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APPLICATION NUMBER:

125151/0

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

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Brand Name	ELAPRASE
Generic Name	Idursulfase
Reviewer	Hong Zhao
Supervisor	Shiew Mei Huang
Division	Clinical Pharmacology Division 5/OCP
Clinical Division	DGP/ODE 3
Sponsor	Transkaryotic Therapeutics (TKT), and Shire
Relevant IND(s)	BB-IND —
Submission Type; Code	NME, Orphan Drug, Fast-Track
Formulation; Strength(s)	Single-use vials containing a 3 mL solution at 2 mg/mL concentration with a pH of approximately 6, diluted in 0.9% Sodium Chloride Injection, USP prior to intravenous administration
Proposed Dosing Regimen	0.5 mg/kg of body weight administered every week (QW) as an intravenous infusion over a period of 1 to 3 hours.
Proposed Indication	For the — treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II)

1 Executive Summary

1.1 Recommendation

The clinical pharmacology and pharmacokinetics (PK) studies of idursulfase are acceptable. The to-be-marketed product is considered comparable to the clinical trial product based on the results of biodistribution, tissue and urine glycosaminoglycans (GAG) level reduction and PK comparability studies.

1.2 Phase IV Commitments

There are no specific Phase IV studies requested from Clinical Pharmacology perspective. There are several Phase IV studies requested from clinical, pharmacology/toxicology and CMC perspectives including completion of TKT024EXT study, evaluation of long-term safety and efficacy data in a registry study of patients with Hunter syndrome being treated with idursulfase, evaluation of efficacy, pharmacokinetics, pharmacodynamics, and safety in children less than 5 years of age — additional toxicity studies, and validation of immunogenicity assays as well as correlation of antibody status with clinical efficacy, safety and urinary GAG levels.

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Introduction: Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2 sulfatase (I2S). Due to the missing or defective I2S enzyme in patients with Hunter syndrome, the glycosaminoglycans (GAG) progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. To date, only symptomatic therapy has been available to individuals afflicted with this disease. Idursulfase is a recombinant form of I2S, and is being developed for — enzyme replacement therapy for patients with Hunter syndrome. The current application contains data from 4 studies of 108 individual male patients with Hunter syndrome, including 96 patients in a Phase II/III, placebo-controlled, double-blind study that assessed several clinical manifestations of this disease. Pharmacokinetics (PK) evaluations were performed in patients with Hunter syndrome in these 4 studies and no studies have been conducted in healthy volunteers. The sponsor claims that in light of the significant morbidity and mortality caused by Hunter syndrome, the safety and efficacy results provided in this submission support a favorable benefit-risk assessment for idursulfase.

Mechanism of Action: Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the GAG dermatan sulfate and heparan sulfate in the lysosomes of various cell types. Treatment of Hunter syndrome patients with idursulfase provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequently catabolism of accumulated GAG.

ADME: Idursulfase is administered by intravenous infusion. The greatest level of idursulfase was found in the liver in both rats and mice (approximately 11% of administered dose in rats and 30 to 40 % in mice). Lower, but appreciable levels of idursulfase were distributed to other major organs and tissues throughout the body (kidneys, heart, spleen, lungs, testes, bone/bone marrow, lymph nodes, pancreas, skin, muscle and adipose tissue). Metabolic degradation of this protein product is expected to occur in cells via normal proteolytic mechanisms. As such, no metabolism studies or *in vitro* and *in vivo* idursulfase-drug interaction studies were conducted in animals or in humans.

Single-Dose and Multiple-Dose PK Parameters at Various Dose Levels: The pharmacokinetics of idursulfase after single doses of 0.15, 0.5 and 1.5 mg/kg have been characterized in a Phase I/II study in 12 patients with Hunter syndrome using an antigen-specific enzyme-linked immunosorbent assay (ELISA) method. Idursulfase exhibits biphasic serum elimination profile following an initial one-hour infusion. Maximum serum concentration (C_{max}) was approximately dose-proportional. Area under the concentration-time curve (AUC_{0-inf}) was greater than dose-proportional across three dose levels. The results suggest that serum clearance mechanism for idursulfase may become saturated at a dose level greater than 0.5 mg/kg. Mean terminal elimination

half-lives for all three dose levels were less than 5 hours (2 to 5 hours), indicating that idursulfase would not accumulate in serum following the dosing frequency of once weekly (QW) in the clinical trials. There are no apparent differences in PK parameter values as a repeat QW dosing of idursulfase.

Serum samples from Phase I/II studies were also analyzed for idursulfase enzyme activity. Serum elimination curves of idursulfase enzyme activity were parallel to serum profiles of idursulfase protein concentration, indicating that idursulfase enzyme activity was not selectively inactivated in patient's serum before binding to cellular receptors.

Rationale for Dose Selection: Due to the rarity of Hunter syndrome, dose and dose frequency were determined via a combination of animal data and clinical data. The dose of 0.5 mg/kg idursulfase was chosen for evaluation in the pivotal clinical study for following reasons: (1) PK data in cynomolgus monkeys suggested that serum clearance mechanisms would saturate in humans around a dose of 0.5 mg/kg, and (2) data from the initial Phase I/II studies indicated that (a) the 0.5 and 1.5 mg/kg doses were likely more effective than the 0.15 mg/kg dose; (b) there was no consistent evidence of further efficacy benefit to the 1.5 mg/kg dose when compared to the 0.5 mg/kg dose; (c) fewer infusion-related reactions at the 0.5 mg/kg dose compared with the 1.5 mg/kg dose, and (d) one patient administered 1.5 mg/kg developed anti-idursulfase antibodies using the initial non-qualified assays.

Rationale for Dosing Schedule Selection: The decision to select QW dose frequency in the Phase II/III pivotal trial was also based on both animal data and clinical data. In an I2S knockout (IKO) mouse model, idursulfase QW dosing appeared to have larger effect on clearance of tissue GAG than every other week (QOW) dosing regimen. In addition, the tissue half-life of idursulfase of 1 to 2 days in animals, suggested that a QW dose may be a better way of providing a consistent presence of enzyme within target tissues than would a QOW dose. The QOW dose regimen was tested in the initial Phase I/II studies. Both QW and QOW dosing regimens were studied in the pivotal clinical trial.

Pharmacokinetics in Special Populations: Hunter syndrome is a rare disease with an estimated incidence of one in approximately 162,000 live births. Despite the heterogeneity in the disease progression, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. The patients at the clinical study entry were 5 to 31 years of age. All patients were male and majority patients were white (88%). Idursulfase was dosed based on body weight. Age was not found to have an appreciable effect on PK parameters of idursulfase. Due to limited number of non-white patients enrolled in the clinical studies, the effect of race on idursulfase PK could not be evaluated.

Exposure-Response: Patients afflicted with Hunter syndrome have significant multi-system dysfunction with severely limited life span due to deficiency of I2S. The primary efficacy outcome assessments were distance walked during six minutes (6 minutes walk test or 6MWT) as a measure of endurance, and percent predicted forced vital capacity (%FVC) as a measure of pulmonary function. Idursulfase has been shown to improve walking capacity. The improvement in 6MWT was statistically significant for 0.5 mg/kg QW regimen, but not for 0.5 mg/kg QOW regimen compared to placebo treatment. The %

FVC was not statistically significant different between QW and placebo or between QOW and placebo. However, when %FVC was analyzed together with 6MWT as a composite score (predefined endpoint), both dosing regimens showed statistically significant differences compared to placebo treatment.

Pharmacodynamic Findings: The ability to reduce urinary GAG excretion in patients and changes in liver and spleen size were the primary biological measures of the clinical activity of idursulfase. All 3 dose levels (0.15, 0.5 and 1.5 mg/kg) of idursulfase resulted in reductions in urine GAG excretion. Over the first 6 months of treatment with idursulfase, the mean baseline normalized urine GAG levels fell by 41%, 44% and 62% in the 0.15, 0.5 and 1.5 mg/kg dose group, respectively (n=4 for each group). The continued clinical activity of long-term idursulfase therapy was monitored by measuring urine GAG levels in patients for up to approximately 3.5 years of treatment in the Phase I/II studies. Among all 64 idursulfase-treated patients in the pivotal clinical trial, 26 patients (16/32, 50% in the idursulfase QW group; 10 of 32, 31% in the idursulfase QOW group) had normalized urine GAG levels below the upper limit of normal (defined as 126.6 µg GAG/mg creatinine) by the end of the study (Week 53) compared to none in the placebo patients.

Of the 50 patients with abnormally large livers at baseline in the idursulfase treatment groups, 40 patients (80%; 20 patients in each idursulfase treatment group) had reductions in liver volume to within the normal range compared to one of 23 in the placebo group at the end of the study. There were 3 of 9 patients in the QW treatment group with abnormally large spleens at baseline had spleen volumes that normalized at the end of the study compare to 2 of 11 patients in the placebo group.

There is no apparent correlation between urinary GAG level and the primary efficacy endpoint (6MWT) or between urinary GAG level and percent of liver size reduction.

Immunogenicity: Anti-idursulfase IgG antibody development occurred in approximately 50% of patients receiving repeat doses of idursulfase. Of the 12 patients who had PK evaluated at the recommended dose regimen, 6 patients tested antibody-positive using qualified assays. PK parameters could not be determined in 2 of the 6 antibody-positive patients at Week 27 due to idursulfase serum concentrations outside the expected ranges as measured by an antibody-based assay (ELISA). There was also a subset of antibody-positive patients in the TKT024EXT study (n=14) whose serum idursulfase exposure could only be measured by an enzyme activity assay suggesting sample interference with the ELISA assay. Factors which may result in ELISA-based assay interference with these patient samples are under evaluation. Investigation of effect of antibody formation on PK was limited to 10 patients who had evaluable PK data for both Week 1 and Week 27. The ratio of clearance (Wk27/Wk1) was similar between the four antibody-positive patients and the six antibody-negative patients (1.30 with range of 0.6 to 2.0 vs. 1.32 with range of 0.8 to 2.5).

Urinary GAG clearance became impaired in patients who developed anti-idursulfase antibodies. The number of patients in the QW group with normalized urine GAG levels below the upper limit of normal (defined as 126.6 µg/mg creatinine) was 5 of 15 for

antibody-positive patients compared to 11 of 16 for antibody negative patients. The impact of immunogenicity on urine GAG level was more profound in the QOW dosing group that the number of patients with normalized urine GAG levels below the upper limit of normal was 2 of 15 for antibody-positive patients compared to 8 of 17 for antibody negative patients. The improvement of 6MWT and liver size reduction appeared not to be affected by anti-idursulfase antibody status. Neutralizing antibodies were found in four of 32 antibody-positive patients.

Hypersensitivity: Severe respiratory distress (bronchospasm, cyanosis, hypoxia) have been reported during idursulfase infusions for patients in both phase II/III and the open-labeled extension study periods. Idursulfase labeling instructs that if severe hypersensitivity or anaphylactic reactions occur, immediately discontinue the infusion of idursulfase and initiate appropriate treatment. Resuscitation measures should be immediately available at all infusion sites.

Adverse Events: Severe infusion-related reactions were reported occasionally in patients with severe underlying obstructive airway disease. Idursulfase labeling states that these patients should be closely monitored and infused with idursulfase in an appropriate clinical setting. The most common infusion-related reactions included cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension, and flushing. Infusion-related reactions were treated or ameliorated by slowing the infusion rate, interrupting the infusion, or by administration of medications, such as antihistamines, antipyretics, low-dose corticosteroids (prednisone and methylprednisolone), or beta-agonist nebulization. No patients discontinued treatment with idursulfase due to an infusion reaction during clinical studies.

Comparability between To-Be-Marketed and Clinical Trial Products: Following completion of the manufacture of idursulfase for the pivotal Phase II/III study, the scale of the manufacturing process was increased to commercial-scale and specific process improvements were implemented. There have been no formulation changes from the initiation of the pivotal efficacy and safety trial onward through commercialization. Comparability evaluations included a physicochemical, nonclinical and clinical program. Biodistribution and pharmacodynamics (tissue and urinary GAG levels) studies were conducted in normal mice and I2S knockout (IKO) mice. PK comparability study was performed in cynomolgus monkeys in a crossover design. Following completion of the comparability assessment, idursulfase produced by the commercial-scale process was introduced into the ongoing clinical studies TKT018 and TKT024EXT and PK data was collected in Study TKT024EXT. The to-be-marketed product is considered comparable to the clinical trial product based on the results of biodistribution, tissue and urinary GAG level reduction and PK comparability studies.

4 Question-Based Review (QBR)

4.1 General Attributes

1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?*

Chemistry and Physical-Chemical Properties: Idursulfase is a purified form of the lysosomal enzyme, iduronate-2-sulfatase (I2S). Idursulfase is produced by recombinant DNA technology in a human cell line providing a human glycosylation profile, which is analogous to the naturally occurring enzyme. Idursulfase hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate in the lysosomes of various cell types. Idursulfase is a 525 amino acid glycoprotein with a molecular weight of approximately 76 kDa. The enzyme contains 8 asparagine-linked glycosylation sites occupied by complex oligosaccharide structures. The enzyme activity of idursulfase is dependent on the post-translational modification of a specific cysteine to formylglycine. Idursulfase has a specific activity ranging from 41 to 77 U/mg (one unit is defined as the amount of enzyme required to hydrolyse 1 μ mol of heparan disaccharide substrate per hour under the specified assay condition).

Formulation: Idursulfase drug product (DP) is a solution for intravenous infusion and is formulated to a concentration of 2 mg/mL. The drug product is supplied as a sterile, nonpyrogenic clear to slightly opalescent solution in single use, 5 mL glass vials containing 3 mL (6 mg) of idursulfase and is diluted in 100 mL of normal saline (0.9% sodium chloride) prior to administration. The extractable volume of 3 mL from each vial provides 6 mg idursulfase, 24.0 mg sodium chloride, 6.75 mg sodium phosphate monobasic monohydrate, 2.97 mg sodium phosphate dibasic heptahydrate, and 0.66 mg polysorbate 20. ELAPRASE does not contain preservatives; vials are for single use only. The placebo formulation used in the pivotal study was identical in composition to the idursulfase DP, with the exception of the active ingredient.

2. *What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?*

Mechanism of Action: Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme I2S. This enzyme acts to cleave oligosaccharide-linked sulfate moieties from two human GAG known as dermatan sulfate and heparan sulfate. Due to the missing or defective I2S enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Treatment of Hunter syndrome patients with idursulfase provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequently catabolism of accumulated GAG.

Proposed Indication: ELAPRASE (Idursulfase) is indicated for the treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). The FDA proposed language under the INDICATION AND USAGE of ELAPRASE labeling is: ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in these patients.

Dosage and Route of Administration: The recommended dosing regimen of ELAPRASE is 0.5 mg/kg of body weight administered every week (QW) as an intravenous infusion. The total volume of infusion should be delivered over a period of 1 to 3 hours. The infusion time can be extended if infusion reactions were to occur.

3. What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The primary efficacy outcome assessments were distance walked during six minutes (6-minute walk test, or 6MWT) as a measure of endurance, and % predicted forced vital capacity (FVC) as a measure of pulmonary function. The primary endpoints are combined these two components into a composite score based on the sum of the ranks of the change from baseline to Week 53 in 6MWT and % predicted FVC, and 6MWT. Evaluations of bioactivity were changes in liver and spleen size, and urinary GAG levels.

4.2 General Clinical Pharmacology

1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy variable was a 2-component composite variable of the sum of the ranks of the change from baseline to Week 53 in the 6MWT and % predicted FVC. These two parameters were also analyzed separately. The sponsor provided the following justifications for choosing these two clinical endpoints as the primary efficacy outcomes: due to a combination of the bone disease, decreased respiratory capacity, and spleen apnea, with or without impaired cardiac function, individuals with Hunter syndrome suffer from chronic, severely diminished endurance; perhaps most devastating to the individuals suffering from Hunter syndrome is the impact that the progressive physical abnormalities have on their quality of life.

The primary biological measure of the clinical activity of idursulfase was the ability to reduce urinary GAG excretion in patients in addition to other measures such as combined liver and spleen volume by MRI and liver and spleen volumes independently, and cardiac left ventricular mass (LVM) by echocardiography. Insufficient levels of I2S lead to

progressive accumulation of these GAG molecules in nearly all organs and body tissues. 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 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.

2. What are the results of clinical efficacy outcomes?

Primary Clinical Efficacy Outcome: A total of 108 male patients with Hunter syndrome were enrolled in 2 randomized, placebo-controlled clinical studies (TKT0018 and TKT024), and have continued treatment in 2 open-label extension studies. Patients in these studies had a broad spectrum of symptoms of the disease. Study TKT024 was a pivotal clinical trial with 3 treatment arms (placebo, 0.5 mg/kg QW and 0.5 mg/kg QOW, n=32 in each arm) and 53 weeks of study duration. The primary clinical efficacy outcome combined two components into a composite score based on the sum of the ranks of the change from baseline to Week 53 in 6MWT and % predicted FVC, and also 6MWT alone. Figure 1 shows the results of the primary efficacy outcomes of the two dosing regimens compared to placebo treatment and the results of statistical analyses are summarized in Table 1.

Figure 1. Plot of Composite (6MWT & Predicted FVC) and 6MWT by Treatment (Mean Adjusted Difference Compared to Placebo)

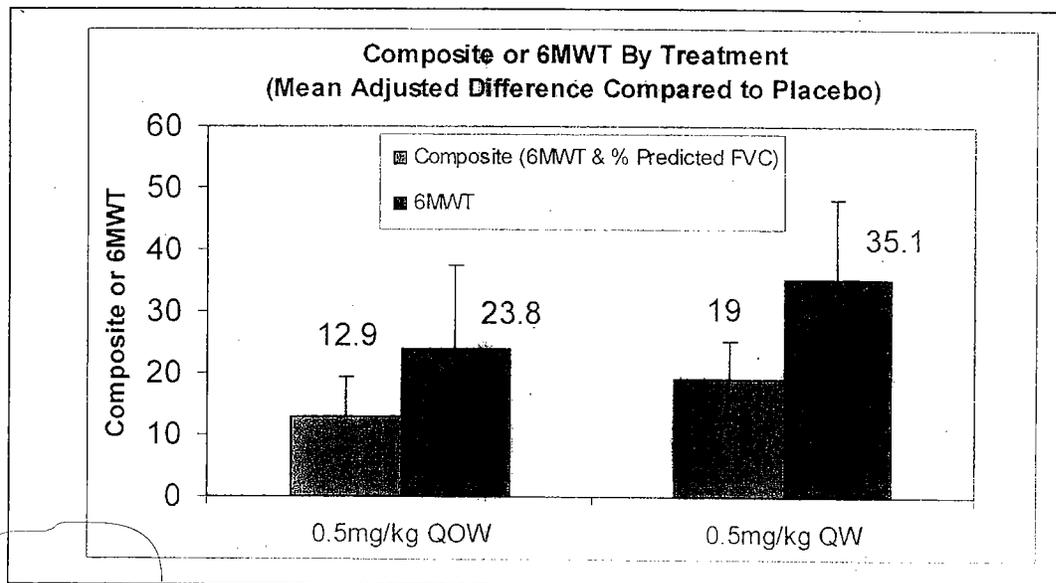


Table 1. Clinical Study Results (Sponsor's Analyses)

Endpoint	Mean Adjusted (SE) Change from Baseline	Mean (SE) Adjusted Difference compared to placebo	p-value compared to placebo
0.5 mg/kg Weekly			
Composite (6MWT & % predicted FVC)	N/A	19.0 (6.5)	0.0049
6MWT (m)	37.0 (10.9)	35.1 (13.7)	0.0131
% Predicted FVC	1.3 (1.7)	4.3 (2.3)	0.0650
FVC Absolute Volume (cc)	180 (40)	190 (60)	0.0011
0.5 mg/kg Every Other Week			
Composite (6MWT & % predicted FVC)	N/A	12.9 (6.2)	0.0416
6MWT (m)	25.9 (10.7)	23.8 (13.0)	0.0732
% Predicted FVC	-1.4 (1.6)	0.1 (2.1)	0.9531
FVC Absolute Volume (cc)	60 (30)	30 (40)	0.3735

Sponsor's Conclusions: The 2-component composite primary endpoint differed statistically significantly from placebo for both QW and the QOW treatment groups (QW idursulfase vs. placebo $p=0.005$; QOW idursulfase vs. placebo $p=0.042$). A total of 11 of 31 (36%) patients in the idursulfase QW group, 8 of 32 (25%) patients in the idursulfase QOW group, and 5 of 31 (16%) patients in the placebo group had an increase in forced expiratory volume in 1 second (FEV₁) of at least 200 cc at or before the end of the study, indicating a dose-related improvement in airway obstruction. The patients in the QW idursulfase-treated group experienced a clinically significant 15% mean improvement in FEV₁ by the end of the study.

Comments: At the pre-BLA meeting, the sponsor was told that the six-minute walk test (6MWT) efficacy endpoint is highly dependent on patient effort. The magnitude of the absolute changes in FVC is of unclear clinical significance. As FVC depends on height and age, it must be interpreted relative to growth over the length of the study and as a percent of predicted. Absolute changes in FVC are also not directly related to clinical benefit. The results of FVC will be interpreted along with the results of the 6MWT, and other secondary and exploratory endpoints (e.g., patient-reported outcome data).

Primary Clinical Outcome Measures (FDA's Analyses): On average, the idursulfase QW dosing regimen statistically significantly improved 6 minute walk distance by 35 meters ($p=0.013$) at the end of the study (Week 53) compared to placebo group as shown in Table 2. There was also a 4.3% predicted FVC improvement of QW dosing regimen compared to placebo ($p=0.065$).

Table 2. Results from the 6-Minute Walk Test (6MWT, meters)

	Baseline	Week 53	Change ^b
Idursulfase QW n=32 ^a	392 ± 108	436 ± 138	44 ± 70
Placebo n=32 ^a	393 ± 106	400 ± 106	7 ± 54
Median Percentiles (25th, 75th)			
Idursulfase QW	397 (317, 486)	429 (369, 533)	31 (1, 94)
Placebo	403 (341, 469)	412 (362, 459)	-4 (-30, 30)
QW – Placebo Difference in Changes		37 ± 16 ^c	35 ± 14 ^{de} ($p=0.01$)

^a One patient in the placebo group and one patient in the Idursulfase group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analyses. ^b Change, calculated as Week 53 minus Baseline. ^c Observed mean ± SE. ^d Model-based mean ± SE, ^e adjusted for baseline disease severity, region, and age.

Individual patient 6MWT changes (the mean of the two measures at Week 53 minus the mean of the two measures at baseline) are calculated. Number of patients with 35 meters or more improvement in 6 minutes walk distance was 15 in QW dosing group, 12 in QOW dosing group and 7 in placebo group.. Number of patients with 10 meters or more decrease in 6 minutes walk distance was 7 in QW dosing group, 5 in QOW dosing group and 12 in placebo group. The mean (\pm SD) values by this calculation for placebo, QW and QOW groups are 16.9 \pm 65.4, 42.9 \pm 68.1 and 31.8 \pm 52.2 meters, respectively.

Pharmacodynamics Measures

Results of other clinical benefit analyses (Urinary GAG levels, % change in liver volume and % change in spleen volume) in the 53-week placebo-controlled study (TKT024) for the idursulfase QW and QOW treated groups are shown in Table 3.

Table 3. Other Clinical Study Results (TKT024, sponsor's results)

Endpoint	Mean adjusted (SE) change from Baseline	Mean (SE) adjusted difference compared to placebo	p-value compared to placebo
0.5 mg/kg QW			
Urine GAG levels	-225 (22)	-276 (30)	<0.0001
% Change in liver volume	-25.6 (1.7)	-25.2 (2.2)	<0.0001
% Change in spleen volume	-25.1 (3.5)	-33.2 (4.8)	<0.0001
0.5 mg/kg QOW			
Urine GAG levels	-225 (22)	-276 (30)	<0.0001
% Change in liver volume	-25.6 (1.7)	-25.2 (2.2)	<0.0001
% Change in spleen volume	-25.1 (3.5)	-33.2 (4.8)	<0.0001

Urinary GAG Level Reduction: The ability to reduce urinary GAG excretion in patients was the primary biological measure of the clinical activity of idursulfase. Urine GAG levels were expressed as micrograms of GAG normalized to milligrams of urine creatinine (μ g GAG/mg creatinine). Among all 64 idursulfase-treated patients in the pivotal trial (TKT024), 26 patients (16/32, 50% in the idursulfase QW group; 10 of 32, 31% in the idursulfase QOW group) had normalized urine GAG levels below the upper limit of normal (defined as 126.6 μ g GAG/mg creatinine) by the end of the study compared to none in the placebo group.

Live Size and Spleen size Reduction: Of the 50 patients with abnormally large livers at baseline in the idursulfase treatment groups, 40 patients (80%; 20 patients in each idursulfase treatment group, QW and QOW) had reductions in liver volume to within the normal range compared to one of 23 patients in the placebo group. There were 3 of 9 patients in the QW treatment group with abnormally large spleens at baseline had spleen volumes normalized at the end of the study compare to 2 of 11 patients in the placebo group.

3. How are dose and dosing regimen selected?

Rationale for Dose Selection

Due to the rarity of Hunter syndrome, dose and dose frequency were determined via a combination of animal data and clinical data. The sponsor states that the dose of 0.5 mg/kg idursulfase was chosen for evaluation in the pivotal clinical study for following reasons: (1)

PK data in cynomolgus monkeys suggested that serum clearance mechanisms would saturate in humans around a dose of 0.5 mg/kg, and (2) data from the initial Phase I/II study indicated that (a) the 0.5 and 1.5 mg/kg doses were likely more effective than the 0.15 mg/kg dose; (b) there was no consistent evidence of further efficacy benefit to the 1.5 mg/kg dose when compared to the 0.5 mg/kg dose; (c) fewer infusion-related reactions at the 0.5 mg/kg dose compared with the 1.5 mg/kg dose, and (d) one patient administered 1.5 mg/kg developed anti-idursulfase antibodies.

Dose Finding Studies (TKT008 and TKT018): The observed urine GAG levels and the mean changes from baseline plotted by treatment group and by visit for up to 2.5 years of treatment are shown in Figures 2 & 3, respectively. All patients were transitioned to 0.5 mg/kg QOW after finishing the initial dose finding study (12 months for 0.15 mg/kg group, and 8 months for 1.5 mg/kg group).

Figure 2. Mean Normalized Urine GAG Levels by Initial TKT 008 Idursulfase Dose Group over Time (n=3 for each dose group, QOW dosing, sponsor's figure)

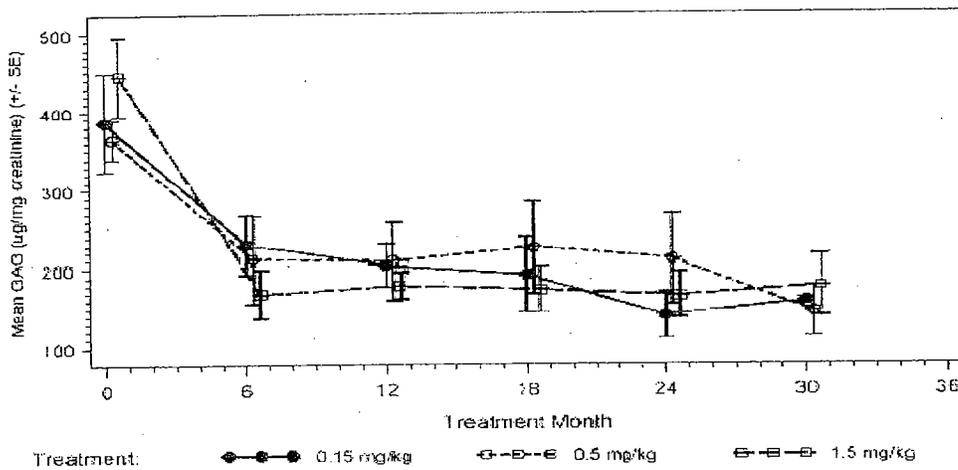
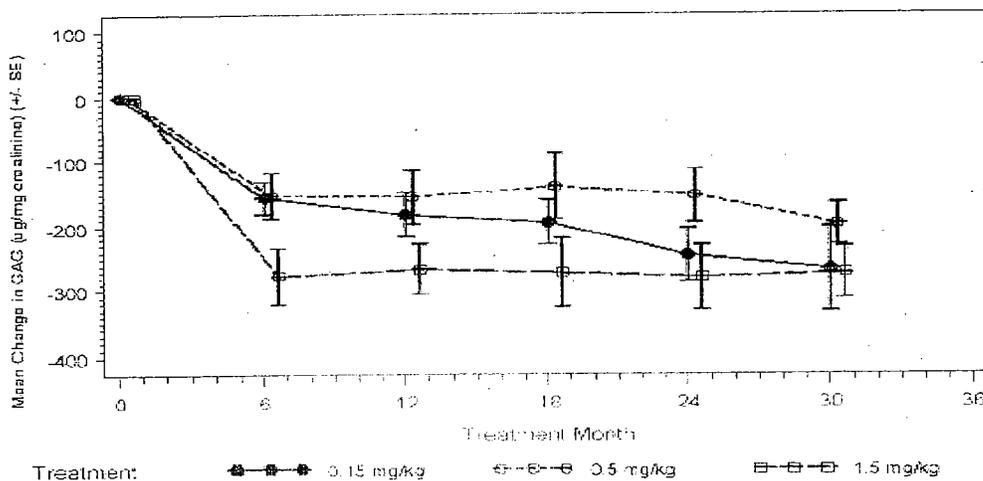
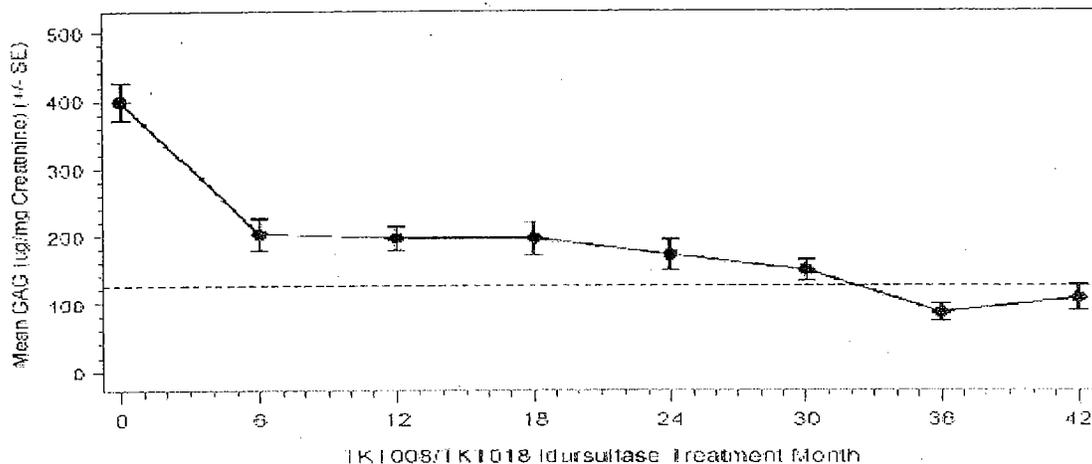


Figure 3. Mean Change from Baseline in Normalized Urine GAG Levels by TKT 008 Idursulfase Dose Group and Months of Treatment ((n=3 for each dose group, QOW dosing, sponsor's figure)



All 3 dose levels of idursulfase resulted in reductions in urine GAG excretion. Over the first 6 months of QOW treatment with idursulfase, the mean baseline normalized urine GAG levels fell by 40.6% , 43.8% and 62.0% in the 0.15, 0.5 and 1.5 mg/kg dose groups, respectively (n=4 in each group). The continued clinical activity of long-term idursulfase therapy was monitored by measuring urine GAG levels in patients for up to approximately 3.5 years of treatment in Studies TKT008/TKT018. Mean normalized urine GAG levels are presented for all patients by treatment month in Figure 4:

Figure 4. Mean Normalized Urine GAG Levels for All Patients from the First Idursulfase Exposure (Studies TKT008/TKT018, sponsor's figure)



Note: The dashed horizontal line represents the upper limit of the normal range; n=12 at Months 30 and 36; n=9 at Month 42

Comments: The pivotal trial dose of 0.5 mg/kg may not be the optimal dose because (a) only 3 dose levels (0.15, 0.5 and 1.5 mg/kg) were explored in patients; (b) serum clearance of idursulfase at 0.5 mg/kg was not saturated in patients; and (c) there was a dose-response in urine GAG level and 1.5 mg/kg dose demonstrated appreciable higher response (62%) than that of 0.5 mg/kg dose (44%) over the first 6 months of QOW treatment.

Rationale for Dosing Regimen Selection

The decision to select QW dosing frequency in the Phase II/III program was also based on both animal data and clinical data. In an I2S knockout (IKO) mouse model, idursulfase QW dosing appeared to have larger effect on clearance of tissue GAG than the QOW dosing regimen. In addition, the tissue half-life of idursulfase of 1 to 2 days in animals, suggested that a QW dosing frequency may be a better way of providing a consistent presence of enzyme within target tissues than would a QOW dosing frequency. The QOW dosing regimen was tested in the initial Phase I/II study. Both QW and QOW dosing regimens were studied in the pivotal clinical trial (TKT024).

4. How effective are the selected dose and dosing regimens in reducing urinary GAG levels in the pivotal clinical trial?

Pivotal Trial (TKT024): Ninety-six (96) patients were enrolled in TKT024 receiving three different treatments (n=32 in each arm): placebo, idursulfase 0.5 mg/kg QW and idursulfase 0.5 mg/kg QOW. Mean normalized urine GAG levels by visit and mean changes from baseline at each visit in normalized urine GAG levels are shown by treatment group for the ITT population in Figures 5 & 6, respectively.

Figure 5. Mean Normalized Urine GAG Levels by Visit and Treatment Group (TKT024 ITT Patient Population, n=32 in each treatment group, sponsor's figure)

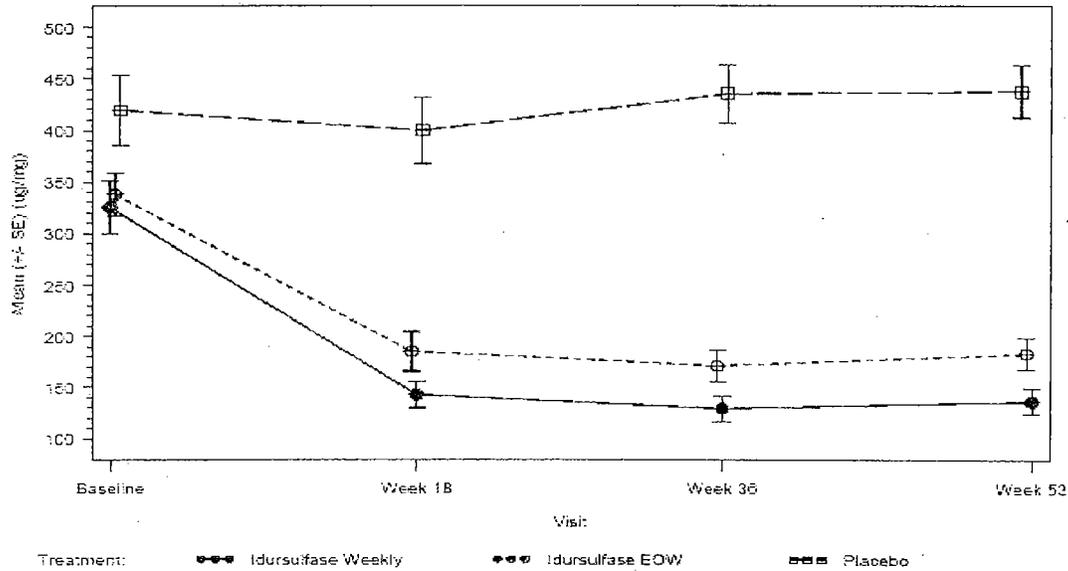
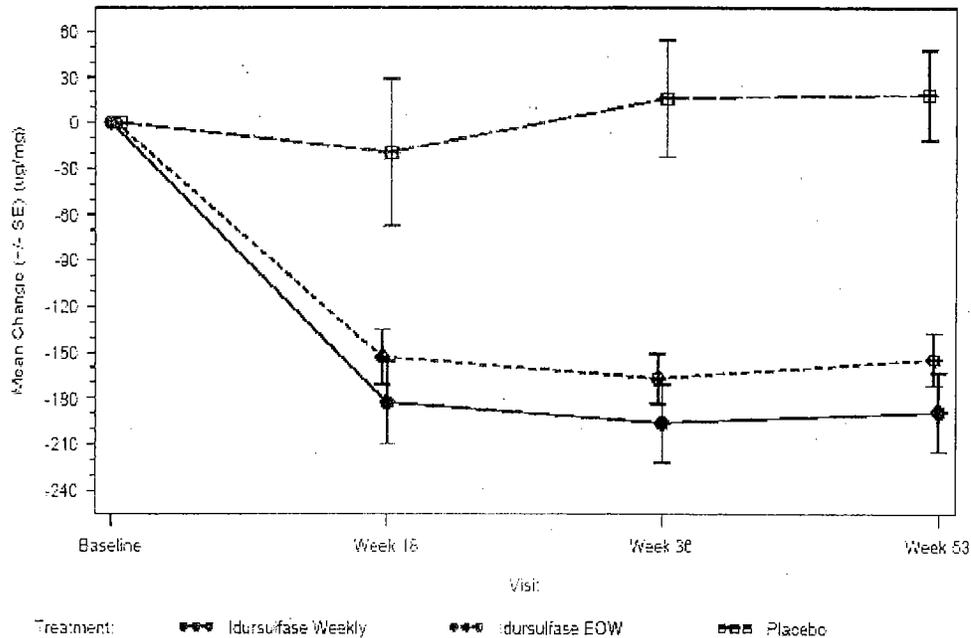


Figure 6. Mean Change from Baseline in Normalized Urine GAG Levels by Visit and Treatment Group (TKT024 ITT Patient Population, n=32 in each treatment group, sponsor's figure)



Individual patient urinary GAG levels at Week 53 (the mean of the two measures at Week 53) are calculated. The mean (\pm SD) values by this calculation for placebo, QW and QOW groups are 422 ± 126 , 136 ± 71 and 183 ± 89 μg GAG/mg creatinine, respectively.

Summary of Urinary GAG Results:

- Mean changes from baseline to Weeks 18, 36, and 53 in normalized urine GAG levels indicated that decreases were first observed at Week 18 for both idursulfase dose regimens, with maximal changes observed at Week 36 for both groups that persisted through Week 53.
- By the end of the study, 16 of 32 (50%) patients in the QW group had urinary GAG levels fell to below the upper limit of normal (defined as 126.6 μg GAG/mg creatinine), while 10 of 32 (31%) patients in the QOW group and no patients in the placebo group had urinary GAG levels fell to below the upper limit of normal by Week 53.

5. How effective are the selected dose and dosing regimens in reducing liver volume in the pivotal clinical trial?

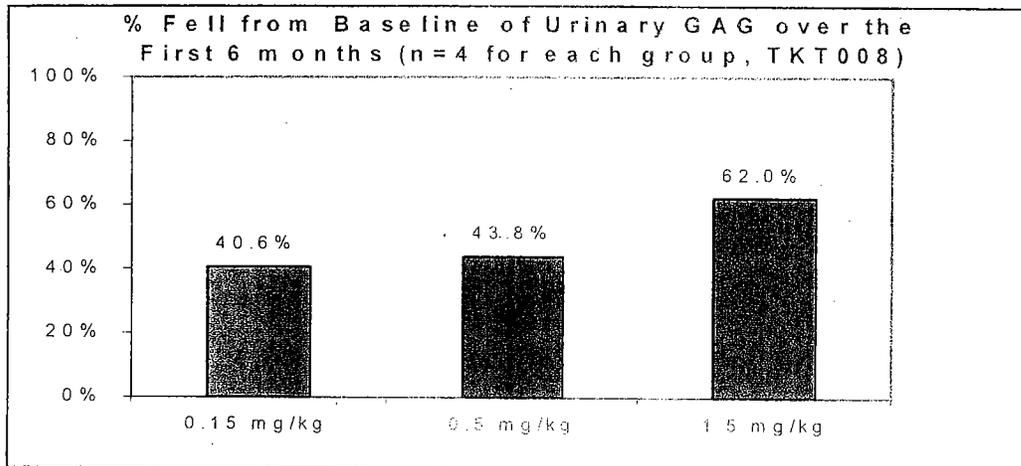
Of the 50 patients with abnormally large livers at baseline in the idursulfase treatment groups, 40 patients (80%; 20 patients in each idursulfase treatment group) had reductions in liver volume to within the normal range. Only one of 23 patients in the placebo group with hepatomegaly at baseline had a normal liver volume by the end of the study.

6. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Dose/Dose Regimen-Response

Dose-response relationship was observed in urinary GAG reduction. Over the first 6 months of QOW treatment with idursulfase, the mean baseline normalized urinary GAG levels fell by 41%, 44% and 62% in the 0.15, 0.5 and 1.5 mg/kg dose group, respectively (Figure 7).

Figure 7. Percent Fell from Baseline of Urinary GAG over the First 6 Months by Dose Levels (TKT008)



Dosing regimen-response relationship was observed in the primary clinical efficacy outcome (6MWT). At the end of the study (Week 53), patients in 0.5 mg/kg QW group walked 43 meters more in average from baseline compared to 32 meters in 0.5 mg/kg QOW group, and 17 meters in placebo group during the 6 minutes walk tests (Figure 8). Dosing regimen-response relationship was also observed in the urinary GAG level reduction to below the upper limit of normal and increased FEV1 ≥ 200 cc at or before the end of the study (Figure 9).

Figure 8. Primary Efficacy Endpoint by Treatment

(Placebo: 16.9 \pm 65.4; QW: 42.9 \pm 68.1; QOW: 31.8 \pm 52.2 meters)

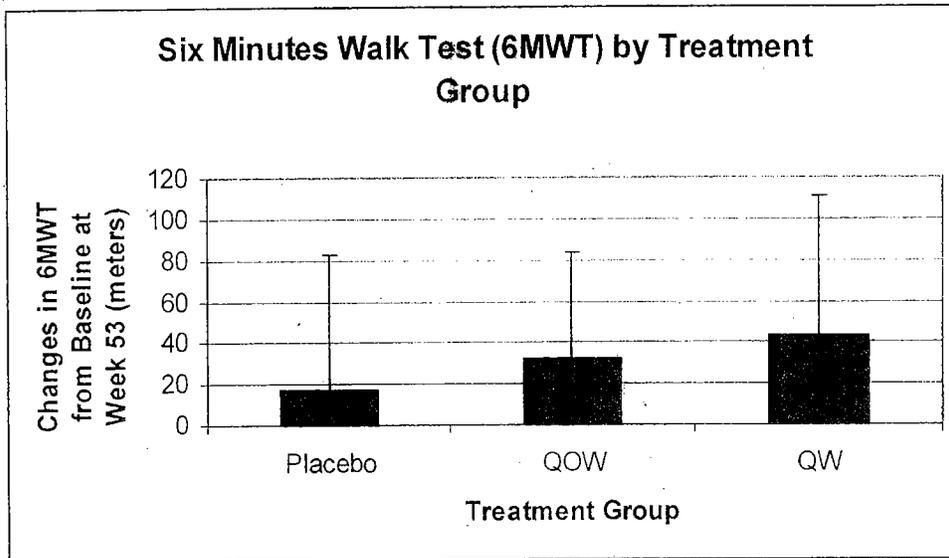
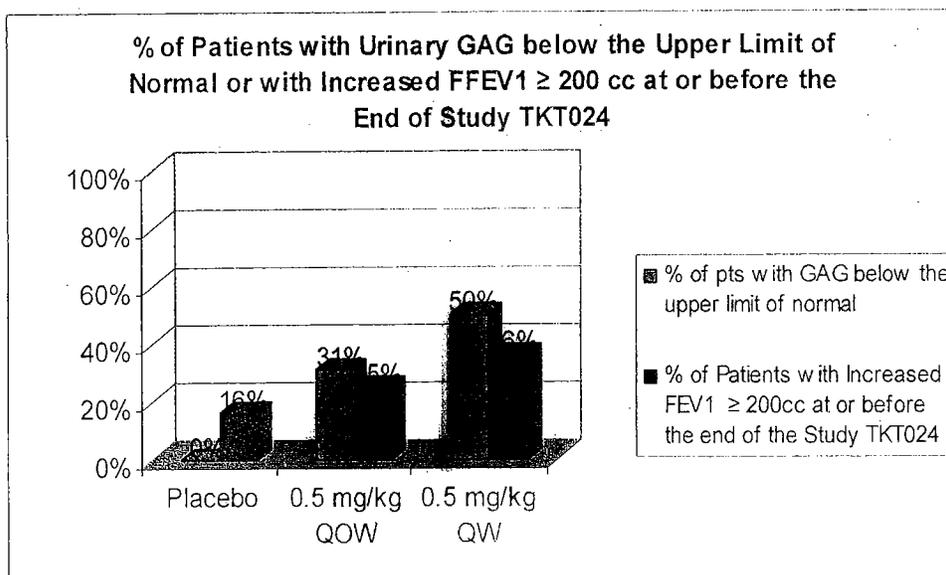


Figure 9. Percent of Patients with Urinary GAG below the Upper Limit of Normal or with Increased FEV1 ≥ 200 cc at or before the End of Study TKT024



Relationships between Clinical Efficacy and Bioactivity Measures

Relationships between 6MWT or liver volume reduction and urinary GAG levels were explored and no correlations are indicated as shown in Figure 10 and 11 below:

Figure 10. Plot of 6MWT Changes from Baseline vs. Urine GAG Levels at Week 53

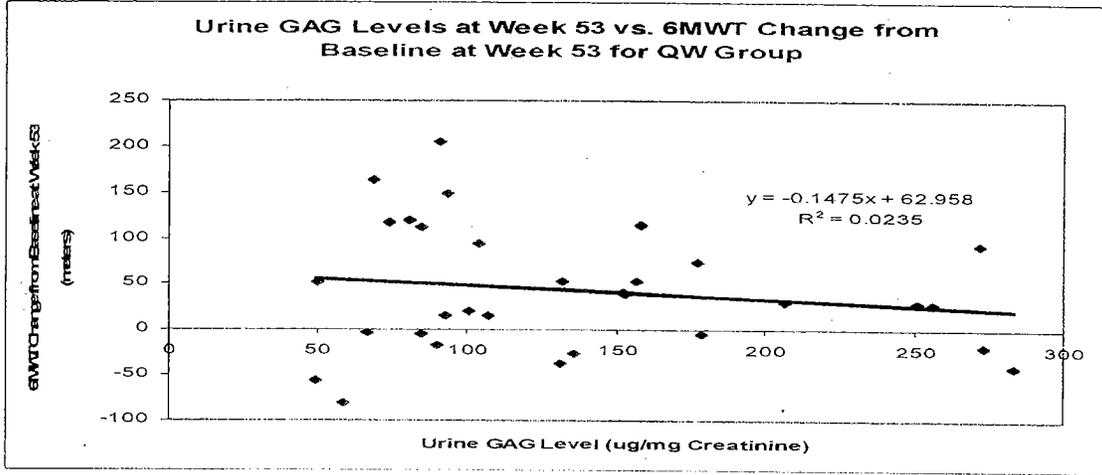
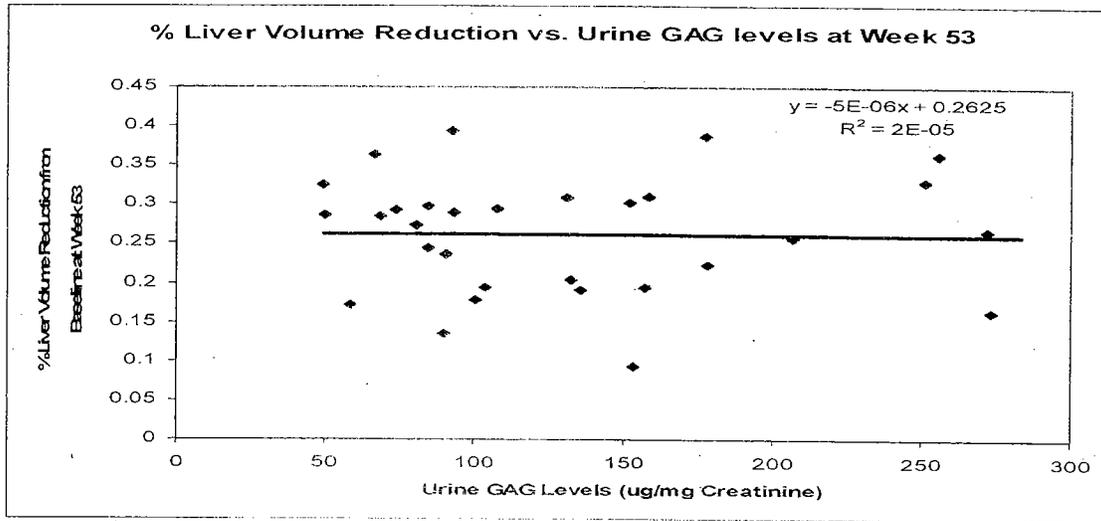


Figure 11. Plot of %Liver Volume Reduction vs. Urine GAG Levels at Week 53



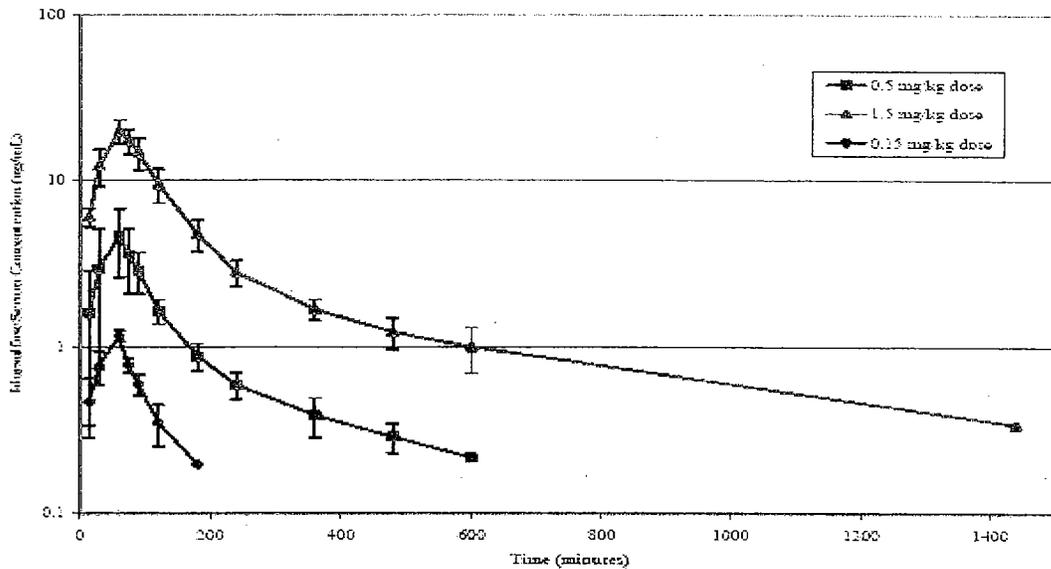
7. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to IV, F, Analytical Section; if no, describe the reasons)

Idursulfase concentrations in serum were determined by an antigen-specific ELISA assay.

a) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The pharmacokinetics of idursulfase after single doses ranging from 0.15 to 1.5 mg/kg have been characterized in 12 patients with Hunter syndrome. Idursulfase exhibits biphasic serum elimination profile following an initial one-hour infusion (Figure 12). Maximum serum concentration (C_{max}) was approximately dose-proportional. Area under the concentration-time curve (AUC_{inf}) was not dose-proportional across three dose levels (Figure 13). The results suggest that serum clearance mechanism for idursulfase may become saturated at a dose level greater than 0.5 mg/kg (Figure 14). Mean terminal elimination half-lives for all three dose levels were 2 to 5 hours, indicating that idursulfase would not accumulate in serum following the dosing frequency of once weekly (QW) or once every other week (QOW) in the clinical trials.

Figure 12. Mean Idursulfase Serum Concentration-time Plot of Dose Groups during and following an Initial 1-hour Infusion (Studies TKT008/TKT018, sponsor's plot)



(Data reflect 1st dose profiles for 3 patients per dose group receiving idursulfase in TKT008, or for the 3 TKT 008 placebo patients receiving their first dose of idursulfase in TKT018)

Figure 13. C_{max} versus Dose (left) and AUC versus Dose (right) Plots following an Initial 1-hour Infusion (Studies TKT008/TKT018, sponsor's plot)

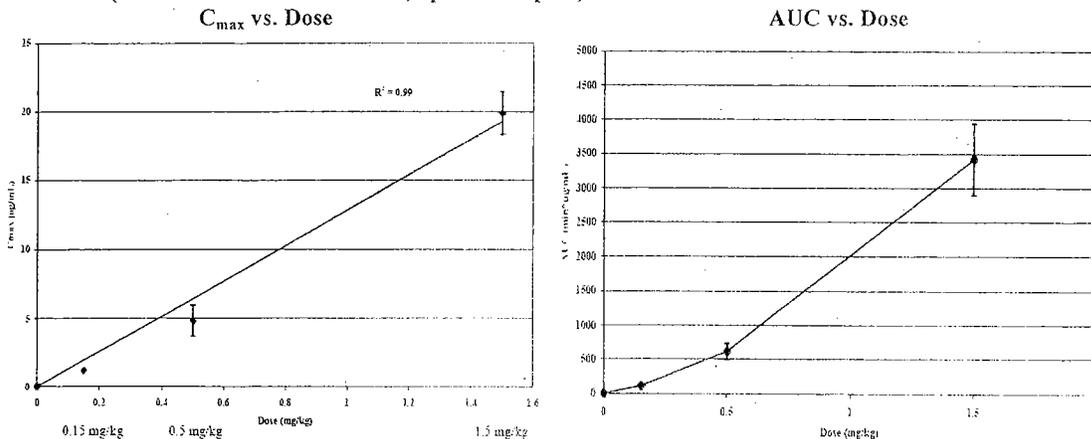
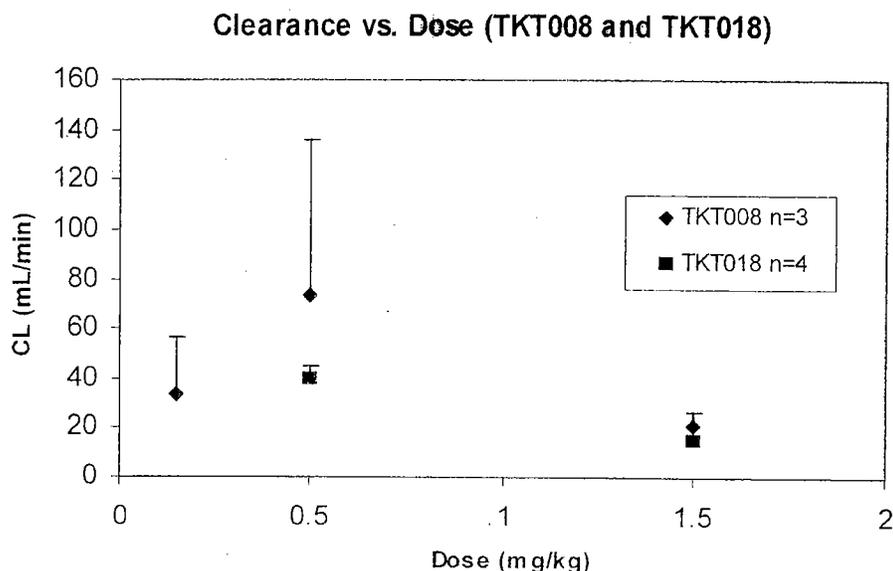
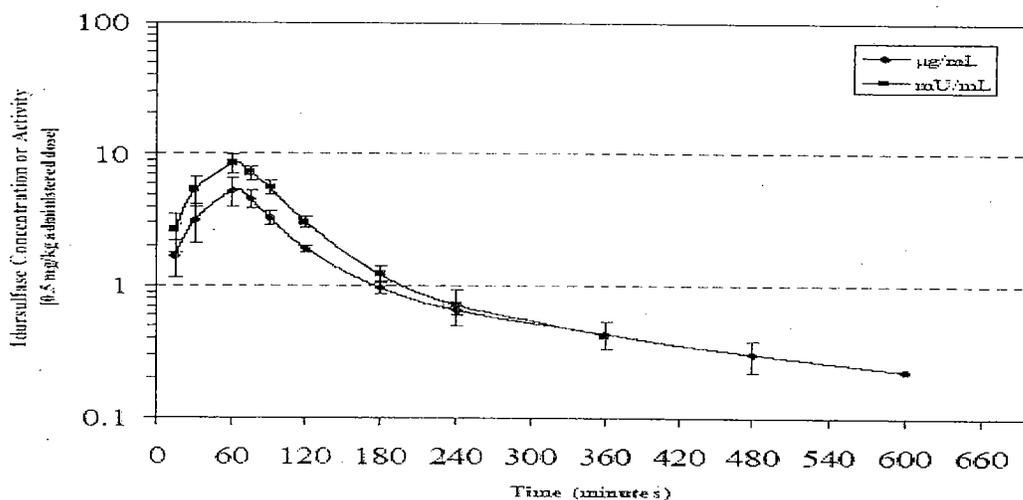


Figure 14. Plot of Idursulfase Clearance vs. Dose (TKT008 and TKT018)



Serum samples from Studies TKT 008 and TKT018 were also analyzed for idursulfase enzyme activity (mU/mL). Serum elimination curves of idursulfase enzyme activity were parallel to serum profiles of idursulfase protein concentration (Figure 15), indicating that idursulfase enzyme activity was not selectively inactivated in patients' plasma before binding to cellular receptors.

Figure 15. Mean Idursulfase Enzyme Activity-time Plot and Serum Concentration-time Plot (Concentration and Activity plots reflect mean data from 5 patients at 0.5 mg/kg dose (n=3 patients from TKT008, and n=2 from TKT018))



b) Do PK parameters change with time following chronic dosing?

PK parameters following repeated infusions of idursulfase in clinical Studies TKT008 and TKT018 appeared similar to PK results following initial infusions (Table 4), but

conclusion cannot be made based on these data due to limited number of patients included in these two studies.

Table 4. Mean Pharmacokinetic Parameters Based on Idursulfase Protein Concentration for All Doses (Studies TKT008 and TKT018, sponsor's table)

PK Parameter	Idursulfase Dose Group (Mean ± SD)		
	0.15 mg/kg	0.5 mg/kg	1.5 mg/kg
C_{max} (µg/mL)			
Week 1 TKT008 (n=3)	1.18 ± 0.22	5.8 ± 1.3	18.5 ± 1.8
Week 1 TKT018 (n=4)	1.17 ± 0.31	NA ^a	NA ^a
Week 25 TKT018 (n=4)	1.36 ± 0.45	NA ^a	NA ^a
AUC (min*µg/mL)			
Week 1 TKT008 (n=3)	NA ^b	708 ± 182	3018 ± 800
Week 1 TKT018 (n=4)	245 ± 156 ^c	312 ± 416	1679 ± 1494
Week 25 TKT018 (n=4)	210 ± 75 ^c	560 ± 453	3177 ± 1446
t_{1/2} (λz) (min)			
Week 1 TKT008 (n=3)	NA ^b	135 ± 18.2	293 ± 163
Week 1 TKT018 (n=4)	280 ± 340 ^c	151 ± 116	198 ± 198
Week 25 TKT018 (n=4)	146 ± 67 ^c	109 ± 95	233 ± 130
MRT (min)			
Week 1 TKT008 (n=3)	NA ^b	138 ± 29.3	276 ± 174
Week 1 TKT018 (n=4)	355 ± 444 ^c	160 ± 84	151 ± 102
Week 25 TKT018 (n=4)	160 ± 74 ^c	137 ± 45	196 ± 78
Cl (mL/min)			
Week 1 TKT008 (n=3)	NA ^b	40.1 ± 6.9	14.9 ± 4.9
Week 1 TKT018 (n=4)	33.6 ± 23.2 ^c	73.2 ± 63.3	20.8 ± 5.3
Week 25 TKT018 (n=4)	32.0 ± 13.3 ^c	65.1 ± 46.4	18.2 ± 6.2
Normalized Cl (mL/min/kg)			
Week 1 TKT008 (n=3)	NA ^b	0.75 ± 0.15	0.51 ± 0.12
Week 1 TKT018 (n=4)	0.75 ± 0.42 ^a	1.69 ± 1.50	0.67 ± 0.33
Week 25 TKT018 (n=4)	0.75 ± 0.24 ^c	1.56 ± 1.22	0.54 ± 0.28
V_{ss} (L)			
Week 1 TKT008 (n=3)	NA ^b	5.50 ± 1.4	3.57 ± 0.9
Week 1 TKT018 (n=4)	5.6 ± 2.2 ^c	8.9 ± 3.3	3.4 ± 1.1
Week 25 TKT018 (n=4)	4.6 ± 1.2 ^c	8.4 ± 5.6	3.3 ± 0.8
V_{ss} (%BW)			
Week 1 TKT008 (n=3)	NA ^b	10.1 ± 3.1%	12.7 ± 4.5%
Week 1 TKT018 (n=4)	15.7 ± 11.3% ^a	20.4 ± 11.2%	9.9 ± 2.2%
Week 25 TKT018 (n=4)	10.8 ± 1.8% ^c	19.0 ± 13.9%	9.4 ± 2.2%

Patient population: Pharmacokinetic population - all randomized patients who received a dose of idursulfase. C_{max}: maximum observed serum concentration; t_{1/2} (λz): terminal elimination half life; V_{ss}: apparent volume of distribution at steady state; V_{ss} (% BW): V_{ss} normalized for body weight; MRT: mean residence time; AUC: area under the curve extrapolated to infinity; SD: standard deviation; NA: Not applicable due to different infusion times.

^a Calculated only for patients with 1-hour infusions.

^b Quantitative PK parameters could not be calculated due to varied infusion times for these patients.

^c n=3

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The PK characteristics of idursulfase were also evaluated at Week 1 and Week 27 in 30 patients who received 0.5 mg/kg idursulfase QW or QOW as a 3-hour infusion in the pivotal clinical trial (Figure 16 and Table 17).

Figure 16. Mean Idursulfase Concentration-time Profile for Weeks 1 and 27 (TKT024, n=21)

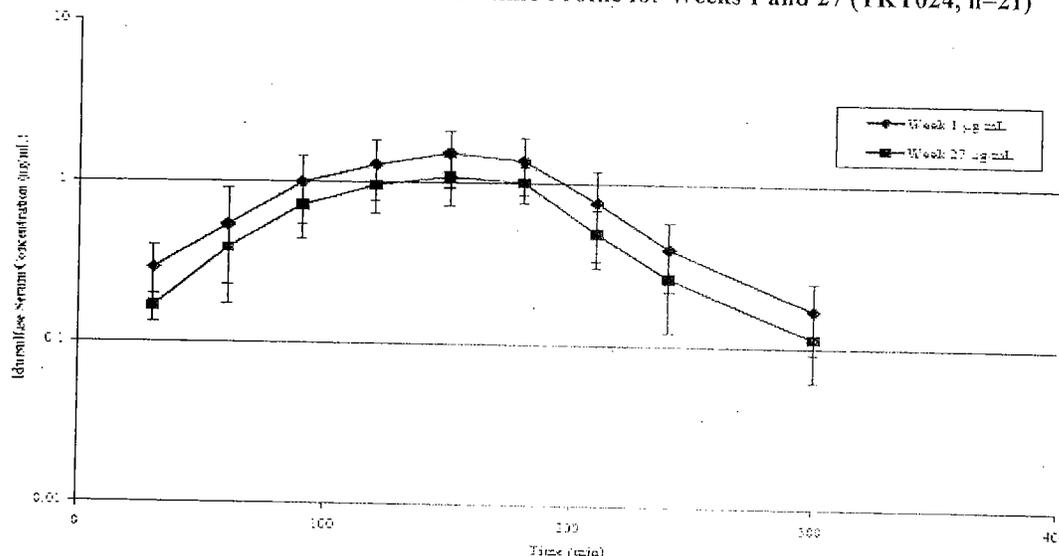


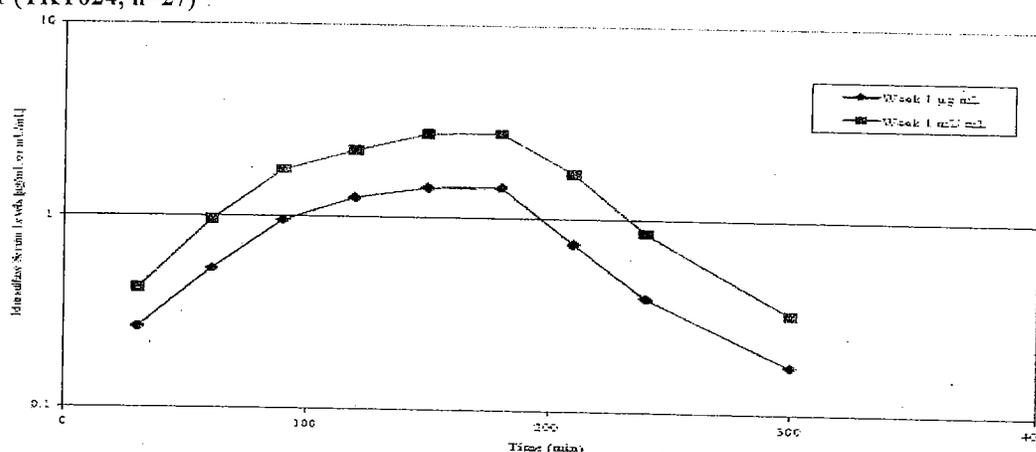
Table 5. Comparison of Week 1 and Week 27 ELISA PK parameters (Study TKT024, sponsor's table)

Study Week ^a (n)	PK Parameter (SD) ^b				
	C _{max} (µg/mL)	AUC (min*µg/mL)	t _{1/2} (min)	CL (mL/min/kg)	V _{ss} (% BW)
Week 1 (n=28)	1.64 (0.55)	234 (82)	50 (36)	2.44 (0.97)	19.2% (7.5%)
Week 27 (n=30)	1.17 (0.41)	165 (48)	39 (17)	3.45 (1.03)	23.3% (10.8%)

^aMean Week 1 results, ^b Mean of all patients irrespective to dose regimens (0.5 mg/kg QW and QOW)

Enzyme activity was measured for the Week 1 samples (Figure 20).

Figure 17. Mean Idursulfase Concentration-time and Serum Enzyme Activity-time Profiles for Week 1 (TKT024, n=27)



Comments: The sponsor's conclusion is that there were no apparent differences in PK parameters as a result of repeat dosing of idursulfase. However, in comparison of PK parameters between Week 27 and Week 1, there were 29% decreases in C_{max} and AUC_{inf}, 41% increase in CL and 21% increase in V_{ss} after repeat dosing (Table 6). The sponsor proposed to include PK parameter values generated from 21 patients who had PK data available at both Week 1 and Week 27 irrespective to dosing regimen in the PK section of the label. The data from 21 patients suggested that there was a 32% increase in CL comparing Week 27 with Week 1 (See Immunogenicity section).

Table 6. Comparison of Mean Week 1 and Week 27 ELISA PK Parameters^a (Study TKT024, all PK evaluable patients irrespective to dose regimen)

Study Week	C _{max} (µg/mL)	AUC _{inf} (min*µg/mL)	CL (mL/min/kg)	V _{ss} (%BW)
All PK evaluable patients				
Week 1 (n=28)	1.64	234	2.44	19.2%
Week 27 (n=30)	1.17	165	3.45	23.3%
(WK 27/WK 1)*100	71%	71%	141%	121%
Patients who had both Week 1 and Week 27 PK data				
Week 1 (n=21)	1.63	233	2.59	18.6%
Week 27 (n=21)	1.16	165	3.42	22.3%
(WK 27/WK 1)*100	71%	71%	132%	119%

^a Mean of all patients irrespective to dose regimen

The PK parameters at the recommended dose regimen (0.5 mg/kg ELAPRASE administered QW as a 3-hour infusion) in patients who had evaluable PK data at both Week 1 and Week 27 are summarized in Table 7. There were no apparent differences in PK parameters between Week 1 and Week 27 in these PK evaluable patients.

Table 7. Comparison of Mean Week 1 and Week 27 ELISA PK Parameters^a (Study TKT024, patients in QW group with evaluable PK data at both Week 1 and Week 27)

Study Week	C _{max} (µg/mL)	AUC _{inf} (min*µg/mL)	t _{1/2} (min)	CL (mL/min/kg)	V _{ss} (%BW)
Week 1 (n=10)	1.5±0.6	206±87	44±19	3.0±1.2	21.3%±8.2%
Week 27 (n=10)	1.1±0.3	169±55	48±21	3.4±1.0	25.4%±8.7%
(WK 27/WK 1)*100	73%	82%	109%	113%	119%

c) How long is the time to the onset and offset of the pharmacological response or clinical endpoint?

The first measurement of urinary GAG levels was at Week 5 of the treatment and the reduction was observed. There is no evidence of waning effect over time with regard to urinary GAG reduction. These data indicate that idursulfase administered weekly at the 0.5 mg/kg dose level is likely to provide a pharmacological response over the course of long-term therapy.

d) Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Two dosing regimens (0.5 mg/kg QW and QOW) were studied in the pivotal clinical trial (TKT024). The serum concentration-time profiles are shown in Figure 18 and PK parameter values generated from these two dosing regimens at Week 27 are shown in Table 8.

Figure 18. Comparison of Mean Idursulfase Serum Concentrations Weekly (QW) vs. Every Other Week (QOW) Dosing at Week 27 (Study TKT024)

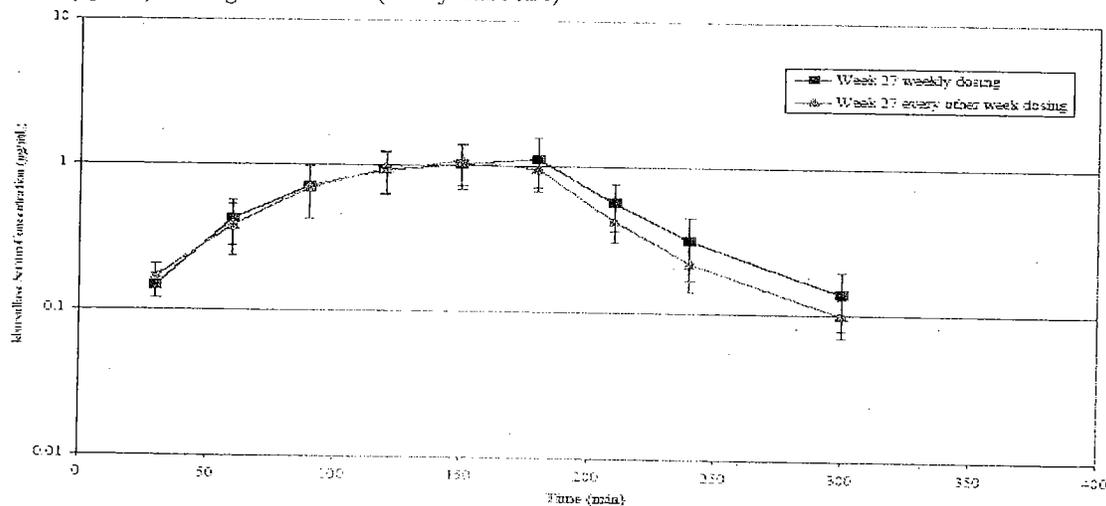


Table 8. Comparison of ELISA PK Parameters at Week 27 between Weekly vs. Every Other Week Dosing (EOW) (Study TKT024)

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%)

Comments: There were 14% higher in AUC and 10% lower in CL of 0.5 mg/kg QW group than those of 0.5 mg/kg QOW group at Week 27. Although the difference in serum exposure of idursulfase in these two dosing regimens is not appreciable, the difference in serum exposure may not reflect the difference in tissue exposure because higher clinical efficacy was achieved in QW dosing group than in the QOW dosing group (also see Immunogenicity section).

8. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

No PK studies were conducted in healthy volunteers. The pharmacokinetic information for intravenously administered idursulfase submitted in this application was obtained from Hunter syndrome patients. As a form of naturally occurring I2S protein, idursulfase is degraded by protein hydrolysis resulting in peptide and amino acid products which are not considered active metabolites.

a) What are the basic PK parameters?

The pharmacokinetics of idursulfase after single doses ranging from 0.15 to 1.5 mg/kg have been characterized in 12 patients with Hunter syndrome (TKT008 and TKT018). The PK of 0.5 mg/kg single dose was also studied in 28 patients in Study TKT024 (Table 9). Idursulfase exhibits biphasic serum elimination profile following an initial one-hour (TKT008 and TKT018) or 3-hour (TKT024) infusion. Maximum serum concentration (C_{max}) was approximately dose-proportional. Area under the concentration-time curve (AUC_{inf}) increased in a greater than dose-proportional manner as the dose increased from 0.15 mg/kg to 1.5 mg/kg following a 1-hour infusion. Mean terminal elimination half-lives for all three dose levels were 1 to 5 hours.

Table 9. Single-Dose PK Parameters for Idursulfase Cross all Studies (Mean±SD)

Dose (mg/kg)	n	C _{max} (µg/ml)	AUC _{0-∞} (µg.min/ml)	t _{1/2} (min)	CL (mL/min/kg)	V _{ss} (%BW)
0.15 (008)	3	1.18±0.22	NA	NA	NA	NA
0.15 (018)	4	1.17±0.31	245±156	280±340	0.75±0.42	15.7±11.3%
0.5 (008)	3	5.8±1.3	708±182	135±18	0.73±0.15	10.1±3.1%
0.5 (018)	4	NA	512±416	151±116	1.69±1.50	20.4±11.2%
0.5 (024)	28	1.64±0.55	234±82	50±36	2.55±0.97	19.2±7.5%
1.5 (008)	3	18.5±1.8	3018±800	293±163	0.51±0.12	12.7±4.5%
1.5 (018)	4	NA	2679±1494	198±198	0.67±0.33	9.9±2.2%

The PK parameter values at Week 25 following QOW in TKT 018 and at Week 27 following 0.5 mg/kg QW and QOW are shown in Table 10. The mean half-life after the recommended dose and dosing regimen (0.5 mg/kg QW) is less than an hour (approximately 40 minutes).

Table 10. Repeat-Dose PK Parameters for Idursulfase Cross all Studies (Mean±SD)

Dose (mg/kg)	n	C _{max} (µg/ml)	AUC _{0-∞} (µg.min/ml)	t _{1/2} (min)	CL (mL/min/kg)	V _{ss} (%BW)
0.15 (018)	4	1.36±0.45	210±75	146±67	0.75±0.24	10.8±1.8%
0.5 (018)	4	NA	560±453	109±95	1.56±1.22	19.0±13.9%
0.5 (024)	30	1.17±0.30	165±48	39±17	3.45±1.03	23.3±10.8%

b) Is this a high extraction ratio or a low extraction ratio drug?

This question is not applicable because idursulfase is an enzyme (protein).

c) Does mass balance study suggest renal or hepatic the major route of elimination?

No mass balance study has been conducted for idursulfase. Idursulfase is an enzyme product. Mass balance studies are not generally performed for enzyme products because they are proteins which are degraded into amino acids that then recycled in the body. However, idursulfase labeled with ¹²⁵I was used in a rat biodistribution study, and groups of rats were sacrificed at 4, 24, and 48 hours after intravenous administration. For major organs, the tissue half-life of idursulfase was estimated at approximately 1 to 2 days.

The greatest level of idursulfase was found in the liver in both rats and mice (approximately 11% of administered dose in rats and 30 to 40% in mice). Lower, but appreciable levels of idursulfase were distributed to other major organs and tissues throughout the body (kidneys, heart, spleen, lungs, testes, bone/bone marrow, lymph nodes, pancreas, skin, muscle and adipose tissue). 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 idursulfase. Biodistribution studies in female mice and male mice indicated that there were no gender related differences in patterns of tissue uptake of idursulfase.

4.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Demographic and Other Characteristics of the Study Population: Hunter syndrome is a serious debilitating disease with a wide spectrum of symptoms that worsen with age. To ensure balance of both patient age and disease severity across the treatment groups in the pivotal trial (TKT024), stratification criteria were applied to the randomization scheme.

The treatment groups in TKT024 were well-balanced with respect to disease severity and patient age. Three age categories (5 to 11, 12 to 18, and >19 years of age) and 3 disease level scores (2, 3 or 4, and 5 or 6) based on a combined score of severity of forced vital capacity (FVC) and 6 minute walk test (6MWT) were defined for TKT024.

Pharmacokinetics in Special Populations: Hunter syndrome is a rare disease with an estimated incidence of one in approximately 162,000 live births. Despite the heterogeneity in the disease progression, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. The age range of patients at clinical study entry was 5 to 31 years. No female patients were enrolled in the clinical studies. Majority patients were white (88%). Idursulfase was dosed based on body weight. Age was not found to have an appreciable effect on PK parameters of idursulfase. Due to limited number of non-white patients enrolled in the clinical studies, the effect of race on idursulfase PK could not be evaluated. No formal clinical studies in patients with hepatic impairment, renal impairment or in elderly populations were conducted with idursulfase.

2. *Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

a) **Elderly**

The age range of patients at clinical study entry was 5 to 31 years. Elderly patients have not been studied. The sponsor proposed the following labeling statement under Geriatric Use: Clinical studies of idursulfase did not include _____ patients aged 65 and over. _____ patients. The FDA proposes the following statement: Clinical studies of ELAPRASE did not include patients _____. It is not known whether older patients respond differently from young patients.

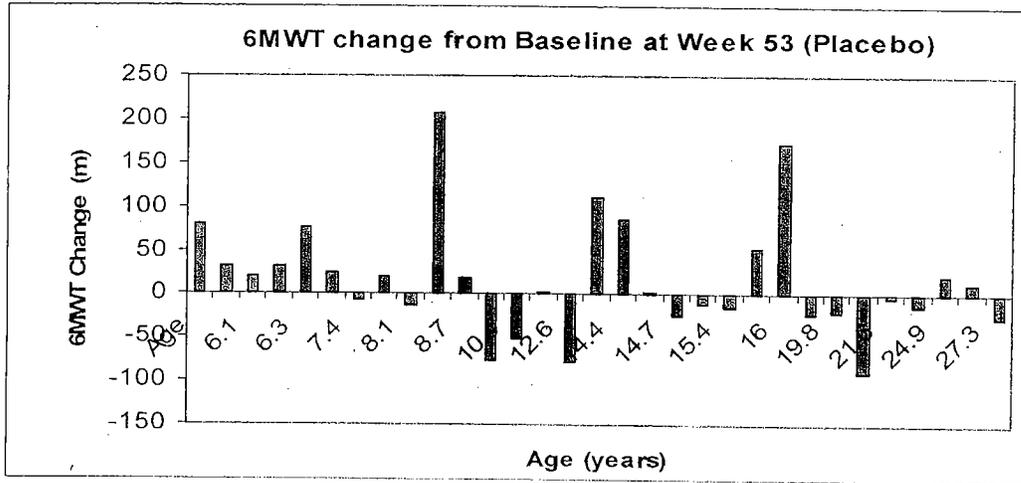
b) **Pediatric Patients**

Patients in the clinical studies were age 5 and older. Sponsor proposed the following labeling statement under Pediatric Use: Children, adolescents, and adults responded similarly to treatment with idursulfase.

The results of the primary efficacy endpoint (6MWT) are plotted by age in Figure 19. Safety and efficacy have not been established in pediatric patients <5 years of age.

The effect of age on idursulfase PK is explored and the results indicate that age does not significantly affect systemic exposure (AUC) and body weight-based clearance (CL, mL/min/kg) of idursulfase as shown in Figure 20 (QW group only) and Figure 21 (combined QW and QOW groups).

Figure 19. Individual Patient 6MWT Change from Baseline at Week 53 by Age (upper panel for Placebo group and lower panel for QW group)
 Placebo: 16.9±65.4 meters



QW: 42.9±68.1 meters

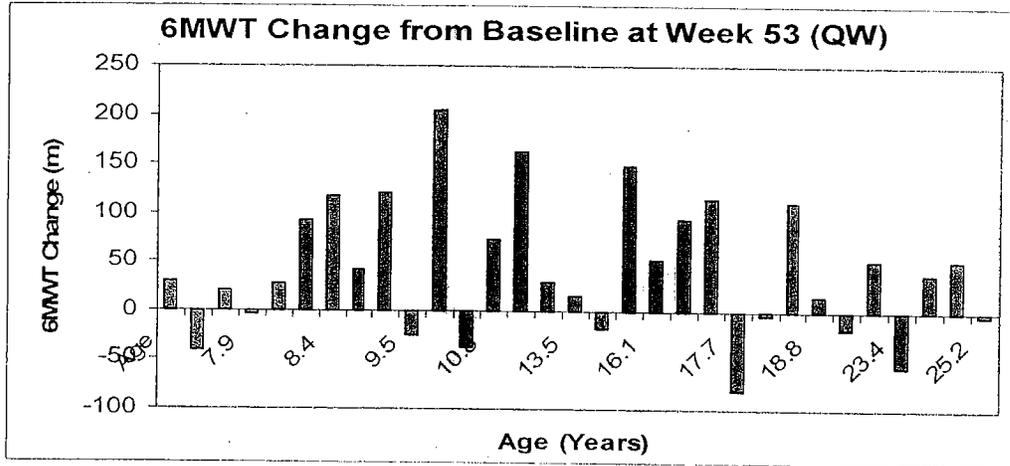
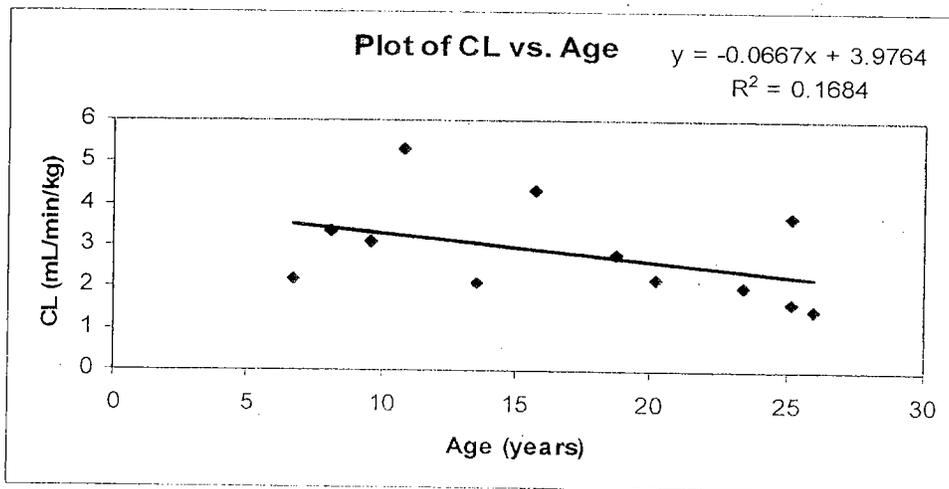


Figure 20. Plots of Clearance vs. Age (upper panel) and AUC vs. Age (lower panel) in QW Group



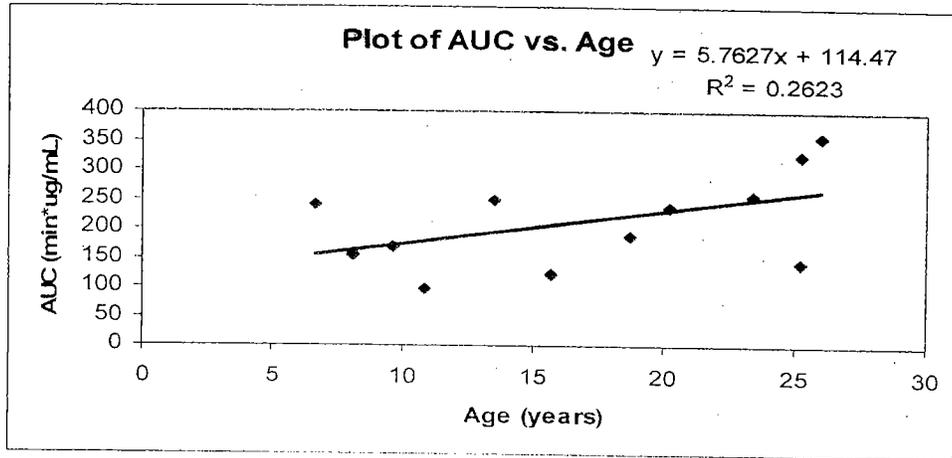
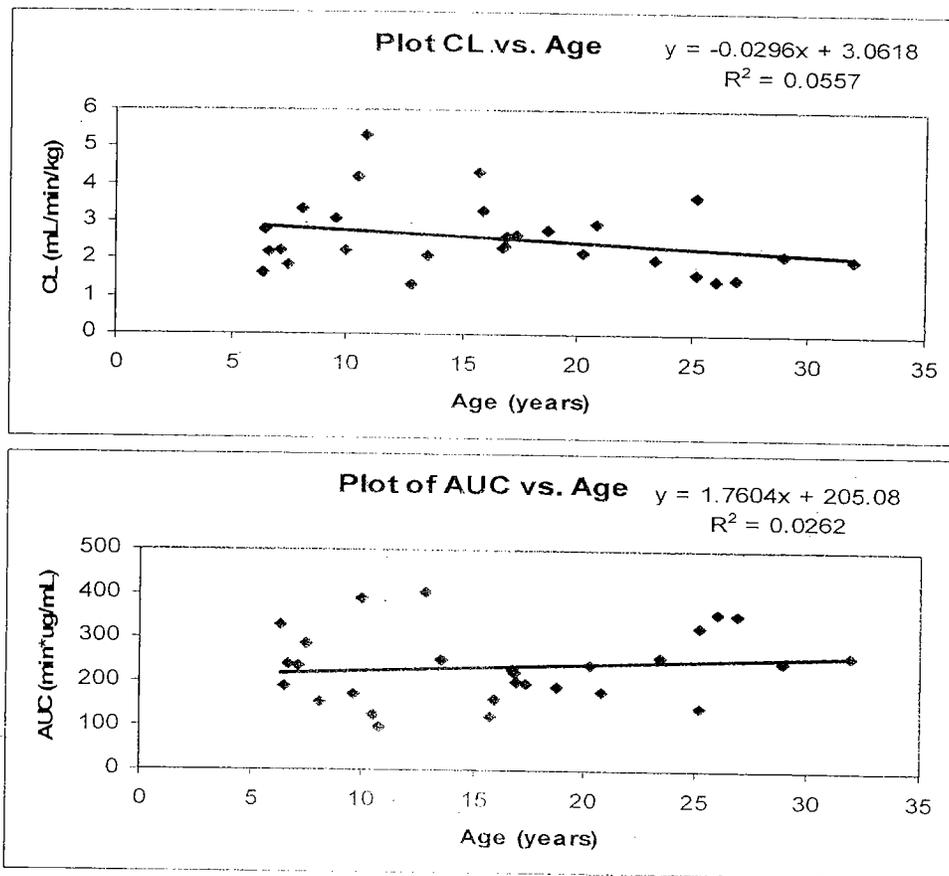


Figure 21. Plots of Clearance vs. Age (upper panel) and AUC vs. Age (lower panel) in QW and QOW Groups



c) Gender

Hunter syndrome is an X-linked recessive disease and the incidence in female is extremely rare. All patients in the clinical studies are male patients.

d) Race

In the pivotal clinical trial, 64 patients received idursulfase 0.5 mg/kg either QW or QOW

and majority patients were white (88%). Due to limited number of non-white patients enrolled in the clinical studies, the effect of race on idursulfase PK could not be evaluated.

e) Renal Impairment

No formal clinical studies in patients with renal impairment were conducted. Idursulfase metabolic degradation is assumed to mainly occur in cells via normal proteolytic mechanisms 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, idursulfase PK is not expected to be affected by renal impairment.

f) Hepatic Impairment

No formal clinical studies in patients with hepatic impairment were conducted. Similarly, idursulfase PK is not expected to be affected by hepatic impairment for the reasons mentioned above.

g) What pregnancy and lactation use information is there in the application?

Pregnancy: The sponsor proposed the following statements for Pregnancy: _____

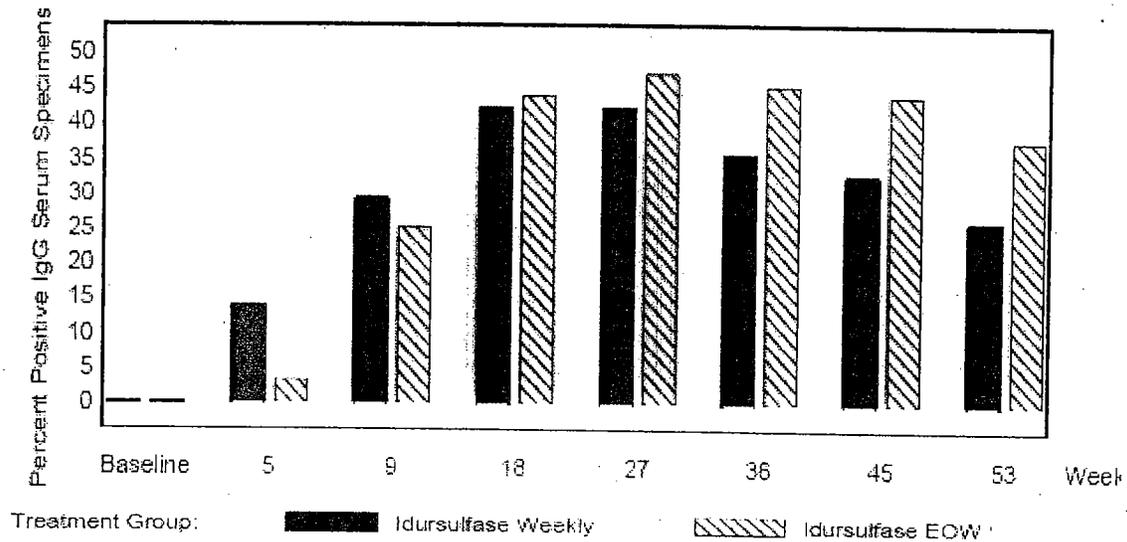
The FDA proposes the following statement: Teratogenic Effects: Category C
Reproduction studies in pregnant female animals have not been conducted with ELAPRASE. It is also not known whether ELAPRASE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELAPRASE should be given to pregnant women only if clearly needed.

Nursing Mothers: Sponsor proposed statement: It is not known whether Idursulfase is excreted in human milk. The FDA proposes the following statements: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELAPRASE is administered to a nursing woman.

h) Other factors that are important to understanding the drug's efficacy and safety

Immunogenicity: As with all therapeutic proteins, idursulfase has the potential to induce an immune response. Since the original application, the sponsor submitted amendment to provide new data on the presence of anti-idursulfase antibodies in patients in clinical studies TKT024 and TKT024EXT using a new validated assay (conformation-specific antibody assay, CSA). This new assay shows that approximately 50% of patients in both studies were positive for anti-idursulfase antibodies at 1 or more time point over the course of treatment, instead of the previously reported 15% using the ELISA-based assay. Figure 22 shows percent of IgG positivity serum specimens by treatment group and week of idursulfase exposure in 53 weeks of TKT024 study. The percent positivity of IgG was higher with QOW regimen than that with QW regimen.

Figure 22. Percent of IgG Antibody Positive Serum Specimens by Treatment Group and Week of Idursulfase Exposure (Safety Population, sponsor's figure 2.7.4.7.3.2.2)



Immunogenicity was also tested during the TKT024EXT study after finishing the 53-week TKT024 study. The results are showing in Figures 23, 24 and 25 for QW, QOW and placebo group (receiving idursulfase in the TKT024EXT study), respectively. The percent positivity of IgG continued to be higher with QOW regimen than that with QW regimen during the extension phase of the study.

Figure 23. Percent of IgG Antibody Positive Serum Specimens by Week of Idursulfase Exposure (QW Safety Population, sponsor's figure 2.7.4.7.2.2.4) (Result of Week 90 is questionable.)

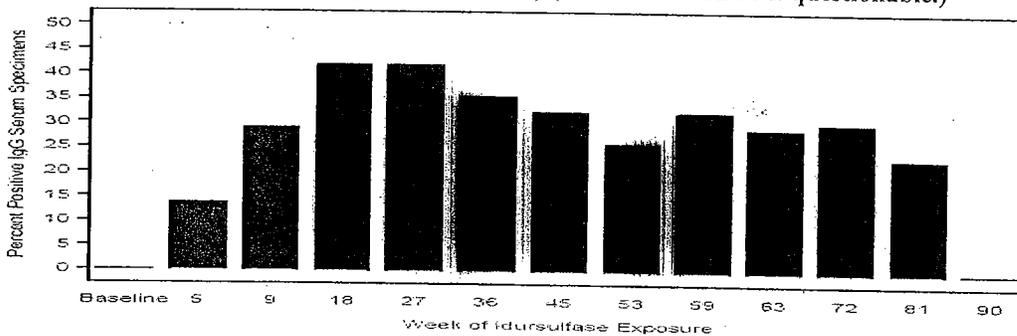


Figure 24. Percent of IgG Antibody Positive Serum Specimens by Week of Idursulfase Exposure (QOW Safety Population, sponsor's figure 2.7.4.7.2.2.4) (Result of Week 90 is questionable)

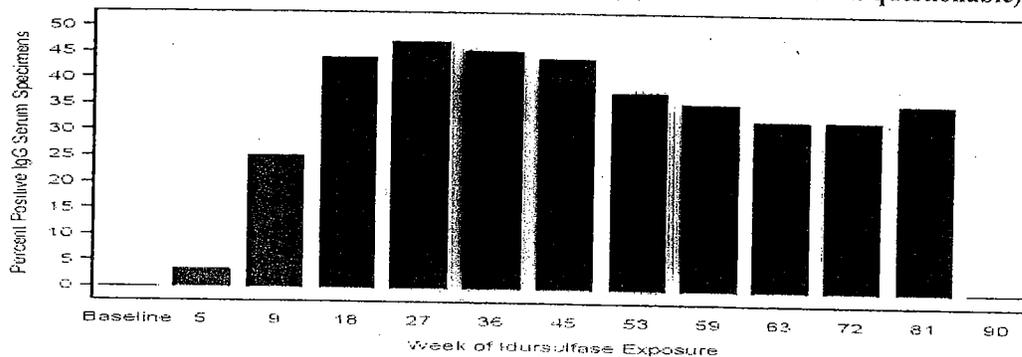
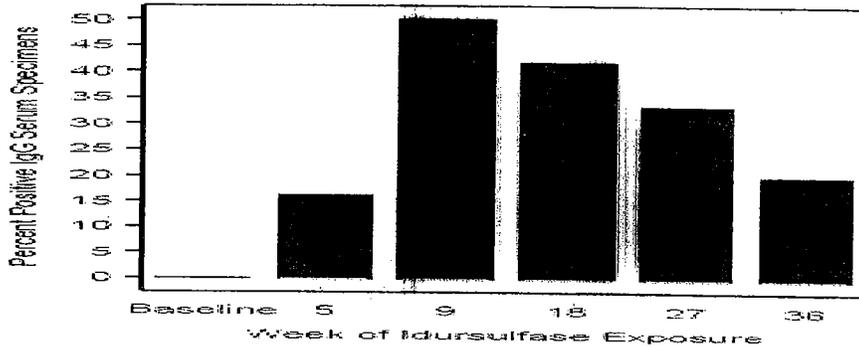


Figure 25. Percent of IgG Antibody Positive Serum Specimens by Week of Idursulfase Exposure (Placebo patients receiving Idursulfase in TKT024EXT, Safety Population, sponsor's figure 2.7.4.7.2.2.4)

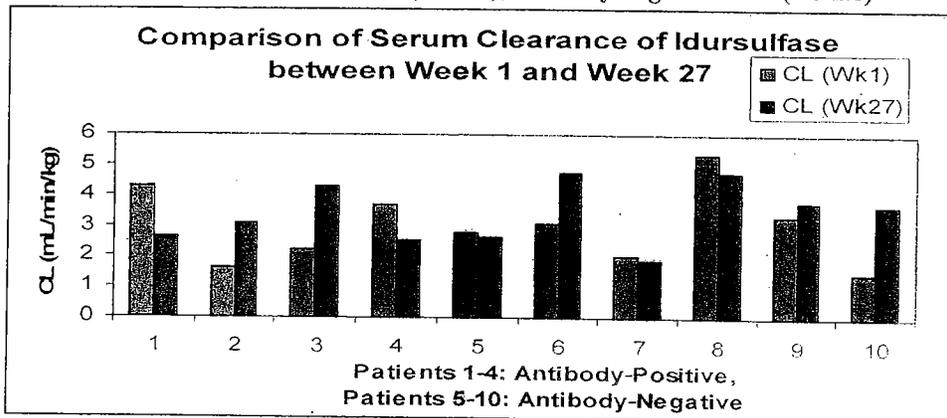


Impact of Immunogenicity on PK: The sponsor did not analyze the impact of immunogenicity on PK due to the limitation of the previously used assay by which only one patient among the patients with PK data available determined IgG antibodies positive by Week 27 in clinical Study TKT024. Of the 12 patients who had PK evaluated at both Week 1 and Week 27, 6 patients tested positive for anti-idursulfase antibodies by the newly developed assays. PK parameters could not be determined in 2 of the 6 antibody positive patients at Week 27 due to idursulfase serum concentrations outside the expected ranges as measured by an antibody-based assay (ELISA). There was a subset of patients in the TKT024EXT study (n=14) whose serum idursulfase exposure could only be measured by an enzyme activity assay suggesting sample interference with the ELISA assay. Factors which may result in ELISA-based assay interference with these patient samples are under evaluation.

Investigation of the effect of antibody formation on PK was limited to 10 patients who had evaluable PK data for both Week 1 and Week 27. The ratio of clearance (Wk27/Wk1) was similar between the four antibody-positive patients and the six antibody-negative patients (1.30 with range of 0.6 to 2.0 vs. 1.32 with range of 0.8 to 2.5). Figure 26 shows serum clearance at Week 1 and Week 27 for each individual patient.

Figure 26. Comparison of Individual Patient's Serum Clearance of Idursulfase between Week 1 and Week 27 (Evaluation of Immunogenicity on PK)

Mean ratio: antibody-positive: 1.30 (0.6-2.0), antibody-negative: 1.32 (0.8-2.5)



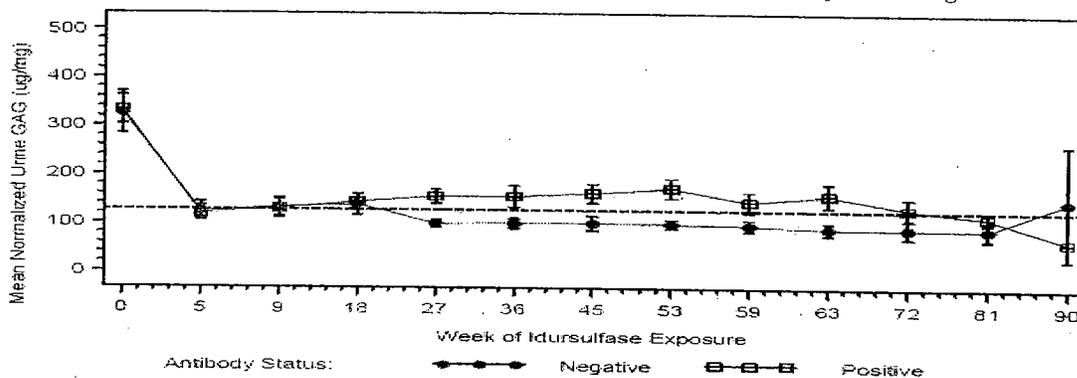
Impact of Immunogenicity on 6MWT: There is no apparent difference in 6MWT between antibody-positive and antibody-negative patients in idursulfase QW dosing group. In QOW dosing group, it appears that antibody-positive patients did better in 6MWT than antibody-negative patients (Table 11).

Table 11. 6MWT Changes (meters) from Baseline at Week 53 by Antibody Status (Mean±SD)

Dosing Regimen	Antibody-Positive	Antibody-Negative
QW	37.9±82.3	48.2±51.2
QOW	43.4±59.8	21.6±43.8

Impact of Immunogenicity on Urinary GAG Level: Approximately 50% of treated patients developed anti-idursulfase antibodies (based on the CSA assay) during the combined TKT024 and TKT024EXT trials. Mean urine GAG levels by study visit and by treatment regimen were compared in Figure 27 (QW), Figure 28 (QOW) and Figure 29 (placebo patients receiving idursulfase in TKT024EXT) for the antibody-negative versus the antibody-positive patients where patients were considered positive if they had at least one seropositive specimen at any study visit.

Figure 27. Mean Normalized Urine GAG (µg/mg) by Antibody Status, TKT024 Treatment Assignment and Week of Idursulfase Exposure (QW Safety Population, sponsor's figure 2.7.4.7.2.2.7)



Dotted line represents the upper limit of normal (126 µg/mL creatinine).

Note: Baseline through Week 53 correspond to TKT024 and Week 59 through Week 90 correspond to Week 5 through Week 36 of TKT024EXT

Figure 28. Mean Normalized Urine GAG (µg/mg) by Antibody Status, TKT024 Treatment Assignment and Week of Idursulfase Exposure (QOW Safety Population, sponsor's figure 2.7.4.7.2.2.7)

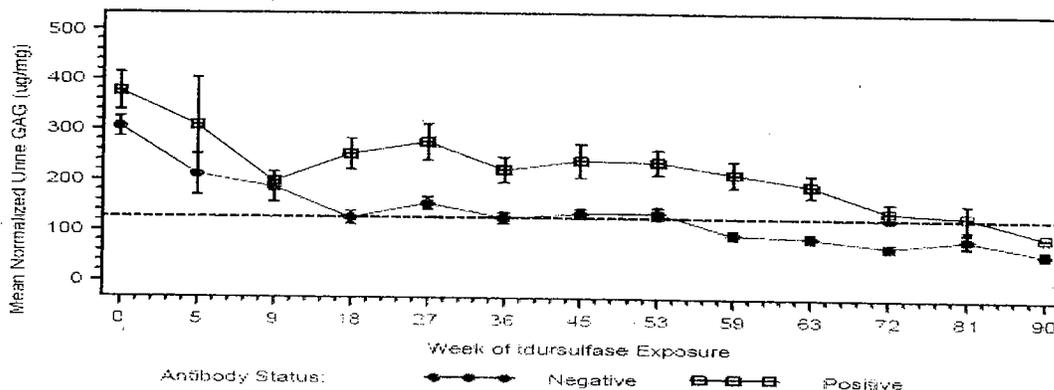
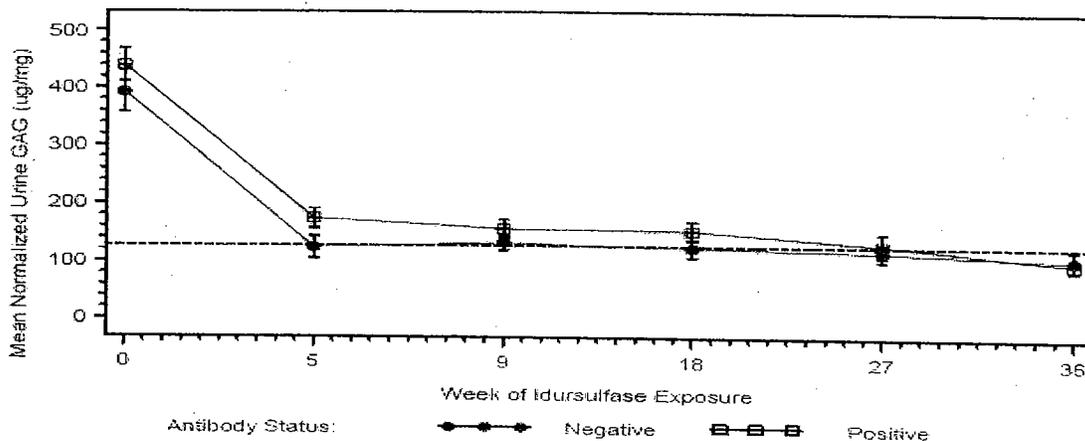


Figure 29. Mean Normalized Urine GAG ($\mu\text{g}/\text{mg}$) by Antibody Status, TKT024 Treatment Assignment and Week of Idursulfase Exposure (Placebo Safety Population, sponsor's figure 2.7.4.7.2.2.7)



As shown in these figures, mean urine GAG levels fell significantly by Week 5 regardless of antibody status, and continued to decrease through Week 9. By Weeks 18 and 27, however, the curves diverged modestly, a time period which was coincident with the observed peak rates of antibody seropositivity. Rates of antibody seropositivity began to decline with continued drug exposure. Urine GAG levels also declined among the antibody seropositive patients with continued drug exposure. After 72 weeks of treatment (i.e., Week 18 visit in TKT024EXT), the curves begin to converge, and ultimately mean GAG levels among the two groups are essentially identical as of the last observation before the data cut-off. The results suggest that idursulfase remains pharmacologically active in patients who form anti-idursulfase antibody, as measured by urinary GAG excretion.

Impact of immunogenicity on urinary GAG level reduction at the end of the pivotal trial (Week 53) is evaluated by individual patient antibody status. Urinary GAG clearance became impaired in patients who developed anti-idursulfase antibodies. The number of patients in the QW group with normalized urine GAG levels below the upper limit of normal (defined as $126.6 \mu\text{g}/\text{mg}$ creatinine) was 5 of 15 for antibody-positive patients compared to 11 of 16 for antibody negative patients. The impact of immunogenicity on urine GAG level was more profound in the QOW dosing group that the number of patients with normalized urine GAG levels below the upper limit of normal was 2 of 15 for antibody-positive patients compared to 8 of 17 for antibody negative patients. The mean values for antibody-positive and antibody-negative patients in each dosing regimen are shown in Table 12.

Table 12. Urinary GAG Levels ($\mu\text{g}/\text{mg}$ creatinine) at the End of Study by Antibody Status (Mean \pm SD)

Dosing Regimen	Antibody-Positive	Antibody-Negative
QW	176 \pm 77	99 \pm 38
QOW	237 \pm 94	136 \pm 49

Impact of Immunogenicity on Liver Volume Reduction: Percent reduction in liver volume was not different between antibody-positive and antibody-negative patients in QW treatment group (antibody-positive: $26.6\pm 9.5\%$; antibody-negative $25.5\pm 5.7\%$).

Impact of Neutralizing Antibody on 6MWT and Urinary GAG Level: Sera from 4 out of 32 radioimmunoprecipitation assay (RIP) confirmed anti-idursulfase antibody-positive patients were found to neutralize idursulfase activity *in vitro*. The incidence of antibodies that inhibit cellular uptake of idursulfase into cells is currently unknown. No apparent impact of neutralizing antibody on the clinical efficacy endpoint (6 MWT) was observed but urinary GAG clearance became impaired in 3 of 4 patients (Table 13).

Table 13. Changes in Six-Minute Walk Tests (6MWT) from Baseline and Urine GAG Levels at Week 53 for Patients with Neutralizing Antibodies

Patient ID	Treatment	Changes in 6MWT from Baseline (meters)	GAG Levels (µg/mg.creatinine)
024-020-0010	0.5 mg/kg QW	-40.5	284
024-059-0006	0.5 mg/kg QW	93	272
024-047-0003	0.5 mg/kg QOW	88.5	341
024-012-0007	0.5 mg/kg QOW	191	108

Impact of Immunogenicity on Infusion-Related Adverse Events (AEs): In TKT024, the rate of infusion-related AEs reported for the idursulfase QW group was higher among IgG antibody-positive patients than among IgG antibody-negative patients. The most commonly reported infusion-related AEs among the antibody-positive patients (at least 3 patients in a treatment group) were headache, hypertension, flushing, pruritus, rash, urticaria, and pyrexia. The sponsor states that the overall rates of infusion-related AEs decreased over time, regardless of antibody status. It is important, therefore, to consider these results with the longer-term results reported during TKT024EXT. Across both studies, the total number of antibody-positive patients for whom the idursulfase safety profile was evaluated was 45 patients. All 45 antibody-positive patients experienced 540 AEs during TKT024EXT compared with 765 AEs reported for 49 antibody-negative patients. Patients who were randomized to placebo during TKT024 switched to 0.5 mg/kg QW in the TKT024EXT phase experienced more AEs than idursulfase QW patients or idursulfase QOW patients, with 16 antibody-positive patients reporting 250 AEs, compared with 14 antibody-positive idursulfase QW patients reporting 113 AEs and 15 antibody-positive idursulfase QOW patients reporting 177 AEs. The higher rate of infusion-related AEs among patients receiving idursulfase for the first time in TKT024EXT was not an unexpected finding based on the experience in TKT024.

4.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

None of these extrinsic factors have been studied. These extrinsic factors are usually not considered influencing exposure of protein products which are given intravenously.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the

exposure-response relationships, describe the basis for the recommendation.

None.

3. Drug-Drug Interactions

a) Is there an in vitro basis to suspect in vivo drug-drug interaction?

Idursulfase metabolic degradation is assumed to mainly occur in cells via normal proteolytic mechanisms. No *in vitro* drug-drug interaction studies have been performed since P450 enzyme system is not expected to play any role in idursulfase biotransformation. As a form of naturally occurring I2S protein, idursulfase is 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.

Metabolism studies are not generally performed for biotechnology-derived products because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to protein metabolism, all of which involve biodegradation of the protein to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed".

b) Is the drug a substrate of CYP enzymes?

As idursulfase is a purified recombinant form of the naturally occurring enzyme I2S, it is an unlikely substrate of cytochrome P450 enzymes.

c) Is the drug an inhibitor and/or an inducer of CYP enzymes?

As idursulfase is a purified recombinant form of the naturally occurring enzyme I2S, it is unlikely an inhibitor and/or inducer of CYP enzymes.

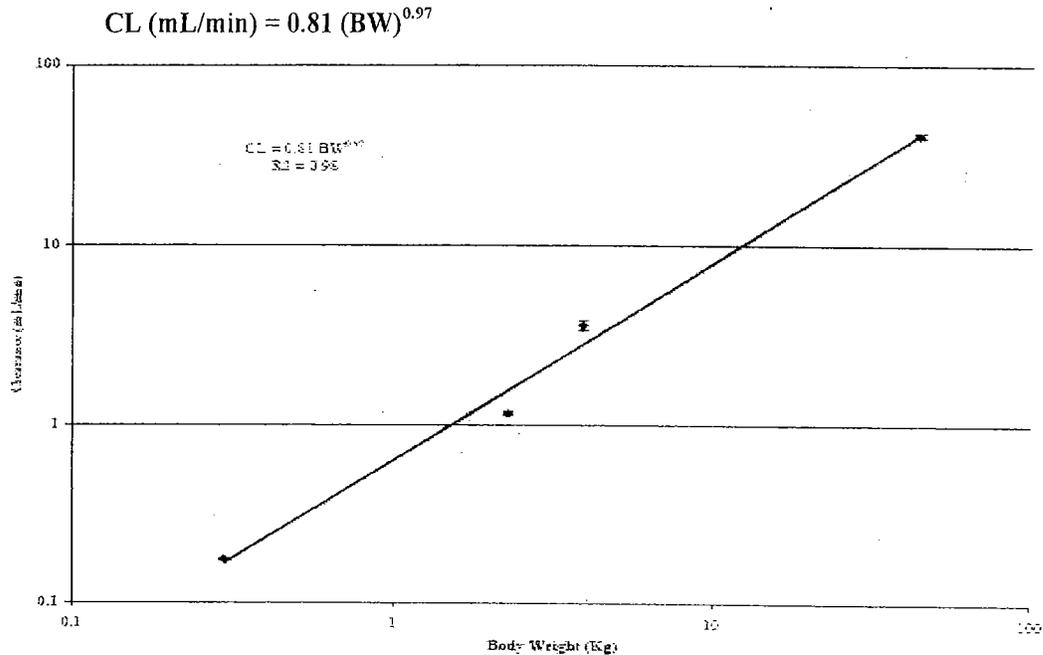
d) Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

As idursulfase is a purified recombinant form of the naturally occurring enzyme I2S, it is unlikely a substrate and/or inhibitor of P-glycoprotein transport processes.

e) Are there other metabolic/transporter pathways that may be important?

Serum Clearance (interspecies comparison): Data derived from rodents, small monkeys, larger monkeys and Hunter syndrome patients (Figure 30) support for a similarity in clearance mechanisms across species. Based on the glycosylation pattern of idursulfase and its action within cellular lysosomes, it is reasonable to assume that idursulfase serum clearance occurs primarily through cellular uptake via cell surface receptors and subsequently transport to cellular lysosomes.

Figure 30. Idursulfase Serum Clearance (mL/min) vs. Body weight



The allometric exponent for serum clearance of small molecules typically ranges from 0.6 to 0.8, with clearance typically occurring via liver metabolism and/or kidney excretion. As kidney and liver also have allometric scaling equations with exponents of 0.6 to 0.8, clearance of typical drugs is proportional to the internal organ size of liver or kidney and is not linearly proportional to body weight. The increased value of the allometric exponent for idursulfase serum clearance (0.97) indicates that, unlike other drugs, its serum clearance is linearly proportional to body weight. This is most likely due to the mechanism of clearance, via cell surface receptors such as the M6P receptor.

f) Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?

Idursulfase is indicated for enzyme replacement therapy. The label does not specify co-administration of another drug. Idursulfase-drug interactions are not expected due to the protein nature of the product and the mechanism of action. Neither *in vitro* interaction studies nor *in vivo* clinical idursulfase-drug interaction studies were conducted. Idursulfase-drug interaction studies may be requested if any evidence of such an interaction observed after treatment with idursulfase.

g) What other co-medications are likely to be administered to the target patient population?

Most commonly used classes of concomitant medications during Study TKT024 (>30% of patients in any treatment group) included anilides, glucocorticoids, anti-infectives, penicillins with extended spectrum, propionic acid derivatives, anesthetics for topical use, amides, selective beta-2-adrenoceptor agonists, fluoroquinolones, comb of penicillins including beta-lactamase inhibitors, macrolides, ACE-inhibitors, plain, cephalosporins and

related substances, heparin group, and aminoalkyl ethers.

h) Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Not applicable.

i) Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Not known.

j) Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Not Known.

4.5 General Biopharmaceutics

1. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Following completion of the manufacture of idursulfase for the pivotal Phase II/III study (TKT024), the scale of the manufacturing process was increased to commercial-scale and specific process improvements were implemented to increase manufacturing efficiency and robustness. The _____ scale was increased by approximately _____ and the _____ increased by approximately _____. There have been no formulation changes from the initiation of the pivotal efficacy and safety trial onward through commercialization.

Comparability evaluations included a physicochemical, nonclinical and clinical program. Biodistribution and pharmacodynamics (tissue and urine GAG levels) studies were conducted in normal mice and I2S knockout (IKO) mice. PK comparability study was performed in cynomolgus monkeys in a crossover design. Following completion of the comparability assessment, idursulfase produced by the commercial-scale process was introduced into the ongoing clinical studies TKT018 and TKT024EXT and PK data was collected in Study TKT024EXT. Since the activity of idursulfase is dependent upon internalization of the enzyme and subsequent transport into the lysosomes, PK comparability studies should be supported by biodistribution, and pharmacodynamic data (tissue and urinary GAG levels). The to-be-marketed product is considered comparable to the clinical trial product based on the results of biodistribution, tissue and urine GAG level reduction and PK comparability studies.

Comparability of Tissue Biodistribution: Tissue distribution patterns in normal mice were studied in normal mice and the results are summarized in Tables 14 and 15. Comparable tissue distribution patterns were established between the two materials in liver, spleen, and heart after 1.0 mg/kg single bolus IV injection of idursulfase.

Table 14. Tissue Biodistribution of Phase II/III and Commercial Scale Idursulfase in Normal Mice (Study TKX47, n=6 in each group, Data from sponsor's table 2.6.4-19)

Tissue	Mean % of Administered Dose (± 1 SD)		Protocol Criteria
	D303-025 (Phase II/III)	DP04-003 (Commercial Process)	
Liver	36.5 \pm 6.0%	30.2 \pm 3.0%	26-46%
Spleen	0.69 \pm 0.15%	0.62 \pm 0.14%	0.5-1.8%
Kidneys	0.56 \pm 0.07%	0.67 \pm 0.10%	0.4-0.7%
Heart	0.09 \pm 0.01%	0.10 \pm 0.02%	0.07-0.14%

*All animals were sacrificed 2 hours post-injection

Table 15. Tissue Biodistribution of Phase II/III and Commercial Scale Idursulfase in Normal Mice (Study TKX47, n=6 in each group, Data from sponsor's table 2.6.4-19)

Tissue	Mean % of Administered Dose (± 1 SD)		Protocol Criteria
	FD924-001 (Phase III)	FDB04-003 (Commercial Process)	
Liver	31.3 \pm 3.0%	31.4 \pm 3.3%	26-46%
Spleen	0.82 \pm 0.08%	0.76 \pm 0.19%	0.5-1.8%
Kidneys	0.64 \pm 0.14%	0.88 \pm 0.17%	0.4-0.7%
Heart	0.11 \pm 0.02%	0.12 \pm 0.01%	0.07-0.14%

*All animals were sacrificed 2 hours post-injection, 1.0 mg/kg single bolus IV injection

Comparability of Tissue and Urine GAG Level Reduction: Consistent with the comparable tissue biodistribution patterns, idursulfase Lots FD924-001 (Phase III clinical lot) and FDB04-003 (commercial lot) reduction of tissue GAG from liver, spleen, kidney, and heart were generally indistinguishable at two different dose levels of idursulfase following 5 weekly bolus IV injections (0.25 and 1.0 mg/kg dose levels, Figure 31). In addition, a potential dose-related decrease in tissue GAG levels was observed in the kidney (35.9 and 26.4 μ g/mg protein for FD924-001; 36.7 and 24.6 μ g/mg protein for FDB04-003; for the 0.25 and 1.0 mg/kg dose group, respectively). Similar urinary GAG level reduction was observed for both products (Figure 32).

Figure 31. Tissue GAG Reduction (IKO mice) Following 5 weekly 1.0 mg/kg Idursulfase bolus injections

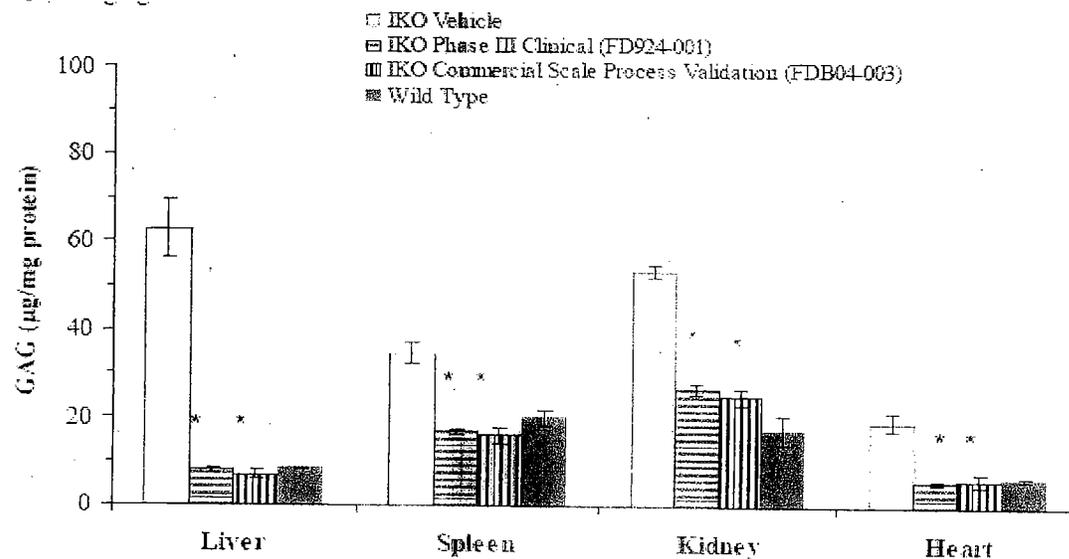
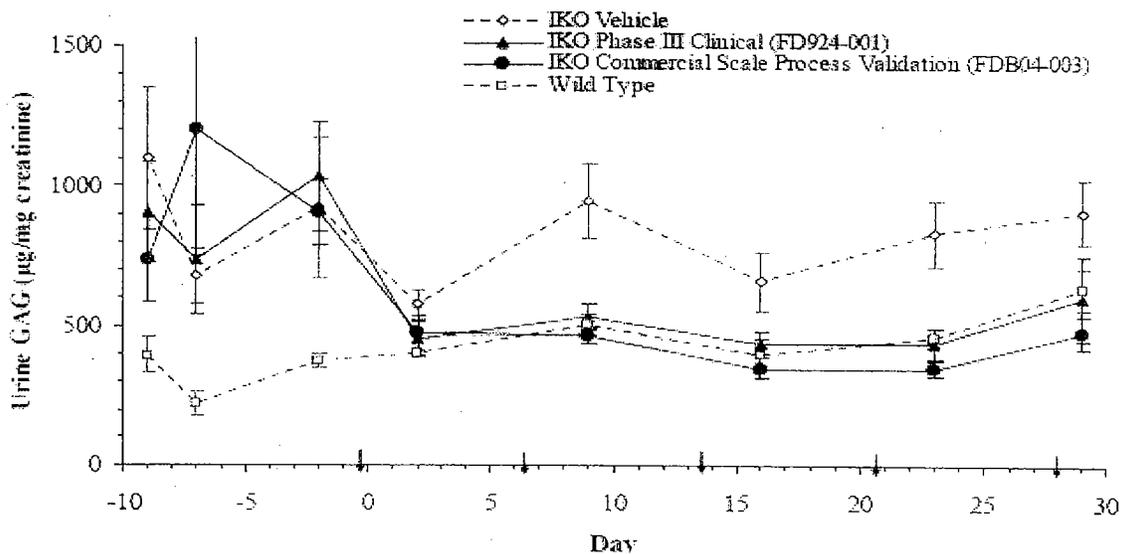


Figure 32. Urinary GAG Reduction (IKO mice) Following 5 weekly 1.0 mg/kg Idursulfase bolus injections



PK comparability in Monkey: Results from the PK study in cynomolgus monkey showed the serum clearance of both manufacturing processes followed essentially identical biphasic patterns, with serum concentrations of idursulfase in all animals being below the limit of quantitation (LOQ) by 24 hours after dosing. PK parameters were statistically indistinguishable between the two manufacturing processes (Table 16).

Table 16. Comparative Idursulfase PK Parameter Values of Commercial Lot (FDB04-003) and Clinical Lot (FD924-002) in Cynomolgus Monkeys (1 mg/kg, Crossover, Data taken from sponsor's Table 2.6.4-22)

Lot	C ₀ (µg/mL)	AUC _{last} (min*µg/mL)	t _{1/2} (λz) (min)	CL (mL/min/kg)	V _{ss} (%BW)
Clinical Lot	26.4±3.4	1376±226	187±42	0.75±0.14	7.3±1.4%
Commercial Lot	27.5±5.4	1398±251	177±41	0.75±0.17	6.7±1.3%
PK Parameter	Ratio Commercial Lot/Clinical Lot				
	Geometric Mean	90% Confidence Interval			
Normalized AUC _{last} Ratio	1.02	(0.98, 1.06)			
Normalized AUC _{0-inf} Ratio	1.02	(0.98, 1.07)			
Normalized C ₀ Ratio	1.04	(0.98, 1.10)			

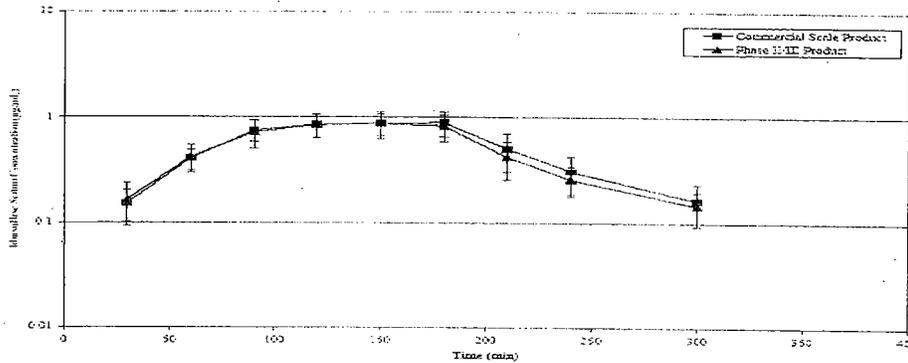
PK Comparability in Patients: A post-hoc PK comparability analysis was performed on the PK data from the 28 previously-placebo patients from TKT024, who received their first infusion of idursulfase during Week 1 of TKT024EXT (Table 17 and sponsor's Figure 2.7.2-13). The results of this analysis indicate that idursulfase produced by the Phase II/III (n=17 patients) and commercial (n=11 patients) processes was slightly outside the 90% confidence range (0.80-1.25 range for acceptance) for AUC_{last} (0.87 to 1.28) on the basis of a parallel-groups analysis. It is important to note that this assessment of comparability was performed on data generated from a study which was not designed as a comparability study. PK data in patients indicate that there were no significant changes in the pharmacokinetic profiles for the material evaluated during Phase II/III and that intended for commercial use.

Table 17. Comparison of Idursulfase PK Parameter Values of Commercial Lot (FDB04-003) and Phase II/III Lots (FD924-001, -002) in Placebo Patients Receiving 0.5 mg/kg QW in TKT024EXT (Data taken from sponsor's Table 2.7-8)

Lot	C _{max} (µg/mL)	AUC _{last} (min*µg/mL)	t _{1/2} (λz) (min)	CL (mL/min/kg)	V _{ss} (%BW)
Phase II/III	0.93±0.23	163±45	67±29	3.38±0.89	26.8±6.7%
Commercial	0.94±0.25	167±52	54±15	3.33±1.26	23.5±5.3%

Phase II/III (n=17), Commercial (n=11). The data excluded one antibody positive patient whose serum concentrations could only be determined by enzyme activity assay.

Figure 2.7.2-13 Mean Idursulfase Serum Concentration Following Initial Dose of Idursulfase (TKT024 Placebo Patients - Week 1 of TKT024EXT)



Note: 11 patients received commercial Drug Product and 17 patients received Phase II/III Drug Product.

Immunogenicity Incidence: Immunogenicity incidence was comparable between the commercial product and the clinical trial product as shown in Table 18.

Table 18. Immunogenicity Comparison between Commercial Product and Clinical Trial Product

Lot	Antibody Positive # of patients	Antibody Negative # of patients	Infusion Reactions # of patients
Phase II/III	n=9	n=8	n=3
Commercial	n=5	n=6	n=4

a) *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?*

Not applicable.

b) *If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?*

Not applicable.

c) *If the formulations are not BE, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation? (e.g., dosage adjustments may be made for injectables)*

Not applicable.

2. *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding*

administration of the product in relation to meals or meal types?

Not applicable. Idursulfase is administered by intravenous infusion and is not an orally administered agent.

3. When would a fed BE study be appropriate and was one conducted?

Not applicable.

4. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Not allocable.

5. Are there any unresolved issues with regard to comparability?

According to the CMC review team, there were some unresolved assay issues in regard to the *in vitro* comparability evaluation. The ELISA assay for serum idursulfase concentration measurement is acceptable for PK studies, but is not an adequate assay for potency measurement. A potency assay which

This assay must be validated and used in drug substance and product release and stability testing. The sponsor has been developing these assays.

For reasons discussed above, the potency assays using the are of limited utility and are not optimal for control in the manufacture of an approved therapeutic enzyme. Upon the request, the sponsor has been

developing and implementing an ————— potency assay using —————

Biochemical Comparability: the side-by-side comparability study should include the following tests:

4.6 Analytical

1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Idursulfase serum concentrations in serum were determined by an antigen-specific ELISA method. Idursulfase enzyme activity in biological samples was measured using the

2. *Which metabolites have been selected for analysis and why?*

None.

3. *For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?*

Not applicable because idursulfase is a protein.

4. *What bioanalytical methods are used to assess concentrations?*

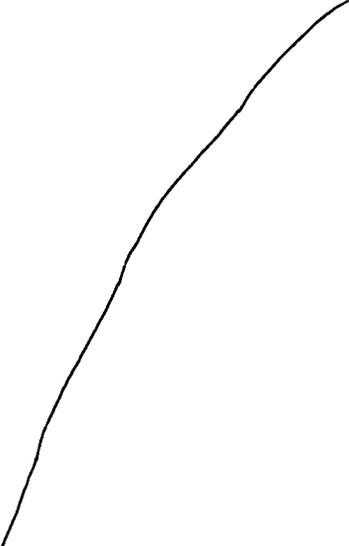
Assay for Quantification of Idursulfase Concentrations: An antigen-specific ELISA assay was used to determine idursulfase serum concentrations. In this assay —————



The assay demonstrates good reproducibility, with intra-assay variation (%RSD) <5.0% and inter-assay variation <12.0%. The assay results were linear ($R^2 = 0.988$) within the reportable range from 12.5 to 50.0 ng/mL idursulfase. Recovery of idursulfase spiked serum was constant at approximately 100% at all concentrations tested.

Serial dilutions of idursulfase Reference Standard were linear within the reportable range of the assay. Specificity of the coating and detection of antibodies approached 100%. Analyst effects were in the range of 9.1 to 13.3%, with day-to-day effects observed in the range of 0.4 to 4.0%. The assay is robust when performed as specified, being affected by <15% by variations in substrate incubation time, plate read lag time, pre-coating/blocking steps, capture IgG antibody coating, or plate readers. The limit of quantitation (LOQ), defined as the mean of the blank serum control sample plus 3 SD (standard deviations) was 0.126 $\mu\text{g/mL}$. The limit of detection (LOD) is defined as the lowest calibration standard (1.6 ng/mL) within the linear region of the calibration curve multiplied by the serum sample dilution (50), and is equal to 0.080 $\mu\text{g/mL}$.

Assay for Quantification of Idursulfase Activity: The method for quantification of idursulfase activity measures idursulfase enzyme activity in biological samples using the



5. *Are there any remaining assay issues?*

Assay Interference: In the PK analyses for patients from TKT024 and TKT024EXT, the majority had PK analyses performed using idursulfase concentration ($\mu\text{g/mL}$, based on ELISA); while a subset of antibody-positive patients (14 patients) had PK analyses performed using enzyme activity levels of idursulfase (mU/mL). Although enzyme activity levels were in the range expected for samples from this subset of patients, idursulfase concentrations were outside the expected ranges as measured by an antibody-based assay (ELISA), suggesting sample interference with the ELISA assay. However, all assay performance specifications, internal assay control limits, and system suitability requirements were met, indicating that factors external to actual assay performance impacted ELISA detection for this patient subset. Factors which may result in ELISA-based assay interference with these patient samples are under evaluation.

The potency assays using the _____ assay are of limited utility and are not optimal for control in the manufacture of an approved therapeutic enzyme. Upon the request, the sponsor has been developing and implementing an enzyme activity potency assay using a more physiologically relevant substrate and evaluating the feasibility of _____. The _____ assay should be replaced with an assay which _____

5 Labeling Recommendation

The sponsor has agreed on the following PK labeling statements:

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic characteristics of idursulfase were evaluated in several studies in patients with hunter syndrome. The serum concentration of idursulfase was quantified using an antigen-specific ELISA assay. The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 0.15 mg/kg to 1.5 mg/kg following a single 1-hour infusion of ELAPRASE. The pharmacokinetic parameters at the recommended dose regimen (0.5 mg/kg ELAPRASE administered weekly as a 3-hour infusion) were determined at Week 1 and Week 27 in 10 patients ages 7 to 27 years (Table 1). There were no apparent differences in PK parameter values between Week 1 and Week 27.

Table 1 Pharmacokinetic Parameters (Mean; Standard Deviation)

Pharmacokinetic Parameter	Week 1	Week 27
C _{max} (µg/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min*µg/mL)	206 (87)	169 (55)
t _{1/2} (min)	44 (18)	48 (20)
CL (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V _{ss} (%BW)	21.3 (8.2)	25.4 (8.7)

The other part of labeling is under negotiation.

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9 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling