SCIENTIFIC DISCUSSION

1. Introduction

Hunter syndrome is a lysosomal storage disease caused by the missing or defective enzyme, iduronate-2-sulfatase (I2S), which acts to cleave O-linked sulfate moieties from two human glycosaminoglycans (GAG) known as dermatan sulfate and heparan sulfate. Insufficient levels of I2S lead to progressive accumulation of these GAG molecules in nearly all organs and body tissues. Hunter syndrome is a rare disease affecting approximately 0.02 in 10,000 persons in the Community when the application was made. Although the disease is heterogeneous with regard to initial presentation, Hunter syndrome is always severe, progressive, and life limiting.

The central, underlying pathophysiological process leading to the clinical manifestations of Hunter syndrome is the chronic accumulation of heparan sulfate and dermatan sulfate inside cellular lysosomes, resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Accumulation of these GAG species affects nearly all cell types, tissues, and organs of the body including the respiratory tract, heart, liver, spleen, leptomeninges, bones, joints, oropharynx, head, neck, and central nervous system. The clinical manifestations of Hunter syndrome vary considerably from patient to patient with pathology in one organ system presenting the most prominent clinical problem in some patients and impairment in other organ systems presenting the biggest challenge in others. Despite the heterogeneity in the disease progression, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course.

As the disease progresses, the phenotypic features typical of the disorder become increasingly apparent. The most common clinical signs and symptoms include slow mental development, enlarged tongue, coarse facial features, hearing loss, abnormal dentition, restrictive lung disease, hepatosplenomegaly, valvular heart disease, decreased joint range of motion, skeletal deformities, and severe short stature. In addition to their restrictive pulmonary disease, oropharyngeal and respiratory deposition of GAG leads to severe airway obstruction due to macroglossia, supraglottic narrowing, and tracheomalacia, further contributing to impaired pulmonary function and sleep apnoea. Perhaps most devastating to the individuals suffering from Hunter syndrome, is the impact that the progressive physical abnormalities have on their quality of life. Due to a combination of the bone disease, decreased respiratory capacity, and sleep apnoea, with or without impaired cardiac function, individuals with Hunter syndrome suffer from chronic, severely diminished endurance. Early on, this may manifest as an inability to keep up with peers in activities that require physical exertion. Later, their ability to walk even short distances may be lost and eventually many patients become wheelchair bound.

In parallel with their loss of ability to perform activities requiring physical endurance, Hunter syndrome patients also lose much of their ability to perform even simple activities of daily living. Over time, the increasing size and protuberance of the tongue causes difficulty with swallowing and also may impair their ability to speak clearly. The progressive decrease in joint mobility and their broad, claw-like short fingers may prevent patients from independently performing many self-care activities including self-dressing, toilet care, and personal grooming. Hunter syndrome patients become entirely dependent on others at an early age for their continued survival. In the latter stages of the disease, continued accumulation of GAG leads to progressive organ failure and significantly shortened life span. In some cases, GAG accumulation in tissues of the central nervous system leads to severe mental retardation and progressive neurological decline, often exacerbated by communicating hydrocephalus and increased intracranial pressure. Death usually occurs in the second or third decade of life most often from respiratory and/or cardiac failure.

The current treatment of Hunter syndrome is palliative and focused on clinical symptoms. For example, surgery to reduce airway obstruction and continuous positive airway pressure (CPAP) has been used to treat sleep apnoea. Although haematopoietic stem cell transplant (HSCT) has been suggested as a way of providing donor cells capable of expressing I2S, long-term results are limited and inadequate to support a recommendation of HSCT for individuals with Hunter syndrome. Bone marrow transplantation has been attempted in a small number of cases with mixed results. However, this procedure is very risky and is not recommended as routine care for patients with Hunter syndrome. Recent advances in genetic engineering technology have made it possible to produce highly purified human proteins for therapeutic use. Because the primary biochemical defect in Hunter

syndrome is now known to be a deficiency in the quantity or enzymatic activity of I2S, the most direct and logical therapeutic approach to this inherited disease is replacement of the missing or defective enzyme. The scientific concepts underpinning enzyme replacement therapy, have already been established in other lysosomal storage diseases, such as Gaucher disease, Fabry disease, MPS I, and MPS VI. Therefore, the likelihood that enzyme replacement therapy would also benefit Hunter syndrome patients is high.

This is a complete independent application through the Centralised Procedure (according to Council Regulation EEC No 726/2004, Article 3(1) and point 1 of Annex 1 (Biotech Medicinal Product). The proposed and approved indication was: "Long-term term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed

The granting of the marketing authorisation by the CHMP was done under exceptional circumstance as the indication for which the product in question is intended is encountered so rarely that the applicant cannot be expected to provide comprehensive data.

On the 26 October 2001 the COMP recommended the designation of this medicinal product, containing iduronate-2-sulfatase, as an orphan medicinal product for the orphan indication "treatment of Mucopolysaccharidosis, type II (Hunter syndrome)", and the product had Orphan Designation granted on 11 December 2001.

Formal Scientific Advice (Protocol Assistance) was given by CPMP/CHMP on 20 February 2003 (EMEA-CPMP-SAWG-637-03) and 29 July 2004 (EMEA/CHMP/SAWP/71/04). Advice given in response to questions on Chemical, Physical and Biological development has been followed on the whole.

Elaprase is a biological product, which does not contain or consist of any genetically modified organisms.

2. Quality aspects

Introduction

Elaprase is an orphan medicinal product indicated for long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II), which is a rare X-linked recessive storage disorder caused by a deficiency or reduced levels of the lysosomal enzyme iduronate-2-sulfatase (I2S). This enzyme is responsible for the hydrolysis of the C2-sulfate ester bonds of the non-reducing iduronic acid residue in both glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate. Reduced or absent activity of this enzyme results in an intracellular accumulation of these GAGs, which causes a progressive and clinically heterogeneous disorder with multiple organ and tissue involvement.

The active substance idursulfase is a recombinant form of iduronate-2-sulfatase. It is produced from a continuous human cell line and secreted into the medium as a mature monomeric protein of approximately 76 kDa.

Idursulfase is purified by a series of chromatography steps, ultrafiltration (UF) steps and a final viral filtration step. The excipients used in the active substance formulation, sodium chloride, a sodium phosphate buffer, polysorbate 20 and water for injections, are commonly employed in parenteral solutions of proteins.

The finished product is manufactured by sterile filtration and aseptic filling of the formulated active substance into vials.

Active Substance

Nomenclature

INN Name:	idursulfase
Compendial name:	not applicable
Chemical name:	iduronate-2-sulfatase

Description of the active substance

Idursulfase is expressed as a monomeric protein of 550 amino acids and is secreted into the medium as a mature protein of 525 amino acids (molecular weight of approximately 76 kDa) following cleavage of the 25 amino acid signal peptide.

Idursulfase contains two disulfide bonds and eight N-linked glycosylation sites occupied by complex, hybrid and high mannose type oligosaccharide chains. The presence of mannose-6-phosphate (M6P) residues allows specific binding of the enzyme to M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs. Biological activity of idursulfase is also dependent on a post-modification of the conserved cysteine (position 59) to formylglycine. Like other sulfatases, idursulfase contains a divalent cation (calcium for idursulfase) that is probably involved in the catalytic activity of the enzyme.

- Manufacture

The active substance is manufactured by Shire, (TK3 facility), Cambridge, MA, USA. This facility was inspected by the MPA in August 2006 and is operated in accordance with current EU GMP.

Development genetics and cell bank system:

An expression plasmid was constructed with the necessary sequences to express idursulfase and a transformed human cell line (HT-1080) was transfected with this expression plasmid constructed. The HT-1080 cell line was chosen due to the specialised nature of the glycosylation requirements for appropriate *in vivo* biological activity of idursulfase. This cell line has been used for the production of two centrally authorised products, Replagal (agalsidase alfa) and Dynepo (epoetin delta). The cell line has been characterized for cell morphology, cell growth properties, tumorigenicity, karyology, identity, virus susceptibility and for adventitious agent contamination.
One stable clone producing idursulfase at high levels was isolated and sub-cloned to establish the Master Cell Bank (MCB) from which the subsequent Working Cell Bank (WCB) was derived. The initial WCB was created from a single ampoule of MCB, based on the same principles as for the MCB and future WCBs will be prepared using an equivalent process.

An extensive range of tests has been performed on the MCB and WCB for their characterisation, in accordance with ICH guidelines, including viability, sterility, identity, stability, presence of adventitious agents (mycoplasma, viral and retroviral contaminants).

Fermentation processs:

The cell culture process consists of two phases, a growth phase and a production phase.
The resulting conditioned production media is concentrated and filtered producing the unpurified bulk active substance for storage. Cell culture conditions, in-process controls (IPC) and action limits have been sufficiently described and are considered appropriate.

Purification process:

Purification is performed by a series of six chromatography steps, two UF steps and a viral filtration step. The resulting material is then formulated with sodium chloride, sodium phosphate and polysorbate 20 following which a final filtration is performed, leading to the formulated bulk active substance (FBDS) which is then frozen and stored at -65ºC – -85ºC.

The applicant has confirmed that reprocessing of a complete batch is not permitted during commercial manufacture of idursulfase.

Operating conditions of the chromatography steps are provided for purification of the active substance. The holding times have been justified. The filtration steps during the purification, the two UF steps and the viral filtration step are well controlled.

The applicant provided a justification for the use of action limits for IPC during cell culture and purification, rather than acceptance criteria.

Manufacturing process development and process validation:

Changes to the active substance manufacturing process were introduced at two stages during development:
a) Prior to initiation of the pivotal Phase II/III study TKT024 in order to increase yield and process efficiency.
b) Subsequently, the scale was increased to the commercial scale process and specific process improvements were made. This commercial product was introduced into the extension studies TKT018 and TKT024EXT.

The rationale for the proposed changes was explained. An extensive comparability exercise was performed, which includes a comprehensive physicochemical characterisation, non-clinical studies (pharmacodynamic, tissue distribution, bioequivalence) and clinical studies (pharmacokinetics). The applicant chose an appropriate range of techniques from the characterisation studies for these comparability studies. Slight differences were observed in the glycosylation but these do not appear to impact on the *in vivo* potency of idursulfase. Stability studies also confirmed comparability in the characteristics of the materials.

A prospective process validation programme was conducted in accordance with ICH guidelines to demonstrate the suitability and robustness of the manufacturing process and the consistent production of idursulfase with the appropriate quality attributes, including identity, purity, potency and microbiological quality. All equipment used during validation was the same as that used for commercial manufacturing and the validation studies were conducted following the applicant's approved production records and standard operating procedures. All lot release assays were validated and in-process assays were qualified as appropriate for use in support of the validation.

The validation for the cell culture process included media preparation, growth and production phases of the cell culture and concentration/filtration of the unpurified bulk. Validation included the manufacture of three consecutive idursulfase unprocessed and unpurified bulk lots. Acceptance criteria were met except for bioburden for which corrective actions have been introduced.

The purification process validation assessed the chromatography and concentration steps, the viral filtration, formulation, dispensing of the bulk active substance and chromatography column cleaning. The acceptance criteria were met during the validation studies. Parameters were defined and the process range for each parameter monitored during the validation studies for the idursulfase active substance manufacturing process.

Characterisation:

a) Elucidation of structure and other characteristics:
The active substance has been comprehensively characterised, using state-of-the-art methods for physicochemical characteristics. The glycosylation, which is important for the biological activity of the product, has been extensively characterised. Biological characterisation included *in vitro* measurement of enzyme activity and uptake in normal human fibroblasts.

a1) Physicochemical characterisation:
- Primary structure:
The observed amino acid composition of purified idursulfase was consistent with the predicted composition. N-terminal sequencing by Edman degradation did not show N-terminal heterogeneity.

Mass spectrometry analysis of the C-terminal sequence showed very low levels of C-terminal truncation.
Partial modification of Cys59 to formylglycine was also confirmed.
- Secondary structure:
Peptide mapping with mass spectrometry analysis confirmed the presence of two disulfide linkages. Data from far UV circular dichroism spectroscopy are consistent with the α/β folding motif reported for other lysosomal sulfatases.
- Glycosylation and charge distribution:
Idursulfase is a heavily glycosylated protein with eight occupied N-linked glycosylation sites, each with varying degrees of branching, sialylation and phosphorylation that leads to charge microheterogeneity.
Appropriate methods have been used to analyse monosaccharide composition, sialic acid content, M6P content, distribution of N-linked oligosaccharides, charge heterogeneity, contribution of charged glycans to the charge distribution.
- Molecular weight distribution:
The expected molecular weight of the amino acid sequence for idursulfase has been confirmed.
It was also shown that the level of aggregates (dimer) in the active substance is very low.

a2) Biological activity:
The specific enzymatic activity was determined using two methods: measurement of the removal of sulfate from a synthetic fluorigenic substrate and an ion chromatography method to quantify the amount of sulfate ions enzymatically released by idursulfase from the naturally-derived substrate.
In order to evaluate the uptake of idursulfase by M6P receptors, internalisation studies were performed using human fibroblasts expressing M6P receptors on their surface. The internalised amount of idursulfase was measured by a specific ELISA method.
b) Impurities:
Process-related impurities consist of host cell-derived impurities, including host cell DNA and host cell proteins, impurities arising from the cell culture medium and potential impurities from the purification process. Product-related impurities include aggregates, fragments, charged variants. The impurity profile has been appropriately analysed.

b) Impurities:
Overall, the purification process showed good consistency in the elimination of both process- and product-related impurities.

A comprehensive series of controls has been established to minimise any potential risk of contamination of idursulfase by non-viral and viral adventitious agents.

For bovine-derived materials, all lots of serum used to manufacture the cell banks and during the fermentation process are obtained from suppliers with appropriate controls in place to adequately verify the sourcing of materials from well-monitored herds who have obtained TSE certificates and can demonstrate compliance with the relevant guidelines. Bovine-derived materials are sourced from Canada, New Zealand and USA. All lots of bovine serum are subject to a heat inactivation step and the bovine calf serum used during the fermentation process is subject to gamma irradiation.

The purification process has been validated for viral clearance using appropriate model viruses to evaluate new and used chromatography resins. The viral filtration step used in the purification process ensures removal of the model viruses tested.

- Specifications

The series of tests proposed for the control of the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity and impurities, potency, content and microbiological quality.

- Stability

The design of the stability testing program, including the testing intervals and temperature storage conditions, are in accordance with current ICH guidelines. The stability acceptance criteria for the tests used in the stability program are the same as those used for release of idursulfase active substance.
The stability data provided were within the specifications and support a shelf life of 24 months at -65°C to -85°C

Finished Product

- Pharmaceutical Development

Formulation development studies showed that the phosphate buffer at the proposed concentration was suitable. The proposed sodium chloride concentration provides an isotonic solution suitable for intravenous administration. Polysorbate 20 at the proposed concentration was a suitable stabilising agent to protect against agitation-induced aggregation and to provide stability of the finished product for shipping and handling. The formulation does not contain any anti-microbial preservatives and direct sterility testing is performed on each lot of finished product. Container closure integrity is tested as part of an ongoing stability program to provide assurance that quality of the product within the vial is maintained throughout shelf life.

Elaprase is for intravenous infusion and must be diluted in 0.9% sodium chloride prior to administration. The compatibility with 0.9% sodium chloride has been established by assessing the stability of diluted idursulfase following storage for up to 8 hours at room temperature (25°C).

- Manufacture of the product

The finished product is manufactured at Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA. This facility was last inspected by the MHRA in February 2006 and is operated in accordance with current EU GMP.

The manufacture of the finished product consists of the sterile filtration and aseptic filling into vials of the formulated active substance. No additional excipients or formulation steps are involved in the manufacture of the finished product. The filling step is followed by stoppering, capping, labelling, packaging and storage of the vials. The media fill and process validation results, lot-to-lot consistency data and critical process controls have shown that the sterile filtration and aseptic filling process are robust and well controlled and that the finished product can be consistently manufactured.

- Product Specification

The tests and rationale for the acceptance criteria were considered acceptable for release testing.

- Stability of the Product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. Based on the data provided, the approvable shelf life for the finished product is 24 months at 2-8°C.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Information on the source and generation of the cell substrate and analysis of the expression construct are considered satisfactory.
The cell bank system used for the manufacture of the active substance is adequately described and an appropriate range of tests has been performed.

In general, the cell culture process and purification process as well as the filling and storage of the active substance have been described in sufficient detail and appropriate IPC and acceptance criteria are in place.
Validation data generally demonstrate that the process consistently produces the active substance.

A number of changes were introduced during development in the active substance manufacturing process, which include changes to increase yield and process efficiency, scale-up and other specific process improvements. The extensive comparability exercise that was performed to support these changes was considered satisfactory.

The active substance has been comprehensively characterised, using state-of-the-art methods for physicochemical characteristics. The glycosylation, which is important for the biological activity of the product, has been extensively characterised. Biological characterisation included *in vitro* measurement of enzyme activity and uptake in normal human fibroblasts.

However, additional information was requested regarding common protein degradation products such as hydrolytic impurities (deamidated forms), oxidation products and truncated forms. It has been demonstrated that oxidised or truncated forms will be detected by the methods currently used. Furthermore, these impurities were not seen in the stability studies. Sufficient justification was provided for the absence of specifications for oxidised and truncated forms.

The active substance and also the finished product release and end-of-shelf-life specifications were considered acceptable
The stability data that was provided for the active substance and finished product support the proposed shelf life of 24 months at -65°C to -85°C and at 2°C to 8°C, respectively, and the proposed in-use storage conditions of 8 hours at 25°C.

The formulation development and manufacturing process development for the finished product have been adequately described.
In general, the validation program has confirmed that the manufacturing process is robust and suitable for routine use and that a finished product of an appropriate quality can be consistently manufactured.

The viral safety and safety concerning other adventitious agents, including TSE, have been sufficiently assured

The last inspection of the active substance and finished product manufacturing facilities showed compliance to the current EU GMP.

Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the quality of Elaprase has been adequately demonstrated.

3. Non-clinical aspects

Introduction

Pharmacodynamic and biodistribution studies conducted in mice were performed according to established protocols, but without quality assurance oversight and thus were considered non-GLP in nature. Safety and toxicology studies were generally conducted in compliance with current international good laboratory practice (GLP) standards. Due to the X-linked recessive nature of Hunter syndrome, all pharmacodynamic non-clinical studies were conducted in male animals.

Pharmacology

Hunter syndrome is a lysosomal storage disease caused by the missing or defective enzyme, iduronate-2-sulfatase (I2S), which acts to cleave O-linked sulfate moieties from two human glycosaminoglycans (GAG) known as dermatan sulfate and heparan sulfate. Due to the intracellular compartmentalization of lysosomes, the pharmacodynamic activity of idursulfase is dependent upon internalization of the enzyme into the lysosomes. The binding of idursulfase via M6P moieties to cell surface M6P receptors

provides a receptor-mediated uptake mechanism for this enzyme, leading to cellular internalization of the enzyme and subsequent targeting to intracellular lysosomes. Sialylation of idursulfase reduces the uptake by hepatic asialoglycoprotein receptors. Treatment of Hunter syndrome patients with IV idursulfase provides exogenous enzyme for uptake into cellular lysosomes and subsequent catabolism of accumulated dermatan sulfate and heparan sulfate.

A model of Hunter syndrome, the iduronate- 2-sulfatase knock-out (IKO) mouse, was created at the University of North Carolina, USA and established by the applicant. The IKO mouse exhibits many of the physical characteristics of Hunter syndrome seen in humans, including coarse features and skeletal defects. Elevated GAG levels are observed in urine and tissues throughout the body and widespread cellular vacuolisation is observed histopathologically.

Male IKO mice are indistinguishable from wild type and carrier littermates at birth. However, affected mice develop progressive gross abnormalities over time. Levels of GAG in IKO mouse urine are 2 to 5-fold higher than that of wild type mice. Consistently higher GAG levels are seen in extracts from all major tissues including the liver, kidneys, heart, and spleen of IKO mice when compared to wild type mice.
The IKO model was used to evaluate the dose levels and dose regimen of idursulfase required to degrade stored GAG in this animal model. The *iv* route of administration was used in animal studies, unless otherwise noted, to conform to the intended clinical route of administration of idursulfase.

- Primary pharmacodynamics

A series of studies were performed to determine the pharmacodynamic effect of idursulfase on GAG accumulation in the IKO (iduronate 2-sulfatase knock-out) mouse model. Using the IKO mouse model, it was demonstrated in several studies that the administration of idursulfase caused marked reductions in GAG in both urine and tissue, in many cases to levels observed in wild type animals. It is therefore concluded that *iv* administered idursulfase reaches relevant tissues throughout the body and is biologically active.

Further studies at doses ranging from 0,1 to 5.0 $mg \cdot kg^{-1}$ in IKO mice concluded that a dose of 1 $mg \cdot kg^{-1}$ idursulfase given weekly and every other week were both effective at reducing urinary and tissue GAG concentrations in a variety of relevant tissues. Both regimens were more effective than monthly administration. Doses of idursulfase as low as 0.15 $mg \cdot kg^{-1}$ reduced urinary and tissue GAG, however, such doses did not provide a maximal effect with respect to GAG reduction.

Idursulfase is found to be sialylated, and the degree of sialylation affects the elimination half-life. Therefore, limits have been defined to the degree of sialylation.

One exception to the *iv* route of administration in the evaluation of pharmacodynamics was a preliminary research study, in which intraperitoneal (*ip*) administration was used in neonatal mice. Due to the technical difficulty of *iv* dosing in neonates, very young mice (4 and 11 days old) received *ip* administration of idursulfase of 5 $mg \cdot kg^{-1}$. Due to unexpected adverse reactions probably associated with the route of administration this study was terminated.

- Secondary pharmacodynamics

No secondary pharmacodynamics studies were performed with Elaprase. The lack of secondary pharmacodynamic studies is not a major omission, due to the enzyme specificity.

- Safety pharmacology programme

A safety pharmacology study in cynomolgus monkeys further described under the Pharmacokinetics section showed no treatment related effects on cardiovascular, respiratory or central nervous system parameters following a single *iv* administration of idursulfase at dose levels of 5, 10, or 20 $mg \cdot kg^{-1}$. The safety pharmacology aspects of this study were GLP compliant.

- Pharmacodynamic drug interactions

Since Elaprase is a recombinant form of human iduronate 2-sulphatase and is removed from serum and transported to lysosomes via specific cell receptors, pharmacodynamic drug interaction studies were not performed. Pharmacodynamic drug interactions are not likely; not performing interaction studies is agreed.

Pharmacokinetics

The pharmacokinetic (PK) properties of idursulfase have been well characterised in the rat and Cynomolgus monkey following bolus *iv* administration.

Single dose PK studies were performed in the rat, while single and repeat-dose PK studies were performed in the monkey. As Hunter syndrome is an X-linked recessive disease the majority of PK studies used male animals, as was also the case for clinical studies. One exception was a monkey PK study that used both male and female animals. Serum availability and tissue biodistribution of *iv* administered idursulfase were also investigated in mice.

Idursulfase lots from 4 phases of drug manufacturing (Research, Phase I/II, Phase II/III, and commercial) were evaluated in nonclinical PK studies.

The amount of idursulfase in animal sera was determined by either measuring the concentration of idursulfase protein by ELISA or the quantification of enzyme activity per ml of serum. Serum samples were compared to a standard curve. The tissue concentrations of idursulfase in mouse biodistribution studies were also determined by an ELISA method.

- *Absorption*

Idursulfase is administered by *iv* injection. Specific absorption studies have not, therefore, been performed. However, studies to determine AUC and $T_{½}$ were performed in the rat and Cynomolgus monkey. These studies also reported C_{max} values (see Tables 1 and 2).

Table 1: Pharmacokinetic Parameters following Single *iv* Administration

PK Parameter	**Idursulfase Dose Level (mg·kg^{1})**		
	0.5	**2.5**	**12.5**
Sprague-Dawley Rat			
Cmax (μg·ml^{-1})	15.1	60.4	419
AUC (μg·min·ml^{-1})	1,074	6,240	51,600
T1/2 (α)	19 min	47 min	52 min
T1/2 (β)	3 h	6 h	4 h
Cl (ml·min^{-1}·kg^{-1})	0.53	0.41	0.24
Cynomolgus Monkey			
Cmax (μg·ml^{-1})	16.6	61.8	377
AUC (μg·min·ml^{-1})	999	8720	80466
T1/2 (α)	20.8 min	1 h 11 min	1 h 28 min
T1/2 (β)	3 h 27 min	9 h 12 min	4 h 55 min
Cl (ml·min^{-1}·kg^{-1})	0.513	0.289	0.161
V_{ss} (% bodyweight)	9.3	9.2	4.7

Adapted from Applicant's tables

Table 2: Pharmacokinetic Parameters for Cynomolgus Monkey following Repeated iv Administration

Parameter	Day 1 (1st Dose)	Day 8 (2nd Dose)	Day 85 (13th Dose)	Day 176 (26th Dose)
Low Dose (0.5 mg·kg^{-1})				
C_{max} (µg·ml^{-1})	16.6	15.1	21.4	22.1
AUC (min*µg·ml^{-1})	999	997	1087	1205
T ½ (α) (min)	20.8	22.7	17.4	19.8
T ½ (ß) (min)	207	225	199	215
Cl (ml·min^{-1}·kg^{-1})	0.513	0.532	0.462	0.417
Vss(% body weight)	9.3 %	9.8 %	7.3 %	7.3 %
Mid-Dose (2.5 mg·kg^{-1})				
C_{max} (µg·ml^{-1})	61.8	97.1	84.2	51.4
AUC (min*µg·ml^{-1})	8,720	9,164	9,595	7,606
T ½ (α) (min)	71.3	70.0	67.4	85.6
T ½ (ß) (min)	552	465	304	336
Cl (ml·min^{-1}·kg^{-1})	0.289	0.273	0.281	0.344
Vss(% body weight)	9.2 %	7.3 %	4.4 %	6.6 %
High Dose (12.5 mg·kg^{-1})				
C_{max} (µg·ml^{-1})	377	382	437	397
AUC (min*µg·ml^{-1})	80,466	78,396	74,520	82,775
T ½ (α) (min)	88.0	128.5	87.7	na
T ½ (ß) (min)	295	358	216	193
Cl (ml·min^{-1}·kg^{-1})	0.161	0.167	0.175	0.152
Vss(% body weight)	4.7 %	4.9%	3.8 %	3.9 %

adapted from applicant's Pharmacokinetics Written Summary
na = not available

The residual amount of administered idursulfase at 24 hours following a single iv dose in the rat was <1.0% of Cmax, indicating that idursulfase would not be expected to accumulate following daily or weekly dosing in this species. C_{max} was proportional to dose, while AUC increased in a greater proportion to dose. Serum clearance normalised for body weight decreased with dose, suggesting that serum clearance mechanisms became saturated.

Following a single *iv* dose to cynomolgus monkeys, C_{max} was dose proportional, while AUC increased more than dose proportionally. The AUC and clearance data for the range of evaluated concentrations further suggested the possibility of clearance saturation mechanisms for idursulfase. Apparent volume of distribution appeared to be independent of dose and fluctuated, indicating that administered idursulfase distributed into intracellular or interstitial fluid in addition to serum.

Following repeated dose iv administration to Cynomolgus monkeys, the residual amount at 24 hours was ≤1.0% of C_{max}, indicating that idursulfase would not be expected to accumulate following weekly dosing in this species. C_{max} increased linearly as dose increased, but AUC again increased more than proportional to dose.

There were few changes in PK parameters following 13 or 26 weekly doses. Mean pharmacokinetic parameters from Days 8, 85, and 176 were almost identical to those observed following the 1st dose and only minor fluctuations were seen in mean serum clearances. The residual amount of

administered protein after 26 weekly *iv* doses was ≤1.0% of C_{max} indicating that idursulfase had not accumulated.

- *Distribution*

Tissue biodistribution studies were conducted in male Sprague-Dawley rats, in normal female mice (ICR strain) and in adult male knockout mice (IKO). The biodistribution study in rats used doses of 0.5 and 12.5 $mg \cdot kg^{-1}$, while the biodistribution studies in mice used a dose of 1 $mg \cdot kg^{-1}$ since this dose was determined to be effective in reducing GAG in pharmacodynamic studies in IKO mice.The greatest level of idursulfase was found in the liver in both rats and mice (approximately 11% of administered dose in rats and from 30 to 40 % in mice). Lower, but significant levels of idursulfase were distributed to other major organs and tissues throughout the body. Detection of idursulfase in tissues and organs throughout the body was consistent with the wide distribution of the mannose-6-phosphate (M6P) receptor in mammals and with known M6P receptor-mediated uptake mechanisms for M6P containing glycoproteins, such as naturally occurring idursulfase. As expected, appreciable amounts of radioactivity were found in blood, thyroid, gastrointestinal contents, and in urine. In the rat biodistribution study using idursulfase labelled with ^{125}I, groups of rats were sacrificed at 4, 24, and 48 hours after administration. Ffor major organs, the tissue half-life of idursulfase was estimated at approximately 1 to 2 days.

Biodistribution studies in female mice and male mice indicated that there were no gender related differences in patterns of tissue uptake of idursulfase.

Idursulfase is a purified, recombinant form of the naturally occurring human lysosomal enzyme and, therefore, plasma protein binding and blood cell distribution patterns of idursulfase are unlikely to differ from those observed in individuals expressing normal iduronate 2-sulphatase levels. The pharmacokinetic studies demonstrated that the vast majority of idursulfase is eliminated from circulation (independent of species examined) within approximately 24 hours of dosing (see below). Consequently, studies examining plasma protein binding and blood cell distribution patterns were not performed.

Hunter syndrome is an X-linked recessive genetic disease with a mostly male prevalence. Therefore, studies examining placental transfer of idursulfase were not performed.

- *Metabolism*

Serum clearance of idursulfase was modelled using allometric scaling to determine the relationship of Cl to body weight across species (rodents, monkeys and humans). The allometric scaling equation derived from these data provided support for a similarity in clearance mechanisms across species. Based on the glycosylation pattern of idursulfase and its site of action within cellular lysosomes, it is reasonable to assume that idursulfase serum clearance occurs primarily through cellular uptake *via* cell surface receptors and subsequent transport to cellular lysosomes.

The allometric exponent for serum clearance of small molecules or other biotherapeutic proteins typically ranges from 0.6 to 0.8, with clearance typically occurring *via* liver metabolism and/or kidney excretion. The increased value of the allometric exponent for idursulfase serum clearance (0.97) indicates that, unlike other drugs, its serum clearance is almost linearly proportional to body weight. This is most likely due to the mechanism of clearance, via cell surface receptors such as the M6P receptor.

As idursulfase is protein it is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

- *Excretion*

As a form of naturally occurring iduronate 2-sulphatase protein, recombinant idursulfase is assumed to be degraded by protein hydrolysis resulting in peptide and amino acid products which enter the body's normal metabolic pools. Based on the known pathways for metabolism and catabolism of amino acids

and peptides, specific studies to determine routes of elimination or the extent of excretion were not performed.

Hunter syndrome is an X-linked recessive disease and only males were included in the clinical studies. Since affected females are extremely rare, studies examining excretion of idursulfase in milk have not been performed.

- Pharmacokinetic Drug Interaction Studies

As a purified, recombinant form of the naturally occurring human lysosomal enzyme iduronate 2-sulphatase, recombinant idursulfase is not likely to interact with other medicinal products. Therefore, specific studies involving idursulfase/drug interactions were not performed.

- Other pharmacokinetic studies

During the development of idursulfase, changes were made to the manufacturing process that were evaluated in an extensive comparability program that incorporated comprehensive analytical characterisation coupled with pharmacodynamic and biodistribution studies. At certain stages, pharmacokinetic studies were also conducted, but were considered to be supportive in nature and were not utilised to draw specific conclusions regarding the comparability of material. The applicant considered that this approach was appropriate since the pharmacodynamic activity of idursulfase occurs in cellular lysosomes, where it catabolises accumulated glycosaminoglycan (GAG) found in nearly all cell types and tissues of Hunter syndrome patients. Thus, to produce a consistent pharmacodynamic effect in patients, the critical factors are tissue uptake (biodistribution) and subsequent GAG reduction (pharmacodynamics) in those tissues.

Evaluation of the serum elimination profile of idursulfase in Sprague-Dawley rats and cynomolgus monkeys demonstrated a time course for removal of enzyme from circulation and presumptively into various tissues and organs; as supported by the enzyme biodistribution data. Serum idursulfase concentrations over time, however, may not directly correlate to pharmacodynamic enzyme activity, which occurs within cellular lysosomes. Nevertheless, pharmacokinetic analysis of idursulfase in these animal studies provided fundamental pharmacokinetic data for idursulfase, including saturation of serum clearance mechanisms and serum elimination half-lives.

Idursulfase manufactured by the Phase I/II and Phase II/III processes demonstrated comparable biodistribution to key organs. For materials produced by both clinical processes, the greatest amount of recovered dose was found in the liver, followed by spleen, kidney, and heart. The relative recoveries in these four tissues were similar as were the dose dependent reductions in urinary and tissue GAG levels. Based on these data coupled with the physicochemical analysis, idursulfase produced by the Phase I/II manufacturing process was considered to be comparable to that produced using the Phase II/III manufacturing process.

Idursulfase produced by the Phase II/III and commercial-scale processes also yielded comparable results in all in vivo studies. Tissue biodistribution patterns in normal mice were comparable between the 2 materials in liver, spleen, and heart. Consistent with the comparable tissue biodistribution patterns, reduction of tissue GAG from liver, spleen, kidney, and heart were generally indistinguishable at 2 different dose levels of idursulfase following 5 weekly bolus iv injections (0.25 and 1.0 mg·kg-1 dose levels).

The inherent variability of the mouse data does not allow for convincing statistical conclusions about the bioequivalence

Results from a pharmacokinetics study in cynomolgus monkey showed the serum clearance of both manufacturing processes followed essentially identical biphasic patterns.

The bioequivalence approach with respect to monkey pharmacokinetic parameters, demonstrated that idursulfase manufactured by both the Phase II/III and commercial processes were therefore comparable.

Toxicology

Several toxicology studies were conducted with idursulfase in Sprague-Dawley rats and cynomolgus monkeys. The iv route of administration was used in all toxicology studies, as this is the intended clinical route of administration. Only male animals were used for these toxicology studies, as Hunter syndrome is an X-linked recessive lysosomal disease.

Idursulfase appeared to be well tolerated in both cynomolgus monkeys and Sprague-Dawley rats following iv bolus administration at single doses of up to 20 mg·kg-1 or repeated doses of up to 12.5 mg·kg-1 for 6 months. The NOAEL for idursulfase in cynomolgus monkeys dosed on a weekly basis provides a safety margin, on a mg·kg-1 basis, of at least 25-fold compared to the proposed weekly clinical dose of 0.5 mg·kg-1.

As expected for a human protein administered to animals, IgG antibodies to idursulfase were detected in some of the monkeys after 13 or 26 weeks of dosing, and in a few knockout mice after 24 weeks of dosing. These anti-idursulfase antibodies had no adverse toxicological effects although there was a trend in decreasing the pharmacodynamic activity of idursulfase.

- Single dose toxicity

Single dose *iv* bolus toxicity studies were conducted in the rat and Cynomolgus monkey using idursulfase produced by the commercial process. The doses of idursulfase that were evaluated (5, 10 and 20 $mg \cdot kg^{-1}$) corresponded to 10 to 40-fold average relative to dosing in the pivotal Phase II/III clinical Study TKT024. No treatment related effects were observed.

Based on these results, the no-observed-adverse-effect level for a single *iv* injection of idursulfase in male Sprague-Dawley rats and male cynomolgus monkeys was 20 $mg \cdot kg^{-1}$.

- Repeat dose toxicity (with toxicokinetics)

A 6 month toxicity study in cynomolgus monkeys was designed to evaluate a more frequent weekly dosing regimen of 0.5, 2.5, and 12.5 $mg \cdot kg^{-1}$ idursulfase and to provide an adequate safety margin relative to the dose range of idursulfase used in clinical trial TKT008 (0.15, 0.5, and 1.5 $mg \cdot kg^{-1}$, administered every two weeks).

The overall study design included an interim evaluation after 3 months of dosing, a one month recovery period following study completion and toxicokinetic evaluations throughout the study.

Idursulfase was well tolerated by male cynomolgus monkeys for 26 weekly *iv* doses. There were no deaths, abnormal clinical signs, changes in food consumption, or effects on body weight indicative of any adverse effect of idursulfase. There were no abnormal ophthalmologic observations or any changes in ECGs related to dosing with idursulfase. There were no changes in clinical pathology parameters (clinical chemistry, haematology, coagulation, or urinalysis) attributable to idursulfase administration. There were no findings at gross necropsy attributed to administration of idursulfase in animals sacrificed after 3 or 6 months of repeat dosing, or following one month of recovery. The injection sites had the expected minimal subcutaneous haemorrhage and fibrosis expected with repeat *iv* injections in both vehicle animals and animals dosed with idursulfase. There was no increase in severity or frequency of findings in animals dosed with idursulfase. There were no effects on organ weights or any histopathological findings in any tissue attributed to treatment with idursulfase.

The toxicokinetic results revealed generally dose-dependent exposure to idursulfase. The AUC values were consistent throughout the 26 weeks of the study for each dose level. A decrease in AUC was observed in 2 animals from both the mid- and high dose groups on Days 85 and 176, which were associated with the presence of antibodies. The C_{max} values were proportional to dose.

The initial distributed half-life, $T_{½}$ (α), increased with dose and ranged from approximately 20 minutes for the low-dose group to approximately 90 to 130 minutes for the high dose group suggesting a possible saturation of clearance mechanisms at the 2 higher dose levels.

Serum samples were collected to assess potential anti-idursulfase antibody development at Weeks 2, 4, 13, 26, and 30 (one month of recovery). Antibodies developed in 0/4, 2/4 and 4/6 animals treated with 0.5, 2.5, or 12.5 $mg \cdot kg^{-1}$, respectively. The majority of antibody positive animals were detected by Week 13, but one animal treated with 2.5 $mg \cdot kg^{-1}$ did not develop antibodies until Week 26. One high dose animal continued to exhibit a positive antibody response throughout Week 30 while another high dose animal's antibody response appeared to decline by Week 26. The development of anti-idursulfase antibodies was not consistently associated with an increase in serum clearance, since 2 high dose animals, which had also developed anti-idursulfase IgG antibodies, did not exhibit any changes in serum clearance. There were no adverse toxicological events associated with the development of anti-idursulfase antibodies.

The toxicity studies in cynomolgus monkeys and rats were not performed in full compliance with GLP. The portions conducted by the applicant, or their designee, which included the placebo control formulation, analysis of formulation samples and bioanalysis of toxicokinetic samples needed clarification. Based on the information provided by the applicant, the CHMP considers that the noted deficiency does not invalidate the studies performed.

- Genotoxicity

Idursulfase has not been evaluated in genotoxicity studies since it is a naturally occurring human protein. Its mechanism of action and site of action (degradation of GAG in cellular lysosomes) do not suggest any genotoxic risk (*e.g.,* idursulfase is not expected to interact directly with DNA or chromosomes).

- Carcinogenicity

No formal carcinogenicity studies have been conducted with idursulfase. The absence of genotoxicity and carcinogenicity studies is considered acceptable given the nature of the product and the indication.

- Reproduction Toxicity

Due to the X-linked recessive nature of Hunter syndrome, only a male rat fertility study was conducted with idursulfase.

This GLP study was designed to determine the potential effects of idursulfase on male rat fertility. Male rats received 2 bolus *iv* doses of idursulfase (0.5, 1.5 or 5 $mg \cdot kg^{-1}$) per week for a period of approximately 9 weeks (4 weeks of pre-mating, during mating, and post-mating until scheduled necropsy). Female rats were not treated and were used solely for mating purposes. The high dose evaluated in this study, 5 $mg \cdot kg^{-1}$, provides a 10-fold safety factor ($mg \cdot kg^{-1}$ basis) compared to the proposed commercial idursulfase dose.

The dosing frequency of 2 times per week was expected to maintain steady-state tissue levels of test article, based on tissue half-lives of 1 to 2 days in rats, for *iv*-administered idursulfase. In addition, dosing at this interval provided an additional safety factor in comparison to the weekly and every other week dosing regimens used in the clinical setting.

After 4 weeks of dosing each male was mated with one untreated female. Approximately 24 to 48 hours after the final dose, all males were sacrificed. Evaluation of effects of idursulfase on male fertility included mating and fertility indices, reproductive organ weights, sperm assessment and histopathological analysis of testes and epididymis. Females were sacrificed on Day 13 of gestation (and were evaluated for pregnancy rate, number of implantations, and number of viable implantations.

There were no significant biological effects of idursulfase treatment on measures of male fertility and treatment with idursulfase had no effect on male reproductive organ weights. Small (8 to 14%), but

statistically significant, increases in cauda epididymis, epididymis and seminal vesicles weights were recorded. However, a lack of dose-dependency in these increases suggests that these changes were not related to treatment with idursulfase. This was supported by a lack of any gross pathological or histopathological findings in these organs. Treatment with idursulfase had no effect on sperm density, morphology or sperm motility.

There was no effect of idursulfase on the mean number of corpora lutea, mean number of implantations, number of resorptions, number of live and dead conceptus, or the percent pre- or post-implantation loss among the females.

Repeated-dosing with idursulfase (2 times per week for approximately 9 weeks) at levels of up to 5 $mg \cdot kg^{-1}$ had no effect on any measure of male rat fertility.

- Local tolerance

No additional studies were specifically designed to evaluate local tolerance effects following *iv* administration of idursulfase. However, histopathological analysis of injection sites (cephalic and saphenous veins) were incorporated into the design of the 6-month repeat dose toxicity study in cynomolgus monkeys. Microscopic evaluations did not reveal any local irritation, inflammation, or necrosis to veins or tissue related to bolus *iv* injection of idursulfase.

Additional data supporting the lack of local injection site reactions were also obtained from single-dose *iv* toxicity studies conducted with idursulfase in male Sprague-Dawley rats and in male cynomolgus monkeys.

- Other toxicity studies

Immunogenicity

Since idursulfase is a human protein being administered to animals it would not be unexpected to see the development of anti-idursulfase antibodies following repeat administration of drug. Studies were not specifically designed to evaluate the development of antibodies to idursulfase but rather were incorporated into the design of two pharmacodynamic studies in IKO mice and a repeat dose toxicology study in cynomolgus monkeys.

The analysis of blood samples for antibody production does not, however, appear to have been conducted in accordance with GLP. However, based on the information provided by the applicant, the CHMP considers that the noted deficiency does not validate the studies performed.

Male IKO mice were treated *iv* with 1 $mg \cdot kg^{-1}$ of idursulfase at weekly or every other week intervals. After 12 weeks half of the animals from each group were sacrificed and the remaining animals were sacrificed after 24 weeks of treatment. At 24 weeks one of the mice treated weekly with idursulfase was found positive for anti-idursulfase antibodies. The 4 mice dosed with 1 $mg \cdot kg^{-1}$ idursulfase every other week for 24 weeks were negative for antibodies to idursulfase.

In a separate study, male IKO mice initially treated *iv* with either 0.15 or 1.0 $mg \cdot kg^{-1}$ of idursulfase for 5 weeks followed by iv doses of 0.15 or 1.0 $mg \cdot kg^{-1}$ idursulfase weekly or once every 4 weeks until Week 24, the end of the study. At the conclusion of the study one of 4 mice treated with monthly doses of 0.15 $mg \cdot kg^{-1}$ and one of 4 mice treated with monthly doses of 1 $mg \cdot kg^{-1}$, were found to be positive for anti-idursulfase antibodies. The development of anti-idursulfase antibodies however had no effect on the pharmacodynamic activity of idursulfase as measured by GAG degradation, indicating that the common pharmacokinetic approach measuring the plasma elimination half-live might be clinically less relevant.

Male cynomolgus monkeys were treated with once weekly *iv* doses of idursulfase for 13 or 26 weeks. Serum samples were collected to assess potential anti-idursulfase antibody development at Weeks 2, 4, 13, 26, and 30 (one month of recovery). Antibodies developed in 0/4, 2/4 and 4/6 animals treated with 0.5, 2.5, or 12.5 $mg \cdot kg^{-1}$, respectively. The majority of antibody positive animals were detected by Week 13, but one animal treated with 2.5 $mg \cdot kg^{-1}$ did not develop antibodies until Week 26. One high

dose animal continued to exhibit a positive antibody response throughout Week 30 while another high dose animal's antibody response appeared to decline by Week 26. The development of anti-idursulfase antibodies was not consistently associated with an increase in serum clearance, although an association could not be excluded.. There were no adverse toxicological events associated with the development of anti-idursulfase antibodies.

Ecotoxicity/environmental risk assessment

Idursulfase is a biological product, which does not contain or consist of any Genetically Modified Organisms. Since idursulfase is a recombinant form of the human lysosomal enzyme, iduronate-2-sulfatase, it is expected that the metabolism and excretion would be similar to that of the naturally occurring enzyme. Therefore no potentially harmful effects to the environment are expected. Metabolic degradation of this protein product is expected to occur in cells *via* normal proteolytic mechanisms.

Idursulfase has received orphan drug designation and is indicated for the treatment of Hunter syndrome, a rare disease with an estimated prevalence of 0.02 in 10,000 people. Therefore the predicted environmental concentration (PEC) from treatment of Hunter syndrome patients will be very low. Elaprase (idursulfase) will be administered by healthcare professionals thus any unused product or waste materials will be disposed of within the local country requirements, therefore limiting a potential environmental exposure.

Discussion on the non-clinical aspects

The pharmacokinetic properties of idursulfase in animal models (mice, rats and monkeys) have been reasonably well characterised. Results from the pharmacokinetic studies of idursulfase in animal models (mice, rats and monkeys) have shown that idursulfase has a biphasic serum elimination profile with mean elimination half-lives of less than 5 to 6 hours in all cases. Values for C_{max} were proportional to dose for all species. However, AUC values were not linearly proportional to dose, indicating that serum clearance mechanisms had become saturated at doses of 0.5 $mg \cdot kg^{-1}$ or higher in monkeys. Clearance saturation was also seen at 2.5 and 12.5 $mg \cdot kg^{-1}$ in rats. However, due to limited dose range tested in rats, it was not possible to confirm the lowest dose of idursulfase which would saturate clearance in this species. Serum clearance of idursulfase followed allometric scaling parameters relative to body weight across species (rodents, monkeys and humans), indicating that clearance of idursulfase from serum likely occurs *via* a common mechanism. In the minority of monkeys in which development of antibodies to idursulfase occurred, this was usually, but not always, associated with enhanced clearance.

Idursulfase was detected in all organs and tissues examined in a ^{125}I-radiolabel rat biodistribution study. Tissue half-lives were similar for the major organs and were approximately 1 to 2 days for liver, kidney, heart, spleen, and bone (including marrow). The accumulation and retention of idursulfase in these organs and tissues is consistent with the distribution of M6P receptors in tissues and organs in mammals, and indicates that the common pharmacokinetic approach defining the serum half-life is less relevant in determining the duration of action.

The role of sialic acid content on *in vivo* properties (PK, tissue biodistribution, and pharmacodynamic activity) of idursulfase was examined. Biodistribution and PD activity parameters were affected by large variations in sialylation of idursulfase. Idursulfase clearance from serum was modified by minor variations in sialic acid content of idursulfase, but was not associated with altered activity from a biodistribution or PD perspective. Results from a comparability program, as part of tissue biodistribution, pharmacodynamic, and pharmacokinetic studies showed that idursulfase, regardless of the manufacturing process, maintained its activity profile.

Toxicokinetic studies in rats and monkeys suggest saturated clearance mechanisms following a single *iv* administration of idursulfase at doses of 10 or 20 $mg \cdot kg^{-1}$, and at 2.5 and 12.5 $mg \cdot kg^{-1}$ following repeat dose administration in cynomolgus monkeys.

There were no signs of local irritation, inflammation, or necrosis to veins or tissue related to multiple bolus *iv* injection of idursulfase.

As expected for a human protein administered to animals, IgG antibodies to idursulfase were detected in some of the monkeys after 13 or 26 weeks of dosing, and in a few knockout mice after 24 weeks of dosing. These anti-idursulfase antibodies had no adverse toxicological effects nor did they impact the pharmacodynamic activity of idursulfase.

4. Clinical aspects

Introduction

Overview of Clinical Studies

The idursulfase clinical development program was designed to test the safety and efficacy of enzyme replacement therapy in patients with Hunter syndrome. **Table 3** presents an overview of the 2 completed, placebo-controlled studies and the 2 ongoing, open-label studies of idursulfase which provide information on the safety and efficacy of idursulfase in this submission.

Table 3 Overview of Idursulfase Clinical Studies

Protocol and Title (Status)	**Doses (mg/kg)**	**Schedule**	**No. Enrolled**	**Age Range at Entry (yrs)**
TKT008: A Phase I/II, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation, Safety and Clinical Activity Study of Iduronate-2-Sulfatase Replacement Therapy in Patients with Mucopolysaccharidosis (MPS) II (Completed)	0.15 0.5 1.5 Placebo	Once every other week for 26 weeks IV	12 (3/dose group)	6.3 – 20.9
TKT024: A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Safety and Efficacy of Weekly and Every Other Week Dosing Regimens of Iduronate-2-Sulfatase Enzyme Replacement Therapy in Patients with MPS II (Completed)	0.5 Placebo	Once weekly or once every other week for 52 weeks IV	96 (32/dose group)	4.9 – 30.9
TKT018: An Open-Label Maintenance Clinical Study of Iduronate-2-Sulfatase Replacement Therapy in Patients with MPS II (Ongoing)	Initially 0.15 0.5 1.5 Then 0.5[a]	Once every other week IV	12 (4/dose group)	6.8 – 21.4
TKT024EXT: An Open-Label Extension of Study TKT024 Evaluating Long-Term Safety and Clinical Outcomes in MPS II Patients Receiving Iduronate-2-Sulfatase Enzyme Replacement Therapy (Ongoing)	0.5	Once weekly for 2 years IV	94	6.0 – 31.9

[a] Subsequent to dose selection for the pivotal study (TKT024), all 8 patients in the 0.15 and 1.5 mg/kg groups in TKT018 transitioned to the 0.5 mg/kg dose group, whereupon all 12 patients have remained on active study drug for approximately 3.5 yrs.

GCP

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

Pharmacokinetics

PK evaluations were performed in all studies. Blood samples were collected from patients enrolled in TKT008 (n=9) and TKT018 (n=12) who received idursulfase; from a subset of patients enrolled in TKT024 (n=36 patients: 18 weekly, 18 every other week dose groups); and from all patients in TKT024EXT (n=94). Urine samples were also collected once per day at specified time points during the clinical studies, and were analyzed in order to quantify patient urine GAG following idursulfase treatment.

The PK parameters analyzed can be seen in tables 4 and 5.

- Methods

The following bioanalytical methods were developed and qualified/validated during the idursulfase clinical development program:

- Assay for Quantification of Idursulfase Concentration
- Assay for Quantification of Urinary Glycosaminoglycans (GAG)
- Screening Assay for Circulating Human Anti-Idursulfase Antibodies
- Radioimmunoprecipitation (RIP) Assay for Circulating Human Anti-Idursulfase Antibodies
- Idursulfase Neutralizing Antibody Assay (NAb)

The pharmacokinetic analyses were performed using a noncompartmental model (WinNonlin™ Professional version 3.2 or 4.1, Model 202, Pharsight Corporation, Mountain, View, CA) .

- Absorption

Idursulfase is administered by intravenous infusion and is not an orally administered agent. Accordingly absorption is not an issue; similarly, 100% bioavailability can be assumed and consequently no bioequivalence, or bioavailability studies were conducted.

- Distribution

The apparent volume of distribution at steady state of Idursulfase was between 3L and 9L (see Table 4). Idursulfase is a protein and an apparent volume of distribution coinciding with blood volume is to be expected.

Table 4 Mean pharmacokinetic parameters of Idursulfase based on protein concentration for all doses after single (week 1 TKT008) and multiple (week 1 TKT018 and week 25 TKT018) dose administration in 12 patients (4 per group).

PK Parameter	Idursulfase Dose Group (Mean ± SD)		
	0.15 mg/kg	**0.5 mg/kg**	**1.5 mg/kg**
AUC (min*µg/mL)			
Single dose[#] (n=4)	NA	617 ± 235	3419 ± 1035
Week 1 TKT018 (n=3)	307 ± 163 [b]	569 ± 490	2031 ± 909
Week 25 TKT018 (n=4)	210 ± 75 [c]	560 ± 453	3177 ± 1446
$t_{½}$ (λz) (min)			
Single dose[#] (n=4)	NA	152 ± 38	339 ± 162

PK Parameter	Idursulfase Dose Group (Mean ± SD)		
	0.15 mg/kg	**0.5 mg/kg**	**1.5 mg/kg**
Week 1 TKT018 (n=3)	380 ±414[b]	133 ± 135	105 ± 83
Week 25 TKT018 (n=4)	146 ± 67[c]	109 ± 95	233 ± 150
Cl (mL/min)			
Single dose[#] (n=4)	NA	41 ± 6	15 ± 4
Week 1 TKT018 (n=3)	23 ± 19[b]	83 ± 73	23 ± 4
Week 25 TKT018 (n=4)	32 ± 13[c]	65 ± 46	18 ± 6
Normalized Cl (mL/min/kg)			
Single dose[#] (n=4)	NA	0.91 ± 0.38	0.46 ± 0.14
Week 1 TKT018 (n=3)	0.54 ± 0.30[b]	1.78 ± 1.83	0.79 ± 0.28
Week 25 TKT018 (n=4)	0.75 ± 0.24[c]	1.56 ± 1.22	0.54 ± 0.28
V_{ss} (L)			
Single dose[#] (n=4)	NA	6.5 ± 2.2	3.9 ± 1.0
Week 1 TKT018 (n=3)	5.9 ± 3.0[b]	8.7 ± 4.0	2.9 ± 0.7
Week 25 TKT018 (n=4)	4.6 ± 1.2[c]	8.4 ± 5.6	3.3 ± 0.7
V_{ss} (%BW)			
Single dose[#] (n=4)	NA	15 ± 11%	12 ± 4%
Week 1 TKT018 (n=3)	18 ± 15%[b]	17 ± 10%	10 ± 3%
Week 25 TKT018 (n=4)	11 ± 2%[c]	19 ± 14%	9 ± 2%

[#]Data from week 1 TKT018 from the placebo-treated patients from study TKT008 were first administration and were therefore combined with TKT008 week1 data in order to be able to compare single versus multiple dose administration of idursulfase.
C_{max}: maximum observed serum concentration; $t_{½}$ (λz): terminal elimination half life; V_{ss}: apparent volume of distribution at steady state; AUC: area under the curve extrapolated to infinity; SD: standard deviation;
NA: Not applicable quantitative PK parameters were not be calculated due to low serum concentrations.
[a] Calculated only for patients with 1-hour infusion (n=1).
[b] Calculated for 2 patients, PK parameters were not be calculated due to low serum concentrations.
[c] Calculated for 3 patients, PK parameters were not be calculated due to low serum concentrations.

- Elimination

Idursulfase is a purified recombinant form of the naturally occurring lysosomal enzyme human idursonate-2-sulfatase, which is removed from serum by specific cell surface receptors and transported to lysosomes. In the dose finding study TKT008, the elimination half-life of idursulfase increased with increasing dose (implying that administered idursulfase enzyme activity was not inactivated in patients' plasma before cellular uptake), but mean terminal half-life was less than 5 hours at the highest concentration tested (1.5 mg/kg). In study TKT024 the estimated half-life was approximately 1 hour (see Table 5). Metabolic degradation of this protein is expected to occur in cells via proteolysis. As such, no metabolism and excretion studies were conducted in humans.

Table 5 Comparison of Initial and Repeat-Dose ELISA PK Parameters from Studies TKT024 and TKT024EXT.

Idursulfase frequency PK parameter	Every week[1]	Every other week[1]
C_{max} (µg/mL)		
Week 1	1.54 ± 0.59	1.72 ± 0.53
Week 27	1.23 ± 0.47	1.12 ± 0.35
Week 52[2]	1.21 ± 0.65	1.16 ± 0.53
AUC (min*µg/mL)		
Week 1	212 ± 80	250 ± 82
Week 27	175 ± 54	154 ± 41
Week 52[2]	211 ± 90	182 ± 64
$t_{½}$ (λz) (min)		
Week 1	46 ± 19	53 ± 45
Week 27	45 ± 18	32 ± 12
Week 52[2]	56 ± 10	55 ± 16
Cl (mL/min/kg)		
Week 1	2.9 ± 1.2	2.3 ± 0.8
Week 27	3.3 ± 1.0	3.6 ± 1.1
Week 52[2]	2.8 ± 1.0	3.1 ± 1.1
V_{ss} (% BW)		
Week 1	21 ± 8	18 ± 7
Week 27	24 ± 8	23 ± 13
Week 52[2]	21 ± 6	24 ± 8

- Dose proportionality and time dependencies

Dose proportionality was studied in study TKT008 and its extension study TKT018. These studies are described in the next section of Clinical Efficacy, Dose Response Studies.

Analysis of idursulfase serum concentrations indicated that idursulfase had a biphasic serum elimination profile following an initial one-hour infusion at all dose levels, 0.15, 0.5, and 1.5 mg/kg (see Table 4). PK parameters presented for the 0.15 mg/kg group should be considered carefully as these data approached assay LOD limit (0.08µg/ml). Maximum serum concentration (C_{max}) appeared proportional to dose when administered as an 1 hour infusion whereas the area under the curve (AUC) was not dose-proportional from 0.5 mg/kg to 1.5 mg/kg. These results suggest that serum clearance mechanisms for idursulfase may become saturated at a dose level near 0.5mg/kg. This was also reflected by an increase in elimination half-life with increasing dose.

Time dependency of idursulfase was assessed from both TKT008 and TKT024 studies and their extension studies TKT018 and TKT024EXT, respectively.
Pharmacokinetics were determined at week 1 of TKT008, week 1 of TKT018 and at week 25 of study TKT018. Idursulfase was administered every other week. Infusion time was 1 hour for the first administration, but was increased to 3-4 hours in 5 out of 8 patients in the 0.5 mg/kg and 1.5 mg/kg groups because of infusion related reactions that occurred with the 1-hour infusion in studies TKT008 and TKT018. Mean C_{max} values could not be estimated in these groups after repeated dosing due to varied infusion times for these patients. The C_{max} for idursulfase generally coincided with the end of the infusion, which varied from 1 to 4 hours in individual patients. Mean elimination half-life was less than 5 hours, no accumulation in serum occurred following the every other week dosing frequency in this study. Serum clearance profiles following repeated dosing were in general not notably different from initial serum profiles.

Infusion period in study TKT024/TKT024EXT was 3 hours. Due to this increased infusion time, the serum concentrations of idursulfase were low and could be followed in time only up to two hours after end of infusion. Therefore, PK parameters from study TKT024 should be considered carefully. From the 32 patients receiving 0.5 mg/kg weekly and the 32 patients receiving 0.5 mg/kg every other week,

pharmacokinetics of idursulfase were determined in a subset of patients (N=36) as single dose (week 1) and after 27 weeks and 52 weeks (=week 1 of TKT024EXT).

A comparison of the mean idursulfase serum concentration and PK parameters (see Table 6) for weekly versus every other week dosing at Week 27 was performed in study TKT024.

Table 6 Comparison of Mean Weekly versus Mean Every Other Week (EOW) ELISA PK Parameters at Week 27: Study TKT024

Dosing Regimen (n)	PK Parameter (SD)				
	C_{max} (µg/mL)	AUC (min*µg/mL)	$t_{1/2}$ (min)	Cl (mL/min/kg)	V_{ss} (% BW)
0.5 mg/kg Weekly (n=15)	1.23 (0.47)	175 (54)	45 (18)	3.27 (0.96)	23.6% (8.1%)
0.5 mg/kg EOW (n=15)	1.12 (0.35)	154 (41)	32 (12)	3.64 (1.11)	23.1% (13.2%)

SD = Standard Deviation

Together with pharmacodynamic data it was seen that the every other week dose schedule is suboptimal compared with the weekly dose schedule, and as such the approved dosing is a weekly dose.

- Special populations

Effect of Gender on Pharmacokinetics
The studies were essentially carried out in males due to the X-linked recessive nature of the disease; however, Hunter syndrome has rarely been reported in females. This being the case, reproductive studies in female animals were not performed, and idursulfase is also not indicated in women of child-bearing potential and this is reflected in the SPC.

Hepatic metabolism
Patients with Hunter syndrome have liver involvement with major organomegaly but with usually minor functional consequences. Liver function tests tended to improve under idursulfase therapy in the clinical trials. In addition, as metabolism of idursulfase is expected to occur by peptide hydrolysis impaired liver function is not expected to affect the pharmacokinetic profile of idursulfase in a clinically significant way. As such, no metabolism studies were conducted in humans, and there is also no clinical experience in patients with hepatic insufficiency.

No clinical investigations were carried out in patients with renal insufficiency.

Idursulfase was not studied in elderly (over 65yrs) or paediatric (under 5 yrs) patients. This point has been specified in section 4.2. of the summary of product characteristics.

Extrinsic Factors
The pivotal study was conducted at 9 sites in the US, EU, and South America. This covered a wide sample of diverse ethnic origin including 4 patients from Japan; however, 82% of the patients were Caucasian. The mutations in the I2S gene responsible for Hunter syndrome occur throughout all races and geographical regions. Therefore, no formal analyses by ethnic origin were conducted.

- Pharmacokinetic interaction studies

Metabolic degradation of idursulfase is expected to occur in cells via proteolysis, therefore as with other enzyme replacement therapy, idursulfase is an unlikely candidate for cytochrome P450 drug-drug interactions. Therefore neither in vitro interaction studies nor in vivo clinical drug interaction

studies were conducted (see section 4.5. of SPC). The applicant has undertaken to monitor any evidence of product interactions observed after treatment with idursulfase.

Pharmacodynamics

- Mechanism of action

Please refer to the section 3.1 Introduction.

- Primary and Secondary pharmacology

The ability to reduce urinary GAG excretion in patients was the primary biological measure of the clinical activity of idursulfase. The elevated excretion of GAG in the urine of Hunter syndrome patients reflects the excessive accumulation and storage of GAG in the body, likely originating from various tissues. As the substrate for I2S, the measurement of urine GAG provides a direct biochemical marker of the enzymatic activity of idursulfase in patients, as well as a measure of GAG reduction. Urine GAG levels were expressed as micrograms of GAG normalized to milligrams of urine creatinine (μg GAG/mg urine creatinine).

In study TKT 008, although the decline in GAG levels for the 0.5 and 1.5 mg/kg groups was more rapid than the 0.15mg/kg dose group, it is notable that the final values of GAG levels at the end of evaluation at 24 weeks were still above the upper limit of normal for all 3 dose groups. Furthermore, while even the highest dose level did not normalise urinary GAG levels, the decreases at week 24 noted with the 0.15 and 0.5 mg appeared to be similar. This suggests that the dosing interval of every other week is suboptimal.

In study TKT 024, both weekly and every other week dose schedules of 0.5 mg/kg showed significant reduction of urinary GAG levels by week 53 at the end of the study. However, it is notable that the mean GAG levels for both groups were above the upper limit of normal, since only 50% of patients in the weekly dose group achieved a reduction of GAG levels below the upper limit of normal compared with 31% in the every other week group. Overall in both groups combined, only 40% of patients achieved urinary GAG levels below the upper limit of normal. It therefore appears that the every other week dose schedule is suboptimal compared with the weekly dose schedule.

Liver and spleen size were measured by abdominal MRI at Baseline 1 (baseline study TKT008) and Baseline 2 (Week 24 of study TKT008), and at Week 25, Week 51, and Week 103 of TKT008/018.
All idursulfase dose groups had marked decreases in liver and spleen volume by 6 to 12 months of idursulfase treatment, even when weight gain was accounted for (normalized for body weight).

The effect of idursulfase therapy on the heart of Hunter syndrome patients was determined by measuring changes in left ventricular mass (LVM) by echocardiography. Of the 15 patients in the idursulfase weekly group with LVH at baseline, 6 patients had normal LVM by Week 53. Of the 9 patients in the idursulfase every other week group with LVH at baseline, 4 patients had normal LVM by Week 53. Of the 9 patients in the placebo group with LVH at baseline, 2 patients had normal LVM by Week 53. The degree of reduction in LV mass, which is needed to be clinically meaningful, is uncertain in Hunter syndrome.

Although the applicant has shown efficacy with respect to non-neurological improvements, no discussion has been put forward regarding neurological development and progression.

A full statistical analysis for the primary endpoint, 6MWT and % Predicted FVC and other endpoints is provided in the table below.

Table 7 Statistical analysis for the primary ands secondary endpoints TKT 024

Endpoint	52 Weeks of Treatment			
	0.5 mg/kg Weekly			
	Marginally Weighted (OM) Mean (SE)		Mean Treatment Difference Compared with Placebo (SE)	P-value (Compared with Placebo)
	Idursulfase	Placebo		
Composite (6MWT and %FVC)	74.5 (4.5)	55.5 (4.5)	19.0 (6.5)	0.0049
6MWT (m)	43.3 (9.6)	8.2 (9.6)	35.1 (13.7)	0.0131
% Predicted FVC	4.2 (1.6)	-0.04 (1.6)	4.3 (2.3)	0.0650
FVC Absolute Volume (cc)	230.0 (40.0)	50.0 (40.0)	190.0 (60.0)	0.0011
Urine GAG Levels (µg GAG/mg creatinine)	-223.3 (20.7)	52.23 (20.7)	-275.5 (30.1)	<0.0001
% Change in Liver Volume	-25.7 (1.5)	-0.5 (1.6)	-25.2 (2.2)	<0.0001
% Change in Spleen Volume	-25.5 (3.3)	7.7 (3.4)	-33.2 (4.8)	<0.0001

Clinical efficacy

Efficacy data included in this application are from a pivotal, 12-month, Phase II/III, double-blind study (TKT024) and from a supportive 6-month, Phase I/II, double-blind study (TKT008) and from 24-months of treatment in an ongoing, Phase I/II, open-label extension study (TKT018). TKT024EXT, the open-label extension of the TKT024 study, was ongoing and no efficacy data were available at the time of submission. The efficacy database is comprised of data from 108 individual patients (96 patients who were enrolled and treated in the pivotal - study TKT024, and 12 patients who participated in study TKT008, and subsequently enrolled into the Phase I/II open-label extension study, TKT018). The patients participating in the idursulfase clinical development program presented a broad spectrum of disease manifestations quite similar to the wide heterogeneity present in the general population of patients with Hunter syndrome.

- Dose response study

Prior to the design and implementation of the pivotal study, the initial clinical safety and pharmacology data were derived from observations in 12 patients with Hunter syndrome who randomly received 1 of 3 dose levels of idursulfase (0.15, 0.5, or 1.5 mg/kg) or placebo as an intravenous infusion every other week for 6 months in a Phase I/II trial (Study TKT008). Begun in 2001, this was a double-blind, placebo-controlled clinical trial designed to assess dose-response of idursulfase. Because this was a sequential, dose-escalation study, patients and study personnel were not blinded to dose cohort, but they were blinded to the treatment assignment (idursulfase versus placebo) within each cohort. This study was conducted at one site in the United States.

- Main study

Protocol No TKT024
METHODS

Multi-centre, double-blind, randomized, placebo/dummy-controlled, 53-week, Phase II/III study of the efficacy and safety of idursulfase 0.5 mg/kg administered either weekly or every other week (EOW) in patients with Hunter syndrome. Patients were stratified by age and disease severity score at baseline and were randomized in a 1:1:1 fashion across centres.

Study Participants

All randomized patients were male between the ages of 5.0 and 30.9 years (1 patient was 4 days short of his 5th birthday at randomization and 5 patients were ≥ 26 years old.). The mean age of patients in this study was 14.22 years old. Nearly 45% of patients in the study were 5 to 11 years old and only 25% of patients were 19 years of age or older. These Hunter syndrome patients were short for their age. The baseline demographic and disease characteristics of all patients in the ITT population are provided in Table 8 and 9.

Table 8 Baseline Patient Demographics: Study TKT024

Demographic Characteristic	**Placebo n=32**	**Idursulfase 0.5 mg/kg**			**All Patients N=96**
		Weekly n=32	**EOW n=32**	**All Idursulfase n=64**	
Age at Randomization (years):					
n	32	32	32	64	96
Mean (SE)	13.12 (1.221)	15.14 (1.113)	14.40 (1.241)	14.77 (0.828)	14.22 (0.687
Median	13.32	15.55	14.06	15.00	)
Min, Max	5.0, 29.0	6.3, 26.0	5.4, 30.9	5.4, 30.9	13.55
					5.0, 30.9
Age Category at Entry (n (%)):					
5 to 11 years	15 (46.9)	14 (43.8)	14 (43.8)	28 (43.8)	43 (44.8)
12 to 18 years	10 (31.3)	10 (31.3)	9 (28.1)	19 (29.7)	29 (30.2)
19 to 25 years	5 (15.6)	7 (21.9)	7 (21.9)	14 (21.9)	19 (19.8)
≥ 26 years	2 (6.3)	1 (3.1)	2 (6.3)	3 (4.7)	5 (5.2)
Baseline Prepubertal Patient (n (%)):					
Yes	17 (53.1)	14 (43.8)	17 (53.1)	31 (48.4)	48 (50.0)
Ethnicity (n (%)):					
Hispanic or Latino	4 (12.5)	7 (21.9)	4 (12.5)	11 (17.2)	15 (15.6)
Non-Hispanic	28 (87.5)	25 (78.1)	28 (87.5)	53 (82.8)	81 (84.4)
Race (n (%)):					
South American Indi	0	1 (3.1)	2 (6.3)	3 (4.7)	3 (3.1)
an	3 (9.4)	0	2 (6.3)	2 (3.1)	5 (5.2)
Asian	4 (12.5)	2 (6.3)	1 (3.1)	3 (4.7)	7 (7.3)
Black	24 (75.0)	28 (87.5)	27 (84.4)	55 (85.9)	79 (82.3)
White	1 (3.1)	1 (3.1)	0	1 (1.6)	2 (2.1)
Other					
Gender (n (%)):					
Male	32 (100.0)	32 (100.0)	32 (100.0)	64 (100.0)	96 (100.0)
Height (cm):					
N	32	32	32	64	96
Mean (SE)	124.19 (2.26	128.54 (2.63	128.03 (2.55	128.29 (1.82	126.92 (1.43
Median	2)	9)	0)	0)	6)
Min, Max	123.40	128.07	127.45	127.45	125.17
	101.2, 158.5	107.0, 166.0	107.4, 170.5	107.0, 170.5	101.2, 170.5

Table 8 Baseline Patient Demographics: Study TKT024

Demographic Characteristic	Placebo n=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly n=32	EOW n=32	All Idursulfase n=64	
Weight (kg):					
n	32	32	32	64	96
Mean (SE)	33.63 (2.284)	37.78 (2.340)	36.66 (2.269)	37.22 (1.618)	36.02
Median	29.75	33.75	33.75	33.75	(1.325)
Min, Max	18.8, 78.2	19.9, 69.8	19.0, 68.8	19.0, 69.8	33.00
					18.8, 78.2
Head Circumference (cm):					
n	32	32	32	64	96
Mean (SE)	56.60 (0.427)	57.32 (0.415)	57.51 (0.424)	57.41 (0.295)	57.14
Median	56.33	57.60	57.45	57.50	(0.244)
Min, Max	51.9, 61.5	52.7, 61.5	52.1, 64.0	52.1, 64.0	57.00
					51.9, 64.0

Note: Percentages are based on all patients in the ITT population within each treatment group. Data were missing where n <32.
ITT=intent-to-treat; EOW=every other week; mg=milligrams; kg=kilograms; SE=standard error; cm=centimetre(s).

Table 9 Baseline Disease Characteristics: Study TKT024

Clinical Characteristic	Placebo n=32	Idursulfase 0.5 mg/kg			All Patients n=96
		Weekly n=32	EOW n=32	All Idursulfase n=64	
Age at Diagnosis of Hunter syndrome (months):					
n	32	32	32	64	96
Mean (SE)	57.09	62.09 (9.144)	52.34 (6.855)	57.22 (5.702)	57.18
Median	(9.410)	48.00	48.00	48.00	(4.899)
Min, Max	36.00	< 1, 240.0	< 1, 180.0	< 1, 240.0	48.00
	< 1, 276.0				< 1, 276.0
Duration of Hunter syndrome from date of diagnosis to date of study entry (months)					
n	32	32	32	64	96
Mean (SE)	99.99 (13.63	119.29 (13.44	120.27 (15.22	119.78 (10.07	113.19 (8.12
Median	3)	6)	2)	4)	4)
Min, Max	77.40	97.80	113.40	101.40	97.80
	8.4, 276.0	13.2, 311.0	4.8, 310.8	4.8, 311.0	4.8, 311.0
Baseline Disease Score (n (%)):					
Score 2	0	2 (6.3)	2 (6.3)	4 (6.3)	4 (4.2)
Score 3	7 (21.9)	7 (21.9)	6 (18.8)	13 (20.3)	20 (20.8)
Score 4	14 (43.8)	10 (31.3)	11 (34.4)	21 (32.8)	35 (36.5)
Score 5	9 (28.1)	10 (31.3)	9 (28.1)	19 (29.7)	28 (29.2)
Score 6	2 (6.3)	3 (9.4)	4 (12.5)	7 (10.9)	9 (9.4)
Baseline % Predicted FVC Severity Score[a] (n (%)):					
Score 1	4 (12.5)	7 (21.9)	6 (18.8)	13 (20.3)	17 (17.7)
Score 2	18 (56.3)	13 (40.6)	12 (37.5)	25 (39.1)	43 (44.8)
Score 3	10 (31.3)	12 (37.5)	14 (43.8)	26 (40.6)	36 (37.5)

Clinical Characteristic	Placebo n=32	Idursulfase 0.5 mg/kg			All Patients n=96
		Weekly n=32	EOW n=32	All Idursulfase n=64	
Baseline % Predicted FVC (%)					
n	32	32	32	64	NA
Mean (SE)	55.567 (2.182)	55.298 (2.802)	55.147 (2.448)	55.222 (1.846)	
Median	57.360	54.885	54.550	54.885	
Min, Max	30.04, 75.75	15.99, 79.84	27.53, 79.25	15.99, 79.84	
Baseline 6MWT Severity Score[b] (n (%)):					
Score 1	4 (12.5)	6 (18.8)	6 (18.8)	12 (18.8)	16 (16.7)
Score 2	24 (75.0)	20 (62.5)	21 (65.6)	41 (64.1)	65 (67.7)
Score 3	4 (12.5)	6 (18.8)	5 (15.6)	11 (17.2)	15 (15.6)
Baseline 6MWT (meters)					
n	32	32	32	64	NA
Mean (SE)	392.5 (18.72)	391.6 (19.10)	400.6 (17.94)	396.1 (13.01)	
Median	403.0	396.5	416.5	407.5	
Min, Max	49, 540	90, 565	156, 554	90, 565	

Note: Percentages are based on all patients in the ITT population within each treatment group. Data missing where n < 32.
ITT=intent-to-treat; EOW=every other week; FVC=forced vital capacity; 6MWT=6-minute walk test; NA=Not Available.
[a] 1 = ≥ 70% to < 80%; 2 = ≥ 50% to < 70%; 3 = < 50% predicted FVC.
[b] 1 = ≥ 500 m; 2 = ≥ 300 m to < 500 m; 3 = severe < 300 m walked in 6 minutes.

Treatments
Patients received 52 weeks of treatment with idursulfase 0.5 mg/kg weekly, idursulfase 0.5 mg/kg EOW, or placebo weekly. Placebo infusions were administered during off weeks in the EOW dose group. Each intravenous (IV) infusion of blinded study drug was to be administered as a 3-hour continuous IV infusion in order to minimize the potential for infusion reactions.

Objectives

Primary Efficacy Objective

The primary objective of this study was to determine the efficacy of weekly dosing of idursulfase (0.5 mg/kg per dose) in the treatment of Hunter syndrome patients.

Secondary Objectives

The secondary objectives of the study were to determine the efficacy of every other week dosing of idursulfase (0.5 mg/kg per dose) in the treatment of Hunter syndrome patients and to evaluate the safety and tolerability of weekly and every other week dosing of idursulfase (0.5 mg/kg per dose) in a large Hunter syndrome patient population.

Outcomes/endpoints

Primary efficacy endpoint was a 2-component composite variable of the sum of the ranks of the change from Baseline to Week 53 in the total distance walked in the 6-minute walk test (6MWT) and in % predicted FVC. The clinical variables of total distance walked in the 6MWT and % predicted FVC were also analyzed separately.

Secondary efficacy endpoints

- Passive joint range of motion (JROM)
- Combined liver and spleen volume by MRI and liver and spleen volumes independently
- Urine glycosaminoglycan (GAG) levels
- Cardiac left ventricular mass (LVM) by echocardiography

Tertiary exploratory efficacy endpoints:

- Additional pulmonary function test parameters of forced expiratory volume in the first second (FEV1), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), and diffusing capacity (DLco).
- Growth velocity in prepubertal patients
- Radiologic skeletal survey
- Childhood Health Assessment Questionnaire (CHAQ) to measure physical function (disability, pain)
- Hunter Syndrome-Functional Outcomes in Clinical Understanding Scale (HS-FOCUS) questionnaire assessing physical disabilities (supplement to CHAQ)
- Quality of Life assessment using the Health Utilities Index (HUI) and the Childhood Health Questionnaire (CHQ) for the parent/care giver and for the child
- A 3-component composite variable consisting of the sum of ranks of the change from baseline to Week 53 in % predicted FVC, total distance walked in 6MWT, and JROM global score

Sample size

- The planned sample size was 90 patients. The final number of enrolled and randomized patients was 96.

Randomisation

Patients were randomised equally to one of three treatment arms: IV infusions of idursulfase either weekly or every other week at a dose of 0.5 mg/kg, or weekly infusions of placebo.

Blinding (masking)

Idursulfase and placebo had the same visual appearance and were bottled and labelled identically. The study drug assignment was unknown to the parents and patients, the investigators, and their study personnel, the study centre pharmacy, and to TKT staff involved in the conduct of the study. The patients randomized to receive every other week infusions of idursulfase were administered placebo in the alternate week to maintain the blinding of the treatment regimen (i.e., weekly dosing).
In order to maintain the study blinded, all magnetic resonance imaging (MRI) studies and echocardiograms were read by an independent, blinded third party.

Statistical methods

Data were summarized by treatment group (and by visit when applicable) with respect to demographic and baseline characteristics, clinical activity variables, safety variables, and PK measurements. Where applicable, each variable was quantified as a change from the baseline value.
Formal statistics with 2-tailed hypothesis testing at the 0.05 level of significance using ANCOVA analysis was performed on the primary endpoint, and other efficacy analyses. Descriptive statistics were performed on the safety data.

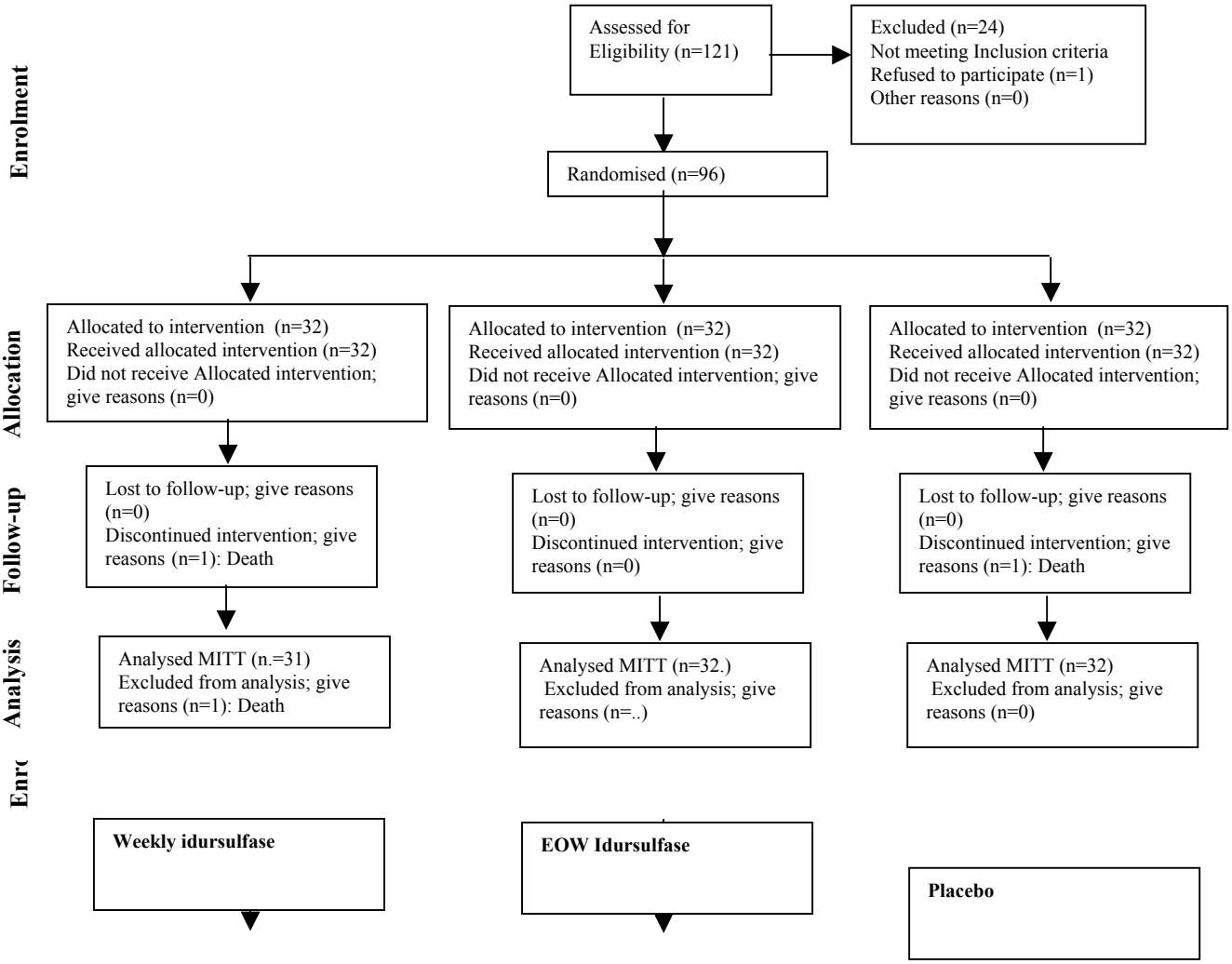
- 96 (32 idursulfase weekly; 32 idursulfase EOW; 32 placebo) were analyzed for efficacy in the intent-to-treat (ITT) population (all randomized patients);
- 95 patients (31 idursulfase weekly, 32 idursulfase EOW, 32 placebo) were analyzed for efficacy in the modified ITT (MITT) population (all patients with a post-baseline assessment); 1 patient in the idursulfase weekly group died of respiratory failure 12 days after his first and only dose and was excluded from the MITT analysis.
- 94 patients (31 idursulfase weekly, 32 idursulfase EOW, 31 placebo) were analyzed for efficacy in the per protocol (PP) population (all randomized patients who met all admission criteria and who completed the 53 weeks of the study, had all baseline and Week 53

measurements of the primary efficacy assessments where a 21-day analysis window after Week 52 infusion was used, received at least 80% of the study drug infusions, had not missed 4 consecutive doses [where a dose was defined as administration of ≥50% of the planned infusion for the efficacy analyses], and had no protocol violations). The 2 patients excluded from the PP analysis were as follows: 1 patient in idursulfase weekly group who died following his first and only dose and was also excluded from the MITT analysis and 1 patient in the placebo group who died of pneumococcal pneumonia 10 days after his Week 34 dose.

- Completer populations were also defined for the secondary and tertiary endpoints, with the actual number of patients for each endpoint being defined by those patients who had each specific endpoint assessment at both Baseline and Week 53
- 96 patients (32 idursulfase weekly; 32 idursulfase EOW; 32 placebo) were analyzed for safety (all patients who received at least 1 infusion, or part of an infusion, of blinded study drug).

RESULTS

Participant flow



Outcomes and estimation

Efficacy was adequately demonstrated for the composite endpoint using the weekly dosage schedule, but it has not been shown for the EOW schedule where the evidence was weak with borderline significance. This was evident for the composite endpoint, which was driven only by one component, namely the 6MWT, with no clear evidence of any effect on pulmonary function by the EOW dose.

Since the effect of the EOW dosing scheme was of borderline significance and seemed to be confined to distance walked with no effect on respiratory function the MA was restricted to weekly dosing only.

The applicant carried out a re-assessment of the risk benefit for the EOW dosing in view of additional data from TKT024EXT, which clearly demonstrated the superiority of weekly dosing over EOW dosing. Accordingly, the treatment is recommended as a weekly dosing for all patients with Hunter syndrome.

Ancillary analyses

To assess the contributions of the treatment differences in the change from baseline to Week 53 in 6MWT distance walked to the outcome of the analysis of the 2-component composite variable analysis, the ranked changes were analysed using an ANCOVA with treatment group and region fitted as factors, and baseline patient age (5 to 11 years, 12 to 18 years, and 19 to 25 years) and baseline disease score (score of 2, score of 3 or 4, and score of 5 or 6) as covariates. A Wilcoxon rank-sum test was also performed.

- Supportive studies

Studies **TKT008 and TKT018** provide the supportive data for this submission which contains a 2- to 2.5-year analysis of efficacy data for these patients, including the first 6 months of idursulfase treatment in TKT008 and a 3- to 3.5-year analysis of safety and clinical activity, including safety data and urinary GAG levels from the first dose of idursulfase in either TKT008 or TKT018.

Patients completing Study TKT008 continued to receive treatment in Study TKT018, an open-label study to further evaluate the long-term safety and efficacy of idursulfase therapy in Hunter syndrome. All 12 patients who completed the Phase I/II testing of idursulfase in TKT008 entered into the open-label extension Study TKT018 starting in October 2001.

No baseline weekly dosing data was available for the dose finding study TKT008, and as such it is not entirely clear, but nevertheless probable, that the dose selected was not optimal for this patient population. Although selection of the dose was also based on pre-clinical data as well, in which a dose of 1.0 mg was studied, this was not clinically evaluated.
It seems probable therefore, judging from urinary GAG levels, that a weekly dose greater than 0.5 mg/kg is more effective in normalising GAG levels rapidly, followed by a lower maintenance dose given weekly or even EOW.

More information on the appropriate dose, dose schedule and infusion time was warranted since the submitted dose finding study was inconclusive. The MAA was asked to submit more elaborate dose finding data especially regarding the efficacy of the comparatively safer weekly 0.15 mg/kg dose, and the safety (3 hour infusion) of the relatively efficacious 1.5 mg/kg dose which needed to be explored further. However, although the applicant stated that there is a lower efficacy with the 0.15 mg/kg (every other week, 1 hour infusion) dose while the higher 1.5 mg/kg (every other week, 1 hour infusion) dose was associated with a higher number of adverse events, detailed analysis did not justify the conclusions of the applicant. In particular, the longer infusion duration for the 1.5 mg/kg dose and the every week dosing of the 0.15 mg/kg had not been explored and will be assessed through the Hunter Outcome Survey..

- Discussion on clinical efficacy

Efficacy was adequately demonstrated in the pivotal trial for the composite endpoint using the weekly dosage schedule, however evidence concerning the EOW was weak with borderline significance seemed to be confined to distance walked with no effect on respiratory function. The applicant carried out a re-assessment of the risk benefit for EOW dosing in view of additional data from TKT024EXT, which has clearly demonstrated the superiority of weekly dosing over EOW dosing, and accordingly, changed the recommended dosing to a weekly schedule for all patients with Hunter syndrome.

Results from the dose finding study showed that it is probable, judging from urinary GAG levels, that a weekly dose greater than 0.5 mg/kg is more effective in normalising GAG levels rapidly, followed by a lower maintenance dose given weekly or even EOW. This issue will be investigated via the Hunter Outcome Survey (HOS) registry.

In trial TK024 the adjusted changes from baseline in the primary endpoint were always lower for all treatment groups than the unadjusted changes, and therefore did not seem to reflect the experience of patients in the trial. Accordingly the applicant was asked to explain how the adjusted means were derived, and to provide results, which more appropriately summarised the data. The applicant supplied the recalculated marginally weighted adjusted means for the primary and other endpoints (absolute changes in FVC, changes in urine GAG levels, liver and spleen volumes), including them in the SPC.

The use of minimisation for treatment allocation in the study TKT024 was a potential concern. The applicant was asked to provide further details of how the minimisation was performed; particularly the element of randomisation in this procedure was to be clearly explained. The applicant clearly described the workings of the dynamic allocation procedure. The p-value from the permutation test (p=0.0197) was not as extreme as that from the original ANOVA (p=0.0049), however statistical significance was still achieved.

With respect to neurological development progress and bioavailability of the enzyme in the CNS, the applicant commented that as a protein, idursulfase was not expected to cross the blood brain barrier and therefore it was not expected to have any effect on CNS disease, if present. Since somatic disease is independent of CNS disease, it was expected that somatic disease would respond to idursulfase regardless of the presence or absence of CNS involvement. The bioavailability of idursulfase within the CNS was not assessed in the pivotal trial.

More information on the appropriate dose, dose schedule and infusion time was warranted since the submitted dose finding study was inconclusive. Accordingly, the applicant has committed to submit, as a post-authorisation follow up measure.

Long-term data on relevant clinical end-points was also requested. The applicant has agreed to gather, as a specific obligation, long-term safety and efficacy data, with comparison to historical data, through establishment of a patient registry; the Hunter Outcome Survey (HOS) with a commitment to continue to analyze data for at least the first 10 years.

Further information was also asked to be provided post-authorisation in the younger population < 5years.The applicant conducted analyses of the effects of age on idursulfase pharmacodynamics, pharmacokinetics and immunogenicity for various age categories above the age of 5. The analysis demonstrated that overall, although younger patients may have higher urinary GAG levels relative to older patients, age however, does not appear to have any clinically relevant effects on idursulfase pharmacokinetics or immunogenicity. However, the applicant has committed to a study in children less than 5 years of age, the protocol for which will be submitted as a follow-up measure. The study is primarily a safety study, although PK, PD and urine GAG will also be evaluated. Any additional information collected through HOS on treatment of patients under 5 will also be evaluated.

Clinical safety

- Patient exposure

All patients receiving any amount of study drug were included in this safety analysis. The safety database includes data from 108 male patients with Hunter syndrome between the ages of 5.0 and 30.9 years at first infusion. The first enrolment dates and cut-off dates for submission of this dossier were the following:

Table 10 Start and cut-off dates for collection of data

Study	First enrolment date	Cut-off date
TKT008	23 APR 2001	26 MAR 2002 (LPV)
TKT018 (ongoing)	08 OCT 2001	30 MAR 2004
TKT024	18 SEP 2003	16 MAR 2005 (LPV)*
TKT024EXT (ongoing)	13 SEP 2004	04 APR 2005*

*Further immunogenicity data for TKT024/024EXT was submitted on the 03 March 2006

Due to differences in study designs, dosing regimens, and dose levels, safety data have not been pooled across studies and an integrated statistical analysis of data was not performed. Therefore, all safety data are summarized descriptively. Safety evaluations included vital sign measurements, oxygen saturation, physical examinations, adverse event (AE) assessments, electrocardiograms (ECG), serum chemistry and haematology laboratory tests, urinalysis, and testing for anti-idursulfase antibodies.

As a conservative measure of safety, any partial infusion administered was counted as a whole dose. A total of 5,321 idursulfase infusions have been administered to date across studies, regardless of dose level or dose regimen. The majority of infusions (3,209) were administered during 1 year of study in TKT024 (see Table 11). Due to differences in dosing intervals and dose levels administered in the idursulfase clinical trials, exposure data have not been integrated for this submission.

Table 11 Total Numbers of Infusions Administered in the Idursulfase Clinical Studies

	TKT008			**TKT018**			**TKT024**		**TKT024EXT**
	Idursulfase Dose Level and Regimen								
	0.15 mg/kg EOW	**0.5 mg/kg EOW**	**1.5 mg/kg EOW**	**0.15 mg/kg EOW**	**0.5 mg/kg EOW**	**1.5 mg/kg EOW**	**0.5 mg/kg Weekly**	**0.5 mg/kg EOW**	**0.5 mg/kg Weekly**
Number of patients	3	3	3	4[a]	12[a,b]	4[a]	32[c]	32	94[d]
Number of infusions	36	35	35	105	811	64	1580	1629	1026

EOW=Every other week.
[a] Includes patients randomized to placebo in TKT008.
[b] All patients were transitioned to 0.5 mg/kg every other week from October to November 2002.
[c] One patient died after receiving only 1 dose of idursulfase in TKT024.
[d] All patients who completed TKT024, including patients randomized to placebo.

In study TKT024 compliance with the treatment regimen was high, with few missed infusions. Of the possible 52 infusions, patients in the idursulfase weekly dose group received an average of 49.4 infusions (range 1 to 52), patients in the idursulfase every other week group received an average of 50.9 infusions (range 49 to 52), and patients in the placebo group received an average of 50.4 infusions (range 34 to 52). Mean durations of exposure also were similar among idursulfase weekly, idursulfase every other week, and placebo groups (49.6, 51.1, and 50.6 weeks, respectively).

For patients enrolled in the ongoing study TKT024EXT, the extent of exposure to idursulfase was calculated from the date of the first infusion after enrolment into the extension study until the day of the last reported infusion as of the data cut-off for this submission. Patients who were randomized to idursulfase every other week in TKT024 had their exposure increased to weekly infusions and patients randomized to placebo in TKT024 received their first infusion of idursulfase in this extension study.

In study TKT008 study drug infusions were administered every other week for 24 weeks, for a total of 12 infusions per patient (3 patients at each of the 3 idursulfase dose levels and 3 patients receiving placebo). Three patients received all 12 infusions of idursulfase at the 0.15 mg/kg dose; 2 patients received 12 infusions and 1 patient received 11 infusions of idursulfase at the 0.5 mg/kg dose; and 2 patients received 12 infusions and 1 patient received 11 infusions of 1.5 mg/kg of idursulfase. The 3 patients randomized to placebo received all 12 infusions of placebo. All patients received treatment for 152 to 154 days.

In TKT018, all 12 patients randomized to treatment in TKT008 received active idursulfase, including the 3 placebo patients in TKT008. During the study, all patients were later transitioned from October to November 2002 to idursulfase 0.5 mg/kg every other week and have continued treatment at this dose to date. Exposure data for TKT018 were calculated from the first active dose of idursulfase in

TKT008 for patients who received idursulfase in TKT008 and from the first dose of idursulfase in TKT018 for patients who had been randomized to placebo in TKT008.

- Adverse events

Controlled studies (Phase III and phase I/II)

No patients withdrew from study TKT024 due to an adverse event. Two patients died during the study (1 idursulfase weekly patient and 1 placebo patient). The patient who was randomized to weekly idursulfase died of cardiac arrest 12 days after receiving only 1 dose of study drug. The placebo patient received 34 infusions of blinded study drug prior to experiencing lung haemorrhage due to streptococcal pneumonia infection and his subsequent death.
Common adverse events in Study TKT 024 are shown in Table 12.

Table 12 Number and Percentage of Patients with the Most Common (at Least 10% of Patients in Any Treatment Group) Treatment Emergent Adverse Events in TKT024, by Treatment Group

System Organ Class Preferred Term	Number (%) of Patients		
	Placebo (n=32)	0.5 mg/kg Idursulfase	
		Weekly (n=32)	EOW (n=32)
Any System Organ Class	32 (100.0)	32 (100.0)	32 (100.0)
Infections and Infestations	25 (78.1)	27 (84.4)	24 (75.0)
Upper Respiratory Tract Infection NOS	10 (31.3)	12 (37.5)	12 (37.5)
Ear Infection NOS	9 (28.1)	8 (25.0)	9 (28.1)
Otitis Media NOS	7 (21.9)	6 (18.8)	7 (21.9)
Otitis Media Serous NOS	4 (12.5)	4 (12.5)	3 (9.4)
Sinusitis NOS	3 (9.4)	5 (15.6)	2 (6.3)
Psychiatric Disorders	5 (15.6)	7 (21.9)	10 (31.3)
Anxiety	0	2 (6.3)	4 (12.5)
Nervous System Disorders	20 (62.5)	22 (68.8)	27 (84.4)
Headache	14 (43.8)	19 (59.4)	21 (65.6)
Dizziness	8 (25.0)	4 (12.5)	6 (18.8)
Ear and Labyrinth Disorders	20 (62.5)	14 (43.8)	20 (62.5)
Otorrhea	9 (28.1)	7 (21.9)	7 (21.9)
Ear Pain	6 (18.8)	7 (21.9)	5 (15.6)
Hypoacusis	4 (12.5)	1 (3.1)	5 (15.6)
Vascular Disorders	15 (46.9)	16 (50.0)	16 (50.0)
Hypertension	7 (21.9)	8 (25.0)	5 (15.6)
Flushing	6 (18.8)	5 (15.6)	5 (15.6)
Hypotension	4 (12.5)	3 (9.4)	2 (6.3)
Poor Venous Access	2 (6.3)	2 (6.3)	4 (12.5)
Respiratory, Thoracic and Mediastinal Disorders	30 (93.8)	31 (96.9)	29 (90.6)
Cough	19 (59.4)	16 (50.0)	16 (50.0)
Nasal Congestion	12 (37.5)	12 (37.5)	16 (50.0)
Pharyngitis	10 (31.3)	13 (40.6)	11 (34.4)
Rhinorrhoea	9 (28.1)	9 (28.1)	10 (31.3)
Nasopharyngitis	5 (15.6)	4 (12.5)	8 (25.0)
Dyspnoea NOS	9 (28.1)	4 (12.5)	3 (9.4)
Wheezing	5 (15.6)	5 (15.6)	5 (15.6)
Rhonchi	5 (15.6)	3 (9.4)	4 (12.5)
Bronchospasm NOS	5 (15.6)	3 (9.4)	2 (6.3)
Epistaxis	5 (15.6)	2 (6.3)	1 (3.1)
Rhinitis NOS	4 (12.5)	4 (12.5)	0
Gastrointestinal Disorders	27 (84.4)	24 (75.0)	26 (81.3)

Table 12 Number and Percentage of Patients with the Most Common (at Least 10% of Patients in Any Treatment Group) Treatment Emergent Adverse Events in TKT024, by Treatment Group

System Organ Class Preferred Term	Number (%) of Patients		
	Placebo (n=32)	0.5 mg/kg Idursulfase	
		Weekly (n=32)	EOW (n=32)
Vomiting NOS	16 (50.0)	8 (25.0)	18 (56.3)
Abdominal Pain NOS	11 (34.4)	11 (34.4)	17 (53.1)
Diarrhoea	15 (46.9)	11 (34.4)	12 (37.5)
Nausea	9 (28.1)	7 (21.9)	9 (28.1)
Abdominal Pain Upper	2 (6.3)	5 (15.6)	2 (6.3)
Dyspepsia	0	4 (12.5)	4 (12.5)
Skin and Subcutaneous Tissue Disorders	22 (68.8)	22 (68.8)	20 (62.5)
Rash	11 (34.4)	8 (25.0)	11 (34.4)
Pruritus	5 (15.6)	10 (31.3)	6 (18.8)
Rash Pruritic	0	5 (15.6)	5 (15.6)
Contusion	2 (6.3)	2 (6.3)	5 (15.6)
Urticaria NOS	0	5 (15.6)	4 (12.5)
Musculoskeletal and Connective Tissue Disorders	21 (65.6)	19 (59.4)	22 (68.8)
Arthralgia	9 (28.1)	10 (31.3)	14 (43.8)
Pain in Limb	10 (31.3)	9 (28.1)	9 (28.1)
Back Pain	8 (25.0)	8 (25.0)	11 (34.4)
Myalgia	3 (9.4)	3 (9.4)	4 (12.5)
Neck Pain	3 (9.4)	3 (9.4)	4 (12.5)
Peripheral Swelling	2 (6.3)	1 (3.1)	4 (12.5)
Chest Wall Pain	0	4 (12.5)	0
General Disorders and Administration Site Conditions	26 (81.3)	26 (81.3)	26 (81.3)
Pyrexia	19 (59.4)	20 (62.5)	18 (56.3)
Influenza-like Illness	4 (12.5)	3 (9.4)	8 (25.0)
Fatigue	3 (9.4)	2 (6.3)	4 (12.5)
Infusion Site Swelling	1 (3.1)	4 (12.5)	4 (12.5)
Malaise	3 (9.4)	5 (15.6)	1 (3.1)
Fall	4 (12.5)	0	4 (12.5)
Injury, Poisoning and Procedural Complications	10 (31.3)	12 (37.5)	15 (46.9)
Head Injury	1 (3.1)	0	4 (12.5)

Patient population: Safety population (all patients who received 1 dose [or partial dose] of study drug).
Patients are counted only once within each system organ class and preferred term.
Most common events occurring in at least 4 patients in any dose group.

The overall incidences of adverse events as well as those adverse events reported most commonly (10% of patients in any treatment group) were similar across treatment groups.

In the Phase I/II study TKT008, all patients in the placebo and idursulfase treatment groups experienced at least 1 adverse event. No patients were withdrawn from the study due to adverse events and no patient died as of the data cut-off for this submission

All 12 patients experienced at least 1 adverse event during the first idursulfase study (TKT008). The incidence of AEs was slightly higher in the 1.5 mg/kg every other week group than in the 0.5 mg/kg group.

Uncontrolled Studies

All 94 patients who completed TKT024 enrolled in TKT024EXT. No patient withdrew from the study due to an adverse event as of the data cut-off. More treatment-emergent adverse events and related adverse events were reported for patients randomized to placebo in TKT024 This was similar to the safety data from TKT024, during which adverse events were reported more frequently during the first 6 months than during the latter 6 months of study. One patient (randomized to idursulfase every other week in TKT024) died during the study.

Erythema, rash NOS, urticaria NOS, flushing, and tachycardia NOS each occurred more frequently in TKT024 placebo patients as compared with patients who received idursulfase weekly or every other week in TKT024.

An overall summary of adverse events (as provided above for Studies TKT008, TKT024 and TKT024EXT) could not be tabulated for TKT018 due to differences in dose levels and dose regimens as well as the different lengths of observation during the study. This also applies for the adverse drug reactions.

- Adverse Drug Reactions

Controlled Studies:

In TKT024, the most common AEs considered possibly or probably related to study drug included:

- Headache (9/32, 28.1%), pruritus, pyrexia (each 7/32, 21.9%), hypertension (6/32, 18.8%), rash NOS, and urticaria NOS (each 5/32 15.6%) in the idursulfase weekly group.
- Pyrexia (7/32, 21.9%), headache, rash NOS (each 6/32, 18.8%), flushing (5/32, 15.6%), hypertension NOS, abdominal pain, pruritus, urticaria NOS, and fatigue (each 4/32, 12.5%) in the idursulfase every other week group.
- Placebo patients most frequently experienced headache, pyrexia, (each 8/32, 25.0%), hypertension NOS, rash NOS (each 6/32, 18.8%), flushing, hypotension NOS, nausea, and pruritus (each 3/32, 9.4%).

In TKT008 the most common adverse events considered possibly or probably related to study drug were flushing, pyrexia, rigors, urticaria NOS, dizziness and headache NOS.

Uncontrolled Studies

During TKT024EXT (up to the data cut-off for this submission), a total of 129 possibly/probably related adverse events were reported in 19 TKT024 placebo patients compared with 34 possibly/probably related adverse events reported in 7 TKT024 idursulfase weekly patients and 19 possibly/probably related adverse events reported in 6 TKT024 idursulfase every other week patients). This result was similar to the safety experience observed in TKT024.

- Serious adverse event/deaths/other significant events

In TKT024 a total of 49 treatment-emergent SAEs occurred in 26 patients during this study (9 patients in the idursulfase weekly group experienced a total of 13 SAEs, 8 patients in the idursulfase EOW group experienced a total of 18 SAEs, and 9 patients in the placebo group experienced a total of 18 SAEs). One additional patient (idursulfase EOW) experienced a SAE, a porta-cath placement that occurred prior to the patient's first idursulfase infusion. Central venous catheterization was prospectively captured as a SAE and was coded as "poor venous access." The incidence of "poor venous access" was similar across treatment groups and was due to the route of administration of idursulfase. The majority of SAEs were considered unrelated to study drug; 3 patients experienced SAEs that were considered to be possibly or probably related to study drug:

- 2 patients in idursulfase weekly group: 1 cyanosis, 1 pulmonary embolism

- 1 patient in placebo group: 1 cutaneous rash

In TKT024EXT 6 patients experienced a total of 8 SAEs up to and including the patient's last infusion before the data cut-off. All SAEs were considered unrelated to study drug.

From the beginning of TKT008, a total of 15 SAEs have been reported in 7 patients. Of the SAEs reported during TKT008 and TKT018, 8 were considered to be infusion-related reactions, including the 2 hypoxia SAEs and 1 respiratory distress SAE reported by 1 patient, facial flushing, facial swelling, rigors, and urticaria, all reported by 1 patient, and the respiratory distress SAE reported by 1 other patient. All of these SAEs occurred while patients were receiving idursulfase 0.5 mg/kg every other week.

Deaths
Four patients died during their participation in idursulfase clinical trials.

- TKT024: 2 patients
- TKT024EXT: 1 patient
- TKT018: 1 patient.

None of the reported deaths was determined to be related to idursulfase.

- Laboratory findings

Haematology Parameters

In the pivotal trial, for red blood cell parameters (haemoglobin, haematocrit, and RBC count), up to 4 patients in each of the 3 treatment groups had values that shifted from normal at baseline, to low at Week 53. Placebo patients had shifts from normal to low in platelet counts, WBC counts, and neutrophil counts. No shifts in haematology parameters, including long-term treatment in TKT018, suggested increased safety risk with either the idursulfase weekly or the idursulfase EOW treatment regimens, compared with placebo.

Chemistry Parameters

In TKT024 shifts from normal to low, or high, in serum chemistry parameters occurred sporadically. More patients in the idursulfase treatment groups (4 patients in each group) compared with the placebo group (1 patient) had high phosphorus values at Week 53. Shifts from high to normal at Week 53 were slightly more common in the idursulfase weekly group than the placebo group for total bilirubin and alkaline phosphatase. None of the shifts in serum chemistry parameters suggested an increased safety risk with either the idursulfase weekly or the idursulfase every other week compared with placebo. In TKT008, no clear dose-related adverse effects could be identified in any of the parameters.

Clinically Significant Laboratory Results

The majority of patients in TKT024 had at least 1 laboratory value that was considered clinically significant during the study. The majority of these values were considered to be related to concurrent disease or unknown causes, rather than to study drug. 7 idursulfase weekly, 3 idursulfase every other week and 4 placebo patients experienced at least 1 clinically significant laboratory value that was considered to be related to study drug. For the idursulfase patients, these laboratory abnormalities were mostly related to infusion reactions (abnormalities in serum tryptase, C3, C4, total serum complement), but also included abnormalities in red blood cells, haemoglobin, haematocrit, alkaline phosphatase, lactic dehydrogenase, and serum uric acid levels. All laboratory AEs considered related to study drug experienced by patients treated with idursulfase were considered mild (Grade 1) in severity, except for increased blood bilirubin, which was considered severe (Grade 3). This patient's bilirubin levels were abnormal at baseline, increased at Week 9, and returned to baseline levels thereafter.

Immunogenicity

The data showed that the majority of infusion-related adverse events (IRAEs) reported during TKT024 occurred during the first 6 months of the study. For both the weekly and EOW groups, a greater incidence of IRAEs were reported among IgG positive patients compared with IgG negative patients. However, the peak rates of IRAEs occurred within the first 6 months and these results seem to

corroborate the results of seropositivity, which also indicated that peak rates were observed within the first 6 months of treatment and declined thereafter. Thus, it appears that patients may develop tolerance to the infusions during long-term treatment. The applicant has committed to evaluate the effects of antibodies on efficacy through the HOS registry.

With respect to infusion reactions as well as respiratory infusion reactions, although comparative AE rates within a given treatment group did not reveal a clear stepwise increase in AE rates as pulmonary function declined, the highest AE rate was observed in subjects with an FVC ≤40% predicted, irrespective of treatment assignment. In addition, IRAEs appeared to be highest in the weekly dosed group in subjects with an FVC ≤40% predicted. It is notable that 81 % of IRAEs in the weekly group occurred in subjects who developed antibodies at some time point in their treatment across all four FVC categories suggesting an association between the likelihood of experiencing an IRAE and the tendency to develop antibodies to idursulfase. With respect to respiratory infusion related adverse events (RIR-AEs) there seemed to be a correlation between increasing number of events with increasing severity of respiratory disease. However, data is still inconclusive due to small numbers and will continue to be collected through Hunter Outcomes Survey.

There do not appear to be any definitive risk factors presently identifiable apart from higher antibody positivity in pre-pubertal patients, however small numbers of patients preclude definitive conclusions to be drawn. The applicant will conduct an evaluation of the genetic mutations in patients from TKT024 in an effort to determine whether there are one or more common genotypes that are highly associated with subsequent antibody formation.

Additional immunogenicity data from TKT024/024EXT using a new validated assay with a conformation specific antibody was submitted on 03 March 2006. Reanalysis of the samples using the new assay showed that in TKT024, 30 of the 64 idursulfase treated patients were determined to be antibody positive during the 52-week study. This compares to 6 of 64 idursulfase treated patients reported initially in the MAA. Four of the 30 antibody positive patients were confirmed to have enzyme neutralizing activity. In study TKT024EXT, 39 of the 94 idursulfase treated patients were determined to be antibody positive. Some of these patients have received up to 88 weeks of treatment in studies TKT024 and TKT024EXT. Seven of the 39 antibody positive patients were confirmed to have enzyme neutralizing activity. Four of these patients were the same as those determined to have neutralizing antibodies during TKT024.

- Safety in special populations

Hunter syndrome is caused by a mutation in the gene for iduronate-2-sulfatase, which results in either an enzyme with deficient activity, or in lack of expression of any enzyme at all. In either case, the mutation causes a clear disease state. Therefore, the alterations in the I2S gene that underlie Hunter syndrome are not considered polymorphisms. There are no known true gene polymorphisms that would be expected to impact the efficacy or safety of enzyme replacement therapy with idursulfase.

Because idursulfase is not cleared through renal or hepatic mechanisms, renal or hepatic insufficiency should not affect the overall safety profile.

All idursulfase doses were calculated on a milligram per kilogram basis. The patient populations evaluated in the clinical studies were primarily paediatric-aged; therefore, no safety-related dose adjustment was made for these patients. The three age categories were defined as 5 to 11 years, 12 to 18 years, and ≥19 years, and were meant to group the study population into pre-pubertal, post-pubertal, and adult patients. Rates of infusion-related AEs by age category and treatment group showed that older patients tended to experience more of these AEs compared to younger patients.

Patients with Hunter syndrome can develop progressive restrictive pulmonary disease mainly due to musculoskeletal involvement and further complicated by severe airway obstruction secondary to oropharyngeal and respiratory deposition of GAG. Respiratory tract infections are common complications in these patients, who may be very sensitive to any additional bronchopulmonary insult. In clinical studies, acute episodes of respiratory distress with hypoxia were reported during idursulfase infusions; they all resolved with appropriate therapeutic measures. Patients at risk were primarily

those with severe underlying obstructive airway disease. Acute respiratory reactions will be monitored as part of the Pharmacovigilance Plan, especially in patients with obstructive airway disease.

- Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with idursulfase.

- Discussion on clinical safety

Overall, therapy with idursulfase was generally well tolerated at a dose level of 0.5 mg/kg administered both weekly and every other week. No patient has withdrawn from a study to date due to an adverse event related to idursulfase The main safety concerns with idursulfase appear to be infusion associated reactions (IARs) and immunogenicity. IARs appear to be related to the dose and the frequency of administration since they were more common in the weekly schedules compared to EOW and no IARs were reported in patients on the lower dose of 0.15 mg. However, the frequency of IARs seems greatest during the first 6-12 months of treatment and decreases over time. Infusion-related AEs were also frequently reported in the placebo group. This appears to suggest that there is a baseline incidence of AEs that may be caused directly by the infusion procedure itself (e.g., vagal reactions). The IARs were manageable either by temporary interruption or slowing of the infusion rate and in some cases by the use of premedication. While the majority of SAEs were considered to be unrelated, it is important to note that some drug-related SAEs do appear to be of particular concern. These were reported in 5 patients treated with 0.5 mg/kg weekly or EOW schedules. Four patients experienced a hypoxic episode during one or several infusions, which necessitated oxygen therapy in 3 patients with severe underlying obstructive airway disease including 2 with a tracheostomy. The most severe episode, which was associated with a short seizure, occurred in a patient who received his infusion while he had a febrile respiratory exacerbation. In the last patient, who had less severe underlying disease, spontaneous resolution occurred shortly after the infusion was interrupted. However, these events did not recur with subsequent infusions using a slower infusion rate and administration of pre-infusion medication, usually with low-dose corticosteroids, antihistamine, and beta-agonist nebulization. The fifth patient, who had pre-existing cardiopathy, was diagnosed with ventricular premature complexes and pulmonary embolism during the study. Nevertheless, it is conceivable that patients with severely compromised airways may also be at particular risk of respiratory insufficiency due to sedative effects of premedication. It is also important to note that in some patients who may have severe underlying cardiopulmonary disease, infusion associated reactions may be less well-tolerated.

Four patients (1 on placebo) died during their participation in the clinical trials. None of the reported deaths were determined to be related to idursulfase.

There were no apparent trends in AE incidence rates and generally the AEs were those expected among a primarily paediatric population over 12 months of study. The most commonly reported AEs were similar among treatment groups.

With respect to infusion reactions as well as respiratory infusion reactions there appears to be an association between the likelihood of experiencing an IRAE and the tendency to develop antibodies to idursulfase. With respect to respiratory infusion related adverse events (RIR-AEs) there also seems to be a correlation between increasing number of events with increasing severity of respiratory disease. However, data is still inconclusive due to small numbers and will continue to be collected as through the Hunter Outcomes Survey.

There do not appear to be any definitive risk factors presently identifiable apart from higher antibody positivity in pre-pubertal patients, however small numbers of patients preclude definitive conclusions to be drawn. The applicant will conduct an evaluation of the genetic mutations in patients from TKT024 in an effort to determine whether there are one or more common genotypes that are highly associated with subsequent antibody formation.

Although the updated safety review provided by the applicant is generally consistent with the data in the original dossier, it should be noted that this only relates to a further 3 months of safety data. This period of follow up was not sufficient to draw firm conclusions on safety with respect to immunogenicity, especially as regards infusion reactions, respiratory infusion reactions and in particular, the sudden increase in vascular and skin reactions with the commercial product. Additionally, the small number of patients included in the analyses preclude firm conclusions to be drawn. The applicant has committed to address these issues through the HOS registry and follow up measures.

In addition, there is no data on patients after re-exposure after temporary discontinuation. In the pivotal study, although antibodies including neutralising antibodies have no clear effect on the efficacy, there is some indication of a loss of efficacy in antibody positive patients. This point will be further addressed in the Hunter Outcome Survey.

The applicant has also committed to monitor the safety of home therapy in the HOS.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAH submitted a risk management plan.

Table 13. Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Respiratory infusion-related reactions	• Continue to monitor through the Hunter Outcome Survey (HOS), clinical studies TKT018, TKT024EXT and TKT031NPU • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Statements included in SPC section 4.4 on infusion reaction symptoms, treatment of patients with severe underlying airway disease and treatment of patients with acute febrile respiratory illness. • Summary of infusion-related events provided in SPC section 4.8
Immunogenicity and hypersensitivity reactions	• Continue to monitor through the Hunter Outcome Survey (HOS), clinical studies TKT018, TKT024EXT and TKT031NPU • HOS immunogenicity sub-study • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings), ongoing monitoring of by request for antibody samples	• Contraindication for patients with known hypersensitivity to the active substance or any excipient in section 4.3 of the SPC • Statement included in SPC section 4.4 on the development of antibodies and management of anaphylactic (allergic-type) reactions. • Summary of immunogenicity observed in the clinical trials provided in SPC section 4.8

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
1-hour infusions	• Continue to monitor through the Hunter Outcome Survey (HOS) and clinical study TKT018 • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings), including specific monitoring of safety of 1-hour infusions in PSURs	• Statement included in SPC section 4.2 that advises physicians that the product should be administered by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.
Patients with hepatic or renal impairment	• Monitor through the Hunter Outcome Survey (HOS) • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Information provided in SPC section 4.2 that there is no clinical experience in patients with renal or hepatic insufficiency, together with statement on clearance mechanisms in section 5.2
Children under 5	• Monitor through the Hunter Outcome Survey (HOS), and HOS under 5 sub-study (TKT038) • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Information provided in SPC section 4.2 that there is no clinical experience in patients under 5 year of age
Female patients	• Monitor through the Hunter Outcome Survey (HOS) • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Section 4.1 of the SPC identifies that there is no clinical trial data in female heterozygous patients
Elderly patients	• Monitor through the Hunter Outcome Survey (HOS) • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Information provided in SPC section 4.2 that there is no clinical experience in patients over 65 years of age.
Home therapy	• Monitor through the Hunter Outcome Survey (HOS) • Routine pharmacovigilance activities (PSURs, AE reporting, monthly internal safety review meetings)	• Information included in SPC section 4.4 on infusion reaction symptoms, treatment of patients with severe underlying airway disease and treatment of patients with acute febrile respiratory illness. • Statement included in SPC section 4.2 that advises physicians that the product should be administered by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance, have been adequately described, controlled and validated. The active substance has been well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications have been set. The manufacturing process of the medicinal product has been satisfactorily described and validated. The quality of the medicinal product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the overall quality of Elaprase is considered acceptable.

Non-clinical pharmacology and toxicology

The pharmacokinetic properties of idursulfase in animal models (mice, rats and monkeys) have been reasonably well characterised. Results have shown that it has a biphasic serum elimination profile with mean elimination half-lives of less than 5 to 6 hours in all cases. Values for C_{max} were proportional to dose for all species. However, AUC values were not linearly proportional to dose, indicating that serum clearance mechanisms had become saturated at doses of 0.5 $mg \cdot kg^{-1}$ or higher in monkeys. Clearance saturation was also seen at 2.5 and 12.5 $mg \cdot kg^{-1}$ in rats. However, due to limited dose range tested in rats, it was not possible to confirm the lowest dose of idursulfase which would saturate clearance in this species. Serum clearance of idursulfase followed allometric scaling parameters relative to body weight across species (rodents, monkeys and humans), indicating that clearance of idursulfase from serum likely occurs *via* a common mechanism. In the minority of monkeys in which development of antibodies to idursulfase occurred, this was usually, but not always, associated with enhanced clearance.

Idursulfase was detected in all organs and tissues examined in a ^{125}I-radiolabel rat biodistribution study. Tissue half-lives were similar for the major organs and were approximately 1 to 2 days for liver, kidney, heart, spleen, and bone (including marrow). The accumulation and retention in these organs and tissues is consistent with the distribution of M6P receptors in tissues and organs in mammals, and indicates that the common pharmacokinetic approach defining the serum half-life is less relevant in determining the duration of action.

The role of sialic acid content on *in vivo* properties (PK, tissue biodistribution, and pharmacodynamic activity) of idursulfase was examined. Biodistribution and PD activity parameters were affected by large variations in sialylation of idursulfase. Idursulfase clearance from serum was modified by minor variations in sialic acid content of idursulfase, but was not associated with altered activity from a biodistribution or PD perspective. Results from a comparability program, as part of tissue biodistribution, pharmacodynamic, and pharmacokinetic studies showed that idursulfase, regardless of the manufacturing process, maintained its activity profile.

Toxicokinetic studies in rats and monkeys suggest saturated clearance mechanisms following a single iv administration of idursulfase at doses of 10 or 20 mg·kg-1, and at 2.5 and 12.5 mg·kg-1 following repeat dose administration in cynomolgus monkeys.

There were no signs of local irritation, inflammation, or necrosis to veins or tissue related to multiple bolus iv injection of idursulfase.

As expected for a human protein administered to animals, IgG antibodies to idursulfase were detected in some of the monkeys after 13 or 26 weeks of dosing, and in a few knockout mice after 24 weeks of dosing. These anti-idursulfase antibodies had no adverse toxicological effects nor did they impact the pharmacodynamic activity of idursulfase.

Efficacy

Efficacy data were provided from a pivotal, 12-month, Phase II/III, double-blind study (TKT024) and from a supportive 6-month, Phase I/II, double-blind study (TKT008) and from 24-months of treatment in an ongoing, Phase I/II, open-label extension study (TKT018). TKT024EXT, the open-label extension of TKT024, is also currently ongoing.

Results from the dose finding study showed that it is probable, judging from urinary GAG levels, that a weekly dose greater than 0.5 mg/kg is more effective in normalising GAG levels rapidly, followed by a lower maintenance dose given weekly or even EOW. However, as no baseline weekly dosing data was available for this study.. This issue will be investigated in the Hunter Outcome Survey (HOS).

In the clinical studies, the data are supportive of efficacy for the weekly 0.5 mg/kg dose in comparison to the every other week (EOW) dose in terms of providing improvement in both individual components of the primary composite endpoint in the pivotal trial namely, the 6MWT and FVC. However, assessment of the evidence of clinical benefit in terms of endurance based on the 6 Minute Walk Test and FVC was complicated by statistical concerns relating to the adjusted changes from baseline presented, which were always lower for all treatment groups than the unadjusted changes, and therefore do not seem to reflect the experience of patients in the trial. Nevertheless, supportive evidence for the primary composite endpoint is provided by the reduction in hepatosplenomegaly and urinary glycosoaminoglycans (GAG) and importantly, the efficacy parameters show no deterioration at long term (1 year). The applicant currently recommends weekly dosing for all patients with Hunter syndrome.

The effect of antibodies has not significantly impacted on PK parameters. It has also been demonstrated that there is no apparent relationship between weight and age with idursulfase pharmacokinetics and consequently therefore, no dose adjustments based on weight or age are necessary. A population PK model is not considered necessary. Concerns regarding immunogenicity affecting PK parameters showed that patient antibody status was not a predominant factor in determining variations in patient PK parameters All PK concerns have now been resolved.

The bioavailability of idursulfase within the CNS was not assessed in the pivotal trial.

Safety

Overall, therapy with idursulfase was generally well-tolerated at a dose level of 0.5 mg/kg administered both weekly and every other week. No patient has withdrawn from a study to date due to an adverse event (AE) related to idursulfase The main safety concerns with idursulfase appear to be infusion associated reactions (IARs) and immunogenicity. Infusion related reactions appear to be related to the dose and the frequency of administration since they were more common in the weekly schedules compared to EOW and no IARs were reported in patients on the lower dose of 0.15 mg. However, the frequency of IARs seems greatest during the first 6-12 months of treatment and decreases over time. Infusion-related AEs were also frequently reported in the placebo group. This appears to suggest that there is a baseline incidence of AEs that may be caused directly by the infusion procedure itself (e.g., vagal reactions). It is also reassuring to note that IARs were manageable either by temporary interruption or slowing of the infusion rate and in some cases by the use of premedication.

Although numbers are limited, antibody positive patients appeared to have increased number of adverse events compared to those who were negative. However, there were no episodes consistent with anaphylactic reaction to idursulfase and no patient developed IgE antibodies.

Antibodies, including neutralising antibodies have no clear effect on the efficacy, however there is some indication of a loss of efficacy in antibody positive patients; this will be addressed in the HOS (Hunter Outcome Survey) registry.

Additional safety data provided by the applicant was generally consistent with the data in the original dossier, but only related to a further 3 months of safety data. This period of follow up is not be sufficient to draw firm conclusions on safety with respect to immunogenicity, especially as regards infusion reactions, respiratory infusion reactions and in particular, the sudden increase in vascular and skin reactions with the commercial product. The applicant will address these issues through the HOS registry..

- User consultation

The target patient groups "user consultation" was assessed as part the applicant's responses to the D120 List of Questions.

Risk-benefit assessment

Although Hunter syndrome is heterogeneous with regard to initial presentation, it is always severe, progressive, and life-limiting, despite the use of any available therapies. Death usually occurs in the second or third decade of life, most often from respiratory and/or cardiac failure. Treatment represents an unmet medical need, since there are no satisfactory treatment options for the majority of patients. It is nevertheless, important to note that idursulfase is not a curative treatment as such but a replacement therapy for the enzyme deficiency in these patients.

There are no major quality or pre-clinical issues. In the clinical studies, the data are supportive of efficacy for the weekly 0.5 mg/kg dose in comparison to the every other week (EOW) dose in terms of providing improvement in both individual components of the primary composite endpoint in the pivotal trial namely, the 6MWT and FVC. However, assessment of the evidence of clinical benefit in terms of endurance based on the 6 Minute Walk Test and FVC was complicated by statistical concerns relating to the adjusted changes from baseline presented, which were always lower for all treatment groups than the unadjusted changes, and therefore do not seem to reflect the experience of patients in the trial. Nevertheless, supportive evidence for the primary composite endpoint is provided by the reduction in hepatosplenomegaly and urinary glycosoaminoglycans and importantly, the efficacy parameters show no deterioration at long term (1 year).

Although adverse events were common, particularly infusion associated reactions; serious adverse events attributable to idursulfase were uncommon. There were 4 deaths during the clinical development, none of which were considered related to idursulfase. The overall limited safety profile does not raise major clinical issues for this focused group of patients and remains consistent with the updated safety data. Nevertheless, an important primary safety concern with idursulfase treatment in a very small proportion of patients, appears to be the management and treatment of those with highly compromised airways, as yet mainly in the older age groups having more severe disease, with respect to the development of severe drug related infusion reactions causing hypoxia and necessitating oxygen therapy. Nevertheless, the risk of such episodes does appear to be minimised by extending the infusion rate over a period of at least 3-4 hours and by the use of premedication with antihistamine and/or steroids and beta-agonist nebulisation. In addition, delaying treatment in patients with acute febrile respiratory illness could possibly contribute in risk minimisation. However, limitation or careful monitoring of antihistamine and other sedative medication use in such patients with compromised airways appears to be important, since it could conceivably, precipitate sleep apnoea. Accordingly, the institution of positive–airway pressure during sleep in clinically appropriate situations is an important consideration and needs to be clearly communicated.

From an immunological perspective, the effect of neutralizing antibodies on efficacy is still to be fully evaluated; therefore, no firm conclusions can be drawn with respect to the effect of neutralizing activity on the safety and efficacy of idursulfase.

Although, the studies did not include patients under the age of 5 or over the age of 31 and females, the Hunter Outcomes Survey proposed by the applicant as part of the risk management plan includes planned sub-studies that will provide the opportunity to further define immunogenicity and study the aforementioned populations.

Considering the progressive nature of MPS II disease and the implications for prognosis, together with the heterogeneity of patients in terms of disease manifestation and age, as well as the problems of reversing the chronic effects caused by long term accumulation of lysosomal storage, the improvements demonstrated in the clinical studies, some albeit limited, appear to represent clinical benefits for MPS II patients. The safety profile from the data submitted does not raise major clinical concerns for the majority of patients. The apparent trend in efficacy has undergone statistical clarification and confirms a positive risk/benefit.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

The granting of the marketing authorisation by the CHMP was done under exceptional circumstance as the indication for which the product in question is intended is encountered so rarely that the applicant cannot be expected to provide comprehensive data.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Elaprase in the Long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II) was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.