six-minute walk test.
Hypothesis testing for the primary efficacy objective was carried out using a Wilcoxon rank-sum test and the primary endpoints was deemed to have been met if the mean change from baseline for both parameters are statistically significantly different at the 0.05 level.

% of Predicted Normal Forced Vital Capacity: After 26 weeks of treatment, the difference between the active and placebo groups in the change from baseline in the mean % of predicted normal FVC was 5.9 percentage points (median difference 3.0 percentage points, p=0.016).
When considering the difference for % of predicted normal FVC seen in this study and calculating an effect size, the resulting effect size is 0.6, which is in the moderate effect size range described by Cohen. Paediatric asthma trials are commonly designed to detect a difference of 5% in pulmonary function tests, which approximates what is seen in this study where 73% of patients are in the paediatric age range.

Six-minute walk exercise tolerance test: The change from baseline to week 26 in the 6-minute walk distance in the rhIDU treatment group was 19.7 meters compared to –18.3 meters in the placebo treatment group. This leads to a mean difference from placebo of 38.1 meters (median difference 38.5 meters, which is close to being statistically significant in favour of the rhIDU treatment group (p=0.066)). When viewing this in terms of effect size, the resulting effect size is 0.6, which is in the moderate effect size range described by Cohen.

Secondary Efficacy Variables

There were four secondary efficacy endpoints: change from baseline to week 26 in the apnea/hypopnea index, liver organ volume, disability score index of the Childhood Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ), and in the shoulder flexion of the Joint Range of Motion (ROM) (the mean of the left and right shoulders was used for the analysis).

Apnea/Hypopnea Index (AHI): Values in the rhIDU treatment group decreased on average by –2.9 whereas the placebo group increased slightly by 0.4. This result was not statistically significant (p=0.145) even though the trend is in favour of the rhIDU treatment group. A *post-hoc* subgroup analysis was performed in patients whose AHI scores at baseline were suggestive of obstructive sleep apnea-hypopnea syndrome. There were nine patients in the rhIDU treatment group with an AHI $\geq$ 20 at baseline. A within-group test on the changes from baseline to week 26 in these nine patients resulted in a mean decrease in the AHI of –7.4, which was statistically significant (p=0.011). Four of these patients reduced their AHI from $\geq$ 20 to below 20.

Hepatomegaly: The % change was statistically significant in favour of the rhIDU treatment group, with a mean decrease of –18.9% in the rhIDU treatment group compared to an increase of 1.3% in the placebo treatment group (p=0.001). Differences between the two treatment groups were seen as early as week 4, which correlates with the improvements seen in FVC in the rhIDU treatment group as early as week 4. Of the 14 patients in the placebo group who were classified as having abnormal baseline liver organ volumes, three patients (21%) were considered normal at week 26; of the 18 patients who

were classified as having abnormal liver organ volumes at baseline in the rhIDU treatment group, 13 patients (72%) were considered normal at week 26.

The CHAQ/HAQ Disability Index evaluates the extent of disability using a scale of 0 to 3 with 3 being the worst score. Changes in the score were small and not statistically significant when looking at the overall population.
Joint Range of Motion (ROM) (Shoulder Flexion): When looking at the overall population for shoulder flexion changes from baseline to week 26, the placebo group decreased by –4.9 degrees compared to –1.5 in the rhIDU treatment group. This difference was not statistically significant (p=0.987).

Tertiary Efficacy Variables
The % change from baseline to week 26 in urinary GAG levels was statistically significant in favour of the rhIDU treatment group with a mean decrease of 54.1% in the rhIDU treatment group compared to an increase of 47.3% in the placebo group ($p < 0.001$). Differences between the two groups were seen as early as week 4 in this surrogate marker. These results corroborate the decreases in urinary GAG levels observed in the phase I/II study.
Other tertiary efficacy variables including the total respiratory index of the sleep study, the Pain Scale of the CHAQ/HAQ, and quality of life measurements failed to reach statistical significance.

Extension study

Phase III study open-label extension (ALID-006-01)
The double-blind phase was followed by an open-label extension phase for 24 weeks, resulting in a total of 50 weeks of treatment. All patients received active therapy with rhIDU although without knowing treatment assignment in the concluded double-blind phase. Efficacy parameters were analysed at baseline (last measurement prior to randomisation in phase III double-blind phase), entry (last measurement prior to enrolment in phase III open-label extension phase) and at weeks 12 and 24 of the study.

Results

The placebo/rhIDU group showed a slight decline (0.6%) in mean FVC (p=0.596) and increase in mean (23.8 metres) Six-minute walk distance (p=0.073) from entry to week 24. The rhIDU/ rhIDU group had a slight increment (0.6%) in mean FVC (p=0.732) and increase in mean (23.2 metres, p=0.015) Six-minute walk distance from entry to week 24. The rhIDU/ rhIDU group showed an overall change from baseline of 5.9 % (p=0.003) in mean FVC and 42.9 metres (p=0.005) Six-minute walking distance. At week 50 a mean reduction of 64.8% in urinary GAG was observed.

Clinical studies in special populations

No studies in special patient groups were performed although the applicant is currently undertaking a study to evaluate the effect of Aldurazyme in children < 5years of age with the most severe phenotype of MPS I. These data will be provided as part of a post-marketing commitment. The lack of data in children <5 years of age and in patients >65 years are reflected in the SPC.

Impact of Antibody Development on the clinical efficacy results

Based on the clinical trials performed, almost all patients are expected to develop IgG antibodies to laronidase, mostly within 3 months of initiation of treatment. All seropositive patients were tested for in-vitro neutralising effects. Three patients showed marginal in-vitro neutralising inhibitory activity, which did not appear to impact clinical efficacy. Two of the patients who initially developed IgG antibodies to laronidase no longer had detectable IgG antibodies after a total of 12 months of Aldurazyme treatment. The presence of antibodies appears not to be related to the incidence of IARs. However, due to the rarity of the condition and the limited experience to date, the effect of antibody formation on safety and efficacy is currently not fully established. The occurrence of IgE antibodies

was not fully explored. The applicant has committed to further investigate the impact of antibody formation on clinical efficacy as a part of the post-marketing commitments.

Clinical safety

Patient exposure

Safety data were reported from the two clinical studies, the extension study and compassionate use/ expanded use programme. The actual safety profile of rhIDU is only based on 68 patients (10 patients in the phase I/II and 45 patients in the phase III study and 13 patients in compassionate use programmes) treated with a formulation including HSA.

Adverse events and serious adverse events/deaths

Phase I/II study (BIO7500-001)

The study provided some insight with respect to long-term effects of the observed immune responses. All 10 patients completed 52 weeks of therapy, 9 patients completed 104 weeks of therapy, and 8 patients completed 152 weeks of therapy. There were two patient deaths during the 152-week period, one due to a systemic viral illness and one case due to complications following spinal fusion surgery for worsening scoliosis. Any relationship to laronidase treatment was deemed unlikely in both cases.

The most commonly reported adverse events occurring on the day of infusion were: rash (80%), abdominal pain (60%), headache (60%), pain (60%), rhinitis (60%), and urticaria (60%).
The most commonly reported adverse events occurring on non-infusion days were: rhinitis (100%), pain (90%), asthenia (80%), cough increased (80%), abdominal pain (70%), fever (70%), headache (70%), vomiting (70%), and sinusitis (70%).

Adverse events that occurred on the day of infusion and were considered related to laronidase could, therefore, be indicative of a hypersensitivity reaction. Events that were known to occur prior to the start of infusion of laronidase were excluded. The types of reactions varied among patients with the most common being rash and urticaria.

In the phase I/II study, all patients developed rhIDU-IgG antibodies (ELISA assays) within 6 to 12 weeks of treatment and 4 patients (40%) experienced specific responses to rhIDU (Western blot). All IDU-specific antibodies declined with time and did not affect the efficacy of the treatment. The effect of the antibodies to rhIDU on enzyme distribution and efficacy was studied by comparing antibody titres with enzyme clearance rates ($t_{1/2}$) and results of therapy (urinary GAG levels). With the exception of allergic reactions, there was no apparent relationship between antibodies, pharmacokinetics, uptake, or efficacy of the enzyme.

Phase II/III study (ALID-003-99)

In the phase III study, 22 patients received an infusion of rhIDU (HSA formulation) weekly (see table below). The following safety parameters were monitored during the phase III trial: adverse events, serious adverse events, infusion-associated reactions, immunogenicity testing, physical examinations, vital signs, brain/cranio-cervical junction MRI, and standard safety laboratory assessments.

All patients in the placebo group and a majority of the patients in the rhIDU group (95%) experienced at least one adverse event during the conduct of the study. None of the patients in either group withdrew due to an adverse event.

Summary of Patients Experiencing Adverse Events During Double-Blind Treatment*

	Placebo (n=23)	Aldurazyme (n=22)
Patients Experiencing Adverse Events	23 (100%)	21 (95%)
Discontinuations Due to Adverse Events	0	0
Patients with Drug-Related Adverse Events	16 (70%)	12 (55%)
Patients with Serious Adverse Events	0 (0%)	3 (14%)
Patients with Severe Adverse Events	2 (9%)	6 (27%)
Patients with Infusion-Associated Reactions	11 (48%)	7 (32%)

*Coded using WHO ART preferred terms

Among adverse events occurring in more than 10% of the patients in the rhIDU treatment group on the day of infusion, the most commonly reported adverse events were: flushing, fever and headache. No clinically significant differences were reported between treatment groups with respect to reports of adverse events occurring on the day of infusion.
Among the AEs occurring in more than 20% of the patients in the rhIDU- and placebo groups on non-infusion days, the most commonly reported adverse events were: headache, fever, rash and rhinitis.
There were three patients who experienced seven serious adverse events during this study. All patients were in the rhIDU treatment group and all events were reported as not related to laronidase. There were no deaths during this study.

All adverse events that occurred on the day of infusion that were reported as causally related and were not a result of a protocol-determined assessment on that day (i.e., physical exam, standard laboratory testing) were considered to be infusion–associated reactions. Eleven patients from the placebo group and seven from the rhIDU treatment group experienced an infusion-associated reaction. The types of reactions varied among patients with the most common being flushing. A majority of the reactions were reported as mild in intensity and none were noted to be severe.
Some patients experienced a positive rechallenge but there were important variations in the clinical presentation, severity and timing of the reactions. Twenty of the 22 rhIDU-treated patients developed specific IgG antibodies but none of the 2 tested patients presented rhIDU-specific IgE antibodies.
None of the patients experiencing infusion-associated reactions had positive results for complement activation and rhIDU-specific IgE.

Phase 3 clinical study – open-label extension (ALID-006-01)
Adverse events were similar in this phase. All except two in the placebo/rhIDU group had developed antibodies. One death occurred due to a respiratory infection and there were 14 serious adverse events. All except one was considered unrelated to test medication. One patient had an anaphylactoid type reaction but recovered without sequelae. Infusion associated reactions were mostly mild in intensity.

Compassionate use (ALID-007-001) / expanded use programme
The patients enrolled received the same treatment regimen as used in the phase III study. In the expanded access protocol, Aldurazyme is administered with HSA while it is administered without HSA in the compassionate use programme. One death was reported in the study ALID-007-001, determined to be unrelated to treatment with rhIDU.

Immunogenicity

Approximately 32% of patients experienced infusion-associated reactions (IARs). Over time the number of these reactions decreased. The majority of the IARs were of mild intensity; the most common reactions consisted of flushing and headache. However, of great concern is a case with pre-existing airway compromise who developed a severe reaction three hours from the start of the infusion (at week 62 of treatment) consisting of urticaria and airway obstruction, requiring tracheostomy. Furthermore, three patients experienced angioedema in the Phase 1/2 study.

There were important variations in the clinical presentation, severity and timing of the hypersensitivity-type reactions. These reactions could be related to the presence of laronidase and/or to impurities. According to the applicant, the addition of human serum albumin (HSA) to the infusate was aimed to reduce anaphylactoid reactions. In both studies, the patients improved from

anaphylactoid reactions after slowing or temporarily stopping the rate of infusion. They were premedicated either with glucocorticoids or antipyretics and/or antihistamines.
IgG testing was performed to further investigate potential immunogenicity. Multiple blood samples per patient were obtained at various timepoints during the study. Samples were tested using an ELISA technique. Overall, 24 patients (4/10 + 20/22) out of 32 developed specific IgG to rhIDU between the 4th and the 16th infusion and 5 patients who received placebo tested positive for IgG antibodies. The mean time to a positive ELISA result was 41 days after initiation of treatment.

The presence of antibodies against the enzyme remains a concern and will need to be assessed following the availability of long-term safety data.

Laboratory findings

There were no clinically important abnormalities in haematology, serum chemistry, or urinalysis results and no indication of immune complex disease following 152 weeks of treatment.

Safety in special populations

No studies in special patients were submitted and this has been sufficiently reflected in the SPC.

Discussion on clinical aspects

Discussion on clinical efficacy

The applicant has demonstrated that the pharmacodynamic effects of Aldurazyme on the reduction of urinary excretion of GAGs were consistent across the two studies. The plasma levels of rhIDU achieved supported the evidence that an adequate drug exposure was achieved as the concentrations remained above the level for half-maximal saturation of uptake into cells. The presence of adequate enzyme levels in buccal mucosa confirms the persistence of enzyme in distal tissues.

The effective dose was based on animal studies where 0.5 mg/kg produced maximum reduction of GAG and further increases had no additional effect (see pre-clinical discussion). Dosage interval was based on steady state urinary GAG levels as a measure of efficacy and data from the phase I/II study on effects of missed infusions.

There was a high degree of intra- and inter-patient variability in pharmacokinetic parameters. The presence of enzyme in leukocytes suggests that variation in pharmacokinetic parameters and/or formation of antibodies did not result in decreased bioavailability of rhIDU at the cellular level. However, in the phase III study an inverse relationship between V_z and antibody level was noted at weeks 12 and 26. This finding might be suggestive that the decrease in V_z could be related to formation of anti-rhIDU antibodies during treatment. In both clinical studies undertaken patients developed enzyme specific antibodies, although according to the applicant this effect was of no clinical significance since the GAGs effects were maintained long-term. Antibody formation seems to be unrelated to clinical efficacy as showed when looking at the primary endpoint as well as uptake of laronidase on a cellular level. It therefore appears that seroconversion is not associated with *in vivo* neutralising activity, although this possibility cannot be completely ruled out.
No data on changes in pharmacokinetics and pharmacodynamics parameters were presented with reference to the severity of illness and this is considered a limitation.

The phase I/II- and phase III studies provided adequate and consistent evidence to support the efficacy of Aldurazyme based on the results on FVC, reduction in liver and spleen and reduction in urinary GAG levels. The percent change from baseline to week 26 in mean liver organ volume was clinically and statistically significant in favour of Aldurazyme, with a mean decrease of 18.9% in the Aldurazyme group compared to an increase of 1.3% in the placebo treated group (p=0.001). Liver volumes that were reported abnormal at baseline became normalised at week 26 in the majority of patients (72% and 80% of patients in the phase III- and the phase I/II studies respectively). The mean percent change in urinary GAG levels for patients in the placebo group was an increase of 47.3%

compared to a decrease of 54.1% for patients in the Aldurazyme group ($p < 0.001$) at week 26 and 64.8% at week 50. These results are very encouraging.

Two primary endpoints were selected for the pivotal study (% of predicted FVC and 6-minute walking distance). The multi-system nature of the disease and its natural history means that no single endpoint can be used as the most relevant representative for the disease spectrum. It seems acceptable to use these endpoints, which assess the respiratory function in the case of FVC and a combined cardio-respiratory and mobility assessment in case of 6-minute walk test.
The median change from baseline to week 26 in the % of predicted normal FVC in the rhIDU treatment group was statistically significant and in favour of the active treatment group. This result indicates an improvement in pulmonary impairment. With reference to improvement in six-minute walk distance, there was a positive trend since this distance increased by a median of 27.5m in the Aldurazyme group compared with a median decrease of 11m in the placebo group. However, since the overall difference was not statistically significant the primary objectives of this study have not been met, as both endpoints were not significant at the 5% level. The size effect was also very limited (3% median improvement of the % of predicted FVC ($p=0.016$) and 38.5 m median improvement of the 6-minute walking distance ($p=0.066$)).

The long-term data (50 weeks) provided by the applicant are of value to assess the durability of the effects observed on the primary endpoints. Although not statistically significant at 24 weeks, the improvement of the 6-minute walk test is further substantiated at 50 weeks in the group that received the active drug in both phases ($p=0.005$). With reference to FVC, however, no further gain in effect size is derived from the extension of treatment of patients (24 weeks).
It is possible that patients would show an improvement in FVC and the six-minute walk during the baseline phase as a result of a training effect rather than as a result of therapy. To account for a potential training effect, baseline measurements for the primary efficacy endpoint were defined as the third and final evaluation performed during the baseline phase just prior to randomisation. Baseline rather than current height was used to try and eliminate the confounding effects of postural changes, growth, and variability associated with repeat height measurements.
A primary endpoint, % of predicted FVC values alone might not adequately reflect the obstructive and restrictive symptoms of the MPS I patients. When also considering the other parameters (TLC: total lung capacity and DL: diffusion capacity), results are far from being statistically significant ($p=0.49$ and $p=0.46$ respectively). However, these parameters are more likely to be affected by skeletal involvement of thorax than FVC and would therefore be less sensitive to treatment.

No direct measures of the main complications of the disease have been evaluated: mental development, neurological and respiratory complications and frequency of intercurrent infections. Due to the molecular weight of the drug, distribution within the brain was not expected. To date no clinical data exist demonstrating a benefit on the neurological manifestations of the disease. This is reflected in the indication proposed, which excludes the neurological manifestations of the disease.

As already discussed, two of the secondary and tertiary endpoints showed significant results: reduction of hepatomegaly and of urinary GAG levels. The other endpoints did not reach statistical significance: apnea/hypopnea index, disability index, joint range of motion, respiratory function, cardiac function pain scales, height, ocular measures, quality of life questionnaires filled up either by patients or parents/guardians. However, although the mean changes in the Apnea/Hypopnea Index (AHI) (Events per hour) were not significantly different between the two treatment groups there was a positive trend in favour of Aldurazyme. A marginal improvement could also be seen in joint ROM and cardiac function.

By observing significant effects on FVC, urinary GAG levels and mean liver organ volume the activity of Aldurazyme has been established. Although not statistically significant at 24 weeks, the improvement of the 6-minute walk test is further substantiated at 50 weeks. This has to be taken into account along with the other parameters reflecting the patients' functional capacity such as joint ROM, which also improved long-term. In view of the potential impact of these improvements in terms of daily life, this is considered to be of clinical relevance. Overall, the observed activity of Aldurazyme seems to translate into a real clinical benefit for patients suffering from MPS I.

Of concern is a possible differential long-term effect on patients with a most severe phenotype of MPS I. Only one patient with Hurler syndrome was included in the clinical programme with Aldurazyme. However, this was expected according to the inclusion (age >5 years) and exclusion (BMT) criteria. This patient progressed to a rapid deterioration after an initial improvement. The applicant will provide data from an ongoing study with the most severe type of MPS I as part of a post-marketing commitment. The lack of data in the most severe patients has been adequately reflected in the SPC (section 5.1).

Animal model studies have indicated a potential preventative effect on bone disease and improvements in liver and spleen enlargement but only partial response in lung involvement. For the Hurler patients, the enzyme therapy is therefore expected to be palliative and is expected to improve physical function but CNS disease may ultimately progress. For the Hurler-Scheie patients, early treatment from diagnosis might be expected to prevent the progressive organ storage, breathing difficulties and airway obstruction. The joint stiffness and contractures may be improved and would not likely progress as without treatment. To the extent that treatment precedes the chronic irreversible disease state, the long-term clinical benefit is expected to be greatest in this group of patients. For the Scheie patients, the therapy has shown improvement in breathing and joint function, which are two important physical problems that limit Scheie patients. Given that these patients have slower disease progression, it may be harder to demonstrate the benefits of treatment in the short-term in these patients.

Although the clinical data from the pivotal clinical study and the supportive phase I/II study have shown that the recommended dose is efficient and safe, efficacy of the dose regimen chosen over a longer time of treatment should be explored. The applicant has committed to perform a clinical study post-authorisation to evaluate alternative dosing regimens.

Although the agent has been used in combination with different medications, such as, per protocol, antipyretics and antihistamine drugs (in both studies) and coricosteroids in the phase I/II study and the frequently used concomitant treatments like antibiotics, potential drug interaction has not been examined in detail. The applicant addressed the issue of a potential drug interaction with chloroquine and other amines through an interference with the delivery of receptor bound enzyme to lysososmes. Further, co-adminstration of heparin and other peptides will be looked at in relation to immunogenicity as a post-marketing commitment. These results will be reported as part of the PSURs.

No studies were performed with rhIDU in patients with renal or hepatic impairment because of its expected metabolism through peptide hydrolysis. Renal clearance is expected to play a minor part, but no data have been presented to correlate the excretion in patients with a different degree of renal impairment. Further, impaired liver function is not expected to affect the pharmacokinetics of laronidase in a clinically significant way.

Further, no data are available in patients below the age of 5 years and above the age of 65 years. The pharmacodymanic, pharmacokinetic and immunogenecity findings would have been desirable stratified according to age, in particular < the age of 5, 5 to 12 years olds, adolescents up to the age of 18 years and adults over the age of 18 years. The applicant has commited to seek Protocol Assistance on proposals to assess safety and efficacy in children less than five years of age. Data from the ongoing study ALID-014-02 in children below the age of five with the most severe form of MPS I will be considered.

The variability of the clinical presentation in MPS I may make it difficult to demonstrate a clinical benefit in the short term. Longer follow-up of efficacy is needed and special groups need to be studied for an accurate assessment of the clinical benefit of Aldurazyme.

Discussion on clinical safety

Overall four patients died during the clinical programme with rhIDU, but none was considered related to Aldurazyme treatment. No patients dropped out due to a drug-related AEs in any of the studies

performed. In the phase III study, the incidence and types of AEs experienced were similar between the placebo and rhIDU groups.

The incidence of IARs was similar between the placebo and rhIDU groups. The number of these reactions decreased with time on treatment. The majority of the IARs were of mild intensity, the most common reactions consisted of flushing and headache. However, some IARs were severe and the main safety concern of Aldurazyme is the anaphylactoid reactions observed. A single patient with pre-existing airway compromise developed a severe reaction three hours from the start of the infusion (at week 62 of treatment) consisting of urticaria and airway obstruction, requiring tracheostomy. Furthermore, three patients experienced angioedema in the phase I/II study.

The hypersensitivity reactions that occurred during the phase I/II study were managed by administration of antihistamines and/or corticosteroids, reduction of infusion rates, or temporarily reducing study drug dosage. In the phase III study, infusion associated reactions were usually managed by decreasing the infusion and administration of antihistamines. Appropriate recommendations have been included in the SPC. Patients treated with Aldurazyme should be closely monitored and all cases of infusion-associated reactions, delayed reactions and possible immunological reactions reported. Antibody status should be regularly monitored and reported.

The difference in the safety profiles reported for the two studies, with the phase I/II study having the worst safety profile, has been attributed to the increased purity of rhIDU manufactured by the proposed commercial process, which was implemented prior to the initiation of the phase III trial.
Almost all patients treated with rhIDU developed protein specific IgG antibodies. The presence of antibodies appears not to be related to the incidence of IARs. However, due to the rarity of the condition and the limited experience to date, the effect of antibody formation on safety and efficacy is currently not fully established. Patients who have developed antibodies or symptoms of IARs should be treated with caution when administering laronidase. Aldurazyme treatment should be supervised by a physician experienced in the management of patients with MPS I or other inherited metabolic diseases. Administration of Aldurazyme should be carried out in an appropriate clinical setting where resuscitation equipment to manage medical emergencies would be readily available.

It is of concern that the patients enrolled in the studies were not suffering from the most severe form of MPS I. The clinical development of rhIDU has targeted the Hurler-Scheie and Scheie patients, only one patient with Hurler syndrome has received laronidase, whereas Hurler is the most critical status to be dealt with in clinical practice (most severe and early alterations). After an initial benefit the condition of this patient with the most severe phenotype of MPS I deteriorated. Therefore, it is arguable that efficacy and safety has only been demonstrated in a population affected by the less severe forms of the disease. The lack of data in the most severe type of the disease has been reflected by section 5.1 of the SPC. However, the applicant will provide data from an ongoing study in patients with the most severe type of MPS I as part of a post-marketing commitment.

Longer follow-up of safety is needed and special patient groups need to be studied before an accurate assessment of the clinical benefit of Aldurazyme can be made.

5. Overall conclusions and benefit/risk assessment

Quality

Apart from a number of points, which can all be addressed as part of post-authorisation commitments, the quality of Aldurazyme is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Viral safety and batch to batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology

Overall, the limited programme of primary pharmacodynamic and pharmacokinetic studies, some in animal models of MPS I, provided adequate evidence for efficacy of laronidase.
It can be concluded that the package of toxicity data as a whole suffices for this compound, provided that careful clinical observations are made and undertakings fulfilled post-marketing. The preclinical findings of potential serious clinical concern relate to immune reactions, anaphylaxis, hypersensitivity and the development of antibodies (see pre-clinical and clinical discussion). This has been appropriately considered in the SPC.
No genotoxicity and carcinogenicity studies were performed with Aldurazyme, which is considered acceptable on the basis of the nature of the product.
Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonal/foetal development, parturition and postnatal development. However, the potential risk for humans is unknown and this has been reflected in the SPC. Aldurazyme should not be used during pregnancy unless clearly necessary and it is recommended to stop breast-feeding during Aldurazyme treatment.

Efficacy

The results from clinical studies support the use of laronidase in the approved indication long-term treatment of MPS I to treat the non-neurological manifestations of the disease. The phase I/II- and phase III studies provided adequate and consistent evidence to support the efficacy of Aldurazyme based on the results on FVC, reduction in liver and spleen and reduction in urinary GAG levels (see clinical discussion). The indication for which the medical product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide more comprehensive evidence/data on the safety and efficacy of the medicinal product in larger numbers and over a longer term at this time.

Safety

Safety data show a relatively mild adverse event profile and reasonable tolerability to Aldurazyme.
While adverse events were common, particularly infusion associated reactions, serious adverse events including death attributable to Aldurazyme were uncommon. Four patients died during the clinical programme for rhIDU, but none was considered related to Aldurazyme treatment.
The main safety concern of Aldurazyme is the anaphylactoid reactions observed (see discussion on clinical safety). Appropriate recommendations have been included in the SPC on pre-treatment and management of patients in case of a hypersensitivity reaction.
The infusion-associated reactions can be potentially severe and anti-laronidase antibody formation gives rise to concern and should be paid special attention in post-authorisation studies. The period of laronidase treatment in the clinical trials does not reflect the life-long treatment necessary for patients with MPS I. Since the indication for which Aldurazyme is intended is very rare, the number of patients who have received laronidase is small, and thus the safety database is not as large as is usually the case for new medicinal products. However, since the structure of laronidase is similar to the enzyme produced naturally in humans, laronidase is not likely to cause unexpected adverse events.

In order to collect additional long-term data, the applicant has committed to complete an extensive programme of clinical studies post-authorisation, the results of which shall form the basis of the annual reassessment of the benefit/risk profile. The applicant has committed to implement a MPS I registry programme, which will collect long term safety and efficacy data in patients treated with Aldurazyme as well as data on the natural progression of the disease in patients not on treatment.

Benefit/risk assessment

Following the assessment of the supplementary documentation provided by the applicant, it was concluded that further data was needed to support the safety and efficacy of the product. Although the majority of these questions could be addressed by the applicant as post-authorisation commitments, a number of key issues were identified that needed further discussion at a CPMP ad hoc Expert meeting on clinical aspects of Aldurazyme treatment.

The conclusions from the Experts were:

The expert group was of the view that Hurler´s syndrome, Hurler-Scheie and Scheie´s syndrome represent a continuum rather than separate well-defined entities. Aldurazyme should be indicated for "long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS I to treat non-neurological manifestations of the disease (see section 5.1)." Section 5.1 should include the outcome of the clinical studies performed and should further include a statement that no data are available in the most severe form of MPS I.

The group considered that the endpoints studied were appropriate and that, although small, the demonstrated efficacy was clinically relevant, especially in the light of the absence of alternative therapies. The efficacy shown was considered sufficient for Marketing Authorisation provided that appropriate commitments were made.
The experts considered that an overall positive benefit-risk ratio had been established for Aldurazyme. However, there was concern regarding the severe infusion reactions reported, including the need for tracheostomy in one case. It was agreed that prescribers should be advised to use appropriate premedication i.e. anti-histamines and antipyrectics and that administration of Aldurazyme should only be carried out in hospitals where resuscitation equipment would be readily available. Advice should also be given in relation to slowing the rate of infusion or discontinuing it in the event of an infusion related reaction.

The experts were of the view that prescribers should initiate treatment in patients corresponding to the proposed target population on the basis of the clinical diagnosis, confirmation of enzymatic deficiency. They also suggested a statement in section 4.2 of the SPC that no safety and efficacy data are available in children below the age of 5 years and no dosage regimen can presently be recommended in these patients, which would alert the treating physicians about the lack of prescribing information in that group.

The expert group considered that there is no further need to investigate the correlation between urinary and tissue GAG levels. The group accepted the position of the Applicant that invasive biopsies are not feasible given difficulties with anaesthesia in these patients. There also appears to be a variation in tissue GAG levels between different tissues from the same patient, which makes extrapolations from one particular sample difficult. Further, experience with bone marrow transplantation has shown such a correlation.

The group encouraged the carrying out of further genotyping as often as considered appropriate but was of the view that this should be regarded as a recommendation and not be made mandatory.

The group considered that it would be useful to further investigate a possible genotype versus treatment/response relationship. The Applicant's proposal to address this issue in a clinical trial of the severe form of MPS I was considered appropriate.

Further, the Applicant should commit to provide data on long-term safety from the clinical studies, which are ongoing. The Applicant should also monitor patients treated with Aldurazyme and report all infusion reactions and all cases of possible immunogenic reactions. In those patients where treatment with Aldurazyme is discontinued for weeks/months, the effects of stopping and restarting treatment should be carefully investigated with reference to safety (incidence of allergic reactions) and antibody formation. The potential influence of antibody formation on the long-term efficacy and safety of Aldurazyme is unknown but remains a concern and should be investigated as part of all ongoing and future clinical studies.

In the light of the outcome of the ad hoc expert meeting, the CPMP considered that there was no longer any need for the applicant to address outstanding issues during an oral explanation before the CPMP.

Following the review of the submitted documentation, and the final SPC and letter of undertaking, and after taking into account the advice from the expert meeting, the CPMP agreed that Aldurazyme has

shown efficacy in patients with MPS I that is encouraging and may be clinically relevant and that allows a conclusion on an acceptable benefit/risk despite the limited efficacy and safety data available. The CPMP concluded that a marketing authorisation for Aldurazyme will be granted under exceptional circumstances, subject to fulfilling the clinical and quality follow-up measures and clinical specific obligations undertaken by the applicant. The indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide more data on the safety and efficacy of the medicinal product at this time. In order to collect additional data, the applicant has committed to complete an extensive programme of clinical studies post-authorisation within pre-specified time frames, the results of which shall form the basis of an annual re-assessment of the benefit/risk profile:

Clinical aspects:

- In order to determine whether children less than five years of age will benefit from treatment, the applicant will seek Protocol Assistance within a pre-defined time frame on proposals to assess safety and efficacy in this population.

- The applicant will seek Protocol Assistance within a pre-defined time frame to discuss the performance of a clinical study to investigate alternative dosing regimens (including maintenance dose).

- The applicant commits to complete the implementation of a MPS I registry programme. Patients treated with Aldurazyme will be monitored and all reported infusion reactions and all cases of possible immunological reactions as well as data on antibody formation specifically reported included in the PSURs.
  Further, the applicant commits to extend the ongoing Open Label Extension study (ALID-006-01) for a total of 4 years.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Aldurazyme, for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.