

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

125151/0

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 24, 2006

FROM: Julie Beitz, MD

SUBJECT: Acting Office Director Memo

TO: BLA STN 125151 Elaprase (idursulfase);
Shire Human Genome Therapies, Inc (formerly Transkaryotic Therapies, Inc)

Elaprase is a formulation of idursulfase, a purified form of the human lysosomal enzyme iduronate-2-sulfatase (I2S) that is produced by recombinant DNA technology in a human cell line. Elaprase provides an exogenous source of I2S that is taken up into cells and transported into lysosomes where it hydrolyzes the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Elaprase has been evaluated in patients with Hunter syndrome (also known as Mucopolysaccharidosis II, or MPS II), an X-linked recessive disease caused by insufficient levels of I2S and accumulation of GAG in lysosomes leading to organomegaly and organ system dysfunction. This memo documents my concurrence with the Division of Gastroenterology Product's approval action for Elaprase, administered by weekly intravenous infusion, for use in patients with Hunter syndrome.

Efficacy

On November 23, 2005, Transkaryotic Therapies, Inc, submitted BLA STN 125151 which was granted a priority review. A request in May 2006 for additional information regarding the occurrence of anaphylactoid and angioedema reactions after idursulfase infusion prompted an extension of the review clock. Elaprase was evaluated in a multicenter, randomized, double-blind, placebo-controlled clinical trial involving 96 male Hunter syndrome patients. Patients aged 5 to 31 years were randomized 1:1:1 to receive either Elaprase 0.5 mg/kg every week, 0.5 mg/kg every other week, or placebo for 53 weeks. Patients had documented I2S deficiency and a percent predicted forced vital capacity (FVC) of <80%. Patients who were unable to perform pulmonary function testing or who could not follow protocol instructions were not enrolled. Compared to placebo-treated patients, those treated with weekly Elaprase performed significantly better when evaluated on a composite endpoint (change from baseline to week 53 in distance walked during a 6 minute walk test and in percent predicted FVC). Improvement was particularly notable in the 6 minute walk test, with patients on the weekly Elaprase regimen experiencing a 35 meter greater mean increase in the distance walked compared to placebo-treated patients. Additional findings in patients treated with weekly Elaprase included: marked reductions at week 53 in mean urinary GAG levels compared to persistent elevations in patients on placebo treatment; and sustained reductions through week 53 in liver and spleen volume compared with no such changes in patients on placebo treatment.

Safety

The safety profile of Elaprase at the recommended dose of 0.5 mg/kg administered by weekly intravenous infusion appears acceptable. Sixteen of 108 (15%) patients experienced infusion reactions involving at least 2 of 3 body systems: cutaneous, respiratory, or cardiovascular. Of these, 11 patients experienced significant reactions, including one patient with a life-threatening reaction comprised of respiratory distress, decreased oxygen saturation from 95% to 88%, and a brief seizure. This patient had a history of severe airways disease and sleep apnea requiring tracheostomy and was infused during a febrile illness. His baseline FVC was 15% of predicted. He recovered and tolerated 74 subsequent infusions with use of premedication. A Boxed Warning has been included in product labeling recommending the availability of appropriate medical support for all patients receiving Elaprase, and additional monitoring for patients with compromised respiratory function or acute respiratory disease.

Severe infusion-related reactions should prompt immediate discontinuation of the infusion and initiation of appropriate treatment. Following a severe reaction, subsequent infusions may be managed with a slower rate of infusion and administration of prophylactic medications such as antihistamines or corticosteroids. Using these measures, no patient in clinical studies discontinued study due to an infusion reaction. The WARNINGS section states that consideration should be given to delaying Elaprase infusion in patients with acute respiratory and/or febrile illness.

The most common adverse reactions requiring intervention were infusion-related reactions. The most frequent serious adverse reactions were hypoxic episodes. The frequency of infusion-related reactions decreased over time with continued Elaprase treatment.

Long-term studies in animals to evaluate carcinogenic or mutagenic potential have not been performed with Elaprase. Elaprase dosed up to 1.6 times the recommended human weekly dose had no effect on fertility and reproductive performance in male rats. Reproductive toxicology studies have not been conducted in pregnant female animals.

Fifty-one percent of patients in clinical trials treated with weekly Elaprase developed anti-idursulfase IgG antibodies. The incidence of IgE antibodies to idursulfase is unknown. Patients who developed IgG antibodies at any time had an increased incidence of infusion reactions, including hypersensitivity reactions. However, the relationship between the development of anti-idursulfase antibodies and clinical efficacy outcomes is unclear.

Tradename Review

The tradename "Elaprase" is acceptable.

Phase 4 Studies

The sponsor has committed to the following phase 4 studies:

- Implementation of a Hunter Outcome Survey, a voluntary patient survey to monitor long-term effects of Elaprase treatment for up to 15 years; survey data will be analyzed yearly and submitted to FDA in annual reports
- Evaluation of pharmacokinetics, pharmacodynamics, and safety in at least 18 Elaprase-treated pediatric patients 5 years of age and under
- Submission of the final study report from Study TKT018, an open-label maintenance study
- Completion and submission of the final study report from Study TKT024EXT, an open-label extension of Study TKT024 evaluating long-term safety and clinical outcomes
- Evaluation of patient samples from Study TKT024 and Study TKT024EXT in an inhibition-of-entry neutralization assay
- Monitoring of binding data and neutralizing antibody formation to assess the potential for loss of immunologic tolerance over time
- A Segment III prenatal and postnatal study in rats
- Evaluation of a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells
- Evaluation of the Conformation Specific Assay in terms of its ability to detect anti-idursulfase antibodies
- Validation of an IgE assay for the detection of anti-idursulfase antibodies
- Evaluation of genetic mutations of iduronate-2-sulfatase in patients enrolled in Study TKT024 and Study TKT024EXT, and correlation of this information with the level of endogenous enzyme levels, antibody response and clinical outcome
- Several CMC commitments including: development and implementation of an improved assay for drug product release and stability testing, and of an improved enzyme potency assay; a laboratory scale study to assess the commercial purification process of the drug substance; modifications to its drug product specifications related to a qualification study to assess its test method for, re-evaluation of analytical methods for the qualification and release of future reference standards; and a commitment to evaluate and revise as

necessary all acceptance criteria for release of drug substance and drug product manufactured at commercial scale.

Julie Beitz

7-24-06

Julie Beitz, MD
Acting Office Director,
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Division of Gastroenterology Products
HFD-180

Date: July 24, 2006
From: John Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Through: Brian Harvey, M.D., Ph.D., Division Director, DGP
Subject: Supervisory Summary Review of BLA/STN 125151/0
Idursulfase for Mucopolysaccharidosis Type II (Hunter Syndrome)
To: BLA 125151/0 File
Julie Beitz, M.D.; Director, ODE 3

John Hyde 7-24-06
Brian E. Harvey
7/24/06
I concur
with this approval
and this walking
Team Leader review

Identifying information

BLA/STN#: 125151
Applicant: Shire Human Genetic Therapies
Biologic name: Idursulfase
Proposed trade name: Elaprase
Submission date: November 23, 2005
Stamp date: November 23, 2005
PDUFA goal date: August 24, 2006
Formulation: 6 mg idursulfase (expressed as protein content) in 3 mL sterile solution, in single use glass vials for injection.
Proposed indication: — treatment of patients with Hunter syndrome.
Proposed regimen: 0.5 mg/kg intravenous infusion every week.

Recommended regulatory action: Approval under 21 CFR 601

Introduction and Regulatory Background

This BLA is for the new molecular entity Elaprase (idursulfase), an exogenous source of enzyme intended to treat deficiency of iduronate-2-sulfatase, the defect causing Mucopolysaccharidosis Type II (MPS II, also known as Hunter syndrome). The enzyme, produced by recombinant DNA technology, is one of the normal variants of the human enzyme. The product is proposed as a treatment for MPS II, and the proposed labeling describes treatment effects of improved walking

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distance, — reduced liver and spleen volumes, and reduced urinary glycosaminoglycans. The product is to be administered weekly at a dose of 0.5 mg/kg as an intravenous infusion over one to three hours.

Clinical studies of idursulfase were conducted by Transkaryotic Therapies (TKT) under BB-IND —, which was received on December 26, 2000. Orphan Designation was granted for this product on November 28, 2001, for the “long term enzyme replacement therapy for patients with MPS II (Hunter syndrome).” Fast Track Designation was granted to TKT on July 14, 2004, for the investigation of idursulfase for “ — in patients with Mucopolysaccharidosis Type II (MPS II) —

An End-of Phase-2 Meeting was held on December 10, 2002, at which TKT presented a proposal for a Phase 3 study using a primary endpoint that was a composite of a walk test, percent predicted forced vital capacity (%FVC), range of motion grading, and liver/spleen volumes. The FDA agreed with the principle of using a composite with a sum of ranks analysis, but the FDA did not agree with including a liver/spleen component, and the FDA requested justification for the criteria for a meaningful change in the range of motion criteria. In subsequent discussions, TKT decided to limit the composite endpoint to a combination of the six-minute walk test and %FVC.

A pre-BLA meeting was held on September 27, 2005, and the BLA submission was received on November 23, 2005. Although the clinical studies in the application did not address the objectives of the Fast Track designation, the application was granted Priority review status because it was viewed as representing, if approved, a significant improvement over currently available therapies. The PDUFA date was set as 5/25/06. A 74-day letter was sent February 3, 2006, identifying CMC deficiencies and requesting additional clinical information. During the course of the review, the Applicant withdrew the request for the proposed dosing of — leaving only weekly dosing. A major amendment, dated 5/12/06, containing additional clinical safety data and analyses of the safety data was received on 5/15/06, and this extended the PDUFA date to 8/24/06. During the course of the review, TKT was acquired by Shire Pharmaceuticals, so that the Applicant is now Shire Human Genetic Therapies (Shire HGT).

No Advisory Committee meeting was convened to discuss this application. However, an Endocrinologic and Metabolic Drugs Advisory Committee meeting was held on January 15, 2003, to discuss the application for Aldurazyme (laronidase) for treatment of Mucopolysaccharidosis Type I. The disease, treatment approach, and clinical evaluation for that application had important similarities to those for this application. The deliberations and recommendations of that committee meeting have direct relevance to the present application, as discussed below.

The primary review disciplines have all written review documents, which should be consulted for more specific details of the application. This memorandum summarizes selected information from these documents. The primary review documents relied upon are the following:

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Clinical Efficacy and Safety Review of J. Ku, dated 7/24/06.
Statistical Review and Evaluation of J. Derr, signed 5/3/06, signoff 5/9/06.
Clinical Pharmacology Review of H. Zhao, signed 5/18/06, signoff 5/19/06.
Pharmacology/Toxicology Review and Evaluation of R. Honchel, signed 4/21/06, signoff 5/7/06.
Supervisory Addendum to Pharmacology Review of J. Choudary, dated 5/7/06.
Pharmacology supervisory E-mail of A. Jacobs, dated 5/9/06, signed 5/9/06.
Immunogenicity Review of J. Wang, dated 7/29/06, signoff 7/3/06.
Product cell line review of L. Xu.
Cell banks review of E. Guan, dated 5/27/06.
Drug substance review of S. Beaucage, dated 5/9/06.
Potency assay review of Y. Fan, dated 7/17/06.
Microbiology product quality review of P. Hughes, dated 5/12/06, signoff 5/28/06.
Drug Product Review of H. Dickensheets, dated 7/18/06.
DSI Clinical Inspection Summary of D. Tesch, dated 4/3/06.
ODS/DDRE Risk Management Plan Review of A. Mackey et. al, dated 4/3/06.
ODS/DMETS Proprietary Name Review of T. Bridges, dated 1/18/06, signoff 4/18/06.
OSE/DMETS proprietary name re-review of T. Bridges, dated 6/28/06, signoff 6/30/06.
DDMAC labeling comment E-mail of M. Brony, dated 5/2/06, signoff 5/11/06.
Pulmonology consult of J. Kaiser, dated 3/29/06, signoff 4/4/06.
Pediatrics consult of H. Sachs, dated 4/21/06, signoff 4/24/06.

Clinical Background

Mucopolysaccharidosis Type II (MPS II, or Hunter syndrome) is a lysosomal storage disease, a category of diseases is characterized by a genetic deficiency in production or function of one or more the lysosomal enzymes. MPS II is X-linked. The deficient enzyme in MPS II is iduronate-2-sulfatase (I2S), which catabolizes the glycosaminoglycans (GAG's) dermatan sulfate and heparan sulfate. GAG's accumulates in lysosomes in cells throughout the body and causes injury to multiple organ systems.

There is considerable variability in the clinical manifestations of Hunter syndrome. Symptoms are not present at birth, but develop and progress as a child ages. All forms of the disease typically involve coarse facial features, joint stiffness and contractures, carpal tunnel syndrome, hepatosplenomegaly, cardiac and valvular disease, and progressive deafness. There is usually pulmonary function impairment secondary to deformities. In severely affected patients, the diagnosis is made at around 2 years, mental retardation is a feature, and life expectancy is 10 to 20 years. In less severely affected patients, mental development may be normal and life expectancy may be as long as into the 60's, but is highly variable.

Urinary GAG levels in MPS II patients (as in other mucopolysaccharidoses) are usually elevated to several times the normal levels; a finding that may be useful in screening for the condition. Diagnosis is confirmed by a blood test for I2S deficiency. Prenatal diagnosis is available if the mother is a carrier.

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The disorder is rare. The incidence is estimated between 1 in 132,000 and 1 in 65,000 live births. Because it is X-linked, it affects almost exclusively males; female cases are exceedingly rare.

There is no approved specific treatment for the disease. The currently available therapeutic options are primarily symptomatic and palliative. Bone marrow transplantation has been used to benefit in a few patients, but it is risky and has limited efficacy. There is a pressing need for new therapies.

Product Issues

The reader is referred to the various CMC reviews cited in the introduction above, and to the Immunogenicity Review by J. Wang.

Chemistry, Manufacturing, and Controls

The drug substance is manufactured by Shire HGT (formerly Transkaryotic Therapies) in Cambridge, MA. Final product manufacturing is done under contract by ———. Quality control testing is performed at a number of sites.

Idursulfase is produced by recombinant DNA technology in a human cell line using a ———

it undergoes sterile filtration and is filled into vials. The final product consists of 6 mg idursulfase in 3 mL sterile solution extractable from stoppered glass vial.

The controls for ——— of the cell banks were found to be adequate. With changes to the drug substance acceptance criteria and the Applicant's agreement to postmarketing commitments, the drug substance reviewer recommended approval. The potency assays were found to be deficient in that the specific activity assay used a substrate (heparin disaccharide) that was not physiologically relevant, and the ——— assay was not able to measure ———. The sponsor developed and agreed to use a ——— potency assay while the specific activity and ——— assays are being re-developed. This was considered adequate for approval. Drug product release specifications were changed by the Applicant at the reviewer's request. With those changes, and the Applicant's commitment to validate and add an ——— release test and to assess the sensitivity of the ——— test, the drug product reviewer recommended approval. Data from stability studies support stability of the commercial Drug Product through 24 months at 2 to 8 °C.

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The manufacturing process for the commercial product differs from that used to manufacture the clinical supplies used in the pivotal study TKT-024. In particular, the scale was increased from _____, certain controls were added and a _____ was eliminated. Comparability of

the clinical and commercial products was established with physico-chemical evaluation, nonclinical evaluation, and clinical evaluation. Pharmacodynamic activity in knockout mice and biodistribution in normal mice were found to be comparable. A two-way crossover PK study in cynomolgus monkeys had essentially identical PK parameters. A parallel PK comparison of the clinical and commercial material conducted in patients in the extension of the pivotal study found comparable PK parameters. The clinical material was judged comparable to the commercial scale material.

The manufacturing facilities were inspected and six Form 483 observations were made. The responses to these observations were deemed adequate, and the application was recommended for approval.

Immunogenicity

The Applicant initially evaluated patient samples for IgG anti-idursulfase antibodies using a validated ELISA assay. However, it was found that the assay failed to detect a majority of positive samples. During the review, the Applicant submitted data using a new, non-validated ELISA assay, the conformation-specific assay (CSA), which has far fewer false negatives compared to the radioimmunoprecipitation assay. Patient samples tested for IgE with a non-validated ELISA have all been negative. The applicant has not developed an assay for measuring antibody-mediated blockade of enzyme uptake into cells.

Using the CSA, the immune response rate was found to be 50%. Enzymatic-activity neutralizing antibody has been found in seven patients. The immunology reviewer noted that in several patients antibodies to the product appeared to interfere with improvement in the six-minute walk test, and that antibodies were associated with impaired urinary clearance of GAG. No association was noted between antibody development and reductions in liver or spleen volume.

More infusion-associated adverse events were seen in antibody positive patients than in antibody negative patients. Presence of antibodies appeared related to cardiac disorders, cyanosis, hypotension, isolated respiratory disorders, and skin disorders. Antibody positivity did not appear to be associated with infection rate or renal problems. All but one of the patients with a hypersensitivity reaction were positive for IgG antibodies.

Conclusions and Recommendations

The product reviewers recommended that the product is approvable with a 24-month expiration date. They felt the substrate (heparin disaccharide) used for the specific activity assay did not seem physiologically relevant, and the performance of the _____ assay was felt to be deficient. The reviewers recommend PMC's to improve these assays.

The product reviewers negotiated post-marketing commitments to use additional substance and product release specifications, to add substance and product release tests, to re-evaluate

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substance and product specifications, and to evaluate alternative methods and enhancements for assays used in production.

The immunogenicity reviewer concluded that the clinical assays needed adequate validation. He recommended post-marketing commitments to develop and validate a neutralizing assay capable of detecting antibodies that inhibit enzyme entry into cells, to evaluate patients samples from TKT024 and its extension using the neutralizing assay, to validate the CSA and IgE assays, to track binding and neutralizing antibodies over time, and to provide data correlating genetic mutation type and antibody response.

Pre-clinical Pharmacology and Toxicology Issues

The reader is referred to the Pre-clinical Pharmacology and Toxicology review by R. Honchel.

Safety pharmacology studies in monkeys using single IV doses up to 20 mg/kg showed no significant findings. Single-dose toxicity studies with doses up to 20 mg/kg in rats and monkeys found no significant adverse effects. A six-month, repeated-dose toxicology study in monkeys using weekly doses of up to 20 mg/kg IV found no significant adverse effects.

Pharmacologic activity of idursulfase was evaluated in studies using I2S knock out (IKO) male mice, an animal model of Hunter syndrome. These mice have little or no tissue I2S activity and they have increased concentrations of GAG in liver, spleen, kidney, and heart, and increased urinary GAG excretion. In several studies with this model, male IKO mice were treated with idursulfase at doses ranging from 0.1 mg/kg to 5 mg/kg. Idursulfase treatment reduced tissue GAG levels and urinary GAG excretion. A dose of 1 mg/kg/week was found to be able to reduce tissue and urinary GAG levels to values similar to those of wild type mice.

Reproductive toxicity studies were conducted on in male rats with IV dosing of 0, 0.5, 1.5 and 5 mg/kg twice weekly. No adverse effects on male fertility or reproductive performance were observed, and there were no effects on the early embryonic development of the pups of treated male rats. No studies of effects on female reproduction were conducted.

No genotoxicity or carcinogenicity studies were conducted.

Conclusions and Recommendations

The pre-clinical reviewer concluded that the product was approvable. He recommended that the pregnancy category should be C, and that the mutagenesis and fertility section of the labeling should refer to the animal studies by dose given.

The reviewer did not recommend requesting any post-marketing commitments to do animal studies.

The supervisory pharmacologist concurred with the approval recommendation and the pregnancy category of C. He noted the prior agreements that the development program could be limited to male animals, but recommended that the applicant be requested to commit to conduct the following postmarketing studies:

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- a) 26-week chronic IV toxicology study in female cynomolgus monkeys.
- b) Segment I. Fertility and reproductive performance study in female rats.
- c) Segment II. Teratology studies in rats and rabbits.
- d) Segment III. Prenatal and postnatal study in rats.

The Pharmacology/Toxicology Director also concurred with the approval recommendation and the pregnancy category of C. However, she recommended that only the Segment II. Teratology study be required.

In subsequent negotiations with the Applicant, and in recognition of the extreme rarity of Hunter syndrome in females, requirements for the other preclinical studies were dropped. However, the requirement for a Segment III. study was reinstated as a means of attempting to obtain some information relevant to neonatal exposure, because technical problems in the neonatal mouse study led to inconclusive results.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology review by H. Zhao.

Pharmacokinetic parameters for idursulfase were evaluated after single, one-hour infusions of 0.15, 0.5, and 1.5 mg/kg in the Phase 1/2 study TKT-008. The C_{max} was approximately dose-proportional, but AUC was greater than dose-proportional, suggesting that the serum clearance mechanism may become saturated at doses greater than 0.5 mg/kg. Elimination was biphasic with a terminal elimination half-life of less than 5 hours for all doses. Analysis of serum samples for enzyme activity showed that the time-activity curves paralleled the time-concentration curves, indicating that there was no selective inactivation in serum prior to uptake.

PK evaluation of repeated dosing was performed in TKT-008 and its extension. The PK parameters appeared similar to those for a single dose, but the number of patients was limited. In the Pivotal study, TKT-024, idursulfase was given at a dose of 0.5 mg/kg weekly or every other week. The PK parameters were estimated at Week 1 and at Week 27. In the 10 patients who were given the recommended dose (0.5 mg/kg weekly) and who also had evaluations at both time points, the PK parameters showed no apparent differences between Weeks 1 and 27. The basic PK parameters as estimated from 28 patients receiving 0.5 mg/kg in the pivotal study are C_{max} of 1.6 $\mu\text{g/mL}$, half-life of 50 minutes, clearance of 2.6 mL/min/kg, and volume of distribution of 19%.

Age was not found to have an effect on PK parameters. Because Hunter syndrome is X-linked, there were no male patients in the clinical studies, so any effect of gender on PK could not be evaluated. Also, there were too few non-white patients to permit a meaningful evaluation of the effect of race on PK parameters. The oldest patient was 31 years, so PK in the elderly was not assessed. There were no studies of idursulfase PK in renal or hepatic impairment; however, based on the known metabolism pathways, no effects would be expected. No drug-drug interaction studies were conducted.

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Anti-idursulfase antibodies developed in four of the ten patients who had PK assessments at Weeks 1 and 27 in study TKT024. Antibody development did not appear to have an effect on PK parameters. Urinary GAG concentration was used as a pharmacodynamic endpoint in these studies. Most patients showed a marked decrease from baseline values by the fifth week of treatment, but average values remained around the upper limit of normal. Mean urinary GAG levels stayed relatively constant after that time, although they tended to be somewhat higher in patients who developed antibodies, particularly in the every other week dosing group. Antibody seropositivity declined with continued exposure, and at 72 weeks, urinary GAG was similar in the antibody positive and antibody negative groups. The clinical pharmacology reviewer concluded that idursulfase remains physiologically active (as measured by urinary GAG excretion) in patients who form anti-idursulfase antibodies.

The clinical study material used substance from a _____ process, while the commercial material is made in a _____ process with certain other process changes. Based on comparable tissues biodistribution in normal mice, comparable tissue and urine GAG reduction in knockout mice, essentially identical PK parameters in cynomolgus monkeys, and similar PK parameter in a post-hoc parallel analysis of 28 patients in the pivotal study extension, the clinical pharmacology reviewer concluded that the to-be-marketed product can be considered comparable to the clinical trial product.

Conclusions and Recommendations

The Clinical Pharmacology reviewer drew the following conclusions:

- Pharmacokinetics were not entirely linear as the AUC at a dose of 1.5 mg/kg was greater than dose-proportional, suggesting serum clearance may become saturated.
- There were no apparent changes in PK parameters with repeated dosing.
- There were no apparent trends in pharmacokinetic parameters as a function of age.
- No effect of antibody development on PK parameters was observed, but antibody development was associated with somewhat lesser urinary GAG reduction. The affect of antibody positivity appeared to diminish with extended exposure.
- The clinical and commercial process materials are comparable.

The reviewer recommended labeling changes to present the PK parameters using only those patients with assessments at Weeks 1 and 27. The reader is referred to the review for specific details of the proposed labeling changes.

The reviewer did not recommend any postmarketing commitments for clinical pharmacology studies.

Clinical/Statistical Issues

The reader is referred to the Clinical review by J. Ku, and to the Statistical Review by J. Derr.

Phase 1/2 Study (TKT-008 and TKT-018)

The initial study of idursulfase was a randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, pharmacokinetics, and pharmacodynamics of idursulfase therapy. Following the initial six-month treatment period (Study TKT-008), patients were rolled over to an open-label extension study (Study TKT-018) for a total of two years of treatment.

A total of 12 patients participated. Patients were required to have a diagnosis of Hunter syndrome, but eligibility was not otherwise restricted. Patients were recruited in three cohorts of four patients, with each cohort assigned a different dose. Within each cohort, three patients were randomized to active treatment, and the fourth received placebo. At the conclusion of six months of treatment, patients were entered into an open-label extension (Study TKT-018) in which all patients received active treatment. All treatments were given by intravenous infusion every other week. Cohort 1 was assigned a dose of 0.15 mg/kg for the six-month blinded period, followed by 0.15 mg/kg for 12 months, followed by 0.5 mg/kg open-label for the remainder of the two-year treatment. Cohort 2 was assigned 0.5 mg/kg for the first six months, as well as 0.5 mg/kg for the remaining treatments. Cohort 3 was assigned 1.5 mg/kg for the first six months, followed by 1.5 mg/kg open-label for an additional six months, followed by 0.5 mg/kg for the remaining period.

Assessments consisted of collection of pharmacokinetic measurements; pharmacodynamic effects as assessed by liver and spleen volumes, pulmonary function testing, and monthly urinary GAG excretion measurements; and safety data. On the basis of this study the Applicant selected a dose of 0.5 mg/kg to carry forward into the Phase 3 study because pharmacodynamic effects of the 0.15 mg/kg dose appeared to be less, while the dose of 1.5 mg/kg did not appear to be consistently more effective but it produced more infusion reactions.

Phase 3 Study (TKT-024)

The sole Phase 3 study was a 96-patient randomized, double-blind comparison of two dosing regimens of Elaprase vs. placebo for 52 weeks to evaluate safety and effects of treatment on tests of physical performance. It also included PK/PD assessments and a variety of secondary and tertiary efficacy measurements.

To be eligible, patients were required to have a diagnosis of MPS II with clinical signs and symptoms, I2S enzyme activity less than 10% of the lower limit of normal, and normal activity of one other sulfatase. Patients were required to be males between the ages of 5 and 25 years, and needed to be capable of performing the required study testing. They were required to be able to stand six minutes and walk at least 5 meters. Percent predicted FVC at baseline was required to be less than 80%. Patients with history of tracheostomy or bone marrow transplant were excluded.

Patients were randomized, stratified by baseline disease severity and age category, with equal probability to:

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- Elaprase 0.5 mg/kg IV every week (EW),
- Elaprase 0.5 mg/kg IV every other week (EOW), or
- Placebo IV.

Treatment was given every week as an intravenous infusion lasting one to three hours. (Details of the infusion could be modified if the patient had infusion reactions – see the clinical review for specific information.) Patients randomized to EOW therapy received a placebo infusion on alternate weeks; placebo patient received weekly placebo infusions. At the conclusion of the study all patients were switched to open-label Elaprase 0.5 mg/kg IV weekly. Patients have continued receiving this dose through two years in the open-label extension study TKT-024EXT.

The primary endpoint was a composite of distance walked on a six-minute walk test (6MWT), and forced vital capacity as a percent of predicted (%FVC). The walk test and pulmonary function testing were conducted at baseline and every four months. The final evaluation was at Week 53. The outcome of the 6MWT at a given visit was defined as the better of two distances walked from two tests done a few days apart. The statistical analysis plan specified for the primary analysis an ANCOVA based on the sums of ranks of the changes in the two components between baseline and Week 53 using the ITT population. The ANCOVA variables were treatment group, study center, baseline age group, and baseline disease score category. The primary comparison was between the placebo and Elaprase weekly groups. Secondary variables were the individual components of the composite, range of motions scores, liver and spleen volumes, left ventricular mass index, and normalized urinary GAG. For ITT analyses, missing values were imputed by carrying the last observation (or rank) forward.

A total of 96 patients participated at nine sites (four in the U.S., three in England, and one each in Germany and Brazil). There were 32 patients randomized to each treatment group. For the group as a whole, the mean age was 14.2 years, mean weight 36 kg, all were male, and 82% were white. Mean age at symptom onset was 28 months, and mean duration of disease prior to study entry was 9.4 years. Mean baseline 6MWT distance was 395 m (range 49 to 565 m), and mean %FVC was 55% (range 16% to 79%). Subjects in the three treatment groups were similar at baseline. Although the placebo patients tended to be younger and smaller than the other groups, and the Elaprase weekly patients tended to have an older age at diagnosis, there was considerable overlap between the groups (see the Clinical Review or the Statistical Review for details).

With the exception of two patients who died during the study, collection of the primary endpoint data was complete. One patient in the Elaprase weekly group died 12 days after his first and only dose. One placebo patient died after Week 34. Compliance with treatment was high: apart from the two who died, all patients received at least 80% of required infusions, and no patient missed more than three consecutive infusions.

The p-value was 0.0049 for the primary analysis, which was a comparison of the Elaprase weekly and placebo groups using ANCOVA with the rank sum composite of changes in 6MWT and %FVC. While providing a valid hypothesis test, the analysis does not provide a clinically interpretable estimate of the treatment effect because it is a composite score and it replaces measured values with ranks. Therefore, the individual components were examined using more conventional analyses as shown below:

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**Distance Walked in Six-Minute Walk Test Mean Change from Baseline to Week 53
ANCOVA Analysis: ITT Population (from BLA)**

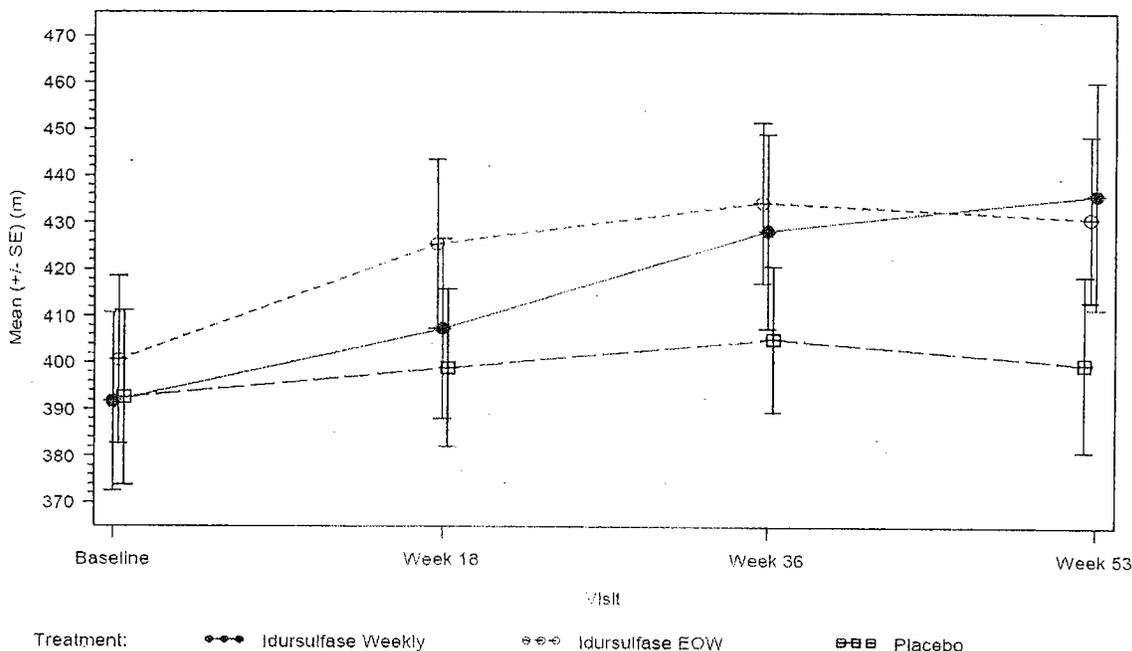
Treatment Comparison	N	Total Distance Walked in 6MWT (m)			Adjusted 95% CI ^a	p-value ^b
		Mean (SE)		Week 53 Change		
		Baseline	Observed			
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.95 (10.89)	7.66, 62.52	0.0131
Placebo	32	392.47 (18.72)	7.28 (9.46)	1.86 (11.84)		
Difference				35.09 (13.69)		
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	25.88 (10.67)	-2.31, 49.91	0.0732
Placebo	32	392.47 (18.72)	7.28 (9.46)	2.08 (11.35)		
Difference				23.80 (13.03)		
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.13 (12.46)	-17.72, 44.09	0.3963
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	22.95 (12.69)		
Difference				13.19 (15.43)		
All Idursulfase vs Placebo						
All Idursulfase	64	396.09 (13.01)	37.30 (7.99)	30.76 (8.39)	5.44, 54.14	0.0171
Placebo	32	392.47 (18.72)	7.28 (9.46)	0.97 (11.55)		
Difference				29.79 (12.25)		

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; 6MWT= 6-minute walk test; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

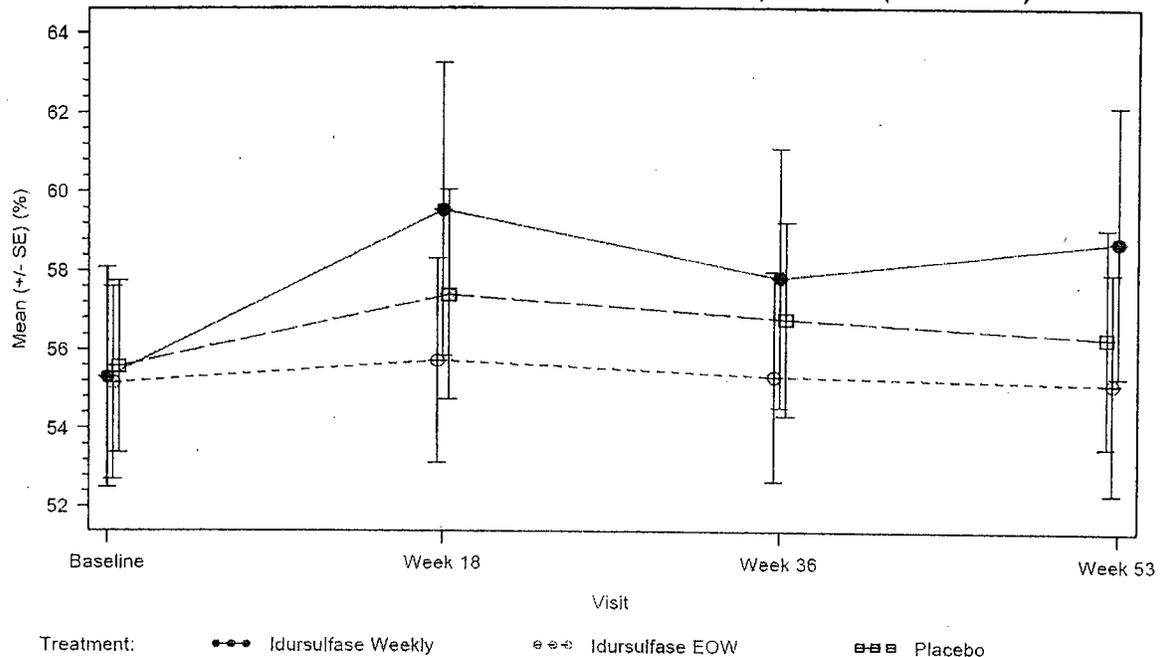
^b p-value for treatment difference based on ANCOVA model containing region, treatment, baseline 6MWT severity score (3 levels), and baseline patient age (3 levels).

Mean Distance Walked in 6MWT by Visit: ITT Population (from BLA)



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Mean Percent Predicted FVC by Visit: ITT Population (from BLA)



**Percent Predicted FVC Mean Change from Baseline to Week 53
ANCOVA Analysis: ITT Population (from BLA)**

Treatment Comparison	N	Observed % Predicted FVC Mean (SE)			Adjusted 95% CI ^a	p-value ^b
		Baseline	Week 53 Change			
			Observed	Adjusted ^a		
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.29 (1.73)	-0.27, 8.83	0.0650
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.99 (1.85)		
Difference			4.28 (2.27)			
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.37 (1.59)	-4.04, 4.28	0.9531
Placebo	32	55.57 (2.18)	0.75 (1.70)	-1.49 (1.67)		
Difference			0.12 (2.08)			
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.82 (1.64)	-0.79, 7.76	0.1079
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.66 (1.68)		
Difference			3.49 (2.13)			
All Idursulfase vs Placebo						
All Idursulfase	64	55.22 (1.85)	1.72 (1.12)	0.00 (1.21)	-1.65, 5.87	0.2675
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.11 (1.69)		
Difference			2.11 (1.89)			

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment and baseline % predicted FVC, baseline patient age (3 levels) and baseline disease score (3 levels).

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For the primary comparison of the Elaprase weekly group vs. placebo, the Elaprase group averaged 37 meters greater gain in the 6MWT over the course of the year. After adjustment, the estimated treatment effect is 35 meters. The effect was nominally statistically significant at $p=0.013$. The benefit in distance walked for the EOW group was not as clear. The effect of Elaprase on change in %FVC was not statistically significant for any of the comparisons.

Following discussions with the Applicant the recommended presentation of the study results in the labeling is as shown in the following table:

Clinical Study Results

	ELAPRASE Weekly n=32 ^a			Placebo n=32 ^a			ELAPRASE Weekly – Placebo
	Baseline	Week 53	Change ^b	Baseline	Week 53	Change ^b	Difference in Change
Results from the 6-Minute Walk Test (Meters)							
Mean ± SD	392 ± 108	436 ± 138	44 ± 70	393 ± 106	400 ± 106	7 ± 54	37 ± 16 ^c 35 ± 14 ^d ($p=0.01$)
Median	397	429	31	403	412	-4	
Percentiles (25 th , 75 th)	316, 488	365, 536	0, 94	400, 469	361, 460	-30, 31	
Results from the Forced Vital Capacity Test (% of Predicted)							
Mean ± SD	55.3 ± 15.9	58.7 ± 19.3	3.4 ± 10.0	55.6 ± 12.3	56.3 ± 15.7	0.8 ± 9.6	2.7 ± 2.5 ^c 4.3 ± 2.3 ^d ($p=0.07$)
Median	54.9	59.2	2.1	57.4	54.6	-2.5	
Percentiles (25 th , 75 th)	43.6, 69.3	44.4, 70.7	-0.8, 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	
^a One patient in the placebo group and one patient in the ELAPRASE group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analysis ^b Change, calculated as Week 53 minus Baseline ^c Observed mean ± SE ^d ANCOVA model based mean ± SE, adjusted for baseline disease severity, region, and age.							

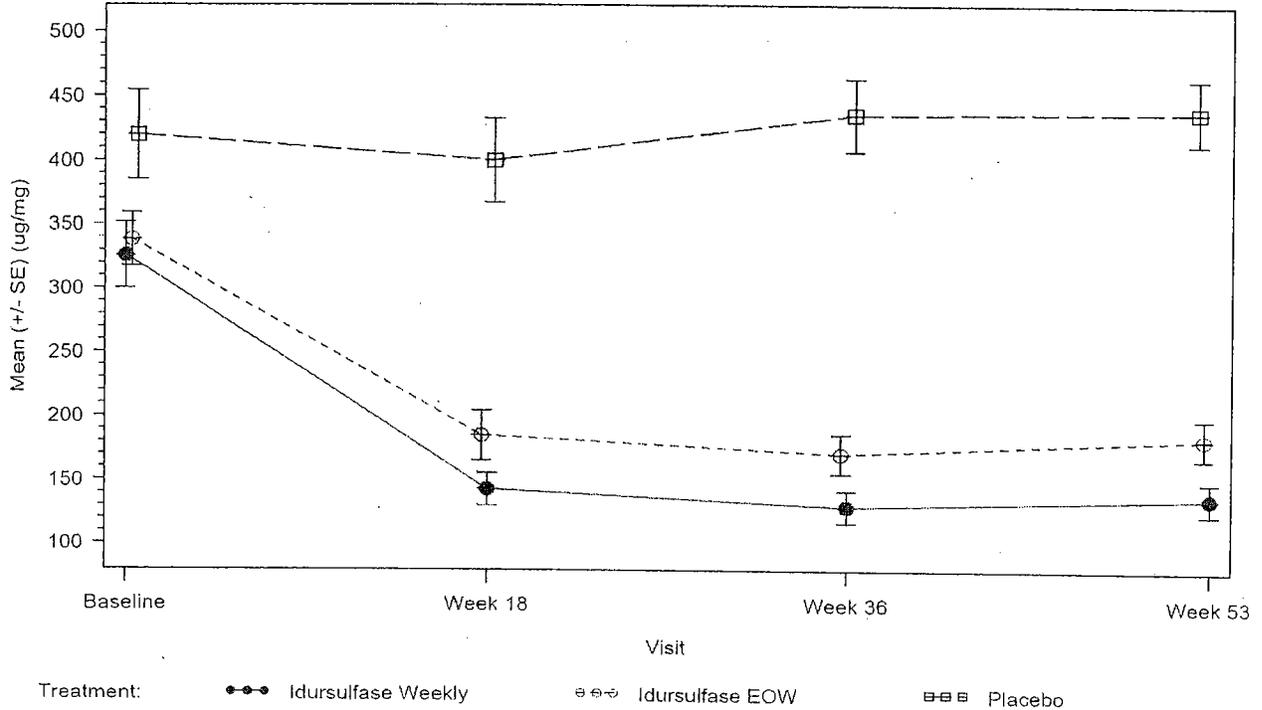
The changes in urinary GAG and liver and spleen volumes, while of uncertain clinical meaningfulness, showed definite evidence of a pharmacodynamic treatment effect. Urinary GAG in the Elaprase weekly group fell markedly and averaged near the upper limit of normal (which is 126.6 µg/mg creatinine), although half of the patients had values that remained above normal.

Liver volume averaged just over 1200 mL for the study population at baseline, and 3/4 of livers were considered to be abnormally enlarged. Liver volumes fell by about one fourth in both of the Elaprase groups but remained essentially unchanged in the placebo group. The Clinical Review also presents a shift table analysis showing a substantial difference between the placebo and Elaprase groups in rates of reverting to normal liver volume. Spleen volumes averaged about 280 mL at baseline, and less than 1/4 of the spleens were considered abnormally enlarged. Spleen volumes fell by about one fourth in the Elaprase weekly group (and by about one fifth in

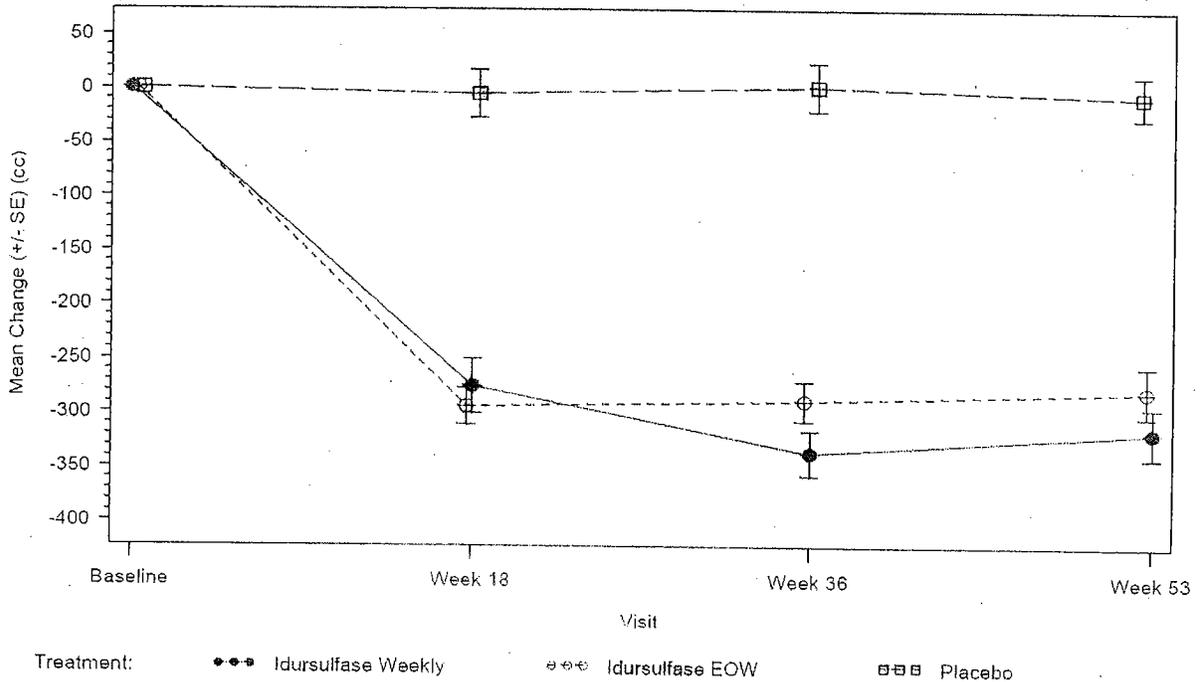
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the EOW group), but the effects seen in the shift table analysis were not striking. Summary pharmacodynamic results are presented in the following graphs:

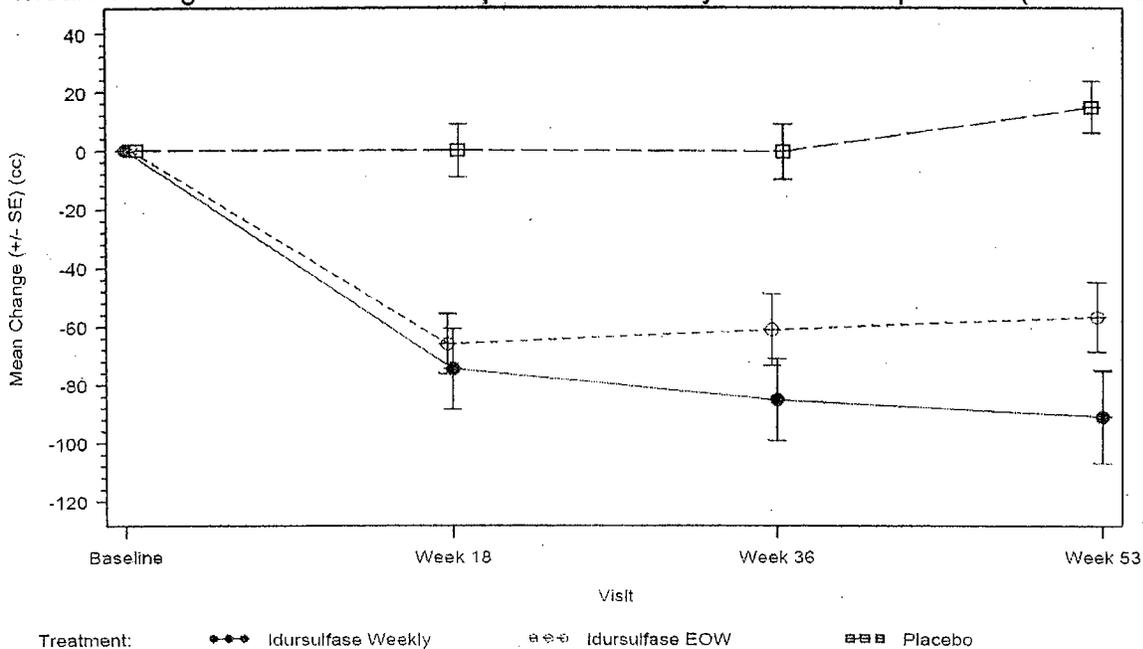
Mean Normalized Urine GAG Levels) by Visit: ITT Population (from BLA)



Mean Change from Baseline in Liver Volume by Visit: ITT Population (from BLA)



Mean Change from Baseline in Spleen Volume by Visit: ITT Population (from: BLA)



The dataset for the pivotal study was small, so that the ability to look at any special subpopulations is severely limited. Because the disease is X-linked, all patients were male, so there was no analysis by gender. There were too few non-white subjects to permit meaningful analyses of any race effects.

The clinical sites in Houston, TX, Chapel Hill, NC, and Porto Alegre, Brazil, were inspected. No discrepancies between source documents and data listings were noted, and no Forms 483 were issued for any of these sites. Data were deemed acceptable for consideration by the review division.

Safety

The reader is referred to Dr. Ku’s review for full details of the safety analysis. The safety database from consisted of the 108 patients enrolled in the two controlled studies and their extensions (12 were enrolled in TKT-001, and 96 were enrolled in TKT-024). All but one of these patients had at least one dose of Elaprase, and 106 had a significant period of exposure.

Identification of drug-related toxicity is challenging because MPS II patients have substantial underlying morbidity, so that serious adverse events would not be unexpected in the course of a year-long study, and the systematic collection of adverse events in a placebo comparison group was limited to essentially 32 patients for one year. Dr. Ku reviewed reports of all deaths and non-fatal serious adverse events, and she performed additional, treatment-blinded categorization

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analyses of all adverse events reported in the clinical studies, pooling events in related groups to increase the sensitivity of the analysis.

Five deaths were included in the safety database. One was in a patient who had only received placebo and who died of pneumonia. Of the four patients who were receiving Elaprase, all had significant respiratory disease at baseline, and the deaths were related to respiratory failure. The investigators did not report any of these events as related to treatment. In the clinical reviewer's assessment, attribution of these deaths to underlying disease and/or undercurrent respiratory infections appeared reasonable, but a possible relationship to study drug could not be ruled out.

The principal safety finding concerned the infusion reactions associated with Elaprase. Significant and possibly serious infusion reactions could be expected based on experience with other therapeutic proteins. Although no patient was found to develop IgE antibodies, the Elaprase safety data contained serious adverse events associated with infusion reactions. In one notable case a patient became hypoxic and cyanotic during an infusion, had a seizure, and lost consciousness. In the course of the safety review, the clinical reviewer recognized that several possible anaphylactoid reactions had not been identified as such because the Applicants analysis had not adequately identified cases by correlating infusion reaction symptoms to identify constellations of events that could suggest anaphylaxis. Also, certain vital sign changes during infusions, such as decreases in blood pressure, had been recorded but not identified as adverse events. This led to a request to the Applicant for a re-analysis of the safety data to identify potential cases of anaphylaxis, and to extend the safety cutoff date for identifying cases for the analysis. The response to this request constituted the major amendment. From analysis of these data the clinical reviewer concluded that the adverse events associated with infusion reactions were serious enough to recommend a boxed warning for hypersensitivity reactions.

From her recoding of the adverse events, the clinical reviewer proposed a revision of the table of common adverse events in which similar adverse events were combined. Also, to eliminate reporting of common non-serious adverse events unlikely to be related to treatment, the proposed table eliminated events that were not more common in the Elaprase-treated patients.

The size of the clinical study patient population is limited by the rarity of the disease. With a sample of 106 patients who received more than nominal exposure, an adverse event would need to affect at least 2.8% of the MPS II population in order to have a 95% probability of having being seen in this clinical program. This limitation underscores the importance of asking Shire HGT to conduct a post-marketing registry study for systematic collection of additional safety data.

Clinical Consults

Pulmonology

The pulmonary consultant (J. Kaiser) noted that the treatment difference in %FVC of 4.28 points was not statistically significant. He also commented that there was no difference in %FVC that has been validated to show a clinically meaningful treatment effect. Concerning the endpoint of absolute FVC, he noted that differences could be affected by growth, but that the absolute FVC

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results were consistent with the %FVC results. He felt it would be difficult to ascribe FVC changes to the observed changes in organomegaly, and that other pulmonary physiologic endpoints did not provide support for the FVC component of the primary endpoint. He recommended that the %FVC should be described in the labeling because it was a part of the primary endpoint, but the clinical significance was uncertain. He also recommended obtaining data on the long-term effects by of idursulfase on pulmonary function by periodic pulmonary function testing.

Pediatrics

The pediatric consultant (H. Sachs) noted that a complication of using %FVC could be the difficulties of measuring height in this patient population. The consultant recommended that labeling indicate effectiveness for _____ and possibly decreasing hepatosplenomegaly _____ The consultant recommended that labeling should not imply _____ and it should indicate that safety and effectiveness have not been established in children less than 5 years. The consultant also recommended that postmarketing commitments should include study of treatment in patients less than five years, and that efficacy could likely be extrapolated on the basis of pharmacokinetics, pharmacodynamics, and safety. The ability to prevent PE tubes, respiratory infections, adenoidectomy, and hearing loss should be explored. Growth should be measured in a standardized manner. For all pediatric patients there should be systematic collection of information on long-term outcomes including neurocognitive function.

Clinical Conclusions and Recommendations

The clinical reviewer concluded that the application provided adequate evidence of efficacy and an acceptable safety profile and was approvable with an indication of improving walking capacity. The reviewer recommended that a boxed warning be added to alert caregivers of the potential for serious hypersensitivity reactions and to have appropriate supportive care readily available. The reviewer recommend clinical post-marketing commitments to conduct a long-term registry study, to provide long-term safety data from the ongoing extension studies, and to obtain pharmacokinetic, pharmacodynamic, and safety data on patients 5 years and younger.

Advisory Committee

This application was not presented to an Advisory Committee. On January 15, 2003, the Endocrinologic and Metabolic Drugs Advisory Committee held a discussion of the application for Aldurazyme (laronidase), an exogenous enzyme therapy for Mucopolysaccharidosis Type I that was approved on April 30, 2003. There are many similarities between the applications for Elaprase and Aldurazyme regarding the nature of the disease, the approach to therapy, and the clinical studies.

For the Aldurazyme submission, the principal clinical data came from a six-month, placebo-controlled study. Urinary GAG was markedly reduced but not normalized. There was a statistically significant difference ($p=.03$) for the modest increase of 4.5 percent predicted in forced vital capacity (FVC) and difference in a six-minute walk test of 38 meters ($p=.066$, or

Regulatory conclusions

In the opinion of this reviewer, the data in this application support approval of Elaprase under 21 CFR 601 for treatment of MPS II at a dosage regimen of 0.5 mg/kg intravenously every week, and provide a basis for construction of product labeling that contains the essential scientific information needed for the safe and effective use of Elaprase.

The product labeling should identify that the benefit was reflected as improvement in walking capacity. Because pulmonary function was a component of the composite primary endpoint, results should be presented in the Clinical Studies section. However, the labeling should identify that the changes in that component were not statistically significant,

The labeling should contain a warning about the risks and management of infusion reactions. Because of the seriousness of some of these reactions, there should be a boxed warning for hypersensitivity reactions that instructs users to have appropriate medical support readily available and to provide additional monitoring for patients with compromised respiratory function. The labeling should indicate the lack of information about safety and efficacy for children younger than five years. The Precautions section should list the pregnancy category as C. The Storage section should include instructions to protect the product from light. Other modifications to the labeling should be made along the lines recommended in the various discipline reviews and as negotiated with the Applicant.

Shire has agreed to appropriate and adequate post-marketing commitments as described above. These include commitments to conduct a long-term registry study to collect additional safety and efficacy data and to provide long-term outcome data from ongoing open-label studies; to collect pharmacokinetic, pharmacodynamic, and safety data in patients 5 years and under; to collect additional clinical data using binding and neutralizing antibody assays; to conduct a Segment III study; to do additional developmental work on several antibody assays; and to make various improvements in the manufacturing processes.

CLINICAL REVIEW

Application Type	BLA
Submission Number	STN 125151
Submission Code	N0
Letter Date	November 23, 2005
Stamp Date	November 23, 2005
PDUFA Goal Date	August 24, 2006
Reviewer Name	Joanna W. Ku MD
Through	John Hyde, MD PhD Clinical Team Leader
Review Completion Date	July 24, 2006
Established Name	Idursulfase
(Proposed) Trade Name	Elaprase™
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Shire Human Genetic Therapies, Inc.
Priority Designation	Priority
Formulation	2mg/mL IV solution
Dosing Regimen	0.5 mg/kg IV weekly
Indication	Mucopolysaccharidosis II
Intended Population	Mucopolysaccharidosis II

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

The reviewer recommends approving this application.

1.2 RECOMMENDATION ON POST-MARKETING ACTIONS

1.2.1 Risk Management Activity

None warranted at the present time.

1.2.2 Required Phase 4 Commitments

The Applicant has committed to the following Phase 4 studies:

- Implementation of a Hunter Outcome Survey, a voluntary patient survey to monitor long-term effects of ELAPRASE™ treatment for up to 15 years; survey data will be analyzed yearly and submitted to FDA in annual reports.
- Evaluation of pharmacokinetics, pharmacodynamics, and safety in at least 18 ELAPRASE™ treated pediatric patients 5 years of age and under.
- Submission of the final study report from study TKT018, an open-label maintenance study.
- Completion and submission of the final study report from study TKT024EXT, an open-label extension of study TKT024 evaluating long-term safety and clinical outcomes.
- Evaluation of patient samples from study TKT024 and TKT024EXT in an inhibition-of-entry neutralization assay.
- Monitoring of binding data and neutralizing antibody formation to assess the potential for loss of immunologic tolerance over time.
- Conducting a Segment III prenatal and postnatal study in rats.
- Evaluation of a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells.
- Evaluation of the Conformation Specific Assay in terms of its ability to detect anti-idursulfase antibodies.
- Validation of an IgE assay for the detection of anti-idursulfase antibodies.
- Evaluation of genetic mutations of iduronate-2-sulfatase in patients enrolled in studies TKT024 and TKT024EXT, and correlation of this information with the level of endogenous enzyme levels, antibody response and clinical outcome.

1.2.3 Other Phase 4 Requests

The Applicant has been asked by the FDA Division of Drug Risk Evaluation (DDRE) to submit reports of anaphylactic events with serious outcomes as 15-Day reports, to Adverse Event Reporting System (AERS) for 12 months after approval.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

ELAPRASE™ is a formulation of idursulfase, a purified form of the human lysosomal enzyme iduronate-2-sulfatase (I2S), which is produced by recombinant DNA technology in a human cell line. Idursulfase provides an exogenous source of I2S that is taken up into cells and transported into lysosomes where it hydrolyzes the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Idursulfase has been evaluated in patients with Hunter syndrome (also known as Mucopolysaccharidosis II, or MPS II), an X-linked recessive disease caused by insufficient levels of I2S and accumulation of GAG in lysosomes leading to organomegaly and organ system dysfunction. Idursulfase is a new molecular entity being proposed as an enzyme replacement therapy for the treatment of Hunter syndrome.

Four clinical studies were performed. These studies are:

- 1) Study TKT008, n=12
- 2) Study TKT018, n=12
- 3) Study TKT024, n=96
- 4) Study TKT024EXT, n=94

Study TKT024 was the pivotal clinical study submitted in support of the approval of idursulfase, and included safety and efficacy outcomes measures that permitted substantive clinical review. Study TKT024 was a multi-center, international, double-blind, placebo-controlled, safety and efficacy study performed in 96 male patients with Hunter syndrome. The study included patients with a documented deficiency in iduronate-2-sulfatase enzyme activity who had a percent predicted forced vital capacity (%-predicted FVC) less than 80%. The patients' ages ranged from 5 to 31 years. Patients who were unable to perform the appropriate pulmonary function testing, or those who could not follow protocol instructions were excluded from the study. Patients received idursulfase 0.5 mg/kg every week (n=32), idursulfase 0.5 mg/kg every other week (EOW) (n=32), or placebo (n=32). The study duration was 53 weeks. The primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to week 53 in distance walked during a 6 Minute Walk Test (6-MWT) and the ranks of the change in %-predicted FVC.

Patients who finished Study TKT024 continued on an open-label, uncontrolled, extension phase of the study, titled TKT024EXT. When the study is completed, these patients will provide at least additional 2 years of long-term pharmacodynamic and safety data associated with chronic idursulfase treatment.

The data submitted from the two remaining studies, TKT008, and its uncontrolled study, extension study TKT018, were of lesser importance due to their small sample size (n=12), and short duration (study TKT008 was a 26 week study). These limited studies primarily provided additional evidence of the pharmacodynamic effects and safety profile.

1.3.2 Efficacy

In the pivotal study TKT024, the primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to Week 53 in distance walked during a 6 Minute Walk Test (6-MWT) and the ranks of the change in %-predicted FVC. This two-component composite primary endpoint differed statistically significantly between the three groups, and the difference was greatest between the placebo group and the weekly treatment group (weekly idursulfase vs. placebo, p=0.0049). Examination of the individual components of the composite score showed that, in the adjusted analysis, the weekly idursulfase-treated group experienced a 35 meter (38 yards) greater mean increase in the distance walked in six minutes compared to placebo. The changes in %-predicted FVC were not statistically significant.

Measures of bioactivity were urinary glycoaminoglycans (GAG) levels and changes in liver and spleen size. Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean urinary GAG levels were markedly reduced in the idursulfase weekly group, although GAG levels still remained above the upper limit of normal in half of the idursulfase-treated patients. Urinary GAG levels remained elevated and essentially unchanged in the placebo group. Sustained reductions in both liver and spleen volumes were observed in the idursulfase weekly group through week 53 compared to placebo. There were essentially no changes in liver and spleen volumes in the placebo group.

1.3.3 Safety

Identification of drug-related toxicity is challenging because Hunter syndrome patients have significant underlying morbidity so that serious adverse events would not be unexpected in the course of a 53-week study, and the systemic collection of adverse events in a placebo comparison group was limited to essentially 96 patients for 53 weeks.

The safety results from the idursulfase clinical development program are notable for the following safety signals, and they are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity reactions, i.e., anaphylactic/anaphylactoid reactions, related to idursulfase infusion was noted late in the initial review cycle. Some of these hypersensitivity reactions were life-threatening, which included: hypoxia, cyanosis, respiratory distress, hypotension, seizure, and loss of consciousness. In clinical trials with idursulfase, 16/108 patients (15%) experienced infusion reactions during 26 of 8274 infusions (0.3%) that involved adverse events that were anaphylactic/anaphylactoid-like. One of these episodes occurred in a patient with tracheostomy and severe airway disease, who received an idursulfase infusion while he had a pre-existing febrile illness, and then experienced respiratory distress, hypoxia, cyanosis, and seizure with loss of consciousness. It is recommended that a black-boxed warning appear in the product

labeling to alert physicians and patients of this noteworthy safety signal. Because of the potential for severe infusion reactions, appropriate medical support should be readily available when idursulfase is administered. When severe infusion reactions occurred during clinical studies, subsequent infusions were managed by use of antihistamines and/or corticosteroids prior to or during infusions, a slower rate of idursulfase administration, and/or early discontinuation of the idursulfase infusion if serious symptoms developed. With these measures, no patient discontinued treatment permanently due to a hypersensitivity reaction. It is recommended also that physicians consider delaying the idursulfase infusion in patients with concomitant acute respiratory and/or febrile illness. If a severe infusion reaction occurs, immediately suspend the infusion of idursulfase and initiate appropriate treatment, depending on the severity of the symptoms. Consider resuming the infusion at a slower rate, or, if the reaction is serious enough to warrant it, discontinue the idursulfase infusion for that visit.

2. Patients with compromised respiratory function, including those with reactive airway disease, may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions (hence they are at a higher risk for life-threatening complications).
3. Other notable serious adverse events that occurred in the idursulfase-weekly treated patients but not in the placebo patients included one case of each of: cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia.
4. Adverse events were commonly reported in association with infusions. The most common infusion-related reactions were headache, fever, cutaneous reactions, and hypertension. The frequency of infusion-related reactions decreased over time with continued idursulfase treatment.
5. The most common (>30%) adverse reactions were pyrexia, headache, and arthralgia.

Safety results are otherwise summarized as follows (not included in the label):

6. Deaths reported in clinical studies were all related to respiratory failure. A causal relationship cannot be determined but appears unlikely, given the high background rate of pulmonary failure deaths in Hunter syndrome patients.
7. However, a safety signal in serious adverse events relating to respiratory issues was detected.
8. Notable adverse events that occurred in the EOW-idursulfase treated patients but not in the placebo patients in the controlled 53 week study included one case of each: syncope, orthostatic hypotension, heart failure, choking, arrhythmia (ventricular extra-systole) requiring medication, and anesthesia intubation complication (airway trauma due to intubation).
9. Other safety signals included: anxiety and depression, thromboembolic events, visual disturbance, musculoskeletal dysfunction, cholestasis, potential for elevation in creatine kinase, pain, and malaise. Of these, pain and malaise will significantly impact on patient's quality of life, and should be considered in the long term assessment of the risk/benefit profile of idursulfase treatment.

The risk/benefit analysis of idursulfase treatment should be individualized to each patient's medical needs.

1.3.4 Dosing Regimen and Administration

Based on the procedures described in the study protocols and the actual experience of the clinical studies, the following recommendation is made to the label:

The recommended dosage regimen of idursulfase is 0.5 mg/kg of body weight administered every week as an intravenous infusion. Idursulfase is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. Each vial of idursulfase contains a 2.0 mg/mL solution of idursulfase protein (6.0 mg) in an extractable volume of 3.0 mL, and is for single use only. Use of an infusion set equipped with a 0.2 micrometer (μm) filter is recommended.

The total volume of infusion may be administered over a period of 1 to 3 hours. Patients may require longer infusion times due to infusion reactions; however, infusion times should not exceed 8 hours (based on product stability). The initial infusion rate should be 8 mL/hr for the first 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr at 15 minute interval increments in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgment, if infusion reactions were to occur. Idursulfase should not be infused with other products in the infusion tubing.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were explored in the idursulfase clinical development program.

1.3.6 Special Populations

Hunter disease is a rare, X-linked recessive, inherited, lysosomal storage disease that is estimated to occur with an incidence of one out of 65,000 to 132,000 births. The entire idursulfase clinical development program has been conducted in Hunter syndrome patients. Children less than 5 years of age were not studied. No data were available geriatric patients (≥ 65 years of age), or in female patients, as Hunter syndrome reduces life expectancy and is exceedingly rare in females. Hunter syndrome occurs worldwide, and patients from the United States, South America, and Europe have been included in clinical studies. However, insufficient information exists to determine a difference in response to idursulfase treatment by ethnic origin.

2 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

Idursulfase (ELAPRASE™) is a purified, man-made enzyme analog of the naturally occurring, endogenous lysosomal enzyme iduronate-2-sulfatase. The rationale for this therapy is that exogenous administration of idursulfase should theoretically replace the deficiency of endogenous enzyme in Hunter syndrome (Mucopolysaccharidosis II, or MPS II) patients. Idursulfase is produced by recombinant DNA technology developed in a human — cell line. Idursulfase is a 525 amino acid glycoprotein with 8 N-linked glycosylation sites that are occupied by complex. — mannose type oligosaccharide chains. Idursulfase has a glycosylation profile that is analogous to the naturally occurring enzyme, and has a molecular weight of approximately 76 kD. After intravenous administration, idursulfase is internalized by cells via cellular membrane mannose-6-phosphate receptors binding to enzyme mannose-6-phosphate residues. The enzyme is then taken up by lysosomes where it begins catabolizing accumulated glycoaminoglycans (GAGs). Idursulfase is thought to be degraded eventually by protein hydrolysis within lysosomes, and the resultant peptide/amino acid products are thought to be incorporated back into the body's amino acids pool.

The proposed trade name is ELAPRASE™. This product is a new molecular entity, a biologic product in the class of human proteins made via recombinant DNA technology. The proposed indication is — based on efficacy evidence of increased distance walked in a 6-Minute Walk Test (6MWT) demonstrated in the pivotal clinical trial. The Applicant proposed that idursulfase would be used for the — treatment of patients with Hunter syndrome administered intravenously weekly f —. The proposed dose is 0.5 mg/kg of body weight,

2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS

Currently there are no available treatments that target the specific disease mechanism of Hunter syndrome. Bone marrow transplantation has been attempted but has only demonstrated limited efficacy while posing substantial risks. All other existing treatments are palliative.

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES

The product is a new molecular entity, therefore not marketed in the US. Since idursulfase is not approved in other countries there is no foreign labeling for review. —

2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS

Other enzyme replacement therapies, notably Aldurazyme™ (laronidase) for treating MPS I, and Naglazyme™ (galsulfase) for treating MPS VI have been approved by the FDA for treatment of these life-threatening diseases. All of these products carry warnings about serious infusion reactions. Aldurazyme™ warnings include severe hypersensitivity and anaphylactic reactions, which consist of airway obstruction and urticaria. Naglazyme™ warnings include severe symptoms, which consist of angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea, and urticaria.

2.5 PRESUBMISSION REGULATORY ACTIVITY

The idursulfase development program was conducted under IND — which was submitted on 12-21-2000, and received by the Agency on 12-26-2000. Idursulfase was granted Orphan Drug status on 11-28-2001, designated as long term enzyme replacement therapy for patients with MPS II (Hunter syndrome). On 12-10-2002 the Applicant and the FDA held an End-of-Phase-2 meeting. Subsequently, it was agreed that it would be acceptable to use a composite primary endpoint consisting of two components: 6-Minute Walk Test (6MWT), and percent predicted forced vital capacity (%-predicted FVC). The IND was granted Fast Track status on 7-14-2004. A pre-BLA meeting was held on 9-27-2005, at which the Division stated that the mildly-affected MPS II patients were not well represented in the patient population in the pivotal study, TKT024, and that it may be insufficient to support a broad indication. The BLA application, which was received on 11-23-05, was granted Priority Review status despite not meeting the objectives of the Fast Track designation, because the product was felt to represent, if approved, a significant improvement over available treatment for prevention of respiratory failure in patients with MPS II who have moderate to severe decreases in FVC. This medical reviewer received the review assignment on 12-19-2005.

2.6 OTHER RELEVANT BACKGROUND INFORMATION

Hunter syndrome, also known as Mucopolysaccharidosis II, or MPS II, is a rare, X-linked recessive disease caused by insufficient activity of lysosomal enzyme iduronate-2-sulfatase. Iduronate-2-sulfatase *in vivo* catabolizes the glycoaminoglycans (GAGs) dermatan sulfate and heparan sulfate by cleavage of oligosaccharide-linked sulfate moieties. Without sufficient amount or activity of iduronate-2-sulfatase, GAGs (also known as mucopolysaccharides) are not degraded properly in patients. Buildups of GAGs in lysosomes occur in a variety of cells, leading to cellular engorgement, widespread tissue destruction, and multi-organ system dysfunction, resulting in Hunter syndrome.

The system organ classes most commonly affected are the musculoskeletal, cardiovascular, pulmonary, ocular, ear/nose/throat, gastrointestinal, neurologic, cutaneous/integument, and cognitive-psychiatric systems. Disease manifestations differ among patients, but there are several unifying themes. Burdened with the illness and frequent medical/surgical visits, many patients are not able to attend school or function socially. Chronic pain is common, and is caused by arthritis, arthralgia, myalgia, and musculoskeletal contractures. Sleep may be interrupted by obstructive apnea. Disabilities include difficulty in ambulation, decrease in manual dexterity, loss of hearing, need for chronic enema or diapers, need for tracheostomy and oxygen support, and inability to carry on activities of daily living such as dressing and washing, among other problems. Quality of life is poor. Many patients undergo

multiple surgeries such as orthopedic procedures, tracheostomy placement, cardiac valvuloplasty, inguinal hernia repair, shunt placement for increased intracranial pressure, tonsillectomy and adenoidectomy, and ear tube placement. The disease has no cure, and those patients who are afflicted with the severe form of the disease die prematurely. The most common cause of death in patients with MPS II is “cardiopulmonary” arrest. This is most likely caused by a host of factors including recurrent upper respiratory and pulmonary infections; restrictive, obstructive, and upper-airway disease; anesthesia complications related to physical anomalies; or, heart disease such as cardiomyopathy, valvular heart disease, heart failure, and conduction abnormalities.

The clinical severity of Hunter syndrome varies from the attenuated to the severe. The attenuated form and the severe form of the disease are separated on clinical grounds, because iduronate-2-sulfatase activity appears equally deficient in both forms¹. Whether the severe and the attenuated forms of Hunter syndrome represent two separate disease entities or simply two extremes on a wide spectrum of clinical severity is unclear. Differentiation is based on three factors: 1) time of onset, 2) life expectancy, and 3) presence/absence of normal intelligence. Patients afflicted with the severe form of the disease have mental retardation, are diagnosed earlier in life (typically between 18-36th months of age), and have a shortened life expectancy of about 10-20 years. Patients afflicted with the attenuated form of MPS II are characterized by later diagnosis, a longer life span (living as long as the 7th decade or beyond, with the longest known survival to age 87²), and intact intelligence. Some patients afflicted with the attenuated form of the disease have almost normal functioning.

Since Hunter syndrome is inherited in an X-linked recessive manner, and males generally do not reproduce, affected females are not expected. Hunter syndrome in females is exceedingly rare. There have been only rare case reports of female patients with well-documented Hunter Syndrome, generally of the mild form. These affected females are heterozygotes in whom some additional genetic event has prevented the expression of the normal allele. Another rare subtype of Hunter Syndrome exists that is autosomal-recessive. Current recommendation is for perspective parents with a family history of Hunter syndrome to undergo genetic testing, which is accomplished in one of two ways. Prenatal diagnosis is possible from chorionic-villus sampling or from amniocentesis. Carrier testing for female relatives of affected males is available via molecular techniques³.

1 The Metabolic & Molecular Bases of Inherited Disease, 8th ed., Volume III, Charles R Scriver et al. (editors) McGraw-Hill Medical Publishing Division, 2001 Authors: Elizabeth F Neufeld and Joseph Muenzer, Chapter 136: 3428-3430

2 Hobolth N, Pedersen C: Six cases of a mild form of Hunter syndrome in five generations. Three affected males with progeny. *Clin Genet* 20:121, 1978.

3 Oski's Principles and Practice of Pediatrics, 2nd ed., DeAngelis C, et al (editors), JB Lippincott Company: 118

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The reader is referred to the review by the FDA product reviewer, Serge Beaucage, PhD, for details.

- Process validation data and release testing results indicate that the manufacturing of idursulfase drug substance is under control, and is consistently producing the drug substance with specified quality attributes in terms of identity, purity, potency, and microbiological quality. It is recommended that the commercial process for the manufacturing of idursulfase drug substance be approved.
- Several CMC commitments are recommended, including: development and implementation of an improved assay for drug product release and stability testing, and of an improved enzyme potency assay; a laboratory scale study to assess the commercial purification process of the drug substance; modifications to its drug product specifications related to , a qualification study to assess its test method for ; re-evaluation of analytical methods for the qualification and release of future reference standards; and a commitment to evaluate and revise as necessary all acceptance criteria for release of drug substance and drug product manufactured at commercial scale

3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY

The pre-clinical data have been extensively reviewed by FDA pharmacology-toxicology reviewer, Ronald Honchel, Ph.D. The reader is referred to Dr. Honchel's review for details.

Since Hunter syndrome is an X-linked recessive disease, non-clinical studies were primarily performed in male animals. There were no significant safety pharmacology and toxicology findings in animals. Idursulfase had no effect on fertility or reproductive performance in male rats, and it had no effect on early embryonic development in the pups of treated male rats. In a series of pharmacodynamics studies, male iduronate-2-sulfatase knock-out (IKO) mice were administered idursulfase at doses ranging from 0.1 to 5 mg/kg/dose. Idursulfase treatment reduced urinary and tissue GAG levels. For reducing urine, liver, and spleen GAG levels in IKO mice to levels similar to those observed in wild-type mice, the most effective dosing regimen was 1/mg/kg/dose.

Two additional observations were made:

- 1) Studies in IKO mice showed that liver effectively took up idursulfase, and liver size was reduced. Similar conclusions, however, could not be made about idursulfase action on reduction of spleen size based on available data.
- 2) Study #720-110-03-449 resulted in the deaths of 3 out of 28 idursulfase-treated mice. The objective of the study was to determine whether administration of idursulfase shortly after birth could reduce the incidence of skeletal abnormalities in growing IKO mice. Male IKO mice were

administered 5 mg/kg/dose idursulfase intraperitoneally on Day 4 and Day 11 of age when they were too small to receive intravenous administration. When they were large enough to receive intravenous cannulation, the mice were administered 1 mg/kg idursulfase intravenously weekly beginning at approximately 1 month of age. The study was halted during the experimental stage when the mice were at 7 weeks of age due to unexpected reactions that had occurred in 20 of 28 idursulfase-treated mice. Three mice (3/28, or 11%) died after intravenous idursulfase administration. Seventeen of the remaining 25 (7/28, 25%) mice experienced various adverse events including ataxia, dyspnea, and mild hypothermia. The Applicant postulated that these unexpected adverse events were due to high doses of idursulfase given intraperitoneally during the neonatal period, which ultimately led to an anaphylactic reaction when animals were given intravenous idursulfase administration later in life. The Applicant did not perform experiments to determine whether intravenous dosing in neonatal animals would have avoided these adverse events.

A number of changes to the non-clinical portion of the label were recommended by the pharmacology-toxicology review team, including a Segment III reproductive toxicology study to examine the effect of maternal administration of idursulfase during pregnancy on neonatal animals. It was felt, however, that overall this submission contained adequate non-clinical studies for marketing approval of idursulfase.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

The idursulfase clinical development program consists of four clinical trials (TKT008, TKT018, TKT024, and TKT024EXT), which are summarized in Table 1, Section 4.2.

4.2 TABLE OF CLINICAL STUDIES

Table 1 Overview of Idursulfase Clinical Studies (Source: BLA Submission)

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

^a Subsequent to dose selection for the pivotal study (TKT024), all 8 patients in the 0.15 and 1.5 mg/kg groups in TKT018 crossed-over to the 0.5 mg/kg every other week dose group, whereupon all 12 patients have remained on active study drug for approximately 3.5 years by the data cut off of 01 April 2005.

4.3 REVIEW STRATEGY

The most important study submitted to this application was the pivotal study, TKT024, a multi-center, international, randomized, double-blind, placebo-controlled, 53 week study in which safety and efficacy were evaluated in 96 patients with Hunter syndrome. In this study, it was found that patients who were treated with weekly administration of idursulfase for one year demonstrated a greater walking capacity during a 6-Minute Walk test (6MWT) than patients who were treated with placebo.

Patients who finished Study TKT024 continued on an open-label, uncontrolled, extension phase of the study, titled study TKT024EXT. When the study is completed, these patients will provide at least additional 2 years of long-term safety data associated with chronic idursulfase treatment. Only interim results of this ongoing study TKT024EXT are available for review at this time.

The data submitted from the two remaining studies, TKT008, and its uncontrolled study, extension study TKT018, were of lesser importance due to their small sample size (N=12), and shorter duration (study TKT008 was a 26 week study). These limited studies primarily provided additional evidence of the pharmacodynamic effects and safety profile.

4.4 DATA QUALITY AND INTEGRITY

Selected patients' case report forms (CRFs) were reviewed. Discrepancies were found in patient's medical history taken at baseline, and at the time that serious adverse events (SAEs) occurred; for example:

1. Patient 024-012-0008 died of respiratory failure secondary to pulmonary infection; his symptoms started 2 days after his first and only dose of blinded idursulfase administration. Patient's SAE/death report stated the he had a history of "severe pulmonary involvement with recurring respiratory tract infections." His baseline medical history, however, did not state that patient had ever had events relating to severe respiratory involvement or recurrent pulmonary infections. This heightens concerns about the patient's death from of a respiratory infection--which started shortly after his first and only idursulfase treatment--when he (possibly) did not have prior history of severe respiratory involvement prior to idursulfase treatment.

The patient's SAE narrative also stated that patient "did not have any cardiac history," but his baseline medical history stated that he did have class II congestive heart failure.

The Applicant explains that these discrepancies stemmed from inconsistent reporting by patient's parent. Although noted, these discrepancies do not appear extensive or severe enough to change the conclusion about the study.

Data regarding pre-medication administrations was confusing, and did not allow analysis regarding pre-medication to be complete. For example, it was listed in the INFUSN.xpt dataset that patient 024-044-0007 received pre-medication for 50 of the 52 infusions during study TKT024; however, the dataset did not actually list what these medications were. A different dataset, CONMED.xpt, recorded that the patient received pre-medication for only 3 (not 50) of the 52 infusions. So it appears that the investigator did not record the indication for all medications listed in the concomitant medication dataset (CONMED.xpt), and the dataset did not necessarily include those medications administered to patients who were known to have received a pre-medication prior infusions. The CONMED.xpt dataset also contained some use of the term "pre-medication" that were for the performance of procedures unrelated to the administration of study medication (e.g., pre-medication for MRIs). In short, although the

Applicant can identify all subjects who received a pre-medication, the Applicant can not associate what actual medications were given in all cases.

Late in the review cycle, the review team noted a worrisome safety signal for hypersensitivity reactions, which was unidentified/unreported in the original BLA submission. The Applicant was asked to screen the adverse event reports for potential cases of anaphylaxis using specific criteria. Cases of anaphylaxis or anaphylactoid reactions were confirmed upon further review. With concurrence of the Applicant, this information was submitted as a major amendment allowing for additional time for review since prominent warnings about these reactions would constitute a major amendment to the label.

Despite these limitations, overall, the content of the submission was sufficient for filing and review. The FDA Division of Scientific Investigation (DSI) performed 3 clinical-site audits:

- 1) Dr. Joseph Muenzer at University of North Carolina at Chapel Hill
- 2) Dr. Christine Eng at Baylor College of Medicine
- 3) Dr. Roberto Giugliani at Hospital de Clinicas de Porto Alegre

These sites were selected because of their high enrollment (#1, 3); unusual pattern of “discarding” patients, i.e., 50% of patients were enrolled but not selected to be randomized to study TKT024 (#2); and/or significant financial contribution to an investigator (#1,3). There was no discrepancy between the source documents and the data listings supplied by the Applicant. The overall observation noted by the DSI Inspector, Ms. Dianne D. Tesch, was that “the studies appear to have been well conducted at all the sites. The data were acceptable for consideration in the BLA review process.”

4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES

The Applicant stated that all studies were conducted in accordance with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

4.6 FINANCIAL DISCLOSURES

Table 2 Financial Disclosures of Investigators

Investigator	Payment received from TKT/Shire:
—	\$121,867 over 8 years — for consulting, speaking, and travel.
—	\$29,041 over 3 years — for consulting. In addition, the — where — is employed and served as a clinical investigator for studies — received \$1,142,898 over 3 years — , a charity which supports a clinic which is part of the — received \$111,777 over 3

Clinical Review
Joanna W. Ku, MD
BLA STN125151-0
Elaprase™ (idursulfase)

	years
	\$248,676 over 5 years, for consulting, research education grant, travel, and TKT sponsorship.

for TKT018, and
for TKT024 did not provide financial disclosure statements.

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5 CLINICAL PHARMACOLOGY

The clinical pharmacology data have been extensively reviewed by the clinical pharmacology and biopharmaceutics reviewer, Hong Zhao, PhD. The reader is referred to Dr. Zhao's review for details. Findings for the pharmacokinetic (PK) and pharmacodynamic (PD) data are briefly summarized below.

5.1 PHARMACOKINETICS

The pharmacokinetic characteristics of idursulfase were evaluated 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 one-hour infusion of ELAPRASE. The pharmacokinetic parameters at the recommended dose regimen (0.5 mg/kg ELAPRASE administered weekly as a three-hour infusion) were determined at Week 1 and Week 27 in ten patients ages 7.7 to 27 years (Table 3). There were no apparent differences in PK parameter values between week 1 and week 27. 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.

Table 3 Pharmacokinetic Parameters (Mean, Standard Deviation) (Source: BLA Submission)

Pharmacokinetic Parameter	Week 1	Week 27
C_{max} ($\mu\text{g/mL}$)	1.5 (0.6)	1.1 (0.3)
AUC ($\text{min} \cdot \mu\text{g/mL}$)	206 (87)	169 (55)
$t_{1/2}$ (min)	44 (19)	48 (21)
Cl (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V_{ss} (% BW)	21 (8)	25 (9)

5.2 PHARMACODYNAMICS

The primary biological measures of the clinical activity of idursulfase were reductions in patients' urinary GAG levels, and in liver and spleen size.

As observed in the Phase 1/2 study, TKT008, at all 3 dose levels (0.15, 0.5 and 1.5 mg/kg), idursulfase resulted in reductions in urine GAG excretion. In study TKT008, over the 6-month treatment with idursulfase, mean urine GAG levels fell by 41%, 44% and 62% in the 0.15, 0.5 and 1.5 mg/kg dose groups, respectively. Similarly, in the Phase 2/3 pivotal study, TKT024, among all 64 idursulfase-treated patients, 26 patients (16/32, 50% in the idursulfase weekly group; 10 of 32, 31% in the idursulfase every-other-week group) had reduction in urine GAG levels below the upper limit of normal (defined as 126.6 μg GAG/mg creatinine) by the end of the study at Week 53. No patient in the placebo group reduced his urinary GAG level below the upper limit of normal, and the mean urinary GAG levels of placebo population remained elevated and essentially unchanged.

In the pivotal study, of the 50 patients with abnormally large livers at baseline in the idursulfase treatment groups (25 in the weekly group, and 25 in the every-other-week group), 40 patients (80%; 20 patients in each idursulfase treatment group) had reduction in liver volume to within the normal range. Only 1 of 23 (3%) patients with hepatomegaly at baseline in the placebo group had reduction in the liver volume to within the normal range.

In the pivotal study, of the 9 patients in the idursulfase-weekly group who had splenomegaly at baseline, 3 patients had normalized spleen volume at the end of the study. Of the 2 patients in the idursulfase-EOW group who had splenomegaly, 1 patient had reduction of splenomegaly to the normal range. Of the 11 patients in the placebo group with splenomegaly, 2 patients had reduction of splenomegaly to the normal range. It appears that although there was statistically significant treatment difference in the change from baseline to week 53 in spleen size between the weekly and the placebo groups, the “shift-to-normal” analysis does not indicate that there was a significant clinical treatment difference in the normalization of spleen volumes between idursulfase-treated and placebo patients.

There was no correlation between the pharmacodynamic effect in reduction in urinary GAG level and the clinical effect in improvement in 6MWT.

5.3 EXPOSURE-RESPONSE RELATIONSHIPS

The improvement in 6MWT was statistically significant, as compared to placebo, for 0.5 mg/kg weekly regimen, but not for 0.5 mg/kg every-other-week regimen. The Applicant has withdrawn the original EOW dosing proposal.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

The Applicant's proposed indication in the labeling is:

ELAPRASE is indicated for the treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

6.1.1 Methods

Clinical data from both of these randomized, double-blind placebo controlled studies (TKT 024 and 008) were analyzed to determine whether a clinical benefit existed for Hunter Syndrome patients who received idursulfase IV therapy. The FDA statistical reviewer, Janice Derr, PhD., confirmed the major efficacy analyses and performed sensitivity analyses to corroborate the findings of the Applicant.

6.1.2 General Discussion of Endpoints

MPS II is an extremely rare condition with unknown worldwide incidence and prevalence. Reports of the incidence of MPS II vary. MPS II occurs as frequently as 1 case in 65,000 births in some reports to as rarely as 1 case in 132,000 births in others. The disease has a wide spectrum of severity and heterogeneous clinical manifestation, with various rates of progression to death. Because of the rarity of the disease and the variation in disease severity and death rates, a large study with robust endpoints such as survival rates, for example, was infeasible. Since no single variable was considered adequate to assess the overall benefit of idursulfase, a wide range of clinical evaluations were selected, among which were prior regulatory endpoints chosen for the other mucopolysaccharidoses that lead to regulatory approval of their respective enzyme replacement therapies: Aldurazyme™ in MPS I, and Naglazyme™ in MPS VII.

The primary efficacy endpoint chosen for the pivotal study TKT024 was a combination of walking performance and pulmonary function. It was defined as a two-component composite score based on the sum of the ranks of the change from baseline to week 53, in 6-Minute Walk Test (6MWT) and forced vital capacity, as a percent of the predicted value (%-predicted FVC). This two-component composite endpoint was agreed by the FDA following the End-of-Phase 2 meeting with the Applicant. The 6MWT, performed according to the American Thoracic Society guidelines, is a sub-maximal exercise tolerance test that measures how far a patient can walk (in meters) during a six minutes period, intended as a surrogate marker for measuring the patient's ability to carry physical activities of daily living, presumably reflective of a combination of the functioning of the patient's respiratory, cardiovascular, and musculoskeletal systems. Forced vital capacity (FVC) is a pulmonary function test that determines whether a patient has restrictive lung disease. The %-predicted FVC is defined as the patient's measured FVC (in liters), expressed as a percentage of the normal value, i.e., that of expected FVC in a healthy individual of comparable age and height. Percent predicted FVC was used rather than the absolute lung volume as a component of the primary end point, because it was thought that the %-predicted FVC allowed comparison between patients, where as absolute lung volume is not directly

comparable between patients since it is affected by extra-pulmonary factors such as age, height, and gender.

As mentioned, the %-predicted FVC is based on the patient's actual measured FVC expressed as a percent of the expected normal value of a healthy individual of the same height and age. Measuring height, however, is difficult in Hunter syndrome patients. In the clinical studies, not all patients were able to stand erect; heights were obtained with some patients standing on their toes. Since heights could not be measured accurately, no conclusion can be drawn from the data regarding %-predicted FVC (see pediatric review by FDA pediatric consultant, Hari Cheryl Sachs, MD). But even if heights could be measured accurately, predicted lung function values in MPS patients is still problematic. As noted by Andrew Wen, MD, a pediatric pulmonologist who interpreted the PFT results for the Applicant in the clinical trial: there is no normative data for pediatric patients with MPS. MPS is associated with musculoskeletal deformities. Patients have limb and chest size abnormalities which make normative data base on height and arm span unreliable. As patients increase in height, it is unclear how much their change in height can be attributed to an increase in chest wall size versus longer limbs or improved posture. Also, height may be changing as body habitus change in these patients. In short, following predicted lung function values based on height is of unclear reliability in this patient population.

FDA pulmonary consultant, James Kaiser, MD delineates these issues further. The Applicant reports that the difference between placebo and weekly treatment in baseline to trial end %-predicted FVC in the ANCOVA was 4.28 points, which was not statistically significant. Aside from the lack of statistical significance, the clinical significance is uncertain. There is no difference in %-predicted FVC that has been validated to show a clinically meaningful treatment effect specifically tailored for Hunter syndrome (even though based on the results of the Aldurazyme™ trial in Hurler and Hurler-Scheie patients, a 4% difference in predicted FVC between control and treated patients was considered to be significant). It is likely that such a validation would have to be made for the disease being studied. In Hunter syndrome, the primary potential pulmonary effects of the disease process are on structures external to the lung, most notably the upper airway, skeleton, and possibly liver and spleen; hence, the FVC and other pulmonary function tests are measures that combine potential effects on the lung itself and structures external to it, not just on the lung alone.

Pulmonary function tests as commonly used are themselves indirect measures, i.e. surrogates, for clinically meaningful changes in the patient. Spirometry does not always correlate with clinical benefit⁴; hence, %FVC is a laboratory-measure outcome that is not itself a measure of clinical efficacy. While it is not unreasonable to expect that changes that affect structures external to the lungs that secondarily affect pulmonary function might allow for use of such testing as a means for detecting changes in the primary disease process, under these circumstances, it would be highly problematic to infer any treatment benefit on the lung itself from a product-related improvement in FVC. A statement by the ATS/ERS was recently published that describes the variability in FVC testing as a hurdle in the interpretation of the test for an individual and gives guidelines on handling this variability. The statement does not give guidelines as to the clinical interpretability of a given change. In fact, it is likely

⁴ Sharek P, et al Agreement among measures of asthma status: a prospective study of low-income children with moderate to severe asthma. *Pediatrics*: 2002; 110 (797-804).

that such a criterion would have to be established in Hunter syndrome, or a class of conditions very similar to it.

In summary: at the present time, there is no established, validated criterion for defining a difference in %-predicted FVC that establishes pulmonary clinical efficacy in Hunter syndrome.

6.1.3 Study Design

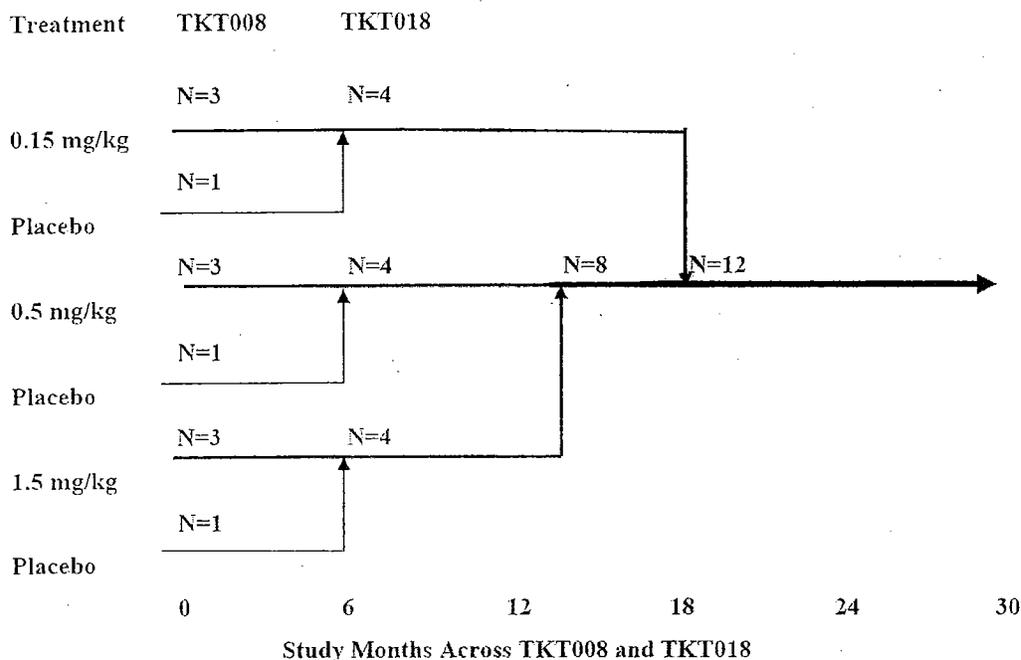
6.1.3.1 Overall Development Program Design

The idursulfase clinical development program consists of four clinical trials, **TKT008**, **TKT018**, **TKT024**, and **TKT024EXT**. Two of the trials (TKT008 and TKT024) were randomized, double-blinded and placebo-controlled studies designed to show superiority over placebo since there is no accepted treatment for Hunter syndrome. The other two are ongoing extensions studies (TKT018 and TKT024EXT) of the two controlled studies.

Study TKT008, the Phase 1/2 study, was a single-center, randomized, double-blind, placebo-controlled, sequential and dose-escalation study of six months duration that involved 12 patients. Patients were assigned by the investigator to one of the three groups of dose-escalation assignments (0.15 mg/kg EOW, 0.5 mg/kg EOW, or 1.5 mg/kg EOW). The four patients in each dosing group were randomized 3:1 to either idursulfase (N=3) or placebo (N=1). Due to the small sample size of study TKT008, no stratification by baseline disease severity or demographic characteristics was performed. The inclusion/exclusion criteria had no limitations on the severity or mildness of disease symptoms. In particular, patients were not excluded if they had tracheostomies or prior bone-marrow transplants. The main objectives of the study was to evaluate the safety and pharmacodynamic (PK) activity of idursulfase when administered at three dose levels every other week for six months by intravenous infusions to Hunter syndrome patients. The primary pharmacodynamic end point was reduction in urine GAG excretion. The study also assessed the pharmacokinetic (PK) parameters of intravenous administered idursulfase.

After patients completed study TKT008, they were enrolled in its extension, open-labeled, multi-center study, **TKT018**. Initially all patients (including the patients who had received placebo in Study TKT008) received intravenous infusions of idursulfase at doses of 0.15, 0.5, or 1.5 mg/kg every-other-week, corresponding to their original dose group in Study TKT008. Subsequently during the study, patients in the 0.15 and 1.5 mg/kg groups were transitioned to a dose of 0.5 mg/kg every-other-week, while the patients in the idursulfase 0.5 mg/kg dose level in Study TKT008 remained on that dose throughout Study TKT018 (see Figure 1). The primary objective of this clinical study was to evaluate the safety of long-term maintenance dosing of idursulfase in patients with MPS II. The secondary objectives included collection of long-term PD and PK data.

Figure 1 Diagram of Treatment Schedules across Studies TKT008 and TKT018 (Source: BLA Submission)



Results from Phase 1/2 study TKT008, in combination with non-clinical data, were used to select the dose, and frequency of idursulfase administration for the pivotal trial, TKT024:

1. The 0.5 and 1.5 mg/kg doses were likely more effective than the 0.15 mg/kg dose.
2. 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.
3. Fewer infusion-related reactions at the 0.5 mg/kg dose compared with the 1.5 mg/kg dose.
4. One patient administered 1.5 mg/kg developed anti-idursulfase antibodies.
5. PK data in monkeys suggested that plasma clearance mechanisms may be likely to saturate in humans around a dose of 0.5 mg/kg.
6. Patients assigned to the every-other-week idursulfase treatment in study TKT008 demonstrated clear evidence of biological activity, as measured by reduction in urinary GAG excretion and liver size.
7. The IKO mouse model, however, suggested that more frequent dosing might have a greater effect on clearance of tissue GAG.
8. The tissue $t_{1/2}$ of idursulfase (~ 1 to 2 days) also suggested that a weekly dose would provide more sustained levels of enzyme in target tissues than an every-other-week dose.

Therefore, the final dose and frequency selection for the pivotal study were: idursulfase 0.5 mg/kg QW; idursulfase 0.5 mg/kg EOW; and, placebo QW.

Study TKT024, the pivotal trial, was an international, double-blind, randomized, placebo-controlled, 53-week, study involving 96 male Hunter syndrome patients treated for one year. This study was designed to evaluate the efficacy and safety of idursulfase 0.5 mg/kg administered either weekly or every-other-week (EOW) in patients with Hunter syndrome. Patients received 52 weeks of treatment with idursulfase 0.5 mg/kg weekly, idursulfase 0.5 mg/kg EOW, or placebo weekly. The open-label extension of study TKT024 is study **TKT024EXT**, which is a multi-center, single-arm, open-labeled, two-year, ongoing safety and clinical outcomes study of idursulfase enzyme replacement therapy in patients who completed study TKT024. All of 94 patients available (two patients of the original 96 patients died during study TKT024) volunteered to continue in this extension study. TKT024EXT was designed to assess safety and clinical outcomes at four-month intervals during the first year of the study and at six-month intervals during the second year. Patients who were unable to complete TKT024EXT because site visits were considered too burdensome were provided the option of discontinuing the study after completion of the Week 18 evaluations. Such patients would be allowed to continue idursulfase treatment at a local infusion site under a designated named patient use protocol. In TKT024EXT, all patients would be administered idursulfase 0.5 mg/kg weekly for at least two years. Until all patients have completed the first year of dosing in TKT024EXT, patients and their families as well as investigators and all clinical site personnel were to remain blinded to the original TKT024 treatment assignments to avoid bias in the assessments of safety and clinical outcomes.

6.1.3.2 Pivotal Study Design, TKT024

The primary objective of the pivotal study was to determine the efficacy and safety of weekly dosing of idursulfase (0.5 mg/kg per dose) in the treatment of Hunter syndrome patients. Patients were initially screened for entry into the study based on their prior medical histories. Qualified patients were given the opportunity to give informed consent to be enrolled if they met inclusion and exclusion criteria:

6.1.3.2.1 Inclusion Criteria

- Diagnosis of Hunter syndrome based upon fulfilling both clinical, and biochemical criteria. For clinical criteria, patients must have at least one of the following considered by the investigator to be Hunter syndrome-related: hepatosplenomegaly, radiographic evidence of dysostosis multiplex, valvular heart disease, evidence of obstructive pulmonary disease. For biochemical criteria, patients must have had *both* of the following: 1) documented deficiency in I2S enzyme activity of $\leq 10\%$ of the lower limit of normal as measured in plasma, fibroblasts, or leukocytes; 2) a normal enzyme activity level of one other sulfatase as measured in plasma, fibroblasts, or leukocytes (based on normal range of measuring laboratory).
- Male, age 5 to 25 years.
- Baseline forced vital capacity of $< 80\%$ of predicted of normal value.
- Ability to adequately perform the required testing, including reproducible pulmonary function testing by spirometry, and to stand for six minutes and walk a minimum of five meters.
- Valid informed consent.

6.1.3.2.2 Exclusion Criteria

- History of a tracheostomy.
- History of a bone-marrow or cord-blood transplant.

- History of receiving treatment with another investigational therapy within the past 60 days.
- Inability to comply with the protocol (e.g., due to a medical condition such as cervical cord compression or uncooperative attitude) or was unlikely to complete the study.
- Known hypersensitivity to any of the components of idursulfase.

6.1.3.2.3 Methods of Assigning Patients to Treatment Groups

In order to achieve balanced allocation, randomization in the pivotal trial was stratified by age category, and baseline disease severity. Age was stratified as 5-11 years of age, 12-18 years of age, and 19-25 years of age, meant to correlate with pre-puberty, puberty, and adulthood. Baseline disease severity was defined as the sum of the %FVC score and the 6 MWT score (see Table 4), for a total baseline disease score. The three strata of total baseline disease score were defined as a score of 2, score of 3 or 4, and score of 5.

Table 4a Scoring of % Predicted Forced Vital Capacity for Inclusion in Total Disease Score for Stratification (Source: BLA Submission)

% of Predicted	Severity Description	Score
≥70% to < 80%	Mild	1
≥50% to < 70%	Moderate to moderately severe	2
< 50%	Severe to very severe	3

Table 4b Scoring of Distance Walked in 6-Minute Walk Test for Inclusion in Total Disease Score for Stratification (Source: BLA Submission)

Distance Walked (meters)	Severity Description	Score
≥500	Mild	1
≥300 to < 500	Moderate to moderately severe	2
< 300	Severe to very severe	3

Reviewer's Comment: This classification system of baseline disease severity was arbitrarily chosen by the investigator for the purpose of this clinical trial, and does not constitute a validated scoring system for disease severity of Hunter syndrome. It does not fully depict the wide disease severity spectrum present in Hunter syndrome patients. The fact that study subjects had to have abilities to follow instructions and carry out testing maneuvers such as the 6MWT and PFTs, suggests that this patient population did not represent the most severely affected Hunters patients, i.e., those who were bed-bound, severely debilitated, or mentally retarded. Therefore, efficacy of idursulfase in treatment in the most severely affected patients has not been established. The study population also excluded patients with %FVC > 80%, indicating that patients without restrictive lung disease were not studied. Other groups excluded from the study were geriatric, younger than 5 year-old (including neonates), and female patients.

6.1.3.2.4 Treatment Plan

In the pivotal trial, 96 patients were randomized to one of three treatment arms with equal probability (1:1:1) so that there were 32 patients per each treatment group:

- intravenous idursulfase 0.5 mg/kg every week (QW): 32 patients

- intravenous idursulfase 0.5 mg/kg every other week (EOW): 32 patients
- intravenous placebo (weekly): 32 patients

In order to maintain the study blind, study drug was administered over 3 hours in order to minimize the potential for infusion reactions. Placebo infusions were administered during off weeks in the EOW dose group. All patients received IV infusions of study drug every week administered over 3 hours. Patients randomized to receive every-other-week infusion of idursulfase were administered placebo infusions in the alternate weeks to maintain the treatment blind. Placebo “drug” was not saline, but rather consisted of the identical formulation of idursulfase drug product without the active drug. Not accounting for minor irregularities over the course of the year-long study:

- Weekly-group patients received a total of 52 doses of idursulfase.
- Every-other-week group patients received a total of 26 doses of idursulfase and 26 doses of placebo.
- Placebo group patients received a total of 52 doses of placebo.

Idursulfase or placebo were diluted with normal saline to a final volume of 100 ml and administered as a 3-hour continuous infusion by the IV route as described in Table 5.

Table 5 Administration Rates for 3-Hour Infusion of the Study Drug (Source: BLA Submission)

Time of Infusion	Rate of Infusion	Volume of Drug During Infusion	Cumulative % of Study Drug Administered
Start	8 mL/hr	2 mL	2%
15 minutes	16 mL/hr	4 mL	6%
30 minutes	24 mL/hr	6 mL	12%
45 minutes	32 mL/hr	8 mL	20% at end of 1 st hr
60 to 180 minutes	40 mL/hr	80 ml	60% at end of 2 nd hr 100% at end of 3 rd hr

Details of the infusion could be modified if the patient had adverse events relating to infusion reactions. Management included the use of antihistamines, and/or corticosteroids prior to or during infusions, a slower rate of idursulfase administration, and/or early discontinuation of idursulfase infusion if serious symptoms developed.

6.1.3.2.5 Efficacy and Safety Variables

The schedule of study procedure is summarized for week 0 (baseline) through Week 53:

Clinical Review
 Joanna W. Ku, MD
 BLA STN125151-0
 Elaprase™ (idursulfase)

Table 6 Flow Chart of Efficacy and Safety Measurements Assessed in Study TKT024 (Source: BLA Submission)

Study Evaluation	Evaluation Weeks													
	0	1	2-8	9	10-17	18	19-26	27	28-35	36	37-44	45	46-52	53
Informed Consent	.													
Blinded Study Drug Infusion
Medical History	.													
Concomitant Medications
Vital Signs (including O2 sat)
AEs ¹
Physical Examination ²	.	.												
Weight and Height ³	.													
Serum Chemistry Laboratory Tests
Hematology Laboratory Tests
Urinalysis
Electrocardiogram (ECG)
Serum Anti-Idursulfase Antibodies (ELISA and neutralizing Abs)
Pulmonary Function Tests ⁴
Echocardiogram
Joint Range of Motion Assessment ⁵
Abdominal MRI
6-Minute Walk Test ⁵
Urine GAG Level (with urine creatinine) ⁶
Functional Disability Measured by CHAQ and Supplemental Questionnaire (HS-FOCUS) ⁷
Full Skeletal Survey (including cervical flexion - extension films) ⁸
Quality of Life Assessments ⁹
Video Documentation of Functional Range of Motion ¹⁰
Pharmacokinetic Study ¹¹	.	.												
Genotype Analysis for Hunter syndrome ¹²	.													

¹ For all patients who were randomized, AE assessment began once patients signed informed consent. While AE assessments occurred weekly at clinic visits, patients and parent(s)/guardian(s) were reminded at every visit to call investigator immediately if the patient experienced any adverse reactions to study drug infusion, or required an unexpected medical visit or hospitalization during the intervening week between study visits.

² Physical examinations included head circumference measurements at baseline and Week 53.

³ Weights taken at baseline, Week 18, and Week 36 were used for the calculation of idursulfase dose for Weeks 1-17, Weeks 18-35, and Weeks 36-52, respectively.

⁴ Performed 2 times at each visit (once per day on 2 different days). At baseline and Week 53, spirometry, lung volume, and DL_{CO} measurements were conducted; at Weeks 18 and 36, spirometry only was conducted.

⁵ Performed 2 times at each visit (once per day on 2 different days).

⁶ Performed 2 times, once per day on 2 different days, at baseline and Week 53; performed only once at Weeks 5, 9, 18, 27, 36, and 45.

⁷ The CHAQ and HS-FOCUS were completed at baseline and at Weeks 18, 36, and 53 of the study. It was completed by the parent/guardian and by the patient (≥12 years of age at the time of enrollment).

⁸ The skeletal survey was not performed at the Children's Hospital at University of Mainz.

⁹ The HUI and CHQ were completed at baseline and at Weeks 18, 36, and 53 of the study. Both instruments were to be completed by the parent/guardian and by the patient (≥12 years of age at the time of enrollment).

¹⁰ Selected study sites participated in the video documentation of functional tasks: Children's Hospital at University of Mainz, Royal Manchester Children's Hospital, Oakland Children's Hospital, and University of North Carolina (UNC) at Chapel Hill.

¹¹ Pharmacokinetic studies were to be performed at the Week 1 and Week 27 infusions of study drug. The pharmacokinetic studies were to be conducted by a subset of study centers: UNC at Chapel Hill, Texas Children's Hospital, Oakland Children's Hospital, St. Louis Children's Hospital, and Hospital de Clinicas de Porto Alegre.

¹² Genotype analyzed at any time during the study, if not previously performed prior to the study. The study center selected the laboratory to perform the analysis.

6.1.4 Efficacy Findings of the Pivotal Study, TKT024

Nine clinical sites participated in this international study (Brazil, Germany, the US, and the UK). Of these, three "satellite" sites were for drug infusion only. The remaining six "main" sites were for purposes of enrollment, randomization, infusion, and efficacy assessment. The number of patients assigned to each of the treatment groups within a center was not necessarily balanced. Rather, the overall study objective was to achieve a balance in baseline age and baseline disease severity across the three treatment groups.

Table 7 List of Investigators Who Enrolled Patients in Study TKT024 (Source: BLA Submission)

Investigator	Site No.	Site
Michael Beck, MD, PhD	012 ^{a, b, d}	Children's University Hospital, Mainz, Germany
Christine M. Eng, MD	048 ^{c, d}	Baylor College of Medicine, Houston, TX, USA
Roberto Giugliani, MD, PhD	020 ^{c, d}	Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil
Paul Harmatz, MD	046 ^{b, c, d}	Children's Hospital Research Center at Oakland, Oakland, CA, USA
Rick A. Martin, MD	045 ^{c, e}	Washington University, St. Louis, MO, USA
Joseph Muenzer, MD, PhD (Principal Investigator)	013 ^{b, c, d}	University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Uma Ramaswami, MD	059 ^f	Addenbrooke's Hospital, Cambridge, UK
Ashok Vellodi, MD	047 ^f	Great Ormond Street Hospital, London, UK
J. Edmond Wraith, MD	044 ^{b, d}	Willink Unit Royal Manchester Children's Hospital, Manchester, UK

^a Did not perform the skeletal survey.

^b Participated in the video documentation of functional tasks.

^c Participated in the pharmacokinetic study.

^d Main center, i.e. performed all major testing at Weeks 0, 18, 36, and 53.

^e Satellite center for main center 013, i.e. performed infusions only.

^f Satellite center for center 044, i.e. performed infusions only.

Patient demographics and baseline clinical characteristics of study TKT024 are summarized:

Table 8 Summary of Patient Demographics at Baseline by Treatment Group: ITT population (Source: BLA Submission)

Clinical Characteristic	Placebo N=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly N=32	EOW N=32	All Idursulfase N=64	
Age at Onset of Hunter syndrome symptoms (months):					
N	31	31	28	59	90 ^a
Mean (SE)	25.39 (3.252)	30.39 (3.751)	27.46 (4.540)	29.00 (2.901)	27.76 (2.204)
Median	24.00	30.00	24.00	24.00	24.00
Min, Max	< 1, 72.0	< 1, 84.0	< 1, 96.0	< 1, 96.0	< 1, 96.0
Age at Diagnosis of Hunter syndrome (months):					
N	32	32	32	64	96
Mean (SE)	57.09 (9.410)	62.09 (9.144)	52.34 (6.855)	57.22 (5.702)	57.18 (4.899)
Median	36.00	48.00	48.00	48.00	48.00
Min, Max	< 1, 276.0	< 1, 240.0	< 1, 180.0	< 1, 240.0	< 1, 276.0
Duration of Hunter syndrome from date of diagnosis to date of study entry (months)					
N	32	32	32	64	96
Mean (SE)	99.99 (13.633)	119.29 (13.446)	120.27 (15.222)	119.78 (10.074)	113.19 (8.124)
Median	77.40	97.80	115.40	101.40	97.80
Min, Max	8.4, 276.0	13.2, 311.0	4.8, 310.8	4.8, 311.0	4.8, 311.0
Baseline Disease Score (N [%]):					
Score 2	0	2 (6.3)	2 (6.3)	4 (6.3)	4 (4.2)
Score 3	7 (21.9)	7 (21.9)	6 (18.8)	13 (20.3)	20 (20.8)
Score 4	14 (43.8)	10 (31.3)	11 (34.4)	21 (32.8)	35 (36.5)
Score 5	9 (28.1)	10 (31.3)	9 (28.1)	19 (29.7)	28 (29.2)
Score 6	2 (6.3)	3 (9.4)	4 (12.5)	7 (10.9)	9 (9.4)
Baseline % Predicted FVC Severity Score* (N [%]):					
Score 1	4 (12.5)	7 (21.9)	6 (18.8)	13 (20.3)	17 (17.7)
Score 2	18 (56.3)	13 (40.6)	12 (37.5)	25 (39.1)	43 (44.8)
Score 3	10 (31.3)	12 (37.5)	14 (43.8)	26 (40.6)	36 (37.5)
Baseline % Predicted FVC (%)					
N	32	32	32	64	NA
Mean (SE)	55.567 (2.182)	55.298 (2.802)	55.147 (2.448)	55.222 (1.846)	
Median	57.360	54.885	54.550	54.885	
Min, Max	30.04, 75.75	15.99, 79.84	27.53, 79.25	15.99, 79.84	

Clinical Characteristic	Placebo N=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly N=32	EOW N=32	All Idursulfase N=64	
Baseline 6MWT Severity Score* (N [%]):					
Score 1	4 (12.5)	6 (18.8)	6 (18.8)	12 (18.8)	16 (16.7)
Score 2	24 (75.0)	20 (62.5)	21 (65.6)	41 (64.1)	65 (67.7)
Score 3	4 (12.5)	6 (18.8)	5 (15.6)	11 (17.2)	15 (15.6)
Baseline 6MWT (meters)					
N	32	32	32	64	NA
Mean (SE)	392.5 (18.72)	391.6 (19.10)	400.6 (17.94)	396.1 (13.01)	
Median	403.0	396.5	416.5	407.5	
Min, Max	49, 540	90, 565	156, 554	90, 565	

Note: Percentages are based on all patients in the ITT population within each treatment group. Data missing where n < 32.

ITT=intent-to-treat; EOW=every other week; FVC=forced vital capacity; 6MWT=6-minute walk test; NA=Not Available.

* 1 = mild (≥ 70% to < 80%); 2 = moderate to severe (≥ 50% to < 70%); 3 = severe to very severe (< 50%).

^a 1 = mild to normal (≥ 500 m); 2 = moderate (≥ 300 m to < 500 m); 3 = severe (< 300 m).

^b Data on age at onset of symptoms of Hunter syndrome were not reported for 6 patients.

Demographic Characteristic	Placebo N=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly N=32	EOW N=32	All Idursulfase N=64	
Head Circumference (cm):					
N	32	32	32	64	96
Mean (SE)	56.60 (0.427)	57.32 (0.415)	57.51 (0.424)	57.41 (0.295)	57.14 (0.244)
Median	56.33	57.60	57.45	57.50	57.00
Min, Max	51.9, 61.5	52.7, 61.5	52.1, 64.0	52.1, 64.0	51.9, 64.0

Note: Percentages are based on all patients in the ITT population within each treatment group. Data were missing where n < 32.

ITT=intent-to-treat; EOW=every other week; mg=milligrams; kg=kilograms; SE=standard error; cm=centimeter(s).

Reviewer's Comment:

Placebo patients were on the average younger, shorter, lighter in weight, and smaller in head circumference, as compared to either of the idursulfase group patients. Also, as compared to the weekly-idursulfase patients, placebo patients were diagnosed earlier with Hunter syndrome, probably correlating with the fact that they showed earlier onset of symptoms. The earlier the diagnosis and onset of the disease, the more severe the form of the disease a patient is likely to have, because severe disease progresses more rapidly. If placebo patients did have a more severe form of the disease, then the improvement gained in idursulfase-weekly treated patients might have been partially contributed by the fact that they had a milder form of the disease to begin with. However, there is considerable overlap among groups for age at onset and baseline disease score.

Four efficacy analysis populations were specified: intent-to-treat population (ITT), modified ITT population (mITT), per-protocol population (PP), and completer population (completer). Because of low dropout rates and good compliance, the ITT, mITT, and the PP were nearly identical in numbers of subjects (See Table 9). The primary efficacy analysis was based on the ITT population, consisting of all 96 randomized patients. Missing observations (patients 024-012-0008 and 024-020-0003) were imputed by carrying forward the last observation or rank, depending on the method of analysis. The modified-ITT (mITT) population excluded only patient 024-12-0008 because he did not have any post-baseline efficacy evaluations before he died after receiving his first and only dose of idursulfase. No imputation method was used for missing data. The PP population included all randomized 96 patients, minus two patients who died: patient 024-012-0008 died after receiving his one and only dose of idursulfase in the weekly group, and patient 024-020-0003 died after receiving 34 placebo infusions in the placebo group. No imputation method was used for missing data. The completer population consisted of all patients who had a baseline and a Week 53 observation. The completer analysis patient population varied for each endpoint analyzed, based on the number of patients who met this definition for the particular endpoint of interest. Ninety-four patients was the maximum number of patients in the completer population (96 randomized patients minus the two patients who died during the course of the study). No imputation method was used for missing data. The primary treatment comparison was made between idursulfase weekly vs. placebo groups in the ITT population.

Table 9 Patient Disposition by Treatment Group: All Enrolled Patients, N (%) in study TKT024 (Source: BLA Submission)

Disposition	Placebo	Idursulfase 0.5 mg/kg			All Patients
		Weekly	EOW	All Idursulfase	
Patients Consented not Randomized					25 ^a
Patients Randomized	32 (100.0)	32 (100.0)	32 (100.0)	64 (100.0)	96 (100.0)
Efficacy Populations:					
ITT	32 (100.0)	32 (100.0)	32 (100.0)	64 (100.0)	96 (100.0)
MITT	32 (100.0)	31 (96.9)	32 (100.0)	63 (98.4)	95 (99.0)
PP	31 (96.9)	31 (96.9)	32 (100.0)	63 (98.4)	94 (97.9)
Completer ^b	31 (96.9)	31 (96.9)	32 (100.0)	63 (98.4)	94 (97.9)
Safety Population	32 (100.0)	32 (100.0)	32 (100.0)	64 (100.0)	96 (100.0)
Study Status:					
Discontinued	1 (3.1)	1 (3.1)	0	1 (1.6)	2 (2.1)
Completed	31 (96.9)	31 (96.9)	32 (100.0)	63 (98.4)	94 (97.9)
Reason(s) for Discontinuation					
Death	1 (3.1)	1 (3.1)	0	1 (1.6)	2 (2.1)

Note: Percentages are based on all randomized patients within each treatment group.
 N=number of patients; ITT=Intent-to-treat; PP=Per Protocol; MITT=Modified Intent-to-treat; AE=Adverse Event; EOW=every other week
^a 24 patients did not meet the entry criteria and 1 patient met the entry criteria but withdrew consent prior to randomization.
^b The completer analysis patient population could have varied for each endpoint analyzed, as it was based on the number of patients who met this definition for the specified endpoint. These 94 patients were the maximum number of patients in the completer population.

Compliance was excellent. In study TKT024, aside from the two patients who died, the remaining 94 patients completed the study, and all received $\geq 80\%$ of their protocol-required 52 infusions with no patient missing more than three consecutive infusions.

Table 10 Treatment Compliance: ITT Patient Population (BLA Submission)

Parameter	Placebo (n=32)	Idursulfase Weekly (n=32)	Idursulfase EOW (n=32)
Total Number of Infusions Received			
Mean (SE)	50.4 (0.6)	49.4 (1.6)	50.9 (0.2)
Median	51	51	51
Min, max	34, 52	1, 52	49, 52
Missed infusions n (%)			
None	16 (50.0)	16 (50.0)	12 (37.5)
1	7 (21.9)	8 (25.0)	9 (28.1)
2 to 4	7 (21.9)	8 (25.0)	11 (34.4)
≥ 5	2 (6.3)	0	0
Study Infusion Compliance n (%) ^a			
Patients receiving $\geq 80\%$ of infusions	31 (96.9)	31 (96.9)	32 (100.0)
Patients missing ≥ 4 consecutive infusions	0	0	0

^a A missed dose is defined as $< 50\%$ of the planned infusion. For the 2 patients who died, compliance was determined using the scheduled doses up until the time of death. Patient 012-0008 (idursulfase weekly) died after receiving the Week 1 infusion and Patient 020-0003 (placebo) died after receiving the Week 34 infusion. EOW=Every other week; SE= Standard error; min=Minimum; max=Maximum.

At baseline, all ITT patients had extensive medical and surgical histories, and they were similar across all treatment groups, except for that in the idursulfase EOW group, patients had a lower incidence of psychiatric histories (12.5%) than the weekly group (43.8%), or the placebo (40.6%) group. The organ systems most affected were ENT, musculoskeletal, GI, cardiovascular, skin, respiratory, and neurologic systems. All four deaths during the course of TKT024 and TKT024EXT were related to respiratory failure but only 84% of patients in the idursulfase groups, and 78% of patients in the placebo group had at least one prior medical condition related to the respiratory system, as compared to 100% of patients who had ENT, and 100% of patients who had musculoskeletal co-morbidities across all three treatment groups. 5.2% of patients were on a bronchodilator when they enrolled in the study, suggesting that only a small percentage of patients had symptomatic obstructive lung disease. There were no clinically important differences among the treatment groups at baseline in the use of concomitant medications, including pain medications, prior to the start of the study. The most common classes of concomitant medication initiated prior to study start among all patients combined were (in decreasing order) angiotensin converting enzyme (ACE-inhibitors) (18.8% of all patients), amides (i.e. lidocaine, prilocaine) (7.3% of all patients), and selective beta-2-adrenoreceptor agonists (5.2% of all patients).

6.1.4.1 The Primary Efficacy Endpoint

The primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to Week 53 in distance walked during a 6-Minute Walk Test (6-MWT) and the ranks of the change in %-predicted FVC. The 2-component composite variable was calculated according to O'Brien's procedure⁵. To derive this combined primary efficacy variable, the change from baseline to the end of the study (at Week 53) in the %-predicted FVC and the 6MWT were

⁵ O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics*. 1984; 40:1079-1087

calculated for each patient. Within each component (6MWT and %-predicted FVC), change in absolute variable were *ranked*. The lowest change value was assigned a rank of 1; the next lowest change was assigned a rank of 2, etc., up to a rank of 96. The more improvement the patient made in that variable (6MWT or %-predicted FVC), the higher his ranking was for that variable. The composite score was simply the sum of the two ranks (one for 6MWT, and one for %-predicted FVC). The following is an example of a formula of how the composite score was calculated and analyzed:

- Y_{ijk} represents the k^{th} variable for the j^{th} patient in treatment group i (where, $k=1, 2$; $j=1, \dots, n_i$; $i=1, 2$). A non-parametric (e.g., rank-sum test) or a parametric (e.g., t-test or ANCOVA) type of test could be applied to the ranked data. R_{ijk} represents the rank of Y_{ijk} among all values of variable k in the pooled treatment groups (i.e., for 1 of the components, for example the 6MWT, the patient data from the 2 (or 3) treatment groups being compared was pooled and then ranked) and S_{ij} was defined as the sum of the ranks assigned to the j^{th} patient in treatment group 1, i.e., $S_{ij} = \text{composite variable} = R_{ij1} + R_{ij2}$.

The treatment groups were then compared on the scores of the composite variable (i.e., S_{ij} values) using an analysis of covariance (ANCOVA) on the ranks, with treatment group and region fitted as factors and baseline patient age (3 stratification levels) and baseline disease score (3 stratification levels) as covariates.

The primary treatment comparison of the two-component composite variable was between the weekly idursulfase treated group and the placebo group. This primary comparison was the pivotal comparison for the determination of idursulfase efficacy. The two-component composite scores were also summarized by region for all treatment groups (idursulfase weekly, idursulfase every other week, placebo, and all idursulfase patients). Clinical interpretation of a significant difference in the two-component composite score between treatment groups was further supported by analysis of the individual components of the composite variable.

FDA statistical reviewer, Janice Derr, PhD selected nine patients, including the two who had imputed endpoints, to follow the steps that were used to construct the primary efficacy endpoint. She was able to confirm calculations for these patients and obtain the same summary statistics that were reported by the Applicant for each treatment group.

As shown in Table 11, the two-component composite score for the idursulfase 0.5 mg/kg weekly group (69.81 ± 7.03) was statistically significantly greater than for the placebo group (50.86 ± 8.07) for the ITT population ($p=0.0049$; 95% CI [5.99, 31.93]), with an adjusted treatment difference of 18.96 ± 6.47 . The greater mean two-component composite score, a measure of the sum of the ranked changes from baseline to week 53 in % predicted FVC and 6MWT distance, seen in the idursulfase weekly group demonstrated that idursulfase 0.5 mg/kg administered as a 3-hour IV infusion weekly met the pre-specified criterion for efficacy in Hunter syndrome.

Table 11 Summary of the Primary Treatment Comparison Based on ANCOVA of the Two-Component Composite Score—Treatment Difference Between Idursulfase Weekly and Placebo in Sum of the Ranked Changes from Baseline to Week 53: ITT Patient Population (Source: BLA Submission)

Treatment Comparison	p-value ^a	Treatment Differences	
		Mean (SE)	95% CI
ITT Population Analysis Primary Endpoint: Idursulfase Weekly vs Placebo	0.0049	18.96 (6.47)	5.99, 31.93

Note: The 2-component composite variable consists of the sum of the ranked changes from baseline to Week 53 for % predicted FVC and 6MWT (distance in meters).

SE: Standard error; ITT= Intent-to-treat; CI=Confidence Interval.

^a p-value for treatment difference based on ANCOVA model containing treatment, region, baseline patient age (3 stratification levels), and baseline disease score (3 stratification levels).

For the ITT population, the two-component composite score of the sum of the ranked changes (adjusted mean ± SE) for the idursulfase weekly and placebo groups and for the idursulfase every-other-week and placebo groups are shown in Figure 2 and Table 12.

Figure 2 Treatment Comparisons of the two-component Composite Score Sum of the Ranked Changes from Baseline to Week 53 (Adjusted Mean ± SE) for the Primary Endpoint of Idursulfase Weekly and Placebo and for the Secondary Treatment Comparison of Idursulfase Every-Other-Week and Placebo: ITT Patient Population (Source: BLA Submission)

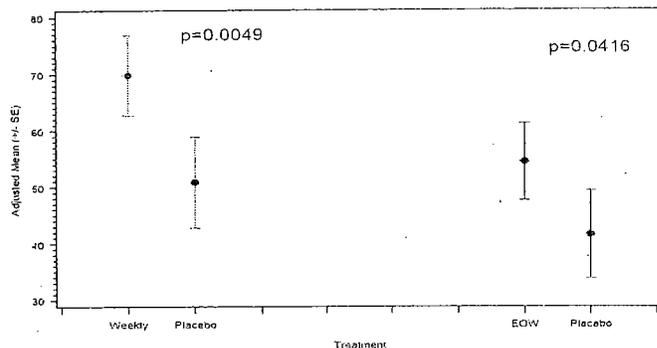


Table 12 Summary of Treatment Comparisons Based on ANCOVA of the Two-Component Composite Score: Sum of the Ranked Changes from Baseline to Week 53 in the ITT Patient Population (Source: modified from BLA Submission)

Treatment Adjusted Comparisons	P-value	Treatment Difference in Mean (SE)	
		95% CI	
Weekly vs. Placebo	0.0049	19.0 (6.7)	6.0 – 31.9
EOW vs. Placebo	0.0416	12.9 (6.2)	0.5 – 15.2
Weekly vs. EOW	0.1329	10.8 (7.1)	-3.4 – 25.1
All (Weekly + EOW) vs. Placebo	0.0069	23.7 (8.6)	6.7 – 40.7

Clinical Review
 Joanna W. Ku, MD
 BLA STN125151-0
 Elaprase™ (idursulfase)

As shown in Table 13, in the ANCOVA model effects baseline patient age and disease score were not statistically significant. But by regions (South America, US, Europe) there was a statistically significant effect (p=0.0225). South America appears to have the lowest mean change in score for both the idursulfase and placebo groups, which may be due to the fact that patients at this site were younger and more than half of the patients in this region had a baseline disease severity score of 5 or 6 as defined by the investigator. An audit by the Applicant of the site did not reveal any procedural explanation(s). Additional sensitivity analysis by the FDA statistical reviewer, Janice Derr, PhD, confirmed that the statistical results did not change with the exclusion of the Brazil site (the only site in the South American region).

Table 13 ANCOVA of the Two-Component Composite Score for Each Treatment Comparison: Sum of the Ranked Changes from Baseline to week 53 in the ITT Population (Source: BLA Submission)

ANCOVA of the Two-Component Composite Score for Each Treatment Comparison
 Sum of the Ranked Changes from Baseline to Week 53
 ITT Patient Population
 Idursulfase Weekly vs Placebo **

	n	Mean (SE)				p-value
		Ranked Baseline	Ranked Week 53 Change	Adjusted Ranked Week 53 Change	Adjusted Ranked 95% CI	
Idursulfase Weekly	32	85.22 (5.67)	73.72 (5.52)	69.81 (7.03)		
Placebo	32	64.78 (4.35)	56.28 (4.14)	59.86 (6.07)		
Treatment Comparison (Change) Idursulfase Weekly vs Placebo **				18.96 (6.47)	5.99, 31.93	0.0049
ANCOVA Model Effects:						
Treatment						0.0049
Region						0.0225
Baseline Patient Age						0.2937
Baseline Disease Score						0.1980

Table 14 Summary Statistics for the 2-Component Composite Variable by Treatment Group and Region—Sum of the Ranked Changes from Baseline to Week 53: ITT Patient Population (Source: BLA Submission)

Treatment Group	2-Component Composite Score			
	Region			
	North America	South America	Europe	All Regions
Idursulfase Weekly				
N	11	7	14	32
Mean (SE)	73.23 (7.61)	48.57 (7.99)	79.50 (9.98)	70.58 (5.66)
Median	80.00	49.00	92.75	71.25
Min, Max	31.0, 104.0	13.0, 75.0	5.0, 123.0	5.0, 123.0
Idursulfase EOW				
N	11	7	14	32
Mean (SE)	63.18 (10.24)	48.00 (8.13)	62.18 (6.43)	59.42 (4.82)
Median	53.00	49.00	60.25	54.00
Min, Max	18.0, 110.0	21.0, 87.0	33.0, 109.0	18.0, 110.0
All Idursulfase				
N	22	14	28	64
Mean (SE)	109.07 (9.12)	78.46 (8.65)	111.98 (8.93)	103.65 (5.54)
Median	121.00	79.00	107.75	102.75
Min, Max	31.0, 167.0	19.5, 139.0	7.0, 186.0	7.0, 186.0
Placebo				
N	12	7	13	32
Mean (SE)	92.00 (10.45)	59.64 (10.93)	89.00 (9.83)	83.70 (6.33)
Median	95.25	60.50	85.50	85.50
Min, Max	18.5, 139.5	22.0, 97.5	42.0, 172.0	18.5, 172.0

Note: The 2-component composite variable consists of the sum of the ranked changes for % predicted FVC and 6MWT (distance in meters). The lowest change value is assigned to the smallest rank. Idursulfase weekly vs placebo is the primary treatment comparison. EOW=every other week; ITT=intent-to-treat; SE=standard error.

Patient with disease score of 5 and 6 appeared to show less improvement than those with a score of 3 or 4 and this improvement was greater in the idursulfase treatment groups than the placebo group (Table 15). There were too few patients with a score of 2 in any treatment group to draw any conclusions about patients in this category.

Table 15 Summary Statistics for the 2-Component Composite Variable by Treatment Group, Baseline Disease Score, and Baseline Patient Age—Sum of the Ranked Changes from Baseline to week 53: ITT Patient Population (Source: BLA Submission)

Treatment Group	2-Component Composite Variable					
	Baseline Disease Score Category			Baseline Patient Age Category (Years)		
	2	3 or 4	5 or 6	5 to 11	12 to 18	19 to 25
Idursulfase Weekly						
N	2	17	13	14	10	8
Mean (SE)	83.00 (21.00)	82.29 (7.64)	61.08 (7.97)	78.75 (8.81)	79.15 (9.00)	58.13 (10.51)
Median	83.00	92.00	62.50	86.50	85.75	66.25
Min, Max	62.0, 104.0	14.5, 123.0	6.0, 102.0	14.5, 123.0	36.0, 116.0	6.0, 97.0
Placebo						
N	0	21	11	15	10	7
Mean (SE)		61.95 (4.86)	45.45 (6.85)	62.73 (6.86)	50.55 (6.78)	50.64 (6.65)
Median		59.00	41.50	59.00	55.25	48.00
Min, Max		22.5, 112.0	15.0, 87.0	15.0, 112.0	15.5, 80.5	27.5, 77.0
Idursulfase EOW						
N	2	17	13	14	9	9
Mean (SE)	41.25 (1.75)	74.47 (7.15)	67.62 (6.81)	73.18 (7.89)	66.06 (11.28)	67.61 (5.80)
Median	41.25	72.00	62.00	71.00	67.00	61.00
Min, Max	39.5, 43.0	25.5, 116.0	22.0, 100.0	38.5, 116.0	22.0, 113.5	42.5, 99.0
Placebo						
N	0	21	11	15	10	7
Mean (SE)		66.81 (5.14)	48.14 (7.18)	66.80 (7.21)	52.75 (7.77)	57.57 (6.30)
Median		64.00	51.00	65.00	59.00	52.00
Min, Max		20.5, 120.0	11.5, 86.5	14.0, 120.0	11.5, 92.0	35.5, 82.0
Idursulfase Weekly						
N	2	17	13	14	10	8
Mean (SE)	79.00 (25.00)	79.00 (7.93)	58.27 (8.06)	75.21 (9.17)	77.00 (9.24)	54.44 (10.33)
Median	79.00	87.00	54.00	81.00	83.00	61.00
Min, Max	54.0, 104.0	13.0, 123.0	5.0, 103.0	13.0, 123.0	37.0, 117.0	5.0, 95.0
Idursulfase EOW						
N	2	17	13	14	9	9
Mean (SE)	33.75 (6.25)	64.24 (7.17)	57.08 (6.77)	63.07 (7.82)	57.44 (10.88)	55.72 (6.44)
Median	33.75	55.00	55.00	56.75	55.00	50.00
Min, Max	27.5, 40.0	21.0, 110.0	18.0, 90.0	27.5, 110.0	18.0, 109.0	30.5, 89.0

The Applicant conducted several pre-specified sensitivity analysis on the primary efficacy endpoint: the ANCOVA analysis was applied to alternative versions of the analysis database, and a Wilcoxon rank-sum test was also used to analyze the composite endpoint. The results remained unchanged with respect to the statistical significance of the outcomes.

As Dr. Derr pointed out in her Statistical Review, the clinical interpretation of the composite endpoint may be challenging because the average summed rank in each treatment group combines endpoints with different scales of measurement. Since the global null hypothesis of no overall treatment effect is rejected, a follow-up evaluation of 6MWT and %FVC is important in providing a clinical interpretation of the action of idursulfase. This relationship between the composite endpoint and its components may best be represented statistically with a multiple comparison procedure. For example, the global test on the composite endpoint could serve as a gatekeeper for the follow-up tests on the components of the endpoint, with appropriate protection for Type I error. Study TKT024 did not specify this gatekeeper approach to evaluating the composite endpoint and its components. The study protocol describes 6MWT and %-predicted FVC as secondary efficacy endpoints. However, in the sense that the primary endpoint serves as a gatekeeper to evaluating all of the secondary efficacy endpoints, the Applicant's

approach may serve a similar purpose from a clinical perspective, the components of the composite endpoint have an important role in the efficacy evaluation. Hence, from a statistical standpoint, the individual components of the composite endpoint have an important role in the efficacy evaluation.

The 6MWT and %-predicted FVC tests were reviewed as if they had been follow-up tests to the global test on the composite endpoint. With the rejection of the global null hypothesis on the composite endpoint at an α of 0.05, the Bonferroni-Holm procedure can be applied to the tests on 6MWT and %FVC. The smaller of the two p-values is evaluated at an α of 0.05, and, if this endpoint is significant, the other endpoint is evaluated at an α of 0.05/2, or 0.025. This procedure, when pre-specified at the protocol stage, would provide strong control of Type I error rate for the composite endpoint and follow-up tests on its components⁶. This analysis of the individual components also allowed determination of the clinical relevance of each component to the observed global benefit.

From a clinical perspective, as well, the concept of a composite primary endpoint may not be as easily understood as the individual components of the composite endpoint. So for both statistical and clinical reasons, individual components (6MWT and %-predicted FVC) of the composite endpoint were examined separately.

6.1.4.1.1 The 6 Minute Walk Test (6MWT)

The first component of the composite endpoint was the 6MWT. In the adjusted analysis, the weekly idursulfase-treated group experienced a 35 meter (38 yard) greater mean increase in the distance walked in the six minutes compared to placebo, and the difference was statistically significant ($p=0.01$). The treatment difference between the idursulfase EOW and placebo group for the mean change from baseline to week 53 in total distance walked in the 6MWT, however, was not statistically significant ($p=0.07$), prompting the Applicant to withdraw the every-other-week dosing regimen from dosing recommendation.

Table 16 Total Distance Walked in Six-Minute Walk Test Observed Mean Change from Baseline to Week 53 ANCOVA Analysis: ITT Patient Population (Source: BLA Submission)

Treatment Comparison	N	Total Distance Walked in 6MWT (m)			Adjusted 95% CI ^a	p-value ^b
		Mean (SE)		Week 53 Change		
		Baseline	Observed			
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.95 (10.89)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	1.86 (11.84)		
Difference				35.09 (13.69)	7.66, 62.52	0.0131
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	25.88 (10.67)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	2.08 (11.35)		
Difference				23.80 (13.03)	-2.31, 49.91	0.0732
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.13 (12.46)		
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	22.95 (12.69)		
Difference				13.19 (15.43)	-17.72, 44.09	0.3963
All Idursulfase vs Placebo						
All Idursulfase	64	396.09 (13.01)	37.30 (7.99)	30.76 (8.39)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	0.97 (11.55)		
Difference				29.79 (12.25)	5.44, 54.14	0.0171

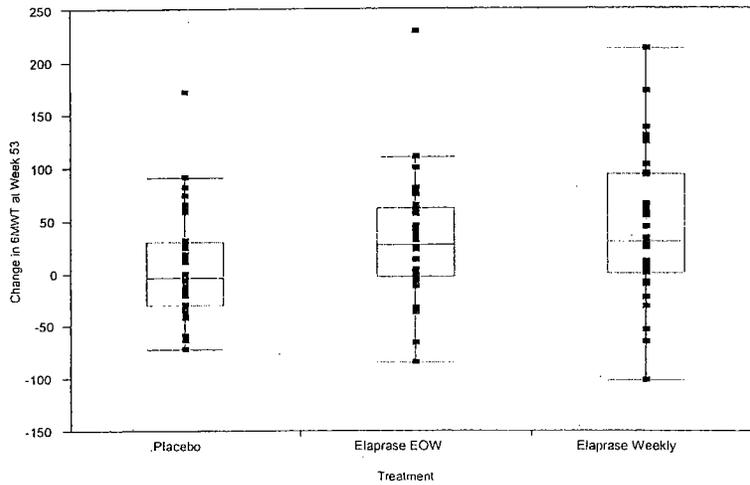
SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; 6MWT= 6-minute walk test; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment, baseline 6MWT severity score (3 levels), and baseline patient age (3 levels)

6 Lehman, W. et al. 1991 Procedures for two-sample comparisons with multiple endpoints controlling the experimentwise error rate. Biometrics, 1991 Vol 47: 511-521

Figure 3 Scatter Plot of Change in 6MWT at Week 53 in Study TKT024, ITT population

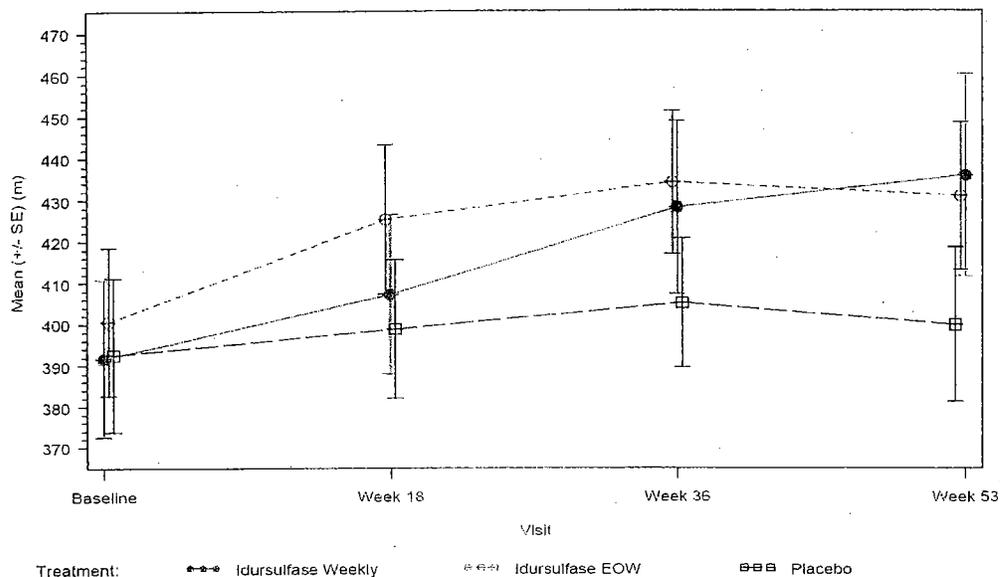


The mean of 6MWT distance walked from baseline by visit and treatment group in the ITT patient population is tabulated and depicted in a graph:

Table 17 Summary Statistics for 6MWT Distance Walked: Observed Values and Change from Baseline by Visit and Treatment Group in the ITT Population (Source: BLA Submission)

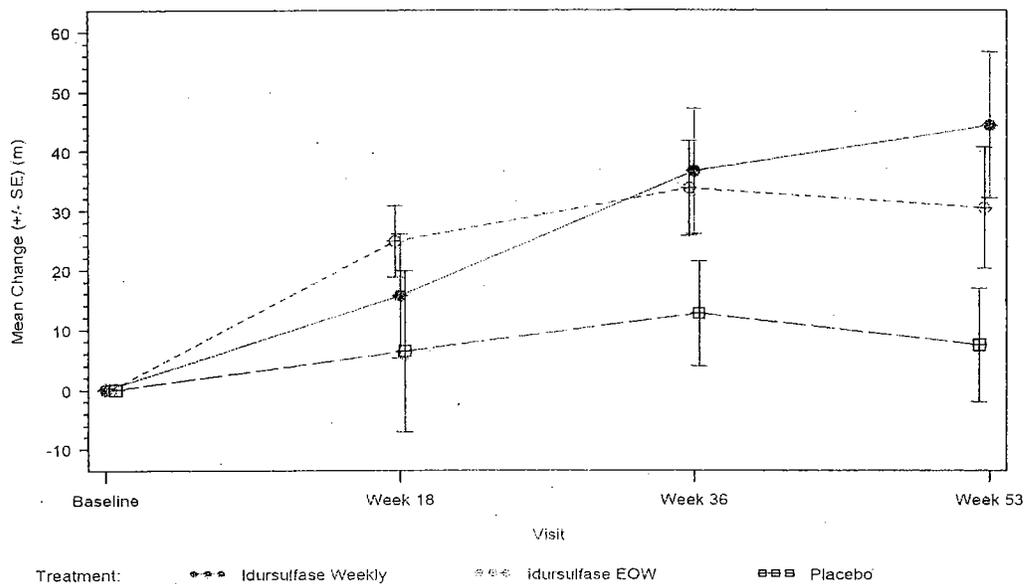
Treatment Group	Statistic	Actual Value				Change From Baseline		
		Baseline	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53
Idursulfase Weekly	n	32	32	32	32	32	32	32
	Mean	391.6	407.2	428.1	435.9	15.6	36.5	44.3
	Std. Err.	19.10	19.29	20.83	24.32	10.39	10.61	12.31
	SD	108.04	109.13	117.81	137.59	58.77	59.99	69.61
	Minimum	90	90	90	90	-134	-54	-102
	Median	396.5	426.5	435.5	429.0	8.5	28.5	30.5
	Maximum	565	562	609	668	207	255	212
Idursulfase EOW	n	32	32	32	32	32	32	32
	Mean	400.6	425.3	434.2	430.9	24.7	33.6	30.3
	Std. Err.	17.94	17.97	17.21	17.81	6.02	8.06	10.25
	SD	101.50	101.68	97.33	100.75	34.05	45.58	57.98
	Minimum	156	180	232	180	-82	-81	-85
	Median	416.5	430.0	455.5	434.0	24.5	35.0	27.5
	Maximum	554	590	584	617	98	137	228
Placebo	n	32	32	32	32	32	32	32
	Mean	392.5	398.8	405.0	399.8	6.3	12.6	7.3
	Std. Err.	18.72	18.81	15.56	18.72	13.46	8.76	9.46
	SD	105.87	95.12	88.03	105.90	76.16	49.57	53.51
	Minimum	49	120	163	37	-88	-64	-72
	Median	403.0	401.0	412.5	411.5	-6.5	10.0	-4.0
	Maximum	540	611	555	588	321	171	171

Figure 4 Mean Observed Total Distance Walked in 6-MWT at Each Visit: ITT Patient Population (Source: BLA Submission)



Mean changes from baseline to each visit in 6MWT distance are depicted graphically:

Figure 5 Mean Changes from Baseline to Each Visit in 6MWT Distance Walked: ITT Patient Population (Source: BLA Submission)



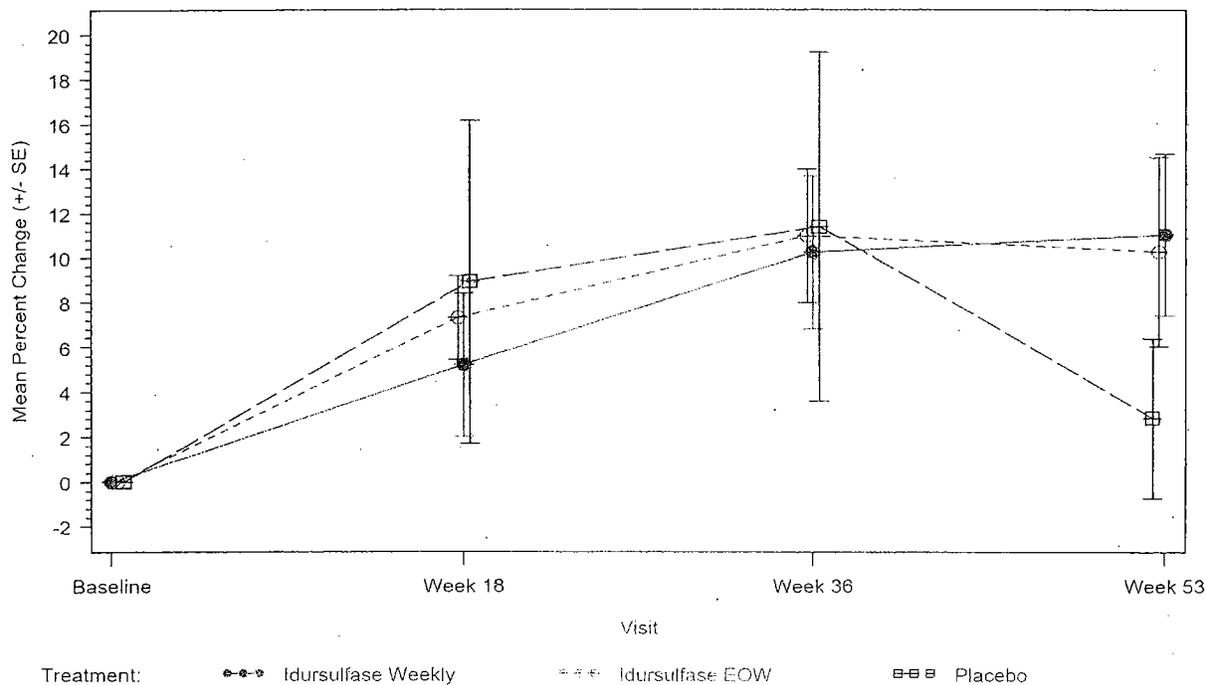
Although the absolute mean change from baseline to Week 53 in total distance walked in the 6MWT for the ITT population (as well as the PP and MITT populations) showed a statistically significant ($p=0.01$) positive treatment difference observed between idursulfase weekly and placebo groups (difference of 35

meters), the adjusted mean *percentage* changes from baseline to week 53 in 6MWT distance walked did not show a statistically significant treatment difference:

Table 18 Summary of Treatment Comparisons Based on ANCOVA of the 6MWT Distance Walked Percent Change from Baseline to Week 53 in the ITT Population (Source: BLA Submission)

Treatment Adjusted Comparisons	p-value	Treatment Difference	
		Mean (SE)	95% CI
Idursulfase Weekly vs Placebo **	0.1187	7.66 (4.64)	-2.03, 17.35
Idursulfase EOW vs Placebo	0.1742	7.16 (5.20)	-3.26, 17.57
Idursulfase Weekly vs EOW	0.9510	0.33 (5.42)	-10.53, 11.20
All Idursulfase vs Placebo	0.1007	7.38 (4.45)	-1.46, 16.22

Figure 6 Mean Percent Change from Baseline in 6MWT Distance Walked (meters) by Visit and Treatment Group: ITT Population (Source: BLA Submission)



Reviewer’s comment: The 6MWT results demonstrated that there although there was a positive treatment effect in the difference between the idursulfase weekly and placebo groups for the absolute mean change from baseline to week 53 in total distance walked in the 6MWT, the difference was modest, i.e. 35 meters. Moreover, the total distance walked at week 53 between treatment groups was not statistically different. Finally, the difference in the mean percentage changes from baseline to week 53 between two groups was not statistically significant. The treatment effect on 6MWT, although demonstrated, is modest.

Additional Sensitivity Analysis: Infusion Reactions and 6MWT

The 6MWT is an effort-dependent test. Because an infusion reaction could un-blind the treatment, which might prompt the patient to make a greater effort or the investigator encourage the patients more, the pivotal trial TKT024 implemented strict measures to minimize such bias during the conduct of the 6MWT. In addition to the precautions taken during conduct of the trial, the question of whether the occurrence of an infusion reaction biased the results of the 6MWT was investigated with several additional analyses by the Applicant.

First, the numbers of patients who actually experienced at least one infusion-related adverse event (defined as *any* related adverse event that occurred within 24 hours after the start of an infusion in the pivotal study) were tabulated and compared. The results showed very similar rates of these infusion reactions adverse events among the three groups on a patient level, as demonstrated by the following table:

Table 19 Number of Patients Experiencing Infusion Reactions

	Treatment Group		
	Weekly Idursulfase N = 32 n (%)	EOW Idursulfase N = 32 n (%)	Placebo N = 32 n (%)
≥ 1 infusion-related AE	22 (68.8)	22 (68.8)	21 (65.6)
≥ 1 infusion reaction	19 (59.4)	19 (59.4)	19 (59.4)
≥ 5 infusion reactions	8 (25.0)	9 (28.1)	6 (18.8)
≥ 5 infusions with at least one infusion reaction/infusion	6 (18.8)	8 (25.0)	6 (18.8)

EOW=Every other week.
 Infusion-related AE was defined as any related AE that occurred within 24 hours after the start of an infusion.

The above per-protocol definition of an infusion-related AE was designed to be conservative on the side of greater sensitive. It captured many non-specific reactions that may not have had any relations to the actual infusion itself, but rather, they happened to have occurred within 24 hours after the start of an infusion.

The question was then reassessed using a more specific definition of an infusion reaction. Several additional analyses were conducted using a more objective definition of an infusion reaction (which was a subset of infusion-related adverse events), and included only objective and quantifiable AEs that were

more characteristic of allergic reactions (i.e. the occurrence of any of the following preferred AE terms within 24 hours of an infusion: tachycardia NOS, cyanosis NOS, hypertension NOS, flushing, hypotension NOS, hot flushes NOS, tachypnoea, wheezing, dyspnoea NOS, hypoxia, swollen tongue, rash NOS, pruritus, urticaria NOS, rash pruritic, erythema, rash macular, face oedema, pruritus generalized, urticaria generalized, pyrexia, rigors, blood pressure increased, or heart rate increase). Subjective or non-specific terms (e.g. malaise, nausea, etc.) were not included in this analysis. The occurrence of any of these infusion reactions may have been more likely to be perceived by the investigators be caused by active study drug. It was also hypothesized that a greater frequency of reactions may have had some bearing on the ability of investigators or patients to the identity of study drug. The number patients who met each of the following criteria were tabulated by arm using the more specific definition of an infusion reaction: 1) presence of at least one infusion reaction during the entire study period, 2) presence of at least five infusions during the entire study period, and 3) presence of at least one infusion reaction/five different infusions. As shown in the following table, the numbers of patients who met these criteria were similar in each treatment arm. Therefore it was unlikely that the occurrence of infusion reaction would enable investigators or patients to deduce treatment assignment for any given patient.

Table 20 Numbers of Patients Experiencing Infusion Reactions in Study TKT024 (Source: BLA Submission)

	Treatment Group		
	Weekly Idursulfase N = 32 n (%)	EOW Idursulfase N = 32 n (%)	Placebo N = 32 n (%)
≥ 1 infusion-related AE	22 (68.8)	22 (68.8)	21 (65.6)
≥ 1 infusion reaction	19 (59.4)	19 (59.4)	19 (59.4)
≥ 5 infusion reactions	8 (25.0)	9 (28.1)	6 (18.8)
≥ 5 infusions with at least one infusion reaction/infusion	6 (18.8)	8 (25.0)	6 (18.8)

EOW=Every other week.

Infusion-related AE was defined as any related AE that occurred within 24 hours after the start of an infusion.

For either the weekly or the placebo group, the occurrence of an infusion reaction did not influence mean distance walked ($p > 0.10$). Based on two-way ANOVA, there was no evidence that the occurrence of an infusion reaction biased the performance during the 6MWT.

Table 21 ANOVA and ANVOCA Results for 6MWT for ITT Weekly and Placebo Patients in Study TKT024 (Source: BLA Submission)

	Regardless of Infusion Reactions	No Infusion Reaction vs. ≥ 1	≥ 5 Infusion Reactions vs. ≥ 5	≥ 5 Infusions with at Least 1 Infusion Reaction vs. ≥ 5
	p-value ^a	p-value ^b	p-value ^b	p-value ^b
Idursulfase weekly vs. placebo treatment difference	0.013	0.041	0.041	0.044
Infusion reaction (+) vs. infusion reaction (-) treatment difference	n/a	0.562	0.494	0.626
Treatment x infusion reaction	n/a	0.174	0.836	0.719
Weekly (infusion reaction difference)	n/a	0.577	0.721	0.928
Placebo (infusion reaction difference)	n/a	0.171	0.549	0.549

^a p-value for treatment difference based on ANCOVA model containing region, treatment, and baseline 6MWT value fitted as factors and baseline patient age (3 levels) and baseline 6MWT score (3 levels) as covariates.

^b p-value based on 2-way ANOVA model containing treatment, infusion reactions (2 levels), and the infusion reaction by treatment interaction, with change from baseline (improvement) in 6MWT as the dependent variable.

6.1.4.1.2 Percent Predicted FVC (%-predicted FVC)

The second component of the composite primary endpoint was the %-predicted FVC. Patients in the idursulfase weekly group had a greater average improvement in percent-predicted FVC at Week 53 compared with the placebo group. However, the 95% confidence interval of this comparison included zero, and the p-value for this comparison was 0.07, not meeting the statistical significance. Neither did the MITT or PP populations reach statistical significance in this variable. Furthermore, the %-predicted FVC change from baseline to Week 53 had a mean difference of only 4.3% between idursulfase weekly and placebo group, which is of unclear clinical significance, as discussed in Section 6.1.2 General Discussion of Endpoints.

Table 22 Percent Predicted Forced Vital Capacity Observed and Adjusted Mean Change from Baseline to Week 53 ANCOVA Analysis: ITT Patient Population (Source: BLA Submission)

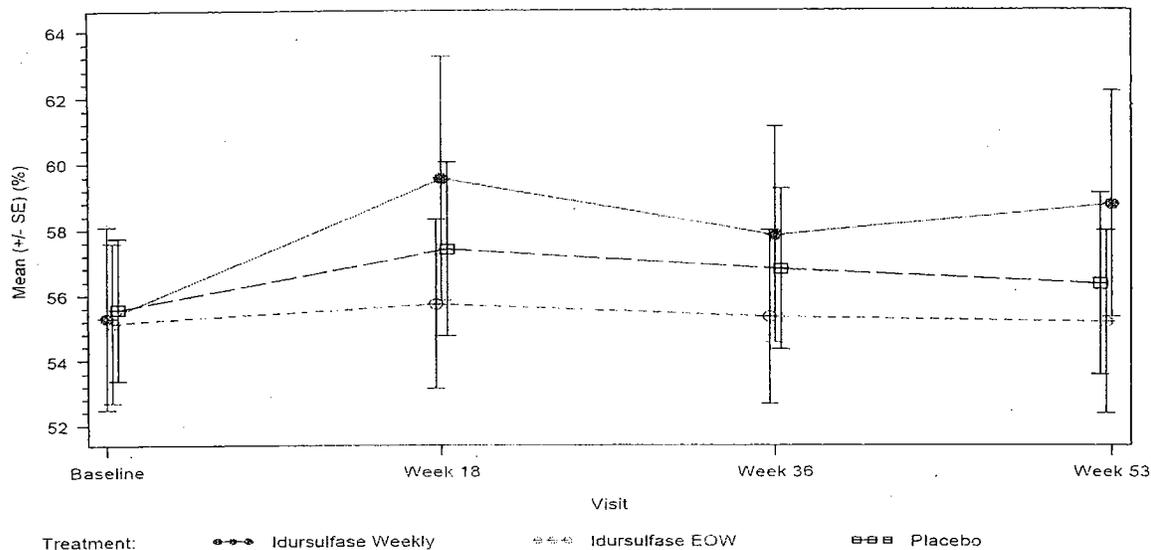
Treatment Comparison	N	Observed % Predicted FVC Mean (SE)			Adjusted 95% CI ^a	p-value ^b
		Baseline	Week 53 Change			
			Observed	Adjusted ^a		
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.29 (1.73)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.99 (1.85)		
Difference				4.28 (2.27)	-0.27, 8.83	0.0650
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.37 (1.59)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-1.49 (1.67)		
Difference				0.12 (2.08)	-4.04, 4.28	0.9531
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.82 (1.64)		
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.66 (1.68)		
Difference				3.49 (2.13)	-0.79, 7.76	0.1079
All Idursulfase vs Placebo						
All Idursulfase	64	55.22 (1.85)	1.72 (1.12)	0.00 (1.21)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.11 (1.69)		
Difference				2.11 (1.89)	-1.65, 5.87	0.2675

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment and baseline %-predicted FVC, baseline patient age (3 levels) and baseline disease score (3 levels).

Figure 7 Mean Percent Predicted FVC (%) by Visit and Treatment Group: ITT Patient Population (Source: BLA submission)



Reviewer's comment: due to lack of statistical significance, uncertainty in clinical significance, and methodological difficulties (discussed in Section 6.1.2 General Discussion of Endpoints), it is problematic to assign clinical significance to the results %-predicted FVC. This single endpoint cannot be expected to serve as a surrogate for the range of possible pulmonary defects in Hunter syndrome, which include upper and lower airway obstruction as well as restriction.

6.1.4.2 Secondary Endpoints

A multitude of secondary and exploratory endpoints were explored to capture any other effects that idursulfase may have on the diverse clinical manifestation of Hunter syndrome.

6.1.4.2.1 Absolute FVC

For populations matched for age, sex, height, and race at baseline, the absolute FVC can be used. A product that has an effect on growth may affect the FVC concomitantly; in which case, the absolute FVC is a surrogate for the growth that has occurred.

The adjusted mean changes from baseline to Week 53 in absolute FVC (difference of 0.19L, or 190 cc) was statistically significant, $p=0.001$, and greater for the idursulfase weekly group compared with the placebo group.

Table 23 Forced Vital Capacity Absolute Volume (L) Mean Change from Baseline to Week 53 ANCOVA Analysis: ITT Patient Population (Source: BLA submission)

Treatment Comparison	N	Actual Baseline FVC (L)	Change to Week 53 in FVC Absolute Volume (L) Mean (SE)		Adjusted 95% CI ^a	p-value ^b
			Observed Change	Adjusted Change ^a		
Idursulfase vs Placebo: Primary Comparison						
Idursulfase Weekly	32	1.19 (0.10)	0.22 (0.05)	0.18 (0.04)	0.08, 0.30	0.0011
Placebo	32	1.09 (0.09)	0.06 (0.03)	-0.01 (0.04)		
Difference				0.19 (0.06)		
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	1.17 (0.10)	0.07 (0.03)	0.06 (0.03)	-0.04, 0.10	0.3735
Placebo	32	1.09 (0.09)	0.06 (0.03)	0.02 (0.03)		
Difference				0.03 (0.04)		
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	1.19 (0.10)	0.22 (0.05)	0.18 (0.04)	0.02, 0.25	0.0176
Idursulfase EOW	32	1.17 (0.10)	0.07 (0.03)	0.05 (0.04)		
Difference				0.13 (0.06)		
All Idursulfase vs Placebo						
All Idursulfase	64	1.18 (0.07)	0.15 (0.03)	0.12 (0.03)	0.02, 0.20	0.0135
Placebo	32	1.09 (0.09)	0.06 (0.03)	0.00 (0.04)		
Difference				0.11 (0.04)		

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week.

^a Adjusted means (LS Means), adjusted SEs from the fitted ANCOVA model, and the difference in the LS means with the corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment and baseline FVC, baseline patient age (3 levels) and baseline FVC severity score (3 levels).

The mean percentage change from baseline to Week 53 in absolute FVC in the ITT population using ANCOVA analyses show that comparing the idursulfase weekly group and the placebo group, there was a difference of 10.6% change (12.4% for idursulfase group, and 1.8% in placebo group), and that this difference was statistically significant (p=0.01).

Table 24 Forced Vital Capacity Absolute Volume Mean Percentage Change from Baseline to Week 53 ANCOVA Analysis: ITT Patient Population (Source: BLA submission)

Treatment Comparison	N	Baseline Mean (SE) FVC (L)	% Change to Week 53 in FVC Absolute Volume Mean (SE)		Adjusted 95% CI ^a	p-value ^b
			Observed % Change	Adjusted % Change ^a		
Idursulfase vs Placebo: Primary Comparison						
Idursulfase Weekly	32	1.19 (0.10)	16.01 (3.36)	12.37 (3.18)	2.26, 18.97	0.0137
Placebo	32	1.09 (0.09)	8.67 (3.23)	1.76 (3.40)		
Difference				10.62 (4.17)		
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	1.17 (0.01)	8.30 (2.59)	6.60 (2.98)	-5.94, 9.66	0.6341
Placebo	32	1.09 (0.09)	8.67 (3.23)	4.74 (3.13)		
Difference				1.86 (3.89)		
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	1.19 (0.10)	16.01 (3.36)	13.04 (2.89)	-0.25, 14.82	0.0577
Idursulfase EOW	32	1.17 (0.10)	8.30 (2.59)	5.75 (2.96)		
Difference				7.28 (3.76)		
All Idursulfase vs Placebo						
All Idursulfase	64	1.18 (0.07)	12.16 (2.16)	9.48 (2.22)	-0.65, 13.08	0.0752
Placebo	32	1.09 (0.09)	8.67 (3.23)	3.26 (3.08)		
Difference				6.22 (3.45)		

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week.

^a Adjusted means (LS Means), adjusted SEs from the fitted ANCOVA model, the difference in the LS means, and the corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment, baseline patient age (3 levels), and baseline FVC severity score (3 levels).

The improvement in absolute FVC, however, appeared to be driven primarily by the 12-18 year olds, a population experiencing pubertal growth spurt (Pediatric Review, H. Sachs, MD)

Table 25 Summary Statistics for Absolute FVC (L): Observed Values and Changes from Baseline by Baseline Patient Age in the ITT Population (Source: BLA submission)

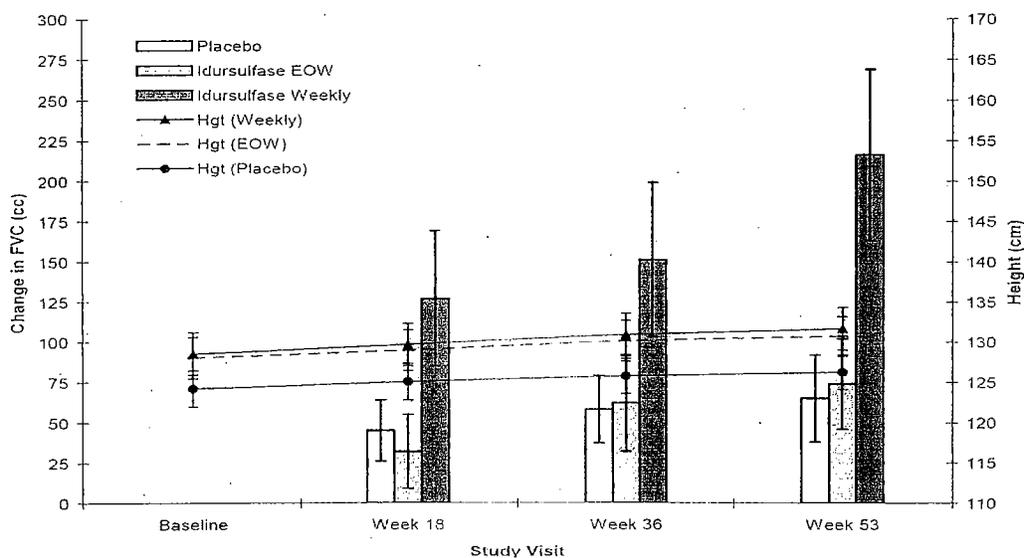
Baseline Patient Age	Treatment Group	n	Actual Value Mean (SE)				Mean Change from Baseline (SE)		
			Baseline	Week 18	Week 36	Week 53	Week 18	Week 36	Week 53
19 to 25 years	Idursulfase Weekly	8	1.06 (0.15)	1.09 (0.15)	1.07 (0.14)	1.11 (0.19)	0.03 (0.03)	0.00 (0.04)	0.05 (0.06)
	Idursulfase EOW	9	1.61 (0.27)	1.55 (0.25)	1.55 (0.27)	1.54 (0.25)	-0.06 (0.03)	-0.06 (0.04)	-0.06 (0.04)
	Placebo	7	1.73 (0.25)	1.70 (0.26)	1.72 (0.25)	1.73 (0.25)	-0.03 (0.05)	-0.01 (0.02)	-0.01 (0.04)
	All Idursulfase	17	1.35 (0.17)	1.33 (0.16)	1.32 (0.16)	1.34 (0.17)	-0.02 (0.02)	-0.03 (0.03)	-0.01 (0.04)
12 to 18 years	Idursulfase Weekly	10	1.57 (0.23)	1.71 (0.31)	1.84 (0.32)	1.91 (0.32)	0.14 (0.10)	0.27 (0.11)	0.34 (0.11)
	Idursulfase EOW	9	1.08 (0.06)	1.20 (0.08)	1.21 (0.09)	1.23 (0.09)	0.10 (0.05)	0.11 (0.07)	0.14 (0.06)
	Placebo	10	1.06 (0.10)	1.09 (0.09)	1.09 (0.08)	1.09 (0.09)	0.04 (0.02)	0.03 (0.03)	0.03 (0.03)
	All Idursulfase	19	1.34 (0.12)	1.47 (0.17)	1.54 (0.16)	1.59 (0.19)	0.12 (0.06)	0.20 (0.07)	0.24 (0.07)
5 to 11 years	Idursulfase Weekly	14	1.00 (0.10)	1.17 (0.13)	1.15 (0.13)	1.22 (0.15)	0.17 (0.06)	0.15 (0.07)	0.22 (0.08)
	Idursulfase EOW	14	0.94 (0.08)	0.98 (0.09)	1.04 (0.10)	1.06 (0.10)	0.04 (0.03)	0.10 (0.04)	0.12 (0.03)
	Placebo	15	0.81 (0.05)	0.89 (0.07)	0.92 (0.07)	0.93 (0.08)	0.09 (0.03)	0.11 (0.03)	0.12 (0.05)
	All Idursulfase	28	0.97 (0.06)	1.08 (0.08)	1.09 (0.08)	1.14 (0.09)	0.11 (0.04)	0.13 (0.04)	0.17 (0.04)

Table 26 Summary Statistics for Absolute FVC (L): Observed Values and Percent Change from Baseline by Baseline Patient Age

Baseline Patient Age	Treatment Group	n	Actual Value Mean (SE)				Mean Percent Change from Baseline (SE)		
			Baseline	Week 18	Week 36	Week 53	Week 18	Week 36	Week 53
19 to 25 years	Idursulfase Weekly	8	1.06 (0.15)	1.09 (0.15)	1.07 (0.14)	1.11 (0.19)	3.19 (2.41)	2.65 (4.69)	2.42 (4.38)
	Idursulfase EOW	9	1.61 (0.27)	1.55 (0.25)	1.55 (0.27)	1.54 (0.25)	-2.00 (2.36)	-2.74 (3.44)	-2.96 (3.03)
	Placebo	7	1.73 (0.25)	1.70 (0.26)	1.72 (0.25)	1.73 (0.25)	-2.30 (2.95)	-0.51 (1.37)	0.07 (2.24)
	All Idursulfase	17	1.35 (0.17)	1.33 (0.16)	1.32 (0.16)	1.34 (0.17)	0.44 (1.76)	-0.20 (2.85)	-0.43 (2.61)
12 to 18 years	Idursulfase Weekly	10	1.57 (0.23)	1.71 (0.31)	1.84 (0.32)	1.91 (0.32)	6.73 (4.13)	15.63 (3.90)	20.78 (4.39)
	Idursulfase EOW	9	1.08 (0.06)	1.20 (0.08)	1.21 (0.09)	1.23 (0.09)	9.58 (4.88)	10.50 (6.08)	12.44 (5.87)
	Placebo	10	1.06 (0.10)	1.09 (0.09)	1.09 (0.08)	1.09 (0.09)	5.38 (2.66)	7.24 (6.48)	5.47 (4.76)
	All Idursulfase	19	1.34 (0.12)	1.47 (0.17)	1.54 (0.16)	1.59 (0.19)	8.08 (3.04)	13.20 (3.47)	16.63 (3.64)
5 to 11 years	Idursulfase Weekly	14	1.00 (0.10)	1.17 (0.13)	1.15 (0.13)	1.22 (0.15)	16.33 (5.26)	14.73 (5.51)	20.37 (5.95)
	Idursulfase EOW	14	0.94 (0.08)	0.98 (0.09)	1.04 (0.10)	1.06 (0.10)	4.62 (2.67)	11.80 (4.45)	12.89 (3.28)
	Placebo	15	0.81 (0.05)	0.89 (0.07)	0.92 (0.07)	0.93 (0.08)	9.84 (3.46)	12.58 (3.88)	14.82 (5.73)
	All Idursulfase	28	0.97 (0.06)	1.08 (0.08)	1.09 (0.08)	1.14 (0.09)	10.47 (3.11)	13.16 (3.49)	16.63 (3.41)

The Applicant, however, proposed that change in absolute FVC was not related to growth, based on the following data:

Figure 8 Mean Height (cm) and Mean Change from Baseline in Absolute FVC Volume (cc) by Treatment Group in the ITT Population (Source: BLA submission)



But, since height could not be measured accurately, no conclusion can be drawn from growth data. Moreover, improvement in absolute FVC would be significant as a solely pulmonary measurement only if a growth effect can be excluded. Such would be the case if data were derived from a population that is not growing (i.e. those post-pubertal patients whose epiphyses have fused). In normal males, the epiphyses fuse at approximately 18 years of age. Inclusion of pre-pubertal or pubertal patients would be problematic in terms of matching treatment groups for height due to difficulties in accurately measuring standing height in this patient. Changes in absolute FVC are more likely to be informative in post-pubertal patients, i.e. patients whose epiphyses have fused.

Reviewer's comment: It appears that although differences in absolute FVC reached statistical significant, its clinical significance is unclear:

6.1.4.2.2 Combined Liver and Spleen Volumes

Changes in liver and spleen volumes were analyzed as a combined volume and as separate volumes. Liver and spleen volumes (expressed in cubic centimeters [cc] or milliliters [mL]) were measured by abdominal MRI at baseline and Weeks 18, 36, and 53. The liver and spleen volumes were summed for each patient to reflect the total organ burden from hepatosplenomegaly (HSM). The outcome of interest was the percent change from baseline to Week 53 in the combined liver and spleen volume. Statistical comparison of the differences between treatment groups for the percent change from baseline to Week

53 was performed using an ANCOVA with treatment and region fitted as a factor and baseline combined volume category and baseline patient age as covariates. (The baseline combined volume category was determined by dividing the entire patient population into tertiles).

Combined liver and spleen volumes decreased in the idursulfase weekly group as compared to placebo group, as shown by ANVOCA analysis of mean percentage changes from baseline to Week 53 in the ITT population (-25.7% in the idursulfase group vs. 0.64% in the placebo group, with a difference of -26.4%, p,0.0001).

Table 27 Combined Liver and Spleen Volumes Percent Change from Baseline to Week 53 ANCOVA Analysis: ITT Population (Source: BLA submission)

	N	Baseline	Combined Liver and Spleen Volumes ^a Mean (SE) % Change to Week 53		Adjusted 95% CI ^a	p-value ^c
			Observed Change	Adjusted Change ^b		
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	31	1578.48 (80.75)	-25.81 (1.44)	-25.72 (1.67)		
Placebo	30	1485.28 (70.19)	0.27 (1.66)	0.64 (1.68)		
Difference				-26.35 (2.24)	-30.85, -21.85	<0.0001
Idursulfase EOW vs Placebo						
Idursulfase EOW	29	1442.22 (63.54)	-23.73 (1.49)	-24.34 (1.72)		
Placebo	30	1485.28 (70.19)	0.27 (1.66)	-0.04 (1.70)		
Difference				-24.30 (2.34)	-29.00, -19.59	<0.0001
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	31	1578.48 (80.75)	-25.81 (1.44)	-25.57 (1.60)		
Idursulfase EOW	29	1442.22 (63.54)	-23.73 (1.49)	-23.46 (1.65)		
Difference				-2.10 (2.23)	-6.57, 2.37	0.3497
All Idursulfase vs Placebo						
All Idursulfase	60	1512.62 (52.13)	-24.80 (1.04)	-24.98 (1.17)		
Placebo	30	1485.28 (70.19)	0.27 (1.66)	0.41 (1.61)		
Difference				-25.40 (1.92)	-29.21, -21.58	<0.0001

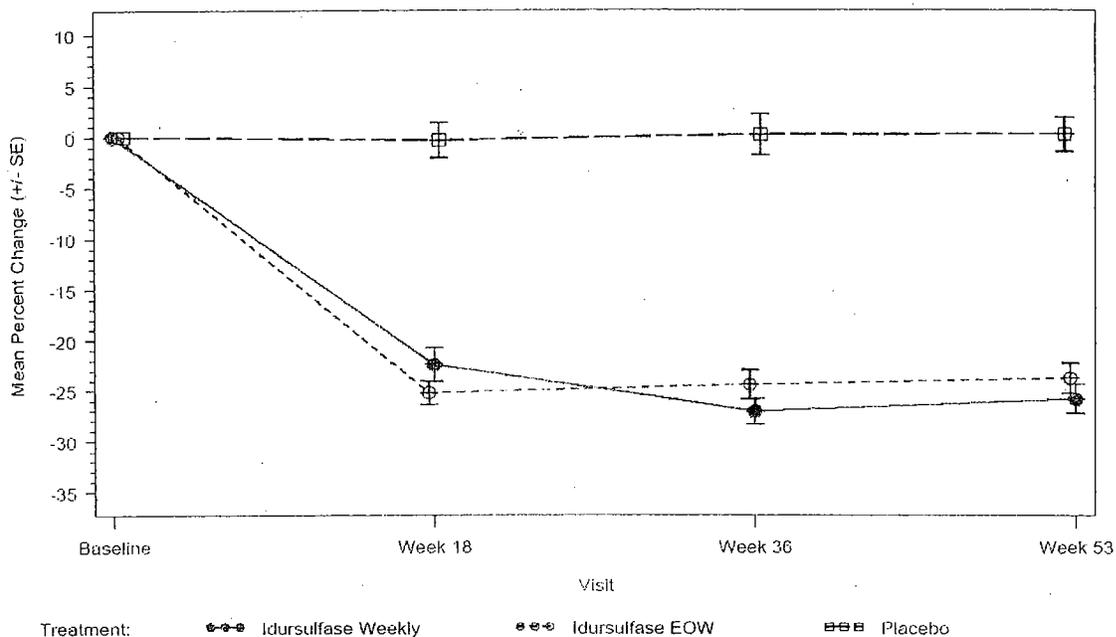
LS Means=Least Squares Means; SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; EOW=every other week.

^a N ≠ 32/treatment group in the ITT patient population because 5 patients (2 placebo, 1 idursulfase weekly, 2 idursulfase every other week) were exempt from having abdominal MRIs performed at any time during the study and 1 patient in the idursulfase every other week group had unreadable images throughout the study.

^b For treatment comparisons, the difference in the adjusted means (LS) and the corresponding 95% CI of the treatment difference are presented.

^c p-value for treatment difference based on ANCOVA model containing region, treatment, and baseline combined liver and spleen volume fitted as factors and baseline patient age (3 levels) and baseline disease score (3 levels) as covariates.

Figure 9 Mean Percent Changes from Baseline in Combined Liver and Spleen Volumes by Visit and Treatment Group: ITT Population (Source: BLA Submission)



Maximum or near maximum decreases in combined liver and spleen volume were observed by week 18 in both idursulfase treatment groups. Maximum changes were -27.1% at week 36 in the idursulfase weekly group. Combined liver and spleen volumes remained essentially unchanged in the placebo group across the 52-week treatment period. The changes from baseline volumes observed among all subgroups for the idursulfase weekly and every other week groups and the differences between these groups and the placebo group were similar to those seen for all patients in each of these treatment groups, indicating idursulfase was effective in Hunter syndrome patients of all age groups, with all grades of disease severity, in all geographical regions, and with all degrees of combined liver and spleen volume.

Reviewer's comment:

While combined liver and spleen size reduction was seen with idursulfase treatment, the clinical significance of this pharmacodynamic effect has not been established.

6.1.4.2.3 Liver Volume

Hepatomegaly was defined by age and the upper bound of the 95% CI for normal liver volume, normalized by body weight. To calculate liver size normalized to body weight expressed as a

percentage, organ density was assumed to be 1 g/mL. Liver size normalized to BM was calculated at each visit using the following formula⁷:

$$\text{Liver size relative to BM} = ((\text{liver volume [mL]})/\text{BW [g]}) \times 100$$

Determination of hepatomegaly, an abnormally enlarged liver volume, was based on the relative liver size expressed as a percentage of body weight using the definitions:

Table 28 Criteria by Age for Determination of Abnormal Liver Volume Where Abnormal Liver Volume was defined as Greater than the Upper Bound of 95% Confidence Interval of Normal Liver Volume Normalized by Body Weight (Source: BLA Submission)

Age (years)	Upper Bound of 95% CI of Normal Liver Volume Normalized by BW
5 to 12	≤ 3.5%
13 to 17	≤ 2.2%
≥ 18	≤ 2.6%

CI=Confidence interval; BW=body weight.

Summary statistics regarding liver volume are:

Table 29 Summary Statistics regarding Liver Volume: Observed Values, Change and Percent Change from Baseline by Visit and Treatment Group in the ITT Population (Source: BLA Submission)

Treatment Group	Statistic	Actual Value			Change From Baseline			Percent Change From Baseline			
		Baseline	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53
Idursulfase Weekly	n	31	31	31	31	31	31	31	31	31	
	Mean	1262.3	986.3	925.2	944.5	-276.0	-337.1	-317.8	-21.9	-26.9	-25.3
	Std. Err.	49.83	44.85	42.53	43.40	25.41	20.75	23.21	1.76	1.34	1.57
	SD	277.42	249.70	236.91	241.66	141.48	115.54	129.24	9.78	7.44	8.74
	Minimum	790	596	561	512	-606	-583	-567	-38	-38	-39
	Maximum	1210.2	964.0	892.6	878.1	-267.9	-344.5	-324.3	-23.8	-28.4	-27.4
Idursulfase EOW	n	29	29	29	29	29	29	29	29	29	
	Mean	1191.4	896.8	902.1	911.6	-294.6	-289.3	-279.6	-24.9	-24.5	-24.0
	Std. Err.	47.78	41.47	41.02	48.59	16.99	18.32	23.21	1.21	1.39	1.66
	SD	257.32	223.33	226.91	261.65	90.98	98.68	124.99	6.49	7.41	8.92
	Minimum	770	531	433	524	-538	-504	-618	-37	-44	-36
	Maximum	1158.5	845.7	877.3	852.4	-309.6	-271.6	-288.3	-26.0	-23.8	-25.0
Placebo	n	30	30	30	30	30	30	30	30	30	
	Mean	1197.8	1192.4	1199.5	1199.8	-5.3	1.9	-7.0	-0.5	0.3	-0.8
	Std. Err.	47.81	54.86	52.13	56.16	22.48	22.46	19.84	1.79	1.96	1.60
	SD	261.85	300.49	285.55	307.63	122.68	123.03	198.68	9.82	10.75	8.74
	Minimum	634	690	649	717	-227	-227	-197	-18	-26	-17
	Maximum	1181.4	1155.4	1172.4	1095.6	-33.0	1.0	-5.1	-2.7	0.1	-0.4

Analysis of the treatment comparisons for the percentage change from baseline to Week 53 in liver volume is:

⁷ Kakkis ED, et al. Enzyme-replacement therapy in Mucopolysaccharidosis I, NEJM 2001, 344:182-188

Table 30 Summary of Treatment Comparison Based on ANCOVA of the Liver Volume (cc): Percent Change from Baseline to Week 53 in the ITT Population (Source: BLA Submission)

Treatment Adjusted Comparisons	p-value	Treatment Difference	
		Mean (SE)	95% CI
Idursulfase Weekly vs Placebo **	<0.0001	-25.16 (2.19)	-29.56, -20.77
Idursulfase EOW vs Placebo	<0.0001	-23.05 (2.26)	-27.58, -18.51
Idursulfase Weekly vs EOW	0.3812	-2.19 (2.48)	-7.18, 2.79
All Idursulfase vs Placebo	<0.0001	-24.18 (1.91)	-27.98, -20.38

Mean volumes and mean changes from baseline in liver volume are presented by visit, depicted in Figures 9 and 10, respectively.

Figure 10 Mean Liver Volumes (cc) by Visit and Treatment Group in the ITT Patient Population (Source: BLA Submission)

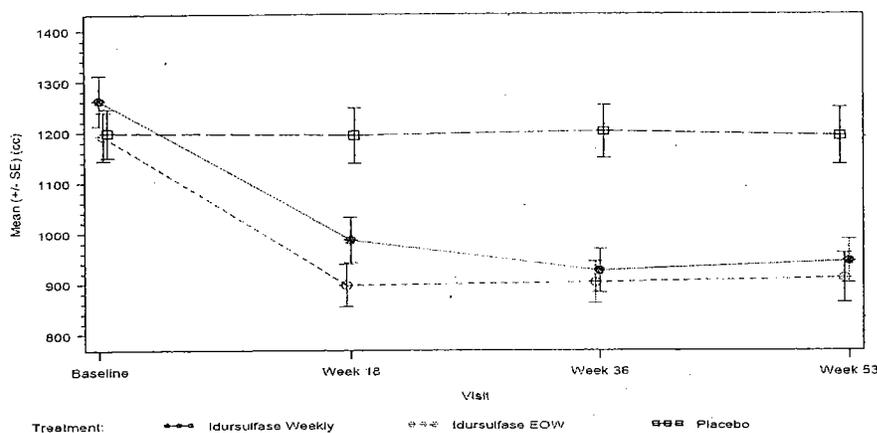
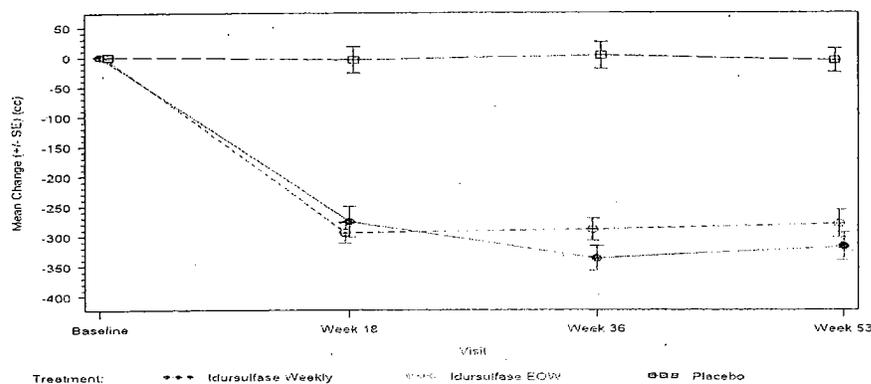


Figure 11 Mean Changes from Baseline in Liver Volume (cc) by Visit and Treatment Group in the ITT Population



Decreases in liver volume were greatest at Week 36 for the idursulfase weekly group. This change persisted through Week 53. Only small changes in liver volume were observed in the placebo group.

Shifts from normal or abnormal are summarized for changes from baseline to Week 53 in liver volume in the following:

Table 31 Summary of Changes from Normal or Abnormal at Baseline to Normal or Abnormal at Week 53 in Liver Volume in the ITT Patient Population (Source: BLA Submission)

Changes from Baseline to Week 53 Relative to Normal Range	Placebo ^a (n=32)	Idursulfase		
		Weekly (n=32)	Every Other Week (n=32)	All Idursulfase (n=64)
Normal to Normal	6	6	4	10
Normal to Abnormal	1	0	0	0
Abnormal to Abnormal	22	5	5	10
Abnormal to Normal	1	20	20	40
Missing ^a	2	1	3	4

^aFive patients (2 placebo, 1 idursulfase weekly, 2 idursulfase every other week patients) were exempt from having abdominal MRIs at all study visits and 1 patient in the idursulfase every other week group had images that were nonreadable at all visits.

The majority of the patients with MRI liver data had hepatomegaly at baseline (25/31 idursulfase weekly, 25/29 idursulfase every other week, and 23/30 placebo). By Week 53, liver volume decreased to within the normal range for most of the patients with hepatomegaly at baseline in the idursulfase weekly and idursulfase every other week groups. 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 improved to within the normal range by Week 53. In contrast, only 1 of 23 (4.3%) patients in the placebo group who had hepatomegaly at baseline improved to normal by Week 53.

Reviewer's Comment:

Results indicated that the decreases in combined liver and spleen volume for the idursulfase treatment groups were primarily due to decreases in liver volume. The reduction in liver size may decrease patients' overall discomfort, the extent of restrict lung disease, or need for umbilical hernia surgery; however, these effects are speculative, and the exact clinical implication of this endpoint has not been established.

6.1.4.2.4 Spleen Volume

Splenomegaly was determined using a regression formula that defined the upper limit of the normal range for spleen volume based on the 95% confidence interval for body weight. An abnormally enlarged spleen volume was calculated according to the following regression formulation, which defines

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the upper limit of the normal range for spleen volume based on body weight (where 0.7 is the y intercept, 4.6 is the slope, and 150 is average width of the 95% confidence interval)⁸:

$$\text{Splenic volume (mL)} = 0.7 + (4.6 \times \text{weight [kg]}) + 150$$

Summary statistics for the spleen volume are provided in the following table.

Table 32 Summary Statistics for Spleen Volume (cc): Observed Values, Change, and Percent Change from Baseline by Visit and Treatment Group in the ITT Population (Source: BLA submission)

Treatment Group	Statistic	Actual Value			Change From Baseline			Percent Change From Baseline			
		Baseline	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53
Idursulfase Weekly	n	31	31	31	31	31	31	31	31	31	31
	Mean	316.2	241.6	230.9	225.1	-74.6	-85.2	-91.0	-21.5	-26.0	-25.1
	Std. Err.	39.46	30.25	28.70	25.99	13.83	14.03	15.87	2.97	2.10	2.36
	SD	219.70	169.45	159.82	144.70	77.03	78.10	88.34	16.53	11.70	13.13
	Minimum	53	64	40	52	-357	-366	-366	-48	-49	-48
	Median	226.2	182.5	170.4	185.5	-54.7	-59.7	-52.0	-25.4	-26.5	-26.0
	Maximum	801	712	634	606	29	0	4	21	0	2
Idursulfase EOW	n	29	29	29	29	29	29	29	29	29	29
	Mean	250.8	184.8	189.6	193.9	-66.0	-61.2	-56.9	-25.0	-22.3	-19.8
	Std. Err.	26.02	21.64	18.64	18.08	10.24	12.32	11.87	3.45	3.65	3.15
	SD	140.10	116.55	100.37	97.34	55.13	66.36	63.92	18.55	20.71	16.97
	Minimum	98	46	51	91	-197	-280	-263	-81	-58	-48
	Median	227.7	157.3	163.8	167.2	-51.8	-46.5	-47.0	-24.1	-26.0	-22.5
	Maximum	807	654	527	544	20	63	29	20	47	13
Placebo	n	30	30	30	30	30	30	30	30	30	30
	Mean	287.5	287.5	287.0	302.2	0.0	-0.4	14.7	3.6	0.9	7.2
	Std. Err.	29.96	27.51	28.03	30.74	9.11	9.52	8.83	3.92	3.13	4.15
	SD	164.09	150.66	153.53	169.35	49.92	52.17	48.36	21.49	17.17	22.71
	Minimum	98	111	96	83	-131	-167	-89	-31	-36	-25
	Median	253.3	269.4	273.1	275.8	4.5	7.0	10.1	1.6	3.0	3.0
	Maximum	848	717	681	842	115	111	117	82	45	73

Statistically significant treatment differences in the percent change from baseline to Week 53 in spleen size were seen between the idursulfase weekly (-33.2%; $\alpha < 0.0001$) and placebo in the ITT population:

⁸ Schlesingere AE, et al. Volume of the spleen in children as measured on CT scans: normal standards as functions of body weight. AJR 1993; 160:1107-1109.

Table 33 Summary of Treatment Comparisons Based on ANCOVA of the Spleen Volume Percent Change from Baseline to Week 53 in the ITT Population (Source: BLA Submission)

Treatment Adjusted Comparisons	p-value	Treatment Difference	
		Mean (SE)	95% CI
Idursulfase Weekly vs Placebo **	<0.0001	-33.22 (4.79)	-42.82, -23.61
Idursulfase EOW vs Placebo	<0.0001	-26.65 (5.67)	-38.03, -15.26
Idursulfase Weekly vs EOW	0.2246	-4.54 (3.69)	-11.95, 2.87
All Idursulfase vs Placebo	<0.0001	-30.78 (4.06)	-38.85, -22.79

The means and mean changes from baseline to Weeks 18, 26, and 53 in spleen volume are shown in the following figures:

Figure 12 Mean Spleen Volumes (cc) by Visit and Treatment Group in the ITT Patient Population (Source: BLA Submission)

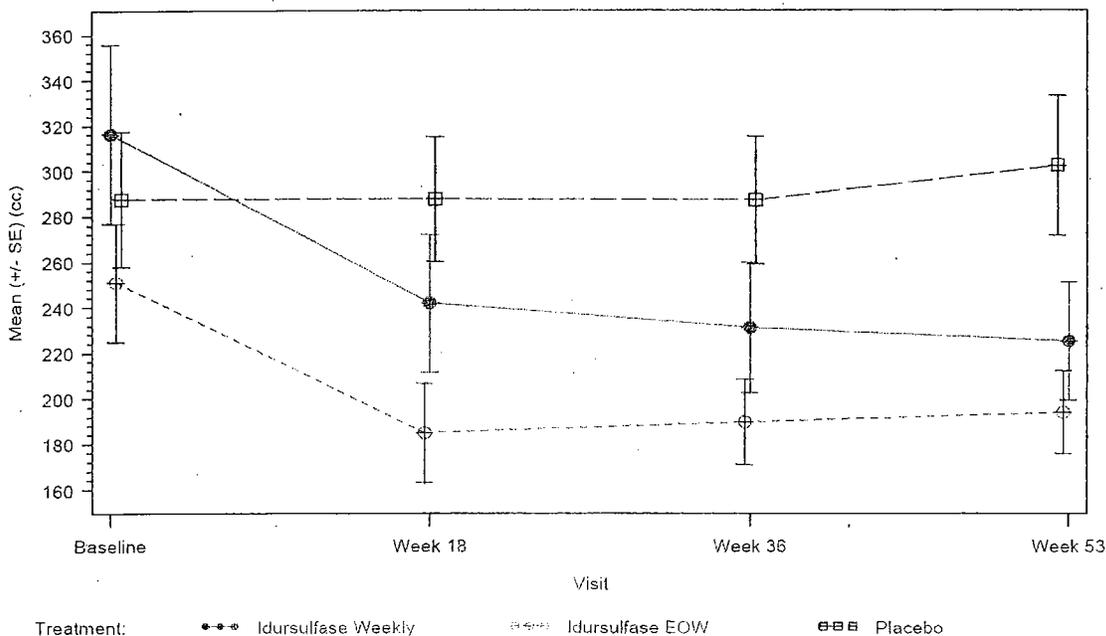
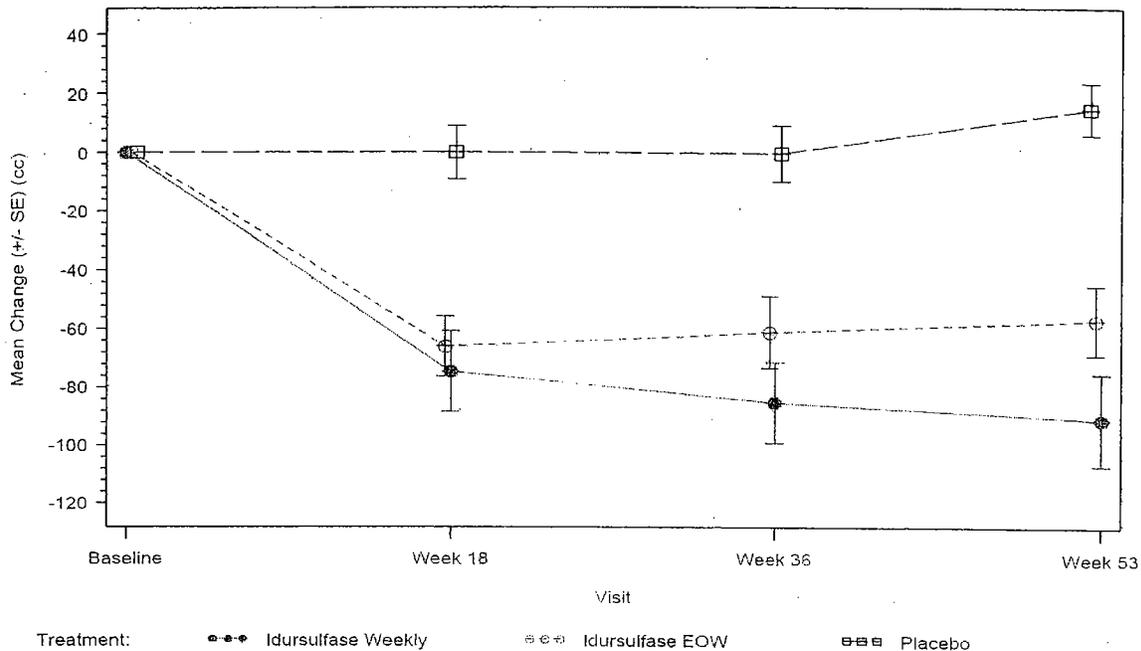


Figure 13 Mean Change from Baseline in Spleen Volume (cc) by Visit and Treatment Group: ITT Patient Population (Source: BLA Submission)



Decreases in spleen volume were greatest at Week 53 for the idursulfase weekly group. Spleen volume remained essentially unchanged in the placebo group. Shifts from normal or abnormal for changes from baseline to Week 53 in spleen volume are summarized:

Table 34 Summary of Changes from Normal or Abnormal at Baseline to Normal or Abnormal at Week 53 in Spleen Volume: ITT Patient Population (Source: BLA Submission)

Changes from Baseline to Week 53 Relative to Normal Range	Placebo ^a (n=32)	Idursulfase		
		Weekly (n=32)	Every Other Week (n=32)	All Idursulfase (n=64)
Normal to Normal	16	22	27	49
Normal to Abnormal	3	0	0	0
Abnormal to Abnormal	9	6	1	7
Abnormal to Normal	2	3	1	4
Missing ^a	2	1	3	4

^a Five patients (2 placebo, 1 idursulfase weekly, 2 idursulfase every other week patients) were exempt from having abdominal MRIs at all study visits and 1 patient in the idursulfase every other week group had images that were non-readable at all visits.

The majority of patients in all three treatment groups had a spleen volume that was normal at baseline. Among patients in the idursulfase weekly group, of the 9 patients with abnormally large spleens at baseline, 3 patients had spleen volumes that normalized by week 53. Among patients in the idursulfase EOW group, of the 2 patients with abnormally large spleens at baseline, 1 patient had spleen volume

that normalized by Week 53. Among the 11 placebo patients who had enlarged spleens at baseline that remained enlarged at Week 53, 2 patients had normal spleen volumes by Week 53.

Reviewer's Comment:

Although statistically significant treatment differences in the percent change from baseline to week 53 in spleen size were seen between the idursulfase weekly group and placebo group, the shift table analysis indicated that the result of shift from splenomegaly to normal was not significantly different between the idursulfase weekly group and the placebo group.

Also, the clinical significance of reduction in splenomegaly is uncertain.

6.1.4.2.5 Urinary GAG Level

Urine samples for the determination of urinary GAG levels were collected at baseline and at various pre-specified week during the one year study. GAG levels were assayed and normalized to urine creatinine obtained from the same urine sample and were reported as μg GAG/mg creatinine. The cut-off of the upper limit of normal level was determined to be >126.6 μg GAG/mg creatinine, as determined by population study. Differences between treatment groups for the mean change and the percent change from baseline to Week 53 in normalized urine GAG levels were analyzed by ANCOVA, where treatment group and region were fitted as factors and baseline GAG category and baseline patient age were covariates. The baseline urine GAG category was determined by dividing the entire patient population into tertiles.

The mean, mean change, and mean percent change from baseline to Weeks 18, 36, and 53 in normalized urine GAG values are summarized in the following tables:

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Table 35 Summary Statistics for Normalized Urine GAG: Observed Values, Change, and Percent Change from Baseline by Visit and Treatment Group in the ITT Population (Source: BLA Submission)

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Treatment Group	Statistic	Actual Value			Change From Baseline			Percent Change From Baseline			
		Baseline	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53
Idursulfase Weekly	n	32	32	32	32	32	32	32	32	32	
	Mean	325.59	142.53	128.18	136.37	-133.07	-196.42	-189.23	-49.46	-55.66	-62.47
	Std. Err.	25.792	12.982	12.550	12.490	20.980	25.222	25.765	5.840	4.876	5.251
	SD	145.993	73.226	70.893	70.855	152.620	142.673	145.740	33.037	27.582	29.793
	Minimum	103.0	45.0	32.2	49.7	-809.4	-606.4	-629.5	-85.5	-86.5	-87.1
	Maximum	391.35	124.85	118.00	111.10	-165.59	-130.45	-158.99	-58.12	-62.37	-60.31
Idursulfase EOW	n	32	32	32	32	32	32	32	32	32	
	Mean	338.49	184.73	170.78	182.16	-153.35	-167.39	-154.98	-45.55	-46.78	-44.63
	Std. Err.	21.034	19.434	15.573	15.666	17.998	16.348	17.178	4.795	3.440	3.973
	SD	118.988	109.936	88.095	88.818	101.768	92.476	97.171	26.613	19.462	22.474
	Minimum	87.9	52.8	63.5	62.6	-316.5	-374.1	-387.1	-77.1	-82.4	-77.4
	Maximum	330.30	157.75	150.10	185.50	-176.25	-171.80	-171.45	-48.30	-54.39	-48.85
Placebo	n	32	32	32	32	32	32	32	32	32	
	Mean	419.40	399.64	435.20	437.56	-19.75	15.61	18.16	24.28	23.67	21.39
	Std. Err.	34.372	32.588	28.114	25.107	48.193	38.513	29.938	20.860	13.466	11.550
	SD	194.435	184.344	159.038	142.028	272.620	217.846	169.352	117.660	76.177	65.335
	Minimum	192.5	153.2	201.5	198.0	-385.5	-676.2	-374.3	-71.1	-60.4	-47.1
	Maximum	405.80	379.40	420.45	412.40	-7.15	27.80	30.20	-2.36	-8.13	-9.59

Statistical analyses of the change from baseline to Week 53 in urine GAG levels normalized by urine creatinine are summarized for the ITT population:

Table 36 Summary of Treatment Comparison Based on ANCOVA of the Normalized Urine GAG Change from Baseline to Week 53 in the ITT Population (Source: BLA Submission)

Treatment Adjusted Comparisons	p-value	Treatment Difference	
		Mean (SE)	95% CI
Idursulfase Weekly vs Placebo **	<0.0001	-275.54 (30.10)	-335.82, -215.25
Idursulfase EOW vs Placebo	<0.0001	-212.06 (28.82)	-269.80, -154.32
Idursulfase Weekly vs EOW	0.0394	-46.57 (22.08)	-90.79, -2.35
All Idursulfase vs Placebo	<0.0001	-241.19 (23.77)	-288.42, -193.95

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Table 37 Summary of Treatment Comparisons Based on ANCOVA of the Normalized Urine GAG Percent Change from Baseline to Week 53 in the ITT Population (Source: BLA Submission)

Treatment Adjusted Comparisons	p-value	Treatment Difference	
		Mean (SE)	95% CI
Idursulfase Weekly vs Placebo **	<0.0001	-89.44 (10.43)	-110.34, -68.54
Idursulfase EOW vs Placebo	<0.0001	-76.14 (9.59)	-95.36, -56.92
Idursulfase Weekly vs EOW	0.1443	-9.09 (6.14)	-21.38, 3.21
All Idursulfase vs Placebo	<0.0001	-79.78 (7.92)	-95.52, -64.03

Mean, mean change, and mean percentage changes from baseline in normalized urine GAG levels are presented graphically for the ITT population in the following figures:

Figure 14 Mean Normalized Urine GAG Levels (µg/mg) by Visit and Treatment Group in the ITT Patient Population (Source: BLA Submission)

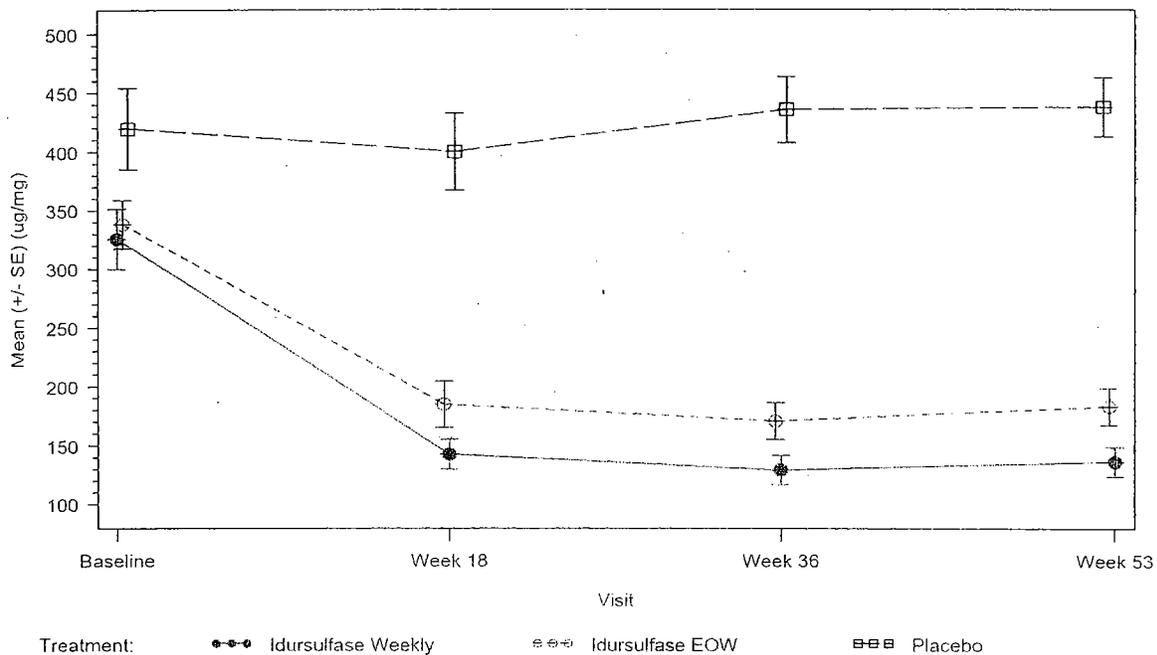


Figure 15 Mean Change from Baseline in Normalized Urine GAG Levels (µg/mg) by Visit and Treatment Group in the ITT Patient Population

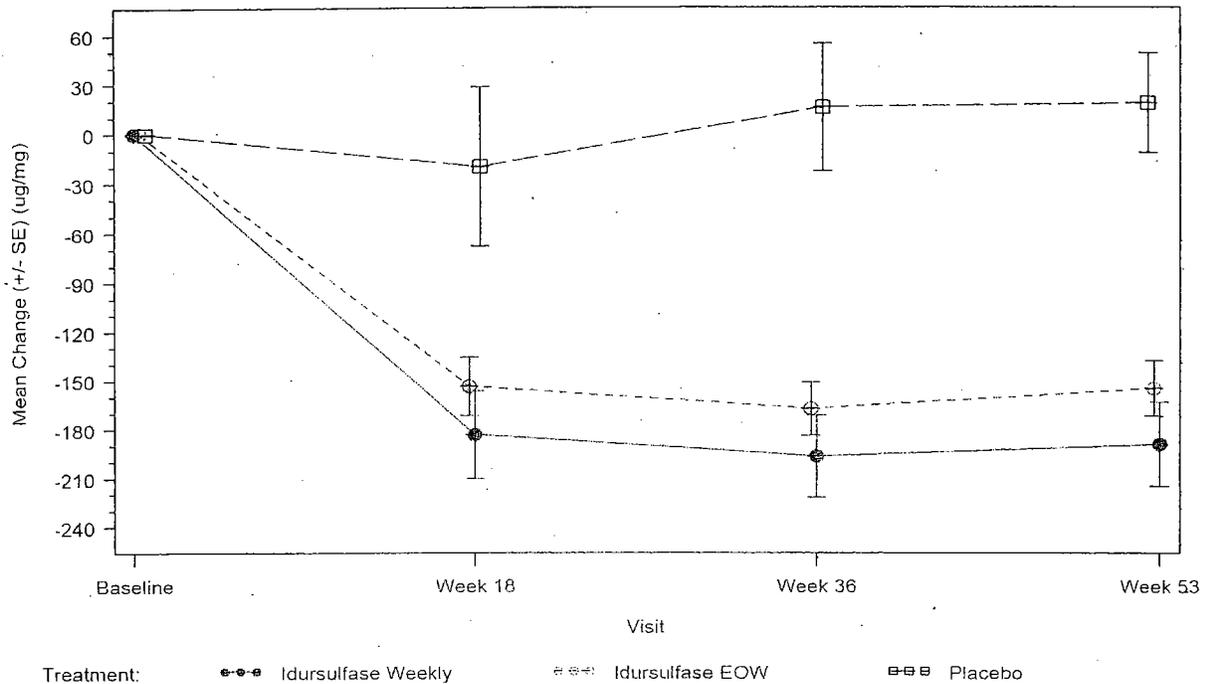
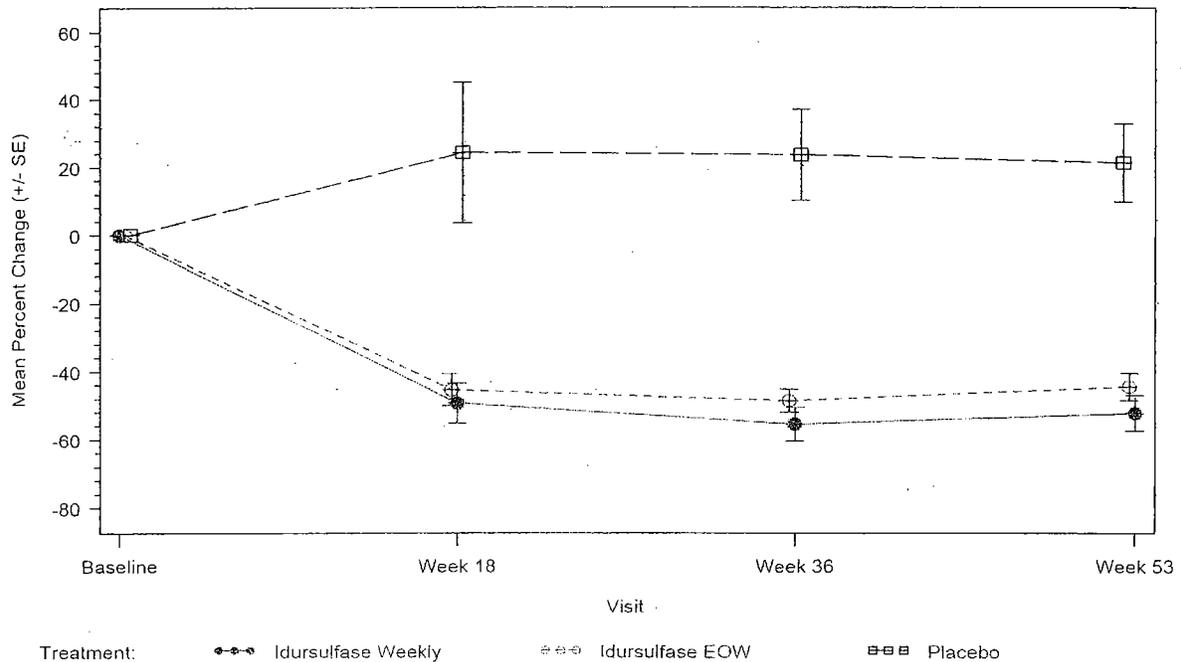


Figure 16 Mean Percent Change from Baseline in Normalized Urine GAG Levels by Visit and Treatment Group in the ITT Population (Source: BLA Submission)



Mean changes and mean percentage changes from baseline to Weeks 18, 36, and 53 in normalized urine GAG values indicated that decreases were observed by Week 18 for both idursulfase weekly and idursulfase every other week, with maximal changes observed at Week 36 for both groups that persisted

through Week 53. Although a slight decrease in mean urine GAG values was seen initially at Week 18 in the placebo group, increases from baseline were observed at Weeks 36 and 53.

Reviewer's Comment:

Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, urinary GAG levels remained elevated and essentially unchanged in the placebo group. Mean urinary GAG levels were significantly reduced in the ELAPRASE treated groups, although GAG levels still remained above the upper limit of normal in half of the ELAPRASE weekly treated patients, which is a significant proportion of the original cohort. In addition, although the pharmacodynamic effect of idursulfase on reduction of urinary GAG excretion has been demonstrated, the overall clinical effect of decreased urinary GAG level is unknown.

6.1.4.3 Exploratory Endpoints:

The following endpoints did not demonstrate treatment benefits from idursulfase treatment during the 53-week placebo controlled study TKT024:

- Passive joint range of motion (JROM) tested bilaterally by goniometry across 7 joints, 23 motions, and 11 combined motions.
- Changes in cardiac left ventricular mass index (LVM) for patients with left ventricular hypertrophy (LVH) at baseline.

Idursulfase weekly patients showed a trend toward improved LV mass index by Week 53 compared with placebo (mean change of $-14.13\% \pm 4.460\%$ versus $+4.31\% \pm 8.827\%$ for idursulfase and placebo; $p=0.1524$). A dose effect was also observed for idursulfase every other week patients (mean change of $-9.64 \pm 5.850\%$ versus $+4.31\% \pm 8.827\%$ for every other week idursulfase and placebo, respectively; $p=0.2893$). Both of the mean reduction values of 14.13% and 9.64% fall within the range of 8 to 15% considered clinically meaningful with antihypertensive subjects. The Applicant states that failure to meet statistical significance in this subset of patients may be due to the lack of sufficient power due to the smaller sample sizes. Based on the prior experience in TKT008, it was anticipated that ~40% of the patients enrolling in TKT024 were likely to have elevated LV mass at baseline. The actual value in this study, however, was 34.4% [33/96] of the enrolled patients having documented LVH upon entry.

- Other pulmonary indices, including FEV₁ (% -predicted and absolute volume), ratio of FEV₁/% predicted FVC for patients a ratio < 0.70 at baseline, %- predicted and absolute lung volumes (TLC, FRC, RV %), % and normalized diffusion capacity (DLco and DLco normalized by alveolar volume DLco/VA] for all patients), and RV/TLC.
- A battery of Health Related Quality of Life (HRQOL) surveys including: Childhood Health Assessment Questionnaire (CHAQ); Hunter Syndrome-Outcomes for Clinical Understanding

Scales Questionnaire (HS-FOCUS); Health Utility Index (HUI); Child Health Questionnaire (CHQ).

The two HRQOL measures (CHQ and HUI) and the disease-specific measure (CHAQ) are considered to be reliable and valid, as well as internationally accepted. The CHAQ has not been validated specifically for patients with Hunter syndrome. The HS-FOCUS has not been validated, and needs further validation. The ability for each measure to detect a response to change varies with disease severity (Pediatric Review, H. Sachs, MD).

Reviewer's Comment:

Although a wide variety of tests were included in assessing the clinical benefit of idursulfase in Hunter syndrome, the only endpoint that demonstrated a beneficial effect of clinical significance with statistical significance was the 6MWT.

6.1.5 Clinical Microbiology

Idursulfase is not an antimicrobial therapy.

6.1.6 Efficacy Conclusions

The efficacy results from the idursulfase clinical program provided evidence of a benefit of treatment with idursulfase as demonstrated in the pivotal study TKT024, where patients who received idursulfase 0.5 mg/kg IV weekly treatment demonstrated superior walking capacity by Week 53 over patients who received placebo. For the 6-Minute Walk Test (6MWT) using the primary analyses model, incorporating adjustment for site, baseline age and disease severity, the estimated difference in improvement is 35 meters (38 yards), which is statistically significant with $p=0.01$. While this improvement is modest, it offers evidence for a novel treatment option for patients with Hunter syndrome. Supportive evidence of the positive effect of idursulfase by way of pharmacodynamic markers came from reduction in urinary GAG level excretion, reduction in hepatomegaly, and, to a lesser degree, reduction in splenomegaly. As only controlled efficacy data up to one year study has been completed and analyzed, long term effect of idursulfase on Hunter syndrome has not been determined at this time.

7 INTEGRATED REVIEW OF SAFETY

7.1 METHODS AND FINDINGS

All patients who received at least one dose (or partial dose) of idursulfase were included in the safety population. Of the 108 patients enrolled in all clinical trials with idursulfase, 107 patients received at least one dose of idursulfase, and collectively their safety data form the basis of current labeling proposal. No formal statistical testing was planned or performed. Safety data submitted for this BLA included complete SAS electronic safety datasets obtained from two randomized, controlled studies: TKT008 and TKT024. Partial data from the respective extension studies, TKT018 and TKT024EXT, submitted as of a cut-off date up to April 2005 (which is approximately 15 months before the approval date) have been reviewed as well. Data regarding possible anaphylactic/anaphylactoid reactions submitted in May 2005 in response to FDA's request had a cut-off-date of 11-15-2005.

The main analysis for this safety review is performed in the pivotal study, TKT024. This reviewer has placed most weight on this study because it is the largest, the longest, and it is placebo-controlled. Supportive evidence comes from the smaller study, TKT008, where 12 patients provided additional data for 6 months. When appropriate, consideration was also given to the two open-labeled, uncontrolled studies, TKT018, and TKT024EXT. The reviewer has examined reports provided on all MedWatch forms associated with idursulfase.

7.1.1 Deaths

Five deaths occurred during the course of idursulfase clinical trials. All five deaths were related to respiratory failure.

Table 38 Deaths in the Idursulfase Clinical Development Program

Patient	Age	Study	Regimen (mg/kg)
024-012-0008	24	TKT024	0.5 weekly ^a
024-059-0002	21	TKT024EXT	0.5 weekly
018-013-0006 (aka 008-013-0006)	24	TKT018	0.5 weekly
024-013-0004 aka TKT031NPU-142-0004)	26	TKT031NPU	0.5 weekly
024-020-0003	6	TKT024	Placebo

- Patient 024-012-0008 was a 24 year old man enrolled at Children's University Hospital in Germany, who was randomized to receive 0.5 mg/kg idursulfase weekly. Patient had both restrictive and obstructive lung disease at baseline: FVC was 0.77L, and FEV₁, 0.74L. He had dyspnea with limited activity level such as walking and conversation. On baseline physical exam he was found to have rales and wheezing, and tachypnea of respiratory rate of 36. He had been taking asthma medications Singulair (montelukast) for six months, and Berotec (Fenoterol, bronchodilator) for eight years prior to the onset of study. He was documented to have Class II congestive heart failure, and sleep apnea. Patient's family reported that two days after patient's first dose of idursulfase, he developed a "respiratory infection," which, in three days progressed into respiratory failure, cardiac arrest, and unconsciousness requiring intubation and intensive

care unit hospitalization. About a week later after the initial intubation, patient developed cardiac arrest for the second time, and died. Final diagnosis was respiratory failure and cardiopulmonary arrest due to respiratory infection. The patient had underlying restrictive and obstructive lung disease. The investigator reported the death as not related to treatment with blinded study medication.

Reviewer's comment:

However, given the close temporal relationship between drug administration and onset of event, a causal relationship could not be ruled out. Also, patient's baseline medical history did not record that he had a history of respiratory infections (but his SAE death report did report such).

- Patient 018-013-0006 was a 24-year old man enrolled at University of North Carolina at Chapel Hill, who was randomized to receive 0.5 mg/kg idursulfase every-other-week, and who participated in both studies TKT080 and 018. At baseline patient had pulmonary disease: FVC was 1.11L, and FEV₁ 0.82L. Patient had exertional dyspnea and a tracheostomy. In addition, patient had a history of episodic peripheral cyanosis; sleep apnea; aortic, tricuspid, and mitral regurgitation; frequent pneumonias as a child, and, prolonged QT interval with RBBB on EKG. When he entered into the study, he had been taking cozaar (for aortic regurgitation), and on an as-needed-basis, lasix. He had multiple allergies: penicillin, Ceclor, Advil, Aspirin, and eggs. He was documented to have a history of hives of unknown origin. His baseline physical exam showed that he had an enlarged tongue, a short neck, and multiple areas of erythematous patches on the skin. Even before entering and throughout the study period of TKT008-018, patient had been experiencing hives and or urticaria, both of which were considered idiopathic in nature, and for which patient was placed on various regimen of steroids, Allegra, and Benadryl on an as-needed-basis. During the 008 study, patient experienced multiple episodes of infusion reactions, the more serious of which included dyspnea, lightheadedness, facial flushing, facial swelling, urticaria, peripheral cyanosis, rigors, suggestive of immune-mediated anaphylactic/anaphlatoid response. In the open label study, patient continued to have episodes of infusion reactions: fevers, chills, hives, and cyanosis.

About a month prior to patient's death, a bronchoscopy was indicated for patient's "increasing airway obstruction." Visualization revealed severe tracheobronchomalacia, severe laryngomalacia, severe adenotonsillar hypertrophy, and suprastomal obstruction by tissue masses. In addition, severe airway obstruction was found at multiple levels: nasopharynx, larynx, suprastomal trachea, distal trachea/proximal main bronchi. It was then recommended that dilatation of the stoma, followed by a placement of a larger tracheostomy tube to help the stent the distal trachea and the orifices of the main bronchi be preformed. Two days after the procedure, approximately 4 years after the first dose of study medication and 4 days after his most recent dose, the patient was hospitalized with increasing dyspnea. Despite of intensive medical therapy, patient's respiratory condition deteriorated. An emergency bronchoscopy was performed that revealed edematous soft tissue at the carina. A repeat bronchoscopy six hours after the initial one demonstrated significantly increased edema and narrowing at the carina, precluding intubation of the left main bronchus as a temporary measure. Due to the inability to adequately ventilate the patient, limited long-term options for improving respiratory status, and

the patient's living will reflecting his wish not to be placed on life support, the decision was made by the family and attending physicians to remove ventilatory support. The patient expired 40 minutes after life support was withdrawn. In the Applicant's opinion the patient's death was unrelated to study medication, which was in agreement with the investigator's assessment.

Reviewer's comment:

The patient had pre-existing severe tracheomalacia, and obstruction of the mainstem bronchi due to his underlying mucopolysaccharidosis. Respiratory failure was probably caused by his progressive airway disease, which is a frequent cause of death in Hunter syndrome. However, a causal relationship cannot be completely ruled out. Whether diffuse swelling of the respiratory tract was exacerbated by angioedema-like reactions secondary idursulfase administration in a patient who demonstrated a significant history of hypersensitivity reactions (including facial swelling) is unknown.

- Patient 024-059-002 was a 21 year-old man enrolled at Addenbrooke's Hospital in England, who was randomized to the idursulfase every-other-weekly group in TKT024, and died during TKT024EXT. At baseline, his FVC was 1.29L, and FEV₁, 0.76L. Past medical history included hypertension, valvular heart disease (aortic and mitral stenoses), asthma, kyphoscoliosis, glossomegaly, and decreased motility requiring wheelchair use. He received all of his scheduled doses in TKT024 and 8 doses of idursulfase in TKT024EXT prior to his death. He did not have any SAEs during the course of the study, and did not have any infusion reactions aside from episodes of pyrexia during 3 separate infusions. Three months into his extension open-labeled study, which was approximately after 15 months of treatment of idursulfase, patient developed a series of events that included asthma exacerbation in the setting of respiratory infection, and hematemesis in the setting of patient's stomach herniating into an umbilical hernia with collapse of the small bowel. Despite of maximum medical support, patient continued to deteriorate, and it was concluded that the patient was experiencing respiratory distress because of the narrow bore of the initial endotracheal tube (a 5.5 ET tube), and that the only option was to introduce a larger bore ET tube through a tracheostomy. Prior to the procedure, a fiber optic examination of the trachea/bronchial tree revealed the right main bronchus almost completely occluded and the left main bronchus 75% occluded. On the CT scanner table, patient arrested; and, despite twenty-five minutes of resuscitation effort, he died of cardiac-pulmonary failure due to upper airway obstruction, mucus plugging, and Hunter disease.

Reviewer's comment:

The cause of death was probably due to Hunter syndrome. However, whether idursulfase treatment lowered the threshold for severe respiratory exacerbation has not been ruled out.

- Patient 024-013-0004 (aka TKT031NPU-142-0004) was a 24 year old man who was enrolled at University of North Carolina at Chapel Hill. Patient was randomized to the placebo group in TKT024. The patient's medical history includes seizure disorder, valvular heart disease, class I angina, tonsil and adenoids hypertrophy, sleep apnea using CPAP at night, difficulty in breathing with poor air movement bilaterally found on physical exam, with a baseline FVC of 1.74L, and FEV₁ of 1.21L. Although obstructive lung disease was not listed as one of his medical problems,

he probably did have symptomatic obstructive lung disease, as his CRF documented that he had been taking a steroid-and- β -2-agonist combination inhaler along with seizure medications prior to the start of the study. He received his first dose of idursulfase on the TKT024EXT protocol, which he participated in for approximately 1 year and 4 months before he transitioned to a named-patient protocol (TKTNPU), in which he could receive drug administration closer to home. During this transition, for approximately the next two months he did not receive any study medication. It was during the two months hiatus that patient developed status epilepticus with aspiration pneumonia for which patient admitted to the ICU where he progressed into respiratory failure requiring mechanical ventilation from which he could not be weaned off over a protracted course of hospitalization. During the course of his hospitalization, he was re-started on idursulfase in the named-patient-use protocol, TKT031NPU. He remained vent-dependent, and about 6 months into his hospitalization, he suffered a cardiac arrest and died. He received his last dose of idursulfase six days prior to death at the age of twenty-six. The investigator reported the death as not related to treatment with idursulfase study medication.

Reviewer's comment:

The cause of death was probably due to Hunter syndrome. However, whether idursulfase treatment lowered the threshold for severe respiratory exacerbation has not been ruled out. If in fact idursulfase lowered the threshold for serious adverse events relating respiratory compromise, it would make ventilator weaning difficult.

- Patient 024-020-0003 was a 6 year old boy enrolled at the Hospital de Clinicas de Porto Alegre in Brazil, who was randomized to receive placebo in the pivotal study TKT024. Patient had both restrictive and obstructive lung disease at baseline: FVC was 0.41L, and FEV₁, 0.41L, though his lung physical exam was normal. He had aortic and mitral valve stenosis, as well as seizure disorder. Two days after his 34th infusion of placebo treatment, patient developed a fever and productive cough. Chest-x ray suggested a left lobar pneumonia in the setting of hypoxic respiratory failure. Blood cultures grew *Streptococcus pneumoniae*. Despite of intensive care supportive therapy, patient's hospital course was complicated by possible GI bleed, secondary to sepsis-associated DIC presumably. Ten days after his 34th infusion of placebo treatment, patient died of cardiopulmonary arrest secondary to pneumonia with a "probable sequence of events summarized as: pneumonia → sepsis → DIC → pulmonary hemorrhage."

Reviewer's comment:

The cause of death was not related to idursulfase since the patient did not receive active drug.

Reviewer's comment:

In the controlled study, TKT024, one patient in the idursulfase weekly group, and one patient in the placebo group died of respiratory-related events. All 5 deaths (4 in the idursulfase-treated groups and 1 in the placebo group) were related to respiratory failures. Except for case of the placebo patient, due to the high prevalence of underlying respiratory illness in Hunter syndrome, it is difficult, if not impossible, to sort out which of these deaths were related to the disease process, and which might have been related to the study drug. As shown below in Section 7.1.2, respiratory signals were detected as serious adverse events and anaphylactoid reactions. Only long term experience will provide more information about a possible connection between idursulfase treatment and respiratory-related deaths.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) that occurred in studies TKT008 (a 6-month study), TKT024 (a 1-year study), TKT018 (up to April 2005), and TKT024EXT (up to April 2005) were pooled by this reviewer. The results showed 39 out of 108 (36%) patients experienced at least one SAE during the studies. Tables 41-44 tabulate all SAEs reported in the four clinical studies.

Table 39 Incidence of Serious Adverse Events in Study TKT008

SAE ^a	0.15 mg/kg EOW N (%) N _{total} =3	0.5 mg/ kg EOW N (%) N _{total} =3
Erythema (including flushing)	0 (0%)	1 (33%)
Feeling cold, shivers, rigors, or chills	0 (0%)	1 (33%)
Hypoxia	0 (0%)	1 (33%)
Infection (pneumonia)	1 (33%)	0 (0%)
Oedema or swelling (face)	0 (0%)	1 (33%)
Respiratory failure	0 (0%)	1 (33%)
Urticaria	0 (0%)	1 (33%)

^aNo SAEs occurred in the 1.5 mg/kg and in the placebo groups

Table 40 Incidence of Serious Adverse Events in Study TKT018 (Data up to April 2005)

SAE	0.5 mg/ kg EOW N (%) N _{total} =12
Dehydration	1 (8%)
Dyspnoea NOS	1 (8%)
Oedema or swelling (throat)	1 (8%)
Pain (headache)	1 (8%)
Respiratory distress	2 (16%)
Respiratory failure	2 (16%)

Table 41 Incidence of Serious Adverse Events in Study TKT024

SAE	0.5 mg/kg EOW N (%) N _{total} =32	0.5 mg/kg QW N (%) N _{total} =32	Placebo N (%) N _{total} =32
Adenoidal hypertrophy	1 (3%)	0 (0%)	0 (0%)
Anaesthesia intubation complication	1 (3%)	0 (0%)	0 (0%)
Appendicitis	0 (0%)	0 (0%)	1 (3%)
Arrhythmia, or EKG changes NOS	1 (3%)	1 (3%)	0 (0%)
Asthma NOS, bronchospasm, or obstructive airway d/o	0 (0%)	1 (3%)	0 (0%)
Bleeding (nose)	0 (0%)	0 (0%)	1 (3%)
Bronchospasm secondary to pneumonia	0 (0%)	0 (0%)	1 (3%)
Carpal Tunnel Syndrome	0 (0%)	1 (3%)	0 (0%)
Cyanosis	0 (0%)	1 (3%)	0 (0%)
Depression, Adjustment Disorder with Depressed Moods	0 (0%)	0 (0%)	1 (3%)
Ear, fluid in	0 (0%)	1 (3%)	0 (0%)
Hearing decrease or loss	0 (0%)	0 (0%)	1 (3%)
Infection (abscess)	0 (0%)	1 (3%)	0 (0%)
Infection (ear)	1 (3%)	0 (0%)	2 (6%)
Infection (pneumonia)	1 (3%)	0 (0%)	1 (3%)
Infection (tooth, or cavity)	2 (6%)	0 (0%)	0 (0%)
Inguinal hernia NOS	0 (0%)	0 (0%)	1 (3%)
Medical device complication	1 (3%)	1 (3%)	0 (0%)
Nausea	1 (3%)	0 (0%)	0 (0%)
Orthostatic hypotension	1 (3%)	0 (0%)	0 (0%)
PCO2 increased	0 (0%)	0 (0%)	1 (3%)
Pain (arthralgia)	0 (0%)	1 (3%)	0 (0%)
Pain (headache)	0 (0%)	0 (0%)	1 (3%)
Pancreatitis acute	0 (0%)	0 (0%)	1 (3%)
Phobia	1 (3%)	0 (0%)	0 (0%)
Poor venous access	3 (9%)	3 (9%)	2 (6%)
Post surgical complication	0 (0%)	0 (0%)	1 (3%)

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Pyrexia	1 (3%)	0 (0%)	0 (0%)
Rash NOS	0 (0%)	0 (0%)	1 (3%)
Respiratory failure	0 (0%)	1 (3%)	0 (0%)
Thrombosis (pulmonary emboli)	0 (0%)	1 (3%)	0 (0%)
Tonsillar hypertrophy	1 (3%)	0 (0%)	0 (0%)
Umbilical hernia NOS	1 (3%)	0 (0%)	0 (0%)
Valvular heart disease	0 (0%)	1 (3%)	2 (6%)

Table 42 Incidence of Serious Adverse Events in Study TKT024EXT (Data up to April 2005)

SAE	0.5 mg/kg QW N (%) N _{total} =94
Arrhythmia, or EKG changes NOS	1 (1%)
Bleeding (nose)	1 (1%)
Cardiac ventricular disorder NOS	1 (1%)
Infection (ear)	1 (1%)
Pain (GI)	1 (1%)
Spinal cord disease NOS	1 (1%)
Thrombosis (central line)	1 (1%)
Umbilical hernia NOS	1 (1%)
Valvular heart disease	1 (1%)
Vomiting NOS	1 (1%)

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Reviewer's comment:

After noting that all five deaths were related to respiratory failure, particular attention was paid to detecting respiratory signals in the SAE category. These SAEs are worrisome by themselves, but they are particularly worrisome in this patient population. Since Hunter syndrome patients usually die of cardiopulmonary arrest, a pulmonary-related serious adverse event could trigger events that may culminate in death. Because many Hunter syndrome patients do not have normal respiratory reserve to withstand a serious triggering event, cardiopulmonary adverse events must be considered with the highest degree of concern.

All the patients who experienced respiratory tract/pulmonary SAEs (those not related to pneumonia, complication of pneumonia, or complication of anesthesia) in study TKT024 were randomized to the idursulfase weekly group. These four patients experienced a total of four respiratory SAEs (see Table 43). Patient 024-012-0008 experienced respiratory failure requiring intubation (and died); patient 024-020-0009 experienced bronchospasm; patient 024-020-0012 experienced cyanosis; and, patient 024-059-0004 experienced pulmonary embolism.

Respiratory SAEs showed a similar trend in the only other controlled study, TKT008. Not counting pneumonia, which is an infection, all respiratory SAEs took place in a single patient: 008-013-0005, who was treated with 0.5 mg/kg EOW idursulfase. Specifically, this patient experienced two separate episodes of hypoxia, and one episode of respiratory failure. When evaluating results from study TKT008, however, one needs to consider that there were three times as many patients enrolled in the idursulfase groups than in placebo group so it was more likely to see any adverse events in the idursulfase treated group than in the placebo group.

In the uncontrolled, open-label study TKT024EXT, as of the cut off date of April 2005, there were no respiratory SAEs. There were, however, five respiratory serious adverse events (that were not related to infections) reported in the extension, open-labeled study TKT018. These respiratory serious adverse events occurred in three patients (25% of the study population of this study of 12 patients). Patient 018-013-0005 experienced three separate episodes of respiratory distress/respiratory failure SAEs; patient 018-013-0007 (who was treated with placebo in TKT008 and crossed over to 0.5 mg/kg EOW in TKT018) experienced one episode of respiratory distress SAE in TKT018 but none while as a placebo patient in study TKT008; patient 018-013-0011 experienced one episode of dyspnea SAE. All of these the patients were being treated with 0.5 mg/kg EOW idursulfase at the time of the event. Patient 018-013-0005 experienced 100% of respiratory SAEs in TKT008, and 60% of respiratory SAEs in TKT018. In total he experienced six separate episodes of respiratory SAEs, and three of these SAEs were considered by the investigator related to infusion reactions. His case study suggests that respiratory SAEs do not necessarily abate with time, and for patients who demonstrate respiratory serious adverse events, especially if on repeat occasions, they may be at higher risk for future respiratory serious adverse events. In such this population risks and benefits of the treatment must be considered judiciously.

In the placebo-controlled, pivotal study TKT024, other notable serious adverse reactions (in addition to the aforementioned respiratory related SAEs) that occurred in the weekly-idursulfase treated patients but not in the placebo patients included one case of each of: cardiac arrhythmia, pilonidal cyst infection, and

arthralgia. Notable SAEs occurred in the EOW-idursulfase treated patients but not in the placebo patients included one case of each: anesthesia intubation complication (airway trauma due to intubation), symptomatic arrhythmia (ventricular extra systole) requiring medication, and orthostatic hypotension. In the uncontrolled, extension study TKT024, notable SAEs included: cardiac arrhythmia, cardiac ventricular disorder, and central line thrombosis.

Of the 27 patients who experienced SAEs during study TKT024, 9 patients received placebo treatment. The remaining 18 patients received idursulfase treatment. Of these 18 patients, 8 patients tested positive for IgG idursulfase antibody, which was screened by Conformation Specific Assay (CSA) ELISA and confirmed by radioimmunoprecipitation assay (RIP).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile

Six patients discontinued idursulfase therapy during the course of the clinical development program. Five patients died (see Section 7.1.1). One patient withdrew from TKT024EXT, citing traveling inconvenience reasons. He was restarted on idursulfase treatment about two months later on a named-patient-use protocol, TKTNPU. In this committed patient population, despite of occurrence of serious adverse events during infusions, patients and their parents have come back for subsequent infusions. There were no adverse events associated with dropout.

7.1.3.2 Other Significant Adverse Events: Anaphylactic/Anaphylactoid Infusion Reactions

The analysis of infusion-related adverse events is an important one to consider when considering the safety profile of any protein-based biologic therapeutic agent. Patients who have little or none of the protein in question can mount immune responses to exogenous or “foreign” proteins used as replacement therapy. These immune hypersensitivity responses can range from tolerable to life-threatening, and the onset can range from immediate to latent. Late-onset immune responses can be difficult to detect in this population because Hunters syndrome patients have multi-organ medical histories at baseline. Immediate immune responses, however, can be characterized by infusion reactions. Of these, the most serious are anaphylactic/anaphylactoid reactions. In July 2005, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN), which included representatives from 16 different organizations or government bodies, convened in the Second Symposium on the Definition and Management of Anaphylaxis, and agreed that anaphylaxis is “one of the most alarming disorders encountered in medicine.” Such reactions “are often life-threatening and almost always unanticipated... [and are] rapid in onset and may cause death.”⁹ The Symposium also addressed the issue of observation after an anaphylactic event. “On the basis of the evidence to date, the participants attending the NIAID/FAAN symposium recommended that

⁹ Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-7

observation periods be individualized on the basis of the severity of the initial reaction, reliability of the patient, and access to care. More caution should be used in patients with reactive airway disease because most fatalities associated with anaphylaxis occur in these patients.”

A by-patient summary of those patients identified as having infusions associated with potential anaphylactic/anaphylactoid reactions is provided in Table 43. Individual patient narratives are provided in Appendix 1. Search strategy of this analysis is addressed in Section 7.1.4.

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Table 43 By-Patient Summary of Patients Experiencing Possible Anaphylactic/Anaphylactoid Reactions

Patient ID (Study No.)	AE Term(s)	Infusion No.	AE Onset (in minutes relative to infusion time)	AE Treatment	Premedication Use ^a	Sponsor's Assessment
018-013-0002 (TKT018)	Facial flushing and Hypotension	27	NA	None	No	Not a reaction
018-013-0005 (TKT008)	Facial flushing ^b	10	NA	None	Yes	Possible
018-013-0006 (TKT008)	Facial flushing and Dyspnoea	7	NA	None	No	Possible
	Facial flushing and swelling, Nasal congestion, Sore throat, Urticaria and Cyanosis in arms; Rigors, and Fever	9	~10	Oxygen; Diphenhydramine IV	No	Possible
018-013-0006 (TKT018)	Urticaria (on hands) ^{ba}	78	NA	Fexofenadine PO	No	Possible
	Rash and Excessive bronchial secretions ^d	108	NA	None	Yes	Not a reaction
018-013-0007 (TKT018)	Facial flushing and Respiratory distress	4	~5	Oxygen; Diphenhydramine IV	No	Possible
	Facial flushing and Dyspnoea	5	NA	Oxygen	Yes	Possible
	Facial flushing and Dyspnoea	6	NA	Oxygen	Yes	Possible

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Patient ID (Study No.)	AE Term(s)	Infusion No.	AE Onset (in minutes relative to infusion time)	AE Treatment	Premedication Use ^a	Sponsor's Assessment
018-013-0010 (TKT008)	Urticaria, rigors ^f	7	NA	None	No	Possible
024-012-0004 (TKT024)	Flush, Urticaria, Swollen tongue, Conjunctivitis ^g	9	15	Prednisolone and Dimetindene IV	No	Possible
024-020-0001 (TKT024)	Wheezing ^g	19	30	Oxygen and Salbutamol INH	Yes	Not likely
024-020-0008 (TKT024)	Rash and Wheezing	7	85	Salbutamol INH; Loratadine PO	Yes	Possible
024-020-0012 (TKT024)	Rash and Dyspnoea	5	60	Fenoterol INH; Diphenhydramine IV	Yes	Possible
	Nausea, Cough, Dyspnoea, Wheezing - then Rash	9	117	Fenoterol INH; Diphenhydramine IV; Metoclopramide IV	Yes	Possible
	Facial erythema and Dyspnoea, Wheezing	13	80	Salbutamol INH; Diphenhydramine and Methylprednisolone IV	Yes	Possible
	Tremor; Skin redness on arms and Perioral cyanosis; Fever - later Facial and Leg oedema for a few days (no time, according to mother)	40	74	Oxygen; Methylprednisolone and Dipyrone IV	No	Possible
024-046-0008 (TKT024)	Pruritic rash (chest, left arm, and cheeks) ^f	22	217	Diphenhydramine PO	Yes	Not likely

Patient ID (Study No.)	AE Term(s)	Infusion No.	AE Onset (in minutes relative to infusion time)	AE Treatment	Premedication Use ^a	Sponsor's Assessment
024-059-0001 (TKT024)	No adverse event recorded ^b	5	65, 180	None	Yes	Not likely
024-013-0010 (TKT024EXT)	Transient rash and Wheezing ("possible exacerbation of underlying reactive airways disease")	23	NA	Salbutamol – Fluticasone INH; Prednisone PO	Yes	Not likely
024-020-0005 (JKT024EXT)	Facial erythema and Bronchospasm: Vomiting	8	30	Oxygen; Salbutamol INH	No	Possible
024-044-0001 (TKT024EXT)	Generalized erythema and Dyspnoea	2	10	Chlorpheniramine PO	No	Possible
024-044-0008 (TKT024EXT)	Facial Flushing and Dyspnoea	9	225	None	Yes	Possible
024-044-0008 (TKT024EXT)	Facial flushing, Rash in the back and Chest tightness (the day after, lasting several days)	11	NA	Piriton PO	Yes	Not likely
024-044-0008 (TKT024EXT)	Face red and swollen and Dyspnoea	12	NA	None	Yes	Possible

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Patient ID (Study No.)	AE Term(s)	Infusion No.	AE Onset (in minutes relative to infusion time)	AE Treatment	Premedication Use ^a	Sponsor's Assessment
024-047-0011 (TKT024EXT)	Urticaria and Wheezing; Pain in the left ear	4	70	Hydrocortisone and Chlorpheniramine IV; salbutamol INH	No	Possible

^a A patient was considered to have potentially experienced an anaphylactic/anaphylactoid reaction if they had events in at least 2 of 3 body systems (respiratory, skin, or vascular) that occurred relative to a given infusion.

^b Sponsor's assessment = Based on medical review of the individual patient's data, the Sponsor believes that the events possibly, not likely, or do not constitute a potential anaphylactic/anaphylactoid reaction.

^c New information is italicized.

^d NA = Not available. The time of an adverse event(s) was not recorded during TKT008 or TKT018; however, time of event was to be recorded during TKT024 and TKT024EXT.

^e Pre-medications used are described in the patient narratives that follow.

^f Patient 018-013-0005 experienced flushing (skin system) and had O₂ saturation change from 95% pre-infusion to 87% thirty minutes after the start of the 10th infusion (i.e., hypoxia, defined as a pre-infusion O₂ saturation >91% and during/after infusion O₂ saturation of <88%, per FDA-specified criteria; see response to Question 2e below). Patient 018-013-0006 experienced urticaria (skin system), had O₂ saturation change from 98% pre-infusion to 81% one hour after the 78th infusion (i.e., hypoxia), and he met the criteria for hypotension (i.e., systolic blood pressure < 80 during an infusion and at least 20 mmHg lower than the pre-infusion systolic blood pressure, as defined in the response to Question 2e below) at the time of his 78th infusion.

^g Patients 018-013-0006, 018-013-0010, 024-012-0004, 024-020-0001, and 024-046-0008 each had an infusion that was associated with 1 skin reaction AND the patient met the criteria for hypotension at that time, therefore only 1 AE term is listed for these patients.

^h Although Patient 018-013-0006 met the criteria for anaphylactic/anaphylactoid reaction associated with infusion 108, review of this patient's history showed that the rash was persistent and that the increased bronchial secretions were part of recurrent episodes of each event.

ⁱ Patient 024-059-0001 did not experience an adverse event, but had had O₂ saturation change from 99% pre infusion to 84% sixty-five minutes after the start of the infusion (i.e., hypoxia) AND he met the criteria for hypotension.

With the exceptions of patient 018-013-0002, who was receiving idursulfase 0.15 mg/kg every other week (during TKT008), and patient 018-013-0010, who was receiving idursulfase 1.5 mg/kg every other week (during TKT008), all patients were receiving idursulfase 0.5 mg/kg (either weekly or every other week) at the time of the potential reaction. Of note, pre-medications were administered to 11 patients who experienced potential anaphylactic/anaphylactoid reactions (however, not necessarily at the time of the reaction). Overall, 8274 idursulfase infusions had been administered as of 11-15-2005. As shown in Table 43, potential anaphylactic/anaphylactoid reactions were associated with a total of 26 infusions (26/8274, 0.3%) in 16 patients (16/108, 14.8%).

To further understand the nature of these potential reactions, the Applicant conducted a detailed medical review of the individual patient data for all patients identified in this analysis. Two (2) potential reactions in 2 patients were considered not anaphylactic/anaphylactoid (patient 018-013-0002 with his 27th infusion [report of hypotension was not supported by the patient's actual systolic blood pressure recordings] and patient 018-013-0006 with his 108th infusion [both events reported were considered recurrent episodes that were coincident with the infusion]). Further details are provided in the individual patient narratives, which can be found in Appendix 1. Five (5) potential reactions in 5 patients were considered not likely to be anaphylactic/anaphylactoid, due to underlying disease (Patient 024-013-0010), unlikely chronology of the events (patient 024-044-0008), or based on a single low blood pressure or oxygen saturation recording that was not noted as adverse event by the investigator and did not prompt any action (patients 024-020-0001, 024-046-0008, 024-059-0001). Based on the Applicant's medical assessment of these data, a total of 19 infusions (19/8274, 0.2%) in 11 patients (11/108, 10.2%) were associated with potential anaphylactic/anaphylactoid reactions. No patient has discontinued any study due to an adverse event associated with idursulfase.

These cases demonstrate some important observations. Anaphylaxis or anaphylactoid response may occur any time, even after 6 months of experience with idursulfase. Anaphylactic/anaphylactoid reactions can breakthrough pre-medication. Patients with severe baseline respiratory compromise (especially those with obstructive/airway reactive lung disease) may be at a greater risk for life-threatening infusion reactions, but patients with less severe respiratory compromise are not immune. Acute respiratory or febrile illnesses may increase the risk of serious infusion; therefore, clinicians should consider delaying idursulfase infusion until the patient has recovered from acute illness. The risk/benefit profile for patients who experienced severe infusion reaction(s) must be weighed judiciously. Other conclusions about anaphylactic/anaphylactoid reactions are included in the FDA approved product label under the BOXED WARNING, WARNINGS, ADVERSE REACTIONS sections, and were derived from evaluation of individual narratives (Appendix 1), MedWatch reports, clinical study protocols, Applicant's safety synopsis, and raw safety datasets.

7.1.4 Other Search Strategies

Regarding the Applicant's initial analysis of infusion reactions, the following issues were identified by the reviewer: 1) It was assumed that because no patient has tested positive for IgE antibodies, there were no anaphylactic reactions, 2) infusion reactions were (partially) defined by the investigator's subjective judgment about drug-relatedness, and 3) the Applicant did not utilize infusion-log vital signs to include episodes of hypoxia and hypotension in counted as symptoms of possible anaphylactic reactions.

During the initial safety review, the following issues led to the reviewer's concern about the adequacy of the Applicant's analyses of infusion reactions:

- Patient 024-044-0007 complained of feeling "like throat closing" during the infusion of 0.5 mg/kg QW idursulfase drug on 2-4-04. This event was coded as an adverse event, but it was not coded as either as a serious adverse event, or an infusion reaction. The same patient, 14 days later, complained of "lump in the throat" during the next infusion. Once again it was not coded as either serious adverse event or infusion reaction because the event was not thought to be related to drug infusion. Pharyngeal-laryngeal edema or spasms are well known symptoms of anaphylaxis/anaphylactoid, or angioedema reactions. But, since these symptoms ("throat closing up," and "lump in the throat") were not judged related to the drug by the investigator, they were not counted as infusion reactions. The result is underestimating possible anaphylactic or anaphylactoid infusion reactions.
- Hypotension and hypoxia that occurred during infusions were missed as infusion reactions. Abnormal vital sign recordings were not always recorded as adverse events, and therefore, not counted as serious adverse events or infusion reactions. Patient 024-059-0006, on 6-02-2004, had a systolic blood pressure of 116 just immediately prior to the start of infusion, but his systolic blood pressure dropped to 61 during the infusion. The episode was not recorded as an AE, and therefore, not an infusion reaction or a serious adverse event. Hypotension is a well known symptom of anaphylaxis or anaphylactoid reactions. Since this incident was not recorded in the adverse events dataset, it was not figured into the infusion reactions analysis. Similarly, hypoxic episodes were missed. Patient 024-048-0008, on 6-16-2004, had an O2 saturation of 95% immediately prior to the start of infusion but his oxygen saturation decreased to 75% at 2 hours time into the infusion. Since this episode of hypoxia was not coded as an adverse reaction, it was not coded as an infusion reaction. The result is underestimating possible anaphylactic or anaphylactoid infusion reactions.

To address these problems, the review team asked the Applicant to provide re-analysis of possible anaphylactic/anaphylactoid infusion reactions, taking into consideration of the following. First, possible anaphylactic/anaphylactoid reactions should be considered even if the patient's IgE antibody status was negative. The IgE antibody assay used by the Applicant has not been validated (see Immunogenicity Review by Jin Hai Wang, MD); moreover, IgE positivity was not identified as a criterion for anaphylaxis by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID-FAAN)⁹. There is no universal agreement on the definition of anaphylaxis or the criteria for diagnosis; the purpose of the Symposium was to continue working toward a universally accepted definition of anaphylaxis based on clinical criteria rather than on laboratory status. The discussion resulted in establishing clinical criteria for diagnosing anaphylaxis (Table 46), and in these criteria, IgE positivity was not identified as a necessary component for establishing events that are likely anaphylaxis. From a clinical perspective, IgE antibody status is not critical for decision-making either, because for both anaphylactic (defined as IgE antibody positive status in conjunction with clinical syndrome), and anaphylactoid, i.e., anaphylaxis-like reactions (defined as IgE antibody negative status in conjunction with clinical syndrome), medical management is the same.

Table 44 Clinical Criteria for Diagnosing Anaphylaxis⁹

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

- b. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
- a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg. Crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
- a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm HG or greater than 30 % decrease from that persons' baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year; less than (70 mm Hg + [2 x age]) from 1 to 10 years; and, less than 90 mm Hg from 11 to 17 years.

Second, the Applicant was asked to screen for possible anaphylactic/anaphylactoid reactions using a set of Division clinical criteria, modified from the criteria set by the Symposium. The analysis would take into consideration vital sign changes during infusions. The analysis would include adverse events based on temporal relatedness, not drug-relatedness. A later cut-off-date of 11-15-2006 would be used.

The Applicant performed the requested analysis, using the criteria described in Figure 16. Results are summarized in Section 7.1.3.2: Other Significant Adverse Events: Anaphylactic/Anaphylactoid Infusion Reactions.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 17 Criteria for Re-Analysis of Anaphylactic/Anaphylactoid Reactions in the Idursulfase Clinical Development Program

Anaphylactic/anaphylactoid reactions have potentially occurred when any 1 of the following 2 criteria was fulfilled:

1. Acute onset of an illness (within 24 hours of the start of an infusion for Studies TKT024 and TKT024EXT, and the day of or the day after infusion for Studies TKT008 and TKT018) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, rash, pruritus, flushing, erythema, urticaria, facial oedema, swollen lips-tongue-uvula), and at least one of the following:
 - a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia [defined as O₂ saturation of < 88% during the infusion AND with corresponding O₂ saturation at least above 91% prior to infusion], respiratory failure or insufficiency, respiratory distress, cyanosis)
 - b. Reduced blood pressure (systolic blood pressure [SBP] less than 80 recorded during an infusion AND at least 20 points lower than the SBP recorded prior to infusion) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope)
2. Two or more of the following that occur rapidly (within 24 hours of the start of an infusion for Studies TKT024 and TKT024EXT, and the day of or the day after infusion for Studies TKT008 and TKT018) after exposure to ELAPRASE:
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, rash, pruritus, flushing, erythema, urticaria, facial oedema, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia [defined as O₂ saturation of <88% during the infusion AND with corresponding O₂ saturation at least above 91% prior to infusion], respiratory failure or insufficiency, respiratory distress, cyanosis)
 - c. Reduced BP (SBP less than 80 recorded during an infusion AND at least 20 points lower than the SBP recorded prior to infusion) or associated symptoms (e.g., hypotonia [collapse], syncope)

**APPEARS THIS WAY
ON ORIGINAL**

7.1.5 Common Adverse Events

7.1.5.1 Applicant's Approach to Eliciting Adverse Events in the Development Program

In the pivotal study TKT024, monitored throughout the study were adverse events (AEs) as observed by the investigator or reported by the patient. AEs were discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or abnormal clinical laboratory values, or abnormal EKG. Information was collected every week at each study visit, when patient was asked, "How do you feel?" and further questions were posed if there was an indication of an AE.

Reviewer's comment:

The open-ended questioning approach allowed capture of unexpected AEs. However, since AEs were not collected by targeted questionnaires, certain categories of adverse events (for example, decreased cognitive or sexual function) may have been missed.

Safety assessments also included concomitant medications and surgeries, vital signs, physical exam, height, weight, laboratory tests (chemistry, hematology, urinalysis, urine and creatinine), serum collection for antibody testing, and EKGs. Serum idursulfase antibodies were screened by enzyme-linked immunosorbent assay (ELISA) and Conformation-specific assay (CSA), and confirmed by radioimmunoprecipitation (RIP) assay. Safety assessments were collected at baseline and at intervals throughout the study (see Table 6 Schedule of Visits and Procedures, Section 6.1.3.2.5).

Reviewer's comment:

Laboratory values of thyroid-stimulating hormone (TSH) and growth hormone (GH) were not included in the study.

The CSA antibody assay has not been validated.

If a patient had an infusion reaction of moderate or severe intensity, laboratory tests for serum tryptase-146 level and total complement were performed to screen for IgE-related anaphylactic/anaphylactoid reactions. The IgE antibody assay has not been validated.

7.1.5.2 Establishing Appropriate Adverse Event Categories and Preferred Terms

The reviewer examined all 5288 adverse events (AEs) listed in the AE.xpt datasets of the four studies containing data up to the cut-off date of April 2005. Verbatim terms were coded by the Applicant into MedDRA preferred terms (PT), which were in turn categorized into System Organ Classifications (SOC). Where terms were too broad or over-inclusive (lumping), the reviewer separated the terms so that important events were not diluted by less important ones. Where terms were too narrow (splitting), resulting in underestimation of the true incidence for a particular event or syndrome, the reviewer lumped the terms together.

The ADVERSE REACTIONS section of the FDA proposed label was derived from the review and recoding of some of the verbatim terms found in the AE.xpt dataset from study TKT024. The majority of the time the reviewer and the Applicant were in agreement as to coding; however, in some instances the verbatim terms were recoded. There were inconsistencies noted in the way that some of the verbatim terms were coded across the four clinical studies. For example, “elevated blood pressure” was coded to “hypertension NOS,” and “elevated BP” was coded to “blood pressure increased”. For consistency, both of these verbatim terms were recoded to the preferred term of “hypertension NOS”. Second, given that MedDRA has over 15,000 preferred terms, such level of granularity can result in a diluting out or over-fragmentation of AE terms. As the exposed population is small, and as we are trying to represent the true AE profile of idursulfase as accurately as possible, recoding of some AE terms was felt to be necessary. For example, the AE preferred terms of “urticaria NOS” and urticaria generalized” were collapsed under the AE term of “urticaria. A similar concern was seen with, for example, the fragmenting of gastrointestinal pain, including such terms as “abdominal pain NOS,” “abdominal pain upper,” “abdominal pain lower,” and “abdominal pain tenderness”. These terms were all coded as Pain (GI). The reviewer acknowledges that coding is an inherently subjective exercise.

Although certain verbatim terms were recoded, the reviewer has found overall categorization of preferred terms, as provided by the Applicant, appropriate.

7.1.5.3 Incidence of Common Adverse Events

Incidence rates of common AEs were analyzed from the AE.xpt datasets. Recurrent or continuing AEs were counted only once in a given patient. AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator (safety or ITT population). The AEs occurring during the double-blind, placebo-controlled studies are of most interest, as these provide the most objective safety data about how idursulfase-treated groups compared to the placebo group patients. There were two placebo-controlled studies: study TKT008, which was a six-month study involving twelve patients, and study TKT024, which was a one-year study involving 96 patients. Common AEs reported in TKT024 are summarized in Tables 47 and 48. The number of all AEs reported declined over time across all studies. During study TKT024 the majority of AEs reported occurred during the first 6 months of the trial.

The most common adverse reactions requiring intervention were infusion-related reactions: headache, fever, cutaneous reactions (rash, pruritus, erythema, and urticaria), and hypertension. The frequency of infusion-related reactions decreased over time with continued idursulfase treatment, and this trend was apparent in all four clinical studies.

Table 47 is a summary of those adverse reactions that occurred in at least 10% of patients (4 or more patients) treated with idursulfase weekly that also occurred more frequently than in the placebo group in the 53-week controlled trial.

Table 45 Summary of Adverse Reactions Occurring in at Least 10% of Patients (4 or More Patients) Treated with Idursulfase Weekly in the 53-Week Controlled Trial, and Occurring More Frequently Than in the Placebo Group

Adverse Event	ELAPRASE 0.5 mg/kg Weekly (n=32)		Placebo (n=32)	
Pyrexia	20	(63%)	19	(59%)
Pain (headache)	19	(59%)	14	(44%)
Pain (arthralgia)	10	(31%)	9	(28%)
Pain (limb)	9	(28%)	8	(25%)
Pruritus	9	(28%)	5	(16%)
Hypertension	8	(25%)	7	(22%)
Malaise	7	(22%)	6	(19%)
Visual disturbance	7	(22%)	2	(6%)
Wheezing	6	(19%)	5	(16%)
Abscess	5	(16%)	0	(0%)
Musculoskeletal dysfunction NOS	5	(16%)	3	(9%)
Pain (Chest wall musculoskeletal)	5	(16%)	0	(0%)
Urticaria	5	(16%)	0	(0%)
Superficial injury	4	(13%)	3	(9%)
Anxiety, irritability	4	(13%)	1	(3%)
Atrial abnormality	4	(13%)	3	(9%)
Adverse events resulting from injury	4	(13%)	2	(6%)
Dyspepsia	4	(13%)	0	(0%)
Infusion site edema	4	(13%)	3	(9%)
Skin disorder NOS	4	(13%)	1	(3%)
Pruritic rash	4	(13%)	0	(0%)

A similar table comparing common adverse events in the EOW idursulfase group and the placebo group is listed in Table 48.

Table 46 Summary of Adverse Reactions Occurring in at Least 10% of Patients (4 or More Patients) Treated with Idursulfase Every-Other-Weekly in the 53-Week Controlled Trial, and Occurring More Frequently Than in the Placebo Group

Adverse Event	ELAPRASE 0.5 mg/kg EOW (n=32)		Placebo (n=32)	
Upper respiratory infection	25	(78%)	24	(75%)
Pain (headache)	22	(69%)	14	(44%)
Vomiting NOS	18	(56%)	16	(50%)
Pain (gastrointestinal)	17	(53%)	11	(34%)
Nasal congestion	16	(50%)	12	(38%)
Pain (arthralgia)	14	(44%)	9	(28%)
Rash NOS	12	(38%)	11	(34%)
Pain (back)	11	(34%)	8	(25%)

Rhinorrhoea	10	(31%)	9	(28%)
Flu-like symptoms	9	(28%)	5	(16%)
Pain (limb)	9	(28%)	8	(25%)
Superficial injury	8	(25%)	3	(9%)
Malaise	7	(22%)	6	(19%)
Arrhythmia, or EKG changes NOS	6	(19%)	4	(13%)
Pruritus	6	(19%)	5	(16%)
Sleep disorder NOS	6	(19%)	2	(6%)
Wheezing	6	(19%)	5	(16%)
Adverse events resulting from fall	5	(16%)	3	(9%)
Adverse events resulting from injury	5	(16%)	2	(6%)
Infusion site edema	5	(16%)	3	(9%)
Pruritic rash	5	(16%)	0	(0%)
Urticaria	5	(16%)	1	(3%)
Anxiety, irritability	4	(13%)	1	(3%)
Dyspepsia	4	(13%)	0	(0%)
Ear congestion	4	(13%)	2	(6%)
Rigors/feeling cold	4	(13%)	1	(3%)
Pneumonia	4	(13%)	3	(9%)
Musculoskeletal dysfunction NOS	4	(13%)	3	(9%)
Pain (myalgia)	4	(13%)	3	(9%)
Pain (neck)	4	(13%)	2	(6%)
Paraesthesia, hypo/hypraesthesia	4	(13%)	3	(9%)
Poor venous access	4	(13%)	2	(6%)

Common adverse events found in both Tables 47 and 48 (Weekly and EOW vs. Placebo) include: pain (headache), pain (arthralgia), pain (limb), pain (chest-wall musculoskeletal), musculoskeletal dysfunction NOS, wheezing, pruritus, malaise, urticaria, superficial injury, adverse events resulting from injury, dyspepsia, catheter site edema, and pruritic rash. Given that the dosing recommendation is weekly idursulfase administration and that the most important common adverse events in Table 48 are also captured in Table 47, the reviewer recommends Table 47 (weekly idursulfase vs. placebo comparison) to be included in the label.

7.1.5.4 Identifying Common and Drug-Related Adverse Events

To establish drug relatedness of adverse events in a small (N=96) controlled study is inherently difficult. It is inappropriate to use hypothesis-testing methods because any reasonable correction for multiplicity would make a finding almost impossible. These small studies are underpowered for statistically valid detection of small differences. Also, high background rate of medical complications due to the disease make small differences are to detect. Given these limitations, the reviewer set an arbitrary definition. A common adverse event is considered an idursulfase-related, common adverse event if it met the following criteria: 1) the event had an incidence rate of occurring in at least 10 percent (i.e., at least four patients) in the idursulfase weekly population; 2) the event occurred in at least 2 or more patients in the

idursulfase weekly group than in the placebo group. Table 49 summarizes these common, drug-related adverse events.

Table 47 Common, Drug-Related Adverse Events in Study TKT024

ADVERSE EVENTS	ELAPRASE 0.5 mg/kg Weekly (n=32)		Placebo (n=32)	
Pain (headache)	19	(59%)	14	(44%)
Pruritus	9	(28%)	5	(16%)
Malaise	8	(25%)	6	(19%)
Visual disturbance	7	(22%)	2	(6%)
Abscess	5	(16%)	0	(0%)
Musculoskeletal dysfunction NOS	5	(16%)	3	(9%)
Pain (chest wall musculoskeletal)	5	(16%)	0	(0%)
Urticaria	5	(16%)	1	(3%)
Anxiety, irritability	4	(13%)	1	(3%)
Adverse events resulting from injury	4	(13%)	2	(6%)
Dyspepsia	4	(13%)	0	(0%)
Pruritic rash	4	(13%)	0	(0%)
Skin disorder NOS	4	(13%)	1	(3%)

In idursulfase-weekly treated patients there was a higher incidence of musculoskeletal injury NOS as compared to placebo patients. Musculoskeletal injury NOS was recoded by the reviewer to include a broad range of verbatim terms relating to musculoskeletal abnormalities: fractured right foot, bad back, calcaneus restriction worsening, decreased hand pincher grasp, decreased grip, increased scoliosis; increased spinal motion at cervical vertebrae, knee stiffness, leg stiffness, limited bilateral knee function, muscle strain, pulled muscle in the neck, ankle sprain, wrist fracture, thumb “clicking”/less mobile, “wobbly legs” secondary to yawns/stretch, neck stiffness, back stiffness, bunion enlarging, whole body stiffness, increased joints stiffness/discomfort, increased scoliosis, ankle torsion, wrist sprain, and synovitis.

Reviewer’s comment:

The finding of increased adverse events of musculoskeletal dysfunction challenges the claim that idursulfase improves comprehensive musculoskeletal functioning, despite that idursulfase has been shown to improve walking capacity in a 6MWT. Patients and treating physicians and patients should understand that idursulfase has not been directly shown to improve global musculoskeletal capacity, and that the exact mechanism by which the 6MWT improvement occurs has not been defined.

Of concern also is that in the idursulfase-weekly treated group, patients experienced a higher incidence of visual disturbance as compared to placebo patients. The recoding of visual disturbance included verbatim terms relating to blurred vision, myopia, astigmatism, hypermetropia, night blindness, seeing flashing colors, farsightedness, and fuzzy vision. No serious visual problem (such as blindness) has been reported to date.

Reviewer's comment:

Whether idursulfase will pose a serious long-term negative effect on the eye is unknown at this time. Some patients will have visual problems (such as ptosis, severe retinal degeneration, discrete corneal opacities, and chronic papilledema) as part Hunter syndrome. In any event, patients will need regular visual acuity exams to see if they needed corrective lenses because since MPS II patients already have ambulation difficulties and are prone to falls and accidents, uncorrected decrease in visual acuity may increase patients' risks of falls and accidents.

Despite observation of an increased incidence rate of abscess infections in the idursulfase-weekly treated patients, an analysis counting all infections and infestations showed that there was no significant difference noted between the idursulfase-weekly versus placebo groups in infection rates.

Reviewer's comment:

Pain and malaise were noted in the table. Pain and malaise pose significant problems in quality of life. Therefore the risk/benefit analysis of idursulfase should be individualized to each patient's medical needs.

7.1.5.6 Additional Analyses and Exploration

Table 14.1.1.8.3 of the TKT024 study report tabulated the finding that there were more idursulfase treated patients who used concomitant pain medications during the study period as compared to placebo patients:

Table 48 Pain Medication Use in Study TKT024 (Source: BLA Submission)

Table 14.1.1.8.3 Protocol No. TKT024				
	Idursulfase Weekly (N=32)	Idursulfase Every-other-week (N=32)	Placebo (N=32)	All patients (N=96)
ANY CONCOMITANT PAIN MEDICATION N (%)	4 (13%)	10 (31%)	1 (3%)	15 (16%)

These medications include acetaminophen and NSAIDs which may have been used as antipyretics. Two patients (6%) in the idursulfase-weekly group, 8 patients (25%) in the idursulfase EOW group, and 3 patients (9%) in the placebo group were initiated on pain medication prior to the start of the study.

More patients in the idursulfase treated groups experienced pain than in the placebo group during the pivotal trial period. The reviewer examined all verbatim terms and MedDRA preferred terms of AEs that contained the word "pain," "ache," "discomfort," "tenderness," "sore," or other similar terms, and counted these pain-related adverse events sorted by anatomical locations.

Table 49 Incidence Table of Pain by Treatment Group in Study TKT024

ADVERSE EVENT: PAIN	ELAPRASE 0.5 mg/kg Weekly (n=32)	ELAPRASE 0.5 mg/kg EOW (n=32)	Placebo (n=32)
PAIN (GI)	11	17	11
PAIN (TMJ OR JAW)	0	1	0
PAIN (ARTHRALGIA)	10	14	9
PAIN (BACK)	8	11	8
PAIN (BONE)	1	1	0
PAIN (BUTTOCK)	0	0	1
PAIN (CATHETER SITE)	3	5	5
PAIN (CHEST WALL MUSCULOSKELETAL)	5	1	0
PAIN (NON-CARDIAC CHEST)	3	2	0
PAIN (DENTAL OR ORAL)	3	1	3
PAIN (EAR)	6	5	6
PAIN (EYE)	3	1	1
PAIN (FLANK)	1	0	1
PAIN (FOOT)	2	1	2
PAIN (GROIN)	1	2	0
PAIN (HEADACHE)	19	22	14
PAIN (HERNIA)	0	1	0
PAIN (INGUINAL HERNIA)	0	0	1
PAIN (LIMB)	9	9	8
PAIN (MICTURATION)	1	0	0
PAIN (MUSCLE CRAMPS)	1	1	0
PAIN (MUSCULOSKELETAL)	1	0	0
PAIN (MYALGIA)	3	4	3
PAIN (NECK)	2	4	2
PAIN (PENIS OR TESTICLE)	2	2	0
PAIN (POST PROCEDURAL)	3	3	4
PAIN (SACRAL)	0	0	1
PAIN (SCIATICA)	0	1	0
PAIN (UMBILICAL HERNIA)	1	1	0
PAIN NOS	1	0	2
TOTAL	100	110	82

Headache accounted for a significant portion of the difference in the incidence of pain among the three groups. The relationship between idursulfase use and pain is not entirely clear at this time but deserves long term observation to guide patients about their choice in continuing idursulfase therapy given that pain is one of the most important components of quality of life.

7.1.6 Less Common Adverse Events

7.1.6.1 Thromboembolic Adverse Events

Three thromboembolic events were reported in patients treated with idursulfase; none was reported in the placebo group. At the time of the event, one patient was randomized to receive idursulfase weekly treatment in study TKT024, and two patients were receiving idursulfase weekly treatment in study

TKT024EXT. Patient 024-059-0004 developed multiple pulmonary emboli while he was on weekly treatment of idursulfase in study TKT024 (about a month after first starting idursulfase). Patient 024-046-0006 developed central line thrombosis while he was on weekly treatment of idursulfase in study TKT024EXT (about 15 months after first starting idursulfase in study TKT024). Patient 024-012-0007 developed thrombosis in the left leg (not specified whether it was a deep venous thrombosis, or an arterial thrombosis) while he was on weekly treatment of idursulfase in study TKT024EXT (about one year after first starting idursulfase treatment in study TKT024). These patients were not identified with hypercoagulable risk factors, and Hunter syndrome is not a recognized risk factor for hypercoagulable tendency (this reviewer searched the PubMed data base and found no connection between Hunter syndrome and thromboembolism). The Applicant attributed the thromboembolic events to underlying cardiac disease (tachyarrhythmia, dilated left atrium, and poor global ventricular function) in the first patient, and Mediport complication in the second patient¹⁰. But, cardiac disease and Mediport placement are common across treatment groups, yet no patient in the placebo group developed thromboembolism. It has been noted that patient 024-059-004 did have severe thrombocytopenia at baseline. Possible connection between thrombocytopenia and risk of thrombosis is beyond the scope of this review¹¹.

Jasti Choudary, PhD, FDA supervising pharmacology-toxicology reviewer, pointed out that the agent danaparoid (ORGARAN®) which contains the active components of heparan sulfate, dermatan sulfate (and a small amount of chondroitin sulfate) was approved for indication for the prophylaxis of post-operative deep venous thrombosis as an anti-thrombotic agent¹². Heparan sulfate and dermatan sulfate act on the coagulation pathway as antithrombotic via thrombin inhibition by anti-Xa and anti-thrombin effects. Lowering GAG levels can, in theory, create a pro-thrombotic state. Although treatment with idursulfase did not lower patient's GAG levels to an abnormally low level, even a disturbance towards lowering GAGs might disrupt the patients' intrinsic hemostatic equilibrium and predispose them to a pro-thrombotic state. Or possibly, by almost normalizing GAG level, idursulfase could unmask a hypercoagulable state.

Supporting this hypothesis is the finding that there was higher bleeding incidence in the placebo-treated group than the idursulfase-treated groups:

Table 50 Bleeding Adverse Events in Study TKT024

Adverse Event Involving Bleeding	0.50 mg/kg EOW N=32	0.50 mg/kg QW N=32	Placebo N=32
Bleeding (GI)	0	1	1
Bleeding (catheter site)	0	1	2
Bleeding (ear)	0	0	2
Bleeding (nose)	1	2	5

10 Revel-Vilk, S. Central venous line-related thrombosis in children. *Acta Haematol.* 2006; 115:201-206.

11 Atsumi T, et al. Antiphospholipid antibody associated thrombocytopenia and the paradoxical risk of thrombosis. *Lupus* 2005; 14(7):499-504

12 Physicians' Desk Reference 56th edition, 2002; 2480-2482

Bleeding (post op)	0	1	0
Bleeding (tooth or gum)	1	0	0
Total	2 (6%)	5 (16%)	10 (31%)

Reviewer's comment:

Pulmonary embolism (and DVT) would pose a serious threat to patients who are already compromised in their respiratory status. These events should be monitored closely in the post-marketing experience.

7.1.6.2 Psychiatric Adverse Event

Over the course of the controlled study TKT024, incidences of psychiatric adverse events including anxiety and depression adverse events were higher in idursulfase-treated groups than in the placebo group. For anxiety/irritability, 4 patients (13%) reported it in the idursulfase weekly group, 4 patients (13%) reported it in the idursulfase EOW group, but only 1 patient (3%) reported it in the placebo group. For depression/depressed mood adverse events, 3 patients (9%) reported it in the idursulfase weekly group, 3 patients (9%) reported it in the idursulfase-every-other-week group, but only 1 patient (3%) reported it in the placebo group.

Table 51 Incidence of Psychiatric Adverse Events in Study TKT024

Psychiatric Adverse Event	0.50 mg/kg EOW N=32	0.50 mg/kg QW N=32	Placebo N=32
Abnormal behaviour NOS	0	2	3
Anxiety, irritability, agitation, or nervousness	4	4	1
Attention deficit/hyperactivity disorder	1	0	1
Depression, Adjustment Disorder with Depressed Moods	3	3	1
Phobia	1	0	0
Stress symptoms	1	0	0
Total	10	9	6

7.1.6.3 Cardiac Adverse Events

Finally, during the controlled study TKT024, heart failure/worsening heart failure occurred in two patients in the idursulfase-weekly group, and one patient in the idursulfase every-other-week group. None was reported in the placebo group. One patient in the EOW idursulfase treated group experienced orthostatic hypotension, and syncope. The episode of orthostatic hypotension was considered a serious adverse event, but syncope was not. The same patient, on another occasion, experienced "cardiac arrhythmia requiring medication" which was described as "ventricular extra-systole (VES)" with symptomatic tachycardia, and the patient was admitted to a hospital Germany for medical treatment, (which was considered a serious adverse event). No patient in the placebo group experienced hypotension or syncope. One patient in the idursulfase weekly group experienced angina in the setting of supraventricular tachycardia that required IV cardioversion with adenosine, but the episode was probably related to the patient's underlying conduction abnormality worsening in the setting of acute

pulmonary emboli. Another patient, randomized to the idursulfase weekly treatment, while on beta-blockers, experienced asymptomatic bradycardia of 27 BPM. Data from the AE.xpt dataset showed that no patient in the placebo group experienced cardiac arrhythmia that required intervention. There were two patients in the EOW idursulfase group, three patients in the weekly idursulfase group, and one patient in the placebo group who experienced cardiac ventricular disorder NOS, which term was recoded by the reviewer to included dyskinetic ventricular septum, left ventricular hypertrophy, and right ventricular hypertrophy. Cardiac hypertrophy can be part of Hunter syndrome, so drug-relatedness is difficult to establish.

Table 52 Incidence of Important Cardiac Adverse Events in Study TKT024

Adverse Events	0.50 mg/kg EOW N=32	0.50 mg/kg QW N=32	Placebo N=32
Angina pectoris	0	1	0
Cardiac ventricular disorder NOS	2	3	1
Heart failure	1	2	0
Total	3	6	1

7.1.7 Laboratory Findings

7.1.7.1 Overview of Laboratory Testing in the Development Program

For each of the four clinical studies, clinical laboratory evaluations (which include serum chemistry, hematology, and urinalysis) were performed at baseline and at various time points throughout (see Section 6.1.3). Investigators were to review all results and designate abnormal values as clinically significant or not. All clinically significant laboratory results were to be reported as adverse events. For the pivotal study TKT024, results of unscheduled lab tests were also included in the principal analyses.

7.1.7.2 Selection of Studies/Analyses for Drug-Control Comparisons of Laboratory Values

All four clinical studies were briefly reviewed for evaluation of the effects of idursulfase in the laboratory values. Since controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test, the focus of this review is on study TKT024. Given timeframe available for the review, these data were reviewed only at a level of detail needed to identify potentially significant general patterns.

7.1.7.3 Standard Analyses and Explorations of Laboratory Data

The reviewer included three standard approaches to the analysis of laboratory data: analyses focused on measure of central tendency (i.e. mean or median of changes), analyses focused on outliers or shifts from normal to abnormal, and analyses focused on marked outliers and dropouts for laboratory abnormalities.

7.1.7.3.1 Analyses Focused on Measures of Central Tendency

For the pivotal study, TKT024, mean creatine kinase (all units in U/L; normal reference value: 18-198) increased with time over the course of the year of study in the two active treatment groups. At baseline for the idursulfase weekly group, the CK mean value was 52, which increased to 80, 91, 90, and 97, respectively at Weeks 9, 18, 36, and 53. The mean, however, never increased to a range out of normal, although it was recorded that the maximum CK value reached 646 during Week 18. Similarly in the idursulfase EOW group, the CK mean increased with time: 57, 64, 69, 70, and 70 (at baseline, Weeks 9, 18, 36, and 53, respectively). This increasing trend of increasing CK with time was not observed in the placebo group, in whom the CK mean actually decreased: 54, 48, 48, 51, and 51 (at baseline, Weeks 9, 18, 36, and 53, respectively). In the extension phase of the study, TKT024EXT, in which all patients received weekly idursulfase treatment, of data available up to 7-19-2005, the mean CK did not rise beyond 145, although it was noted that the maximum CK value did reach 1901. The reason or implication for this level has not been provided by the Applicant since the study is still ongoing. Data from study TKT024 and available data from TKT024EXT suggested, however, that within the first year of treatment, there was an idursulfase dose- and time-dependent effect on the CK value (the higher the dose and the longer the duration of therapy, the higher the CK mean), and that with longer term use, CK may reach a higher level exceeding upper normal limit. The clinical significance of elevated CK is unclear.

Mean values at baseline and across the 52 weeks of treatment for serum hematology and urine analysis parameters for all treatment groups were unremarkable.

7.1.7.3.2 Analyses Focused on Outliers or Shifts from Normal to Abnormal

Shift tables for laboratory studies were reviewed. There were minor shifts in various lab values, but the number of patients involved was too small to make meaning conclusions from the analysis. There were no apparent trend of interest.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Laboratory abnormalities that were considered by the investigator to be clinically significant were coded as adverse events. This collection represents a very small subset of all out-of-range laboratory results. There were no dropouts due to laboratory abnormalities. The following table lists these adverse events that occurred in at least one patient in either idursulfase weekly group or idursulfase EOW group during study TKT024.

Table 53 Adverse Events of Laboratory Abnormalities in TKT024

Laboratory Abnormality	Incidence in idursulfase weekly group (N=32)	Incidence in idursulfase biweekly group (N=32)	Incidence in placebo group (N=32)
†Alkaline phosphatase	1	3	1
†Creatine Kinase	0	1	0
Hypokalemia	2	0	1
†LDH	1	3	0
Lymphocytosis secondary to infection	1	0	0

↓Hemoglobin, or anemia	2	0	4 ^a
Hematuria	2	0	0
Leukopenia	0	1	1 ^a
Thrombocytopenia	1	0	2 ^a
↓Ferritin	1	0	0
↑Phosphorus	0	1	0
↑Total bilirubin	1	0	0
↑Triglyceride	0	2	0
↑Uric acid	1	0	1

^aPatient 024-045-0001 had pancytopenia, hence he is counted three times in this table: under anemia, thrombocytopenia, and leucopenia.

None of these events was considered a serious adverse event by the investigator. Only one laboratory abnormality in the idursulfase groups was coded as severe (grade 3), and the rest were moderate or mild (grade 2 or 1, respectively). The only grade 3 laboratory adverse event was in the increased total bilirubin level in patient 024-020-0007, who was randomized to the idursulfase weekly group. His total bilirubin was abnormally high at 2.2 mg/dl at baseline, peaked at 3.9 by Week 9, then decreased to 1.3 by the end of the study (normal reference 0.2 to 1.2). No explanation was given for this patient's bilirubin pattern.

7.1.7.4 Special Assessments: Hepatotoxicity

Given that idursulfase showed an effect on decreasing mean liver volume, the potential for hepatotoxicity was examined.

The reviewer noted that three patients had total bilirubin levels that were abnormally elevated at baseline (but not higher than 1.5 times the upper limit of normal [1.5 x ULN]) that reached a level higher than 1.5 x ULN during the study period of study TKT024.

Patient ID	Treatment group	Time Course (Total Bilirubin mg/dL) ^{a,b}
024-012-0005	EOW	Baseline: (1.7)→ week 9: (0.9)→ week 18: (0.2)→ week 36 (2.5)→ week 53: (2.7)^c
024-013-0014	EOW	Baseline: (2.3)→ week 18: (3.3)→ week 20: (3.5)^c → week 36: (1.9)→ Week 53: (2.2)
024-020-0007	Weekly	Baseline: (2.2)→ week 9: (3.9)^c → week 18: (1.6)→ week 36: (2.1)→ week 53: (1.3)

^aNon-standard unit is listed in this table because this is the more familiar unit to clinicians practicing in the US.
^bNormal range: 0.2-1.2 mg/dL. (1.5 x UNL is 1.8 md/dL)
^cBolded entries: peak total bilirubin value for the patient

No patient in the placebo group had total bilirubin value higher than 1.5 x ULN any point (including at baseline) during the study. The study was too small and too short to make conclusions about the likelihood or clinical implication of elevated total bilirubin levels.

In analyzing transaminases, no patient in the idursulfase treated groups experienced an AST elevation that was as high as 3 x ULN. In the ALT analysis, the only idursulfase-treated patient who experienced elevation of ALT that was greater than 3 x ULN occurred in patient 024-013-0007, who was randomized to the EOW idursulfase group. His baseline ALT was 107 (U/L), which peaked to 177 at week 20, and decreased to 55 by week 53 (normal range: 6-34 U/L; 3 x UNL is 102 U/L).

In analysis of alkaline phosphatase (AP), two patients in the weekly idursulfase group, and one patient in the every-other-week group had elevation that was 1.5 x ULN that was not seen at baseline. Patient 024-020-0007 was randomized to idursulfase weekly treatment; his AP was 182 at baseline, which peaked to 228 at Week 18 (upper normal limit was 129; 1.5 times UNL was 194), but returned to within normal limit by Week 53. Patient 024-046-0005 was also randomized to weekly idursulfase treatment; his baseline AP was 345 (upper normal limit was 250; 1.5 times UNL was 375), and peaked at Week 53 to 396 (upper normal limit was 129; 1.5 times upper normal limit was 194). Patient 024-020-0017 was randomized to the every-other-weekly idursulfase group; his baseline AP was within normal limit, but by Week 53, it increased to 388 U/L (upper normal limit was 250; 1.5 times UNL was 375). The clinical significance of these elevated AP levels is unknown.

Reviewer's comment:

In summary, however, it does not appear that idursulfase exhibits any serious liver toxicity. But there was at least one patient, 024-020-0007, who experienced cholestasis during idursulfase treatment (indicated by his elevated bilirubin and AP levels).

7.1.8 Vital Signs

Vital signs were recorded in several ways in the pivotal study. First, vital signs taken as part of physical exams in TKT024 were collected at scheduled physical exams as outlined in Figure 8, in Section 6.1.3. Analysis of this data showed there were no significant changes in the means of vital signs during the study period that differed across treatment groups.

Second, vital signs collected that were considered clinically significant changes by the investigator were reported as adverse events (AEs). In this analysis of abnormal vital signs as adverse events there were no significant differences across study groups.

Third, vital signs were collected at specific time points during drug infusion. At the request of the review team, episodes of hypotension and hypoxia were counted toward symptoms of possible anaphylactic/ anaphylactoid events (see Section 7.1.3.2 Anaphylactic/Anaphylactoid Reactions).

7.1.9 Electrocardiograms (ECGs)

ECGs were not necessarily read by cardiologists. No notable, relevant, or remarkable findings for changes in ECGs were seen, other than those mentioned in Section 7.1.6.3 Cardiac Adverse Events. No events of torsades de pointes or clinically significant QT prolongation were reported by the Applicant. The Applicant also verified that no other types of worrisome/life-threatening arrhythmia occurred in patients who received idursulfase treatment.

7.1.10 Immunogenicity

Immunogenicity data have been reviewed by FDA reviewer, Jin Hai Wang, MD. The reader is referred to Dr Wang's review for detail.

- Thirty-two out of 63 patients (32/63, 51%) in the ELAPRASE-treated groups in the pivotal and its extension clinical study (TKT024, TKT024EXT) developed anti-idursulfase IgG antibodies as assessed by either classic ELISA or Conformation Specific Assay (CSA), and confirmed by radioimmunoprecipitation assay (RIP). Sera from 4 out of 32 RIP-confirmed anti-idursulfase antibody positive patients were found to neutralize idursulfase enzymatic activity in vitro.
- The incidence of antibodies that inhibit cellular uptake of idursulfase into cells is currently unknown.
- Patients who developed IgG antibodies at any time had an increased incidence of infusion reactions and hypersensitivity reactions. Also, the reduction of urinary GAG excretion was less in patients in whom circulating anti-idursulfase antibodies were detected. Liver size reduction appeared not to be affected by anti-idursulfase antibody status.
- The relationship between anti-idursulfase antibodies and clinical efficacy (6MWT) is unclear.
- Enzymatic-activity neutralizing antibody was detected in patients in TKT024 and TKT024EXT. An assay to measure antibody mediated blockade of enzyme uptake into cells has not been developed. When this is developed patient samples positive in the screening assay will need to be tested.
- The incidence of IgE antibodies to idursulfase is currently unknown. The assay has not been validated.
- A number of post-marketing commitments were recommended to address these aforementioned issues.
- The data reflect the percentage of patients whose test results were positive for antibodies to idursulfase in specific assays, and are highly dependent on the sensitivity and specificity of these assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to idursulfase with the incidence of antibodies to other products may be misleading (e.g. enzyme replacement therapies for other MPSs).

7.1.11 Human Carcinogenicity

Pre-clinical genotoxicity and carcinogenicity studies were not submitted since idursulfase is a recombinant endogenous human protein, which is not expected to interact with cellular DNA. Idursulfase is taken up into the cell by endocytosis and remains in the lysosomal system until degradation. Genotoxicity and carcinogenicity studies are usually not required for biological therapeutics. No cases of malignancy have been diagnosed in patients during the idursulfase clinical development program to date.

7.1.12 Special Safety Studies

None performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None known.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies with idursulfase have been conducted in pregnant women. Hunter syndrome is exceedingly rare in females.

7.1.15 Assessment of Effect on Growth

Due to the difficulties with obtaining accurate height measurements in Hunter syndrome patients in this clinical development program, claims regarding growth cannot be made (Pediatric review, H. Sachs, MD).

7.1.16 Overdose Experience

All patients in the study program were treated with idursulfase at the proposed protocol doses. There have been no reports of overdose with idursulfase.

7.1.17 Postmarketing Experience

Since idursulfase is not licensed, approved, or marketed in any country there is no postmarketing experience.

7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The Applicant, Human Genetic Therapies, provided primary source data with data collected from applicant sponsored clinical trials.

The entire idursulfase clinical program was conducted in Hunter syndrome patients, and given the rarity of this disease, the entire idursulfase-exposed population, for whom data were submitted to this application, was adequate. This application includes clinical safety information from four Shire-sponsored clinical studies, two of which were placebo-controlled. Additional data consisted of MedWatch reports submitted by the Applicant to the Agency for serious, expedited Adverse Events (AEs), and an analysis on hypersensitivity and infusion reactions that were submitted to the application at the request of the Division. The total patient exposure to idursulfase is 108 male patients.

In the opinion of this reviewer, the overall clinical experience, animal testing, routine clinical testing, and safety experience of idursulfase was felt to have been adequately described in the data contained in this application.

7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS

The safety results from the idursulfase clinical development program are notable for the following safety signals and concerns that are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity reactions, i.e., anaphylactic/anaphylactoid reactions, related to idursulfase infusion was noted late in the initial review cycle. Some of these hypersensitivity reactions were life-threatening, which included: hypoxia, cyanosis, respiratory distress, hypotension, seizure, and loss of consciousness. In clinical trials with idursulfase, 16/108 patients (15%) experienced infusion reactions during 26 of 8274 infusions (0.3%) that involved adverse events that were anaphylactic/anaphylactoid-like. One of these episodes occurred in a patient with tracheostomy and severe airway disease, who received an idursulfase infusion while he had a pre-existing febrile illness, and then experienced respiratory distress, hypoxia, cyanosis, and seizure with loss of consciousness. It is recommended that a black-boxed warning appear in the product labeling to alert physicians and patients of this noteworthy safety signal.

Because of the potential for severe infusion reactions, appropriate medical support should be readily available when idursulfase is administered. When severe infusion reactions occurred during clinical studies, subsequent infusions were managed by use of antihistamines and/or corticosteroids prior to or during infusions, a slower rate of idursulfase administration, and/or early discontinuation of the idursulfase infusion if serious symptoms developed. With these measures, no patient discontinued treatment permanently due to a hypersensitivity reaction. It is recommended also that physicians consider delaying the idursulfase infusion in patients with concomitant acute respiratory and/or febrile illness. If a severe infusion reaction occurs, immediately suspend the infusion of idursulfase and initiate appropriate treatment, depending on the severity of the symptoms. Consider resuming the infusion at a slower rate, or, if the reaction is serious enough to warrant it, discontinue the idursulfase infusion for that visit.

2. Patients with compromised respiratory function, including those with reactive airway disease, may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions (hence they are at a higher risk for life-threatening complications).
3. Other serious adverse events that occurred in the idursulfase-weekly treated patients but not in the placebo patients included one case of each of: cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia.
4. Adverse events were commonly reported in association with infusions. The most common infusion-related reactions were headache, fever, cutaneous reactions, and hypertension. The frequency of infusion-related reactions decreased over time with continued idursulfase treatment.

5. The most common (>30%) adverse reactions were pyrexia, headache, and arthralgia.
6. A table for common adverse reactions occurring in at least 10% of weekly idursulfase-treated patients (and occurring more frequently than in the placebo group) in the 53 week controlled trial is to be provided in the label.

Safety results are otherwise summarized as follows:

7. Deaths reported in clinical studies were all related to respiratory failure. A causal relationship cannot be determined but appear unlikely, given the high background rate of pulmonary failure deaths in Hunter syndrome patients.
8. However, a signal in serious adverse events relating to respiratory issues was detected in the clinical development program.
9. Notable adverse events that occurred in the EOW-idursulfase treated patients but not in the placebo patients in the controlled 53 week study included one case of each: syncope, orthostatic hypotension, heart failure, arrhythmia (ventricular extra-systole) requiring medication, choking, and anesthesia intubation complication (airway trauma due to intubation).
10. Other safety signals noted include: anxiety and depression, thromboembolic events, visual disturbance, musculoskeletal dysfunction, cholestasis, potential for elevation in creatine kinase, pain, and malaise. Of these, pain and malaise will significantly impact a patient's quality of life, and should be considered in the long term assessment of the risk/benefit profile of idursulfase treatment.

7.4 GENERAL METHODOLOGY

Please refer to Section 7.1 for a discussion of the methodology used in the review of safety.

8 ADDITIONAL CLINICAL ISSUES

8.1 DOSING REGIMEN AND ADMINISTRATION

Based on the procedures described in the study protocols and the actual experience of the clinical studies, the following recommendation is made to the label:

The recommended dosage regimen of idursulfase is 0.5 mg/kg of body weight administered every week as an intravenous infusion. Idursulfase is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. Each vial of idursulfase contains a 2.0 mg/mL solution of idursulfase protein (6.0 mg) in an extractable volume of 3.0 mL, and is for single use only. Use of an infusion set equipped with a 0.2 micrometer (μm) filter is recommended. The total volume of infusion may be administered over a period of 1 to 3 hours. Patients may require longer infusion times due to infusion reactions; however, infusion times should not exceed 8 hours (based on product stability). The initial infusion rate should be 8 mL/hr for the first 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr at 15 minute interval increments in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgment, if infusion reactions were to occur. Idursulfase should not be infused with other products in the infusion tubing.

8.2 DRUG-DRUG INTERACTIONS

There were no specific studies conducted on drug-drug interactions with idursulfase.

8.3 SPECIAL POPULATIONS

Hunter syndrome is a rare, X-linked inborn error of metabolism. The entire idursulfase clinical development program has been conducted in male, Hunter syndrome patients only.

8.4 PEDIATRICS

FDA pediatric consultant, Hari Cheryl Sachs, MD, concludes that since heights could not be measured accurately, no conclusions can be drawn from the growth data. Furthermore, given the difficulties in obtaining accurate height measurements, the %-predicted FVC is unlikely to be clinically meaningful in these patients. The improvement in %-predicted FVC and absolute FVC appears to be driven by the population that is likely to be the fastest growing, i.e., the patients aged 12-18 years who are entering the pubertal growth spurt.

The Pediatric Use section should indicate that safety and effectiveness have not been established in children less than 5 years of age. Postmarketing commitment should include study of patients less than 5 years of age, at a time before changes due to GAG accumulations become potentially irreversible. The ability of idursulfase to prevent the need for PE tubes, respiratory infections, adenoidectomy and the development of hearing loss should be explored. Growth (height, weight, and head circumference)

should be measured in a standardized manner. Height measurements should be correlated with degree of deformity and joint contracture. Weight measurements should be correlated with modes of feeding (e.g. G-tube vs. oral).

8.5 ADVISORY COMMITTEE MEETING

There was no advisory committee meeting held for this BLA application.

8.6 LITERATURE REVIEW

References have been included as endnotes throughout the review.

8.7 POSTMARKETING RISK MANAGEMENT PLAN

None warranted at the present time. The Applicant has committed to conducting a registry (Hunter Outcome Survey) to monitor long term safety.

**APPEARS THIS WAY
ON ORIGINAL**

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS

The efficacy results from the idursulfase clinical program provided evidence of a benefit of treatment with idursulfase in the Hunter syndrome patient population. Evidence of a treatment benefit was demonstrated in Study TKT024, where treatment of Hunter syndrome patients with weekly intravenous administration with idursulfase resulted in a 35 meter greater mean increase in the distance walked in the 6 Minute Walk Test compared to placebo patients. The changes in %-predicted FVC were not statistically significant.

Identification of drug-related toxicity is challenging because Hunter syndrome patients have significant underlying morbidity so that serious adverse events would not be unexpected in the course of a 53-week study, and the systemic collection of adverse events in a placebo comparison group was limited to essentially 96 patients for 53 weeks.

With these limitations in mind, the results from the idursulfase clinical development program are notable for the following safety signals, and they are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity infusion reactions was noted. Some of these hypersensitivity reactions have been life-threatening, and were anaphylactic or anaphylactoid in nature. Reactions included symptoms such as cyanosis, hypoxia, respiratory distress, hypotension, seizure, and loss of consciousness. In clinical trials with idursulfase, 16/108 patients (15%) experienced infusion reactions. Out of 8274 infusions, 26 involved adverse events in at least two of the following three body systems: cutaneous, respiratory, or cardiovascular. One of these episodes occurred in a patient with a tracheostomy and severe airway disease, who received an idursulfase infusion while he had a pre-existing febrile illness, and then experienced respiratory distress, hypoxia, cyanosis, and seizure with loss of consciousness.
2. In clinical studies, the most frequent serious adverse events related to the use of idursulfase were hypoxic episodes.
3. Other notable serious adverse events that occurred in the idursulfase-weekly treated patients but not in the placebo patients included one case of each of: cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia.
4. Adverse events were commonly reported in association with infusions. The most common infusion-related reactions were headache, fever, cutaneous reactions (rash, pruritus, erythema, and urticaria), and hypertension. The frequency of infusion-related reactions decreased over time with continued idursulfase treatment.
5. The most common (>30%) adverse reactions were pyrexia, headache, and arthralgia.

6. Common adverse reactions occurring in at least 10% of patients treated with idursulfase weekly in the 53-week controlled trial and occurring more frequently than in the placebo group is to be tabulated in the product label (Table 3 in ELAPRASE™ label).

Safety results are otherwise summarized as follows (not included in the label):

7. Deaths reported in clinical studies were all related to respiratory failure. A causal relationship cannot be determined but appears unlikely, given the high background rate of pulmonary failure deaths in Hunter syndrome patients.
8. However, a signal in serious adverse events relating to respiratory distress/failure was detected.
9. Notable adverse events that occurred in the EOW-idursulfase treated patients but not in the placebo patients in the controlled 53 week study included one case of each: syncope, orthostatic hypotension, heart failure, choking, arrhythmia requiring medication (ventricular extra-systole), and anesthesia intubation complication (airway trauma due to intubation).
10. Other safety signals noted include: anxiety and depression, thromboembolic events, visual disturbance, musculoskeletal dysfunction, cholestasis, potential for elevation in creatine kinase, pain, and malaise. Of these, pain and malaise are the most concerning because they will significantly impact on reducing patient's quality of life, and should be considered in the long term assessment of the risk/benefit profile the therapy.

Although in theory enzyme replacement should work dramatically, the treatment benefit shown in the clinical study was modest in the reviewer's opinion: an improvement of 35 meters in walking distance in a 6-MWT after weekly treatment for a year. The total distance walked at Week 53 between treatment groups was not statistically different. And, the difference in the mean percentage changes from baseline to Week 53 between the idursulfase weekly and placebo groups was not statistically significant. Moreover, a wide range of testing failed to show impact on other relevant endpoints (e.g., passive and functional joint range of motion testing, echocardiogram parameters, health related quality-of-life surveys, growth velocity in pre-pubertal patients, other pulmonary function test components, and radiographic skeletal surveys). Reductions in urinary GAG levels and liver size were demonstrated, but these pharmacodynamic markers do not prove clinical efficacy.

The efficacy of idursulfase in the most severe patients, i.e., those patients who have neuro-cognitive deficits, has not been established. Its effects in female patients are unknown. Idursulfase has not been used in children younger than five years of age, including neonatal patients.

Short term experience of clinical trials, however, may not reflect the full potential of this enzyme replacement therapy. With longer treatment, patients might experience greater benefits, and if treatment were to begin early in life, before irreversible damages have occurred, idursulfase may exert even greater benefits—but these potential effects were not assessed by this clinical development program and remain speculative.

The reviewer is concerned about the increased incidence of pain and malaise in idursulfase treated patients. Pain and malaise will impact negatively on quality of life. In addition, weekly steroid use to prevent anaphylactic reactions might bring about the attended risks associated with long-term steroid use. Finally, a commitment to life-long therapy of weekly, multi-hour infusions (which may be accompanied by severe infusion reactions,) starting from birth to death, should not be underestimated as an easy or entirely benign task for any patient or his family.

In conclusion: the risk/benefit analysis of idursulfase treatment must be individualized to each patient's medical needs.

9.2 RECOMMENDATION ON REGULATORY ACTION

The application provided adequate evidence of efficacy and an acceptable safety profile. Without availability of this treatment, there is no other targeted treatment for Hunter syndrome. Not approving this therapy would deprive patients and families of a choice in treatment options. Given the gravity, the urgency, lack of treatment for Hunter syndrome, and the real, if modest, clinical benefit demonstrated, even in the presence of serious adverse events, this application is approvable.

9.3 RECOMMENDATION ON POSTMARKETING ACTIONS

9.3.1 Risk Management Activity

None warranted at the present time.

9.3.2 Required Phase 4 Commitments

The Applicant commits to the following clinical recommended Postmarketing Commitments (PMCs). There are preclinical and product recommended commitments as well (see respective reviews).

- Implementation of a Hunter Outcome Survey, a voluntary patient survey to monitor long-term effects of ELAPRASE™ treatment for up to 15 years; survey data will be analyzed yearly and submitted to FDA in annual reports.
- Evaluation of pharmacokinetics, pharmacodynamics, and safety in at least 18 ELAPRASE™ treated pediatric patients 5 years of age and under.
- Submission of the final study report from study TKT018, an open-label maintenance study.
- Completion and submission of the final study report from study TKT024EXT, an open-label extension of study TKT024 evaluating long-term safety and clinical outcomes.
- Evaluation of patient samples from study TKT024 and TKT024EXT in an inhibition-of-entry neutralization assay.
- Monitoring of binding data and neutralizing antibody formation to assess the potential for loss of immunologic tolerance over time.
- Conducting a Segment III prenatal and postnatal study in rats.
- Evaluation of a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells.
- Evaluation of the Conformation Specific Assay in terms of its ability to detect anti-idursulfase antibodies.
- Validation of an IgE assay for the detection of anti-idursulfase antibodies.
- Evaluation of genetic mutations of iduronate-2-sulfatase in patients enrolled in studies TKT024 and TKT024EXT, and correlation of this information with the level of endogenous enzyme levels, antibody response and clinical outcome.

9.3.3 Other Phase 4 Requests

The Applicant has been asked by the Division of Drug Risk Evaluation (DDRE) to submit reports of anaphylactic events with serious outcomes as 15-Day reports, to Adverse Event Reporting System (AERS) for 12 months after approval.

9.4 LABELING REVIEW

Extension labeling negotiations were held between the Division and the Applicant. With concurrence by the Applicant, a Box Warning was placed to prominently alert physicians and patients the potential for anaphylactic/anaphylactoid reactions with idursulfase treatment. Please see the approved ELAPRASE™ label.

9.5 COMMENTS TO APPLICANT

None.

10 APPENDICES

10.1 APPENDIX 1

Narratives of Cases Identified as Possible Anaphylactoid Reactions **(Source: BLA Amendment 15)**

Study TKT008/TKT018

- A 9-year-old patient (008/018-013-0002) with a baseline FVC of 68% predicted received idursulfase 0.15 mg/kg every other week. Facial flushing and hypotension were reported as non-serious adverse events during his 27th 1-hour infusion; no treatment was given. However, his BP records did not support the determination of hypotension since his blood pressure only fell from 105/29 to 91/38 mmHg.
- A 20-year old patient (008/018-013-0005) had severe obstructive disease and sleep apnea with a baseline FVC of 15% predicted, which required a tracheostomy and initially only supplemental oxygen at night. Later he received oxygen during the day as needed and mechanical ventilation at night. He experienced three serious episodes of respiratory distress with hypoxia over a period of 11 months of idursulfase treatment at 0.5 mg/kg every other week. During his 5th infusion, his oxygen saturation fell from 88 to 47%. The infusion was discontinued and blow-by oxygen was administered, followed by humidified oxygen via his tracheostomy. His oxygen saturation rapidly increased to 96%. It was initially thought that this was due to a mucus plug in the patient's upper airway. During his 6th infusion, while on 35% supplemental oxygen, his oxygen saturation fell to 75%. The infusion was discontinued and the supplemental oxygen was increased to 100%, which rapidly induced an increase in his oxygen saturation above 90%. Subsequent study drug infusions were managed with a longer infusion time (3 hours) and premedication with IV diphenhydramine and levosalbutamol nebulization. During his 10th infusion, the patient experienced a non-serious reaction of facial flushing with a decrease in oxygen saturation from 95% to 87% which was recorded 30 minutes after the end of the infusion. The rate of infusion was not modified and no treatment was applied. He again experienced infusion reactions during his 15th and 18th infusion with rigors and dyspnea or cyanosis, which were managed by transitory interruption of the infusion. When he was due to receive his 24th infusion, he was found to have labored breathing with wheezing and a fever at 38.2°C. His oxygen saturation was 92% on room air and 28% oxygen was initiated via his tracheostomy to maintain his saturations above 95%. He was administered a nebulization of levosalbutamol before the infusion. During the infusion, he experienced rigors, cold hands and cyanosis with some respiratory distress. His oxygen saturation decreased to 88%. The infusion was discontinued and further respiratory assistance was required. The patient subsequently experienced a short seizure. Apart from oxygen therapy, he was administered IV diphenhydramine, then epinephrine, salbutamol nebulization, and IV methylprednisolone. The episode resolved the same day. The patient subsequently received 74 infusions over the last 3

years while being pre-medicated with low-dose corticosteroids (oral prednisone and IV methylprednisolone), IV diphenhydramine and levosalbutamol nebulization. No further adverse reactions were reported apart from isolated hypotension (from 75/40 to 65/29 mmHg) occurring on one occasion (without other symptoms of a potential anaphylactic/anaphylactoid reaction).

- A 20-year-old patient (008/018-013-0006) had a baseline FVC of 34% predicted with severe obstructive pulmonary disease requiring a tracheostomy; he also suffered from idiopathic urticaria, for which he received antihistamines as needed. He received idursulfase treatment at 0.5 mg/kg every other week. During his 7th infusion, which was administered over 1 hour, the patient experienced non-serious, transient facial flushing and dyspnea; no action was taken. During his 9th infusion, despite routine medication with oral diphenhydramine and fexofenadine for his urticaria, the patient experienced nasal congestion followed by facial flushing, redness and swelling, and a sore throat. Urticaria was also observed on the patient's upper back and shoulders. The infusion was stopped after 14 minutes and IV diphenhydramine was administered. An episode of hypotension was recorded 46 minutes later, the blood pressure falling from 98/44 mmHg before the infusion to 75/62 and 75/46 mmHg; this episode lasted for approximately 10 minutes. The patient developed rigors and cyanosis in his arms, which prompted the administration of oxygen (35%). The rigors resolved after 1 hour and oxygen was discontinued 10 minutes later with oxygen saturation recorded as 93 to 94% on room air. The patient also had a fever (up to 39°C) for a few hours but was discharged from the hospital the same day. This reaction was rated as serious by the investigator. Subsequent infusions were managed by lengthening the infusion time to 3 hours. Although the investigator decided not to premedicate, the patient was already being routinely treated with daily fexofenadine and diphenhydramine as needed for his idiopathic urticaria. The 14th infusion was transiently interrupted because the patient experienced rigors and fever, and his nail beds were becoming dusky. Rigors were reported during his 18th infusion. On the day of his 78th infusion, he had urticaria on his hands and his oxygen saturation was recorded as 81% 1 hour after the end of the infusion (98% before the infusion). A drop in his systolic blood pressure from 95/48 to 78/34 mmHg was also noted 1 hour after the start of the infusion; no treatment was given apart from oral fexofenadine for the urticaria. Subsequently no further adverse reactions occurred until his 85th infusion, which was interrupted due to non-serious urticaria. The investigator decided to routinely premedicate after that and no reactions were observed for the subsequent 21 infusions. On the day of his 108th infusion, rash and excessive bronchial secretion were noted; these events lasted for 14 and 19 days, respectively. This rash was considered a persistent event as it lasted for 14 days. Further, increased respiratory secretion had occurred previously for approximately 6 weeks (from May 2005 to June 2005); based on this patient's history, this is considered a recurrent episode. Therefore, based on medical judgment, the occurrence of these 2 events on the infusion day does not likely constitute an anaphylactoid reaction.
- A 13-year-old patient (008/018-013-0007) had severe oropharyngeal and respiratory involvement with obstructive sleep apnea and a baseline FVC of 46% predicted. He received idursulfase treatment at 0.5 mg/kg every other week. During his 4th infusion, he experienced a serious episode of respiratory distress. Five minutes into the infusion the patient was noted to have facial flushing and he complained of dyspnea. The infusion was stopped immediately. His oxygen saturation was 91% on room air and his blood pressure was 86/56 mmHg with a pulse of

93 bpm. He was administered 50% oxygen via a facial mask and IV diphenhydramine. The episode resolved quickly and supplemental oxygen was discontinued 75 minutes after the start of the episode, while the oxygen saturation was 99%. Before the 5th and 6th infusion he was only premedicated with levosalbutamol nebulization; he again experienced facial flushing and dyspnea with a decrease in oxygen saturation (91%). In both instances, the infusion was transiently interrupted and oxygen was administered; overall, the infusion was administered over a period of 4.5 hours. The patient was subsequently pre-medicated with low-dose corticosteroids (oral and IV methylprednisolone), IV diphenhydramine and levosalbutamol nebulization. The only infusion-related reactions reported afterwards were rigors and fever after the 7th, 9th, and 12th infusion; during this last one, he also experienced dyspnea, which was managed by temporary infusion discontinuation and oxygen. Although the nature of the respiratory events was similar only the first one was considered to be serious. The patient subsequently received 75 infusions over the last 3 years without any reaction.

- An 8-year-old patient (008/018-013-0010) with a baseline FVC of 78% and with aortic valvular disease received idursulfase 1.5 mg/kg every other week. He experienced his first infusion-related reaction during his 4th infusion, which was stopped after 6 minutes but no treatment was administered; its manifestations were urticaria with ear and nose discomfort, cough, and headache. During his 6th infusion, he again developed urticaria with flushing of the ears; the infusion was interrupted after 108 minutes and re-started at a slower rate. During his 7th infusion, he again developed urticaria with rigors; the infusion was interrupted after 2 hours for 36 minutes. Fourteen minutes after re-starting the infusion, a drop in systolic blood pressure was recorded from 113/43 mmHg before the infusion to 77/61 mmHg; the subsequent reading 15 minutes later was 109/56 mmHg. No treatment was administered and the full dose was infused over 3.5 hours. The patient continued to experience reactions to all his subsequent infusions until his 17th infusion; symptoms reported were usually urticaria with fever and rigors, sometimes nasal congestion and/or throat irritation, and at one occasion dyspnea with agitation, headache, or nausea. No treatment was ever administered. The duration of the infusions was increased up to 4 hours as needed. No infusion reaction was reported after the first 8 months of treatment except for two possible febrile episodes.

Study TKT024

- A 20-year-old patient (024-012-0004) with a baseline FVC of 27% predicted and significant cardiac involvement (cardiomyopathy, valvulopathy and Class II congestive heart failure) received idursulfase 0.5 mg/kg weekly. Fifteen minutes after the start of his 9th infusion (event occurred at Week 10, however this patient missed 1 infusion) without any premedication, he experienced flushing and showed urticaria with a swollen tongue and conjunctivitis; his oxygen saturation fell from 98 to 86% within 20 minutes. The infusion was stopped and he was administered IV prednisolone and dimetindene. Serum complement and tryptase levels at 30 minutes were within the normal range. Under premedication with IV prednisolone and oral dimetindene he only experienced mild urticaria during the two subsequent infusions.
- A 6-year-old patient (024-020-0001) with a baseline FVC of 47%, a history of asthmatic episodes and aortic valvular disease received idursulfase 0.5 mg/kg every other week. Thirty

minutes after the beginning of his 19th infusion of active drug he developed wheezing, and 2 hours later, his blood pressure was measured at 79/55 mmHg as compared to a pre-infusion value of 108/68 mmHg; the next reading 35 minutes later was 120/67 mmHg. The patient had an underlying upper airway infection, which had started 3 days before the day of the infusion, and he was administered oxygen and salbutamol nebulization. The respiratory event was considered non-serious and the single low value of blood pressure was not reported as hypotensive event by the investigator. Apart from a previous episode of abdominal pain this was the only infusion reaction observed.

- A 5-year-old patient (024-020-0008) with a baseline FVC of 36% predicted and obstructive sleep apnea received idursulfase 0.5 mg/kg every other week; he also had known allergies (eggs). Due to the occurrence of a rash with his 10th infusion (placebo) he was subsequently premedicated with oral prednisone and loratadine on the day before the infusion and IV diphenhydramine and methylprednisolone on the day of the infusion. In spite of this prophylaxis, he again had a rash with his next infusion (6th infusion of active) and the duration of the infusion was extended to 5 hours. Approximately 1.5 hours after the start of his 7th active infusion, he experienced a non-serious rash associated with wheezing, which were treated with fenoterol nebulization and IV diphenhydramine, and the infusion was completed. The duration of the infusion was later reduced again to about 3 hours and under premedication he had only occasional rashes.
- A 20-year-old patient (024-020-0012) with a baseline FVC of 40%, obstructive sleep apnea, and a history of asthmatic episodes predicted received idursulfase 0.5 mg/kg weekly. He experienced a series of non-serious, infusion-related reactions as of his 4th infusion (nausea and rash). A slower infusion rate (up to 5 hours) and premedication with oral prednisolone as well as IV methylprednisolone and diphenhydramine were initiated. During his 5th infusion, he experienced rash and dyspnea; the infusion was stopped and he received fenoterol nebulization and IV diphenhydramine. During his 9th infusion, he experienced after 2 hours nausea, cough, dyspnea, wheezing and rash; he received fenoterol nebulization and IV diphenhydramine and metoclopramide. During his 13th infusion, he experienced facial erythema, dyspnea, and wheezing; he received salbutamol nebulization and IV diphenhydramine and methylprednisolone. The patient's condition stabilized with no infusion-related symptoms except minor flushing. After 31 infusions the patient was successfully weaned off his pre-medications. Seven weeks later, 74 minutes following the beginning of his 40th infusion, the patient experienced tremors with increasing intensity followed by significant perioral cyanosis and redness of upper limbs. His blood pressure was 133/78 mmHg, heart rate 114 bpm and he had an oxygen saturation measured at 86% (pre-infusion baseline 99%). The infusion was stopped immediately and the cyanosis and low oxygen saturation resolved in approximately 1 minute. The patient was given IV methylprednisolone and later metamizole due to slightly elevated temperature (38.2°C). His oxygen saturation being 98% the infusion was subsequently completed and the fever resolved shortly. The patient's mother later reported that the patient experienced mild facial and leg oedema for a few days following this event. The patient received his subsequent 33 infusions with premedication of IV methyl-prednisolone and diphenhydramine over a period of 4.5 hours (maximum infusion rate of 24 mL/hr). Only mild facial erythema was occasionally reported.

- A 7-year-old patient (024-046-0008) with a history of respiratory distress episodes and allergies (pollen) and with aortic and mitral valvular disease received idursulfase 0.5 mg/kg weekly. Thirty seven minutes after the end of his 22nd infusion he developed a non-serious pruritic rash on his chest, left arm and cheeks, which was treated with oral diphenhydramine. In addition, one single low value was noted amongst his blood pressure recordings 65 minutes after the start of the infusion: 78/46 mmHg as compared to a pre-infusion value of 125/63 mmHg. The next reading 25 minutes later was 121/41 mmHg and this was not reported as hypotensive event by the investigator. The patient was subsequently premedicated with IV diphenhydramine and no further rash was observed.
- A 9-year-old patient (024-059-0001) with a baseline FVC of 47% and with aortic and mitral valvular disease received idursulfase 0.5 mg/kg every other week. During his 5th infusion of active drug the monitoring of the patient's vital signs showed two abnormal determinations: one oxygen saturation at 84% (pre-infusion 99%) 65 minutes after the beginning of the infusion and one blood pressure at 79/48 mmHg (pre-infusion 107/60 mmHg) immediately after the end of the 3-hour infusion. These two isolated low values were not reported as an adverse event by the investigator and no measure was taken. The only adverse drug reaction reported for this patient was occasional pyrexia (three times associated with the active drug and once with placebo).

Study TKT024EXT

- A 6-year-old patient (024-013-0010) with a history of asthma and multiple allergies was under prophylactic treatment with cetirizine and montelukast. His baseline FEV1/FVC ratio was 78%. He received idursulfase 0.5 mg/kg weekly. During his 5th and 6th infusions he developed a non-serious urticaria. He was subsequently premedicated with IV methylprednisolone and diphenhydramine and oral ibuprofen and prednisone. Over the study period he had several asthmatic episodes, which were treated with inhalations of beta-2 adrenergics and corticosteroids. During the week preceding his 23rd infusion he developed wheezing and wet cough; during the infusion itself, he had a transient red rash and wheezing, which was reported as a possible exacerbation of his underlying reactive airways disease. On the same day, fever and increased white blood cells were also reported. The infusion was stopped and the patient received a nebulization of salbutamol, followed by maintenance treatment with salbutamol and fluticasone inhalations with oral prednisone for two weeks. The patient did not experience similar reactions thereafter.
- An 8-year-old patient (024-020-0005) with a baseline FVC of 41% predicted received idursulfase 0.5 mg/kg weekly. Thirty minutes after the beginning of his 8th infusion he developed a non serious-reaction of facial erythema with bronchospasm and vomiting; the infusion was interrupted and he was given oxygen and salbutamol nebulization. He experienced a similar reaction (facial oxygen and berotec nebulization and no further reactions were reported.
- A 16-year-old patient (024-044-0001) with a baseline FVC of 59% predicted received idursulfase 0.5 mg/kg weekly. Ten minutes after the start of his 2nd infusion he experienced a non-serious reaction of generalized erythema with dyspnea; the infusion was stopped and he

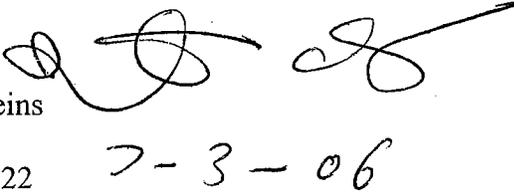
received oral chlorpheniramine. He was subsequently premedicated with oral prednisolone and the duration of the infusion was extended to 5 hours. He experienced cutaneous reactions (rash/erythema) to the 4 subsequent infusions. About 4 hours after the start of his 9th infusion he experienced facial flushing and dyspnea; no treatment was given. Afterwards, he occasionally experienced mild facial flushing and the duration of the infusion was progressively reduced to 3.5 hours again.

- A 25-year-old patient (024-044-0008) with a baseline FVC of 29% predicted received idursulfase 0.5 mg/kg weekly. He had his first reaction to the 6th infusion with nausea, headache, hot feeling, and erythema of the face and arms; serum CH50 and tryptase levels were found to be elevated. He was subsequently premedicated with oral prednisolone, paracetamol and hydroxyzine while the duration of the infusion was extended to 5 hours. However, he still experienced facial flushing and occasional rashes (with a swollen face once) with all subsequent infusions; he also reported chest tightness the day after his 11th infusion, which lasted for several days. At the occasion of his 12th infusion, he experienced a non-serious reaction of facial erythema and swelling with dyspnea; no treatment was given. He had only occasional facial flushing afterwards.
- A 9-year-old patient (024-047-0011) with a baseline FVC of 70% received idursulfase 0.5 mg/kg weekly. About one hour after the beginning of his 4th infusion he developed a non-serious reaction with urticaria, wheezing, and pain in left ear; the infusion was stopped and he was treated with salbutamol nebulization and IV hydrocortisone with chlorpheniramine. He was subsequently premedicated with IV hydrocortisone and chlorpheniramine and did not develop any further infusion reaction.

**APPEARS THIS WAY
ON ORIGINAL**

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 - 9. Impact on infusion reactions
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 - D. Impact of antibodies on Hunter Syndrome: Cross reaction on endogenous
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June 29, 2006
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7-3-06

To: BLA125151
Through: Amy Rosenberg, M.D., Director, DTP, HFD-122
Elizabeth Shores, Ph.D., Acting Deputy Director, OBP, HFD-122



Re: Immunogenicity Review of BLA 125151/0, Idursulfase

Sponsor: Shire Human Genetic Therapies, Inc (TKT) 617-613-4531 (Nik Mehta)
Date received: November 23, 2005
The first action due date: **May 25, 2006**

I. Proposed PMCs for the sponsor

1. Shire commits to test and provide data from studies TKT024 and TKT024EXT using patient samples that are positive in the screening assay, in the inhibition-of-entry neutralization assay, to assess whether patient antibodies block entry of enzyme into cells. The information will be submitted to FDA by September 30, 2007.
2. Shire commits to track binding and neutralizing antibodies using sensitive and validated assays over an extended time period to assess the potential loss of antibodies (immunologic tolerance) to ELAPRASE. Individual patient data should be provided as a function of time and a correlation of antibody status with clinical efficacy and GAG levels provided. This information will be submitted to FDA by December 31, 2008.
3. Shire commits to develop, describe, and provide validation data for a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells. This information will be submitted to FDA by May 31, 2007.
4. Shire commits to provide complete validation data for the Conformation Specific Assay (CSA),

particularly with regard to sensitivity (ng/mL) and specificity of detection of the assay. This information will be submitted to FDA by December 31, 2006.

5. Shire commits to fully validate an IgE assay for detection of anti-idursulfase IgE antibodies. This information will be submitted to FDA by June 30, 2007.
6. Shire commits to investigate and provide data on the nature of the genetic mutations of iduronate-2-sulfatase in patients in study TKT024, titled "A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Safety and Efficacy of Weekly and Every Other Week Dosing Regimens of Iduronate-2-Sulfatase Enzyme Replacement Therapy in Patients with MPS II," and to correlate findings with the level of endogenous enzyme (via protein, not enzyme activity assessment), the antibody response (binding, neutralizing and IgE), and clinical outcome in TKT024 and TKT024EXT, titled "An Open Label Extension study of TKT024 Evaluating Long-term Safety and Clinical Outcomes of MPS II Patients Receiving I2S Enzyme Replacement Therapy". This information will be submitted to FDA by January 31, 2008.

II. Proposed Label (from FDA)

Immunogenicity

Fifty-one percent (32 of 63) of patients in the weekly ELAPRASE treatment arm in the clinical study (53-week placebo-controlled study with an open-label extension) developed anti-idursulfase IgG antibodies as assessed by ELISA or conformation specific antibody assay and confirmed by radioimmunoprecipitation assay (RIP). Sera from 4 out of 32 RIP confirmed anti-idursulfase antibody positive patients were found to neutralize idursulfase enzymatic activity in vitro. The incidence of antibodies that inhibit cellular uptake of idursulfase into cells is currently unknown, and the incidence of IgE antibodies to idursulfase is not known. Patients who developed IgG antibodies at any time had an increased incidence of infusion reactions and hypersensitivity reactions. The reduction of urinary GAG excretion was less in patients in whom circulating anti-idursulfase antibodies were detected. The relationship between the presence of anti-idursulfase antibodies and clinical efficacy outcomes is unknown.

The data reflect the percentage of patients whose test results were positive for antibodies to ELAPRASE in specific assays, and are highly dependent on the sensitivity and specificity of these assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELAPRASE with the incidence of antibodies to other products may be misleading.

III. Summary

Mucopolysaccharidosis II (Hunter's syndrome) is a mucopolysaccharidosis caused by deficiency of iduronate-2-sulfatase and the only X-linked recessive traits (all other MPS are inherited as autosomal recessive traits). MPS II is a progressive disorder and characterized by involvement of multiple organs and excretion of unmodified dermatan sulfate and heparan sulfate in the urine.

Immunogenicity is determined by multiple product and host factors. The nature of the assay, assay validation and the time of serum sample collection also have significant impacts on the reported incidence of immunogenicity. For this trial, dosing was performed either on weekly or every other week (EOW) basis. It was reported by sponsor that blood samples were taken just prior to the next infusion. In TKT024, no I2S was detectable in serum 24 hours after infusion of clinical dose of I2S. Therefore, it is unlikely that there was significant interference from on-board product (see review).

The sponsor initially validated a classic ELISA assay where they confirmed results with a validated radio-immuno-assay (RIP). Although the assay appeared sensitive (135 ng/ml), subsequently it was found that it failed to detect the majority of positive samples. During the BLA review process the sponsor submitted a new non-validated binding assay, the conformation specific assay (CSA) that detected anti-I2S antibodies in a large number of samples confirmed to be positive by RIP. Consequently, the determination of the incidence of antibody positive patients was based on a positive result in either the classic ELISA or the CSA ELISA with confirmation by the RIP assay. When these results were combined, the immune response rate was determined to be 50% (47/94) in TKT024 and TKT024EXT. Because of the withdrawal of the Every Other Week treatment part of the study (EOW), the immune response rate for weekly I2S is 50.79% (32/63). Enzymatic-activity neutralizing antibody was detected in 7 patients in TKT024 and TKT024EXT. An assay to measure antibody mediated blockade of enzyme uptake into cells has not been developed. When this is developed patient samples positive in the screening assay will need to be tested.

Regarding efficacy, in the TKT024 weekly study, an improvement in 6 Minute Walk Test (6MWT), and reduction in urinary GAG and liver volume were observed. In several patients, antibodies to the product appeared to interfere with improvement in the 6MWT. Antibodies were also associated with impaired clearance of urinary GAG. There appeared to be no association between the development of antibodies and liver volume and spleen volume reduction. The effects of antibody on I2S tissue distribution were not reported.

Regarding safety, there were more infusion associated adverse events (IAEs, total 241 events) in antibody positive patient undergoing weekly treatment in TKT024 and TKT034EXT than in antibody negative patients (104 events). There were more cardiac disorders in antibody positive patients (14 events) than antibody negative patients (1 event). Events such as arrhythmia, cyanosis and hypotension were only found in antibody positive patients. Isolated respiratory disorders were found uniquely in antibody positive patients who experienced dyspnoea, bronchospasm and throat tightness. Skin disorders contributed significantly to the increased IAEs in antibody positive patients. The high rate of infections was not changed after I2S treatment and antibodies did not seem to impact that finding. No renal problems were reported in antibody positive patients.

The incidence of reported allergic reactions was 38% (24/63) in TKT024 weekly and TKT024EXT placebo. It is higher in IgG + patients (56%, 18/32) and less in IgG negative patients (19%, 6/31). All test samples were negative for IgE (IgE ELISA was not validated yet). Sponsor submitted their new analysis regarding anaphylactic/anaphylactoid reactions according to the requirement of at least two system involvement (skin, cardiac, or respiratory) in BLA125151-0-0013 on May 15, 2006. 11 patients were listed with hypersensitivity reactions [11%, or 11/(94+12) (without EOW group it is 13%, 10/(64+12). Of note, patients with hypersensitivity reactions were all positive for IgG antibody except patient 018-013-0002. Therefore, there were more hypersensitivity reactions in IgG positive patients, although it is not clear whether such patients also have IgE antibodies.

The sponsor reported that total treatment emergent AEs in antibody positive patients were not more than that in antibody negative patients in TKT weekly and TKT024EXT placebo. However, there were more cardiac and skin disorders in antibody positive patients than in antibody negative patients. No correlation was found between the death of four patients during the studies and the antibody status.

IV. Review

Mucopolysaccharidosis II(Hunter's syndrome) is one of a group diseases that caused by deficiency of lysosomal enzymes involved in the degradation of mucopolysaccharides (glycosaminoglycans). MPS II is a mucopolysaccharidosis caused by deficiency of iduronate-2-sulfatase and the only X- linked recessive traits (all other MPS are inherited as autosomal recessive traits). MPS II is a progressive disorder and characterized by involvement of multiple organs (including CNS) and excretion of dermatan sulfate and heparin sulfate in the urine.

The product is Elaprase, a purified form of human iduronate-2-sulfatase — from a human cell line — It is formulated as following:

Table 3.2.P.3.2-1 Batch Formula

Component	Specification	Quantity per Liter
Idursulfase Drug Substance	In-house Monograph	
Sodium chloride	Ph Eur, USP	
Sodium phosphate dibasic, heptahydrate	USP	
Sodium phosphate monobasic, monohydrate	USP	
Polysorbate 20	Ph Eur, NF	

A. Assay Validation

1. Classic Binding Assay – IgG ELISA

Method

Cut point

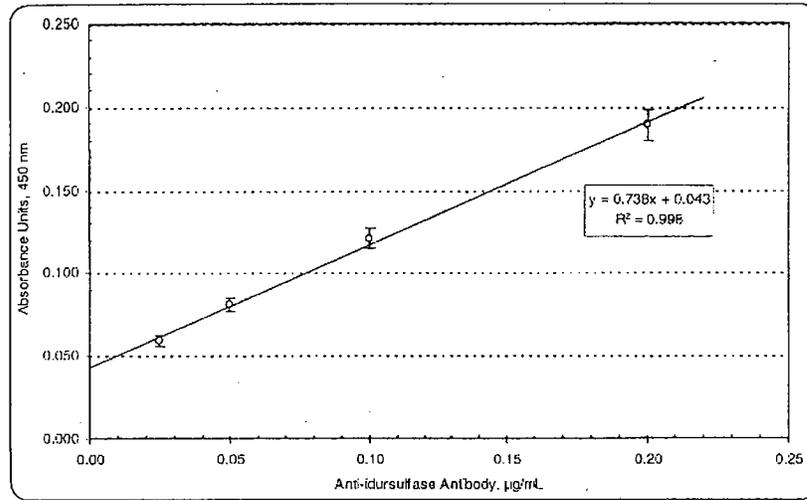
Cutpoint was determined by naïve patient serum for each isotype.

Table 1. Cut Point

Antibody Isotype	N	% Outliers	95%CI Cut Point $A_{450(nm)}$
IgG	98	11.2	0.047
IgM	96	8.3	0.036
IgA	96	10.4	0.030
IgE	96	4.2	0.027

Sensitivity

Figure 3. Affinity-purified Human Anti-Idursulfase IgG Dose Response



LOD = $3.3\sigma/S$ [σ = SD of the blank, S = slope of the dose response curve]
Based on linear regression analysis

$$Y = 0.738x + 0.043 \quad (R^2 = 0.998, \sigma = 0.00151)$$

[Y = A_{450nm} , X = antibody concentration in $\mu\text{g/mL}$]

$$\text{LOD} = (3.3 \times 0.00151) / 0.738 = 0.00675 \mu\text{g/mL} \text{ or } 6.75 \text{ ng/mL}$$

Because of 1;20 dilution, so LOD is $6.75 \times 20 = 135 \text{ ng/mL}$.

LOD = 135 ng/mL (Recommended assay sensitivity is < 500 ng/mL)

Precision

Inter-assay and Intra-assay Precision were determined with anti-I2S serum of high, medium, and low titer and are with specifications.

Table 2. Inter-assay and Intra-assay Precision

	Intra-assay Mean						Inter-assay
	Day 1	Day 2	Day 3	Day 4	Day 5	%RSD	%RSD
High	1.08	1.05	1.04	1.04	1.08	2.0-	4.0
Medi	0.53	0.52	0.52	0.52	0.53	1.7-	4.5
Low	0.18	0.19	0.15	0.17	0.18	8.2-	12.9
Negative	0.027	0.044	0.046	0.032	0.023	2.3-15.0	25.3

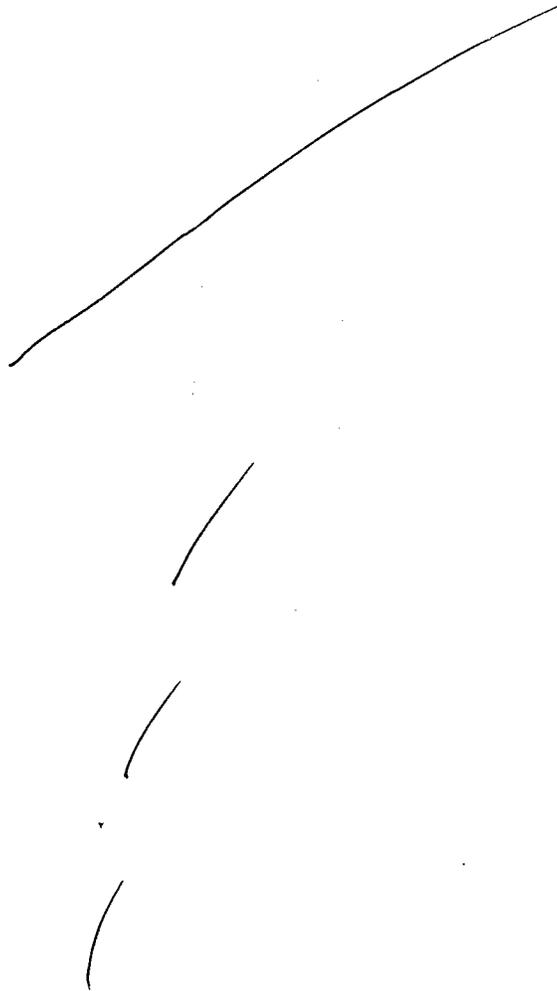
N= 10 determinants per sample per day

Intra-assay precision for high, medium, and low samples was less than 18% RSD and inter-assay precision for the three samples was less than 13% RSD.

The positive control is human anti-idursulfase positive serum pool from two patients (one from TKT008, the other from TKT018). It is likely to represent a relatively high affinity antibody as it seems to document very good sensitivity of the assay yet subsequent data demonstrated the assay missed many positive patients upon screening.

2. Binding Assay – Conformation Specific Anti-idursulfase antibody assay

Method



Assay cut point

250 serum sample from 31 Hunter Syndrome patients receiving placebo were analyzed by three analysts. Samples were diluted 1:50 in 1X idursulfase dilution buffer (contains 8 ng/ml of idursulfase) and analyzed in duplicate. The assay positive cut point was established from the 95% confidence interval using the formula:

$$\text{Assay positive cut point} = \text{Mean} - 1.645 \text{ SD}$$

Table 3. Assay Positive Cut Point (CSA Ratio)

Donor Source	N (Data Points)	Dilution Factor	Mean	SD	Cut Point
Hunter Syndrome Patients	654	1:50	1.07	0.19	0.76

Table 5. Precision (CSA Ratio)

Assay Reference	Sample ID					
	PC 1:100 Mean	PC 1:100 % RSD	PC 1:500 Mean	PC 1:500 % RSD	PC 1:1000 Mean	PC 1:1000 % RSD
Intra - 30NOV05LP	0.13	3.4%	0.46	2.1%	0.67	2.2%
Intra - 01DEC05LP	0.11	3.2%	0.43	0.6%	0.66	0.8%
Intra - 02DEC05LP	0.12	7.8%	0.45	4.9%	0.65	3.7%
Intra - 05DEC05LP	0.11	2.2%	0.43	0.8%	0.67	1.9%
Intra - 07DEC05LP	0.10	2.5%	0.39	1.2%	0.60	2.3%
Inter Assay (five days)	0.11	10.6%	0.43	5.8%	0.65	4.3%

The CSA Ratio is determined by the result of a specific time point divided by the result of baseline. The less diluted samples contain more antibodies, form more immune complex so contain less detectable free I2S, therefore less absorbent and small CSA ratio. The % relative SD for all three dilutions is less than 11%. However, it has not been demonstrated that the inhibition is due to human IgG.

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Inter-day precision: The mean, SD, and %RSD were calculated from nine results per sample obtained by each analyst over three days as showed in Table 7.

Overall precision: The mean, SD, and %RSD were calculated from eighteen results per sample obtained by two analysts over three days as showed in Table 7.

The %RSD was used to determine inter-day and overall precision.

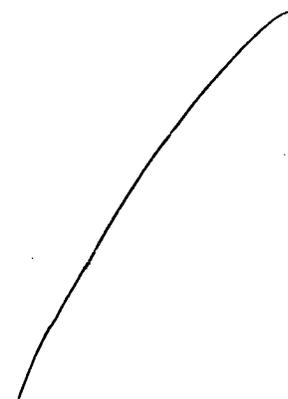
Table 7. Inter-Day Precision and Overall Precision (CSA Ratio)

Analyst	Sample ID					
	PC 1:100 Mean	PC 1:100 % RSD	PC 1:500 Mean	PC 1:500 % RSD	PC 1:1000 Mean	PC 1:1000 % RSD
Inter-day (LH)	0.12	6.2%	0.46	3.8%	0.67	1.9%
Inter-day (LP)	0.11	9.5%	0.42	6.1%	0.64	5.0%
Overall Precision	0.11	8.5%	0.44	6.4%	0.66	4.3%

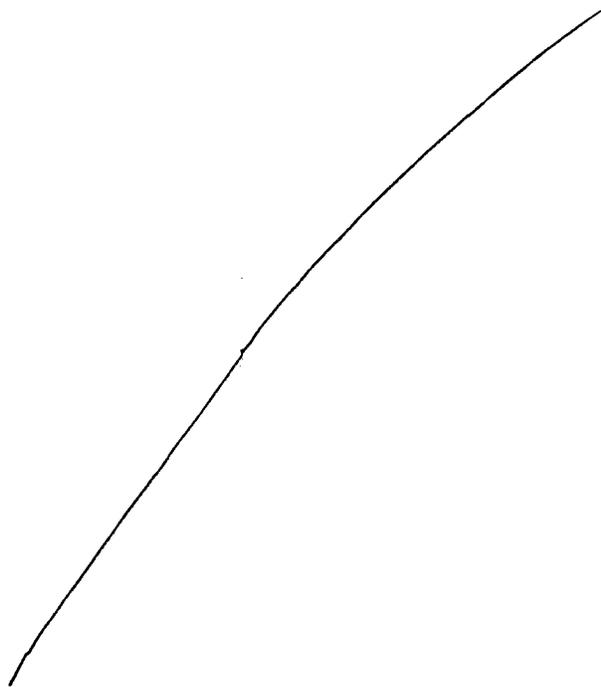
The inter-assay precision is less than 9%RSD for all three dilutions with two analysts.

Based on the validation report, the specificity and sensitivity of the assay in terms of anti-I2S antibody IgG have not been demonstrated. It is all reported in terms of the amount of I2S.

3. Radio Immune-Precipitation (RIP) Confirmation Assay Method



Confirmation Assay- Radioimmunoprecipitation



Validation Data

Table 1. Acceptance Criteria and Validation Results

Validation Parameter	Acceptance Criteria	Results
Reproducibility	<ul style="list-style-type: none"> • %RSD* ≤ 15% 	<ul style="list-style-type: none"> • Intra-assay: 1.5 to 10.5% • Inter-assay: 6.5 to 8.4 %
Linearity	<ul style="list-style-type: none"> • R² ≥ 0.950 	<ul style="list-style-type: none"> • R² ≥ 0.987
Specificity	<ul style="list-style-type: none"> • Characterization of the immune complex: — • Competition assay: R² of competition curve ≥ 0.900 	<ul style="list-style-type: none"> • R² ≥ 0.965
Ruggedness	<ul style="list-style-type: none"> • Analyst % Effect ≤ 15% • Day-to-day % Effect ≤ 15% 	<ul style="list-style-type: none"> • Analyst % Effect = 8.7% • Day-to-day Effect = 0% (ratio > cut point)
Robustness	<ul style="list-style-type: none"> • Effect of ¹²⁵I-labeled idursulfase concentration on positive sample/total counts ratio ≤ 15% 	<ul style="list-style-type: none"> • 4.4 -7.4% change in ratio

*RSD = Relative Standard Deviation

Cut point

The positive cut point is determined by three analysts each assayed 81 naïve Hunter patient serum samples over three days. The upper negative cut point of 95% was calculated using the mean plus 1.645 SD, where 1.645 is the 95th percentile of the normal distribution. Results were expressed as the ratio of the positive control assayed concurrently with the unknown samples. Samples with ratio >0.180 will be assessed as positive.

Table 5: Cut Point Determination

Antibody Isotype	N	Number of Outliers	% Outliers	Mean	Cut Point Mean + 1.645 SD
IgG	243	12	4.9	0.07	0.180

*Ratio \geq cut point

Linearity

Linearity was demonstrated with goat-anti-I2S (Figure 1) and three ELISA positive patient samples (Figure 2).

Figure 1: Goat anti-Idursulfase: RIP Assay Concentration Dependent Binding

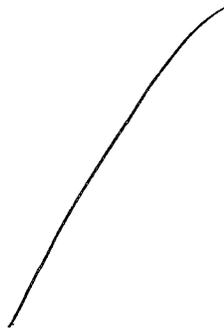
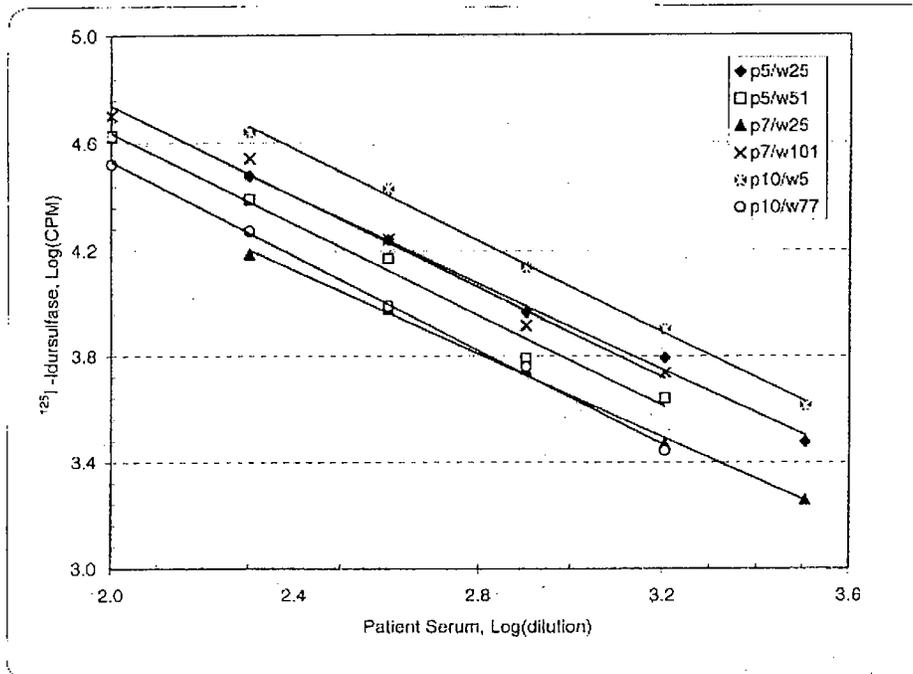


Figure 2: Idursulfase Binding by Positive Patient Sera Collected on Two Different Dates

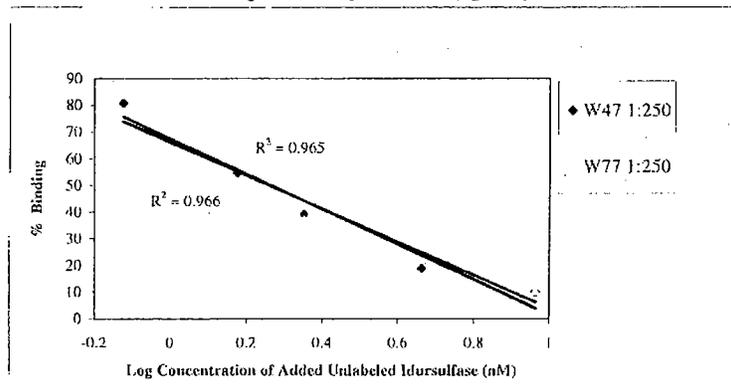


Legend: (p5/w25), patient 5, week 25 of enzyme replacement therapy (ERT); (p5/w51), patient 5, week 51 of ERT; (p7/w25), patient 7, week 25 of ERT; (p7/w101), patient 7, week 101 of ERT; (p10/w5), patient 10, week 5 of ERT; (p10/w77), patient 10, week 77 of ERT.

Specificity

250,000 cpm of ^{125}I -labeled idursulfase was mixed with indicated unlabeled idursulfase, then anti-I2S positive sera W47 or W77 (both diluted 1:250) was added and assayed by RIP. Percent binding was calculated relative to the mixture without unlabeled idursulfase. Dose dependent competition by cold I2S was demonstrated, indicating the assay is specific.

Figure 6: Competitive Binding Assay



RIP Summary

RIP assay was validated for specificity, linearity, precision, and ruggedness. The sensitivity of the assay in terms of anti-I2S IgG mass unit has not been determined.

4. Enzyme Activity Neutralization Assay

Method

Summary of Validation Studies to date

Activity neutralization assay was qualified for reproducibility, ruggedness, and robustness, but the specificity (IgG dependent and do not neutralize other enzymes) of the assay has not been demonstrated.

Table 1: Acceptance Criteria and Validation Results

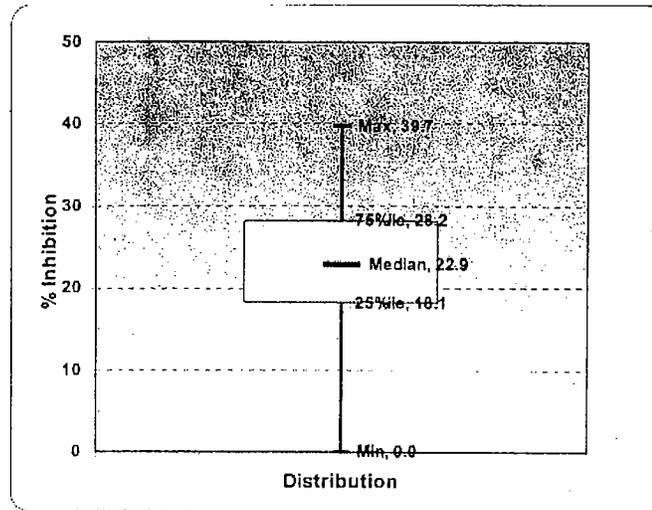
Validation Parameter	Acceptance Criteria	Validation Result		
Reproducibility	% RSD \leq 15% % RSD < 20%	Inter-assay: %RSD \leq 2.6% Intra-assay: %RSD \leq 3.5%		
Ruggedness	1) Analyst % Effect \leq 15 % 2) Day-to-Day % Effect \leq 15 %	1) Analyst % Effect = 9.0% 2) Day-to-Day % Effect = 4.9%		
Robustness	Pre-Incubation Time % Effect	Controls	120 minutes	240 minutes
	\pm 15 % relative to standard incubation	Positive	3.8%	23.0%
		Negative	3.2%	2.1%
	\pm 10% in DRX006A Concentration must produce a % Effect \leq 15 %	% Effect = 4.0-6.9%		

RSD= relative standard deviation, IQR= interquartile range

Matrix Effects

Strong matrix effects were shown below with 82 naïve patients' sera that were negative for anti-I2S antibody. There are no reports of GAG or non-Ig inhibitors of I2S in sera of Hunter patients.

Figure 1. Effect of Naïve Hunter Patient Serum in the Neutralizing Antibody Assay



5. Uptake Neutralization Assay: Not Yet Developed

Importance

The target of I2S is inside cells (lysosome) and the uptake of I2S is essential for its function. Therefore it should be assessed whether patients' sera Ig can inhibit the uptake of I2S and therefore the function of I2S.

Anti-I2S antibody could affect the clearance of the product as well as the entry of the product into cells. Therefore it is important to establish an uptake based neutralization assay.

Comment in the 74 day letter

"Please develop and provide validation data for a neutralizing antibody assay that can detect the presence of antibodies that inhibit the entry of I2S into cells. Please test and provide data from patient samples that are positive in the screening assay with this inhibition-of-entry neutralization assay."

In addition to the comment below, the sponsor should be notified to address other issues. Specifically, the specificity of the uptake should be demonstrated by (1) competition by unlabeled product, but not by irrelevant proteins; (2) whether it is IgG dependent.

B. Incidence of Specific Antibodies

1. Antibody response in monkey

Monkeys in four groups: Vehicle (6 monkeys), 0.5 mg/kg/week (4), 2.5 mg/kg/week (4), and 12.5 mg/kg/week, were injected with indicated dose of I2S. Serum samples were collected on non-dosing days (9, 23, 87, 177, 206). Anti-I2S

antibody was detected in five monkeys at day 87. Clearance was enhanced in two antibody positive monkeys, but not in others.

Antibody response and product clearance

Group #	Animal #	Antibody Assay		Clearance (ml/min/kg)	
		Prestudy	Day 87/177	Day 1	Day 85/176
3	F11735M	0.084	0.227	0.272	0.433
	F13101M	0.030	0.057/0.166	0.264	0.221/0.415
4	F11703M	0.091	0.424	0.179	0.130
	F11722M	0.094	0.445	0.158	0.248
	F13144M	0.210	0.572	0.119	0.180
	F13171M	0.166	0.414	0.136	0.165

2. Binding antibody in TKT008 via classic ELISA

Patient 013-0010 was tested positive by IgG ELISA and confirmed by RIP at week 13 and 24. The other eleven patients were negative for IgG ELISA. It should be noted that the incident may be higher than perceived as the IgG ELISA was later found to be unable to detect many positive patients.

3. Binding antibody in TKT018 via classic ELISA

Five out of twelve patients test positive for IgG antibody by ELISA and confirmed by RIP during TKT018 study. They included 013-0005, 013-0006, 013-0007, 013-0010, 013-0012.

4. Binding antibody in TKT024 and TKT025EXT via classic ELISA

In TKT024EXT all patients were treated with weekly I2S. As shown in Table 8.7-1, no IgE was detected in any patient (the assay has not been validated yet). 5 patients were IgM positive with classic ELISA in TKT024 and TKT024EXT. 10/94 (10.6%) patients were IgG positive with classic ELISA (Please refer to following CSA results). All IgM positive patients were positive for IgG by CSA assay.

Table 8.7-1 Summary of Anti-Idursulfase Antibody Development

	Placebo (N=31)	Idursulfase Weekly (N=31)	Idursulfase EOW (N=32)	All Patients (N=94)
IgG				
Positive (N [%])	3 (9.7) ^a	5 (16.1)	2 (6.3)	10 (10.6)
Negative (N [%])	28 (90.3)	26 (83.9)	30 (93.8)	84 (89.4)
IgE				
Positive (N [%])	0	0	0	0
Negative (N [%])	31 (100.0)	31 (100.0)	32 (100.0)	94 (100.0)
IgM^b				
Positive (N [%])	3 (9.7) ^a	1 (3.2)	1 (3.1)	5 (5.3)
Negative (N [%])	28 (90.3)	30 (96.8)	31 (96.9)	89 (94.7)

EOW=Every other week.

Patient Population: Safety population: all patients who received at least 1 dose (or partial dose) of study drug in TKT024EXT.

Antibody positivity is defined as positive result at any time point during TKT024 through the data cut-off date for TKT024EXT (04 April 2005).

^a TKT024 placebo patients were positive for antibodies in TKT024EXT only.

^b A confirmatory RIP assay for IgM antibodies was being developed and validated at the time this report was prepared.

Data source: Table 14.3.7.

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Table 2.7.2-12 listed the titer and timing of each patient that were positive for the ELISA assay. The titers are low.

Table 2.7.2-12 Antibody Status by Patient and Study Week: TKT024 and TKT024EXT

Treatment Group and Patient	TKT024								TKT024EXT		
	Baseline	Week 5	Week 9	Week 18	Week 27	Week 36	Week 45	Week 53	Week 5	Week 9	Week 18
IgG Antibody Status											
Idursulfase weekly											
013-0001	-	-	-	20	-	-	-	-	-	-	-
020-0010	-	-	-	-	40	200	40/+	80/+	160/+	160	NV
020-0012	-	-	-	-	-	-	20 ^a	-	-	NV ^a	NV
048-0005	-	-	-	-	-	-	-	-	-	160	160
059-0006	-	-	40	20/+	-	-	-	-	-	-	NV
Idursulfase EOW											
047-0003	-	-	80 ^c	-	-	-	40/+	20/+	160/+	160/+	NV
012-0007	-	-	320	20	20	20	-	20/+	-	-	NV
Placebo											
046-0013	-	-	-	-	-	-	-	-	-	20	20
047-0006	-	-	-	-	-	-	-	-	20	20	NV
047-0011	-	-	-	-	-	-	-	-	40	80	NV
IgM Antibody Status^d											
Idursulfase weekly											
046-0008	-	80	-	-	-	-	-	-	-	-	NV
Idursulfase EOW											
012-0015	-	-	20	20	-	-	-	-	-	NV	NV
Placebo											
012-0009	-	-	-	-	-	-	-	-	40	40	NV
044-0005	-	-	-	-	-	-	-	-	-	20	NV
047-0002	-	-	-	-	-	-	-	-	20	-	NV

Note: Numbers indicate antibody titer; EOW = Every other week; - indicates antibody negative; + indicates neutralizing antibody positive; NV = No Visit

^a Patient 020-0012 was positive for IgG antibodies when evaluated at Week 40 only.

^b Due to staggered patient enrollment this visit was not scheduled to occur prior to the 04 April 2005 cut-off date for this patient.

^c Patient 047-0003 was also IgG antibody positive at Week 10 (neutralizing activity negative).

^d IgM antibody status has not been confirmed in Study TKT024EXT.

5. RIP-based Confirmatory Antibody Findings of IgG ELISA positive patients in TKT024

Based on the >0.180 ratio positive cut point, 6 out of 13 ELISA IgG antibody positive patients were confirmed positive for anti-idursulfase IgG isotype antibodies by RIP IgG assay.

- Patients 013-0001, 020-0010, 020-0012, 047-0003, 059-0006 and 012-0007 were positive by RIP.
- Patients 013-0010, 020-0003, 020-0025, 020-0031, 046-0013, 047-0006, and 059-0008 (baseline only) were negative.

These 6 antibody-positive patients were 4 in the weekly group and 2 in the every other week group.

6. RIP-based Confirmatory Antibody Findings of IgG ELISA and CSA positive patients in TKT024 and TKT024EXT

The CSA assay was introduced to as a means to screen patients and incidence was re-evaluated with this assay.

Table 2.7.4-15 Antibody Status by Assay Method (TKT024)

	Idursulfase Weekly n=32	Idursulfase EOW n=32	Placebo n=32	All Patients N=96
Antibody Status TKT024	n (%)	n (%)	n (%)	n (%)
Negative	17 (53.1)	17 (53.1)	32 (100.0)	66 (68.8)
Positive				
ELISA A ₄₅₀	4 (12.5)	2 (6.3)	0	6 (6.3)
CSA	14 (43.8)	15 (46.9)	0	29 (30.2)
Either ELISA A ₄₅₀ or CSA	15 (46.9)	15 (46.9)	0	30 (31.3)
Both ELISA A ₄₅₀ and CSA	3 (9.4)	2 (6.3)	0	5 (5.2)

Patient population: Safety population (all patients who received at least 1 dose [or partial dose] of idursulfase.
EOW=Every other week.; CSA=conformation-specific antibody; ELISA=enzyme-linked immunosorbence assay.
Data source: Table 2.7.4.7.3.1.33.

Table 2.7.4-16 Antibody Status by Assay Method (TKT024EXT, by TKT024 Treatment Assignment)

	Idursulfase Weekly n=31	Idursulfase EOW n=32	Placebo n=31	All Patients N=94
Antibody Status TKT024EXT	n (%)	n (%)	n (%)	n (%)
Negative	21 (67.7)	20 (62.5)	14 (45.2)	55 (58.5)
Positive				
ELISA A ₄₅₀	3 (9.7)	2 (6.3)	6 (19.4)	11 (11.7)
CSA	10 (32.3)	12 (37.5)	16 (51.6)	38 (40.4)
Either ELISA A ₄₅₀ or CSA	10 (32.3)	12 (37.5)	17 (54.8)	39 (41.5)
Both ELISA A ₄₅₀ and CSA	3 (9.7)	2 (6.3)	5 (16.1)	10 (10.6)

Patient population: Safety population (all patients who received at least 1 dose [or partial dose] of idursulfase.
EOW=Every other week.; CSA=conformation-specific antibody; ELISA=enzyme-linked immunosorbence assay.
Data source: Table 2.7.4.7.2.1.68.

Although the CSA assay has not been fully validated, the assay results were confirmed by the validated RIP assay (>0.180 ratio positive cut point) in 29 out of 31 CSA positive patients in TKT024. Of the 13 ELISA positive patients 6 were confirmed by RIP. Of the 6 ELISA and RIP positive patients, one was negative for CSA. In addition, RIP assay found 30 out of 63 patients in I2S treatment groups are positive for anti-I2S IgG in TKT024 trial.

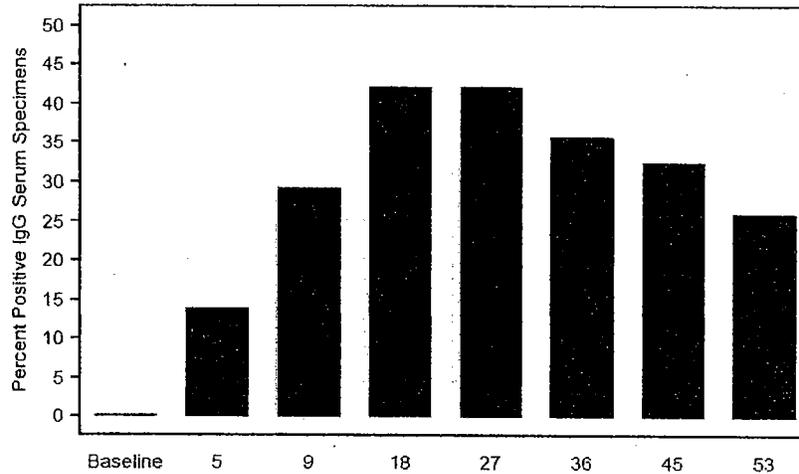
In TKT024EXT there were 37 RIP confirmed CSA positive patients and one CSA negative but ELISA positive patients were confirmed by RIP IgG assay. There were 17 RIP confirmed IgG positive patients (16 CSA+/RIP+ and one ELISA+/RIP+) in newly treated placebo group.

7. Serum conversion

Serum conversion over time of RIP confirmed CSA or ELISA positive patients in weekly and every other week groups are shown as below:

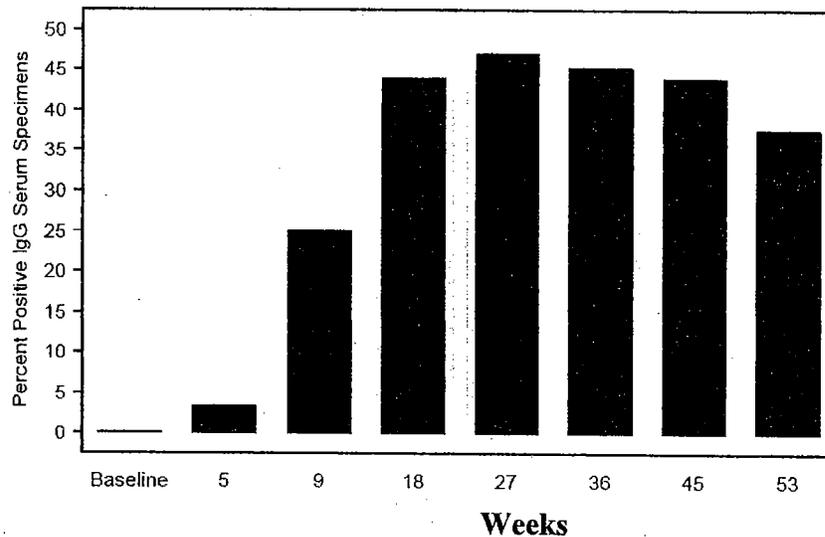
Protocol No. TKT024

Figure 2.7.4.7.3.2.1
Percent of IgG Antibody Positive Serum Specimens by Treatment Group and Visit
Idursulfase Weekly Patients
Safety Population



Protocol No. TKT024

Figure 2.7.4.7.3.2.1
Percent of IgG Antibody Positive Serum Specimens by Treatment Group and Visit
Idursulfase EOW Patients
Safety Population



Most seroconversions occurred between week 5 to week 18 for both weekly and EOW groups. 6 out of 15 IgG positive patients in weekly group became negative at week 53, a 40% tolerance within one year although only one measurement was positive in two patients. Less tolerance was found in the EOW group at week 53.

8. Activity Neutralization Antibody

- 5/30 RIP positive/64 treated patients developed neutralizing antibody (> 40% inhibition) in TKT024.
- 7/39 RIP IgG positive patients developed Nab (> 40% inhibition) in TKT024EXT.

	Groups	TKT024	TKT024EXT
024-012-0007	EOW	+(wk49)	+(wk9,18,27)
024-012-0014	EOW	-	+(wk5)
024-020-0010	Weekly	+ (wk 45, 53)	+(wk5)
024-044-0001	Placebo	-	+(wk18,27)
024-044-0009	Weekly	+(wk27)	+(wk27)
024-047-0003	EOW	+(wk18,27,36,45,53)	+(wk5,9,18)
024-059-0006	Weekly	+(wk18,27,36,45)	+(wk5,9)

The highest inhibition is 99% in patient 024-047-0003 at week 18 of TKT024EXT.

9. Summary of antibody incidence

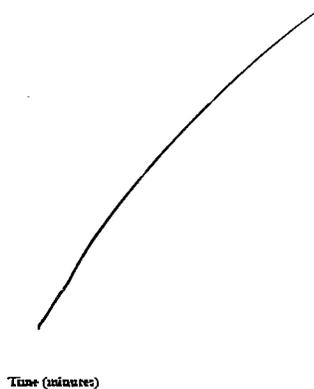
In summary, there were a total of 47 patients (30 in TKT024 I2S treatment groups and 17 new serum conversions in TKT024 placebo patients treated with I2S under TKT024EXT study) that tested positive by the CSA assay or ELISA and confirmed by RIP assay in TKT024 and TKT024EXT. Therefore, the incidence of immune response in TKT024/TKT024EXT is 50% (47/94). As per email of Dr. Ku EOW was withdrawn from the protocol and only weekly treatment will be on the list for approval. Therefore the incidence of IgG binding antibody immune response in TKT024/TKT024EXT is **50.79%** [(15 in 024 weekly + 17 new cases in 024EXT placebo)/63]. The incidence of activity neutralizing antibody is 6% (4/63, 3 in weekly + one in 024EXT placebo). The incidence of uptake neutralizing antibody is yet to be determined.

Most CSA positive patients were also positive by RIP. In contrast, only 6 patients out of 13 patients that tested antibody positive by ELISA were confirmed positive by RIP. These data show that there is strong correlation between CSA and RIP results and that the CSA is likely a more sensitive and accurate assay for detecting antibody-positive samples, than is the ELISA assay. **It is worth noting that 7 out of 13 ELISA positive cases were negative by RIP, indicating that there were false positive cases in ELISA. The ELISA was so bad that the 13 ELISA positive patients were not more specific than random selection in terms of immune response (53%) detected by RIP, which is comparable to the 51% response rate for the entire patient population as assessed by the combined CSA/ELISA and RIP. Therefore, it is unlikely that RIP is more sensitive and will detect more positive cases than the combination of ELISA and CSA.** However, without

testing the answer is unknown. It is unclear what causes the assay difference among ELISA, CSA and RIP. One possible factor is in ELISA,

Possible reasons for reports of low incidence antibody by classic ELISA

- 1) Assay sensitivity: LOD of this classic ELISA is 135 ng/ml. The recommended LOD is < 500 ng/ml. Even though the LOD is lower than the recommended, the assay failed to detect most of the CSA positive samples, suggesting that factors other than sensitivity and specificity are also very important. LOD of CSA has not been determined yet in terms of IgG.
- 2) There were products in serum sample? – Timing of serum sampling is known to be critical. Based on the March 14, 2006 Fax from TKT, serum samples for antibody testing were to be obtained on the day of the designated study visit, just prior to the infusion of study drug. As shown below, there is unlikely to be much product interference at the time of sample collection.



3) It is unclear whether _____ contribute to the assay difference

ELISA	/	/
CSA		
RIP		

C. Relationship of Anti-I2S antibodies to clinical efficacy and safety

1. Relationship of antibody status to primary clinical endpoints

The primary efficacy endpoint in the pivotal trial TKT024 was a single composite variable that combined 2 clinical measurements of function:

- 6-minute walk test as a measure of functional capacity and endurance, and
- forced vital capacity as a measure of respiratory function.

Table 1 P-values and 95% Confidence Intervals for Treatment Differences in Primary Efficacy Variables in Study TKT024: ITT Patient Population

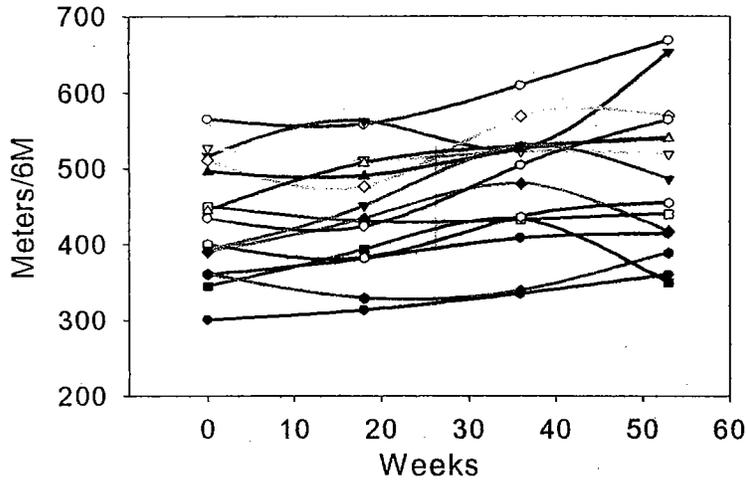
Efficacy Endpoint	Treatment Comparison		
	Weekly vs Placebo	EOW vs Placebo	Weekly vs EOW
Primary Endpoint: ITT Patient Population			
2-Component Composite			
p-value	0.0049	0.0416	0.1329
95% CI	5.99, 31.93	0.51, 25.22	-3.40, 25.07
Components of the Primary Endpoint: ITT Patient Population			
6-Minute Walk Test Distance			
6MWT Distance (Mean Change from Baseline)			
p-value	0.0131	0.0732	0.3963
95% CI	7.66, 62.52	-2.31, 49.91	-17.72, 44.09
% Change in 6MWT Distance			
p-value	0.1187	0.1742	0.9510
95% CI	-2.03, 17.35	-3.26, 17.57	-10.53, 11.20

The p value of primary endpoint and 6MWT distance for weekly vs placebo, but not EOW vs placebo is significant. TKT has withdrawn the EOW treatment.

No analysis was provided that examined the correlation between antibody positivity (based on RIP confirmed CSA and ELISA) and outcome of the 6MW. 6MW data of all antibody positive patients in weekly treatment group were shown below with antibody status at testing week 0, 9, 18, 27, 36, 45, and 53. A negative sign,“-“ indicates antibody negativity. “9” or “18” indicates that binding antibody was positive at week 9 or 18. “9, 18, 27” indicates that binding antibody was positive at weeks 9, 18, and 27.

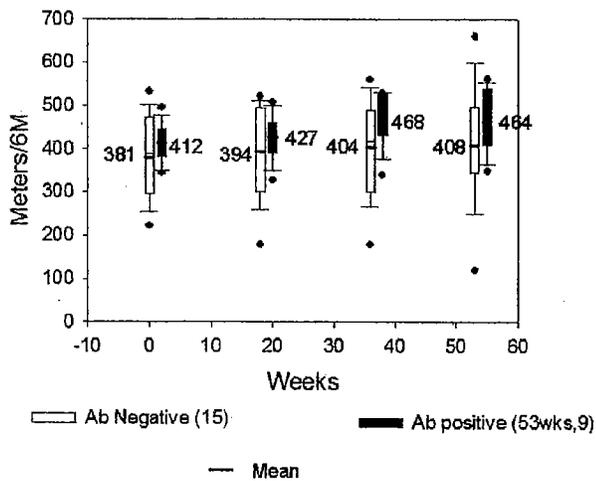
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6MW data of all RIP confirmed CSA and ELISA antibody positive patients in weekly treatment group.



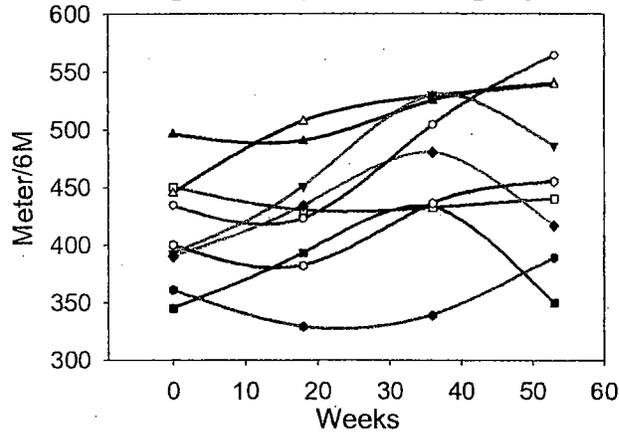
Id	IgG+ (at weeks)
024-012-0004	-, -, -, 27, 36, -, -
024-012-0012	-, -, 18, 27, 36, 45, -
024-013-0001	-, -, 18, -, -, -, -
024-013-0002	5, 9, 18, 27, -, -, -
024-020-0010	5, 9, 18, 27, 36, 45, 53
024-020-0012	5, 9, 18, 27, 36, 45, 53
024-044-0009	-, 9, 18, 27, 36, 45, 53
024-045-0017	-, 9, 18, 27, -, -, -
024-045-0020	-, -, -, 27, 36, 45, 53
024-046-0005	-, -, 18, 27, 36, 45, 53
024-046-0008	5, 9, 18, 27, 36, 45, 53
024-048-0005	-, 9, 18, 27, 36, 45, 53
024-048-0008	-, -, 18, -, -, -, -
024-059-0004	5, 9, 18, 27, 36, 45, 53
024-059-0006	5, 9, 18, 27, 36, 45, 53

6MW of Weekly Treatment Group



The mean (percent) change for patients who were antibody positive at week 53 is 52 meters (12.6%), which is not statistically different from antibody negative patients at the same time point (27 meter, 7.1%).

Neutralizing antibody and loss of progress in 6MWT

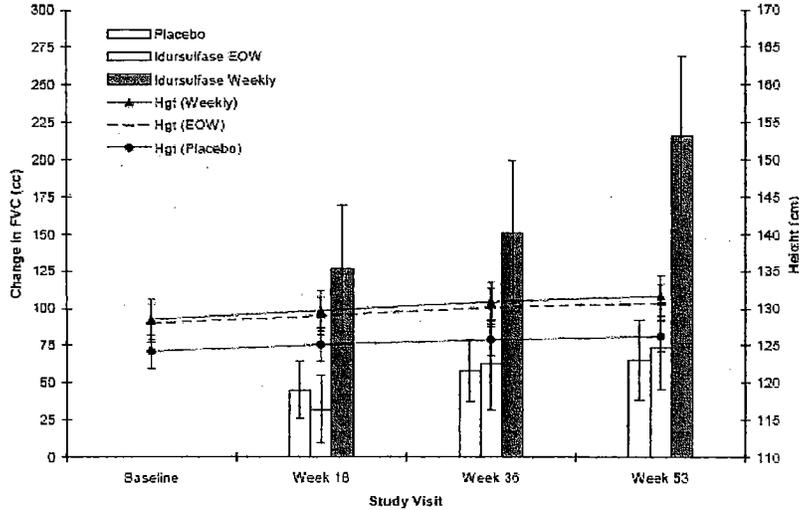


ID	IgG+ (weeks)
024-020-0010	5, 9, 18, 27, 36, 45, 53 NAb
024-020-0012	5, 9, 18, 27, 36, 45, 53
024-044-0009	-, 9, 18, 27, 36, 45, 53 Uptake?
024-045-0020	-, -, -, 27, 36, 45, 53
024-046-0005	-, -, 18, 27, 36, 45, 53
024-046-0008	5, 9, 18, 27, 36, 45, 53
024-048-0005	-, 9, 18, 27, 36, 45, 53
024-059-0004	5, 9, 18, 27, 36, 45, 53
024-059-0006	5, 9, 18, 27, 36, 45, 53 NAb

Summary: Three patients lost progress in 6MWT. Among them activity neutralizing antibody was detected in patient 024-020-0010 at week 45 and 53 and in patient 024-059-0006 from week 18 to week 45, suggesting the possibility that antibody may affect outcome. It is unknown as to whether these patients' antibodies can inhibit cell uptake. No activity neutralizing antibody was detected in the third patient (024-044-0009) who also lost progress in 6MWT. It should be determined whether this patient has uptake inhibition antibodies. Because the likelihood of antibodies being able to target lysosomal I2S is very low, enzyme neutralizing antibodies are unlikely be a major problem unless they also have other effects (e.g. inhibit uptake, change PK, or tissue distribution).

2. Relationship of antibody status to Forced vital capacity

Figure 11.4-5 Mean Height (cm) and Mean Change from Baseline in Absolute FVC Volume (cc) by Treatment Group: ITT Patient Population



Efficacy endpoint

	Weekly vs Placebo	EOW vs Placebo	Weekly vs EOW
Forced Vital Capacity:			
% Predicted FVC (Mean Change from Baseline)			
p-value	0.0650	0.9531	0.1079
95% CI	-0.27, 8.83	-4.04, 4.28	-0.79, 7.76
Absolute FVC (L) (Mean Change from Baseline)			
p-value	0.0011	0.3735	0.0176
95% CI	0.08, 0.30	-0.04, 0.10	0.02, 0.25
% Change in Absolute FVC			
p-value	0.0137	0.6341	0.0577
95% CI	2.26, 18.97	-5.94, 9.66	-0.25, 14.82

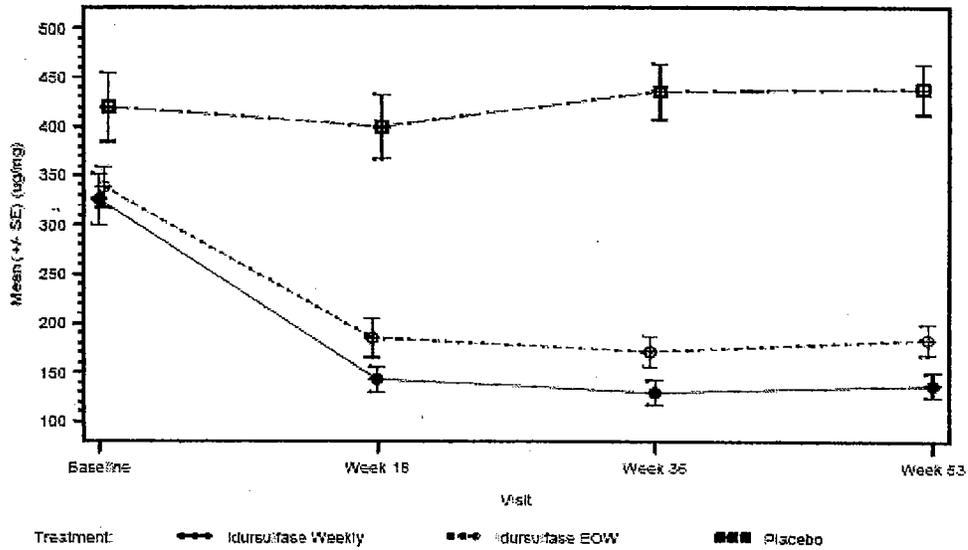
Summary: The forced vital capacity absolute value was increased in weekly treatment group but not in every other week treatment group. P value of absolute FVC (L) is significant for weekly vs placebo, but not EOW vs placebo.

The mean value of FVC in IgG positive patients is 243.6 cc that is not less than the value (205.9 cc) of antibody negative patients in TKT024 weekly group. The FVC value for the 9 patients who were tested positive at 53 weeks in weekly group is 155.6 cc, a 50 cc drop than that of negative patients. FVC value was not increased in 10 patients (4 patients were antibody positive, 6 patients were antibody negative).

3. Relationship of antibody status to Urine GAG levels

The upper limit of urine GAG/creatinine (ug/mg) in healthy pediatric urine samples is 126.6 (the mean is 61.89). Urine GAG levels are significantly increased in patients with Hunter's syndrome. Urine GAG levels in both weekly and every other week treatment groups were reduced, indicating patients are sensitive to I2S treatment in general.

Figure 11.4-11 Mean Normalized Urine GAG Levels ($\mu\text{g GAG}/\text{mg creatinine}$) by Visit and Treatment Group: ITT Patient Population



In four out of six anti-I2S IgG ELISA positive patient's urine GAG levels rebounded after initial decrease (see the following figure). Among them three have neutralizing activity in the activity based neutralization assay. This suggests that significant levels of antibodies or antibodies that neutralize may diminish product efficacy.

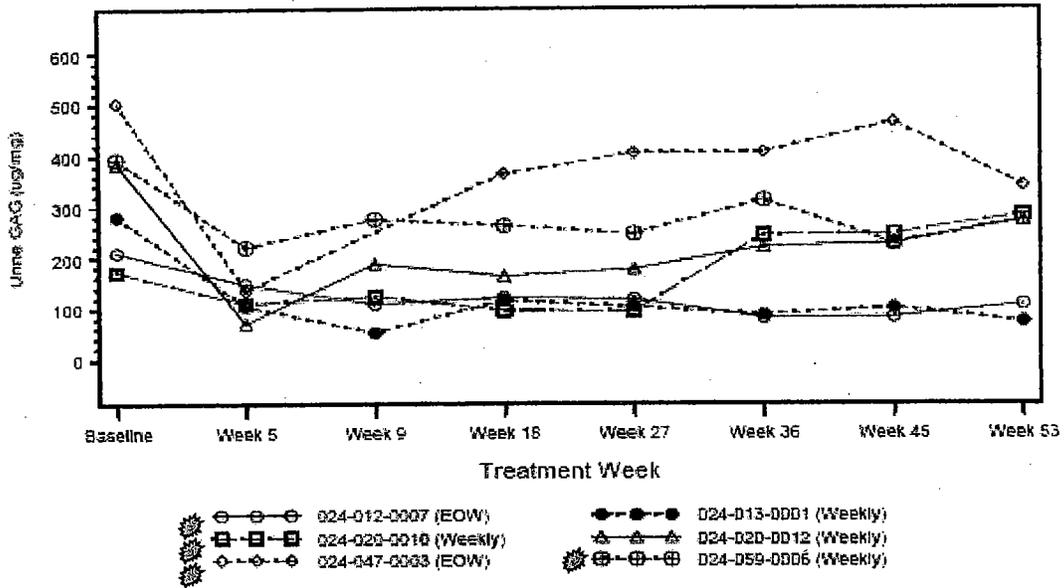
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Rebound of urine GAG levels in antibody positive patients

Transkaryotic Therapies, Inc.
Protocol No. TKT024

Page 1 of 1

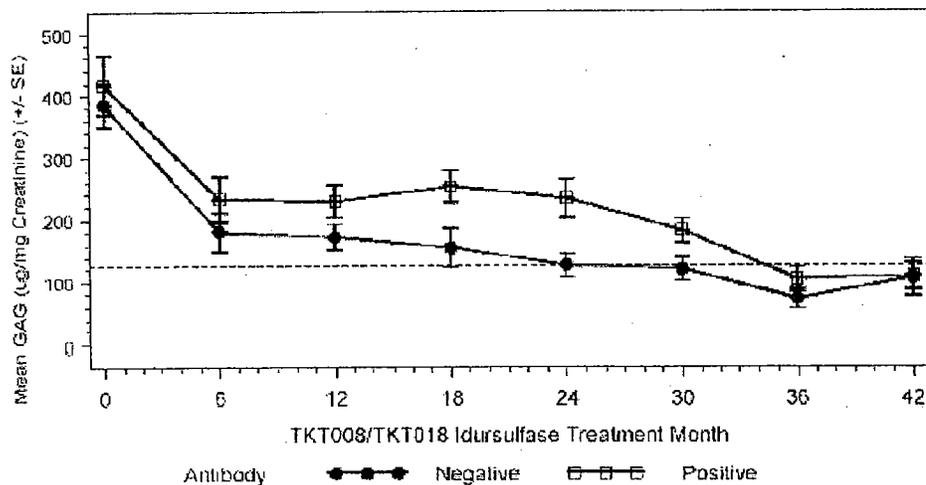
Figure 14.2.1.33
Normalized Urine GAG Levels (ug/mg) by Visit per Patient
IgG Positive Patients
ITT Patient Population



Enzymatic Neutralization antibody positive

As shown in Figure 2.7.2-18 (below), after prolonged treatment (up to 36 months) urine GAG levels fell below the upper limit of normal range in anti-I2S antibody ELISA positive patients of phase I/II study, indicating tolerance might be induced that could due to the disappearance of antibody in these patients (No patients tested positive for IgG at the Week 155 time point for phase I/II trial as shown in Table 2.7.2-11). Patients in the phase II/III studies should be monitored for extended time period in order to observe whether tolerance will also be induced in this patient population.

Figure 2.7.2-18 Mean Normalized Urine GAG Levels from the First Idursulfase Exposure, by Antibody Status and Month: Studies TKT008/TKT018



Note: The dashed horizontal line represents the upper limit of the normal range

Table 2.7.2-11 TKT018 IgG Antibody Status by Patient and Study Week

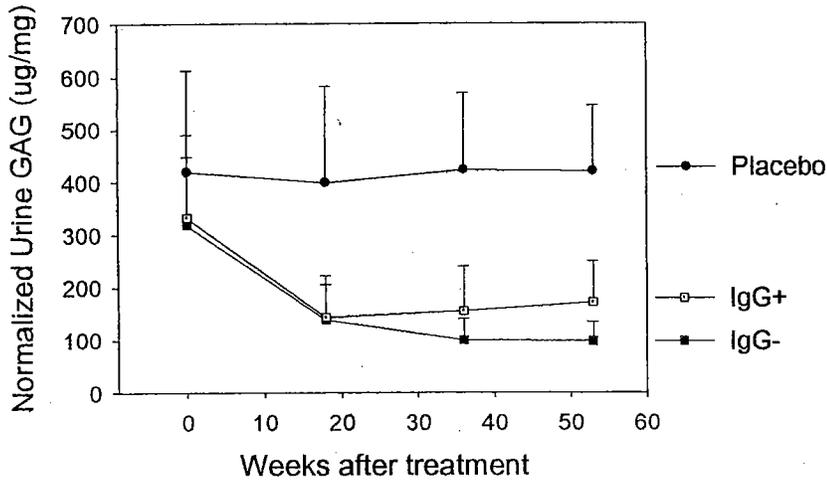
Patient ID ^a	Study Weeks 5 to 47															
	5	9	11	13	15	17	19	21	23	25	29	31	33	39	43	47
013-0005	20	*	*	1280	*	640	*	640	320	80	*	*	*	20	20	20
013-0006	*	40	*	40	*	40	*	40	*	40	*	40	*	40	40	40
013-0007	N	*	*	80	80	80	*	*	*	160	*	*	80	40	40	40
013-0010	1280	*	*	640	*	*	160	*	80	80	80	*	80	40	*	*
013-0012	80	*	80	*	80	80	*	80	*	80	N	*	N	N	*	*
Patient ID ^a	Study Weeks 51 to 155															
	51	55	57	59	63	67	69	71	73	77	81	85	101	103	129	155
013-0005	20	*	*	20	20	*	20	20	*	20	*	*	*	20	N	N
013-0006	40	*	40	*	40	80	*	80	*	80	80	*	*	20	N	N
013-0007	80	*	*	*	80	80	*	40	*	160	20	40	40	*	40	N
013-0010	80	80	*	40	N	*	N	*	40	80	*	*	*	20	N	N
013-0012	n	*	*	N	N	*	*	N	*	N	*	*	*	N	N	N

Note: Numbers indicate antibody titer; N indicates antibody negative; * indicates not tested; patient samples not evaluated for neutralizing antibodies
^a Patients 013-0001, 013-0002, 013-0003, 013-0004, 013-0008, 013-0009, and 013-0011 tested negative by ELISA or were confirmed negative by RIP for antibodies at all time points evaluated in this study

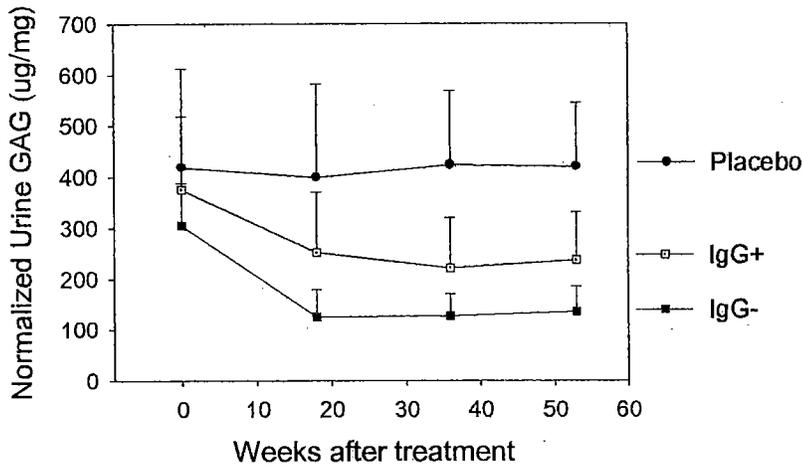
When patients were grouped according to CSA antibody status, a delayed clearance of urine GAG was also observed in TKT024, especially in EOW treatment group.

As shown below, the placebo group started with higher urine GAG. IgG + group includes all patients that were positive by CSA and RIP at any time. The mean urine GAG levels were below the normal upper limit at week 36 and 53 in IgG negative patients, but above the limit in IgG positive patients.

Effects of antibody status on urine GAG of Weekly Group



Effects of antibody status on urine GAG of EOW Group

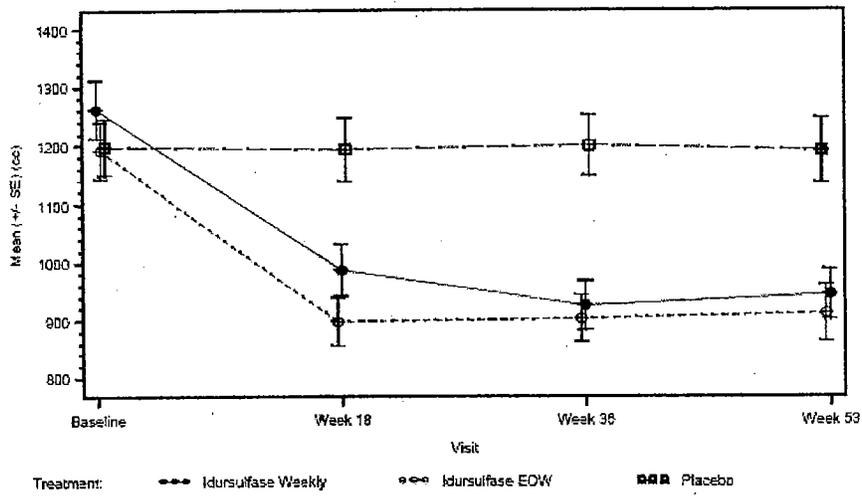


Summary: A moderate rebound of urinary GAG was seen in antibody positive patients in weekly group and a slow clearance was seen in antibody positive patients in EOW group, suggesting that antibody may affect product activity.

4. Relationship of antibody status to Mean liver volume.

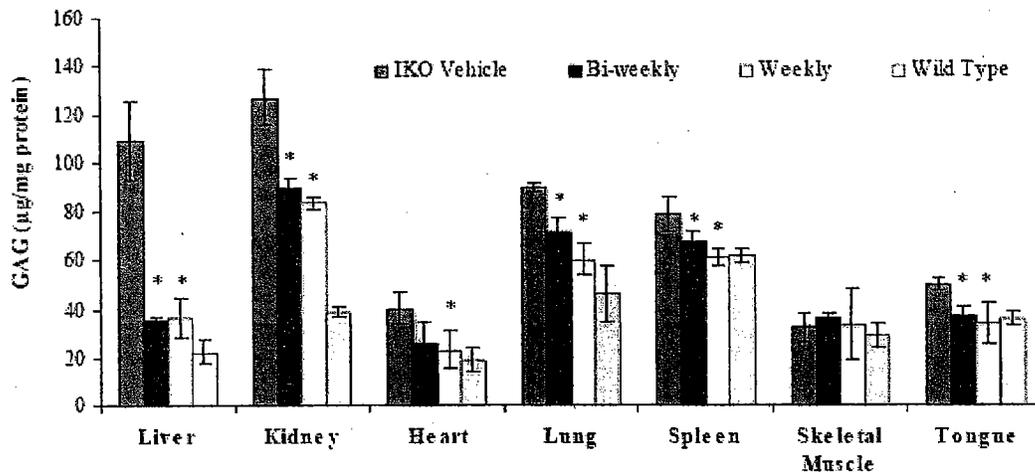
Liver volume was very sensitive to both weekly and every other week treatments and it correlates very well with the facts that I2S has high uptake in liver due to the known high levels of M6PR on human hepatocytes.

Figure 11.4-7 Mean Liver Volume (cc) by Visit and Treatment Group: ITT Patient Population

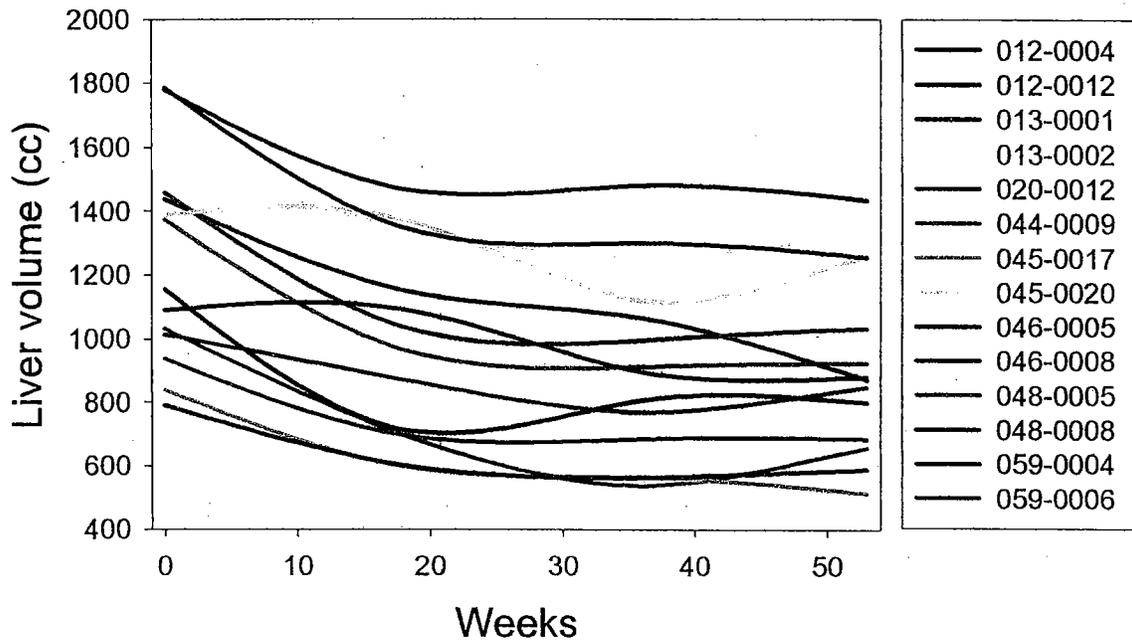


Mean liver volume also correlated very well with GAG reduction in IKO mice treated with product.

Figure 7A: TKX 29: Tissue Extract GAG reduction in IKO Mice Treated Weekly (1.0 mg/kg) or Biweekly for 24 Weeks. Absolute GAG Concentrations (error bars: ± 1 SD)



Liver volume (cc) in antibody positive patients of TKT024 weekly group



Data from the above fourteen patients indicate IgG+ patients were sensitive to treatment in general with exception of slight rebound in three patients. Data of patient 024-020-0010 (IgG positive, with a decreased from week 36 to week 53 in 6MWT) were missing.

5. Relationship of Hunter Syndrome and anti-I2S antibodies to incidence of infections

Infection occurred in 78% patients. It is unclear why infection occurred in most patients. I2S treatment did not reduce the infection rate (84% and 75% in weekly and every other week treatment group, respectively). There were more infections in antibody positive patients in TKT024. I2S reduced spleen volume by more than 20% in 24/32 patients (including 12 antibody positive patients) in the TKT024 weekly group, indicating that I2S can enter spleen cells, although the relationship of after treatment spleen sizes to normal age-adjusted spleen size is unclear. Spleen GAG was increased around 30% in I2S knockout mice and significantly reduced by I2S treatment, indicating that cells in murine spleen expressed I2S receptors. I2S-radiolabel was detected in lymph node (0.03%) and thymus (0.05%) in a tissue distribution study in the rat, but no data of peripheral leukocytes were reported. The therapeutic effect of I2S is dependent on expression of M6PR on target cells and on the M6P ligand on carbohydrates of I2S. M6PR was detected on human monocytes (Rom WN. 1991. Human mononuclear phagocytes express the insulin-like growth factor-II/mannose-6-phosphate receptor. *Am J Respir Cell Mol Biol*. Ohnuma et al. 2001). However, human resting peripheral T cells do not express M6PR (Ikushima et al. 2000). There is no report regarding whether GAG is increased in human T lymphocytes

of Hunter's patients despite early reports show that Hunter patients had 1-2% normal iduronate sulfatase activity in lymphocytes (Liebaers 1976). It may help in identification of factors that cause the high rate of infections if it can be determined whether lymphocytes in Hunter patients have normal function or whether I2S can be effectively endocytosed by lymphocytes. Regarding B cell and DC, EBV-transformed human lymphoblasts express M6PR (Lu, et al. PNAS 1996), whereas it is unclear whether normal human B cells and dendritic cells also express M6PR. Hunter PBLs have effectively been transduced by I2S viral vectors and believed to take up I2S secreted into medium (Pan, et al. Human Gene Therapy 1999).

The following table presents the rate and site of infections in TKT024.

System Organ Class/ Preferred Term	Idursulfase Weekly		Idursulfase EON		Placebo	
	Patients (N=32)	Events (N=1063)	Patients (N=32)	Events (N=1163)	Patients (N=32)	Events (N=992)
	n (%)	n (%)				
ANY SYSTEM ORGAN CLASS	32 (100.0)	1063 (100.00)	32 (100.0)	1163 (100.00)	32 (100.0)	992 (100.00)
INFECTIONS AND INFESTATIONS	27 (84.4)	96 (9.03)	24 (75.0)	113 (9.72)	25 (78.1)	36 (6.87)
UPPER RESPIRATORY TRACT INFECTION NOS	12 (37.5)	26 (2.45)	12 (37.5)	34 (2.92)	10 (31.3)	19 (1.92)
EAR INFECTION NOS	6 (18.8)	15 (1.41)	9 (28.1)	17 (1.46)	9 (28.1)	19 (1.92)
OTITIS MEDIA NOS	6 (18.8)	3 (0.28)	7 (21.9)	11 (0.95)	7 (21.9)	9 (0.91)
OTITIS MEDIA SEROUS NOS	4 (12.5)	8 (0.75)	3 (9.4)	3 (0.69)	4 (12.5)	6 (0.60)
SINUSITIS NOS	5 (15.6)	5 (0.47)	2 (6.3)	5 (0.43)	3 (9.4)	4 (0.40)
TONSILLITIS	2 (6.3)	2 (0.19)	3 (9.4)	3 (0.26)	1 (3.1)	1 (0.10)
HORDOOLIM	0	0	2 (6.3)	2 (0.17)	3 (9.4)	3 (0.30)
TRACHEOSBRONCHITIS	1 (3.1)	1 (0.09)	1 (3.1)	1 (0.09)	3 (9.4)	4 (0.40)
FURUNCLE	1 (3.1)	1 (0.09)	2 (6.3)	3 (0.26)	1 (3.1)	1 (0.10)
INFLUENZA	2 (6.3)	2 (0.19)	1 (3.1)	1 (0.09)	1 (3.1)	2 (0.20)
LEICE INFESTATION	2 (6.3)	2 (0.19)	0	0	2 (6.3)	2 (0.20)
RESPIRATORY TRACT INFECTION NOS	1 (3.1)	1 (0.09)	2 (6.3)	2 (0.17)	1 (3.1)	1 (0.10)
VIRAL INFECTION NOS	1 (3.1)	1 (0.09)	1 (3.1)	1 (0.09)	2 (6.3)	2 (0.20)
HERPES SIMPLEX	2 (6.3)	2 (0.19)	1 (3.1)	4 (0.34)	0	0
LOCALISED INFECTION	0	0	3 (9.4)	4 (0.34)	0	0
LOWER RESPIRATORY TRACT INFECTION NOS	0	0	2 (6.3)	2 (0.17)	1 (3.1)	1 (0.10)

6. Relationship of antibody status to tissue distribution

No comparative data of tissue distribution in the presence and absence of antibody were reported.

7. Relationship of antibody status to mortality

The below listed four patients died during phase I/II and phase II/III study

Patient number	Treatment	Cause of death	Antibody status
• 024-059-0002	I2S	Respiratory F.	Ab negative by ELISA and CSA
• 024-012-0008	I2S	Cardiac F.	Only reported baseline
• 024-020-0003	Placebo	Pneumonia	Not treated by I2S
• 018-013-0006*	I2S	Respiratory F.	Ab positive by ELISA

* 24-year-old, Enrolled 2001. Tracheostomy eight years ago. July 2005, severe airway obstruction by bronchoscopy.

— , 4 days after most recent dose, dyspnea, treated in ICU on full ventilatory support.

Ventilatory support was removed because of patient's living will, decision of family and physicians. Patient 018-013-0006 died of respiratory failure.

It is clear that IgG antibodies did not play any role in the death of patient 024-059-0002 and 024-020-0003. However, it is unclear whether patient 024-012-0008 became IgG positive at the time of cardiac failure or death. For patient 018-013-0006 with pre-existing lung disease (severe airway obstruction on multiple levels), it is a question as to whether IgG antibody played a role in accelerating disease progression.

8. Relationship of antibody status to adverse events

Adverse Events

TKT024	Placebo	Weekly	EOW
AEs:	992	1063	1163
IARs:	128/21/32	202/22/32	145/22/32
SAEs:	18/9/32	13/9/32	18/8/32

“128/21/32” means there were 128 IARs in 21 patients out of a group with 32 patients.

Common AEs were headache, pruritus, pyrexia, hypertension, and rash.

Common IARs were headache, flushing, erythema, urticaria, rash, pyrexia, vomiting and tachycardia.

Treatment emergent adverse events in CSA antibody positive patients in comparison with that in negative patients (TKT024)

System affected	Positive		Negative	
	Patients (N=29)	Events (N=1067)	Patients (N=35)	Events (N=1159)
Infections	25	130	26	79
Upper R. track	16	43	8	17
NS	21	113	28	219
Headache	14	88	26	162
Cardiac	10	23	8	11
Vascular	15	36	17	33
Respiratory	28	194	32	149
Cough, nasal congestion, pharyngitis, rhinorrhoea		113		87
Pulmonary embolism	1	1	0	0
Respiratory F.	0	0	1	1
GI	25	102	25	194
Skin	22	120	20	70
Musculoskeletal	18	73	23	127
Renal	2	2	4	8

There were more cardiac, respiratory, skin and infectious adverse events in antibody positive patients. *Among cardiac disorders in TKT024, arrhythmia, atrioventricular block first degree, bundle branch block right, atrial tachycardia, and supraventricular tachycardia, were only found in antibody positive patients.*

For treatment emergent adverse events of O24EXT please refer to Appendix Table 1.

Treatment Emergent Adverse Events of TKT024 weekly and TKT024EXT placebo of RIP confirmed IgG positive and IgG negative patients

Disorders	IgG positive		IgG negative	
	Patients	Events	Patients	Events
	30	768	32	797
Cardiac&Vascular	16	50	12	19
Respiratory	28	121	31	118
Skin	29	129	21	79
O ₂ saturation decreased	1	1	0	0
Arterial pressure ↑	1	1	0	0

There were more cardiac and skin adverse events in 024 weekly and O24EXT placebo.

9. Relationship of antibody status to infusion related events.

There are more infusion related adverse events in antibody positive patients in TKT024 (Appendix Table 2). Skin disorders and pyrexia contribute significantly to the difference, but there are also more hypertensive, hypotensive, and dyspneic episodes in antibody positive patients. There is one each of embolism, arrhythmia, and anemia in antibody positive patients. No renal problems were reported in antibody positive patients. There were more respiratory and cardiac (mainly tachycardia) events in antibody positive patients in 024ext (Appendix Table 3).

Infusion Associated Adverse Events of TKT024 Weekly and TKT024EXT placebo groups according to RIP status

	RIP positive		RIP negative	
	Patients (N=32)	Events (N=241)	Patients (N=31)	Events (N=104)
Total	25	241	18	104
Respiratory disorders	6	19	5	7
Dyspnoea	2	7	0	0
Bronchospasm	1	1	0	0
Throat tightness	1	1	0	0
Wheezing	2	3	1	1

Cardiac disorders	4	14	1	1
Arrhythmia	1	1	0	0
Cyanosis	1	1	0	0
Tachycardia	2	12	0	0
Vascular Disorders	10	32	5	15
Hypertension	4	15	2	4
Hypotension	2	3	0	0
Flushing	4	14	3	11
Skin disorders	16	77	3	21

Weekly treatment is the regimen for approval. TKT024 weekly and TKT024EXT placebo represent the weekly treatment.

CONCLUSION: *From the above table it is clear that infusion related adverse events were more than doubled in antibody positive patients. Specifically there were more cardiac, respiratory and skin disorders in antibody positive patients. Severe events, such as arrhythmia, bronchospasm, throat tightness, hypotension, were only found in antibody positive patients.*

10. Infusional associated reactions and hypersensitivity

IgE was negative in all patients, although this study is not informative as the ELISA assay for IgE has not been validated yet for critical assay characteristics that bear on detection of positives.

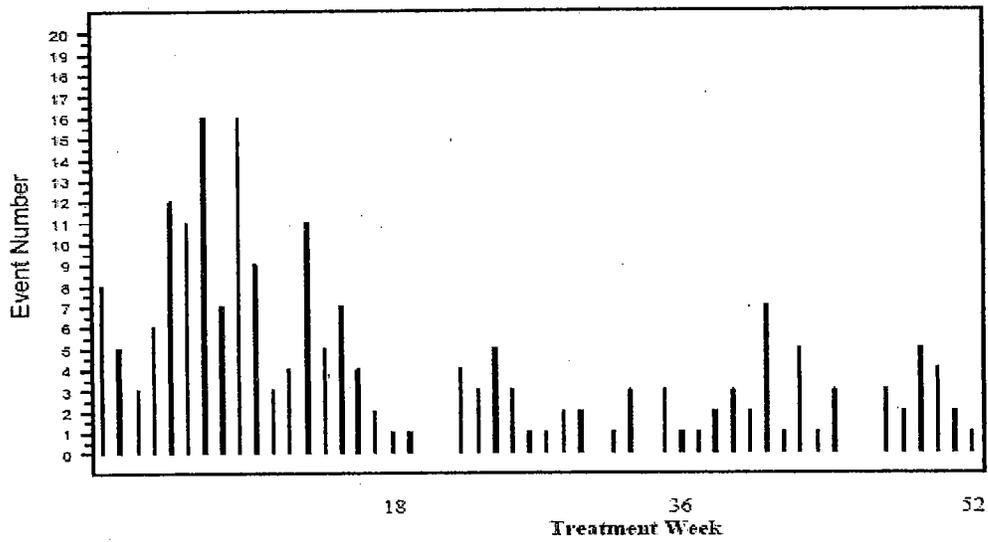
There were more infusion reactions in weekly (202 events/22 patients), EOW (145 events/22 patients) than in placebo (128 events/ 21 patients). As shown in the following Figures, on an events/week basis, more infusion reactions occurred in the first 18 weeks than other weeks.

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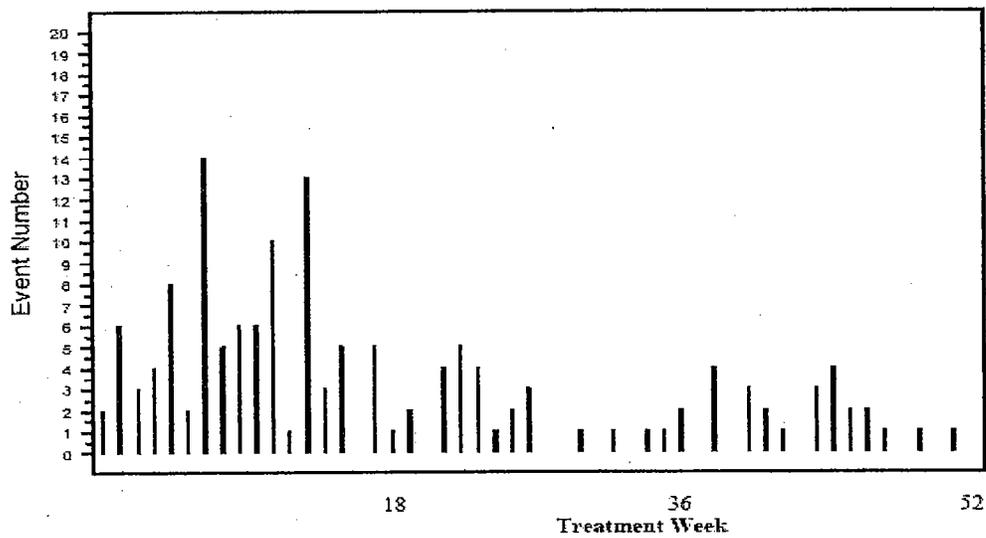
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Figure 2.7.4-3 Number of Infusion-related Adverse Events Per Week 1 Treatment Group and Treatment Week in TKT024

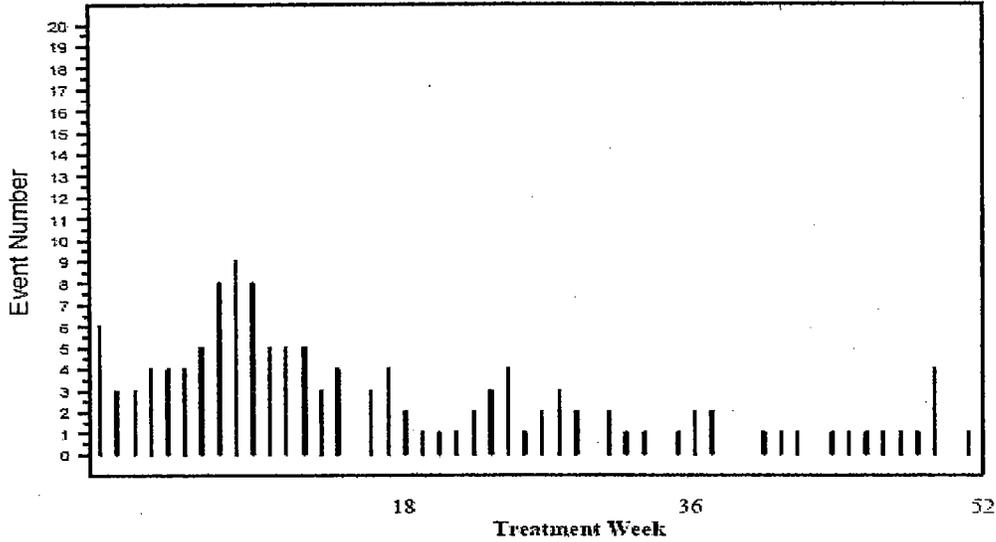
A. Idursulfase Weekly



B. Idursulfase Every Other Week



C. Placebo



Anaphylactoid reactions were defined as IgE negative responses involving at least two organ systems (skin, cardiac, or respiratory). *In TKT024EXT, a high percentage (29%, 5/17) of antibody positive patients had anaphylactoid reactions, but none were observed (0/15) in IgG negative patients.* The sponsor has different criteria for hypersensitivity reactions. According to reported data from sponsor, 24 patients had allergic reactions in TKT024 weekly and TKT024EXT placebo, that is 38% (24/63). The reported allergic reactions in IgG positive patients in the above two groups are 56% (18/32). It is 19% in IgG negative patients.

Hypersensitivity reactions and IgG antibody status of patients in TKT024EXT placebo

Placebo	Infusion	IgG+ weeks	Reported allergic reactions	Symptoms
024-012-0001				
024-012-0009		18		
024-012-0011		18		
024-012-0017	IAR		Allergic R Wk7 EXT	Abdominal pain
024-012-0018				
024-012-0025				
024-013-0003	IAR			pain
024-013-0004	IAR			Headache, hypotension
024-013-0008	IAR		Allergic R wk10 in 024	Abdominal pain

024-013-0010	IAR	9,18,27	Allergic R Wk6 EXT	Urticaria
024-013-0012	Anaphylactoid	6,9	Allergic R Wk6 EXT	Urticaria, oxygen saturation ↓
024-020-0003		NA		
024-020-0005	Anaphylactoid	9	Allergic R Wk8,10 EXT	Brochospasm, facial erythema, vomiting, pain
024-020-0019				
024-020-0020	IAR	9,18	Allergic R Wk5,6,7 EXT	Urticaria, tremor
024-020-0023	IAR	9,18	Allergic R Wk6 EXT	Erythema
024-020-0025	IAR	5,9,18	Allergic R Wk15,16 EXT	Fever, chills, vomiting
024-020-0031	IAR			Fever, headache, nausea
024-044-0001	Anaphylactoid	2,4,5,9,18,27	Allergic R Wk2,4 Ext	Breathless, tachycardia, blisters/rash, vomiting, head throbbing, fever
024-044-0005	IAR	9,18,27	Allergic R Wk6 EXT	Red skin, Head throbbing, headache, abdominal pain
024-044-0008	IAR		Allergic R Wk6 EXT	Red, head throbbing, headache, 2 month later multiple body parts pain
024-045-0001	Anaphylactoid	9	Allergic R Wk6 EXT	Tachycardia, rash, dizziness
024-045-0002		9		
024-046-0007	IAR			Itching
024-046-0013	IAR	9,18,27,36	Allergic R Wk15,16 EXT	Hives on face, neck, trunk, chest, abdomen
024-046-0014	IAR	9,18,27		Nasal congestion
024-047-0002		5,9,18		
024-047-0006		5,9,18		
024-047-0011	Anaphylactoid	5,9,18	Allergic R Wk5 024, EXT4	Urticaria, wheeze, pain
024-048-0002				
024-048-0004			Allergic R Wk38 024	
024-059-0003	IAR			Fever
Idursulfase Weekly	IAR	IgG+ weeks		
024-012-0002	0			
024-012-0004	6	27,36	Allergic R Wk 18	
024-012-0006	0			
024-012-0008	0	Baseline only		
024-012-0012	0	18,27,36,45		
024-012-0013	0			
024-012-0019	0			
024-013-0001		18		
024-013-0002		6 9,18,27	Allergic R Wk7	
024-020-0007	1			

024-020-0009	2			
024-020-0010	2	5,9,18,27,36, 45,53	Allergic R wk11,12,13	IgG- 11,12,13
024-020-0011	3			
024-020-0012	29	5,9,13,18,27, 36,40,45,53	Allergic R Wk4, 13, 40	IgG-4
024-020-0013	0			
024-020-0015	0			
024-044-0003	0			
024-044-0007	3		Allergic R Wk55, ext wk3	
024-044-0009	1	9,18,27,36, 45,53		
024-045-0007	8			
024-045-0010	1			
024-045-0017	0	9,18,27		
024-045-0020	11	27,36,45,53	Allergic R Wk7	
024-046-0004	0			
024-046-0005	3	18,27,36,45, 53	Allergic R Wk6,7	
024-046-0008	2	5,9,18,27,36, 45,53		
024-047-0001	0		Allergic R Wk12	
024-048-0005	8	9,18,27,36, 45,53		
024-048-0008	9			
024-059-0004	0	5,9,18,27,36, 45,53		
024-059-0006	25	5,9,18,27,36, 40,45,53	Allergic R Wk40, EXT WK3	
024-059-0009	0			

Regarding anaphylactic/anaphylactoid reactions, the sponsor submitted their new analysis in BLA125151-0-0013 on May 15, 2006. Table 1 (provided by sponsor) listed 11 patients with hypersensitivity reactions. Of note, all patients except 018-013-0002 were positive for IgG antibody. Since TKT018 patients were only screened with the ELISA, and not the CSA, it is not clear whether 018-013-0002 would be positive by CSA assay. Therefore, the incidence of hypersensitivity reactions in antibody positive and negative patients is 19% [10/(47 TKT024/024EXT + 5 TKT008/018)] and 2% [1/(47 +7)], respectively.

Table 1 Overall Summary of Patients Who Experienced Potential Anaphylactic/Anaphylactoid Reactions, by Body System

Patient ID (Study)	System Class		
	Respiratory	Skin	Vascular
018-013-0002 (TKT008/018)	No	Yes	Yes
018-013-0005 (TKT008/018)	Yes	Yes	No
018-013-0006 (TKT008/018)	Yes	Yes	No
018-013-0007 (TKT008/018)	Yes	Yes	No
024-012-0004 (TKT024)	Yes	Yes	No
024-020-0008 (TKT024)	Yes	Yes	No
024-020-0012 (TKT024)	Yes	Yes	No
024-020-0005 (TKT024EXT)	Yes	Yes	No
024-044-0001 (TKT024EXT)	Yes	Yes	No
024-044-0008 (TKT024EXT)	Yes	Yes	No
024-047-0011 (TKT024EXT)	Yes	Yes	No

A patient was considered to have potentially experienced an anaphylactic/anaphylactoid reaction if they had events in at least 2 of 3 body systems (respiratory, skin, or vascular) that occurred relative to a given infusion.

D. Impact of Antibodies on Hunter Syndrome: Cross reactivity on Endogenous I2S

Hunter patients may have more than 1% of normal I2S activity which is very important for maintaining their limited functions. In this trial, less than 10% of normal I2S level is one of the inclusion criteria. Depletion of endogenous I2S may have deleterious effects on patients. Because multiple organs and systems are affected in Hunter patients, depleting the endogenous remaining I2S in any organ or system could impact the patient significantly. However, since I2S is an intracellular, lysosomal enzyme, it is highly unlikely that antibodies can access the normal stores of the enzyme. Even if antibody did enter cells through FcR (monocytes, dendritic cells, endothelial cells of blood vessels, B cells, neutrophils), antibody would be expected to be dissociated and degraded and to lack activity in the environment of the lysosome (MELLMAN 1984).

E. Possible Impact of antibodies on Immune Complex Syndrome

No immune complex syndrome was reported in this BLA. Immune complex mediated AEs may develop in antibody positive patients. There is a report of nephrotic syndrome in one GAA treated Pompe patient during tolerance induction with increased doses of GAA. Therefore, the sponsor should monitor for immune complex syndrome (such as vasculitis and glomerulonephritis) for all antibody positive patients, particularly if dosaging is increased.

That having been said, the relationship of drug induced immune complex with specific immune disorders is unclear. Goodpasture's Syndrome, and Hashimoto's Thyroiditis belong to a family of diseases mediated by cytotoxic antibody. These

antibodies react with specific antigens in the basement membrane of kidney glomeruli and lung alveoli or with thyroid antigens. Although no specific immune complex syndromes were reported for I2S yet, patients with persistent antibody response should be closely monitored

Appendix Table 1

Treatment emergent adverse events in CSA antibody positive patients in comparison with that in negative patients (TKT024EXT)

	CSA positive		CSA negative	
	Patients (N=47)	Events (N=605)	Patients (N=47)	Events (N=700)
Total AEs	44	605	46	700
Infections	27	67	33	75
Renal	0	0	5	10
Muscle	19	42	20	62
Skin	24	75	17	91
Urticaria	5	10	2	17
Pruritus	1	1	4	13
GI	26	55	25	90
Respiratory	31	111	35	85
Bronchospasm	1	1	0	0
Obstructive airways	0	0	1	1
Cardiac	6	18	12	14
Tachycardia	2	14	2	3
Congestive F.	1	1	1	1
Vascular	13	28	8	20
Hypotension	2	2	1	1

Tachycardia was the main cardiac disorders in antibody positive patients in TKT024EXT. Many other types of cardiac disorders were present in antibody negative patients.

Appendix Table 2

Infusion related adverse events in CSA antibody positive patients in comparison with that in negative patients (TKT024)

	CSA positive		CSA negative	
	Patients (N=29)	Events (N=1067)	Patients (N=35)	Events (N=1159)
Total IAEs	24	219	20	128
Skin	13	64	7	26
Urticaria	5	14	3	3
Erythema	2	11	1	1
Respiratory	4	11	5	7
Dyspnoea	1	5	0	0
Embolicism	1	1	0	0
Cardiac	3	4	2	3

Arrhythmia	1	1	0	0
Cyanosis	1	1	0	0
Hypertension	4	15	6	9
Hypotension	3	5	1	1
Anemia	1	1	0	0
Pyrexia	8	41	6	13
Rigors	3	8	1	1
Renal	0	0	1	2
Muscle	3	8	4	7
GI	9	16	7	14

Appendix Table 3

Infusion related adverse events in CSA antibody positive patients in comparison with that in negative patients (TKT024EXT)

	CSA positive		CSA negative	
	Patients (N=47)	Events (N=605)	Patients (N=47)	Events (N=700)
Total IAEs	21	131	20	137
Respiratory	5	11	3	3
Brochospasm	1	1	0	0
Cardiac	2	12	2	2
Tachycardia	2	12	1	1

**APPEARS THIS WAY
ON ORIGINAL**

MEDICAL OFFICER CONSULT

Division Of Pediatric Drug Development HFD 960

SPONSORS: Transkaryotic Therapies, Inc.

NAME: Elaprase (idursulfase)

NUMBER: STN BLA 125151

CLASS: Enzyme Replacement Therapy

MEDICAL OFFICER: Hari Cheryl Sachs, MD, FAAP

REVIEW DATE: April 21, 2006

REVIEW SUMMARY:

Idursulfase is an enzyme replacement therapy developed for the treatment of Hunter's syndrome. The Division of Pediatric Drug Development was asked to comment on the: 1) Quality of life measurements used as exploratory efficacy measures in the trials 2) Changes expected in pulmonary function testing with growth and 3) Proposed pediatric labeling and post-marketing commitments.

The two health-related quality of life measures, Child Health Questionnaire (CHQ) and Health Utilities Index (HUI), and the disease specific measure, Child Health Assessment Questionnaire (CHAQ), are considered to be reliable and valid, as well as internationally accepted measurements. The CHAQ has not been validated specifically for patients with Hunter syndrome. The Hunter Syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS) needs further validation. Therefore, these disease-specific measures will provide supplemental information to the CHQ and HUI.

With regard to the pulmonary function testing, the predicted FVC which is a function of height is unlikely to be meaningful in patients with Hunter's syndrome given the difficulties in obtaining accurate height measurements in these patients. Using arm span to predict lung function in these patients should be considered. In addition, changes in absolute FVC are likely to be more informative in post-pubertal patients, i.e. in patients whose epiphyses have fused. For descriptive purposes only, consideration should be given to analysis of the changes in absolute FVC by pubertal status along with age, height and arm span.

In general, the labeling should be consistent with that of laronidase, indicating that ELAPRASE (idursulfase) is effective for the treatment of Hunter's syndrome and decrease hepatosplenomegaly. The labeling should not imply _____ . Due to the aforementioned difficulties with obtaining accurate height measurements, _____ . At best, the findings with regard to

absolute FVC can be described. The Pediatric Use section should indicate that safety and effectiveness have not been established in children less than 5 years of age. Recommendations for post-marketing commitments should include a phase IV pharmacokinetic, pharmacodynamic and safety trial in children < 5 years old and systemic collection of adverse events and long term outcomes.

SIGNATURES

Reviewer:

Hari Cheryl Sachs, MD, FAAP _____ **Date:** 4/17/2006

Acting Team Leader:

Jean Temeck, MD *JT*

Date: 4/17/2006/4/24/06

Acting Division Director:

Lisa Mathis, M.D. *LLM*

Date: 4/24/06

M E M O R A N D U M

Date received: March 6, 2006
Date assigned: March 8, 2006
Date review completed: April 17, 2006
Due Date requested: April 21, 2006

From: Hari Cheryl Sachs, M.D., Medical Officer
Division of Pediatric Drug Development
Office of Counter Terrorism and Pediatric Drug Development

Through: Jean Temeck, M.D., Acting Team Leader
Lisa Mathis, M.D. Acting Division Director
Division of Pediatric Drug Development
Office of Counter Terrorism and Pediatric Drug Development

To: Brian Harvey, MD
Division Director
Division of Gastroenterology Drug Products

Subject: BLA 125151

Name of Drug: Elaprase (idursulfase)

Sponsor: Transkaryotic Therapies, Inc

Formulation: intravenous

Approved Indications: none

Consult question: The Division of Pediatric Drug Development was asked to comment on the:
1) Quality of life measurements used as exploratory endpoints in the efficacy trials
2) Changes expected in pulmonary function testing with growth
3) Proposed pediatric labeling and post-marketing commitments

Material Reviewed

Brief review of Sponsor's submission- Dec 2, 2005
Brief literature review of the scales used in trials, Hunter's syndrome, spirometry and growth in children
Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children (Posted 11/6/2001)
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Issued 2/2/2006), Posted 2/2/2006)

Background Information:

Idursulfase, a recombinant form of iduronate-2-sulfatase is the first enzyme replacement therapy (ERT) for Hunter syndrome (Mucopolysaccharidosis II, MPS II). This rare (< 1/100,000) X-linked disorder is one of the lysosomal storage diseases. Patients with Hunter's syndrome have a defective or absent iduronate sulfatase which results in the progressive accumulations of glycosaminoglycans, particularly dermatin sulfate and heparan sulfate in lysosomes of all tissues. Multiple organs are affected, including respiratory tract, heart, liver, spleen, bones, joints, and CNS. The clinical phenotype is heterogeneous depending on the organs involved and the age of onset of symptoms. (Neufeld 2001) Two clinical forms are recognized: mild and severe (Young 1983, 1982). Typically, patients develop symptoms in early childhood between ages 2.5 (for the severe form) to 4.5 years (for the mild form). Thus, an early age of onset is generally associated with more severe disease. Mortality occurs on average at age 22 years in the milder forms (Young 1982) and age 12 years in the more severe forms (Young 1983). The disease is rare, but not unheard of, in females (Tuschl 2005). Carrier detection is via molecular genetic techniques and prenatal diagnosis is possible from chorionic villus sampling or amniocentesis (Oski 1999).

Classically, patients with Hunter's syndrome develop slow mentation, coarse facial features, hirsutism, enlarged tongue, restrictive lung disease, hepatosplenomegaly, cardiac disease, skeletal deformities [dysostosis multiplex (distinct abnormal radiographic pattern including misshapen skull, vertebral bodies, ribs, metacarpals, humerus and pelvis), arthrogyriposis of fingers and toes and kyphosis], deafness, skin nodules and short stature. Mortality is usually due to respiratory and/or cardiac failure (Tuschl 2005). Morbidity is experienced from progressive loss of endurance (limiting walking); difficulty with eating/talking due to large tongue; arthrogyriposis (fixed deformities) in hands preventing self-care; and mental retardation from CNS changes and/or hydrocephalus.

Currently, treatment is palliative only. A handful of patients have undergone bone marrow (Takahashi 2001) or stem cell transplantation (Ochiai 2005). However, although these patients may experience normalization of liver and spleen size, improvement in cutaneous findings such as hirsutism and skin thickness and also improvement in joint mobility, the degree of neurocognitive recovery and survival is unclear (Ochiai 2005). The level of accumulated mucopolysaccharidosis in white matter may be normalized when lesions are absent but not if lesions are present (Takahashi 2001). Skeletal dysplasias also may not improve (Haddad 1998). New modalities of treatment such as substrate deprivation or gene therapy are not yet feasible (Schiffman 2002).

Enzyme replacement therapy (ERT) with laronidase has been approved for patients with Hurler and Hurler-Scheie syndrome (MPS 1). These patients have a similar clinical course to Hunter's syndrome; however patients with Hurler's syndrome exhibit more severe skeletal deformities and corneal clouding (Oski 1999). The approval of laronidase was based on improvement in exercise tolerance measured by the six minute walk test (6MWT) and pulmonary function measured by forced vital capacity (FVC). ERT is also approved for Gaucher's disease and Fabry's disease and it is approvable for Pompe's disease.

Summary of submission under evaluation

Transkaryotic Therapies, Inc. submitted the results from two completed placebo-controlled studies, TKT008 and TKT024, and preliminary results from two open label studies: TKT1018 and TKT024 EXT.

TKT008 was a double blind, placebo-controlled dose-escalation trial (0.15, 0.5 and 1.5 mg/kg dose) in 12 patients. The primary endpoint was reduction in urinary glycosaminoglycan (GAG) levels after

every other week 1-hour infusions. Additional endpoints included pulmonary function studies, abdominal and central nervous system MRI (CNS MRI), echocardiography, 6MWT, joint mobility, sleep study, quality of life measures, idursulfase antibody testing, and routine laboratory testing.

Trial TKT024 was an international (Brazil, Germany, United Kingdom and the United States), multi-center efficacy and safety trial. 96 patients with Hunter's syndrome, aged 5 to adulthood, were enrolled. Patients were stratified by disease severity and age. Age stratifications were: ages 5-11 (n=43), 12-18 (n=29), 19-25 (n=19) and ≥ 26 (n=5) years. Disease severity was based on a composite of 6MWT and FVC (See Appendix I). Among the inclusion criteria were the ability to perform pulmonary function testing and the 6MWT. Patients were to have evidence of decreased lung function, defined as $<80\%$ predicted FVC. They received either weekly or every other week infusions of idursulfase, 0.5 mg/kg x 3 hrs. The primary outcome for the trial was based on a composite variable of 6MWT and percent predicted FVC. A clinically significant difference between treatment and placebo was modeled after that detected in the laronidase trials, namely a 38 meter difference in the 6MWT and a 4 percent difference in predicted FVC. Secondary endpoints included joint range of motion, liver and spleen size, urine GAG and cardiac left ventricular mass. Exploratory efficacy endpoints included growth rate in prepubertal patients, radiologic skeletal survey, additional lung function parameters, and quality of life measures. Safety evaluations included vital signs, physical examination, adverse events, EKGs, serum chemistry and laboratory tests, urinalysis and anti-idursulfase antibodies. Efficacy and safety endpoints were collected at baseline (week 0) and at approximately 4 month intervals (weeks 18, 36 and 53). Preliminary review of the efficacy data (per Dr. Joanna Ku) suggests that statistical differences in favor of idursulfase are the improvements

Patients were continued in an open label study, TKT018 or TKT024 EXT. Patients on placebo or idursulfase qow were converted to idursulfase q week.

Safety outcomes were reported on all patients given idursulfase in any of these trials.

Discussion

I. Quality of life and functional outcomes

These trials utilized four surveys: the Child Health Questionnaire (CHQ), Health Utilities Index (HUI) Child Health Assessment Questionnaire (CHAQ) and Hunter Syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS). All measures were administered at baseline, and weeks 18, 36 and 53 by the parent or by both the parent and child for patients > 12 years. No physician ratings were collected.

The HUI and CHQ are generic quality of life measures designed to assess both health status and functional status. A generic measure permits comparisons across illnesses and provides normative reference data. The CHAQ and HS-FOCUS are disease specific measures; developed for arthritis and Hunter's syndrome patients, respectively. Disease-specific measures in general are thought to be more responsive to change than generic measures. The following table summarizes these four scales used to evaluate Hunter's syndrome patients.

Quality of Life and Disease-Specific Measures Used to Evaluate Hunter Patients

List of abbreviations at end of table

Scale	Age Limits	Population Used to Validate	Assesses	Reliability and Validity	Applications	Comments/Limitations
Generic Quality of Life Measures						
CHQ (Landgraf 1996)	5-18 years	391 (US)	<p>Psychosocial functioning</p> <ul style="list-style-type: none"> Mental health Role/Social limitations (Emotional) Role/Social limitations (Behavioral) Behavior Self Esteem <p>Physical functioning</p> <ul style="list-style-type: none"> Physical functioning Role/Social limitations (physical) Bodily pain/discomfort General Health perceptions 	<p>CHQ- CF87 ICC 0.67- 0.89</p> <p>CHQ-CF50 ICC >0.70</p> <p>Test-retest No health change- 0.54-0.73 Health change- 0.118-0.77</p> <p>Construct validity > 0.31</p> <p>Concurrent validity with HUI, PODCI, PEDI and GMFM</p>	<p>Asthma, attention deficit hyperactivity disorder (ADHD), stem cell transplantation, cancer, chemotherapy, congenital heart disease (CHD), connective tissue disorders (dermatomyositis, Juvenile Rheumatoid arthritis (JRA), Systemic Lupus Erythematosus), cystic fibrosis, diabetes, epilepsy, immunodeficiency (HIV), kidney disease, medication (Fentanyl), musculoskeletal disorders (MSKDs, cerebral palsy, spina bifida), sickle cell disease, surgery (tonsillectomy)</p>	<p>Versions:</p> <p>CHQ-PF 50 (parental questionnaire), ages 5-13</p> <p>CHQ- CF87 (child form), ages 10-18</p> <p>CHQ-PF28 (brief parent version)</p> <p>CF-87 designed for 10 years and older but in practice >12</p> <p>Gold standard for rheumatology trials</p> <p>International, translated into 32 languages</p> <p>Moderate ceiling effect (difficulty documenting improvements in higher functioning patients)</p>
HUI (Feeny 1992, Torrance 1995)	6 years-adult	<p>HUI3 256 parents</p> <p>HUI2 194 parents</p> <p>(Ontario Canada)</p>	<p>Functional status</p> <ul style="list-style-type: none"> Vision Hearing Speech Ambulation Dexterity Emotion Cognition Pain <p>Utility function</p>	<p>ICC >0.60-0.99</p> <p>Test-retest- > 0.58 (cancer)</p> <p>Construct validity</p> <p>Concurrent validity with CHQ, GMFCS</p>	<p>Asthma, ADHD, atopic dermatitis, cancer, cochlear implants, cystic fibrosis, hydrocephalus, low birthweight infants, liver transplantation, MSKDs (cerebral palsy, spina bifida, myelomeningocele), meningitis, national health surveys, otitis media, pediatric intensive care</p>	<p>Version</p> <p>HUI3: 972,000 health states</p> <p>HUI2: 24,000 health states</p> <p>International, translated into 14 languages</p> <p>Parents may underestimate degree of impairment</p>
Disease-specific measures						
CHAQ (Singh 1990)	1-19 years	72 JRA patients 22 control	<p>Discomfort</p> <p>Disability in</p> <ul style="list-style-type: none"> Dressing and grooming Arising Eating Walking Hygiene Reach Grip Activities 	<p>Disability index $\alpha = 0.94$</p> <p>Test-retest ICC, $r = 0.94$</p> <p>Preliminary Hunter's (n=12) $\alpha > 0.83$</p> <p>Test-retest: $r > 0.81$</p>	<p>Connective tissue disorders (JRA, dermatomyositis, SLE), MSKDs (myopathy), spina bifida</p>	<p>Gold standard for rheumatology trials</p> <p>International, translated into 32 languages</p> <p>Parent and child scores highly correlated (Spearman 0.84)</p> <p>Difficulty detecting improvements in patients with mild disease</p> <p>Not specifically validated for Hunter's syndrome patients</p>
HS-FOCUS	> 12 years to adult	12 Hunter's syndrome patients	<ul style="list-style-type: none"> Walking/standing Grip/Reach Sleeping Schooling/work Activities Breathing Satisfaction Botheredness Parent satisfaction Parent botheredness 	<p>Preliminary reliability: $\alpha > 0.83$</p> <p>Preliminary test-retest $r > 0.71$</p> <p>Preliminary ICC with functional disability >0.69</p>	<p>Hunter's syndrome (MPS II)</p>	<p>Not validated, designed for this trial</p>

CHQ- Children's Health Questionnaire

CHAQ- Child Health Assessment Questionnaire

GMFCS- Gross Motor Function Classification System

GMFM- Gross Motor Function Measure

HUI- Health Utility Index

HS-FOCUS

ICC- Intraclass Correlation Coefficient

PEDI- Pediatric Evaluation & Disability Inventory

PODCI- Pediatric Outcomes Data Collection Instrument

Children's Health Questionnaire- CHQ-PF50

The CHQ is a generic health-related quality of life (HRQOL) questionnaire regarding physical and psychosocial functioning in children and adolescents. A generic HRQOL questionnaire, as opposed to a disease specific questionnaire, permits comparison between the general population and patients with health conditions. The versions used by the Sponsor (the CHQ-PF50 and CHQ-CF97) contain 50 and 87 questions, respectively. These questions address 14 different aspects of a child's abilities and the affect of a child's illness on physical, mental, school, and social functioning, as well as the impact on family and parents. Scoring for each dimension is based on four- to six-point Likert scales which generate raw scores that are transformed into two summary scores: Psychosocial and Physical Health. Higher summary scores represent better levels of functioning. The maximum score is 100, mean is 50 with a standard deviation of 10. (Landgraf 1998, Sawyer 1999, Raat 2002, Schmidt 2002)

In addition to the versions utilized by the Sponsor, the long (CHQ-PF87) and abbreviated (CHQ-PF28) versions are available (Riley 2004). A version for children 2 months to 5 years of age is undergoing validation studies (Hack 1999, Raat 2002)

The CHQ has been used in assessments of HRQOL in a large number (>10,000) of children and a wide spectrum of clinical disorders. Clinical applications include asthma (Rutishauser 1998), attention deficit disorder (Rentz 2005), cancer (Sawyer 1999, Speechley 1999), connective tissue disorders (JRA, dermatomyositi, Moretti 2005), neonatal intensive care survivors (Hack 1999) and neuromuscular disorders (McCarthy 2002, Vitale 2005).

This scale is widely used internationally and has been translated into 32 languages (Ruperto 2004). The CHQ is considered to be cross-cultural (Brunner 2003) and has been validated in many countries, including those represented by these trials (Landgraf 1998, Lollar 2000, Brunner 2003, Waters 2003) as well as in over 1000 Chinese (Ng 2005) and 5000 Australian children (Waters 2000).

Both parent and child versions possess discriminant and construct validity (Schmidt 2002). According to a recent review on outcomes research in children, substantial research has been conducted on the CHQ's psychometric properties (Lollar 2000). In addition, the CHQ has concurrent validity with the HUI (Speechley 1999, Raat 2002, Sung 2003) in childhood cancer studies and the physical scales of the PEDI, GMFM and PODCI in patients with cerebral palsy (McCarthy 2002, Vitale 2005). Moreover, the different versions of the CHQ have been used to validate disease-specific measures for asthma, cancer, cerebral palsy, school performance and tonsillectomy (Bukstein 2000, Bhatia 2002, Daltroy 1998, Edmunds 2005, Stewart 2001).

Reviewer comment:

Although designed for children > 10 years of age, younger children encounter difficulties completing child's version and some studies, including these ERT trials, use the CHQ only for patients > 12 years of age (Riley 2004). Parents' ratings may not correlate with that of children (Eiser 2004). A literature search detected 137 citations of the CHQ with 16 randomized controlled trials. Although a floor effect is minimal in healthy children (Ng 2005), a ceiling effect has been detected in several trials (Asmussen 2000, McCarthy 2002, Ng 2005, and Vitale 2005). [Ceiling effect is the tendency for healthy patients to cluster at the higher range of scoring while a floor effect is the tendency for disabled patients to cluster at the lower range of scoring. The ceiling and floor effects result in a lower ability to demonstrate improvement for high-or low-functioning patients respectively.] The CHQ is often used concurrently in cancer trials with the HUI. Compared to the HUI, the CHQ is more behaviorally based (Speechley 1999). While the CHQ is considered to be

responsive to change (Rentz 2005), it may not necessarily be responsive to changes in physiologic function (Ginsberg 2004) or acute changes (Gorelick 2003). In trials of patients with arthritis, the CHQ was more responsive to change than the CHAQ (Moretti 2005). While the CHQ is capable of detecting the wide range of physical abilities of patients with cerebral palsy (Vitale 2005), the PEDI appears to be more reliable than the CHQ for patients with cerebral palsy (McCarthy 2002).

Health Utilities Index Mark 2 and 3 (HUI2/3)

The Health Utilities Index systems are generic HRQOL questionnaire regarding capabilities of children and adolescents, ages 6 years to adulthood. The HUI classification systems are linked to specific functional domains which provide both single-attribute and global utility scores. The single-attribute scores range from highly impaired (0) to normal (1), while the global score is anchored by perfect health (1.00) and death (0.00) (Speechley 1999, Barr 1999).

The Health Utilities Mark 2 and 3 (HUI2/3) were used in the clinical trials for idursulfatase. The HUI3 assesses eight dimensions of functional status: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain; while the HUI2 examines seven dimensions: sensation (vision, hearing, and speech), mobility, emotion, cognition, self-care, pain and fertility. Each dimension is ranked on a score from 1 (severely impaired) to 5 or 6 (normal). The rankings are converted to utility scores (Kennes 2002). The dimensions of the two Marks differ in terms of components and constructs. The HUI2 includes self-care and fertility while the HUI3 includes dexterity. Emotion in the HUI 2 is linked to worry and anxiety while the HUI3 is linked to happiness. Pain in the HUI2 includes pain medications required while the HUI3 rates pain via disruption in normal activities. The ability to walk determines the HUI mobility status, while the ability to walk, bend and lift is part of the HUI2 mobility status (Speechley 1999).

The HUI has been used to assess health related quality of life in national (Canadian) health surveys (Speechley 1999) as well as in children with arthritis (Brunner 2003), cancer (Speechley 1999), cerebral palsy (Kennes 2002), cochlear implants (Bichey 2002), otitis media (Kubba 2004), pediatric intensive care (Janse 2005) and preterm birth (Hille 2005).

According to the developer's web site (www.healthutilities.com), the HUI system has been used in greater than 20 countries and in over 200, 000 patients and has been translated into 14 languages. The literature confirms that the HUI has been translated into multiple languages and validated in the countries participating in the trial (Barr 1999, Felder-Puig 2000, Janse 2005, Shimoda 2005).

The Health Utilities Index has concurrent validity with many features of the CHQ (Speechley 1999, Raat 2002) and the Gross Motor Function Classification System (GMFCS, Kennes 2002). In children with medulloblastoma, IQ and cognition scores on the HUI are significantly correlated (Mulhern 1999). Motor function on the GMFCS and mobility scores on the HUI are also correlated (Kennes 2002). In contrast, pain scores do not correlate with the Visual Analogue Scale of Pain (Sung 2003). This measure has been used to validate disease specific measures for chronic illness and hydrocephalus (Detmar 2005, Kulkarni 2004).

Reviewer comment: Literature search for applications of the HUI to children yielded 66 citations with multiple validation studies in several languages and six randomized controlled clinical trials. The Health Utilities index compliments other generic measures such as the CHQ because it examines capability in contrast to performance, which may be influenced by environment and preferences (Speechley 1999). Substantial differences in perceptions for emotion and pain between parent and physicians have been reported (Janse 2005). Since parents underestimated the degree of impairment in a heterogeneous group of children with musculoskeletal disorder (Brunner 2003, blinded physician

ratings may be informative. The HUI was highly reliable but not responsive to acute change in asthmatic patients (Juniper 1997).

Child Health Assessment Questionnaire (CHAQ)

The Child Health Assessment Questionnaire is a disease specific measure for arthritis (Duffy 1997) with two components: discomfort and disability index. The discomfort index is based on a visual analogue scale ranging from pain to no pain. The disability index examines function in activities of daily living and consists of 30 items. Each item is rated based on the difficulty in performing, use of aids, or assistance required which is translated into a 4 point scale (0-3) related to: no difficulty (0), some (1), much difficulty (2), unable (3) or does not apply. Thus, lower scores represent a higher degree of functioning.

In children with arthritis and other connective tissue disorders, the CHAQ is considered to have reliability and validity (Duffy 1997, Brunner 2003), good discriminative value (Duffy 1997, Garcia 2000, Brunner 2003), and responsiveness to change (Brunner 2003). This measure has been used internationally and is translated into 32 languages (Brunner 2003, Ruperto 2004), including those used in these ERT trials (Garcia 2000, Muller-Godeffroy 2005, Brunner 2003). The CHAQ has been used primarily in connective tissue disorders. However, the effect of several myopathies, spina bifida and other neuromuscular disorders has been evaluated by this measure (Brunner 2003, Huber 2001, Alman 1996).

Reviewer comment: Literature search for CHAQ and children revealed 90 citations, numerous validation studies in multiple languages and identified six randomized controlled clinical trials. The CHAQ is considered to be a validated quality of life instrument by international research networks in rheumatology (Brunner 2003, Ruperto 2004). This measure tends to have a floor effect (Brunner 2003) [Floor effect is a tendency for a large proportion of patients to cluster at the lower end of the scale; consequently improvements in mildly affected patients are difficult to measure.] Depending on the patient population, the CHAQ may be variably responsive to change. For patients requiring intraarticular corticosteroid injections, the CHAQ was responsive to change at 6 weeks and 6 months after treatment (Brown 2005). In contrast, in patients with arthritis with low scores, the CHAQ has been less responsive to change than the CHQ (Moretti 2005).

This measure has not been validated specifically for patients with Hunter's syndrome. The Sponsor submitted an abstract which was presented at a May 2004 International Society for Pharmacoeconomics and Outcomes Research Conference (ISPOR) and suggests good reliability and reproducibility in a pilot study of 12 MPS II patients. However, the authors state further assessment is warranted. Thus, results from the CHAQ will most likely compliment the results from the CHQ and HUI.

Hunter Syndrome Functional Outcome in Clinical Understanding Scale (HS-FOCUS)

The HS-FOCUS is a disease specific measure developed by Abt Associates in Cambridge Massachusetts. The HS FOCUS contains items assessing six functional domains (walking/standing, grip/reach, sleeping, schooling/work, activities and breathing) along with patient and parental satisfaction and inconvenience ("botheredness") scores. Each domain is assessed by several tasks. Performance of each task is rated by the parent or child as without ANY difficulty, with SOME difficulty, with MUCH difficulty, VARIES: may or may not be able to do, UNABLE to do or not applicable.

Reviewer comment: A literature search for this outcome measure did not yield any citations. The Sponsor submitted 3 abstracts which were presented at a May 2004 ISPOR Conference), which preliminarily suggest good reliability and reproducibility. However, the authors conclude that the measure needs further assessment. Therefore, the results from the HS-FOCUS will be complimentary to the CHQ and HUI. The Sponsor can be referred to a guidance entitled: "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Issued 2/2/2006), Posted 2/2/2006)."

Conclusion:

The two HRQOL measures (CHQ and HUI) and the disease specific measure (CHAQ) are considered to be reliable and valid, as well as internationally accepted measurements. The CHAQ has not been validated specifically for patients with Hunter syndrome. The HS-FOCUS has not been validated and needs further validation. The ability for each measure to detect a response to change varies with the severity of disease. Consequently, the results from the CHQ and HUI are likely to be complimented by the findings from the CHAQ and HS-FOCUS.

II. Growth and Pulmonary function testing

A. Growth

In order to ensure accuracy of the height measurements in children, height should be measured via calibrated stadiometer with repeated measurements at each time point [(see Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children (Posted 11/6/2001)]. The growth rate in prepubertal patients is 4-6 cm/year (McMillan 1999). Typically growth velocity is greatest during the adolescent growth spurt (Lebowitz 1995). Weight gain is more variable and ranges from 2-5 kg/year depending on nutritional status and activity. Head growth typically levels off after age 3 years (McMillan 1999).

Texts describe that patients with Hunter's syndrome experience joint contracture and short bones resulting in short stature (McMillan 1999, Neufeld 2001). The literature is relatively scanty with regards to growth in Hunter's syndrome yielding two reports of large case series that describe growth in the mild (n=32) and severe (n=52) forms of the disease (Young 1982, 1983). In contrast to the normal growth pattern, patients with Hunter's syndrome exhibit a marked decline in linear growth by 4-6 years of age. Historically, by age 12 years, most patients' heights are below the third percentile for height (Young 1982, 1983). Macrocephaly (head circumference > 97 %) is evident in most patients with the severe form of Hunter's syndrome by age 2 years and may decline after age 6-7 years. In the milder form, patients head sizes are more variable and cluster above the 50th percentile for age. Most head sizes in patients reaching adulthood are > 95th percentile.

Heights were obtained via stadiometer or similar calibrated instrument; measurements were performed in triplicate.

Weight measurements were performed on a balance beam or digital scale. Calibrations were performed weekly. Head circumferences were measured in duplicate at each visit using a flexible tape measure.

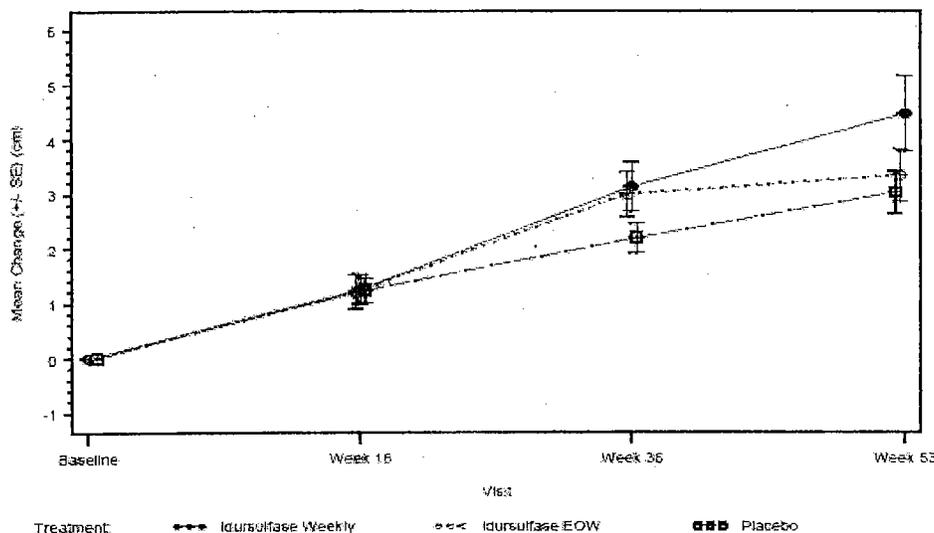
The changes in growth parameters are reported in the following table:

Table 2.7.3-21 Change from Baseline to Week 53 in Height, Weight, and Head Circumference in Prepubertal Patients

	Change / Year			
	Placebo	Idursulfase 0.5 mg/kg		
		Weekly	EOW	All Idursulfase
Change in Height (cm)				
n	15	12	12	24
Mean (SE)	3.02 (0.393)	4.49 (0.689)	3.36 (0.486)	3.92 (0.429)
Median	2.93	4.63	3.82	3.92
Min, max	0.9, 5.5	-0.2, 8.1	0.5, 6.2	-0.2, 8.1
Change in Weight (kg)				
n	15	12	12	24
Mean (SE)	2.11 (0.482)	2.76 (0.969)	2.42 (0.414)	2.59 (0.517)
Median	1.70	1.60	2.10	1.90
Min, max	-0.3, 7.5	-3.0, 7.6	0.5, 5.4	-3.0, 7.6
Change in Head Circumference (cm)				
n	15	12	12	24
Mean (SE)	0.62 (0.218)	0.71 (0.199)	0.12 (0.201)	0.41 (0.152)
Median	0.25	0.80	0.18	0.48
Min, max	-0.5, 2.3	-0.5, 2.0	-1.4, 1.3	-1.4, 2.0

EOW=every other week; SE=Standard error; cm=centimeter(s); kg=kilogram(s); min=minimum; max=maximum.
 Completer Population Study TKT024; Data Source: See CSR TKT024, Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, In-text Table 11.4-20

Figure 2.7.3-8 Mean Change in Height for Prepubertal Patients: Completer Population Study TKT024



Data Source: See CSR TKT024, Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, In-text Figure 11.4-15.

Reviewer comment: The Sponsor reported that not all patients were able to stand erect and heights were obtained with some patients standing on their toes. Bone age was not obtained to confirm cessation of growth. Height velocity was not reported for the baseline period. Note, that in the pre-pubertal patients, the standard deviations in each of the treatment groups are large (7.4 to 11.8 cm),

particularly when compared with an expected mean annual change of 4-6 cm/year. The individual height data reveals a decline in height by 2 cm or more in at least 2/15 prepubertal patients in the idursulfase group. Since, heights could not be measured accurately, no conclusions can be drawn from the growth data. Weight was not correlated with nutritional status. Thus, modest changes in weight are difficult to interpret. Since head growth is expected to vary with disease severity, the head circumference data are also difficult to interpret.

B. Changes in lung function

The Sponsor submitted data on predicted FVC and absolute FVCs, along with exploratory variables in FEV1, total lung capacity, functional residual capacity, residual volume and diffusing capacity. A detailed analysis of the findings is beyond the scope of the consult and is addressed in part by the consult from DPAP. The comments below primarily address normal lung growth, changes in pulmonary function tests with growth, and ability to interpret predicted FVC and absolute FVC given the difficulties with accurately measuring height.

Normal pattern of Lung Growth

During puberty, the lungs expand in both diameter and length. The diameter's peak velocity occurs temporally with peak height velocity while peak expansion in length lags 6 months behind peak height velocity. Chest growth is also delayed compared to height and leg growth. Consequently, vital capacity increases up to age 25 years; well after adult height is reached (Lebowitz 1995).

In healthy children, spirometric measurements have been successfully obtained in preschoolers (Nystaad 2002, Kozlowski 2005) and are considered to be reliable in children > age 5 years (Miller 2005). In order to ensure the accuracy of spirometric measurements, the American Thoracic Society recommends obtaining at least 3 measurements with < 5 % variability (Miller 2005).

Growth curves are available for following FVC and FEV1 in children > 3 years (Wang 1993, Nystad 2002, Pelligrino 2005) with predicted values related to height in children over 90 cm (Nystad 2002). In general, spirometric values increase with age and height in healthy children (Nystad 2002, Al-Riyami 2004, Pelligrino 2005). FVC growth is approximately linear with age until after the adolescent growth spurt (Wang 1993). Peak change in FEV1 and FVC usually lags behind the height spurt (Wang 1993, Lebowitz 1995, Pelligrino 2005). Depending on how early the height spurt occurs, the delay can be from 6 months to 1 year, with longer gaps occurring in children with earlier growth spurts (Wang 2003). Therefore, although patterns of growth are similar, individual variations in the time of onset and magnitude of change occur (Wang 1993). Standing height is considered to be the most useful predictor for the lung function (Quanjer 1995, Morton 1976). However, during the pubertal growth spurt the correlation between height and FVC or FEV declines (Schrader 1984).

Spirometry measures airway, lung and chest-wall function (Gauld 2005); all of which may be impacted by MPSII. The upper airway is blocked by macroglossia, gingival hyperplasia, adenoid hypertrophy and thick rhinorrhea (Hukins 2000, Morehead 1993). Lung function may be further compromised by small chest size and impaired mobility of the ribs. Kyphoscoliosis may contribute to chest restriction (Morehead 1993). The degree of reduction in vital capacity may or may not be correlated with the severity of deformity (Muirhead 1985). Hepatosplenomegaly may interfere with diaphragmatic expansion (Morehead 1993).

Predicted FVC

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Since absolute spirometric measurement values change with somatic growth, reference values have been derived from population studies based on age, sex, standing height and arm-span, sitting height and ethnicity (Pfaff 1994). Most commonly, reference values for FVC are related to height and age (Kurzawa 1999, Krause 2003, Li 2005, Pelligino 2005). Predicted FVC can be calculated with corrective factors based on age and height (Hankinson 1998, Subbarao 2004, Pelligino 2005). These predictions are unlikely to be adequate for children outside the height or age of the population in which the equations were developed (Subbarao 2004).

In the trials submitted by TTK, predicted FVC was performed according to American Thoracic Society guidelines (1995) and calculated on published reference values (Hankinson 1999, Polgar 1971), which use height and age in the equations. Based on the results of the laronidase trial in Hurler and Hurler-Scheie patients, a 4 % difference in predicted FVC between control and treated patients was considered to be significant. A significant change in predicted FVC was not observed (per Dr. Joanna Ku). The improvement in FVC appears to be driven by the 12-18 year olds (see Figures below).

Figure 14.2.1.4.1
Mean Change from Baseline in Percent Predicted FVC (%)
by Visit, Treatment Group and Baseline Patient Age Category
ITT Patient Population
5 to 11 years

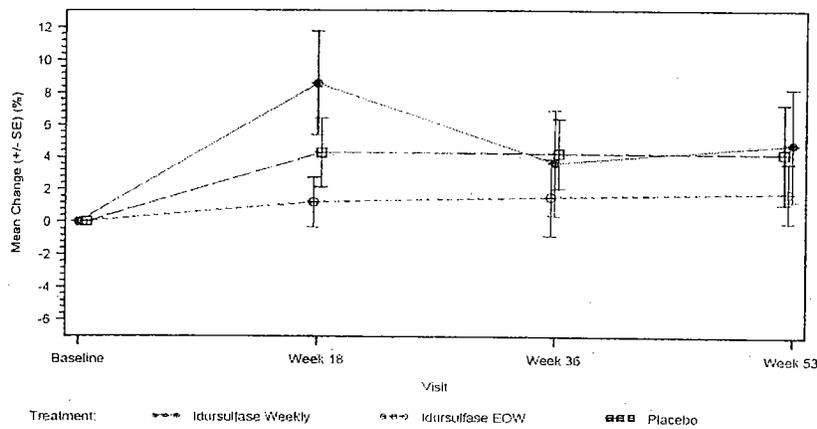


Figure 14.2.1.4.1
Mean Change from Baseline in Percent Predicted FVC (%)
by Visit, Treatment Group and Baseline Patient Age Category
ITT Patient Population
12 to 18 years

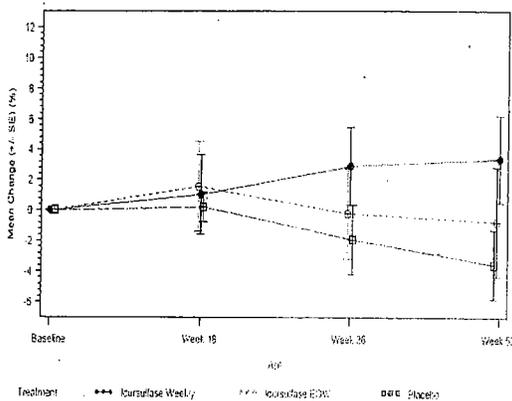
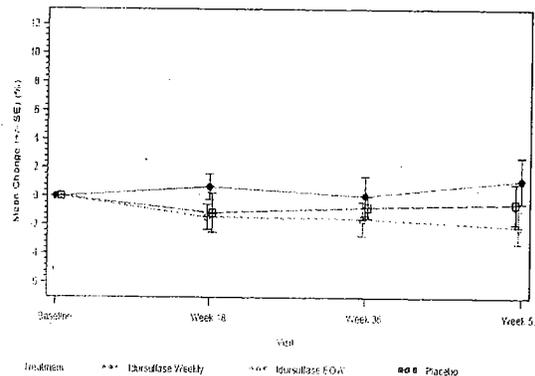


Figure 14.2.1.4.1
Mean Change from Baseline in Percent Predicted FVC (%)
by Visit, Treatment Group and Baseline Patient Age Category
ITT Patient Population
19 to 25 years



Reviewer comment: The improvement in predicted FVC was driven by the subset of patients, aged 12-18 years. Of note, improvement in the 6MWT, the other primary efficacy endpoint in this composite outcome, was driven by two subsets of patients, those aged 5-11 years and those aged 12-18 years.

The pulmonary division was consulted regarding the interpretation of the pulmonary function results and they concluded that other measures than predicted FVC should be used. Since standing height measurements in Hunter's syndrome patients were likely to be unreliable, DPAP also suggested that arm span could be utilized to predict FVC.

Reviewer comment: We agree that abnormalities in growth patterns in patients with Hunter's syndrome complicate interpretation of the predicted FVC data. Given the difficulties in obtaining accurate height measurements, the predicted FVC is unlikely to be meaningful in these patients. Although in normal individuals standing height is considered ideal for predicting lung function, using arm span as a reference to predict lung function in patients with skeletal deformities is recommended in the American Thoracic Society's guidelines (Miller 2005, Pelligrino 2005). Reference values for children have been developed relating arm span to spirometric norms (Morton 1976, Mary 1999). Arm span has been used in assessment of lung function for children with neuromuscular diseases (Mulreany 2003), scoliosis (Muirhead 1985), myelomeningocele (Sherman 1997) and Duchenne Muscular Dystrophy (Phillips 2001).

As noted above, the improvement in FVC appears to be driven by the population that is likely to be the fastest growing, i.e. the patients aged 12-18 years who are entering the pubertal growth spurt. In contrast, predicted FVC did not demonstrate steady improvements in pre-pubertal or adult patients.

The ability to perform pulmonary function testing is affected by intelligence and behavior (Gauld 2005) and effort (Miller 2005) which may explain the variability of the PFTs. In addition, 4-7 % of patients in the trial used medications that are likely to affect pulmonary function (e.g., steroids, bronchodilators).

Absolute FVC

The Sponsor analyzed changes in absolute FVC because, "the formulae for percent predicted FVC assume normal statural growth and the ability to accurately measure height. Neither of these assumptions applies to patients with Hunter syndrome because these patients are growth-impaired and may be unable to stand erect. Therefore, it is uncertain whether percent predicted FVC for a growth-impaired child of a certain age with Hunter syndrome would be the same as that for a normal child, even if the changes in height during therapy could be accurately measured. To assess further the impact of idursulfase therapy on the restrictive component of Hunter-related lung disease, changes in absolute FVC volumes were also calculated."

Absolute FVC significantly increased in treated patients compared with untreated patients (per Dr. Joanna Ku).

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Table 11.4-10 Forced Vital Capacity Absolute Volume Mean Percentage Change From Baseline to Week 53 ANCOVA Analysis: ITT Patient Population

Treatment Comparison	N	Baseline Mean (SE) FVC (L)	% Change to Week 53 in FVC Absolute Volume Mean (SE)		Adjusted 95% CI ^a	p-value ^b
			Observed % Change	Adjusted % Change ^a		
Idursulfase vs Placebo: Primary Comparison						
Idursulfase	32	1.19 (0.10)	16.01 (3.36)	12.37 (3.18)		
Weekly	32	1.09 (0.09)	8.67 (3.23)	1.76 (3.40)		
Placebo						
Difference				10.62 (4.17)	2.26, 18.97	0.0137
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	1.17 (0.01)	8.30 (2.59)	6.60 (2.98)		
Placebo	32	1.09 (0.09)	8.67 (3.23)	4.74 (3.13)		
Difference				1.86 (3.89)	-5.94, 9.66	0.6341
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase	32	1.19 (0.10)	16.01 (3.36)	13.04 (2.89)		
Weekly	32	1.17 (0.10)	8.30 (2.59)	5.75 (2.96)		
Idursulfase EOW						
Difference				7.28 (3.76)	-0.25, 14.82	0.0577
All Idursulfase vs Placebo						
All Idursulfase	64	1.18 (0.07)	12.16 (2.16)	9.48 (2.22)		
Placebo	32	1.09 (0.09)	8.67 (3.23)	3.26 (3.08)		
Difference				6.22 (3.45)	-0.65, 13.08	0.0752

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week.

^a Adjusted means (LS Means), adjusted SEs from the fitted ANCOVA model, the difference in the LS means, and the corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment, baseline patient age (3 levels), and baseline FVC severity score (3 levels).

Data Source: Table 14.2.1.1.8.1.

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Table 14.2.1.1.7.2.2
Summary Statistics for Absolute FVC (L)
Observed Values and Change from Baseline by Baseline FVC Severity, Baseline Patient Age and Region
ITT Patient Population

Baseline Patient Age	Treatment Group	n	Actual Value Mean (SE)				Mean Change from Baseline (SE)		
			Baseline	Week 18	Week 32	Week 53	Week 18	Week 36	Week 53
19 to 25 years	Idursulfase	8	1.06 (0.15)	1.08 (0.15)	1.07 (0.14)	1.11 (0.19)	0.03 (0.03)	0.00 (0.04)	1.05 (1.06)
	Weekly								
	Idursulfase EOW	9	1.81 (0.27)	1.55 (0.25)	1.55 (0.27)	1.84 (0.25)	-0.26 (0.03)	-0.06 (0.04)	-0.06 (0.04)
	Placebo	7	1.73 (0.25)	1.70 (0.26)	1.72 (0.25)	1.73 (0.25)	-0.03 (0.05)	-0.01 (0.02)	-0.01 (0.04)
	All Idursulfase	17	1.35 (0.17)	1.33 (0.16)	1.32 (0.16)	1.34 (0.17)	-0.02 (0.02)	-0.02 (0.02)	-0.04 (0.04)
12 to 18 years	Idursulfase	10	1.57 (0.23)	1.71 (0.31)	1.84 (0.32)	1.91 (0.32)	0.14 (0.10)	0.27 (0.11)	0.34 (0.11)
	Weekly								
	Idursulfase EOW	9	1.09 (0.06)	1.20 (0.08)	1.21 (0.09)	1.23 (0.09)	0.10 (0.05)	0.11 (0.07)	0.14 (0.06)
	Placebo	10	1.06 (0.10)	1.09 (0.09)	1.09 (0.08)	1.09 (0.09)	0.04 (0.02)	0.03 (0.03)	0.03 (0.03)
	All Idursulfase	19	1.34 (0.13)	1.47 (0.17)	1.54 (0.18)	1.55 (0.19)	0.12 (0.06)	0.20 (0.07)	0.24 (0.07)
5 to 11 years	Idursulfase	14	1.00 (0.10)	1.17 (0.13)	1.15 (0.13)	1.22 (0.15)	0.17 (0.06)	0.18 (0.07)	0.22 (0.09)
	Weekly								
	Idursulfase EOW	14	0.94 (0.08)	0.92 (0.09)	1.04 (0.10)	1.06 (0.10)	0.04 (0.03)	0.10 (0.04)	0.12 (0.03)
	Placebo	15	0.81 (0.05)	0.89 (0.07)	0.92 (0.07)	0.93 (0.08)	0.09 (0.03)	0.11 (0.03)	0.12 (0.05)
	All Idursulfase	28	0.97 (0.06)	1.08 (0.09)	1.09 (0.08)	1.14 (0.09)	0.11 (0.04)	0.13 (0.04)	0.17 (0.04)

The Sponsor claims that the change in absolute FVC is not related to growth, as evidenced by the following Figures:

Mean height (cm) and mean changes from baseline in absolute FVC (cc) are summarized in Figure 11.4-5.

Figure 11.4-5 Mean Height (cm) and Mean Change from Baseline in Absolute FVC Volume (cc) by Treatment Group: ITT Patient Population

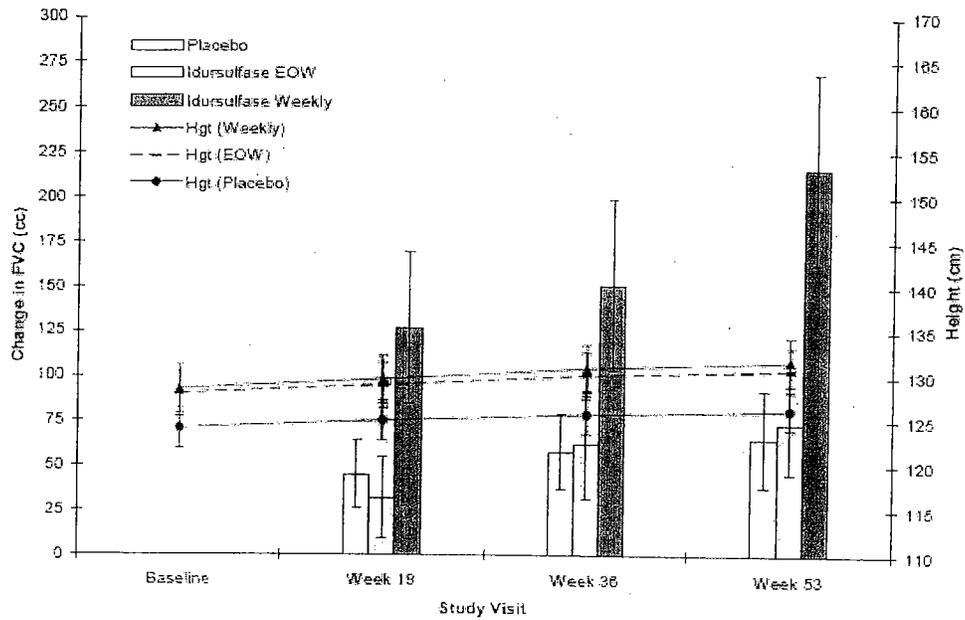
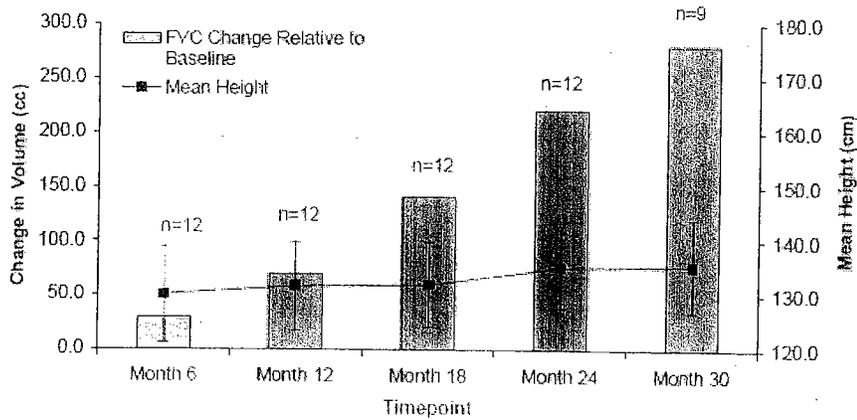


Figure 2.7.3-14 Change in Mean FVC (cc) and Height (cm) Relative to Baseline: Studies TKT008/TKT018



ITT Patient Population: Note: Twelve (12) patients had data available out to 24 months and 9 patients (3 TKT008 placebo patients excluded) had data available out to 30 months.

As far as changes in absolute FVC, the pulmonary division concluded that changes in absolute FVC would not be meaningful unless the effect of growth could be ruled out.

Reviewer comment: Since no conclusion can be drawn from the height data, Figure 2.7.3-14 depicted above is not meaningful. We agree with DPAP that improvements in absolute FVC would be significant if a growth effect can be excluded. Such would be the case if data were derived from a population that is not growing (i.e., those post-pubertal patients whose epiphyses have fused). In normal males, the epiphyses fuse at approximately 18 years of age. Inclusion of pre-pubertal or pubertal patients would be problematic in terms of matching treatment groups for height due to difficulties in accurately measuring standing height in these patients. In addition, DPDD defers to DPAP regarding what would constitute a clinically meaningful difference in absolute FVC between placebo and treated groups in a population with fused epiphyses.

Although pulmonary function testing is useful for monitoring lung function in an individual patient, spirometry does not always correlate with clinical benefit (Sharek 2002). Nonetheless, spirometry has been used to monitor other neuromuscular disorders (Gauld 200) and has prognostic value. For example, a vital capacity < 1 Liter is associated with a 5 year survival < 10 % in patients with Duchenne Muscular Dystrophy (Phillips 2001).

Conclusion: Pulmonary function testing

Given the difficulties in obtaining accurate height measurements in patients with Hunter's syndrome, the predicted FVC is unlikely to be clinically meaningful. Using arm span to predict lung function in these patients should be considered. Changes in absolute FVC are more likely to be informative in post-pubertal patients, i.e. patients whose epiphyses have fused. For descriptive purposes only, consideration should be given to analyzing changes in absolute FVC by pubertal status along with age, height and arm span.

III. Pediatric labeling and post-marketing commitments

Specific labeling recommendations will be discussed during the labeling meetings. In general, the labeling should be consistent with that of laronidase, indicating that ELAPRASE (idursulfase) is effective for the treatment of Hunter's syndrome and possibly to decrease hepatosplenomegaly. The labeling should not imply

— Due to the aforementioned difficulties with obtaining accurate height measurements,

— The Pediatric

Use section should indicate that safety and effectiveness have not been established in children less than 5 years of age.

The Sponsor has indicated that long-term clinical outcomes (cardiac, respiratory, musculoskeletal and neurologic), along with safety will be assessed. In addition, the Sponsor's draft labeling refers to a Registry that will be established. Data is to be collected during routine follow-up via multispecialty clinics and may include laboratory testing and optional investigations. These optional investigations include cerebral and abdominal imaging, ophthalmology, audiometry, pulmonary function testing, electrocardiogram, echocardiogram, joint mobility testing, 6MWT, neurophysiology, polysomnography, bronchoscopy and barium swallow. Laboratory testing is "Hunter specific" along with routine hematology, chemistry and urinalysis.

Postmarketing commitments should include the study of this therapy in patients < 5 years before changes due to GAG accumulation are irreversible. Since the pathogenesis of Hunter's syndrome is the same for these patients, efficacy can likely be extrapolated provided pharmacokinetic/ pharmacodynamic and safety studies are performed. The ability of ERT to prevent the need for PE tubes, respiratory infections, adenoidectomy and the development of hearing loss should be explored. Growth (height, weight, and head circumference) should be measured in a standardized manner. Height measurements should be correlated with degree of deformity and joint contracture and weight with nutritional status.

For all patients, the long-term outcomes suggested by the Sponsor should be collected in a systematic manner. Adverse events should be correlated with antibody development. In addition, neurologic outcomes should include evaluation of neurocognitive function such as the Weschler family of tests based on age (WPPSI and WISC-III). Since long term improvement in neural manifestations with therapy is unknown, consideration should be given to examining neuronal accumulation of GAG. Bone marrow transplant studies in Hunter's syndrome have included assessment of peripheral nerve GAG accumulation (via rectal or cutaneous nerve biopsy) and MRI spectroscopy (Okane 1998, Takahashi 2001). As DPAP suggests, calculating lung function with height and arm span as well as measures of peak cough flow to assess mucociliary clearance may augment pulmonary function studies and polysomnography (Gauld 2005).

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Appendix I- Idursulfase Clinical Studies

Table 2.7.3-4 Idursulfase Clinical Studies

Study ID/ Study Status (Study Dates)	Objectives of the Study	Study Design and Type of Control	Inclusion / Exclusion Criteria	Idursulfase Dose (mg/kg) (No. of patients)	Schedule / Route of Administration	Duration of Treatment	Information Included (Location in CTD)
Controlled Studies							
TKT008 Completed (April 2001 to March 2002)	Phase I/II, dose- finding, safety and efficacy; PK and PD	Randomized, double-blind, placebo-controlled, dose escalation	Male patients, \geq 5 years of age, with Hunter syndrome; able to adequately perform required testing	0.15 EOW (n = 3) 0.5 EOW (n = 3) 1.5 EOW (n = 3) Placebo EOW (n = 3)	Once every other week for 24 weeks / IV	6 months	Safety and efficacy data in full CSR (Section 5.3.5.1)
TKT024 Completed (September 2003 to March 2005)	Pivotal, Phase II/III, safety, efficacy, and PK	Randomized, double-blind, placebo-controlled study	Male patients, 5 to 25 years of age, with Hunter syndrome; forced vital capacity of $<$ 80% of predicted; able to adequately perform required testing	0.5 Weekly (n = 32) 0.5 EOW (n = 32) Placebo Weekly (n = 32)	Once weekly or once every other week for 52 weeks / IV	12 months	Safety and efficacy data in full CSR (Section 5.3.5.1)
Uncontrolled Studies							
TKT018 Ongoing (study start October 2001)	Phase III, safety and long-term treatment dosing, efficacy, and PK	Open-label, extension study of TKT008	Patients who completed Study TKT008 (ie, completed the final evaluation at Week 24)	Initially ^a 0.15 EOW (n = 4) 0.5 EOW (n = 4) 1.5 EOW (n = 4) Then ^b 0.5 EOW (n = 12)	Once every other week / IV	Ongoing ^c	Efficacy data up to 2 years of treatment in full CSR (Section 5.3.5.2) Safety data up to 01 April 2005 in synopsis (Section 5.3.5.3)
TKT024EXT Ongoing (study start September 2004)	Long-term, 2-year, safety, PK, and clinical outcome; safety data for commercial product	Open-label, single arm, extension study of TKT024	Patients who completed enrollment in the double-blind phase of Study TKT024 (ie, completed the Week 53 final evaluations)	0.5 Weekly (n = 94)	Once weekly for 2 years / IV	Ongoing ^d	Safety data up to 04 April 2005 in synopsis (Section 5.3.5.2)

mg/kg = milligrams per kilogram; PD = pharmacodynamic(s); PK = pharmacokinetic(s); EOW = Every Other Week; IV = Intravenous; CSR = Clinical Study Report

^a All 12 patients enrolled after completing participation in Study TKT008.

^b All patients were transitioned to 0.5 mg/kg every other week in October to November 2002.

^c This submission contains approximately 3 years of safety and 2 years of efficacy data for patients enrolled in this study.

^d At the time of this submission, efficacy data were not available; up to 6 months of safety data for patients enrolled in this study are presented in Section 2.7.4 Summary of Clinical Safety

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Appendix II

Severity score (source Clinical Study Report TKT024 Oct 2005 Vol 1-138 p66)

The patient's FVC and 6MWT baseline results will be scored on severity as shown in Tables 3 and 4. (The highest FVC value and farthest distance walked of the 2 tests at baseline will be used for the scoring).

Table 3. Scoring for Forced Vital Capacity*

% of Predicted	Severity	Score
$\geq 70\%$ to $< 80\%$	Mild	1
$\geq 50\%$ to $< 70\%$	Moderate to moderate severe	2
$< 50\%$	Severe to very severe	3

*Modified from the American Thoracic Society guidelines on lung function testing (7).

Table 4. Scoring for 6-Minute Walk Test

Distance Walked (m)	Severity	Score
≥ 500	Mild to normal	1
≥ 300 to < 500	Moderate	2
< 300	Severe	3

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$$\% \text{ predicted FVC} = (\text{FVC highest} + \text{FVC predicted}) \times 100$$

Table 9.7-1 Reference Equations Used to Derive Predicted Forced Vital Capacity Values

Age (years)	Equations for Predicted FVC
5 to 7 ^a	$= 4.4 \times 10^{-3} \times [\text{Height (cm)}^{2.67}] / 1000$
8 to 19 ^b	$= -0.2584 - 0.20415 \times \text{Age} + 0.010133 \times \text{Age}^2 + 0.00018642 \times [\text{Height (cm)}]^2$
$\geq 20^b$	$= -0.1933 + 0.00064 \times \text{Age} - 0.000269 \times \text{Age}^2 + 0.00018642 \times [\text{Height (cm)}]^2$

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ON ORIGINAL**



MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 13, 2006

TO: Brian Harvey, MD, Director
Division of Gastrointestinal Products

THROUGH: Gerald Dal Pan, MD, MHS, Director
Office of Drug Safety

FROM: ODS Idursulfase RMP Review Team

DRUG: Idursulfase (iduronate-2-sulfatase, I2S, DRX006A)

BLA#: 125151/0

SPONSOR: Transkaryotic Therapies, Inc.

SUBJECT: Risk Management Plan, submitted November 23, 2005

PID #: D060003

INTRODUCTION/BACKGROUND

This consult follows a request from the Division of Gastrointestinal Products (DGP) for the Office of Drug Safety (ODS) to review and comment on the proposed Risk Management Plan (RMP) for idursulfase.

Idursulfase is an enzyme replacement product used in patients with Hunter syndrome (also known as mucopolysaccharidosis II, MPS II), a lysosomal storage disease caused by a deficiency of iduronate-2-sulfatase (I2S). I2S is an enzyme that cleaves O-linked sulfate moieties from two human glycosaminoglycans (GAG) known as dermatan sulfate and heparan sulfate. Insufficient I2S leads to an accumulation of the GAG molecules in nearly all cells resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. The disease is almost always progressive and increasingly disabling. In later stages of the disease, GAG continues to accumulate leading to progressive end-organ failure and a shortened life span. The disease is rare with an

incidence of about 1 in 162,000 live births. Because it is so rare, the safety database is limited (n=108¹) and did not include children less than 5 years of age.²

The most frequent and concerning adverse drug related event associated with idursulfase treatment during the clinical trials were mild to moderate infusion-related reactions. These were characterized by flushing, dizziness, urticaria, rigors, and headache. Most resolved in subsequent infusions with pre-medication with antihistamines such as diphenhydramine or, for more severe reactions, with an antihistamine plus a corticosteroid, and sometimes with ibuprofen or acetaminophen, and/or by slowing the infusion rate³. The most severe reactions were episodes of hypoxia that occurred in about 3.7% (4/108) patients with underlying obstructive airway disease.

PROPOSED RISK MANAGEMENT PLAN

In addition to the open-label extensions of the two clinical trials still ongoing⁴ (n=106), Transkaryotic Therapies, Inc (TKT) is proposing the following studies in the postmarketing period:

- Hunter Outcome Survey (HOS) – this is a post-marketing observational study on clinical and laboratory tests that are part of standard medical care for patients with Hunter syndrome. This study will be open to all patients with Hunter syndrome and will provide additional information beyond that available in the Hunter registration program, currently the largest and longest of its kind. The objectives of this study are to enhance the understanding of its natural history, to monitor the safety and efficacy of enzyme replacement therapy with idursulfase, and to provide a basis for the development of clinical management guidelines for Hunter syndrome.
- Immungenicity Sub-Study – the objective of this study is to collect data on up to 100 patients for a period of at least 3 years. The Sponsor will collect serum at baseline and on a regular basis during idursulfase treatment. Samples will be analyzed for IgG, M and E antibodies. Antibody positive samples will be evaluated for neutralizing activity. The Sponsor also plans to collect urine samples at the same time points for measurement of GAG levels.
- Specific Sub-Population Studies – the Sponsor plans to study children

¹ BLA 125151/0, Module 2, Section 2.7 Clinical Summary; pg 4.

² BLA 125151/0. Module 5, Section 2.1.2.1, pg 5.

³ BLA 125151/0. Module 5, Section 2.1.2.3.2, pg 9.

⁴ Phase II/III study – 94 patients receiving 0.5 mg/kg of idursulfase over 3 hours weekly and Phase I/II – all 12 patients transitioned to 0.5 mg/kg idursulfase every other week, BLA 125151/0. Module 5, Section 3.4.1; pg 19.

TKT is proposing to have collect and report suspected adverse events in accordance with current worldwide regulations and ICH guidelines⁵. Sources of safety information will include:

- Direct reports to the Sponsor's affiliates or licensees, including:
 - Spontaneous notification from health care professionals about commercial product
 - Compassionate/named patient use
 - Ongoing open-label extension clinical trials
- HOS (described above) - All suspected adverse drug reactions and all serious adverse events identified in the survey will be entered into the pharmacovigilance database.
- Literature reports
- Regulatory authorities

ODS COMMENTS, QUESTIONS, AND RECOMMENDATIONS

- For Postmarketing safety reporting, we remind the Sponsor of the final Guidance to Industry "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report" at <http://www.fda.gov/cder/guidance/1830fn1.pdf>. It states,
"The FDA has determined, for purposes of postmarketing safety reporting under 21 CFR 310.305, 314.80, 314.98, and 600.80, that information concerning potential adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., company sponsored patient support programs, disease management programs) should be handled as safety information obtained from a postmarketing study. Applicants, manufacturers, and licensed manufacturers should not report safety information obtained through these types of patient contacts unless the adverse event meets the regulatory definitions of serious and unexpected and there is a reasonable possibility that the drug or biological product caused the adverse experience (see 21 CFR 310.305(c)(1)(ii), 314.80(c)(2)(iii), 314.80(e), 600.80(c)(2)(iii), and 600.80(e))."

Under the guidance, the sponsor of idursulfase should report within 15 days serious, unexpected events during active solicitation from the observational study and other studies for which they believe there is a reasonable possibility that the product caused the adverse experience. The sponsor may be requested to send in other reports expeditiously from the studies or other sources regardless of causality if there was concern about particular adverse events.

- A Hunter registration program already exists, and the company is proposing a Hunter Outcome Study (HOS) on standard medical care. Apparently there will be input from the Hunter registration program in the HOS, however the submission does not

⁵ BLA 125151/0. Module 5, Section 3.2; pg 17..

provide sufficient details regarding the HOS and whether it will adequately collect adverse event data.

We recommend that the Sponsor:

- Encourage health care providers to solicit enrollment of all Hunter patients, especially those exposed to idursulfase in the existing Hunter registry program.
 - Develop a reliable mechanism for collecting data, including data on adverse events, risk factors, disease severity, and organ involvement in order to provide earlier signal detection of adverse events.
 - Develop incentives to increase the participation of providers; examples might include access to summary findings from the registry, contacts with specialists when needed.
 - Report to FDA, in the routine periodic drug adverse event report (quarterly for the first 3 years after approval and annually thereafter), a summary analysis of all adverse events identified including any risk factors or etiologic explanations; the interventions used and an assessment of their benefit; and an incidence rate with a description of the patients exposed if possible.
- We also request the Sponsor provide additional clarification as follows on the Hunter registration program and the Hunter Outcome Survey that further describes these programs, the patients enrolled, the information gained and the dissemination of that information for the benefit of the patients:
 - the number of Hunter patients already in these programs compared to the number of Hunter patients total and why those not enrolled are not registered
 - the means of enrolling patients: current or proposed methods of enrollment, who enrolls in the program - the patient or healthcare professional, reasons for patients not being enrolled
 - methods used to follow these patients: means of contact, frequency of follow-up, number lost to follow-up and why they were lost to follow-up
 - information collected: what information is collected, how often information is collected, how information is stored
 - means of analyzing the data: inclusion/exclusion criteria, missing data, types of analyses planned for evaluation of the data
 - how findings are communicated: method of communication, types of reports, frequency of reports, etc.

CONCLUSION

Idursulfase is not likely to be used in a large population of patients because of the rarity of the disease. According to the Sponsor, those that are to be treated are likely closely monitored and followed by their physician and/or other specialized health care provider. Currently there is a Hunter registration program. The most concerning adverse events as described in the Sponsor's submission are infusion-related reactions. These were

managed by slowing the infusion rate and pre-medicating patients prior to infusion. This type of adverse event is generally handled in the postmarketing setting in product labeling and we agree with the Sponsor's proposal to include the appropriate precautions and instructions in the product labeling to minimize this risk. We also agree with the Sponsor's proposal to conduct the Hunter Outcomes Study (HOS), an observational study that is open to all Hunter patients, and additional sub-studies to further understand the safety of this product particularly in populations that were not studied (e.g., children

If the Sponsor or the Review Division determine that a safety concern warrants consideration of a Risk Minimization Action Plan (RiskMAP), please refer to the following Guidance document: Development and Use of Risk Minimization Action Plans: <http://www.fda.gov/cder/guidance/6358fnl.htm>. Should the review division want ODS to review a future RiskMAP submission please send a consult to ODS and notify the ODS-IO Project Manager, Mary Dempsey, at 301-796-0147.

ODS Idursulfase RMP Review Team

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Office of Drug Safety

**DIVISION OF PULMONARY AND ALLERGY PRODUCTS MEDICAL
OFFICER CONSULTATION**

Date:	29 March 2006
To:	Joanna Ku, M.D. Medical Officer OND/ODE3/DGP CDER
From:	James Kaiser, M.D. Medical Officer Division of Pulmonary and Allergy Products (DPAP) <i>James Kaiser 3/29/06</i>
Through:	Peter Starke, M.D. Medical Team Leader DPAP <i>P. Starke 3/29/06</i>
Through:	Badrul Chowdhury, M.D., Ph.D. Division Director, DPAP <i>Badrul A. Chowdhury 4/4/06</i>
Subject:	Consult regarding endpoints in clinical trial of Hunter syndrome

General Information

Request From:	Joanna Ku, M.D. , Division of Gastroenterology Products (DGP)
Date of Request:	1 March 2006
Date Received:	1 March 2006
Materials Reviewed:	TKT summary of efficacy in trial TKT024 Medical Officer's draft review of efficacy of trial TKT024

Introduction

The Division of Gastroenterology Products has requested consultation with DPAP on the clinical meaning of changes in pulmonary physiology seen in a proposed pivotal trial of iduronate-2-sulfatase (established name, Idursulfase) in Hunter syndrome.

Hunter syndrome (mucopolysaccharidosis-II, or MPS-II) is an X-linked, recessive disorder in which aberrant catabolism and deposition of glycosaminoglycans occurs due to the deficiency of the enzyme iduronate-2-sulfatase. Upper airway obstruction may occur from enlarged tongue, gums, soft tissues of the nasopharynx tonsils, and adenoids. Tracheal or lower airway obstruction may occur from abnormalities of tracheal cartilage, redundant respiratory epithelium, or nodules.¹ Sleep apnea is described. Enlargement of the liver and spleen may occur. Dysostosis multiplex may result abnormalities of vertebral bodies with kyphosis and pulmonary restriction. Shortened stature may also result also from shortened long bones. The disease occurs in severe and mild forms. The severe form usually has its onset at 2-4 years of age and results in death at as young as less than 10 years usually from obstructive airway disease and cardiac failure.² Mildly affected individuals survive into early teenage years to as late as 87 years old; death is usually due to airway obstruction and cardiac failure.² Patients with Hunter syndrome may receive tracheostomies to avoid upper airway obstruction or positive pressure airway assistance at night to avoid sleep apnea. The discussion in this consultation does not detail the numerous other manifestations of Hunter syndrome, including other skeletal abnormalities, neurologic, hepatic, and dermatologic manifestations.

TKT024 tested a weekly and a biweekly doses of Idursulfase compared to placebo in 96 subjects with Hunter Syndrome for 52 weeks. The primary endpoint incorporated two measurements, FVC % predicted and the 6-minute walk test. Ranks for these two endpoints were summed into a composite endpoint and analyzed by ANCOVA. The primary comparison, which was statistically significant, was between the every-week treatment and placebo. The clinical interpretation of this composite endpoint is complex and beyond the scope of this consultation. However, the statistic plan did call for examination of the components. This consultation concerns the pulmonary physiology part of the primary endpoint.

Patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) have disostosis multiplex and die from obstructive lung disease as do patients with Hunter syndrome. Aldurazyme (α -L-iduronidase) is approved to improve pulmonary function and walking distance for these patients. The pivotal trial demonstrated a 4-point difference between treated and placebo groups in the mean FVC% predicted and a mean difference of 38 meters walked in the 6-minute walk test. The endpoints were measured at 26 weeks.

DGP's questions

1. Regarding %FVC:
 - a. Does the difference in the %FVC seen in study TKT024 represent a clinically meaningful treatment effect?
 - b. Given that the formula for %FVC involves a corrective factor for race, do we need to take race into account into the analysis of this end point (e.g. stratified analysis for race)?
2. Regarding the absolute FVC:
 - Given that this is a growing population with skeletal abnormality and that the treatment has effects on organomegaly please comment on the appropriateness of absolute FVC as a measurement of pulmonary function, and how the results should be interpreted.
3. Given the lack of statistical significant differences among treatment groups in all other pulmonary indices studied, are the findings regarding FVC meaningful in terms of describing the overall pulmonary status of Hunter patients? In particular, is the effect of idursulfase on pulmonary function of sufficient significance that we should consider including it in the indication and/or describing it in the clinical study section?
4. Do you have any recommendations of how pulmonary function should be assessed in post marketing registry studies or any post market clinical trials?

Summary of DPAP responses

Preliminary Comments:

In Hunter syndrome, the primary potential pulmonary effects of the disease process are on structures external to the lung, most notably the upper airway, skeleton, and possibly liver and spleen. The FVC and other pulmonary function tests are measures that combine potential effects on the lung itself and structures external to it. In addition, we note that pulmonary function tests as commonly used are themselves indirect measures, i.e. surrogates, for clinically meaningful changes in the patient. While it is not unreasonable to expect that changes that affect structures external to the lungs that secondarily affect pulmonary function might allow for use of such testing as a means

for detecting changes in the primary disease process, under these circumstances, it would be highly problematic to infer any treatment benefit on the lung itself from a product-related improvement in FVC. With this in mind, we offer our comments and answers to the specific questions posed in the consult.

The summary of primary endpoint results submitted by the applicant shows no notable difference from placebo in the every-other-week active treatment arm so the comments in this consultation are restricted to comparisons of the every-week dosing arm. It is beyond the scope of this review to examine the robustness of the statistical analysis. For example, we have not examined the effect of missing data, nor the consistency across subgroups of subjects.

Although it was not a subject of consultation, we note that the trial showed an increase in the treated group compared to placebo in the 6-minute walk test distance. It is not clear by what mechanism the effect occurred. Pulmonary physiology may have been one component of the difference.

Answers to specific questions: 1. The applicant reports that the difference between placebo and every-week treatment in baseline to trial-end FVC % predicted in the ANCOVA was 4.28 points (see appendix), which was not statistically significant. Aside from the statistical interpretation, there is no difference in FVC % predicted that has been validated to show a clinically meaningful treatment effect. It is likely that such a validation would have to be made for the disease being studied, or at least for this class of diseases (of which the mucopolysaccharidoses may be an example or unique in their class).

If the corrective factor for race was used for each subject there is no need for an adjusted analysis.

2. For populations matched for age, sex, height, and race at baseline, the absolute FVC can be used. A product that has an effect on growth may affect the FVC concomitantly, in which case the FVC is a surrogate for the growth that has occurred. The applicant reports that in a subpopulation of the study there was a difference in growth, but this may be unreliable. If the differences in growth are small, the absolute FVC is a reasonable measure. The absolute FVC results in the current trial are consistent with the FVC % predicted results (see appendix).

It is problematic to ascribe changes in pulmonary function to given changes in liver and spleen size. In fact trial results show that the sum of mean changes in liver and spleen size were much greater than the mean change in absolute FVC.

3. We agree that physiologic endpoints did not provide support for the FVC component of the primary endpoint; however, each endpoint measures a different physiologic parameter. This single endpoint cannot be expected to serve as a surrogate for the range of possible pulmonary defects in Hunter syndrome, which include upper and lower airway obstruction as well as restriction. As the FVC % predicted was a component of the primary endpoint, it should be described in the clinical studies section of labeling should the product be approved. However, its clinical significance is uncertain.

4. We recommend that further information on the long-term effect of the product be determined by periodic determination of pulmonary function using standard testing procedures. Although to our knowledge the correlation of arm span and height over time has not been formally tested in Hunter Syndrome, we recommend consideration of the calculation of predicted FVC using arm span as well as height. We also recommend that upper airway obstruction be measured using flow-volume

measurements. Despite the analytical issues posed by the noncontrolled nature of postmarketing data, these measurements may provide some insight into the long-term effect of the product on pulmonary function in Hunter Syndrome.

Individual responses to CBER's questions

1a.

FVC % predicted is a laboratory-measured outcome that is not itself a measure of clinical efficacy. There is no established, validated criterion for a difference in FVC % predicted that correlates with clinical efficacy. A statement by the ATS/ERS was recently published³ that describes the variability in FVC testing as a hurdle in the interpretation of the test for an individual and gives guidelines on handling this variability. However, the statement does not give guidelines as to the clinical interpretability of a given change. In fact, it is likely that such a criterion would have to be established in Hunter Syndrome, or a class of conditions very similar to it (like the mucopolysaccharidoses). It is the opinion of DPAP that other data from the clinical trial must be used to interpret the clinical benefit of the experimental agent in this trial.

Regarding the use of FVC% predicted, the submission states,

For the majority of % predicted FVC analyses, current standing height was used to calculate the % predicted FVC; however, the formulae for % predicted FVC assume normal statural growth and the ability to accurately measure height. Neither of these assumptions apply to patients with Hunter syndrome because these patients are growth-impaired and may be unable to stand erect.

We agree that interpretation of FVC% predicted data is complicated by abnormalities in growth patterns and inaccuracies in measuring height. How inaccurate the measurements were is beyond the scope of this consultation.

b. If the corrective factor for race was used for each subject there is no need for an adjusted analysis.

2. As the question implies, FVC is determined by various factors. In populations of normal stature matched for age, race, sex, and height, the absolute FVC can be a valid comparator. (An additional potential confounder might be imbalances in statural abnormalities at baseline (thoracic as compared to long bones). The balance in FVC% predicted at baseline suggests that the structural abnormalities were balanced.) However, the interpretation of an increase in absolute FVC in the active arm of a trial is complicated if a product increases growth markedly. In this case, increases in FVC are not necessarily indicative of an increase in lung function, but a surrogate for the growth effects. If, however, a product has a beneficial effect preferentially on the shape of the thoracic cavity, one meaningful measurement of the benefit of this could be an improvement in pulmonary function as measured by FVC.

The growth analysis submitted by TKT shows a small effect in a subset of prepubertal subjects, amounting to about 1% of baseline height. A full analysis of the growth effect claim in the submission is beyond the scope of this review. Growth measurements may have been inaccurate, as stated in the submission.

The question poses the issue of organomegaly and its effect on FVC. Extrathoracic compression can result in a lower FVC; reduction in organomegaly can reduce the restrictive process and increase FVC. However, the effects of a given reduction in liver or spleen size in an individual are probably variable. It is problematic to ascribe changes in pulmonary function to given changes in liver and spleen size.

The absolute FVC results, showing a difference between treatment groups of 0.19 liters, are consistent with the FVC % predicted results. However, it should be noted that the placebo and every-week treatment group were somewhat imbalanced for height and age (see appendix). What effect these factors had on the difference is not certain.

3. The applicant performed numerous exploratory analyses of spirometry related to FEV₁ (total sample size ($n=94$), total lung capacity (TLC, $n=57$), and diffusing capacity of the lung for carbon monoxide (DL_{CO}, $n=38$): FEV₁ absolute and % predicted; FEV₁/FVC for subjects whose baseline ratio was <0.7 at baseline (n not stated, probably 94); % predicted total lung volume; absolute total lung volume; RV/TLC.

An improvement in FEV₁ may be due to the alleviation of the restrictive process that depresses FVC; when the changes occur in the same direction it is problematic to interpret them as independent changes. An independent measure of obstruction could be obtained by analyzing the FEV₁/FVC ratio in an adequate population (i.e., an adequately sized population that is abnormal at baseline). The applicant's analysis of FEV₁ in subjects who showed an obstructive pattern (whose FEV₁/FVC ratio was <0.7 at baseline) does not provide independent confirmation of the results (in addition, it failed to reach even the nominal p-value of 0.05).

Among the physiological parameters only FEV₁ was analyzed for an adequate sample size (although the analyses were conducted on a "completer" population, this excluded only 1 placebo subject and 1 subject from the every-week treatment arm). Differences were noted in the comparison of active treatment to placebo in change from baseline to end of treatment in FEV₁% predicted (observed values differences in means, 2.5) and absolute FEV₁ (observed values differences in means, 0.11). These differences are consistent in direction with the FVC results. However, it is not appropriate to accept the applicant's claim of statistical significance for the absolute FEV₁ result, as there was no adjustment for multiplicity of analyses. Moreover, the comparison of every-week treatment to placebo in baseline to end-of-treatment in FEV₁ % predicted was not statistically significant according to the applicant's analyses.

TLC and DL_{CO} analyses were conducted on insufficient numbers of subjects for any estimate of a treatment effect to be drawn.

Overall, these results provide no support for the primary endpoint in that they do not provide evidence of independent pulmonary effects.

4. We recommend that further information on the long-term effect of the product be determined by periodic determination of pulmonary function using standard testing procedures. Current ATS/ERS guidelines state, "When height cannot be measured, options include using stated height or estimating height from arm span, as indicated in a previous document from this series and other publications..."³ Although to our knowledge the correlation of arm span and height over time has not been formally tested in Hunter Syndrome, we recommend consideration of the calculation of predicted FVC using arm span as well as height. Upper airway obstruction is a major clinical problem in Hunter Syndrome. We recommend that upper airway obstruction be determined using flow-volume measurements. Despite the analytical issues posed by the noncontrolled nature of postmarketing data, these measurements may provide some insight into the long-term effect of the product on pulmonary function in Hunter Syndrome.

References

1. Kakkis E and Wraith E. Complications and management of the mucopolysaccharidoses. UpToDate, July 18, 2005.
2. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease, 8th ed. New York, NY: McGraw-Hill; 2001:3421-3452.
3. Pellegrino R et al., Interpretative strategies for lung function tests. Eur. Respir. J. 2005; 26(5): 948-968.

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Appendices:

TKT024: Baseline demographics
Table 11.2-1 Summary of Patient Demographics at Baseline by Treatment Group: ITT Patient Population

Demographic Characteristic	Placebo N=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly N=32	EOW N=32	All Idursulfase N=64	
Age at Randomization (years):					
N	32	32	32	64	96
Mean (SE)	13.12 (1.221)	15.14 (1.113)	14.40 (1.241)	14.77 (0.828)	14.22 (0.687)
Median	13.32	15.55	14.06	15.00	13.55
Min, Max	5.0, 29.0	6.3, 26.0	5.4, 30.9	5.4, 30.9	5.0, 30.9
Age Category at Entry (N [%]):					
5 to 11 years	15 (46.9)	14 (43.8)	14 (43.8)	28 (43.8)	43 (44.8)
12 to 18 years	10 (31.3)	10 (31.3)	9 (28.1)	19 (29.7)	29 (30.2)
19 to 25 years	5 (15.6)	7 (21.9)	7 (21.9)	14 (21.9)	19 (19.8)
≥ 26 years	2 (6.3)	1 (3.1)	2 (6.3)	3 (4.7)	5 (5.2)
Baseline Prepubertal Patient (N [%]):					
Yes	17 (53.1)	14 (43.8)	17 (53.1)	31 (48.4)	48 (50.0)
Ethnicity (N [%]):					
Hispanic or Latino	4 (12.5)	7 (21.9)	4 (12.5)	11 (17.2)	15 (15.6)
Non-Hispanic	28 (87.5)	25 (78.1)	28 (87.5)	53 (82.8)	81 (84.4)
Race (N [%]):					
South American Indian	0	1 (3.1)	2 (6.3)	3 (4.7)	3 (3.1)
Asian	3 (9.4)	0	2 (6.3)	2 (3.1)	5 (5.2)
Black	4 (12.5)	2 (6.3)	1 (3.1)	3 (4.7)	7 (7.3)
White	24 (75.0)	28 (87.5)	27 (84.4)	55 (85.9)	79 (82.3)
Other	1 (3.1)	1 (3.1)	0	1 (1.6)	2 (2.1)
Gender (N [%]):					
Male	32 (100.0)	32 (100.0)	32 (100.0)	64 (100.0)	96 (100.0)
Height (cm):					
N	32	32	32	64	96
Mean (SE)	124.19 (2.262)	128.54 (2.639)	128.03 (2.550)	128.29 (1.820)	126.92 (1.436)
Median	123.40	128.07	127.45	127.45	125.17
Min, Max	101.2, 158.5	107.0, 166.0	107.4, 170.5	107.0, 170.5	101.2, 170.5
Weight (kg):					
N	32	32	32	64	96
Mean (SE)	33.63 (2.284)	37.78 (2.340)	36.66 (2.269)	37.22 (1.618)	36.02 (1.325)
Median	29.75	33.75	33.75	33.75	33.00
Min, Max	18.8, 78.2	19.9, 69.8	19.0, 68.8	19.0, 69.8	18.8, 78.2

TKT024: Baseline disease characteristics
Table 11.2-2 Summary of Baseline Disease Characteristics by Treatment Group: ITT Patient Population

Clinical Characteristic	Placebo N=32	Idursulfase 0.5 mg/kg			All Patients N=96
		Weekly N=32	EOW N=32	All Idursulfase N=64	
Age at Onset of Hunter syndrome symptoms (months):					
N	31	31	28	59	90 ^a
Mean (SE)	25.39 (3.252)	30.39 (3.751)	27.46 (4.540)	29.00 (2.901)	27.76 (2.204)
Median	24.00	30.00	24.00	24.00	24.00
Min, Max	< 1, 72.0	< 1, 84.0	< 1, 96.0	< 1, 96.0	< 1, 96.0
Age at Diagnosis of Hunter syndrome (months):					
N	32	32	32	64	96
Mean (SE)	57.09 (9.410)	62.09 (9.144)	52.34 (6.855)	57.22 (5.702)	57.18 (4.899)
Median	36.00	48.00	48.00	48.00	48.00
Min, Max	< 1, 276.0	< 1, 240.0	< 1, 180.0	< 1, 240.0	< 1, 276.0
Duration of Hunter syndrome from date of diagnosis to date of study entry (months)					
N	32	32	32	64	96
Mean (SE)	99.99 (13.633)	119.29 (13.446)	120.27 (15.222)	119.78 (10.074)	113.19 (8.124)
Median	77.40	97.80	113.40	101.40	97.80
Min, Max	8.4, 276.0	13.2, 311.0	4.8, 310.8	4.8, 311.0	4.8, 311.0

TKT024: FVC% predicted results

Table 11.4-8 Percent Predicted Forced Vital Capacity Observed and Adjusted Mean Change From Baseline to Week 53 ANCOVA Analysis: ITT Patient Population

Treatment Comparison	N	Observed % Predicted FVC			Adjusted 95% CI ^a	p-value ^b
		Baseline	Week 53 Change			
			Observed	Adjusted ^a		
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.29 (1.73)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.99 (1.85)		
Difference				4.28 (2.27)	-0.27, 8.83	0.0650
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.37 (1.59)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-1.49 (1.67)		
Difference				0.12 (2.08)	-4.04, 4.28	0.9531
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	55.30 (2.80)	3.45 (1.77)	1.82 (1.64)		
Idursulfase EOW	32	55.15 (2.45)	0.00 (1.32)	-1.66 (1.68)		
Difference				3.49 (2.13)	-0.79, 7.76	0.1079
All Idursulfase vs Placebo						
All Idursulfase	64	55.22 (1.85)	1.72 (1.12)	0.00 (1.21)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.11 (1.69)		
Difference				2.11 (1.89)	-1.65, 5.87	0.2675

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment and baseline % predicted FVC, baseline patient age (3 levels) and baseline disease score (3 levels).

Data Source: Table 14.2.1.1.5.1.

TKT024: FVC absolute results

Table 11.4-9 Forced Vital Capacity Absolute Volume (L) Mean Change From Baseline to Week 53 ANCOVA Analysis: ITT Patient Population

Treatment Comparison	N	Actual Baseline FVC (L)	Change to Week 53 in FVC Absolute Volume (L)		Adjusted 95% CI ^a	p-value ^b
			Mean (SE)			
			Observed Change	Adjusted Change ^a		
Idursulfase vs Placebo: Primary Comparison						
Idursulfase Weekly	32	1.19 (0.10)	0.22 (0.05)	0.18 (0.04)		
Placebo	32	1.09 (0.09)	0.06 (0.03)	-0.01 (0.04)		
Difference				0.19 (0.06)	0.08, 0.30	0.0011
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	1.17 (0.10)	0.07 (0.03)	0.06 (0.03)		
Placebo	32	1.09 (0.09)	0.06 (0.03)	0.02 (0.03)		
Difference				0.03 (0.04)	-0.04, 0.10	0.3735
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	1.19 (0.10)	0.22 (0.05)	0.18 (0.04)		
Idursulfase EOW	32	1.17 (0.10)	0.07 (0.03)	0.05 (0.04)		
Difference				0.13 (0.06)	0.02, 0.25	0.0176
All Idursulfase vs Placebo						
All Idursulfase	64	1.18 (0.07)	0.15 (0.03)	0.12 (0.03)		
Placebo	32	1.09 (0.09)	0.06 (0.03)	0.00 (0.04)		
Difference				0.11 (0.04)	0.02, 0.20	0.0135

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FVC=forced vital capacity; EOW=every other week.

^a Adjusted means (LS Means), adjusted SEs from the fitted ANCOVA model, and the difference in the LS means with the corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment and baseline FVC, baseline patient age (3 levels) and baseline FVC severity score (3 levels).

Data Source: Table 14.2.1.1.7.1.

TKT024: FEV₁ % predicted results

Table 14.2.3.1.1.2.1
Summary Statistics for the % Predicted FEV₁
Observed Values and Change From Baseline by Visit and Treatment Group
Completer Analysis Patient Population

Treatment Group	Statistic	Actual Value				Change From Baseline		
		Baseline	Wk 18	Wk 36	Wk 53	Wk 18	Wk 36	Wk 53
Idursulfase Weekly	n	31	31	31	31	31	31	31
	Mean	49.652	52.317	51.075	51.738	2.664	1.422	2.085
	Std. Err.	3.042	3.622	3.517	3.423	1.677	1.562	1.944
	SD	16.938	20.165	19.580	19.061	9.337	6.699	10.824
	Minimum	15.23	18.50	17.92	16.37	-12.47	-19.15	-35.35
	Maximum	48.340	49.310	49.150	50.100	1.370	0.930	2.660
Idursulfase EOW	n	32	32	32	32	32	32	32
	Mean	47.079	49.203	47.556	47.876	2.125	0.477	0.797
	Std. Err.	2.581	2.765	2.819	2.863	1.335	1.810	1.762
	SD	14.603	15.640	15.945	16.194	7.553	10.236	9.968
	Minimum	22.87	25.06	22.50	23.18	-10.04	-21.21	-13.36
	Maximum	45.595	45.685	43.930	43.015	1.490	-0.675	-1.045
Placebo	n	31	31	31	31	31	31	31
	Mean	51.280	51.918	51.436	50.862	0.640	0.159	-0.417
	Std. Err.	2.466	2.884	2.760	3.112	1.323	1.212	1.657
	SD	13.728	16.057	15.369	17.326	7.366	6.750	9.224
	Minimum	26.08	26.89	20.88	23.27	-13.65	-10.34	-13.04
	Maximum	54.310	51.086	50.470	47.210	-0.440	-0.280	-2.210
	Maximum	70.00	89.19	84.50	85.77	26.03	21.33	22.60

TKT024: FEV₁ absolute differences

Table 11.4-19 Forced Expiratory Volume in 1 Second Absolute Volume Change From Baseline to Week 53 ANCOVA Analysis: Completer Patient Population

Treatment Comparison	N	Baseline	FEV ₁ Absolute Volume (L) Mean (SE) Change to Week 53		Adjusted 95% CI ^a	p-value ^b
			Observed Change	Adjusted Change ^a		
Idursulfase Weekly vs Placebo						
Idursulfase Weekly	31	0.96 (0.08)	0.15 (0.05)	0.12 (0.04)		
Placebo	31	0.90 (0.06)	0.04 (0.03)	-0.02 (0.04)		
Difference				0.14 (0.05)	0.04, 0.24	0.0077
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	0.87 (0.06)	0.07 (0.03)	0.06 (0.03)		
Placebo	31	0.90 (0.06)	-0.04 (0.03)	0.02 (0.03)		
Difference				0.04 (0.04)	-0.03, 0.12	0.2667
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	31	0.96 (0.08)	0.15 (0.05)	0.12 (0.04)		
Idursulfase EOW	32	0.87 (0.06)	0.07 (0.03)	0.06 (0.04)		
Difference				0.07 (0.05)	-0.04, 0.17	0.2268
All Idursulfase vs Placebo						
All Idursulfase	63	0.92 (0.05)	0.11 (0.03)	0.09 (0.03)		
Placebo	31	0.90 (0.06)	0.04 (0.03)	-0.00 (0.04)		
Difference				0.09 (0.04)	0.01, 0.18	0.0294

LS Means=Least Squares Means; SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; FEV₁: forced expiratory volume in the first second; EOW=every other week; L=liter(s).

^a Adjusted means (LS Means) and adjusted SEs from the fitted ANCOVA model. For treatment comparisons, the difference in the LS means is presented along with the corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment, and baseline FEV₁/FVC as factors.

TKT024:6-minute walk test results
Table 11.4-7 Total Distance Walked in Six-Minute Walk Test Observed Mean Change From Baseline to Week 53 ANCOVA Analysis: ITT Patient Population

Treatment Comparison	N	Total Distance Walked in 6MWT (m) Mean (SE)			Adjusted 95% CI ^a	p-value ^b
		Baseline	Week 53 Change			
			Observed	Adjusted ^a		
Idursulfase Weekly vs Placebo: Primary Treatment Comparison						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.95 (10.89)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	1.86 (11.84)		
Difference				35.09 (13.69)	7.66, 62.52	0.0131
Idursulfase EOW vs Placebo						
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	25.88 (10.67)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	2.08 (11.35)		
Difference				23.80 (13.03)	-2.31, 49.91	0.0732
Idursulfase Weekly vs Idursulfase EOW						
Idursulfase Weekly	32	391.63 (19.10)	44.28 (12.31)	36.13 (12.46)		
Idursulfase EOW	32	400.56 (17.94)	30.31 (10.25)	22.95 (12.69)		
Difference				13.19 (15.43)	-17.72, 44.09	0.3963
All Idursulfase vs Placebo						
All Idursulfase	64	396.09 (13.01)	37.30 (7.99)	30.76 (8.39)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	0.97 (11.55)		
Difference				29.79 (12.25)	5.44, 54.14	0.0171

SE=Standard error; CI=Confidence Interval; ANCOVA=Analysis of Covariance; 6MWT= 6-minute walk test; EOW=every other week; LS=Least squares.

^a Adjusted (LS) means and SEs from the fitted ANCOVA model with corresponding 95% CI of the treatment difference.

^b p-value for treatment difference based on ANCOVA model containing region, treatment, baseline 6MWT severity score (3 levels), and baseline patient age (3 levels).

TKT024: Reference equations for FVC % predicted

Age (years)	Equations for Predicted FVC
5 to 7 ^a	$= 4.4 \times 10^{-3} \times [\text{Height (cm)}^{2.67}]/1000$
8 to 19 ^b	$= -0.2584 - 0.20415 \times \text{Age} + 0.010133 \times \text{Age}^2 + 0.00018642 \times [\text{Height (cm)}]^2$
≥ 20 ^b	$= -0.1933 + 0.00064 \times \text{Age} - 0.000269 \times \text{Age}^2 + 0.00018642 \times [\text{Height (cm)}]^2$

**APPEARS THIS WAY
ON ORIGINAL**