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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Drug Name: Idursulfase (Iduronate-2-Sulfatase) solution for intravenous infusion

Indication(s): Mucopolysaccharidosis II (MPS II; Hunter's syndrome)

Applicant: Shire Pharmaceuticals

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions:

This reviewer concludes that the statistical results of the Phase 2/3 study in patients with Hunters syndrome support the applicant's conclusion that Idursulfase is superior to the placebo with respect to the pre-specified primary efficacy endpoint. The primary efficacy endpoint was a composite endpoint that combined the results from the six-minute walk test (6MWT) and the forced vital capacity (FVC % Predicted). Each component was expressed as a change from week 53 compared to baseline. The pre-specified method of combining these two different clinical measurements involved ranking each patient's change from baseline separately on the two endpoints, and then adding together the ranks (as described in O'Brien (1984¹)).

Results from the analysis of the 6MWT component of the composite endpoint supported the overall conclusion that Idursulfase is superior to the placebo with respect to the average improvement in 6 minute walk distance between week 53 and baseline. Results from the analysis of the FVC % Predicted component of the composite endpoint were supportive but less conclusive. Results of the analysis of other secondary efficacy endpoints, such as urinary GAG, liver volume and spleen volume, also supported the efficacy conclusion about Idursulfase.

Hunters syndrome is a rare disease, and the overall number of patients treated with Idursulfase in the Phase 2/3 study (92 Hunter syndrome patients total, with 64 allocated to Idursulfase) and other supportive studies is small. The small size of the Phase 2/3 study may limit the extent to which the results can be generalized to the target population. However, this reviewer notes the consistency of supportive findings in the secondary efficacy endpoints.

Safety Conclusions:

With respect to safety, the inclusion of a warning about infusion reactions and a description of adverse reactions in the labeling text appear to be appropriate from a statistical perspective, given the findings on adverse events and infusion-associated reactions.

Recommendations:

Because the results from the composite endpoint may be challenging to interpret from a clinical perspective, and because the 6MWT component had a p-value less than 0.05 while the FVC % Predicted component did not, this reviewer suggested the following table for presenting the efficacy results in the labeling text under the Clinical Studies heading:

¹ O'Brien, P.C. 1984. Procedures for comparing samples with multiple endpoints. *Biometrics* 40:1079-1087.

Results from the 6-Minute Walk Test (Meters)

	Idursulfase Weekly n=32 ^a			Placebo n=32 ^a			Idursulfase Weekly – Placebo
	Baseline	Week 53	Change	Baseline	Week 53	Change	Difference in Changes
Mean ± SD	391.6 ± 108.0	435.9 ± 137.6	44.3 ± 69.6	392.5 ± 105.9	399.8 ± 105.9	7.3 ± 53.5	37.0 ± 15.5 ^b 35.1 ± 13.7 ^c
Median	396.5	429.0	30.5	403.0	411.5	-4.0	
Percentiles (25 th , 75 th)	316.3, 487.5	364.5, 536.0	0.3, 93.8	— 468.8	360.8, 460.3	-30.0, 30.5	

^a One patient in the placebo group and one patient in the Idursulfase group died before week 53; imputation was by last observation carried forward in the intention-to-treat database

1.2 Brief Overview of Clinical Studies

Idursulfase is proposed to be indicated in the treatment of patients with MPS II disease, or Hunter syndrome. The evaluation of the effectiveness and safety of Idursulfase is based on one Phase 1/2 study that was extended to an open-label maintenance clinical study, and a Phase 2/3 study that had an open-label extension. In the Phase 1/2 study, a total of twelve patients with Hunter syndrome were enrolled in three groups of four, with a dose-escalating design to evaluate 0.15, 0.5 and 1.5 mg/kg dose levels. After six months of weekly dose administration, the open-label maintenance phase evaluated the 0.5 mg/kg weekly dose in all twelve patients.

In the Phase 2/3 study, 96 patients with Hunter syndrome were randomized to three treatment groups in a 1:1:1 allocation; placebo, Idursulfase 0.5 mg/kg weekly and Idursulfase 0.5 mg/kg every other week (EOW). The study involved six centers, located in the U.S., Germany, England and Germany. After 53 weeks of therapy, patients who had been assigned to either placebo or Idursulfase EOW were transitioned to treatment with Idursulfase weekly 0.5 mg/kg. At the time of this NDA submission, the open-label extension study was still ongoing, with a total duration planned for two years.

1.3 Statistical Issues and Findings

This reviewer explored, examined, and analyzed the applicant's data from the phase 2/3 study. This reviewer verified the applicant's findings for the primary efficacy composite variable and its components. As an exploratory evaluation, this reviewer applied a multiple comparisons procedure to the statistical results of the composite variable and its components, 6MWT and

FVC % Predicted. With the rejection of the global null hypothesis on the composite endpoint at an α of 0.05 serving as the gatekeeper, the Bonferroni-Holm procedure was applied to the tests on the components. This approach, if it had been pre-specified at the protocol stage, would have provided strong control of Type I error rate for the composite endpoint and follow-up tests on its components (Lehmacher, et al. 1991)². In the post-hoc exploratory evaluation of this approach, this reviewer found that the statistical conclusions about the composite endpoint and its components were not changed.

The Phase 2/3 study was small (92 MPS II patients total, with 64 allocated to Idursulfase) because MPS II is a relatively rare disorder. This small study may limit the extent to which the results can be generalized to the target population. However, this reviewer notes the consistency of supportive findings in the secondary efficacy endpoints.

The small study also limits the interpretation of results from subgroups of the study. The results from subgroups suggest that age and level of baseline disease severity may influence a patient's response to Idursulfase therapy. However, the study was too small to establish these relationships with certainty.

2. INTRODUCTION

2.1 Overview

Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) is a subgroup of lysosomal storage disorders in which each type of MPS is caused by the deficiency of a special lysosomal enzyme required for the catabolism of glycosaminoglycans (GAGs). MPS II, or Hunter syndrome, is a serious, debilitating, life-threatening disease that is caused by the deficiency of the lysosomal enzyme, iduronate-2-sulfatase (I2S). Insufficient levels of I2S lead to progressive accumulation of two glycosaminoglycans (GAG), dermatan sulfate and heparin sulfate, in nearly all organs and body tissues. The clinical manifestations of Hunter syndrome vary considerably from patient to patient with pathology in one organ system presenting the most prominent clinical problem in some patients and impairment in other organ systems presenting the biggest challenge in others. Despite the heterogeneity in the disease progression, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. The most common clinical signs and symptoms include slow mental development, enlarged tongue, coarse facial features, hearing loss, abnormal dentition, restrictive lung disease, hepatosplenomegaly, valvular heart disease, decreased joint range of motion, skeletal deformities and severe short stature. Due to a combination of bone disease, decreased respiratory capacity, and sleep apnea, with or without impaired cardiac function, individuals with Hunter syndrome suffer from chronic, severely diminished endurance.

² Lehmacher, W.; G. Wassmer and P. Reitmier. 1991 Procedures for two-sample comparisons with multiple endpoints controlling the experimentwise error rate.

In the latter stages of the disease, continued accumulation of GAG leads to progressive end-organ failure and significantly shortened life span. Death usually occurs in the second or third decade of life is most often from respiratory and/or cardiac failure.

Hunter syndrome is a rare disease with an estimated incidence of 1 in approximately 162,000 live births. The applicant reports that the current treatment of Hunter syndrome is palliative and focused on clinical symptoms. Bone marrow transplantation has been attempted in a small number of cases with mixed results.

Class and Indication

The investigational drug product is Idursulfase, or iduronate-2-sulfatase. Idursulfase is produced by recombinant DNA technology in a human cell line providing a human glycosylation profile, which is analogous to the naturally occurring enzyme. Idursulfase is being developed for the treatment of patients with Hunter syndrome. Idursulfase drug product is a solution for intravenous infusion and is formulated to a concentration of 2 mg/mL.

The proposed indication for Idursulfase is for the treatment of patients with Hunter syndrome.

History of Drug Development

In accordance with its potential to address a serious, unmet medical need, Idursulfase received Fast-Track designation in the US on July 14, 2004. Orphan Drug designation was granted on November 2001 by the Agency for long-term enzyme replacement therapy for patients with Hunter syndrome. Idursulfase was also designated an orphan medicinal product in the European Union on December 11, 2001 for treatment of MPS II on the grounds that at present, no satisfactory treatment has been authorized for patients affected by this disease.

Nonclinical studies with Idursulfase provided the basis for selecting the dose and regimens appropriate for further evaluation of Idursulfase in clinical trials.

The initial phase I/II trial, TKT008, explored the safety and clinical activity of Idursulfase compared with placebo in 12 patients with Hunter syndrome. Study TKT018 was an extension of TKT008, and extended Idursulfase therapy for the 12 patients for approximately 3.5 years. Study TKT018 was still ongoing at the time of this NDA submission. Results from TKT008, in combination with nonclinical data, were then used to select the dose of 0.5 mg/kg for the Phase II/III program. However, the optimal dose frequency was considered to be an open question at the end of TKT008. For this reason, two dose frequencies were evaluated in the Phase II/III program; weekly administration or every-other-week administration. The final study report for TKT024 is part of this NDA submission. The open-label extension of TKT024 is study TKT025EXT. Study TKT025EXT was still ongoing at the time of submission of this NDA.

Specific Studies Reviewed

TABLE 1 Clinical studies of Idursulfase in patients with Hunters syndrome

Protocol and Title (Status)	Doses (mg/kg)	Schedule	No. Enrolled	Age Range at Entry (yrs)
TKT008: A Phase I/II, randomized, placebo-controlled, multiple-dose, dose-escalation, safety and clinical activity study of iduronate-2-sulfatase replacement therapy in patients with mucopolysaccharidosis (MPS) II (Completed)	0.15 0.5 1.5 Placebo	Once every other week for 26 weeks IV	12 (3/dose group)	6.3-20.9
TKT024: A Phase II/III, randomized, double-blind, placebo-controlled clinical study evaluating the safety and efficacy of weekly and every other week dosing regimens of iduronate-2-sulfatase enzyme replacement therapy in patients with MPS II (Completed)	0.5 Placebo	Once weekly or once every other week for 52 weeks IV	96 (32/dose group)	4.9-30.9
TKT018: An open-label maintenance clinical study of iduronate-2-sulfatase replacement therapy in patients with MPS II (Ongoing)	Initially 0.15 0.5 1.5 then 0.5	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

Below are descriptions of the studies that are included in this application.

Study TKT008 was the first study of Idursulfase in humans, and enrolled twelve patients. This was a placebo-controlled, double-blind, dose-ranging study that was conducted to test the safety and clinical activity of Idursulfase in patients with Hunter syndrome. Three dose levels of Idursulfase were evaluated (0.15, 0.5 and 1.5 mg/kg) in a sequential, dose-escalating study design. Three groups of four patients per group (a total of 12 patients) were enrolled sequentially to receive the 3 escalating doses of Idursulfase, i.e., the first group received the 0.15 mg/kg dose or placebo, the second group received the 0.5 mg/kg dose or placebo, and the third group received the 1.5 mg/kg dose or placebo. Within each dose group, patients were randomized to receive Idursulfase or placebo in a 3:1 ratio. A single dose of Idursulfase or placebo was administered every other week for 6 months (12 doses). Because this was the first use of Idursulfase in humans, an extensive battery of tests and evaluations was performed. These included pulmonary function tests, abdominal/cerebral magnetic resonance imaging, echocardiograms, 6MWT, sleep studies, joint mobility assessments, quality-of-life assessments, urine GAG levels, serum Idursulfase antibody levels and routine laboratory tests.

The primary endpoint of the study was measurement of urinary GAG levels, selected as a potential predictor of clinical efficacy. The statistical methodology was primary descriptive, with inferential approaches employed only for changes in urine GAG levels. The efficacy assessments in TKT008 were based on the percent change from baseline and the mean change from baseline.

Study TKT018 was the open-label extension study of TKT008, and all twelve patients from TKT008 consented to participate in TKT018. Patients who had received active study drug in TKT008 continued on the same dose, and each of the three individual placebo patients were assigned to receive one of the three original TKT008 doses (i.e., 0.15, 0.5 and 1.5 mg/kg). Upon final analysis of the results from TKT008, all patients were then transitioned to a common dose of 0.5 mg/kg (October or November 2002). The study endpoints and patient assessments evaluated in TKT008 were also evaluated in TKT018. The study report for TKT018 submitted with this NDQA provides an analysis of two years of treatment with Idursulfase.

Study TKT024 was a randomized, double-blind, placebo-controlled Phase II/III clinical study. This study was conducted in four countries: Brazil, Germany, the US and the UK. Patients were enrolled and randomized equally (1:1:1) to 1 of 3 treatment arms: IV infusions of Idursulfase 0.5 mg/kg administered on either a weekly or every other week basis, or weekly IV infusions of placebo. Patients randomized to receive every other week infusions of Idursulfase were administered placebo infusions in the alternate weeks to maintain the treatment blind. All patients received IV infusions of study drug administered over 3 hours every week for 1 year (or a total of 52 infusions) on an out-patient basis. Efficacy and safety outcomes were determined at baseline (week 0) and at 4 month intervals (weeks 18, 36 and 53).

TABLE 2 Study TKT024; Randomization of patients by study center

Study Center	Idursulfase Weekly	Idursulfase Every Other Week	Placebo
Chapel Hill, NC and St. Louis, MO ¹	6	7	7
Oakland, CA	3	2	3
Houston, TX	2	2	2
Total in US	11	11	12
Porto Alegre, Brazil	7	7	7
Mainz, Germany	7	6	6
Manchester, London, and Cambridge, UK ²	7	8	7
Total in non-US countries	21	21	20
Overall Totals	32	32	32

¹ The St. Louis, MO study site was an infusion-only satellite site for Chapel Hill, NC
² The London and Cambridge study sites were infusion-only satellite sites for Manchester, UK

The study's inclusion criteria included patients with a confirmed diagnosis of Hunter syndrome, aged 5 to 25 years, who were able to comply with protocol requirements. Patients who met the initial screening criteria based on their medical histories and who signed an informed consent were enrolled on a preliminary basis. Immediately following enrollment in the study, pulmonary function testing was performed twice on two separate days to determine their continued eligibility for the study. As one of the entry criteria, patients were required to have an abnormal FVC, expressed as the percent of the predicted FVC for that patient's age and height. This variable will be called "FVC % Predicted" in this review. An abnormal level of FVC % Predicted was an entry criterion so that it would be possible to detect an improvement in this variable as a response to therapy. Patients whose FVC was less than 80% of predicted were eligible to complete the remaining baseline evaluations during week 0. The results of all baseline evaluations were reviewed to determine final eligibility for participation in the study. Eligible patients were then randomized and received their first infusion of study drug within 7 days of completion of the baseline evaluations.

The primary efficacy endpoint was a composite variable based on two clinical endpoints: (1) the change in baseline to week 53 in FVC % predicted and (2) the change in baseline to week 52 in the 6MWT. This endpoint is discussed in greater detail in part 3.1 of this review. The primary comparison in TK024 was between the Idursulfase weekly treatment vs. placebo.

Study TKT024EXT is the open-label two-year extension study of TKT024. Upon their completion of TKT024, patients who had been assigned to either placebo or EOW Idursulfase were transitioned to treatment with weekly 0.5 mg/kg Idursulfase. Efficacy is scheduled to be assessed every 4 months during the first year and every six months during the second year. At the time of this NDA submission, study TKT024EXT was ongoing. Safety data but not efficacy data is included in this submission from study TKT024EXT.

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

The phase II/III clinical study TKT024 was selected for a full statistical review and evaluation because it is the only randomized, double-blind, placebo-controlled study in this application. Data from this study may provide most of the substantial evidence for efficacy and safety of Idursulfase for this proposed indication.

Major Statistical Issue: The composite endpoint

The primary efficacy endpoint was a single composite variable which combined two individual clinical measurements: (1) the distance walked (in meters) in the six-minute walk test (6MWT); and (2) the forced vital capacity (FVC), measured as FVC % Predicted. Each endpoint was expressed as a change from week 53 relative to baseline. The method of combining these two different aspects of the Hunter syndrome involved ranking each patient's change from baseline

separately on the two endpoints, and then adding together the ranks (as described in O'Brien (1984³)).

The protocol for study TKT024 specified the composite of $k=2$ endpoints, 6MWT and FVC % Predicted as the primary efficacy endpoint. This reviewer notes that the composite of k endpoints may be appropriate in situations where no single endpoint fully captures the clinical response to treatment. From a statistical perspective, the composite endpoint can provide a reasonable test of the global null hypothesis of no overall treatment effect. This is because the test is sensitive to the alternative hypothesis that the components show a response in one direction, as might occur in a clinical response to treatment (O'Brien, 1984).

From a clinical perspective, the components of the composite endpoint have an important role in the efficacy evaluation. 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. If the global null hypothesis of no overall treatment effect is rejected, a follow-up evaluation of 6MWT and FVC % Predicted may be very 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 FVC % Predicted 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.

2.2 Data Sources

The applicant submitted this BLA including the data to the FDA CBER Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in TABLE 3. All the data submitted are in SAS v.5 transport format.

TABLE 3 Study TKT024; Data source

Document: BLA 125151/0	Company: Transkaryotic Therapies Inc.
CBER EDR link: \\... \BLA125151\roadmap.pdf	
Letter Date: 12/2/2005	Stamp Date: 12/2/2005
Drug: Idursulfase; iduronate-2-sulfatase	Path \crt\datasets\TKT024\

³ O'Brien, P.C. 1984. Procedures for comparing samples with multiple endpoints. *Biometrics* 40:1079-1087.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Randomization

The allocation of patients across treatment groups and the stratification variables used in randomization was reasonably well balanced. Randomization was stratified by baseline disease severity and age category. Baseline disease severity had three ordered levels and was based on the sum of two baseline scores, baseline FVC % Predicted and baseline distance walked in the 6-minute walk test (6MWT), as shown in TABLE 4. Although the randomization strata were based on the overall baseline disease severity score, the distribution of patients across each component of the sum was also relatively balanced (TABLE 4). TABLE 6 summarizes the distribution of patients across the three age strata (5 to 11 years, 12 to 18 years, and 19 to 25 years). The allocation across three regions represented by centers in the study was also relatively balanced, and is shown in TABLE 5.

TABLE 4 Allocation of patients across treatment groups and levels of baseline disease severity

Baseline Forced Vital Capacity (FVC % Predicted)						
% of Predicted	Severity	Score	number randomized ¹			
			Placebo	Idursulfase Weekly	Idursulfase EOW	
≥ 70% to < 80%	Mild	1	4	7	6	
≥ 50% to < 70%	Moderate to moderate severe	2	18	13	12	
< 50%	Severe to very severe	3	10	12	14	
Total			32	32	32	
Baseline 6-Minute Walk Test (6MWT)						
Distance Walked (m)	Severity	Score	Placebo	Idursulfase Weekly	Idursulfase EOW	
≥ 500	Mild to normal	1	4	6	6	
≥ 300 to < 500	Moderate	2	24	20	21	
< 300	Severe	3	4	6	5	
Total			32	32	32	
Baseline Disease Severity Score (FVC % Predicted + 6MWT)						
Baseline FVC + 6MWT scores		Score	Placebo	Idursulfase Weekly	Idursulfase EOW	
2		1	0	2	2	
3-4		2	21	17	17	
5-6		3	11	13	13	
Total			32	32	32	

TABLE 5 Allocation of treatment group assignment across region

	Placebo	Idursulfase Weekly	Idursulfase EOW	Totals
North America	12 (35.3%)	11 (32.4%)	11 (32.4%)	34
South America	7 (33.3%)	7 (33.3%)	7 (33.3%)	21
Europe	13 (31.7%)	14 (34.1%)	14 (34.1%)	41
				96

3.1.2. Patient disposition

A total of 96 patients, 32 in each of the three treatment groups, were randomized into the study. Of the 96 patients randomized, 94 completed one year of treatment (31/32 in the placebo, 31/32 in weekly Idursulfase and 32/32 in Idursulfase EOW). Two patients died during the study: Patient 012-0008 in the Idursulfase weekly group died 12 days after his first and only dose of the study drug due to respiratory insufficiency leading to cardiac arrest. Patient 020-0003 in the placebo group died 10 days after his week 34 dose due to pneumonia.

3.1.3. Patient demographic and baseline characteristics

A summary of patient demographic characteristics is provided in TABLE 6 . Baseline disease characteristics are summarized in TABLE 7 .

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TABLE 6 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

Source: Study TKT024 Clinical Study Report, Table 11.2-1

TABLE 7 Summary of baseline disease characteristics by treatment group: ITT 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) ¹					
n	31	31	28	59	90
Mean (SE)	25.4 (3.3)	30.4 (3.8)	27.5 (4.5)	29.9 (2.9)	27.8 (2.2)
Median	24.0	30.0	24.0	24.0	24.0
Min, Max	<1, 72.0	<1, 84.0	<1, 96.0	<1, 96.0	<1, 96.0
Duration of Hunter syndrome from date of diagnosis to date of study entry (months)					
n	32	32	32	64	96
Mean (SE)	100.0 (13.6)	119.3 (13.4)	120.3 (15.2)	119.8 (10.1)	113.2 (8.2)
Median	77.4	97.8	113.4	101.4	97.8
Min, Max	8.4, 276.0	13.2, 311.0	4.8, 310.8	4.8, 311.0	4.8, 311.0
Baseline FVC % Predicted (%)					
n	32	32	32	64	Not combined
Mean (SE)	55.6 (2.2)	55.3 (2.8)	55.1 (2.4)	55.2 (1.8)	
Median	57.4	54.9	54.6	54.9	
Min, Max	30.0, 75.8	16.0, 79.8	27.5, 79.3	16.0, 79.8	
Baseline 6MWT (meters)					
n	32	32	32	64	Not combined
Mean (SE)	392.5 (18.7)	391.6 (19.1)	400.6 (17.9)	396.1 (13.0)	
Median	403.0	396.5	416.5	407.5	
Min, Max	49, 540	90, 565	156, 554	90, 565	
¹ Data on age of onset of symptoms of Hunter syndrome were not reported for 6 patients					
Source: Study TKT025 Clinical Study Report, Table 11.2-2					

3.1.4. Analysis databases

Because 94 of the 96 patients who were randomized also completed the study, the pre-defined analysis populations were fairly similar to each other (see section 3.1.2. for more detail). The analysis population for the primary efficacy analysis was based on the intention-to-treat (ITT) population, consisting of all 96 randomized patients. Missing observations from patients 012-0008 and 020-0003 were imputed by carrying forward either the last observation or the last rank, depending on the method of analysis. The modified-ITT (MITT) population excluded only patient 012-0008 because he did not have any post-baseline efficacy evaluations. The remaining 94 patients were included in the completer population, and they also all met the criteria for the per protocol (PP) population.

The safety analyses for study TKT024 were conducted using the safety population, consisting of all patients who received at least one dose, or partial dose, of study drug.

3.1.5. Primary efficacy endpoints and analyses

Primary efficacy endpoint: The primary efficacy endpoint was a single composite variable which combined two individual clinical measurements: (1) the distance walked (in meters) in the six-minute walk test (6MWT); and (2) the forced vital capacity (FVC), measured as FVC % Predicted. The method of combining these two different aspects of the Hunter syndrome involved ranking each patient separately on the two endpoints, and then adding together the ranks (as described in O'Brien (1984)). The process of developing the composite primary endpoint is described in more detail in TABLE 8, TABLE 9, and TABLE 10.

This reviewer selected nine patients, including the two who had imputed endpoints, to follow the steps that were used to construct the primary efficacy endpoint. This reviewer confirmed the calculations for these patients, and also obtained the same summary statistics that were reported by the applicant for each treatment group. The results for the nine selected patients are shown in TABLE 10.

TABLE 8 Steps for determining the final form of the 6MWT endpoint for the composite endpoint

Steps	6MWT term	Description
1	6MWT _{time}	A patient's 6MWT measurement at a given evaluation time
2	6MTW _{week53-baseline}	The difference in 6MWT between week 53 and baseline
3	Rank[6MWT _{week53-baseline}]	The rank of the difference, among all 96 patients. The smallest change value is assigned a rank of 1, the next larger change value is assigned a rank of 2, and so on; the largest change value has a rank of 96.
<p>Imputation for Step 1: 6MWT is determined at baseline and weeks 18, 36 and 53. The 6MWT is performed twice at each of the visits (once per day on two different days). The highest 6MWT reading reflecting the patient's best effort of the two tests will be used for all analyses. If one of the tests is not done then the data from the remaining test will be used in the analysis.</p> <p>Imputation for Step 3: If 6MWT is missing a week 53 value, then the Last Rank Carried Forward (LRCF) method, based on the entire pool of patients, will be used for imputation.</p>		

TABLE 9 Steps for determining the final form of the FVC endpoint for the composite endpoint

Steps	FVC term	Description
1.	FVC_{time}	A patient's FVC measurement at a given evaluation time
2.	$FVC \% \text{ Predicted}_{time} = (FVC_{time} \div FVC \text{ Predicted}_{time}) \times 100$	
	<u>Age group</u>	<u>FVC Predicted</u>
	Age 5 to 7 years ^a	$=(4.4 \times 10^{-3} \times \text{Height(cm)}^{2.67})/1000$
	Age 8 to 19 years ^b	$= -0.2584 + -0.20415 \times \text{Age} + 0.010133 \times \text{Age}^2 + 0.00018642 \times \text{Height(cm)}^2$
	Age \geq 20 years ^b	$= -0.1933 + 0.00064 \times \text{Age} + -0.000269 \times \text{Age}^2 + 0.00018642 \times [\text{Height(cm)}]^2$
3.	$FVC \% \text{ predicted}_{\text{week53-baseline}}$	The difference in % predicted FVC between week 53 and baseline.
4.	$\text{Rank}[FVC \% \text{ predicted}_{\text{week53-baseline}}]$	The rank of the difference, among all patients
<p>Imputation for Step 1: FVC is determined at baseline and weeks 18, 36 and 53. The spirometry testing is performed twice at each of the visits (once per day on two different days). The highest FVC reading reflecting the patient's best effort of the two tests will be used for all analyses. If one of the tests is not done then the data from the remaining test will be used in the analysis.</p> <p>Imputation for Step 4: If FVC % Predicted is missing a week 53 value, then the Last Rank Carried Forward (LRCF) method, based on the entire pool of patients, will be used for imputation.</p> <p>^a Polgar, G. and V. Promodhat. 1971. Pulmonary function testing in children: techniques and standards. W.B. Saunders (Philadelphia).</p> <p>^b Hankinson, J.L., J.R. Odencrantz, and K.B. Fedan. 1999. Spirometric reference values from a sample of the general U.S. population. <i>Am J Respir Crit Care Med</i> 159: 179-187.</p>		

TABLE 10 6MWT°FVC Composite primary endpoint, with examples of calculations

Subj ID and group P=Placebo IW=Idursulfase weekly	6MWT _{week53-baseline} (m)	FVC % predicted week53-baseline	Rank [6MWT week53-baseline]	+ Rank [FVC % predicted week53-baseline]	= 6MWT° FVC composite endpoint
012-0001 (P)	588-514 = 74	47.9-48.4= -0.5	52	+ 28.5	= 80.5
012-0002 (IW)	120-222 = -102	64.8-63.4 = 1.4	1	+ 35	= 36
012-0004 (IW)	414-360 = 54	26.0-27.1 = -1.1	44	+ 26	= 70
012-0006 (IW)	460-288= 172	67.5-75.1 = -7.6	63	+ 11	= 74
012-0009 (P)	445-459= -14	62.8-65.4= -2.6	18	+ 23	= 41
012-0011 (P)	360-189= 171	54.8-63.4 = -8.6	62	+ 8	= 70
012-0012 (IW)	668-565= 103	84.5-65.0 = 19.5	57	+ 59	= 116
012-0008 ^a (IW)	[.] - 90.0 = [.]	[.] -30.3= [.]	[2]	+ [4]	= [6]
020-0003 ^b (P)	[420]-484=[-64]	[37.1]-41.3=[-4.2]	[5]	+ [10]	= [15]

[Numbers in square brackets] indicate situations where primary imputation rules were used.
^a Subject 012-0008 died on day 12. The rank of the change at week 53 was imputed from the rank at baseline.
^b Subject 020-0003 died after week 34. The rank of the change at week 53 was imputed from the rank of the change at week 18.

Statistical considerations in the use of a composite endpoint: The protocol for study TKT024 specified the composite of $k=2$ endpoints, 6MWT and FVC % Predicted as the primary efficacy endpoint. This reviewer notes that the composite of k endpoints may be appropriate in situations where no single endpoint fully captures the clinical response to treatment. From a statistical perspective, the composite endpoint can provide a reasonable test of the global null hypothesis of no overall treatment effect. This is because the test is sensitive to the alternative hypothesis that the components show a response in one direction, as might occur in a clinical response to treatment (O'Brien, 1984).

From a clinical perspective, the components of the composite endpoint have an important role in the efficacy evaluation. 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. If the global null hypothesis of no overall treatment effect is rejected, a follow-up evaluation of 6MWT and FVC % Predicted may be very 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 FVC % Predicted 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.

For exploratory purposes, this reviewer evaluated the 6MWT and FVC % Predicted tests 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 % Predicted. 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 components (Lehmacher, et al. 1991)⁴.

Primary statistical analysis method for primary efficacy endpoint: The primary efficacy analysis of the FVC*6MWT composite variable was an analysis of covariance (ANCOVA). Treatment group and study center were factors, and baseline age group (three stratification levels) and baseline disease score (three stratification levels) were covariates. The primary comparison was between the patients treated weekly with Idursulfase and the patients treated with placebo.

Results of the primary analysis: This reviewer confirmed the results of the primary analysis of the composite endpoint. The Idursulfase weekly group was significantly different from the placebo group with respect to the change from week 53 to baseline (TABLE 11). This difference was in the direction of a greater improvement in the combined response of 6MWT and FVC % Predicted in the Idursulfase weekly group compared with the placebo (TABLE 11).

This reviewer also confirmed the results of the analysis of covariance of the two component endpoints. Patients in the Idursulfase weekly group had a greater average improvement in 6MWT distance at week 53 compared with the placebo group. This comparison had a p-value of 0.01. Patients in the Idursulfase weekly group had a greater average improvement in FVC % Predicted at week 53 compared with the placebo group; however, the 95% confidence interval of this comparison included 0 and the p-value for this comparison was 0.07.

⁴ Lehmacher, W., G. Wassmer and P. Reitnuer. 1991. Procedures for two-sample comparisons with multiple endpoints controlling the experimentwise error rate.

TABLE 11 Summary of the primary efficacy analysis for the composite endpoint and for its components, 6MWT and FVC % Predicted: (1) Using the full ITT population, and (2) Excluding the Brazilian site

	Idursulfase Weekly Week53-Baseline Mean (SE)	Placebo Week53- Baseline Mean (SE)	Idursulfase Weekly – Placebo Mean (95% CI)	p-value
(1) Primary efficacy analysis ^a: ITT population				
	n=32	n=32		
6MWT•FVC composite endpoint	69.8 (7.0)	50.9 (8.1)	19.0 (6.0, 31.9)	0.0049
6MWT ^b	36.9 m (10.9)	1.9 m (11.8)	35.1 (7.7, 62.5)	0.0131
FVC % Predicted	1.3% (1.7)	-3.0% (1.9)	4.3 (-0.3, 8.8)	0.0650
(2) Additional sensitivity analysis: ITT population, excluding Brazilian site (So. American region)				
	n=25	n=25		
6MWT•FVC composite endpoint	77.3 (7.1)	55.3 (8.4)	21.9 (6.8, 37.1)	0.0055
6MWT	58.6 m (12.7)	20.4 m (13.8)	38.2 (3.9, 72.4)	0.0298
FVC % Predicted	3.0% (1.9)	-2.0% (2.0)	5.0 (-0.3, 10.3)	0.0661
<p>^a The analysis of covariance (ANCOVA) model for the composite endpoint included treatment group and study center as factors. The covariates were baseline age group (three stratification levels) and baseline disease score (three stratification levels). The correlation between the ranked values of 6MWT and FVC % Predicted in the primary efficacy endpoint is 0.19.</p> <p>^b The ANCOVA model for 6MWT used the original scale of measurement (distance walked in meters). Treatment group and study center were factors. The covariates were baseline age group and baseline 6MWT. The ANCOVA model for FVC%Predicted used the original scale of measurement (% of Predicted FVC). Treatment group and study center were factors. The covariates were baseline age group and baseline FVC % Predicted. The correlation between the model residuals from the ANCOVA of 6MWT and the ANCOVA of FVC % Predicted was -0.07.</p>				

This reviewer notes that the exploratory application of the gatekeeper / Bonferroni-Holmes procedure for multiple comparisons resulted in a similar conclusion about efficacy. First, the global null hypothesis on the composite endpoint would be rejected. Second, the follow-up test on the 6MWT component had the smaller of the two p-values, which would be significant at an α of 0.05. Finally, the follow-up test on the FVC % Predicted component would not be significant at an α of 0.025 (TABLE 11).

Sensitivity analysis for primary efficacy endpoint: The applicant conducted several pre-specified sensitivity analyses on the primary efficacy endpoint. The ANCOVA analysis was applied to alternate 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.

This reviewer also evaluated the composite endpoint and its components in the subset of the ITT database formed by excluding the 21 patients from the Brazilian site. This was the only site in the South American region. The reason for the exclusion was to assess the influence of this site on the overall study results. The statistical results were not changed with the exclusion of the Brazilian site (TABLE 11).

3.1.6. Secondary efficacy endpoints and analysis

The results from the analysis of secondary efficacy endpoints were generally supportive of the efficacy evaluation of Idursulfase (TABLE 12). Secondary efficacy endpoints included the joint range of motion (JROM), liver volume, spleen volume, level of urine glycosaminoglycan (GAG) and cardiac left ventricular mass. Each of these variables was expressed as a change from baseline to week 53, and analyzed by an ANCOVA. The results for urine GAG, liver volume and spleen volume in the Idursulfase groups showed reductions at week 53 compared to baseline. A reduction in these endpoints would support the efficacy of Idursulfase. The comparison of the Idursulfase groups to placebo in the reduction of liver volume, spleen volume, and level of urine GAG all have p-values less than 0.05 (TABLE 12). The results for JROM and cardiac left ventricular mass were inconclusive (TABLE 12).

The comparisons between the Idursulfase EOW group and the placebo for the 6MWT•FVC composite endpoint and its two components, 6MWT and FVC % Predicted, were also considered a secondary efficacy analysis. Of these, the comparison of Idursulfase EOW vs. placebo in the composite endpoint had a p-value less than 0.05 ((TABLE 12). However, the average improvement of the Idursulfase EOW group was generally larger than the average in the placebo group for 6MWT and FVC % Predicted at week 53 compared to baseline.

TABLE 12 Secondary efficacy endpoints and comparisons between treatment groups with ITT patient population

ITT Population		Difference between groups Week 53 - Baseline		
Endpoint (units)	Treatment Comparison	p-value	Mean (SE)	95% CI
6MWT•FVC composite endpoint (summed ranks)				
	Idursulfase EOW vs Placebo	0.04	12.9 (6.2)	0.5, 25.2
	Idursulfase Weekly vs EOW	0.13	10.8 (7.1)	-3.4, 25.1
	All Idursulfase vs. Placebo	0.01	23.7 (8.6)	6.7, 40.7
6MWT (m)				
	Idursulfase EOW vs Placebo	0.07	23.8 (13.0)	-2.3, 49.9
	Idursulfase Weekly vs EOW	0.40	13.2 (15.4)	-17.7, 44.1
	All Idursulfase vs. Placebo	0.02	29.8 (12.3)	5.4, 54.1

ITT Population		Difference between groups Week 53 - Baseline		
Endpoint (units)	Treatment Comparison	p-value	Mean (SE)	95% CI
FVC % Predicted (%)				
	Idursulfase EOW vs Placebo	0.95	0.1 (2.1)	-4.0, 4.3
	Idursulfase Weekly vs EOW	0.11	3.5 (2.1)	-0.8, 7.8
	All Idursulfase vs. Placebo	0.27	2.1 (1.9)	-1.7, 5.9
Global JROM Score				
	Idursulfase Weekly vs Placebo	0.73	0.4 (1.2)	-2.0, 2.9
	Idursulfase EOW vs. Placebo	0.35	-1.2 (1.3)	-3.8, 1.4
	Idursulfase Weekly vs. EOW	0.19	1.5 (1.1)	-0.8, 3.7
	All Idursulfase vs. Placebo	0.67	-0.5 (1.1)	-2.6, 1.7
Liver Volume (cc; Percent change)				
	Idursulfase Weekly vs Placebo	<0.01	-25.2 (2.2)	-29.6, -20.8
	Idursulfase EOW vs. Placebo	<0.01	-23.1 (2.2)	-27.5, -18.5
	Idursulfase Weekly vs. EOW	0.38	-2.2 (2.5)	-7.2, 2.8
	All Idursulfase vs. Placebo	<0.01	-24.2 (1.9)	-28.0, -20.4
Spleen Volume (cc; Percent change)				
	Idursulfase Weekly vs Placebo	<0.01	-33.2 (4.8)	-42.8, -23.6
	Idursulfase EOW vs. Placebo	<0.01	-26.7 (5.7)	-38.0, -15.3
	Idursulfase Weekly vs. EOW	0.22	-4.5 (3.7)	-12.0, 2.9
	All Idursulfase vs. Placebo	<0.01	-30.8 (4.1)	-39.0, -22.7
Normalized Urine Glycosaminoglycan levels (µg GAG/mg Creatinine)				
	Idursulfase Weekly vs Placebo	<0.01	-275.5 (30.1)	-335.8, 215.3
	Idursulfase EOW vs. Placebo	<0.01	-212.1 (28.8)	-269.8, -154.3
	Idursulfase Weekly vs. EOW	0.04	-46.6 (22.1)	-90.8, -2.4
	All Idursulfase vs. Placebo	<0.01	-241.2 (23.8)	-288.4, -194.0
Cardiac Left Ventricular Mass Index				
	Idursulfase Weekly vs Placebo	0.60	-3.3 (6.4)	-16.1, 9.4
	Idursulfase EOW vs. Placebo	0.62	2.8 (5.6)	-8.4, 14.0
	Idursulfase Weekly vs. EOW	0.56	-3.3 (5.6)	-14.5, 7.9
	All Idursulfase vs. Placebo	0.99	0.0 (5.0)	-10.0, 10.0

The Medical Division requested an exploration of the correlation between selected efficacy endpoints: the 6MWT•FVC composite endpoint and its components, liver and spleen volume, and urinary GAG. However, this reviewer noted that the correlation estimates, apart from the expected high correlations between the composite endpoint and its components, were not very stable. Correlation estimates were subject to change, depending on whether and how missing data from a small number of subjects was imputed, and whether or not a rank-based correlation was calculated. The small size of the study may have contributed to this instability. A more detailed exploration of the relationships among these endpoints, including an assessment of possible time lags in their expression, and the influence of other factors, is beyond the scope of the present review.

3.1.7. Efficacy conclusions

This reviewer confirmed the results of the primary analysis of the primary efficacy endpoint, the composite endpoint 6MWT•FVC. The Idursulfase weekly group had a significantly greater improvement from week 53 to baseline compared to placebo, with respect to the composite 6MWT•FVC endpoint ($p=0.0416$). The pre-specified primary analysis was an analysis of covariance on the intention-to-treat (ITT) database.

The components of the endpoint were pre-specified as secondary efficacy endpoints. This reviewer confirmed that patients in the Idursulfase weekly group had a greater average improvement in 6MWT distance at week 53 compared with the placebo group ($p=0.0131$). Patients in the Idursulfase weekly group had a greater average improvement in FVC % Predicted at week 53 compared with the placebo group; however, the 95% confidence interval of this comparison included 0 and the p-value for this comparison was 0.0650.

The pre-specified sensitivity analysis of the primary efficacy endpoint did not change the statistical findings. The sensitivity analysis involved the primary analysis method with alternate versions of the analysis database, and an alternative analysis method (the Wilcoxon rank-sum test) with the ITT database and the alternate analysis databases. However, the pre-defined analysis databases were relatively similar to each other, because 94 of the 96 patients who were randomized also completed the study. This reviewer also evaluated the composite endpoint and its components in the subset of the ITT database formed by excluding the 21 patients from the Brazilian site (the only site in the South American region). The statistical results were not changed with the exclusion of the Brazilian site.

The results from the analysis of secondary efficacy endpoints were generally supportive of the efficacy evaluation of Idursulfase. The results for urine GAG, liver volume and spleen volume in the Idursulfase groups showed reductions at week 53 compared to baseline. A reduction in these endpoints would support the efficacy of Idursulfase. The comparison of the Idursulfase groups to placebo in the reduction of liver volume, spleen volume, and level of urine GAG all have p-values less than 0.05. The results for JROM and cardiac left ventricular mass were inclusive.

3.1.8. Recommendations for labeling on efficacy results

Because the results from the composite endpoint may be challenging to interpret from a clinical perspective, and because the 6MWT component had a p-value less than 0.05 while the FVC % Predicted component did not, this reviewer suggested the following format for presenting the efficacy results in the labeling text under the Clinical Studies heading (TABLE 13):

TABLE 13 Recommended table for summarizing the 6 minute walk test in labeling

Results from the 6-Minute Walk Test (Meters)

	Idursulfase Weekly n=32 ^a			Placebo n=32 ^a			Idursulfase Weekly – Placebo
	Baseline	Week 53	Change	Baseline	Week 53	Change	Difference in Changes
Mean ± SD	391.6 ± 108.0	435.9 ± 137.6	44.3 ± 69.6	392.5 ± 105.9	399.8 ± 105.9	7.3 ± 53.5	37.0 ± 15.5 ^b 35.1 ± 13.7 ^c
Median	396.5	429.0	30.5	403.0	411.5	-4.0	
Percentiles (25 th , 75 th)	316.3, 487.5	364.5, 536.0	0.3, 93.8	316.3, 468.8	360.8, 460.3	-30.0, 30.5	

^a One patient in the placebo group and one patient in the Idursulfase group died before week 53; imputation was by last observation carried forward in the intention-to-treat database

3.2 Evaluation of Safety

The safety portion of the statistical review addresses specific issues that were of interest to the medical division. These issues include the infusion reactions and the immunogenicity response from Study TKT024 and its open-label extension Study TKT024EXT. Of special interest were the relationships among the occurrence of Idursulfase antibodies, the occurrence of infusion-related reactions, the level of urinary GAG, and the change in 6MWT from baseline to week 53 in study TKT024. Although urinary GAG and 6MWT are efficacy endpoints, the exploration of how the safety endpoints interact with the efficacy outcomes will be included in this section of the review.

The applicant submitted a safety update on January 30, 2006 which summarized data that was available up to July 19, 2005. This update also provided new information concerning the immunogenicity status of patients, following the results of a new assay for Idursulfase antibodies. Due to differences in study designs, dosing regimens and dose levels, the applicant did not pool safety data across studies for an integrated statistical analysis of data. Instead, the safety report was organized by study.

Exposure to Idursulfase: The overall exposure to Idursulfase in the safety database, as of July 19, 2005, expressed as the total number of infusions administered in the Idursulfase clinical studies, is summarized in TABLE 14.

TABLE 14 Total numbers of infusions administered in the Idursulfase clinical studies

	TKT008/TKT018			TKT024		TKT024EXT
	0.15 mg/kg EOW	0.5 mg/kg EOW	1.5 mg/kg EOW	0.5 mg/kg Weekly	0.5 mg/kg EOW	0.5 mg/kg Weekly
Number of Patients	4 ^a	12 ^{a,b}	4 ^a	32 ^c	32	94 ^d
Total Number of Infusions	415	949	376	1580	1629	2373
Total Number of Clinical Infusions ^e	376	828	335	1580	1629	393
Total Number of Commercial Infusions	0	121	0	0	0	2000

EOW=Every other week.

^a Includes patients randomized to placebo in TKT008.

^b All patients were transitioned to 0.5 mg/kg every other week from October to November 2002.

^c One patient died after receiving only 1 dose of idursulfase in TKT024.

^d All patients who completed TKT024, including patients randomized to placebo.

^e During TKT008/018, patients received both Phase I/II Drug Product and Phase II/III Drug Product. Patients in TKT018 also received commercial Drug Product. During TKT024 patients received only Phase II/III Drug Product. During TKT024EXT, patients received Phase II/III and commercial Drug Product.

Antibody status: For purposes of this reviewer's exploration of the relationship between antibody status and other outcomes, a patient was classified as "antibody negative" if he/she had no serum samples with Idursulfase antibodies during the study that is being analyzed, and "antibody positive" if he/she had at least one serum sample with Idursulfase antibodies during the course of the study.

During the course of TKT024, 30 of the 64 patients treated with Idursulfase in TKT024 were determined to be antibody positive. A total of 47 of the 94 patients treated with Idursulfase during the course of TKT024 and TKT024EXT were determined to be positive for Idursulfase antibodies. The positive determination was for IgG antibodies.

Antibody status and overall adverse event rate: Antibody status did not appreciably affect the overall rate of reporting adverse events (AE). All 30 IgG antibody-positive patients in TKT024 experienced a total of 1136 AEs, for an average event rate of 37.9 events per patient (TABLE 15). This adverse event rate is somewhat greater than the adverse event rate in the antibody-negative patients, but the difference is not very great: The 34 antibody-negative patients experienced a total of 1090 AEs, for an average event rate of 32.1 AEs per patient (TABLE 16). The adverse event rate in the placebo group of TKT024 is somewhat smaller: 32 antibody-negative patients in the placebo group experienced a total of 992 AEs, for an average event rate of 31.0 AEs per patient (TABLE 17).

Infusion-related adverse events: The applicant defined an infusion-related adverse event as an AE that met two criteria: (1) the AE was either probably or possibly related to study drug; and (2) the AE occurred within 24 hours from the start of an infusion. Overall, 202 infusion-related AEs were experienced by 22 patients in the Idursulfase weekly groups (22/32, 68.8%; TABLE 15), 145 infusion-related AEs were experienced by 22 patients in the Idursulfase EOW group (22/32, 68.8%; TABLE 16), and 128 infusion-related AEs were experienced by the 21 patients in the

placebo group (21/32, 65.6%; TABLE 17). The most frequently reported infusion-related AEs were similar among all dose groups and included headache, pruritus, pyrexia, hypertension, rash, urticaria, flushing, hypertension NOS, abdominal pain NOS and fatigue.

Antibody status and infusion-related adverse events: Patients in the antibody positive subgroup of the Idursulfase weekly group appeared to have more infusion-related AEs than patients in the antibody negative subgroup. Fourteen of 15 patients in the antibody positive subgroup experienced at least one infusion-related AE (93.3%), and 164 infusion-related AEs were reported for this subgroup, giving an average infusion-related AE rate of 10.7/patient (TABLE 15). In contrast, 8 of 17 patients in the antibody negative subgroup experienced at least one infusion-related AE (47.1%), and 38 infusion-related AEs were reported in this subgroup, giving an average infusion-related AE event rate of 2.2/patient. The largest difference between the two subgroups in the frequency of AEs appeared to be in the system-organ-class categories of “skin and subcutaneous tissue disorders,” and “general disorders and administrative site conditions,” although in general the number of events recorded for the antibody positive subgroup were greater than in the antibody negative subgroup for all of the categories shown in TABLE 15.

In contrast to the tendency for more infusion-related AEs in the antibody positive subgroup of the Idursulfase weekly group than in the antibody negative subgroup, the two subgroups in the Idursulfase EOW group appeared to be relatively similar in infusion-related adverse events. Eleven out of 15 patients in the antibody positive subgroup of Idursulfase EOW experienced at least one infusion-related AE (73.3%) and 68 infusion-related AEs were reported for this subgroup, giving an average infusion-related AE rate of 4.5/patient (TABLE 16). Similarly, 11 out of 17 patients in the antibody negative subgroup experienced at least one infusion-related AE (64.7%), and 77 infusion-related AEs were reported in this subgroup, also giving an average infusion-related AE event rate of 4.5/patient (TABLE 16).

In the extension study TKT024EXT, 21 of the 47 antibody positive patients experienced at least one infusion-related AE (44.7%), and 131 infusion-related AEs were reported for this subgroup, giving an average infusion-related AE rate of 2.8/patient (TABLE 18). In the antibody negative subgroup, 20 of 47 patients experienced at least one infusion-related AE (42.6%), and 137 infusion-related AEs were reported in this subgroup, giving an average infusion-related AE event rate of 2.9/patient (TABLE 18). This reviewer notes that this summary includes the increase in infusion-related AEs that would take place during the first several weeks of TKT024EXT while the placebo patients from TKT024 crossed over to Idursulfase weekly treatments.

TABLE 15 Study TKT024, Idursulfase Weekly group; Summary of the most common infusion-related AEs for patients in subgroups determined by antibody status

System Organ Class Preferred Term ²	Idursulfase Weekly			
	IgG Positive ¹ n=15		IgG Negative n=17	
	Patients	Events	Patients	Events
All patients with treatment-emergent AEs	15	587	17	476
All infusion-related AEs from any system organ class	14/15 93%	164/587 28%	8/17 47%	38/476 8%
Nervous system disorders	6/15 40%	14/587 2%	4/17 24%	7/476 2%
• Headache	5/15 33%	8/587 1%	4/17 24%	6/476 1%
Vascular disorders	6/15 40%	20/587 3%	3/17 18%	9/476 2%
• Hypertension NOS	4/15 27%	15/587 3%	2/17 12%	4/476 1%
• Flushing	2/15 13%	2/587 0%	1/17 6%	5/476 1%
Skin and subcutaneous tissue disorders	8/15 53%	40/587 7%	3/17 18%	9/476 2%
• Pruritis	4/15 27%	7/587 1%	3/17 18%	4/476 1%
• Rash NOS	3/15 20%	6/587 1%	2/17 12%	2/476 0%
• Urticaria NOS	3/15 20%	8/587 1%	2/17 12%	2/476 0%
General disorders and administrative site conditions	9/15 60%	46/587 8%	2/17 12%	2/476 0%
• Pyrexia	6/15 40%	34/587 6%	1/17 6%	1/476 0%

Notes:
¹A patient was classified as “IgG positive” if at least one serum sample collected over the course of TKT024 tested positive for IgG with either the ELISA or the CSA assay.
²A system-organ-class was included if at least 3 antibody-positive patients experienced an AE in this s-o-c category.
Sources: TKT024 Clinical Study Report Tables 14.3.1.8 and 14.3.1.1; ISS/Amendment 003 Table 2.7.4-19

TABLE 16 Study TKT024, Idursulfase EOW group; Summary of the most common infusion-related AEs for patients in subgroups determined by antibody status

System Organ Class Preferred Term ²	Idursulfase EOW			
	IgG Positive ¹ n=15		IgG Negative n=17	
	Patients	Events	Patients	Events
All patients with treatment-emergent AEs	15	549	17	614
All infusion-related AEs from any system organ class	11/15 73%	68/549 12%	11/17 65%	77/614 13%
Nervous system disorders	2/15 13%	9/549 2%	5/17 29%	10/614 2%
• Headache	1/15 7%	8/549 2%	5/17 29%	8/614 1%
Vascular disorders	4/15 27%	7/549 1%	7/17 41%	11/614 3%
• Hypertension NOS	0/15 0%	0/549 0%	4/17 24%	2/614 1%
• Flushing	3/15 20%	4/549 1%	2/17 12%	2/614 1%
Skin and subcutaneous tissue disorders	6/15 40%	26/549 5%	3/17 18%	15/614 2%
• Pruritis	2/15 13%	5/549 1%	2/17 12%	2/614 0%
• Rash NOS	3/15 20%	11/549 2%	3/17 18%	10/614 2%
• Urticaria NOS	2/15 13%	6/549 1%	1/17 6%	1/614 0%
General disorders and administrative site conditions	3/15 20%	15/549 3%	8/17 47%	18/614 3%
• Pyrexia	2/15 13%	7/549 1%	5/17 29%	12/614 2%

Notes:

¹A patient was classified as "IgG positive" if at least one serum sample collected over the course of TKT024 tested positive for IgG with either the ELISA or the CSA assay.

²A system-organ-class was included if at least 3 antibody-positive patients experienced an AE in this s-o-c category.

Sources: TKT024 Clinical Study Report Tables 14.3.1.8 and 14.3.1.1; ISS/Amendment 003 Table 2.7.4-19

TABLE 17 Study TKT024, Placebo group; Summary of the most common infusion-related AEs based on results from the Idursulfase groups

System Organ Class Preferred Term	Placebo Group n=32	
	Patients	Events
All patients with treatment-emergent AEs	32	992
All infusion-related AEs from any system organ class	21/32 66%	128/992 13%
Nervous system disorders	9/21 43%	16/992 2%
• Headache	7/21 33%	11/992 1%
Vascular disorders	10/21 48%	19/992 2%
• Hypertension NOS	6/21 29%	8/992 1%
• Flushing	3/21 14%	4/992 0%
Skin and subcutaneous tissue disorders	8/21 38%	32/992 3%
• Pruritis	3/21 14%	6/992 1%
• Rash NOS	6/21 29%	23/992 2%
• Urticaria NOS	0/21 0%	0/992 0%
General disorders and administrative site conditions	9/21 43%	27/992 3%
• Pyrexia	8/21 38%	24/992 2%

Notes:
¹All placebo patients were antibody negative.
²A system-organ-class was included in this table if at least 3 antibody-positive patients in the Idursulfase groups experienced an AE in this s-o-c category.

Sources: TKT024 Clinical Study Report Tables 14.3.1.8 and 14.3.1.1

TABLE 18 Study TKT024EXT, all patients; Summary of the most common infusion-related AEs for patients in subgroups determined by antibody status

System Organ Class Preferred Term ²	All Patients ¹			
	IgG Positive n=47		IgG Negative n=47	
	Patients	Events	Patients	Events
All patients with treatment-emergent AEs	47	605	47	700
All infusion-related AEs from any system organ class	21/47 45%	131/605 22%	20/47 43%	137/700 20%
Nervous system disorders	6/47 13%	13/605 2%	10/47 22%	18/700 3%
• Headache	4/47 9%	10/605 2%	8/47 17%	13/700 2%
Vascular disorders	6/47 13%	16/605 3%	4/47 9%	11/700 2%
• Flushing	4/47 9%	14/605 2%	3/47 6%	9/700 1%
Gastrointestinal disorders	7/47 15%	11/605 2%	5/47 11%	9/700 1%
• Vomiting NOS	3/47 6%	4/605 1%	0/47 0%	0/700 0%
Skin and subcutaneous disorders	11/47 23%	42/605 7%	4/47 9%	64/700 9%
• Erythema	5/47 11%	15/605 3%	2/47 4%	15/700 2%
• Urticaria NOS	4/47 9%	9/605 2%	2/47 4%	16/700 2%
• Rash NOS	3/47 6%	5/605 1%	2/47 4%	9/700 1%
General disorders and administration site conditions	3/47 6%	16/605 3%	9/47 19%	22/700 3%
• Pyrexia	3/47 6%	10/605 1.7%	3/47 6%	6/700 1%
• Rigors	3/47 6%	4/605 1%	0/47 0%	0/700 0%

Notes:

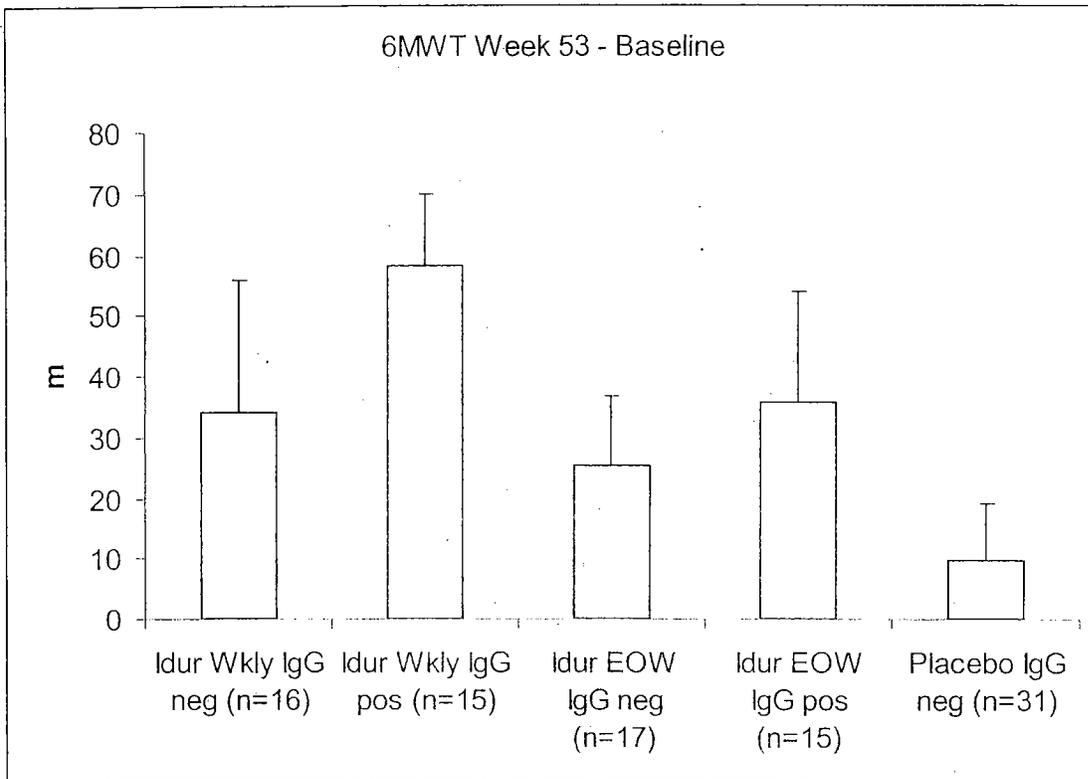
¹A patient was classified as “IgG positive” if at least one serum sample collected over the course of TKT024 and TKT024EXT tested positive for IgG with either the ELISA or the CSA assay.

System Organ Class Preferred Term ²	All Patients ¹			
	IgG Positive n=47		IgG Negative n=47	
	Patients	Events	Patients	Events
² A system-organ-class was included if at least 3 patients experienced an AE in this s-o-c category. Source: ISS/Amendment 003; Table 2.7.4-21				

Antibody status and 6MWT: This reviewer explored the 6MWT results (change from baseline to week 53 in TKT024) in subgroups defined by antibody status. The purpose of this assessment was to address a concern that a patient’s overall improvement, as measured by the 6MWT, might decline in the presence of Idursulfase antibodies. If this were the case, then patients who tested positive for Idursulfase antibodies might show less improvement in the 6MWT than patients in the same treatment group who tested negative. The exploration of subgroups did not detect a pattern consistent with the concern that Idursulfase antibodies might interfere with improvement on the 6MWT (FIGURE 1). In fact, the average improvement in 6MWT was somewhat greater in the subgroup of patients who were antibody positive than in the subgroup who were antibody negative. However, the differences between group means are not large compared with the variability of response in each subgroup. This exploratory finding is consistent with the interpretation that the occurrence of Idursulfase antibodies did not decrease the performance on the 6MWT efficacy at 53 weeks compared to baseline. However, this reviewer notes that it may be difficult to detect this pattern and separate it from other influences on the patients’ performance on the 6MWT.

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FIGURE 1 6MWT results and Idursulfase antibody status in TKT024



Mean + SE for patients who completed the 53 week study. A patient was classified as IgG positive ("IgG pos") with one or more positive serum samples during the study. Otherwise the patient was classified as IgG negative ("IgG neg").

Infusion reactions and 6MWT: The applicant defined an infusion reaction as an infusion-related AE that was characteristic of allergic reactions. An infusion reaction was a subset of all of the infusion-related AEs that included: tachycardia NOS, cyanosis NOS, hypertension NOS, flushing, hypotension NOS, hot flushes NOS, tachypnoea, wheezing, dyspnoea NOS, hypoxia, swollen tongue, rash NOS, pruritis, urticaria NOS, rash pruritic, erythema, rash macular, face oedema, pruritus generalized, urticaria generalized, pyrexia, rigors, blood pressure increased or heart rate increased.

Infusion reactions occurred at a relatively similar rate across the treatment groups in TKT024, using three different methods of summarizing infusion reactions per patient (TABLE 19).

TABLE 19 Study TKT024; Rate of infusion reactions by week 53, ITT patient population

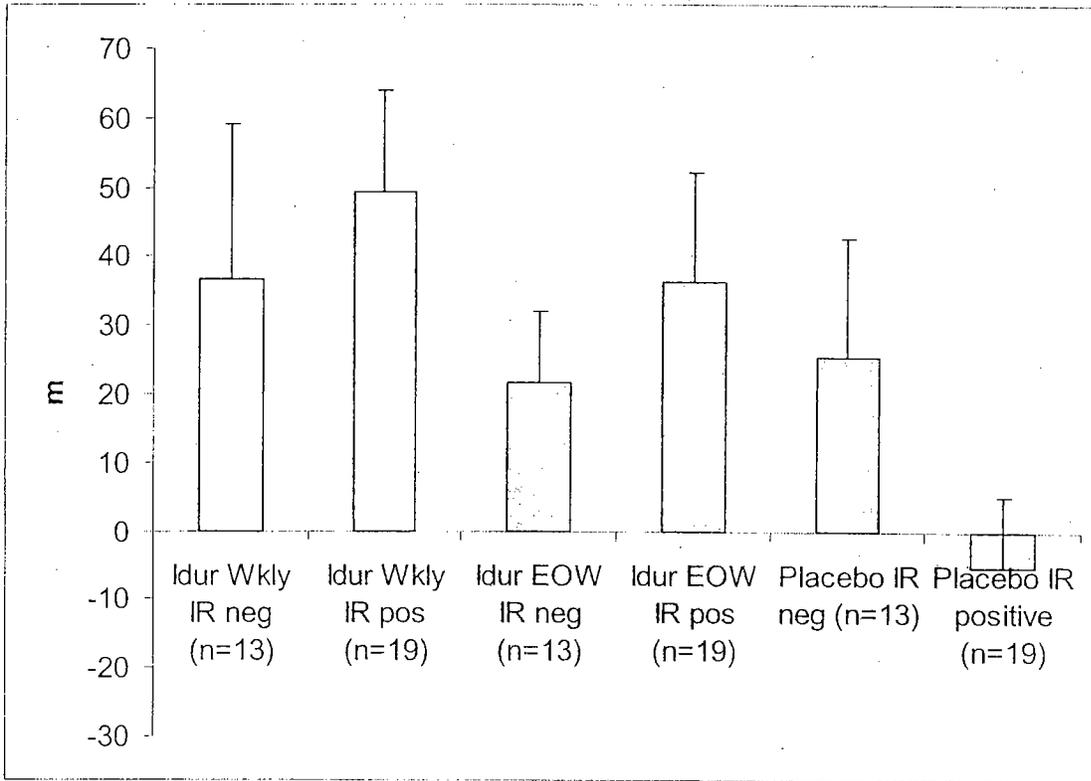
Definition of infusion reaction	Idursulfase Weekly	Idursulfase EOW	Placebo
Patients with at least one infusion-related AE ¹	22/32 (69%)	22/32 (69%)	21/32 (66%)
Patients with at least one infusion reaction ²	19/32 (59%)	19/32 (59%)	19/32 (59%)
Patients with at least 5 infusion reactions	8/32 (25%)	9/32 (28%)	6/32 (19%)
Patients with at least 5 infusions with infusion reactions	6/32 (19%)	8/32 (25%)	6/32 (19%)

¹ An infusion-related AE was defined as any related AE that occurred within 24 hours after the start of an infusion
² An infusion reaction was a subset of the infusion-related AEs that met certain criteria for allergic reactions
 Source: TKT024 Clinical Study Report, section 11.4.2.8.8, Table 11.4-26, Table 14.4.3 and Table 14.4.1.1

Out of a concern that if a patient had an infusion reaction the investigator may guess at the identity of the study medication, and because the 6MWT has a voluntary component, the protocol for study TKT024 included several measures to minimize such bias during the conduct of the 6MWT. These measures included: (1) a requirement that each site have only one individual administer all of six-minute walk tests at all study visits, and that that individual be independent of the immediate study staff, including the investigator and the site coordinator; (2) a requirement that the test administrator not have contact with the family; and (3) specific instructions on how to conduct the test, including a script for the test administrator to follow during the test.

This reviewer evaluated the 6MWT endpoint, the change from baseline to week 53, in two subgroups; one subgroup of patients who had not experienced any infusion reactions and one subgroup of patients who had experienced one or more. If there were some bias associated with the infusion reaction, then patients who experienced one or more infusion reactions might tend to show more improvement on the 6MWT than patients in the same treatment group who did not. However, an analysis of subgroups did not detect this pattern (FIGURE 2). The average improvement in 6MWT was actually somewhat greater in patients in the Idursulfase groups who experienced at least one infusion reaction than in those who did not. In the placebo group, the average improvement in 6MWT in patients who experienced at least one infusion reaction was less than the average improvement in patients who did not experience one. As an exploratory analysis, the applicant also fit several analysis of covariance models. None of these models detected an effect of infusion reaction on the average improvement in 6MWT (see Tables 14.4.4.1 and 14.4.4.2 of the TKT024 Clinical Study Report).

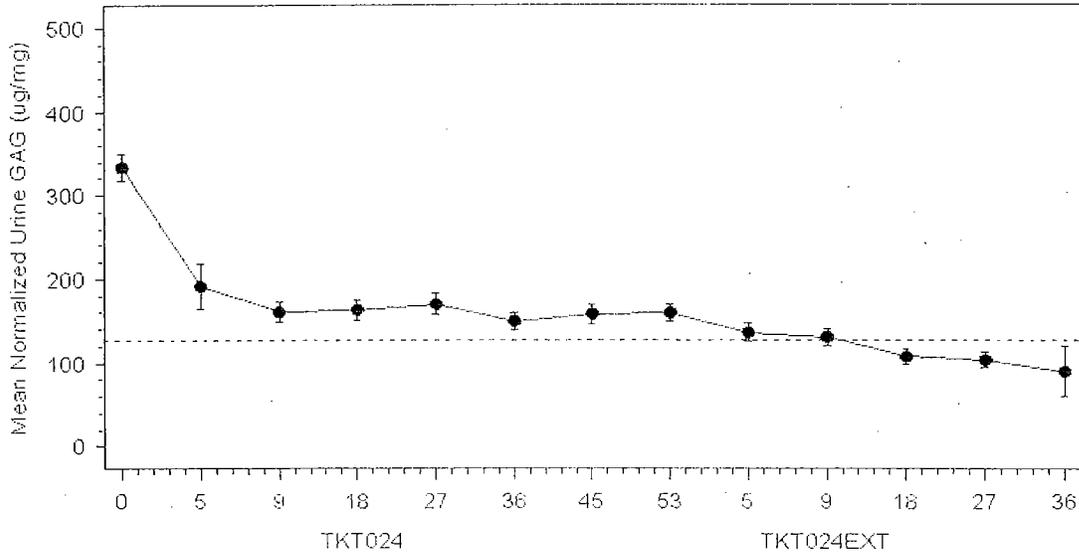
FIGURE 2 Study TKT024; 6MWT results in patients with and without one or more infusion reactions



Source: TKT024 Clinical Study Report, Table 14.4.1.1. IR neg: Patients who did not experience any infusion reactions, baseline to week 53; IR pos: Patients who experienced at least one infusion reaction, baseline to week 53; 6MWT is the average change from baseline to week 53 in total distance (m)

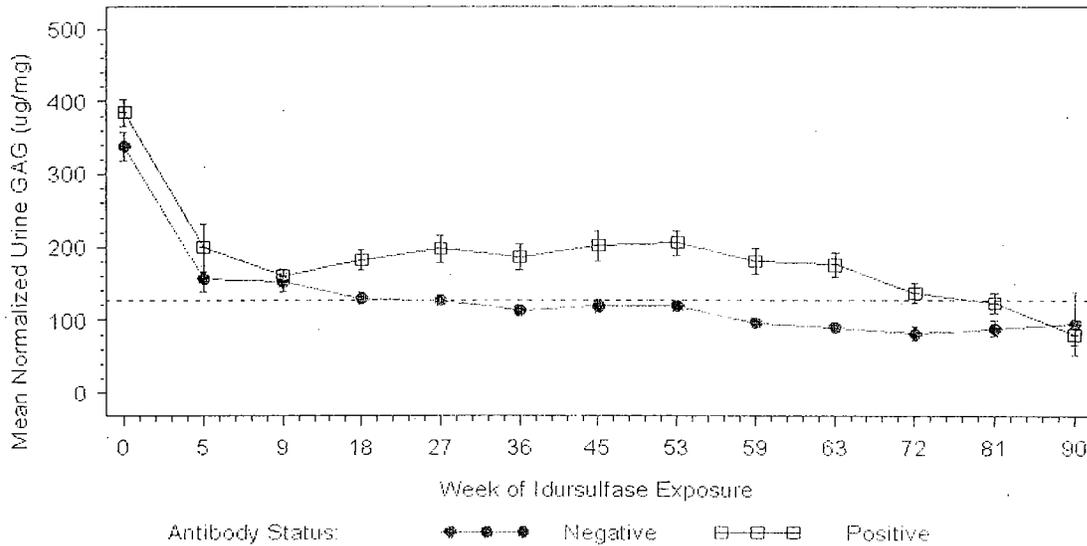
Antibody status and urine GAG levels: Mean urine GAG levels for all treated patients decreased by week 5 compared to baseline, and continued to decline through the last available sample point (week 36 in TKT024EXT; FIGURE 3). The two antibody subgroups (antibody positive and antibody negative) had a similar profile of mean urine GAG levels over time until week 18. After week 18, the antibody positive patients had a larger mean urine GAG than the antibody negative patients (FIGURE 4). After 72 weeks of treatment (the week 18 visit in TKT024EXT), the profiles of the two subgroups began to converge.

FIGURE 3 Mean normalized urine GAG levels for all patients treated with Idursulfase from the first infusion (TKE024 and TKT024EXT)



Source: Figure 2.7.4-11. The dotted line represents the upper limit of normal (126 $\mu\text{g}/\text{mL}$ creatinine)

FIGURE 4 Mean normalized urine GAG levels for all patients treated with Idursulfase from the first infusion, by antibody status (TKT024 and TKT024EXT)



Source: Figure 2.7.4-12. The dotted line represents the upper limit of normal (126 $\mu\text{g}/\text{mL}$ creatinine).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The results from an examination of the age subgroups in study TKT024 suggest that age may influence a patient’s response to Idursulfase therapy. However, the study is too small to establish this relationship with certainty. Because all study subjects were male, and the majority were Caucasian (TABLE 6), part 4.1 of this review concerns only the age subgroups. In age groups 5 to 11 years and 12 to 18 years, the patients in the Idursulfase weekly group showed more improvement than the placebo, and also more improvement than the Idursulfase EOW group, with respect to 6MWT and FVC % Predicted (TABLE 20). The oldest patients, aged 19 to 25, appeared to show more improvement in the Idursulfase EOW group than the Idursulfase weekly group relative to the placebo (TABLE 20), for the 6MWT.

TABLE 20 Summary statistics by baseline age group and treatment group for 6MWT and FVC % Predicted, expressed as change from baseline to week 53

		Baseline Age Category in Years		
		Mean (SE), Week 53 - Baseline		
		5 to 11	12 to 18	19 to 25 ¹
6MWT (m)	Idursulfase Weekly	59.1 (20.9)	47.1 (23.3)	14.8 (14.5)
	Idursulfase EOW	24.2 (16.0)	27.7 (11.5)	42.4 (25.3)
	Placebo	10.2 (11.9)	15.6 (23.4)	-10.9 (15.0)
FVC % Predicted (%)	Idursulfase Weekly	4.8 (3.5)	3.4 (2.8)	1.2 (1.6)
	Idursulfase EOW	1.8 (1.8)	-0.8 (3.6)	-2.1 (1.2)
	Placebo	4.2 (3.1)	-3.6 (2.3)	-0.5 (1.4)
Number of subjects per group				
	Idursulfase weekly	14	10	8
	Idursulfase EOW	14	9	9
	Placebo	15	10	7

¹ The 19 to 25 age group included 5 subjects who were over 25 years: 2 in the placebo group, 1 in the Idursulfase weekly group and 2 in the Idursulfase EOW group.

4.2 Other Special/Subgroup Populations

Level of severity at baseline: The results from subgroups of this study suggest that age and level of baseline disease severity may influence a patient’s response to Idursulfase therapy. However, the study is too small to establish these relationships with certainty. In the subgroups that did not have the most severely affected status at baseline, patients in the Idursulfase weekly group showed more improvement than either the placebo or the Idursulfase EOW group (TABLE 21). Patients in the most severely affected baseline status showed somewhat more improvement in the

Idursulfase EOW group than in the Idursulfase weekly group, with respect to 6MWT and FVC % Predicted.

The younger patients were more likely to be in the more severely affected categories at baseline than the older patients (TABLE 22). The applicant also noted that patients in the Brazilian site (the only site in the South America region) had the lowest mean change in score for both the Idursulfase and placebo groups. This site/region had more patients in the younger age group than the other regions, and more than half of the patients in this site/region had a baseline disease severity score of 5 or 6 (TABLE 23).

TABLE 21 Summary statistics by level of baseline severity and treatment group for 6MWT and FVC % Predicted

Mean (SE), Week 53 - Baseline			
Baseline 6MWT categories			
6MWT (m)	1 ≥ 500 m	2 ≥ 300 to < 500 m	3 <300 m
Idursulfase Weekly	73.7 (23.9) n=6	35.3 (14.4) n=20	45.0 (39.8) n=6
Idursulfase EOW	-1.5 (27.4) n=6	30.1 (9.0) n=21	69.4 (41.1) n=5
Placebo	0.0 (30.5) n=4	4.7 (9.4) n=24	30.0 (47.3) n=4
Baseline FVC categories			
FVC % Predicted (%)	1 ≥ 70% to < 80%	2 ≥ 50% to < 70%	3 <50%
Idursulfase Weekly	28.0 (8.7) n=7	46.2 (4.6) n=13	29.8 (3.8) n=12
Idursulfase EOW	28.3 (7.3) n=6	33.4 (6.3) n=12	33.9 (3.8) n=14
Placebo	17.3 (7.6) n=4	33.4 (4.6) n=18	25.7 (4.9) n=10

TABLE 22 Age and level of disease severity at baseline

	Baseline Age Category in Years		
	5 to 11	12 to 18	19 to 25 ¹
Baseline Disease Status categories ²			
2	---	1 (3.4%)	3 (7.0%)
3-4	7 (29.2%)	16 (55.2%)	32 (74.4%)
5-6	17 (70.8%)	12 (41.4%)	8 (18.6%)
Baseline 6MWT categories			
1 (≥ 500 m)	3 (12.5%)	4 (13.8%)	9 (20.1%)
2 (≥ 300 to < 500 m)	13 (54.2%)	20 (69.0%)	32 (74.4%)
3 (< 300 m)	8 (33.3%)	5 (17.2%)	2 (4.7%)
Baseline FVC categories			
1 ($\geq 70\%$ to $< 80\%$)	1 (4.2%)	4 (13.8%)	12 (27.9%)
2 ($\geq 50\%$ to $< 70\%$)	6 (25.0%)	15 (51.7%)	22 (51.2%)
3 ($< 50\%$)	17 (70.8%)	10 (34.5%)	9 (20.9%)

¹ The 19 to 25 age group included 5 subjects who were over 25 years: 2 in the placebo group, 1 in the Idursulfase weekly group and 2 in the Idursulfase EOW group.

² The Baseline Disease Status categories result from the sum of the baseline 6MWT categories and the baseline FVC categories.

TABLE 23 Summary statistics by region and treatment group for 6MWT and FVC % Predicted

		Mean (SE), Week 53 - Baseline		
		Region		
		North America	South America	Europe
6MWT (m)	Idursulfase Weekly	51.9 (12.0)	-12.7 (9.8)	66.8 (23.4)
	Idursulfase EOW	41.0 (14.3)	-3.3 (16.7)	38.7 (18.2)
	Placebo	-6.4 (10.1)	-34.0 (13.6)	42.2 (15.5)
FVC % Predicted (%)	Idursulfase Weekly	1.0 (2.9)	0.2 (3.0)	7.0 (2.9)
	Idursulfase EOW	-0.3 (2.2)	-1.3 (2.4)	0.9 (2.3)
	Placebo	5.9 (3.1)	-0.9 (2.5)	-3.1 (2.3)
Number of subjects	Idursulfase Weekly	11	7	14
	Idursulfase EOW	11	7	14
	Placebo	12	7	13

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical considerations in the use of a composite endpoint: At the protocol stage of study TKT024, the Agency concurred with the composite of $k=2$ endpoints, 6MWT and FVC % Predicted, as the primary efficacy endpoint. The composite of k endpoints may be appropriate in situations where no single endpoint fully captures the clinical response to treatment. From a statistical perspective, the composite endpoint can provide a reasonable test of the global null hypothesis of no overall treatment effect. This is because the test is sensitive to the alternative hypothesis that the components show a response in one direction, as might occur in a clinical response to treatment (O'Brien, 1984).

From a clinical perspective, the components of the composite endpoint have an important role in the efficacy evaluation. 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. If the global null hypothesis of no overall treatment effect is rejected, a follow-up evaluation of 6MWT and FVC % Predicted may be very 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 FVC % Predicted 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.

For exploratory purposes, this reviewer evaluated the 6MWT and FVC % Predicted tests 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 % Predicted. 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 components (Lehmacher, et al. 1991)⁵. This exploratory approach did not change the statistical conclusions.

⁵ Lehmacher, W., G. Wassmer and P. Reitmier. 1991. Procedures for two-sample comparisons with multiple endpoints controlling the experimentwise error rate.

5.2 Conclusions and Recommendations

Efficacy

Based on an evaluation of the applicant's analysis, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust to different approaches to the analysis. The results from the statistical analysis support the conclusion that Idursulfase is superior to placebo with respect to the composite 6MWT•FVC endpoint.

Results from the analysis of the 6MWT component of the composite endpoint supported the overall conclusion that Idursulfase is superior to the placebo with respect to the improvement in 6MWT between week 53 and baseline. Results from the analysis of the FVC % Predicted component of the composite endpoint were supportive but less conclusive. Results of the analysis of other secondary efficacy endpoints, such as urinary GAG, liver volume and spleen volume, were also supportive of the overall conclusion concerning the efficacy of Idursulfase in patients with Hunter's syndrome.

This reviewer provided recommendations for revising the draft labeling text and tables concerning the statistical findings from study TKT024.

Safety

With respect to safety, the inclusion of a warning about infusion reactions and a description of adverse reactions in the labeling text appear to be appropriate from a statistical perspective, given the findings on adverse events and infusion-associated reactions.

SIGNATURES/DISTRIBUTION LIST

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Mathematical Statistician

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Stella Grosser, Ph.D. *Stella Grosser 5/3/06*

S. Edward Nevius, Ph.D. *S. Edward Nevius 5/9/06*

cc:

BLA 125151/0
HFD-180/CStark, JKu, JHyde, BHarvey
HFD-715/ENevius, SGrosser
HFD-700/LPatrician, RO'Neill