Aldurazyme® (laronidase)

Biologics License Application BL 128058

Sponsor Briefing Document for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Aldurazyme® (laronidase) is a recombinant form of human α-L-iduronidase under investigation as an enzyme replacement therapy for patients deficient in the enzyme who have the lysosomal storage disorder, mucopolysaccharidosis I (MPS I). This briefing document contains a summary of the key information that supports the safety and efficacy of Aldurazyme to treat MPS I patients. These key points are:

1) MPS I is a rare, progressive and life threatening disorder with a challenging breadth, depth and heterogeneity of symptoms. MPS I represents an unmet medical need; the treatment options for the majority of MPS I patients are limited to symptomatic care.
2) Aldurazyme contains the recombinant form of the normal human α-L-iduronidase enzyme that is taken up efficiently by affected cells. It replaces the deficient enzyme and has been demonstrated to be effective in both in vitro and in vivo models.
3) MPS I patients treated with Aldurazyme have a rapid decrease in lysosomal storage as measured by reduced liver and spleen size, and urinary GAG excretion, demonstrating that the enzyme can correct the enzyme deficiency.
4) MPS I patients experienced significant clinical benefit after treatment with Aldurazyme as demonstrated by improvements in respiratory function (pulmonary function and airway obstruction) and functional capacity (walking and joint function) as well as improvements in other heterogeneous aspects of MPS I disease.
5) Aldurazyme has an acceptable safety profile and infusion-associated reactions are manageable.
6) Aldurazyme has a favorable risk-benefit profile.

This section of the document contains an executive summary that reviews the main points of the briefing document. The body of the document contains an introduction to MPS I and the rationale for enzyme replacement therapy. This is followed by an overview of the preclinical pharmacology and toxicology. The clinical development program is outlined and data on clinical pharmacology, efficacy, and safety in the Phase 3 Double-Blind Study, the Phase 3 Open-Label Extension Study and the Phase 1/2 Study are summarized. Finally, a risk-benefit assessment is made based on the data within the Biologics License Application for Aldurazyme.

1.1 Description of the Disease: Mucopolysaccharidosis I (MPS I)

Mucopolysaccharidosis I (MPS I) is a rare (1:100,000 births), progressive, and life-threatening lysosomal storage disorder that results in the accumulation of excessive amounts of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate in all organs and tissues of the body (Neufeld, 2001, McGraw-Hill). The disease affects children and is most commonly diagnosed in early childhood beginning as young as 1-2 years of age. The pathophysiology of MPS I is based on the effects of lysosomal storage in all tissues and body systems that causes a complex combination of disease symptoms of varying onset, severity and progression. Hurler, Hurler-Scheie and Scheie syndrome are the common terms used to describe the severe, intermediate and milder points on the spectrum of clinical severity. Patients with any form of MPS I are deficient in α-L-iduronidase and have substantial medical morbidity and mortality.

Cardiopulmonary disease and functional impairment are consistently among the most important clinical manifestations of MPS I. Progressive storage in the airway, heart and lungs as well as alterations of the thoracic and vertebral skeleton lead to decreased respiratory function and serious complications such as respiratory insufficiency, airway obstruction, and complex congestive heart failure. In addition to decreased cardiopulmonary function, joint stiffness, pain and contractures contribute to reduced physical functional ability such as walking or running. Common daily activities such as brushing teeth or putting on a sweater become impossible tasks due to the progressive storage in the joints and connective tissues. A variety of other important clinical manifestations occur in MPS I patients and all are caused by progressive lysosomal storage. In patients with severe disease, mental retardation and neurodegeneration begin early in life. In all MPS I patients, the continued progression of disease leads to diminished physical activity and functional status, resulting in immobility and, often, a bedridden state. Most MPS I patients die in late childhood and early adulthood from pulmonary or cardiac causes. (Neufeld, 2001, McGraw-Hill)

The treatment options for the majority of MPS I patients are limited to symptomatic care. Bone marrow transplantation (BMT) has been used in patients with the severe phenotype (Hurler) and has demonstrated some efficacy in patients who survive the procedure and engraft (Vellodi, 1997, Arch Dis Child)(Peters, 1998, Blood).

Since the storage of GAG is the fundamental pathophysiology underlying MPS I, an effective and safe therapeutic for MPS I must treat the underlying lysosomal storage in order to address the impairments in respiratory and physical function and the variety of other major medical problems experienced by MPS I patients.

1.2 Description of the Drug Product: Aldurazyme (laronidase)

Aldurazyme (laronidase) contains a recombinant form of human α-L-iduronidase (rhIDU), a normal lysosomal enzyme involved in the stepwise degradation of the GAGs, heparan sulfate and dermatan sulfate. Aldurazyme is under investigation as an enzyme replacement therapy for patients genetically deficient in α-L-iduronidase with the lysosomal storage disorder MPS I.

The recombinant form of human α-L-iduronidase is produced in Chinese hamster ovary cells transfected with the human iduronidase cDNA. The enzyme is secreted into the medium and purified to 99% or greater purity. The enzyme is a soluble monomeric glycoprotein with an apparent molecular weight of 83 kD. The secereted enzyme contains mannose 6-phosphate moieties on its N-linked carbohydrates that mediate high affinity uptake by the large mannose 6-phosphate receptor present on the surface of virtually all cells. Uptake via this receptor targets the enzyme for transport to the lysosome. This efficient uptake and targeting process is the fundamental feature of Aldurazyme that allows it to correct the deficiency of α-L-iduronidase that occurs in patients with MPS I.

1.3 Rationale for Aldurazyme as Enzyme Replacement Therapy for MPS I

The rationale for rhIDU treatment is based on the fundamental biology of lysosomal enzymes derived from scientific research of the last 30 years. Dr. Neufeld and colleagues demonstrated correction of the defect in MPS I fibroblasts in 1968 but were unable to apply the treatment to patients due to the lack of an adequate source of high-uptake enzyme (Fratantoni, 1969, Proc Natl Acad Sci USA). The corrective activity of rhIDU enzyme is dependent on mannose-6-phosphate markers on its N-linked oligosaccharides that have been shown to mediate high-affinity uptake of the enzyme at concentrations in the ~1 nanomolar range and correction of GAG storage in the ~1 picomolar range in vitro (Sando, 1977, Cell).

The efficiency of the uptake mechanism and the efficacy of enzyme replacement in MPS I in vivo have been established in a series of preclinical studies (Shull, 1994, Proc Natl Acad Sci USA)(Kakkis, 1996, Biochem Mol Med)(Kakkis, 2001, Mol Genet Metab). The results from these studies formed the basis for the clinical studies of rhIDU, which used a dose that is known from canine MPS I studies to provide receptor-saturating concentrations of rhIDU in the bloodstream and to correct lysosomal storage (Kakkis, 1996, Biochem Mol Med). The data did not show significant reduction of storage within the brain as expected due to the blood-brain barrier. The in vitro and animal studies have demonstrated the rational biologic basis for enzyme replacement therapy in MPS I and verified that the mechanisms of enzyme replacement described in vitro 30 years ago do function in animal models of MPS disease.

1.4 Overview of Clinical Development Program

A series of 3 clinical trials have been performed to evaluate the clinical pharmacology, efficacy, and safety of weekly intravenous administration of rhIDU at a dose of 100 units/kg (0.58 mg/kg) in human MPS I patients:

1. Phase 3 Double-Blind Study (ALID-003-99)—a 26-week, placebo-controlled, multinational, multi center study of 45 patients (23 randomized to placebo and 22 to rhIDU). The primary efficacy variables were the percent of predicted normal forced vital capacity (FVC) and the 6-Minute Walk Test. Secondary efficacy variables were liver size, apnea-hypopnea index, shoulder flexion range of motion and the Child Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ).
2. Phase 3 Open-Label Extension Study (ALID-006-01)—an open-label, extension of the Phase 3 Double-Blind Study in which all 45 patients received active rhIDU treatment; 24-week data from this ongoing study are reported; rhIDU/rhIDU patients also received rhIDU during the Phase 3 Double-Blind Study for a total of 50 weeks rhIDU treatment; placebo/rhIDU patients received placebo during the Phase 3 Double-Blind Study for a total of 24 weeks of rhIDU treatment. The efficacy variables were the same as the double-blind phase but comparisons within groups pre and post treatment are made for statistical purposes. For the primary efficacy variables, data through the 36-week timepoint are also reported.
3. Phase 1/2 Study (BIO7500-001)—an open-label study of 10 patients; efficacy evaluations through Week 152 and safety reporting up to Week 235 from this ongoing study are reported. The primary efficacy variables were liver and spleen size, and urinary GAG excretion. Secondary and other variables include cardiac function (NYHA score), sleep apnea, joint range of motion, visual acuity, skeletal disease, height growth and weight growth among others.

In addition to the clinical studies, there is an ongoing Expanded Access Program that provides treatment for patients with late-stage MPS I who are seriously ill and do not meet the selection criteria for participation in ongoing clinical studies. As of December 2002, a total of 16 patients have received rhIDU treatment for varying periods of time in this worldwide program, bringing the total number of patients treated with rhIDU to 71. The results for clinical pharmacology, efficacy and safety are presented below.

1.5 Summary of Clinical Pharmacology

Clinical pharmacology was evaluated in the Phase 1/2 Study (BIO7500-001) and the Phase 3 Double-Blind Study (ALID-003-99). These studies were performed in patients with a confirmed diagnosis of MPS I based on IDU levels.

The dosing regimen used in both of these studies, 100 U/kg (0.58 mg/kg) as a 3 – 4 hour intravenous infusion once weekly, is that proposed for commercial use in humans. Both the Phase 1/2 and Phase 3 pharmacokinetic studies demonstrated that slow intravenous infusions

at a dose of 100 U/kg (0.58 mg/kg) once weekly produces significant circulating plasma IDU activity. These levels were sufficient to reach 20-30 times the concentration for half-maximal uptake (half-maximal saturation ~1 nM; 0.01 U/ml) for periods of 3 hours or more. These levels suggest that rhIDU is fully saturating available mannose 6-phosphate receptors during the infusion period.

In both studies, urinary GAG excretion was utilized as marker for in vivo pharmacodynamic activity based on the data obtained in the MPS I animal model studies. In both Phase 3 and Phase 1/2 Studies, weekly enzyme infusions produced a rapid (within 4 weeks) decline in urinary GAG excretion. These decreases were maintained over the duration of each study and were both statistically significant ($p<0.001$) and clinically relevant. The data are further discussed in Section 6.

The substantial decrease and near normalization of urinary GAG indicates that enzyme is reaching and correcting storage in the renal distal tubules and other distal tissues of treated patients, as predicted by nonclinical studies (Kakkis, 1996, Biochem Mol Med).

1.6 Overall Summary of Efficacy

The efficacy of rhIDU treatment was evaluated in the Phase 3 Double-Blind Study (ALID-003-99), the Phase 3 Open-Label Extension Study (ALID-006-01), and the Phase 1/2 Study (BIO7500-001). An integrated overview of the efficacy results is presented below, while a complete summary of efficacy is in Section 6. The clinical data supporting efficacy are based on the demonstration of a reduction in measures of storage (liver size and urinary GAG excretion), an improvement in respiratory function (pulmonary function [FVC] and airway obstruction [apnea/hypopnea index (AHI)]), an improvement in functional capacity (6-minute walk test, joint range of motion, NYHA scores) and other improvements in smaller numbers of patients with other diverse manisfestations of MPS I. The data show that treatment with rhIDU is associated with the expected reductions in lysosomal storage that are the rational basis for treatment of this disorder. The reduction in lysosomal storage leads to clinically meaningful improvements that are clinically relevant to MPS I disease.

1.6.1 Reduction in Lysosomal Storage

Liver size by MRI and urinary GAG excretion were assessed in all 3 studies as the primary measures of lysosomal storage. In all studies, significant decreases in lysosomal storage were observed within a few weeks of initiating rhIDU therapy demonstrating a potent effect of rhIDU on lysosomal storage in human MPS I patients as predicted by preclinical studies.

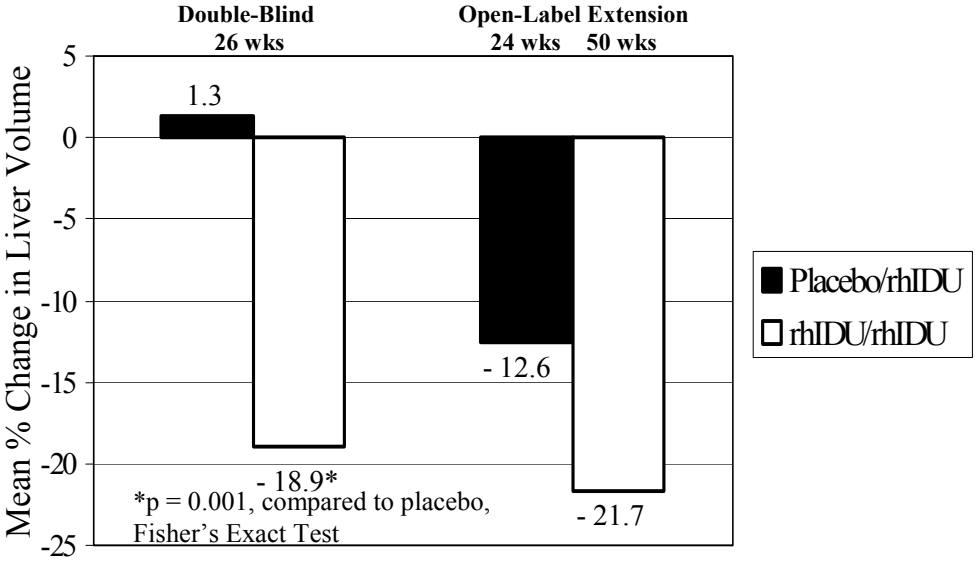
Disease Relevance. Hepatomegaly and elevated urinary GAG excretion are relatively consistent features of MPS I that reflect excessive accumulation of GAG in the body and are important markers of GAG reduction based on studies of rhIDU treatment of MPS I canines.

Although hepatomegaly could be considered a surrogate marker of disease, it is an important problem as reported by patients and reduction in liver size may have several clinical benefits, including improved diaphragm excursion, ability to bend over, physical appearance (decreased clothing size), self-esteem, comfort and appetite. At baseline, 73% (32/44) of patients in the Phase 3 Double-Blind Study had hepatomegaly and all patients showed elevated urinary GAG levels.

Consolidated Findings. In the Phase 1/2 Study, treatment with rhIDU reduced liver size as early as Week 2 by physical examination and as early as Week 6 by MRI. In the Phase 3 Double-Blind Study, patients treated with rhIDU showed an 18.9% reduction in liver volume after 26 weeks, followed by a 3.6 % reduction over the next 24 weeks, for a total reduction of 21.7% after 50 weeks. The difference between the rhIDU and placebo treatment groups for percent change in liver volume after 26 weeks was statistically significant ($p = 0.001$), favoring the rhIDU group. In the Phase 3 Open-Label Extension Study, the placebo/rhIDU patients showed a 12.6% reduction in liver volume (Figure 1).

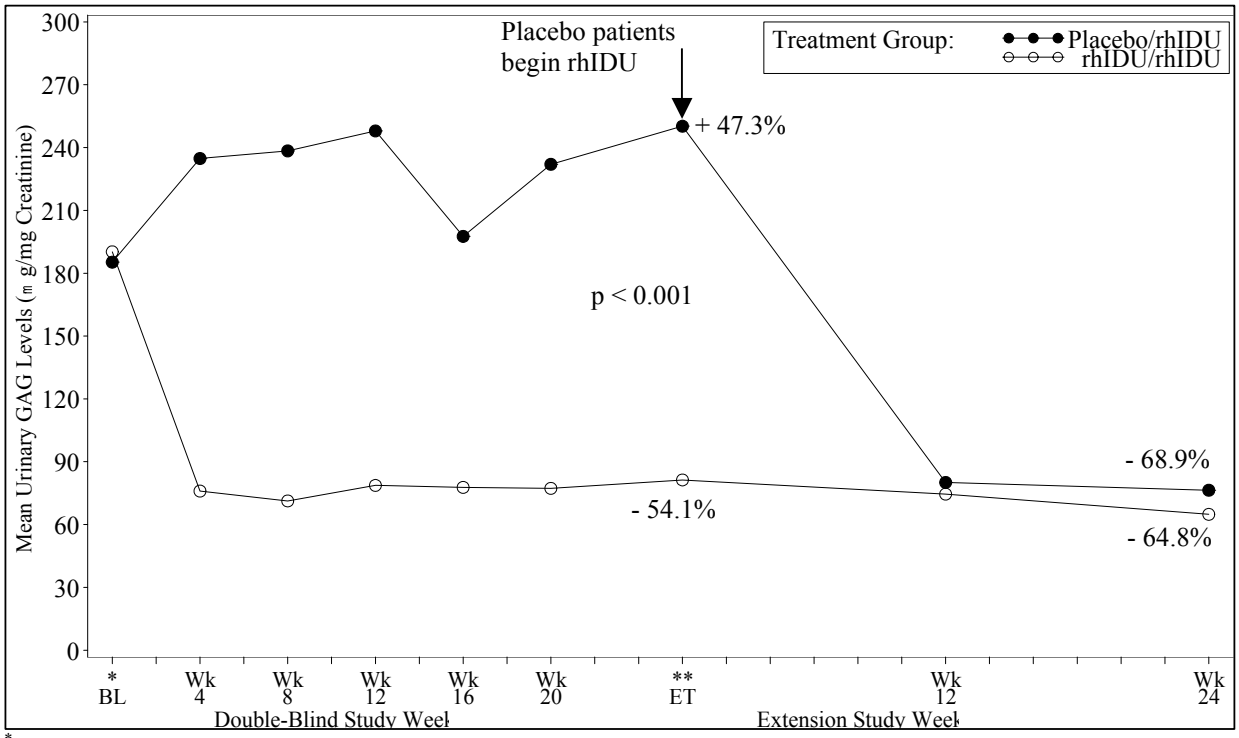
In the Phase 3 Double-Blind Study, 64% (18/28) of patients with abnormal liver size at the time of initiation of rhIDU treatment had normalized their liver volumes within 6 months. In the Phase 1/2 Study, 8 of 10 patients had a normal liver size at 6 weeks after 5 doses of rhIDU and 9 of 10 patients normalized their liver volumes by Week 52. This study met its primary endpoint of two-thirds of patients showing a ≥20% reduction in liver or spleen volume since by Week 26, 80% (8/10). Spleen volumes also decreased, with 50% (5/10) of patients showing ≥20% reduction in spleen size at Weeks 26 and 52.

Figure 1: rhIDU Decreases Hepatomegaly



In the Phase 1/2 and Phase 3 Double-Blind Study, a rapid decline in urinary GAG excretion was observed by Week 4, with slow further reduction over several months to near normal age-specific levels. The decreases in urinary GAG levels from baseline were similar (approximately -60%) between patient groups following 6 to 12 months of rhIDU treatment. By Week 24 of the Phase 3 Open-Label Extension Study, 6 patients in the rhIDU/rhIDU group and 3 patients in the placebo/rhIDU had achieved a normal GAG level (Figure 2). In the Phase 1/2 Study by 152 weeks, 8/10 patients had achieved a normal GAG level.

Figure 2: rhIDU Reduces Urinary GAG Levels



* BL = baseline, last measurement prior to randomization in the Phase 3 Double-Blind Study

** ET = entry, last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study

Clinical Significance. Overall, large reductions in mean liver volume and urinary GAG level were observed for patients in all 3 clinical studies. The high percentage of patients who normalized their liver volumes and had near normal urinary GAG levels after 52 weeks of treatment suggests that the rhIDU dose regimen is effective in removing accumulated GAG from tissues. Patients in all 3 clinical studies reported that the reduction in organ size improved their comfort and ability to breathe and eat. The clinical benefit associated with a reduction in organ size was important to these patients.

1.7 Improvement in Respiratory Function

An improvement in respiratory function following treatment with rhIDU was demonstrated by the results of forced vital capacity (FVC) testing (co-primary endpoint in the Phase 3 Studies). Supportive data are available from the results of apnea/hypopnea testing (a secondary endpoint in both the Phase 3 and Phase 1/2 clinical studies) in more severely affected patients. Together, the improvement in respiratory function and reduction in airway obstruction are important benefits for MPS I patients.

1.7.1 Percent of Predicted Normal Forced Vital Capacity

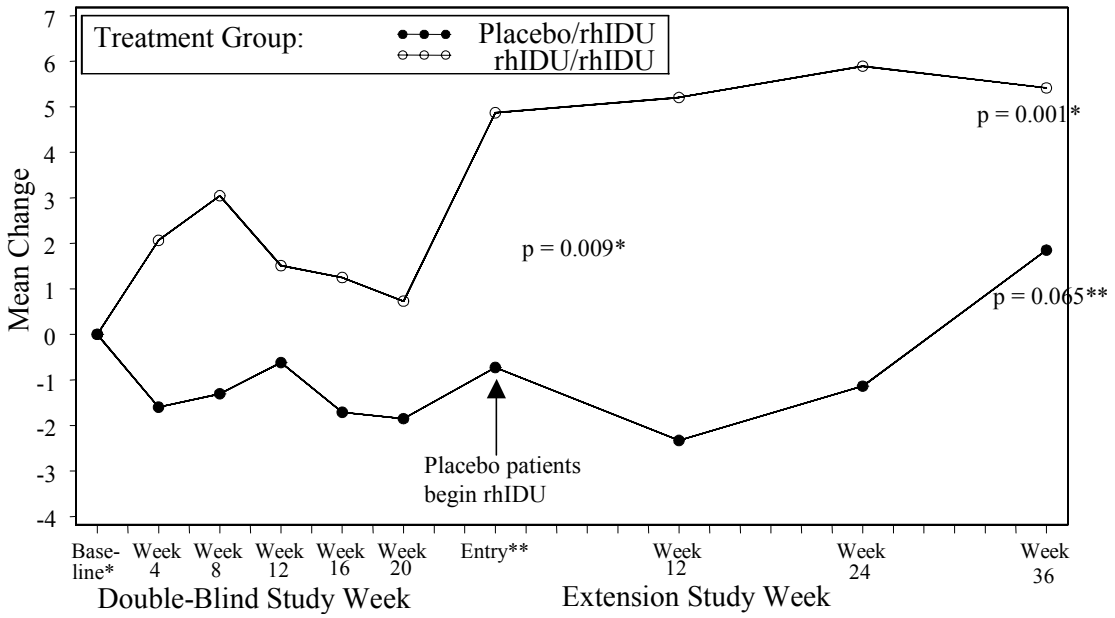
Disease Relevance. Progressive respiratory insufficiency is an important aspect of MPS I disease and is a major cause of morbidity and mortality. Patients exhibit reduced lung capacity that manifests functionally as a restrictive-type abnormality and clinically as hypoventilation syndrome, leading to atelectasis, pulmonary infections, and impaired gas exchange. In conjunction with airway obstruction, reduced lung capacity can lead to sleep apnea, hypoxemia and right heart failure (Semenza, 1988, Medicine).

All patients enrolled in the the Phase 3 Double-Blind Study were required to have ≤ 80% of predicted normal FVC at baseline. The mean baseline FVC value was 51.4%, reflecting a loss of nearly half of vital lung volume and constitutes a moderate-to-severe restriction-type abnormality (ATS, 1991, Am Rev Respir Dis). Reduction in FVC is caused by several features of MPS I, including limitation of diaphragmatic excursion by hepatosplenomegaly, chest wall rigidity, spinal deformity, infiltration of the lung parenchyma with GAG, and premature closure of the glottis by redundant tissue during exhalation.

Consolidated Findings. Percent of predicted normal FVC was used as a measure of respiratory function in both the Phase 3 Double-Blind and the Phase 3 Open-Label Extension Studies where it was 1 of 2 co-primary efficacy variables.

After 26 weeks of treatment in the Phase 3 Double-Blind Study, the rhIDU group showed a 5.6 percentage point difference from placebo in percent of predicted normal FVC (median difference from placebo was 3.0 percentage points, $p = 0.009$). Following an additional 36 weeks of treatment, the rhIDU/rhIDU group maintained its prior improvement in FVC with a statistically significant 5.4 percentage point increase from baseline ($p = 0.001$; see Figure 3). Similar results were observed in the placebo patients who switched to treatment with rhIDU in the Phase 3 Open-Label Extension Study. After 36 weeks of receiving rhIDU, the placebo/rhIDU patients showed a 2.6 percentage point increase in FVC ($p = 0.065$) compared to a –0.7 percentage point decrease in the placebo phase of the study. The smaller and delayed treatment response in placebo/rhIDU patients may be related to their relatively less pulmonary restriction (higher FVC) at baseline or other factors such as seasonal effects (assessments were done during winter), or missed infusions.

Figure 3: Mean Changes in Percent of Predicted FVC (%) from Baseline* and Entry through Week 36 (ITT Population)**
(Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study: 36-Week Data)



* BL=baseline, last measurement prior to randomization in the Phase 3 Double-Blind Study.
**ET=Entry, last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.
Note: The percent of predicted FVC was calculated using baseline standing height.

Clinical Significance. The mean increase in percent of predicted FVC corresponds to a 10% relative improvement over baseline FVC of 48.4%, which is considered by the American Thoracic Society (ATS) to be a clinically significant change and not due to week-to-week variability. (ATS, 1991, Am Rev Respir Dis) This improvement is even more meaningful given that MPS I is a progressive disorder and most patients in this study had moderate or severe restrictive lung disease. Much of the restriction in these MPS I patients is due to skeletal deformity that would probably not respond to treatment. Even so, the magnitude of change in lung function observed in this study is similar to changes in respiratory function test measurements used to support the efficacy claims of approved drugs to treat asthma and cystic fibrosis.

1.7.2 Obstructive Sleep Apnea (Apnea/Hypopnea Index)

Disease Relevance. Upper airway obstruction is a significant contributor to morbidity and mortality in MPS I patients and compounds the problems with pulmonary insufficiency and respiratory infections in these patients. The most important clinical manifestations are obstructive sleep apnea, which can lead to numerous medical problems and difficulty with

intubation, which makes these patients high anesthesia risks. Sleep apnea may have several consequences, including excessive sleepiness, poor endurance, morning headaches, and, in children, neurobehavioral changes such as learning disabilities, attention deficit, and hyperactivity (American Academy Pediatrics, 2002). Systemic hypertension (Nieto, 2000, JAMA) as well as pulmonary hypertension with right-heart failure, are medical complications that correlate with apnea/hypopnea index (AHI) level.

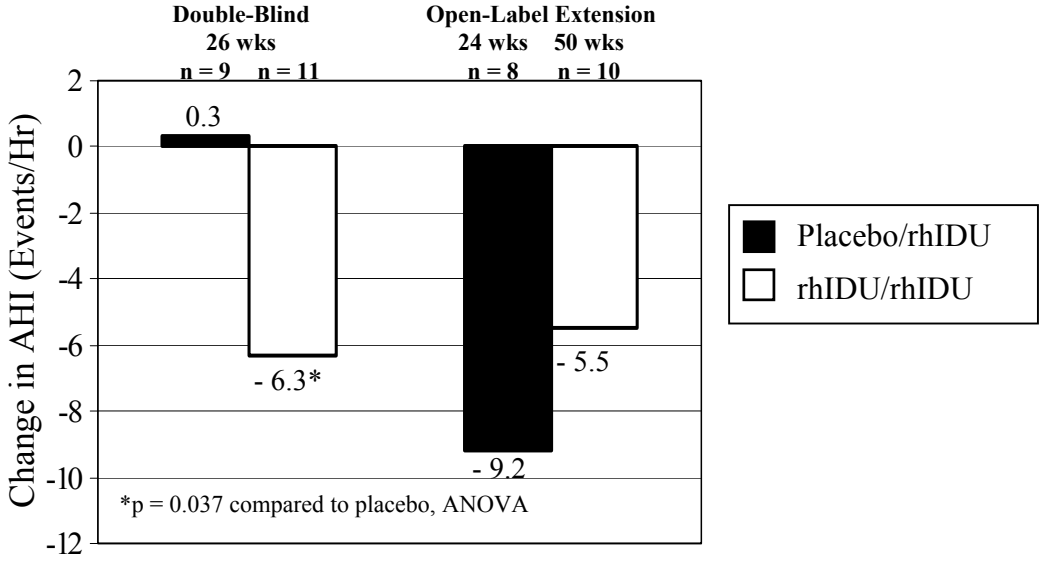
At baseline, approximately half of the patients had AHI values consistent with sleep apnea but only 9% were being treated with nasal CPAP. Although most patients with MPS I do undergo tonsillectomy and adenoidectomy, which is the treatment of choice for sleep apnea in otherwise healthy children, patients are not rendered symptom-free long-term because of other obstructive airway components and the recurrence of lymphoid tissue storage.

Consolidated Findings. Improvement in obstructive sleep apnea following treatment with rhIDU was demonstrated in all 3 studies, particularly in patients who had significant sleep apnea at baseline.

The primary analysis of the Phase 3 Double-Blind Study showed a trend to improvement in rhIDU treated patients with a decrease of 3.6 apnea or hypopnea events per hour ($p=0.145$). Since only patients with sleep apnea could be expected to improve, a post-hoc analysis of patients who had an abnormal AHI at baseline (≥ 10 AHI for children, ≥ 15 AHI for adults) was performed. This subgroup of patients treated with rhIDU showed a mean decrease of 6.3 events per hour over the first 26 weeks of treatment which was significantly different from placebo ($p=0.037$). This improvement was maintained through 50 weeks of treatment. The same effective subset of placebo/rhIDU patients showed a similar improvement with a mean decrease of 9.2 events per hour during the Phase 3 Open-Label Extension Study. The latter represents a 40% decrease, and a change in the mean AHI value to below 15, the Medicare threshold for initiation of CPAP (Tunis, 2001, Centers for Medicare and Medicaid Services Admin File) (Figure 4).

In the Phase 1/2 Study, the methodology used to measure obstructive events was different than that used in the Phase 3 Studies, resulting in a different scoring system (normal AHI <1). Nevertheless, mean AHI decreased from 2.08 at pretreatment to a mean of 0.97 at Week 26, a 53% reduction, and the 3 patients with clinically significant sleep apnea all improved.

Figure 4: rhIDU Reduces AHI



Clinical Significance. The improvements in AHI seen in MPS I patients with sleep apnea who were treated with rhIDU are most likely due to a reduction in GAG substrates from the tissues surrounding the upper airway, the tongue and within the respiratory epithelium, thereby relieving airway obstruction. Although not formally assessed in the Phase 3 Studies, reduction in GAG in the tongue, pharynx, and trachea is expected to make the airway easier to intubate, thereby decreasing the risk of complications with anesthesia.

The minimum clinically significant change in AHI has not been established. A change in AHI of at least 10 events per hour is reasonable as it is above the test-retest variability of placebo-treated patients, similar in magnitude to the upper range of normal for children (10 events per hour) and adults (15 events per hour), and approximately 20% of the evaluable range for sleep apnea (10 to 60). In the Phase 3 Double-Blind Study, 44% (20/45) of patients had AHI scores suggestive of sleep apnea at baseline based upon an AHI $\geq$10 for pediatric patients and AHI $\geq$ 15 for adult patients. Using a threshold of change of at least 10 events per hour, 20% (4/20) of rhIDU patients improved compared to 10% (2/21) of placebo patients. Conversely, no rhIDU patient deteriorated compared to 14% (3/21) of placebo patients. Overall, there was net improvement in 20% (4/20) of rhIDU patients versus a net decline in 5% (1/21) of placebo patients.

1.8 Improvement in Functional Capacity

An improvement in functional capacity following treatment with rhIDU was demonstrated by the results of the 6-Minute Walk Test (co-primary endpoint in the Phase 3 Studies) and the joint range of motion (ROM) testing (secondary and tertiary endpoints in the Phase 3 Studies

and a secondary endpoint in the Phase 1/2 Study) in patients with more severe baseline disease. The results of the New York Heart Association (NYHA) classifications (secondary endpoint in the Phase 1/2 study) provide further evidence of improvements in functional capacity.

1.8.1 6-Minute Walk Test and NYHA Classification

Disease Relevance. Impaired mobility and ambulation is a prevalent and significant disability for patients with MPS I. As is the case for FVC, the ability to walk is likely affected by the varied symptoms of MPS I, including cardiorespiratory disease, hepatomegaly, musculoskeletal disease (bony deformities and joint contractures, stiffness, and pain), and spinal cord compression with myelopathy. Even though the Phase 3 Double-Blind Study patients predominantly had the intermediate form of MPS I disease, 31% (14/45) of patients used a wheelchair, 7% (3/45) used a walker, and 2% (1/45) used a cane. One-third of patients (15/45) were unable to walk more than 330 m in 6 minutes. Although no normative data exist in children, this 6-Minute Walk Test distance approximates the lower limit of normal for healthy adult women (310 m) (Enright, 1998, Respir Crit Care Med) and the lower limit of normal for "community ambulation" (332 m) (Robinett,1988, Phys Ther) (Menard-Rothe, 1997, J Cardiopulm Rehabil). Independent community ambulation, defined as the ability to walk at a near normal speed of 80 m/min for 332 m, is considered to be functionally important for activities such as crossing a street or performing an errand in the neighborhood. In the Phase 3 Double-Blind Study, patients walked at a mean speed of 57 m/min at baseline. In the Phase 1/2 Study, patients also showed clinically significant functional limitations, with none of the 10 patients identified as Class I (no symptoms) in the NYHA Classification at baseline.

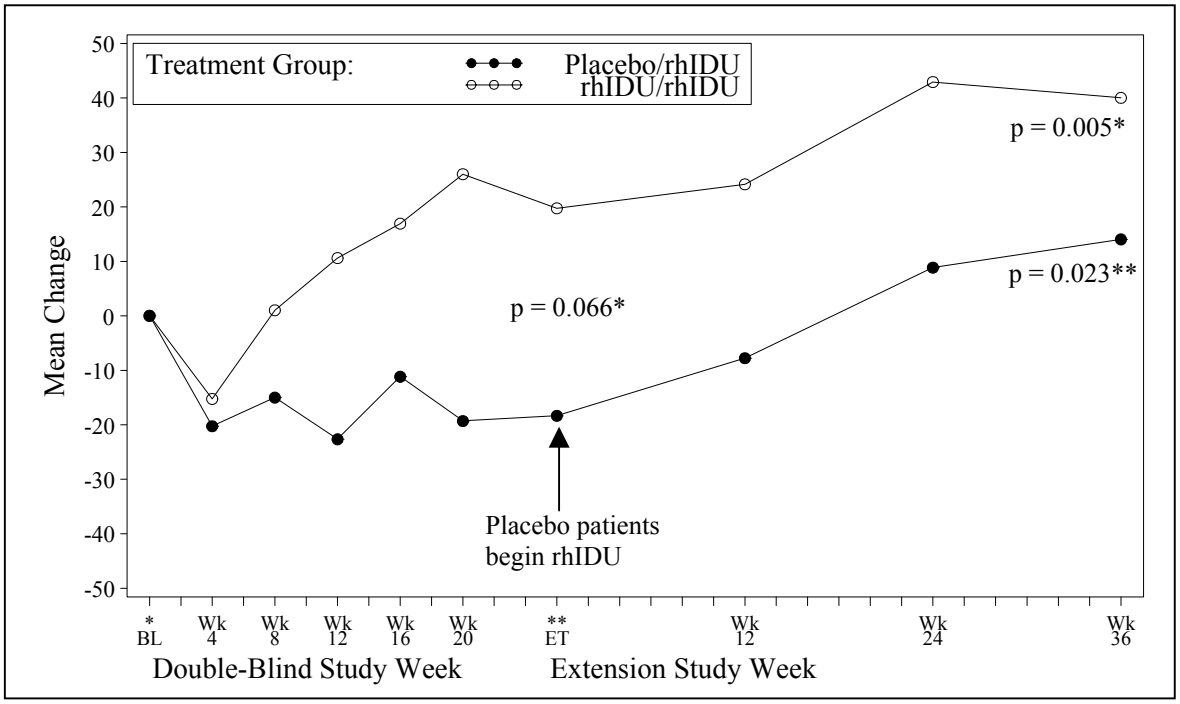
Consolidated Findings. The 6-Minute Walk Test was used as a measure of functional capacity in the Phase 3 Double-Blind and Phase 3 Open-Label Extension Studies, and the NYHA Classification was used as a measure in the Phase 1/2. Patients showed increased functional capacity and endurance following 6 to 12 months of treatment with rhIDU.

Improvements in the 6-Minute Walk Test were consistent after initiation of rhIDU treatment in the Phase 3 Double-Blind and Open-Label Extension Studies. Patients treated with rhIDU in the double-blind study showed a 19.7 m mean increase after 26 weeks (median difference from placebo of 38.5 m, $p=0.066$ versus placebo) (Figure 5). While this difference from placebo did not reach statistical significance in the primary analysis, the wide variation in height, baseline walk distance, gender and stage of disease make it difficult to achieve significance in a study of MPS I patients. Because of the known patient heterogeneity, an analysis of covariance (ANCOVA) was discussed with the Agency and prespecified to account for baseline differences between groups that might affect outcome, including center,

baseline 6-Minute Walk Test, gender, height, and liver volume. The ANCOVA showed a difference from placebo that was statistically significant (p=0.039).

The initial rhIDU treatment group showed an additional 20.3 m mean increase (p=0.146 versus entry value) after 36 more weeks of treatment, for a total mean increase of 40.0 m (p=0.005 versus baseline value) over 62 weeks. The placebo/rhIDU patients showed a 18.4 m mean decrease during treatment with placebo followed by a 32.4 m mean increase after 36 weeks of rhIDU treatment (p = 0.023 versus entry value) (Figure 5).

Figure 5: Mean Changes in 6-Minute Walk Test Distance (m) from Baseline* and Entry through Week 36 (ITT Population)**
(Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study: 36-Week Data)



* Last measurement prior to randomization in the Phase 3 Double-Blind Study.
** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

In the Phase 1/2 study, the NYHA Classification improved in all patients after 52 weeks (n=10) and 104 weeks (n=9) of treatment. The mean change in NYHA Classification from baseline was statistically significant at Week 52 (p = 0.002) and was maintained through Week 104. With treatment, 50% of patients (5/10) improved to Class I after 52 weeks and 67% of patients (6/9) improved to Class I by 104 weeks.

Clinical Significance. The 38.1-m difference between groups after 26 weeks and the 42.9-m change within the rhIDU/rhIDU group after 50 weeks of rhIDU treatment in the Phase 3 studies are comparable to the 54-m difference (95% CI, 37 to 71 m) that is frequently cited in

the literature as the minimal clinically significant difference perceived by individuals in the 6-Minute Walk Test. (Redelmeier, 1997, Am J Respir Crit Care Med). This distance was based on the testing of elderly adults with chronic obstructive pulmonary disease, as opposed to children with MPS I, and may overestimate the change needed to be perceived as clinically significant because of the shorter stride length in the younger and shorter MPS I patients who participated in these Phase 3 studies. This 54-meter difference is also considerably higher than the training effect observed during the 3 successive baseline evaluations of patients in the Phase 3 Double-Blind Study.

Using the 54-m threshold, a clinically significant improvement was seen in 41% (9/22) of rhIDU patients versus 13% (3/23) of placebo patients, whereas a $\geq$54 m decline was seen in 18% (4/22) of rhIDU patients versus 26% (6/23) of placebo patients.

The 6-Minute Walk Test is among the most widely used sub-maximal exercise tolerance tests for patients with cardiovascular and pulmonary disease. The distance walked in 6 minutes is a strong independent predictor of morbidity and mortality in patients with congestive heart failure (Bittner, 1993, JAMA)(Shah, 2001, Am J Card) and with primary pulmonary hypertension (Miyamoto, 2000, Am J Respir Crit Care). Two pulmonary hypertension medications [Tracleer™ (bosentan) and Flolan® (epoprostenol sodium)] have been approved with the 6-Minute Walk Test as the primary endpoint, with improvements similar to the mean change occurring in the Phase 3 Double-Blind Study. The improvements in the NYHA score were statistically significant and are intrinsically clinically meaningful based on the clinical status categories that the NYHA score represents.

1.8.2 Shoulder Flexion and other Joint Range of Motion

Disease Relevance Joint stiffness and pain is a prevalent feature of MPS I disease that limits activities of daily living and mobility. Reduced joint ROM is a physiologic consequence of accumulation of GAG in the synovium, periarticular connective tissues as well as secondary bony changes. At baseline in the Phase 3 Double-Blind Study, 78% of patients complained of joint stiffness, 53% of joint contractures, and 31% of joint pain. Mean shoulder flexion was 92.7 degrees, which approximate the horizontal and reflect significant limitation. Using 150 degrees as the lower limit of the normal range for shoulder flexion (Norkin C.C, 1995, Allied Health: Jean-Francois Vilain), 98% (44/45) of patients showed reduced flexion, and 60% (27/45) had flexion less than 100 degrees.

Consolidated Findings. Increased shoulder flexion and other joint ROM were observed in all 3 studies and treatment over longer period of times in the Phase 1/2 patients showed more improvement than treatment after shorter periods of time.

In the Phase 3 Double-Blind Study, when shoulder flexion was evaluated in all patients, or in all patients except for two with symptomatic cervical cord compression, there was a modest

mean treatment effect in favor of rhIDU-treated patients but the primary analysis was not statistically significant. Based on the earlier results from the Phase 1/2 Study in which more severely restricted patients showed greater improvement, patients with greater shoulder restriction at baseline of the Phase 3 Double-Blind Study (below the median subset) were analyzed and showed an almost 10-degree mean increase in the rhIDU group compared to a 5-degree decrease in the placebo group. The change was still not statistically significant. In the Phase 3 Open-Label Extension Study, patients with more severely restricted shoulder flexion in the rhIDU/rhIDU group showed a mean increase in shoulder flexion of 6.6 degrees from Week 24 to Week 50, for a total mean increase of 8.7 degrees after 50 weeks. The placebo/rhIDU group showed a mean increase of 15.2 degrees from entry to Week 24.

In the Phase 1/2 Study, right and left shoulder flexion improved by 10.75 and 8.25 degrees, respectively, after 26 weeks and by 28.13 ($p<0.001$) and 26.12 degrees ($p<0.002$), respectively, by Week 52. In both the Phase 3 and Phase 1/2 Studies, rhIDU-treated patients also demonstrated trends or significant improvements in other joint ROM measures (shoulder extension, knee flexion/extension, and elbow extension) with patients showing severe joint restriction at baseline demonstrating larger improvements.

Clinical Significance. Shoulder function is necessary for self-care skills and functional independence and, for patients with significant shoulder restriction, increased active joint ROM is a prerequisite for improved shoulder function. Joint function is also an important component of walking and functional capacity. The combination of improvements observed in joint range of motion suggest that patient mobility is overall improved with rhIDU. Based on the results of long-term treatment with rhIDU in the Phase 1/2 study, joint range of motion is expected to continue to improve with time.

1.9 Supporting Measures of Benefit

In addition to effects on lysosomal storage, respiratory function, and functional capacity, individual patients showed improvement in a number of other important parameters of the disease. Results from the following secondary and tertiary efficacy endpoints in the 3 clinical studies support the ability of treatment with rhIDU to limit or reverse the progressive nature of the disease.

Quality of Life (QoL) Assessments. In the patients treated with rhIDU for 50 weeks during the Phase 3 Open-Label Extension Study, there were several physical and general health domains in the patient Childhood Health Questionnaire (CHQ)-CF-87 assessment that showed improvements. Patients treated for 26 weeks in the Phase 3 Double-Blind Study or for 24 weeks in the Open-Label Extension Study did not show clinically significant changes in either the parent CHQ-PF-50 or the patient CHQ-CF-87, suggesting that these improvements take time and are not a placebo effect. Although no formal measures of QoL

were assessed, the patients in the Phase 1/2 Study reported improvements in daily activity levels.

Visual Acuity. In the Phase 3 Double-Blind Study, there was a consistent trend towards improvement in visual acuity in the patients treated with rhIDU compared with the placebo group, particularly in the patients with corrected vision of 20/60 or worse. In this subgroup, left and right eye visual acuity improved by >10 Snellen units in 5/7 and 5/6 rhIDU-treated patients, respectively, compared to 2/4 and 0/6 placebo-treated patients.

In the Phase 3 Open-Label Extension Study, in patients with corrected vision of 20/60 or worse, 6 patients treated for 50 weeks showed improvement from baseline of >10 Snellen units and 3 patients treated for 24 weeks showed improvement of >10 Snellen units.

Visual acuity improved in at least one eye in each of the 3 patients with the worst vision in the Phase 1/2 Study.

1.10 A Responder Analysis Based on a Composite Endpoint Approach

Significant improvements were observed in measures of respiratory function, functional capacity, and lysosomal storage across all studies of rhIDU in MPS I patients. In other clinical measures, such as sleep apnea, joint ROM, and visual acuity, improvements occurred in the more severely affected patients. Based on these studies, it is clear that more severely affected subsets for individual efficacy variables demonstrated greater benefit in general and that each patient had a different array of MPS disease at varying stages of progression. This variability makes it difficult to effectively study MPS I patients using traditional group mean comparisons and does not adequately assess the effect of therapy in an individual across the many symptoms of MPS I.

To address the benefit of rhIDU treatment in this variable population, a composite clinical efficacy endpoint was used as an alternative analytical method to evaluate the treatment effect of rhIDU in MPS I patients on an individual basis. This approach complements the traditional analysis design employed in the Phase 3 Double-Blind Study (single endpoints for single clinical measures) by capturing clinical benefit across multiple organ systems simultaneously in a responder analysis.

Post-hoc analysis of the Phase 3 Double-Blind Study data using a composite clinical endpoint and responder approach at the level of the individual patient lends further support for a rhIDU treatment effect. The composite endpoint consists of clinically significant changes in FVC, 6-Minute Walk Test, AHI, shoulder flexion, and visual acuity (refer to Appendix I). A responder is defined as a patient who shows net improvement (domains improved>domains declined) across the 5 domains. Specifically, there were 59% responders in the rhIDU group compared to 22% in the placebo group ($p=0.016$). Most rhIDU-treated patients improved in

more than 1 domain and showed net overall improvement (+1.00 domains/patient), whereas most placebo patients showed little improvement with an average decline in 1 domain and a slight net decline overall (-0.39 domains/patient).

1.11 Overall Summary of Clinical Safety

The evaluation of safety variables monitored in patients treated with rhIDU in this clinical development program, including adverse event (AE) reporting, physical examination findings, vital signs, electrocardiography (ECG), echocardiography (ECHO), and standard clinical laboratory and immunogenicity testing, indicates that rhIDU has an acceptable safety profile in patients receiving both short-term and long-term treatment.

Almost all of the patients enrolled in the 3 clinical studies experienced at least 1 AE, including patients receiving placebo treatment in the Phase 3 Double-Blind Study. This is not unexpected given the nature of the disease under study, which affects multiple organ systems by lysosomal storage of GAGs. In the Phase 3 Double-Blind study, the overall patient incidence and types of adverse events were similar between the placebo and rhIDU treated patient. In the Phase 3 Open-Label Extension Study, the overall patient incidence and types of adverse events observed for both treatment groups were similar to those seen in the Phase 3 Double-Blind Study, even with the approximately 50% greater exposure time in the latter group.

In the Phase 3 Studies, infusion-associated reactions (IARs) were defined as those AEs reported by the investigator as related to study drug that occurred on the day of infusion, excluding those AEs identified by protocol-required assessments that were performed prior to drug infusion. IARs were reported in one-third to one-half of patients in both Phase 3 Studies, regardless of treatment group. The vast majority of these were mild and did not require intervention. The incidence of patients experiencing IARs, as well as the type and number of IARs reported, was similar between treatment groups in both Phase 3 Studies. Over time, the number of patients experiencing IARs remained the same, while the number of IARs reported decreased.

Almost all of the patients in the Phase 3 Studies developed measurable levels of antibody to rhIDU. When comparing results of the Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study, the presence of IgG antibodies to rhIDU does not appear to have an effect on overall safety. The lack of significant proteinuria in patients further suggests that there has been no significant clinical manifestation of immune complex disease. Given that rhIDU and placebo were similarly well tolerated, it seems unlikely that the development of IgG antibodies had any clinically significant effect on overall safety. Finally, none of the patients who were tested for immunoglobulin E (IgE) antibodies to rhIDU was found to test IgE-positive.

Assessment of neutralizing antibody titers at Week 24 of the Phase 3 Open-Label Extension Study revealed that a majority of patients do not show a significant rise in inhibitory activity from the start of rhIDU treatment through Week 24. There was no discernible association between patients experiencing IARs and inhibitory activity.

The majority of the AEs experienced by the patients in the Phase 3 Studies occurred on non-infusion days and were judged by the investigators to be unrelated to study treatment. Each of the AEs experienced on non-infusion days that were reported to be treatment-related by the investigator, occurred in a single patient, in almost all instances.

In the Phase 1/2 Study, all patients experienced at least 1 AE. Urticarial rashes on the day of infusion was noted more commonly in the Phase 1/2 Study, but were infrequently seen in the Phase 3 Studies. Angioedema symptoms occurred infrequently and in general, were manageable using increased premedication and slowed infusion rate. The difference in frequency of urticaria and related symptoms may be due to the difference between the drug product administered during the majority of the Phase 1/2 Study and the product of increased purity administered in the later studies. Forty percent of the patients in the Phase 1/2 Study developed IgG antibodies that were specific to rhIDU based on Western blot analysis, although no consistent relationship between these findings and the treatment-related AEs on the day of infusion was seen.

Among the 55 patients who have received rhIDU treatment in clinical studies, there have been 4 reported deaths—1 in the Phase 3 Open-Label Extension Study (Week 16), and 3 in the Phase 1/2 Study through (Weeks 103, 139, and 234). All deaths were reported by the investigators to be unrelated to rhIDU treatment. There have been 2 deaths, reported as unrelated to rhIDU treatment, among the 16 patients who have received rhIDU in the Expanded Access Program.

There were no discontinuations due to adverse events, other than patients who died.

In both Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study (up to Week 24), all serious adverse events (SAEs) were reported by the investigator to be unrelated to rhIDU treatment and consistent with complications of the underlying disease. A total of 11 patients experienced 21 SAEs during the Phase 3 Double-Blind and Open-Label Extension Studies, including 1 patient who experienced SAEs in both studies. Three rhIDU-treated patients experienced 7 SAEs in the Phase 3 Double-Blind Study, while in the Phase 3 Open-Label Extension Study, 6 patients formerly treated with placebo experienced 11 SAEs and 3 patients formerly treated with rhIDU experienced 3 SAEs. Of the 9 SAEs experienced by 5 patients during the Update period, all were unrelated except for an expected event of dyspnoea that was reported by the investigator as possibly related.

In the Phase 1/2 Study, 8 patients experienced 32 SAEs over a 3-year period of treatment. A majority of these SAEs (23) were judged by the investigator to be unrelated to rhIDU treatment. Nine SAEs were reported to be related to rhIDU treatment, and all but 1 were considered allergic reactions. None of the three SAEs experienced by 2 patients during the Update period were related to study drug treatment.

No new trends were noted in safety variables monitored in patients treated with rhIDU in the update period, including AE reporting, physical exam findings, vital signs, ECG, ECHO, and standard clinical laboratory and immunogenicity testing.

The evaluation of safety data collected in this clinical development program indicates that short-term and long-term treatment in patients with MPS I disease have an acceptable safety profile.

1.12 Overall Conclusion

rhIDU reduces lysosomal storage and provides significant clinical benefit to MPS I patients. The in vitro and canine MPS I model data demonstrate the potency and efficiency of the uptake of rhIDU and its effects on reduction of lysosomal storage. Clinical studies have demonstrated a parallel effect in reducing lysosomal storage in patients, with a rapid reduction and normalization of liver enlargement and a reduction in urinary GAG excretion. Consistent with these reductions in lysosomal storage, the studies demonstrate clinical benefit in a variety of endpoints. Improvements were observed in respiratory function (FVC and sleep apnea), functional capacity (6-Minute Walk Test, NYHA classification, and joint ROM), and a variety of other MPS I problems. Given the progressive nature of the disease, the heterogeneity of patients in terms of disease manifestation and age, and the challenges in reversing the chronic effects caused by years of lysosomal storage, these improvements represent important clinical benefit to MPS I patients. The risks of the treatment primarily relate to infusion-associated reactions that were in general manageable and not life-threatening .

MPS I disease represents an unmet medical need because the currently available treatments are not satisfactory for the majority of patients with MPS I. The data show that enzyme replacement therapy with rhIDU improves many clinical aspects of the disease and reduces lysosomal storage as well. The safety and efficacy data provided in this application combine to support a positive risk-benefit profile for rhIDU.

2. INTRODUCTION

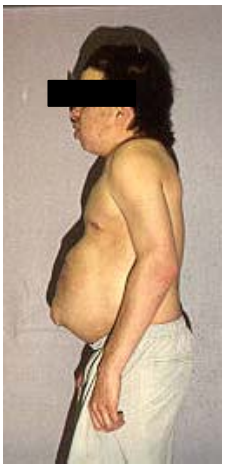
2.1 MPS I Disease

Mucopolysaccharidosis I (MPS I) is a rare, progressive and life-threatening lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-L-iduronidase (Neufeld, 2001, McGraw-Hill). Patients with MPS I accumulate excessive amounts of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate in all organs and tissues of the body. MPS I is an autosomal recessive disorder that has an incidence of approximately 1 in 100,000 live births. It is estimated that there are 1,000 MPS I patients in the United States.

Historically, MPS I patients have been broadly categorized as Hurler, Hurler/Scheie, and Scheie, representing the most severe, intermediate, and less severe clinical phenotypes, respectively. These classifications are arbitrary categorizations of points on a spectrum of patient phenotypes and MPS I disease. Although the degree of severity may vary between patients, MPS I is always a serious and life-threatening disease. While the pathophysiologic basis for MPS I is clear, the diverse combination of medical problems and the rate of progression of specific clinical symptoms varies greatly between patients, and there is significant patient-to-patient heterogeneity. Clinical symptoms begin in infancy to late childhood, progress over a period of years, and ultimately lead to death from cardiopulmonary disease during the first or second decade of life in most patients. Despite this heterogeneity, MPS I is consistently characterized by enlargement of the liver and spleen and excessive levels of urinary GAG excretion. Additionally, cardiopulmonary and functional effects are consistently among the most important clinical manifestations of the disease (Neufeld, 2001, McGraw-Hill).

Lysosomal storage in MPS I is most clearly manifested clinically by massive enlargement of the liver and spleen due to engorgement of macrophages, as well as parenchymal cells, with GAG (Neufeld, 2001, McGraw-Hill) (Figure 6).

Figure 6: Illustration of Hepatomegaly in MPS I Patient

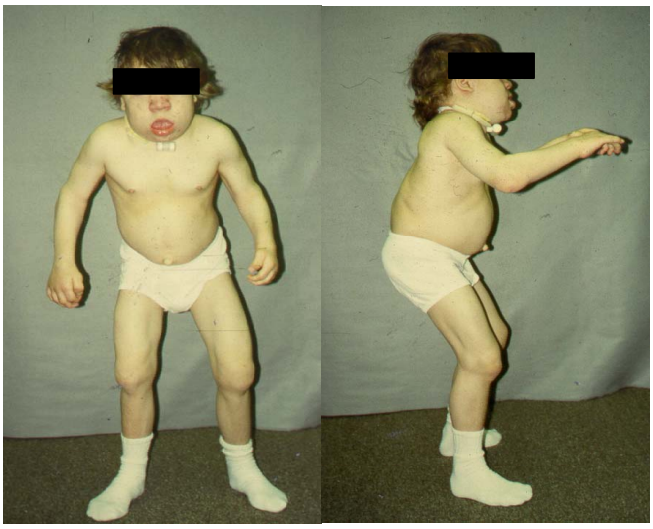


A 22 year old Hurler-Scheie patient from the Phase 1/2 Study with hepatomegaly.

Enlargement of the liver and spleen may have a number of clinical consequences, including limitation of diaphragmatic excursion causing shortness of breath, early satiety, abdominal discomfort, poor self-image, and difficulty bending over. In addition, the excessive storage particularly within the kidney and collecting tubules, leads to the excretion of excessive amounts of GAG in the urine. For this reason, urinary GAG levels are commonly used in the diagnosis of suspected MPS I disease. The storage of GAG is present in every tissue and nearly every cell type, as might be expected for a widespread macromolecule such as GAG. Stored GAG substrate also leads to coarsened facial features, abnormal bones, large tongue, and stiffened joints, in part due to synovial engorgement with GAG.

The functional capacity of MPS I patients is also profoundly affected by GAG storage in a variety of tissues (Figure 7). Decreased cardiopulmonary function contributes to reduced physical ability (Semenza, 1988, Medicine), and direct accumulation of GAG within connective tissues affects mobility in MPS I patients (Neufeld, 2001, McGraw-Hill). Joint stiffness, decreased range of motion, and pain often limit the usual activities of daily living, including walking. Skeletal storage causes short stature and skeletal deformities, which can also affect mobility. Ocular abnormalities include decreased visual acuity, corneal clouding, and glaucoma, which also affect daily activities (Kakkis, 1996, McGraw-Hill). In patients with severe disease, mental retardation and neurodegeneration begin early in life. In all MPS I patients, the continued progression of disease leads to diminished physical activity and functional status, resulting in immobility and, often, a bedridden state.

Figure 7: Illustration of Broad Anatomic Effect of GAG Storage in MPS I Patient



A 17 year old Hurler-Scheie patient is shown from the Phase 1/2 Study. Note the coarsened facial features, hepatomegaly, and stiff and contractured knees, hips and elbows. The patient is lifting his arms as high as possible on the right demonstrating substantial limitation of shoulder flexion.

MPS I patients exhibit severe progressive airway obstruction due to lysosomal GAG storage in the lymphoid and soft tissues of the pharynx and airway itself. Patients have decreased pulmonary function due to a restrictive-type abnormality caused by the small immobile thorax, hepatomegaly limiting diaphragmatic excursion, and, to some extent, storage in the lung itself. The combination of upper airway obstruction and decreased pulmonary function makes patients more susceptible to obstructive sleep apnea, with clinical features that may include fatigue, daytime somnolence, pulmonary hypertension, and cor pulmonale (Mahowald, 1989, Sleep Res)(Ruckenstein, 1991, J Otolaryng)(Bredenkamp, 1992, Ann Otol Rhinol Laryngol). Upper airway obstruction also poses high anesthesia risks because of difficulty with intubation during the myriad of procedures these patients must endure, such as hernia repair, spinal fusion surgery, open-heart surgery, and ventriculoperitoneal (VP) shunt placement. Many patients have died or required tracheostomies following airway problems during anesthesia (Belani, 1993, J Ped Surg). The pulmonary problems are further compounded by frequent pulmonary and upper respiratory tract infections that produce excessive thick secretions and chronic changes in the respiratory tract (Semenza, 1988, Medicine). In addition, primary cardiac problems, including endocardial fibroelastosis, cardiomyopathy, pulmonary hypertension, and valvular disease, can lead to poor cardiac function that exacerbates the respiratory dysfunction due to pulmonary edema and poor cardiac output (Dangel, 1998, Eur J Pediatr).

MPS I patients are heterogeneous and can present with a variable constellation of MPS I symptoms. Each symptom may vary with regard to severity and the rate of progression even among patients of similar overall severity or among siblings within a family. In addition, there are few diseases that can match the breadth of physical involvement and complexity of

disease in every tissue and every body system, and the resulting burden of illness that MPS I patients carry. MPS I patients in the clinical studies described below often have more than 10 major medical problems and have had multiple surgeries by their teens. The combination of progressive, pervasive disease and chronic, irreversible changes in connective tissues and organ structure make MPS I a very difficult disease to study and to treat.

2.2 Current Therapy

The treatment options for the majority of MPS I patients are limited to symptomatic care. MPS I patients typically receive physical and occupational therapies for their stiff joints, but surgery is often required to correct conditions such as carpal tunnel syndrome and joint contractures. In addition, surgery may be needed to fuse vertebrae because of congenital underdevelopment or scoliosis. Many patients use walkers or wheelchairs because of impaired ambulation secondary to joint stiffness, joint pain, and low endurance. Hearing loss can be treated with hearing aids and decreased visual acuity with corrective lenses. Glaucoma can be managed with medication. Recurrent upper respiratory infections are generally treated with antibiotics and myringotomy tube placement. Surgical removal of tonsils and adenoids is usually needed to temporarily relieve upper airway obstruction and, in severe cases, tracheostomy is required. Nighttime oxygen and/or a respiratory device (continuous positive air pressure [CPAP] or bi-level positive air pressure [BiPAP]) are also used to treat obstructive sleep apnea and cor pulmonale. Surgery is also commonly used to repair umbilical and inguinal hernias and to replace heart valves. Available symptomatic care options are unable to treat the underlying cause of MPS I, thus allowing the continued progression of the disease.

Bone marrow transplantation (BMT) has been used in patients with the severe phenotype (Hurler) and has demonstrated some efficacy in patients who survive the procedure and engraft (Vellodi, 1997, Arch Dis Child)(Peters, 1998, Blood). In those patients with adequate engraftment, there are improvements in liver and spleen storage, urinary GAG excretion, and in some functional areas. Corneal clouding improves in most patients, as does mobility. However, pain and stiffness of the hips and knees and spinal curvature increase after approximately 5-6 years post BMT (Vellodi, 1997, Arch Dis Child). Bone disease remains progressive after BMT. BMT in patients younger than 2 years old, prior to developmental decline, has been shown to slow or prevent the inevitable mental degeneration of Hurler patients (Peters, 1998, Blood). Late BMT is not effective in preventing or reversing the decline in mental function, presumably because changes that precede and cause the decline have already occurred. Many patients with severe MPS I undergo BMT, but the morbidity and mortality risk is high; specifically, mortality rates have been reported in the 10–50+% range, depending on the time of follow-up, whether the donor is related, and the degree of tissue match. As many as 50% of surviving engrafting patients develop graft versus host

disease (Peters, 1998, Blood)(Vellodi, 1997, Arch Dis Child)
(Whitley, 1993, Am J Med Genet). In intermediate and less severe MPS I disease, patients rarely undergo BMT because the risk/benefit ratio of BMT is unfavorable.

2.3 Rationale for Enzyme Replacement Therapy

The rationale for rhIDU treatment is based on the fundamental biology of lysosomal enzymes derived from scientific research of the last 30 years. Dr. Neufeld and colleagues demonstrated correction of the defect in MPS I fibroblasts in 1968 but were unable to apply the treatment to patients due to the lack of an adequate source of high-uptake enzyme. The corrective activity of rhIDU enzyme is dependent on mannose-6-phosphate markers on its N-linked oligosaccharides that have been shown to mediate high-affinity uptake of the enzyme at concentrations in the ~1 nanomolar range and correction of GAG storage in the ~1 picomolar range in vitro (Sando, 1977, Cell).

The efficiency of the uptake mechanism and the efficacy of enzyme replacement in MPS I in vivo have been established in a series of preclinical studies (Shull, 1994, Proc Natl Acad Sci USA)(Kakkis, 1996, Biochem Mol Med)(Kakkis, 2001, Mol Genet Metab). The results from these studies formed the basis for the clinical studies of rhIDU, which used a dose that is known from canine MPS I studies to provide receptor-saturating concentrations of rhIDU in the bloodstream and to correct lysosomal storage (Kakkis, 1996, Biochem Mol Med). The data did not show significant reduction of storage within the brain as expected due to the blood-brain barrier. The in vitro and animal studies have demonstrated the rational biologic basis for enzyme replacement therapy in MPS I and verified that the mechanisms of enzyme replacement described in vitro 30 years ago do function in animal models of MPS disease.

2.4 Regulatory History

Aldurazyme® was designated an Orphan Drug in September 1997 and a Fast Track product in September 1998. The BLA filing was completed on July 26, 2002 and granted priority review.

Aldurazyme has been developed in accordance with relevant FDA and ICH guidelines and regulations. Aldurazyme development has included frequent, detailed collaboration between the Sponsor and the FDA, including standard meetings prior to the filing of the IND, after the completion of the Phase 1/2 clinical trial, and prior to the filing of the BLA. The Phase 3 clinical protocol was designed with input from relevant experts in MPS I disease and the FDA. The Phase 3 statistical analysis plan was also developed in collaboration with the FDA.

2.5 Description of Aldurazyme (laronidase)

Laronidase, or rhIDU, the recombinant form of human α-L-iduronidase, is produced in Chinese hamster ovary cells transfected with the human iduronidase cDNA. The enzyme is secreted into the medium and purified to 99% or greater purity. The enzyme is a soluble monomeric glycoprotein with an apparent molecular weight of 83 kD. The secreted enzyme contains mannose 6-phosphate moieties on its N-linked carbohydrates that mediate high affinity uptake by the large mannose 6-phosphate receptor present on the surface of virtually all cells. Uptake via this receptor targets the enzyme for transport to the lysosome. This efficient uptake and targeting process is the fundamental feature of Aldurazyme that allows it to correct the deficiency of α-L-iduronidase that occurs in patients with MPS I.

2.6 Proposed Indication

Aldurazyme® (laronidase) is indicated as long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; α- L –iduronidase deficiency) to treat the non-central nervous system manifestations of the disease.

3. PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

3.1 Toxicology

Acute intravenous toxicity studies of rhIDU were conducted in the rat and canine. Overall, there were no treatment-related findings in the acute rat and canine toxicity studies at doses up to approximately 1.7- and 10-fold, respectively, the recommended human dose of 100 U/kg (0.58 mg/kg).

A repeat dose intravenous toxicity study was conducted in 32 cynomolgus monkeys. rhIDU caused no significant toxicity (ophthalmic, electrocardiographic, organ weight, or macroscopic and microscopic pathology) when administered IV weekly for 26 weeks at doses up to 16.6 mg/kg. This dose is equivalent on a surface area basis to a dose of approximately 5.5 mg/kg in humans, which is approximately 10-fold the dose administered in the Phase 1/2 and Phase 3 studies (0.58 mg/kg). All of the monkeys treated with rhIDU developed antibodies in a dose-dependent manner. Antibody levels declined in approximately half of the monkeys between Weeks 13 and 26; levels rose in the remaining animals. The change in antibody levels between Weeks 13 and 26 was not dose-dependent. Only one event consistent with a mild hypersensitivity response to administration of drug was observed in this study. Edema developed at Week 4 in one male monkey in the 16.6 mg/kg dose group.

An 8-week repeat intravenous dose study in canines was undertaken to assess the possible effects of infusate diluents on the ability of the current clinical drug product to provoke anaphylactoid reactions in normal canines. None of the three different infusion formulations of rhIDU (saline, saline plus canine serum albumin, and saline with polysorbate 80) induced an anaphylactoid reaction, although transient infusion-associated reactions developed during the third dose (Week 3) that resolved with subsequent infusions. The status of the cardiovascular system during these events was found to be within normal limits. All canines developed IgG antibodies in this study and fixed complement during the infusions where infusion-associated reactions occurred.

3.2 Pharmacodynamics

Seven studies in MPS-affected animals (six canine and one feline) were conducted to assess the potential pharmacodynamic effects (efficacy, dosing rationale and safety) of rhIDU over a dose range of 0.1 – 2.0 mg/kg.

3.2.1 Efficacy and Dosing Rationale

Overall, the results from the six efficacy studies in MPS I canines indicated that a dose of at least 0.5 mg/kg/week of rhIDU was necessary to obtain measurable levels of enzyme activity in all tissues examined. This resulted in decreased GAG storage in many tissues, particularly in liver, kidney and spleen. However, even though low levels of enzyme activity were

detected in brain tissues, no histopathological evidence of improvement was found in the CNS in any study. This finding may be due to uptake by brain endothelial cells of rhIDU, which then fails to cross the blood brain barrier. Increasing the dose to 2.0 mg/kg/week resulted in increased tissue enzyme levels; however, the dose of 0.5 mg/kg/week was adequate to result in the highest achievable reduction of GAG in most tissues. This latter dose is similar to the recommended human dose, 0.58 mg/kg.

Thus, studies of the efficacy of rhIDU in lowering tissue GAG, together with the 5-day half-life of rhIDU taken up by fibroblasts from MPS I patients *in vitro* (Kakkis, 1994, Protein Expr Purif), support the recommended human dose of 0.58 mg/kg given weekly.

3.2.2 Safety Pharmacology

Treatment of MPS I canines or cats with rhIDU was well tolerated with no adverse clinical, clinical pathology or histomorphological findings with the exception of anaphylactoid reactions. These reactions, which could be severe, occurred during the early studies, and were managed successfully by stopping the infusion, administering IV fluids and, if necessary, oxygen. The probable cause of the reactions was shown to be IgG-mediated complement activation and in most subsequent studies animals were pretreated with antihistamines prior to infusions.

A two-stage infusion regimen was developed to manage the anaphylactoid reactions wherein the enzyme, diluted in phosphate buffered saline containing 1 mg/mL canine serum albumin, was infused at a slow rate (12 μg/kg /hour) for one hour followed by faster rates of 155 μg/kg/hour or 244 μg/kg/hour for the next one or two hours, respectively. These regimens were used successfully to treat the animals for 67 weeks in this study without further anaphylactoid reactions. Relative to the material used in these studies, the rhIDU used in the subsequent toxicology studies and the Phase 3 clinical study contained less impurities and was formulated in a buffer that contained polysorbate 80. No anaphylactoid reactions were observed in the 26-week IV infusion toxicity study in monkeys, no albumin was used in the infusate, and the animals were not pre-treated with antihistamine drugs.

3.2.3 Biodistribution Studies

The biodistribution of rhIDU in the tissues of MPS I canines was studied as part of the six pharmacodynamic studies. Overall, these studies demonstrated that, at IV doses of 0.5 mg/kg/week and higher, α-L-iduronidase activity was found in all tissues assayed. The levels varied greatly between tissues; those containing reticuloendothelial cells such as the liver, spleen and lymph nodes had the highest levels and the brain tissues had the lowest levels. In some tissues, such as the intestine, kidney, liver, lung, lymph nodes, rib cartilage and synovium, the levels exceeded those found in the same tissues in normal carrier canines.

3.3 Reproduction Toxicology Studies

3.3.1 Intravenous Fertility and General Reproduction Toxicity Study of rhIDU in Rats

No effects on mating and fertility parameters were observed in this study, and there were no treatment-related effects on sperm parameters or findings on gross necropsy. There was no effect on litter parameters or treatment-related fetal effects. Male rats received rhIDU or vehicle from 28 days before cohabitation until sacrifice after 7 days of cohabitation. Female rats received rhIDU or vehicle from 15 days before cohabitation until the seventh day of gestation (DG 7); they were sacrificed on DG 21. In contrast to the once-per-week dosing in efficacy studies, the rats in this study received once daily IV doses of 0, 0.036, 0.36 or 3.6 mg/kg/day. Symptoms of anaphylaxis were observed at 0.36 mg/kg and 3.6 mg/kg and consequently all rhIDU-treated rats were treated thereafter with decreasing (with time) doses of diphenhydramine. There were no other treatment-related clinical signs, mortality or dose/treatment-related effects on male body weights or feed consumption. A significant decrease in body weight gain was observed in females at 3.6 mg/kg on DG 0 to 8.

The NOAEL determined in this study was $\geq$3.6 mg/kg males and $\geq$0.36 mg/kg in females. There was no reproductive toxicity at doses up to 3.6 mg/kg.

3.3.2 Intravenous Developmental Toxicity Study of rhIDU in Rats

In this study, no rhIDU-treatment related effects on litter parameters were observed after ten consecutive daily infusions of rhIDU (0.036, 0.36 or 3.6 mg/kg/day). Symptoms of anaphylaxis were observed at 0.36 mg/kg/day and consequently all rhIDU-treated rats were treated thereafter with IV doses of diphenhydramine. No mortality or other treatment-related clinical signs were observed. Body weight gains were significantly reduced on DG 10 to 12 and body weights were slightly reduced vs. controls on DG 7 to 18 at 0.36 and 3.6 mg/kg. At these doses, there was also a significant reduction in absolute and relative food consumption on DG 15 to 18. Body weights and food consumption were unaffected at 0.036 mg/kg dose.

The maternal NOAEL determined in this study was $\geq$0.36 mg/kg. The developmental NOAEL for rhIDU was determined to be $\geq$3.6 mg/kg.

3.4 Mutagenic and Carcinogenic Potential

Studies to assess the mutagenic and carcinogenic potential of rhIDU have not been conducted. Mutagenic potential would not be anticipated with Aldurazyme based on the structure of the drug substance (a recombinant human glycoprotein), its impurity profile and the excipients in the final product (polysorbate 80, sodium phosphate, and sodium chloride).

Carcinogenic potential would not be anticipated with rhIDU based on the structure of the drug substance (a recombinant human glycoprotein) and its impurity profile. The

biochemical properties of α-L-iduronidase are well characterized, and there are no known interactions with DNA.

4. OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

4.1 Overview

Three clinical studies have been conducted to demonstrate the safety and efficacy of rhIDU in treating patients with MPS I. A summary of all clinical study protocols is shown in Table 1.

Table 2 summarizes the objectives, study design, number of patients enrolled, duration, and eligibility criteria (inclusion and exclusion criteria) of the Phase 3 Double-Blind Study and the Phase 1/2 Study. The 2 studies differed in design, including number of patients and study duration, but had similarities in patient eligibility requirements and some efficacy assessments.

All 45 patients who completed the Phase 3 Double-Blind Study were enrolled in the ongoing Phase 3 Open-Label Extension Study. Additional eligibility criteria for enrollment into the Extension Study were successful completion of the Phase 3 Double-Blind Study, including having received 21 of the 26 consecutive weekly infusions and having experienced no safety issues that would contraindicate participation in the Extension Study. Other differences between the 2 studies included a change in study design from a randomized placebo-controlled, double-blind study of 26 weeks to an ongoing open-label study in which all patients receive active rhIDU treatment. Results of the Extension Study reflect the safety and efficacy of long-term rhIDU treatment.

Table 3 summarizes the efficacy variables of the studies. The efficacy variables in the Phase 3 Double-Blind and Phase 3 Open-Label Extension Studies and the Phase 1/2 Study were chosen as appropriate measures of clinical benefit and lysosomal GAG storage. While the 2 studies did not include identical variables to assess clinical benefit, both studies evaluated the effect of rhIDU treatment on pulmonary function, functional capacity, and obstructive sleep apnea, as well as on measures of disease burden and general well-being.

Table 1: Summary of All Clinical Studies

Protocol No.	Study Design	Completion Status/Study Dates	Location/ No. of Centers	Treatment Doses (IV infusion)	Data Included in this Report	No. of Patients Entered/ Evaluable	Age: (years)	Sex (M/F)	Race* C/B/H/A/Other
ALID-003-99	Phase 3 Double-Blind, Placebo-Controlled, randomized	Completed 28DEC00 to 6SEP01	USA: 2 Canada: 1 UK: 1 Germany: 1	100 U/kg (0.58 mg/kg) once weekly	26 weeks	45/45	Mean 15.5 (Range: 6 to 43)	22/23	37/0/4/2/2
ALID-006-01	Phase 3 Open-Label, non-randomized extension	Ongoing Start date: 29MAY01	USA: 13 Canada: 2 UK: 1 Germany: 2 (this report)	100 U/kg (0.58 mg/kg) once weekly	24 weeks (36 weeks for primary endpoints and safety data)	45/45	Mean 15.5 (Range: 6 to 43)	22/23	37/0/4/2/2
BIO7500-001	Phase 1/2 Open-label, non-randomized	Ongoing Start date: 28NOV97	USA: 13	100 U/kg (0.58 mg/kg) once weekly	through 152 weeks (efficacy) up to 235 weeks (safety)	10/10	Mean 12.3 (Range: 5 to 22)	6/4	10/0/0/0/0
Expanded Access Program	Special access program for individual patients	Ongoing	Australia: 3 Brazil: 1 Czech Rep.: 1 Finland: 1 Germany: 3 Italy: 3 Netherlands: 1 Spain: 1 Taiwan: 1	100 U/kg (0.58 mg/kg) once weekly	Case-by-case basis per patient (through 30SEP02)	15/15 (SAE and IAR** reporting through 30SEP02)	Range: 2 - 39	6/ 9	unknown
	Protocol No. ALID 007 01 (Special access protocol for an individual patient)	Completed (pt. died)	USA: 1	100 U/kg (0.58 mg/kg) once weekly	28 weeks (As of 29APR02)	1/1 (SAE and IAR** reporting through 29APR02)	10	0/1	1/0/0/0/0

* C = Caucasian; B = Black; H = Hispanic; A = Asian.

** Infusion-associated reaction.

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Table 2: Study Design and Patient Eligibility

	Phase 3 Double-Blind Study	Phase 1/2 Study
Protocol No.	ALID-003-99	BIO7500-001
Design	Randomized, placebo-controlled, double-blind, multinational multicenter	Open-label
Objectives	To confirm the safety and efficacy of rhIDU in the treatment of MPS I	To evaluate the safety and efficacy of rhIDU in the treatment of MPS I
No. Patients	45 (22 rhIDU, 23 placebo)	10
Study Duration	26 Weeks (all patients enrolled into the ongoing open-label extension study ALID-006-01)	152 Weeks (ongoing)
Inclusion Criteria	Patients who: • had a documented diagnosis of MPS I, confirmed by measurable clinical signs and symptoms of MPS I, and a documented fibroblast or leukocyte α-L-iduronidase enzyme activity level of less than 10% of the lower limit of the normal range of the measuring laboratory • were males or females ≥5 years old • provided signed, written informed consent prior to performing any study-related procedures (or patient's legal guardian) • if a female of childbearing age, had a negative pregnancy test (urine β-hCG) at baseline. Note: All female patients of childbearing potential and sexually mature males were advised to use a medically accepted method of contraception throughout the study • were capable of standing independently a minimum of 6 minutes and walking a minimum of 5 meters within 6 minutes • were capable of performing a reproducible FVC maneuver • had a baseline FVC value that was less than or equal to 80% of the patient's predicted FVC value based on Polgar or Hankinson predicted values	Patients who: • were male or female and had a diagnosis of MPS I confirmed by clinical and enzymatic assessments, who: • were ≥5 years old • had significant physical disease indicative of MPS I, including enlarged liver or spleen size (≥ 1.5 times normal for age) and elevated urinary GAG (≥ 5 times normal for age) • were capable of providing at least a minimum level of consent and had a parent or legal guardian who consented • were able to attend (with at least 1 parent or legal guardian) the Harbor-UCLA Clinical Research Center for the first 6 weeks of the study • had a coordinating physician located in a geographic region nearby who was able and willing to administer the enzyme with the proper safety monitoring procedures and collect the required specimens for evaluation
Exclusion Criteria	Patients who: • had undergone a tracheostomy • had previously undergone BMT • were pregnant or lactating • had received an investigational drug within 30 days prior to study enrollment • had a medical condition, serious intercurrent illness, or other extenuating circumstance that significantly interfered with study compliance including all prescribed evaluations and follow-up activities • had a known hypersensitivity to rhIDU or to components of the test solutions.	Patients who: • were <5 years old • were, in the judgment of the investigator, uncooperative, incapable of performing clinical assessments, or likely to be noncompliant • were critically ill • required acute clinical procedures for life-threatening or harmful conditions • had previously undergone bone marrow transplant • received an investigational drug or procedure within 30 days of study enrollment

Table 3: Efficacy Variables in the Phase 3 Double-Blind Study, the Phase 3 Open-Label Extension Study and the Phase 1/2 Study

	Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study*	Phase 1/2 Study
Primary Variables	• FVC • 6–Minute Walk Test	• Liver and Spleen Volume • Urinary GAG Excretion
Secondary Variables	• Apnea/hypopnea index (AHI) • Liver Volume • Disability Index (CHAQ/HAQ) • Shoulder Flexion	• Joint Range of Motion (ROM) • Cardiac Function, including New York Heart Association (NYHA) Classification • Airway Obstruction (AHI and airway index) • Eye Disease
Tertiary Variables	• Urinary GAG Levels • Pain Score (CHAQ/HAQ) • Joint Range of Motion (ROM) • Patient Quality of Life (QoL) • Height • Visual Acuity, Tonometry, and Ophthalmologic Parameters • Cardiac Function • Investigator Global Assessment (Phase 3 Double-Blind Study only) • Forced Expiratory Volume (FEV_1), Total Lung Capacity (TLC), and Diffusing Capacity (D_L) • Parent/Primary Care-giver QoL • Resource Utilization • Heart Rate, Respiratory Rate, and O_2 Saturation	• Central Nervous System (CNS) Abnormalities • Bone Evaluations • Height and Weight Growth Rates in Prepubertal Patients

* The Phase 3 Open-Label Extension Study continues to assess the same efficacy variables measured in the Phase 3 Double-Blind Study, except for the Investigator Global Assessment.

4.2 Dosage Selection and Timing

Based on the data from the preclinical studies, the optimum dose for adequate delivery of enzyme to all tissues was determined to be 0.58 mg/kg (100 U/kg) once weekly for the Phase 1/2 Study in MPS I patients. Use of this dose was expected to provide enzyme levels sufficient to demonstrate biochemical and clinical improvement in disease. The results from the Phase 1/2 Study confirmed that 0.58 mg/kg (100 U/kg) was sufficient to demonstrate biochemical and clinical improvement in MPS I patients.

Therefore, the dose of 0.58 mg/kg (100U/kg) was also chosen for use in the Phase 3 Double-Blind Study, Phase 3 Open-Label Extension Study, and the Single Patient and Expanded Access Program.

The choice of weekly infusions was suggested by in vitro studies using fibroblasts from MPS I patients, in which the half-life of the enzyme was 5 days after uptake into the lysosome (Kakkis,

1994, Protein Expr Purif). The weekly regimen was shown to be effective in the MPS I canine (Kakkis, 1996, Biochem Mol Med).

5. CLINICAL PHARMACOLOGY

5.1 Human Pharmacokinetics

The pharmacokinetic profiles from the Phase 1/2 Study and the Phase 3 Double-Blind Study were in generally good agreement with comparable C_{max} (maximum plasma concentration), T_{max} (time to peak plasma concentration), V_{ss} (apparent volume of distribution at steady state), and MRT (mean residence time) values. There was a trend toward a faster CL (clearance) and shorter $t_{1/2}$ (elimination half-life) in the Phase 1/2 Study compared to the Phase 3, but given the individual variations within each study it is unlikely this difference is of clinical significance.

Table 4 summarizes the plasma pharmacokinetics of rhIDU determined in the Phase 3 Double-Blind Study.

Table 4: Pharmacokinetic Parameters for IDU Following Intravenous Infusion of rhIDU 0.58 mg/kg (100 U/kg) to Patients with MPS I: Study ALID-003-99

Parameter[1,2]	Infusion Number			p-value[3]
	1	12	26	
Dose (U/kg)	105.0 ± 5.0	103.9 ± 3.3	103.1 ± 3.2	–
Infusion Time (h) (Min., Max.)	3.98 (3.83, 4.33)	4.00 (3.83, 4.17)	3.96 (3.92, 4.25)	–
C_{max} (U/mL)	0.197 ± 0.052	0.210 ± 0.079	0.302 ± 0.089	< 0.001
T_{max} (h)	3.93	3.83	3.92	0.273
AUC_{0-t} (h.U/mL)	0.806 ± 0.218	0.713 ± 0.312	1.098 ± 0.389	–
AUC_{∞} (h.U/mL)	0.930 ± 0.214	0.913 ± 0.445	1.191 ± 0.451	0.247
CL (mL/min/kg)	1.96 ± 0.495	2.31 ± 1.13	1.68 ± 0.763	0.074
CL (mL/min)	65.4 ± 20.1	77.6 ± 43.9	60.7 ± 21.8	0.247
V_z (L/kg)	0.604 ± 0.172	0.307 ± 0.143	0.239 ± 0.128	0.022
V_z (L)	19.3 ± 3.01	9.97 ± 4.38	9.16 ± 5.33	0.022
V_{ss} (L/kg)	0.440 ± 0.125	0.252 ± 0.079	0.217 ± 0.081	0.015
V_{ss} (L)	14.1 ± 2.03	8.38 ± 2.68	8.00 ± 2.68	0.015
Elimination rate constant (h^{-1})	0.202 ± 0.046	0.773 ± 1.01	0.596 ± 0.522	–
$t_{½}$ (h)	3.61 ± 0.894	2.02 ± 1.26	1.94 ± 1.09	0.247
MRT (h)	3.83 ± 1.04	2.23 ± 1.21	2.36 ± 0.830	–

1 Mean ± standard deviation (SD) except for the infusion time for which the median and range are reported and T_{max} for which the median is reported.

2 Number of patients included for the different pharmacokinetic parameters varied from 10 to 12 for infusions 1 and 26, and 6 to 11 for infusion 12.

3 Friedman's test for comparison among the three infusions.

Following the infusion, the plasma IDU concentration remained above concentration for half-maximal saturation of uptake into cells (0.7 nM; 0.01 U/ml) for approximately 3–4 hours.

There was significant inter- and intra-patient variability in several pharmacokinetic parameters over time. C_{max} showed an increase over time, which was possibly due to a concomitant 50% reduction in V_z (volume of distribution). The reduction in V_z may also account for the trend towards a reduction in $t_{½}$ over time.

There was an inverse relationship between V_z and antibody level at Weeks 12 and 26, suggesting that the decrease in V_z could be related to formation of anti-rhIDU antibodies during treatment. Antibody-bound enzyme may have different distribution characteristics than unbound enzyme, thus increasing the fraction of the total body load of enzyme in the plasma and reducing the volume of distribution. However, CL did not appear to be affected by the duration of the treatment period (26 weeks), indicating that the irreversible transport of rhIDU out of the plasma was not affected.

5.2 Biodistribution

Tissue enzyme activity in a remote or distal anatomic compartment and in the intravascular compartment was also assessed in the Phase 1/2 Study by evaluation of IDU enzyme levels in buccal brushings and leukocytes, respectively. The demonstration of lowest trough IDU levels (i.e., one week after the last infusion and just before the next dose) in buccal brushings of about 1% of normal is expected to be corrective and sufficient to reduce lysosomal storage based on previous canine data evaluating enzyme levels and lysosomal storage in distal tissues. Leukocyte IDU mean trough levels reached an average of 18% of normal at Week 26, 12% of normal at Week 52, and 35% of normal at Week 104 (a level comparable to that seen in asymptomatic carriers). These values represent a substantial amount of enzyme further supporting that enzyme is being delivered to different cell types and demonstrates that, as expected, a higher level of enzyme uptake is achieved in cells that are in direct contact with the circulation.

No other patient tissue samples were collected in either clinical study.

5.3 Pharmacodynamic Evaluation

A mean reduction of 54.1% in urinary GAG levels was achieved in the Phase 3 Double-Blind Study, while a >50% reduction in urinary GAG was achieved in 8 out of 10 subjects (mean reduction of 65% across all 10) in the Phase 1/2 Study. A reduction of urinary GAG excretion due to removal of excess dermatan sulfate and heparan sulfate was selected as a pharmacodynamic endpoint and was one of the efficacy parameters. Based on MPS I canine studies, a 50% or greater reductions in urinary GAG levels was associated with reductions in other tissues (Kakkis,1996, Biochem Mol Med). BMT studies in humans that showed a reduction in urinary GAG following successful engraftment was associated with clinical improvements (Guffon, 1998, J Pediatrics). These studies suggested that a 50% reduction in urinary GAG would be an appropriate surrogate marker for clinical improvements.

6. EFFICACY

6.1 Results of the Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study

6.1.1 Patient Disposition in the Phase 3 Double-Blind Study

Forty-five patients were randomized into the study. Between 6 and 12 patients were entered at each of the 5 study centers. Of the 45 patients who were randomized, 23 patients were randomized to the placebo treatment group and 22 were randomized to receive rhIDU.

All 45 randomized patients completed the study and were included in the safety population. Randomization between treatment groups was well balanced at each of the study sites. The disposition of all randomized study patients is summarized in Table 5.

Table 5: Summary of Patient Disposition (Phase 3 Double-Blind Study)

Category	Summary Statistic	Placebo	rhIDU	Overall
Total Number of Patients Enrolled	n	NA	NA	47
Number of Patients Randomized	n	23	22	45
Number of Randomized Patients Completing the Study	n (%)	23 (100)	22 (100)	45 (100)
Safety Population	n	23	22	45

Note: NA = not applicable (enrollment occurred pre-randomization).

6.1.2 Patient Disposition in the Phase 3 Open–Label Extension Study

As this Phase 3 Open-Label Extension Study (ALID-006-01) is an extension of the placebo-controlled Phase 3 Double-Blind Study (ALID-003-99), the 2 treatment groups represented in the reporting of the Phase 3 Open-Label Extension Study data are as follows:

- placebo/rhIDU treatment group- patients received 26 weeks of placebo in the Phase 3 Double-Blind Study and are receiving ongoing rhIDU treatment in the Phase 3 Open-Label Extension Study.
- rhIDU/rhIDU treatment group - patients received 26 weeks of rhIDU treatment in the Phase 3 Double-Blind Study and are receiving ongoing rhIDU treatment in the Phase 3 Open-Label Extension Study.

At the time of this report, primary efficacy and safety data was available through Week 36. Data for other efficacy variables was available through Week 24.

Table 6 summarizes patient disposition through Week 36 of the ongoing Phase 3 Open-Label Extension Study.

Table 6: Summary of Patient Disposition from Entry* to Week 36 (Phase 3 Open-Label Extension Study)

Category	Summary Statistic	Treatment Group		
		Placebo/rhIDU	rhIDU/rhIDU	Overall
Total Number of Patients Enrolled	N	23	22	45
Number of Patients Completing Study	n	21	22	43
Number of Patients not Completing the Study	n	2	0	2
Reason for Withdrawal:				
Adverse Events	n	1**	0	1
Wishes to Withdraw	n	1***	0	1

*Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.
** One patient died due to an unrelated AE (Section 7.3.6).
***One patient chose to discontinue participation in the study because she became needle-phobic.

6.1.3 Patient Demographics in the Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study

Demographic and baseline characteristics for all randomized Phase 3 Double-Blind Study patients are summarized in Table 7.

Table 7: Demographic and Baseline Characteristics (Phase 3 Double-Blind Study)

Parameter	Summary Statistic	Treatment Group (ITT Population)		
		Placebo (n = 23)	rhIDU (n = 22)	Overall (N = 45)
Gender:				
Male	n (%)	11 (48)	11 (50)	22 (49)
Female	n (%)	12 (52)	11 (50)	23 (51)
Race:				
Caucasian	n (%)	21 (91)	16 (73)	37 (82)
Black	n (%)	0 (0)	0 (0)	0 (0)
Hispanic	n (%)	0 (0)	4 (18)	4 (9)
Asian	n (%)	1 (4)	1 (5)	2 (4)
Other	n (%)	1 (4)	1 (5)	2 (4)
MPS I Subtype				
Hurler	n (%)	1 (4)	0 (0)	1 (2)
Hurler-Scheie	n (%)	19 (83)	18 (82)	37 (82)
Scheie	n (%)	3 (13)	4 (18)	7 (16)
Age Group:				
≤ 12 years	n (%)	10 (43)	12 (55)	22 (49)
13 to ≤ 18 years	n (%)	8 (35)	3 (14)	11 (24)
19 to ≤ 65 years	n (%)	5 (22)	7 (32)	12 (27)
Age (years)	n	23	22	45
	Mean	15.4	15.6	15.5
	Median	14.1	12.4	13.8
	Std Dev	7.63	8.63	8.04
	Min, Max	6, 39	7, 43	6, 43
Weight (kg)	n	23	22	45
	Mean	40.3	35.3	37.9
	Median	35.7	33.1	33.8
	Std Dev	13.04	12.45	12.86
	Min, Max	22.5, 74.6	17.8, 61.5	17.8, 74.6
Standing Height (cm)	n	23	22	45
	Mean	137.2	133.5	135.4
	Median	136.0	133.6	136.0
	Std Dev	12.05	16.07	14.12
	Min, Max	117.7, 163.8	97.2, 159.9	97.2, 163.8

Note: The percentages are based on the total number of ITT patients.

There were no significant differences between treatment groups with respect to baseline characteristics or demographics.

Classification of MPS I disease subtype was based on investigator opinion. The MPS I disease subtype for the majority of patients, over 80% in both treatment groups, was Hurler-Scheie syndrome. The distribution between the treatment groups for Hurler syndrome and Scheie syndrome, the other 2 categories of MPS I, were comparable.

Baseline measures of patient MPS I characteristics are displayed in Table 8.

Table 8: Patient Baseline MPS I Characteristics (Phase 3 Double-Blind Study)

Parameter	Summary Statistic	Placebo (n=23)	rhIDU (n=22)	Overall (N=45)
Enzyme Activity Level (% of lower normal range)	n	23	22	45
	Mean	1.9	1.2	1.6
	Std Dev	3.20	2.13	2.72
	Min, Max	0.0, 9.9	0.0, 6.5	0.0, 9.9
Percent of Predicted FVC	n	23	22	45
	Mean	54.2	48.4	51.4
	Median	53.6	51.1	51.9
	Std Dev	16.00	14.85	15.55
	Min, Max	18, 77	15, 70	15, 77
6–Minute Walk Test (m)	n	23	22	45
	Mean	366.7	319.0	343.4
	Median	360.0	348.5	358.0
	Std Dev	113.68	131.41	123.62
	Min, Max	60, 571	14, 591	14, 591

There were no statistically significant differences at baseline between groups with respect to MPS I characteristics.

6.1.4 Extent of Exposure in the Phase 3 Double-Blind Study

All 45 randomized patients completed 26 weeks of the study. The mean number of days on study for the placebo and rhIDU groups was 182.0 and 181.5, respectively. The mean number of study drug infusions was similar between the 2 treatment groups (placebo 25.4 infusions and rhIDU 25.3 infusions). The mean volume of double-blind study medication infused was similar between the 2 groups during each infusion week.

6.1.5 Extent of Exposure in the Phase 3 Open-Label Extension Study

Forty-three of the 45 patients enrolled in this study completed 24 weeks of treatment in this ongoing open-label extension study. One patient in the placebo/rhIDU group died at Week 16

due to an upper respiratory tract infection that was judged to be not-related to rhIDU treatment, per the investigator. One of the remaining 44 patients chose to discontinue participation in the study at the Week 24 visit and did not receive the Week 24 infusion. Exposure to rhIDU during this period, as measured by time in the study and number of infusions, was similar in both treatment groups. The mean volume of rhIDU infused was also similar between the 2 groups during each infusion week.

Table 9 presents the total exposure to active study medication during the combined Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study periods. As anticipated, overall exposure for the rhIDU/rhIDU group, as measured by time in the study and number of infusions administered, was more than twice that of patients in the placebo/rhIDU group.

Table 9: Patient Cumulative Exposure to Study Medication from Baseline* through Week 36

Parameter	Summary Statistic	Placebo/rhIDU	rhIDU/rhIDU
Number of Days in Study	**N**	23	22
	Mean	234.5	426.2
	Median	246.0	427.5
	Standard Deviation	31.84	6.88
	Minimum, Maximum	112, 252	407, 435
Number of Study Drug Infusions	**N**	23	22
	Mean	31.8	58.6
	Median	33.0	59.0
	Standard Deviation	5.31	3.17
	Minimum, Maximum	16, 36	47, 62

* Last measurement prior to randomization in the Phase 3 Double-Blind Study
Note: Placebo/rhIDU patients did not receive any rhIDU administrations during the Phase 3 Double-Blind Study (ALID-003-99).

6.1.6 Primary Efficacy Results of the Phase 3 Studies: FVC and 6–Minute Walk Test

6.1.6.1 FVC in the Phase 3 Double-Blind Study

The changes from baseline to Week 26 for the percent of predicted FVC were initially calculated using the patient's current height at that visit and were compared between treatment groups. After 26 weeks of double-blind treatment, the change in the median value for the percent of predicted FVC for the rhIDU group was a 1.0 percentage point increase, while for the placebo group it was a -1.1 percentage point decrease. The difference between treatment groups in the median change from baseline to Week 26 for percent of predicted FVC was statistically significant ($p = 0.028$) favoring the rhIDU group.

The choice of current vs. baseline height for calculation of percent of predicted FVC was not prespecified in the statistical analysis plan. Review of the FVC results with clinical experts led to the recommendation to use baseline height for the calculation of the percent of predicted FVC to eliminate the confounding effects of postural changes, growth, and variability associated with repeat height measurements. The reasoning behind this decision was based on three issues identified through analysis of the percent of predicted FVC data:

1. Height is difficult to measure in the MPS I population due to skeletal and joint disease and repeated height measurements lead to increased variation.
2. Changes in joint stiffness and posture due to rhIDU treatment confounds the height measurements and leads to a systematic reduction in the apparent effect on FVC.
3. The decline in percent of predicted normal FVC in placebo patients using current height measurements was driven by a change in height, not lung volume, and led to an incorrect impression of declining lung volume in this group.

Therefore, baseline height was used to normalize the FVC for all patients; this baseline height was used throughout the study. Using this approach, the change in percent of predicted normal FVC in these studies represents changes in lung volume and not confounding variables, and at the same time, the effect of patient size variation at baseline is minimized.

Table 10 summarizes changes from baseline in percent of predicted FVC when baseline height is used to calculate percent of predicted FVC. These data are presented in graphical form in Figure 8.

Table 10: Changes from Baseline (Percentage Points) to Week 26 in Percent of Predicted FVC (ITT Population - Baseline Height) (Phase 3 Double-Blind Study)

	Placebo			rhIDU			Difference From Placebo	p-Value*
Statistic	**Baseline**	**Week 26**	**Change**	**Baseline**	**Week 26**	**Change**		
n	23	23	23	22	22	22	—	0.009
Mean	54.2	53.5	−0.7	48.4	53.3	4.9	5.6	
Median	53.6	56.4	0.0	51.1	54.2	3.0	3.0	
Std. Dev.	16.00	14.15	5.92	14.85	18.49	8.71	—	
Min., Max.	18, 77	30, 76	−19, 12	16, 70	19, 89	−18, 23	—	

* Hypothesis testing was on the median change.

When baseline height is used to calculate percent of predicted FVC, the difference between the 2 treatment groups is greater. After 26 weeks of double-blind treatment, the difference between the treatment groups in the change in mean percent of predicted FVC between the 2 treatment groups was 5.6 percentage points (median difference 3.0 percentage points, p=0.009).

In addition, an analysis of covariance (ANCOVA), described prospectively in the statistical analysis plan, was performed to account for baseline differences between groups. This analysis demonstrated that the treatment effect was maintained ($p = 0.040$) when taking into account center, baseline FVC, baseline AHI, baseline TLC, baseline liver volume, and baseline GAG level. Relative to the 48.4% of predicted baseline value for rhIDU patient, the 4.9 percentage point increase represents a 10% improvement.

Mean changes in percent of predicted FVC values are displayed for each study visit for the placebo and rhIDU treatment groups in Figure 8, along with the results from the Open-Label Extension Study.

An overall improvement in mean values over the 26-week treatment period was observed for the rhIDU group while mean change values declined for the placebo group. During the study, the percent of predicted FVC for the rhIDU treatment group showed a downward trend at Weeks 12, 16, and 20 but always remained higher than placebo. A similar downward trend from Week 12 to 20 was also observed in the placebo group. Various factors may have contributed to this downward trend, including intercurrent illness, assessment following an infusion, seasonal effects, or patient fatigue from repeat study visits. Nevertheless, the percent of predicted FVC for the rhIDU treatment group remained above the corresponding value for the placebo group at every time point during the study. The largest separation between groups occurred at the end of the study (Week 26).

6.1.6.2 FVC in the Phase 3 Open-Label Extension Study

The mean changes from baseline (last measurement prior to randomization in the Phase 3 Double-Blind Study) and entry (last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study) to Week 36 for the percent of predicted FVC for the placebo/rhIDU and the rhIDU/rhIDU treatment groups are displayed in Table 11.

Table 11: Changes in Percent of Predicted FVC through Week 36 (ITT Population) (Phase 3 Open-Label Extension Study: 36-Week Data)

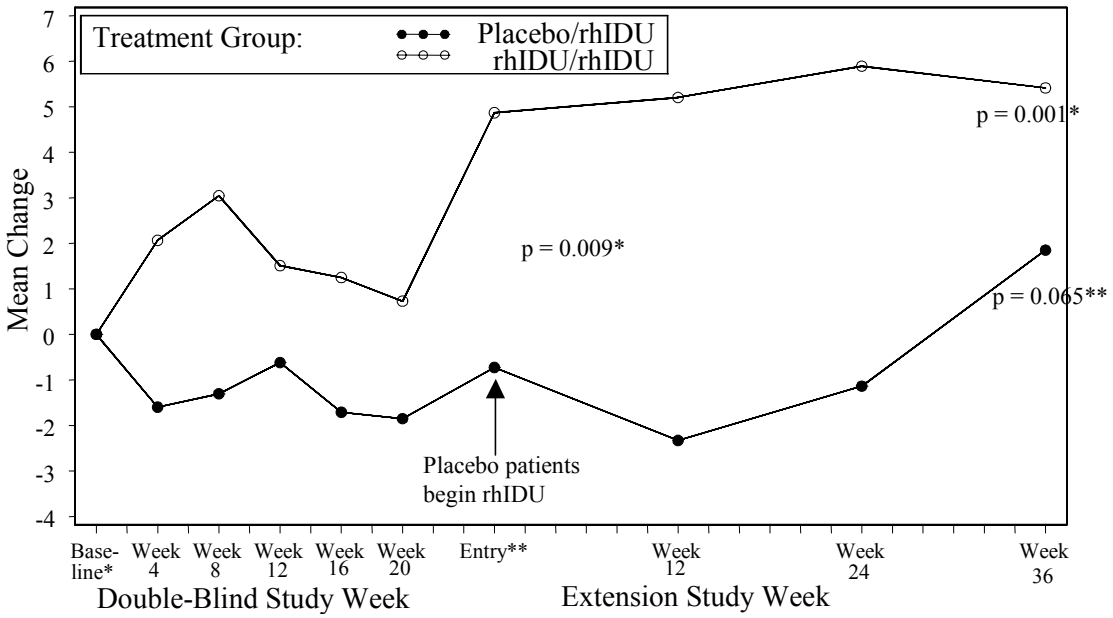
Summary Statistic	Baseline*	Entry**	Week 36	Change from Baseline* to Entry**	Change from Entry** to Week 36	Change from Baseline* to Week 36
Placebo/rhIDU Patients (n = 23)						
Mean (p-value)***	54.2	53.5	56.1	−0.7	2.6 (0.065)	1.8 (0.271)
Median	53.6	56.4	58.5	0.0	1.6	1.9
Std. Dev	16.00	14.15	16.03	5.92	6.36	7.86
Min., Max	17.8, 77.4	30.2, 76.3	21.9, 87.8	−19, 12	−8.3, 19.2	−20.2, 19.3
rhIDU/rhIDU Patients (n = 22)						
Mean (p-value)***	48.4	53.3	53.8	4.9	0.5 (0.773)	5.4 (0.001)
Median	51.1	54.2	57.4	3.0	0.6	4.6
Std. Dev	14.85	18.49	18.82	8.71	8.77	6.29
Min., Max	15.5, 70.4	18.9, 88.5	17.7, 83.7	−18, 23	−15.3, 26.9	−9.1, 16.9

* Last measurement prior to randomization in the Phase 3 Double-Blind Study.
** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.
*** p-value from within-group t-test.

From baseline to Week 36, the mean change in percent of predicted FVC for the rhIDU/rhIDU group was 5.4 percentage points, demonstrating that the improvement observed over the first 26 weeks of treatment was maintained. From entry to Week 36, the placebo/rhIDU group showed a 2.6 percentage point increase in percent of predicted FVC, with most of the improvement occurring between Weeks 24 and 36. The increase was not as high as in the rhIDU/rhIDU group and occured more slowly, which could be due to baseline disease severity, a seasonal effect or missed infusions.

The mean changes in percent of predicted FVC from baseline of the Phase 3 Double-Blind Study through the study time points of the Phase 3 Double-Blind Study and the Open-Label Extension Study are displayed for the rhIDU/rhIDU group and the placebo/rhIDU group in Figure 8.

Figure 8: Mean Changes in Percent of Predicted FVC (%) from Baseline* and Entry through Week 36 (ITT Population)**
(Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study: 36-Week Data)



* BL = baseline, last measurement prior to randomization in the Phase 3 Double-Blind Study.
** ET = Entry, last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.
Note: The percent of predicted FVC was calculated using baseline standing height.

6.1.6.3 6–Minute Walk Test in the Phase 3 Double-Blind Study

The changes from baseline to Week 26 in the distance in meters (m) that patients were able to walk in 6 minutes are shown in Table 12. These data are presented in graphical form in Figure 2.

Table 12: Changes from Baseline (m) to Week 26 in the 6-Minute Walk Test Distance (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo	p-Value*
	Baseline	Week 26	Change	Baseline	Week 26	Change		
n	23	23	23	22	22	22	—	0.066
Mean	366.7	348.3	−18.4	319.1	338.8	19.7	38.1	
Median	360.0	405.0	−11.0	348.5	359.5	27.5	38.5	
Std. Dev.	113.68	128.82	67.49	131.41	127.06	68.56	—	
Min., Max.	60, 571	30, 505	−170, 94	14, 591	33, 517	−100, 155	—	

* Hypothesis testing was on the median change.

The median change in distance walked for the rhIDU group was an increase of 27.5 meters while the median distance walked decreased by 11.0 meters in the placebo group after 26 weeks of double-blind treatment. The overall difference between treatment groups for median change in distance walked, 38.5 m, approached statistical significance (p=0.066).

A prospectively-defined ANCOVA was also performed to account for disease heterogeneity and baseline differences between groups. Center, baseline 6-Minute Walk Test, gender, baseline standing height, and baseline liver volume were the covariates used in the model. The resulting treatment effect achieved statistical significance using this analysis approach (p = 0.039). Relative to the baseline value for rhIDU-treated patients, the 19.7 meter increase represents a 6.2% improvement in meters walked.

The mean changes in the 6–Minute Walk Test at each study visit for the placebo and rhIDU treatment groups are displayed in Figure 9, along with the data from the Open-Label Extension Study.

Mean changes in the 6–Minute Walk Test distance over time show that the separation of the 2 treatment groups first occurs after 4 weeks into treatment in favor of the rhIDU group and continues throughout the 26 week treatment period. The baseline measurements were repeated 3 times and the last measurement prior to randomization was used as the baseline measurement. The data suggest that there may be a training effect of 15–20 meters taking place during the baseline evaluation that may lead to a higher distance walked at baseline than for example, at Week 4 and onward, for which only 1 measurement was taken. Week 4 may be more of a true baseline for the patients and hence separation is seen for the 2 treatment groups after Week 4.

6.1.6.4 6–Minute Walk Test in the Phase 3 Open-Label Extension Study

The mean changes from baseline and entry to Week 36 for the distance, in meters (m), that patients were able to walk in 6 minutes are displayed in Table 13.

Table 13: Changes in 6-Minute Walk Test Distance (m) through Week 36 (ITT Population) (Phase 3 Open-Label Extension Study)

Summary Statistic	Baseline*	Entry**	Week 36	Change from Baseline* to Entry**	Change from Entry** to Week 36	Change from Baseline* to Week 36
Placebo/rhIDU Patients (n = 23)						
Mean (p-value)* **	367.6	352.7	380.7	−18.4	32.4 (0.023)	14.0 (0.285)
Median	369.0	405.5	375.0	−11.0	30.0	15.0
Std. Dev	116.25	130.05	127.02	67.49	63.49	61.47
Min., Max	60.0, 571.0	30.0, 505.0	60.0, 590.0	−170, 94	- 103.0, 225.0	−144.0, 154.0
rhIDU/rhIDU Patients (n = 22)						
Mean (p-value)* **	319.0	338.8	359.0	19.7	20.3 (0.146)	40.0 (0.005)
Median	348.5	359.5	383.0	27.5	13.5	51.5
Std. Dev	131.41	127.06	112.36	68.56	62.92	60.50
Min., Max	14.0, 591.0	33.0, 517.0	77.0, 515.0	−100, 155	- 81.0, 145.0	−95.0, 185.0

* Last measurement prior to randomization in the Phase 3 Double-Blind Study.

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

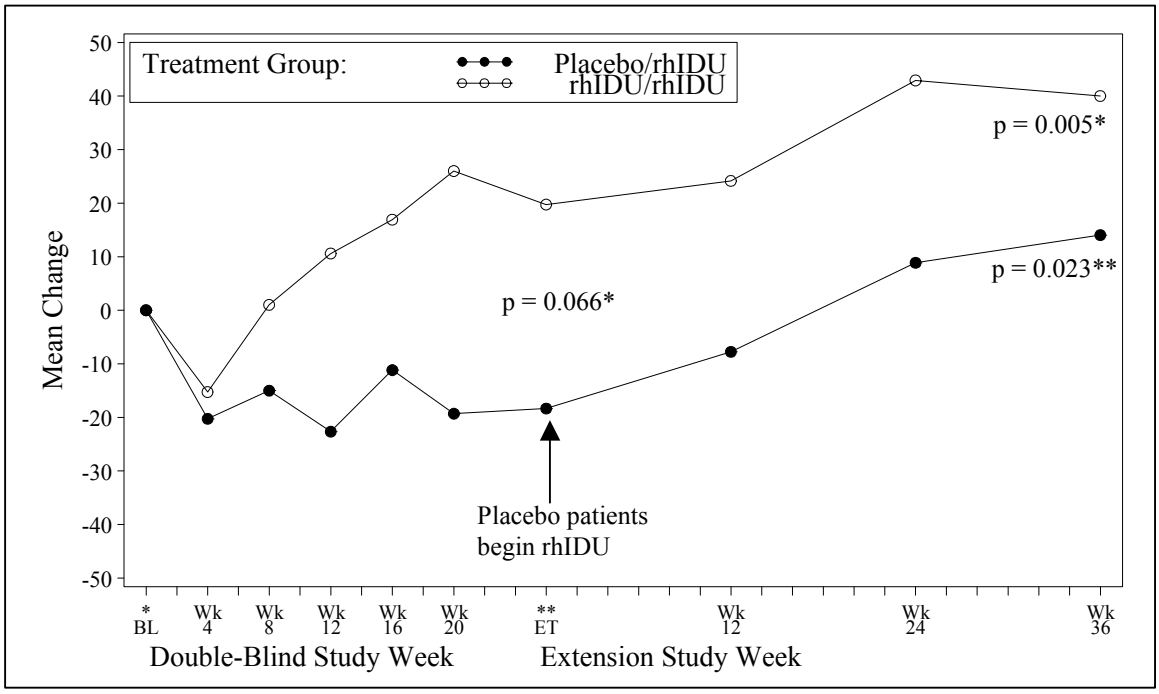
*** p-value from within-group t-test.

Note: Numbers of patients are displayed according to the number of patients with baseline, entry, and Week 36 values in the Phase 3 Open-Label Extension Study, except the Change from Baseline to Entry Column, in which the number of patients with Baseline and Week 26 data in the Phase 3 Double-Blind Study are presented.

From baseline of the Phase 3 Double-Blind study to Week 36 of the Phase 3 Open-Label Extension Study, the mean change in distance walked for the rhIDU/rhIDU group increased 40.0 m ($p = 0.005$). The increase that occurred between Week 26 of the Phase 3 Double-Blind Study and Week 36 of the Phase 3 Open-Label Extension Study was of similar magnitude to that observed during the first 26 weeks of treatment. From entry of the Phase 3 Open-Label Extension Study to Week 36, the mean distance walked for the placebo/rhIDU group increased 32.4 m ($p = 0.023$).

The changes from baseline of the Phase 3 Double-Blind Study to the study time points of the Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study in the mean 6-Minute Walk Test distance at each patient visit are displayed in Figure 9.

Figure 9: Mean Changes in 6-Minute Walk Test Distance (m) from Baseline* and Entry through Week 36 (ITT Population) (Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study: 36-Week Data)**



* Last measurement prior to randomization in the Phase 3 Double-Blind Study.
** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

Together, the results from the 2 groups, rhIDU/rhIDU and placebo/rhIDU, show a consistent treatment effect and have continued to increase with time.

6.1.7 Secondary Efficacy Results of the Phase 3 Studies

6.1.7.1 Apnea/Hypopnea Index (AHI) in the Phase 3 Studies

6.1.7.1.1 AHI in the Phase 3 Double-Blind Study

The change in the AHI from baseline to 26 weeks was compared between the treated and placebo groups as shown in Table 14.

Table 14: Changes in AHI (Events per Hour) from Baseline to Week 26 (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo*	p-Value
	Baseline	Week 26	Change*	Baseline	Week 26	Change*		
n	21	19	19	20	20	20	−3.6	0.145
Mean	14.7	15.5	0.4	20.5	17.6	−2.9		
Median	10.1	9.9	0.4	13.7	12.6	0.1		
Std. Dev.	15.20	14.93	8.55	19.04	16.75	6.66		
Min., Max.	1.9, 61.4	0.6, 52.9	−16.7, 18.1	2.9, 78.9	1.2, 69.8	−13.6, 7.8		

* Difference in adjusted mean changes calculated using the ANOVA model.

Although the trend was in favor of the rhIDU-treated patients, the difference from placebo, –3.6 events per hour, was not statistically significant (p=0.145).

A significant proportion of the patients had normal AHI scores at baseline that may have obscured an efficacy effect in patients with sleep apnea. While still blinded, the independent expert who interpreted the sleep studies recommended analyzing results from pediatric patients (≤15 years) with AHI scores ≥10 and adult patients (>15 years) with AHI scores ≥ 15, based on recently published guidelines for evaluating obstructive sleep apnea-hypopnea syndrome (Goodwin, 2001, Sleep)(Tunis, 2001, Centers for Medicare and Medicaid Services Admin File).

Restricting the analysis to those patients with sleep apnea at baseline (AHI ≥10 for children, ≥15 for adults), 10 placebo and 11 rhIDU patients were identified as affected as shown in Table 15.

Table 15: Changes in AHI (Events per Hour) from Baseline to Week 26 in Children with AHI ≥10 and in Adults with AHI ≥15 (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo*	p-Value
	Baseline	Week 26	Change*	Baseline	Week 26	Change*		
n	10	9	9	11	11	11	−9.1	0.037
Mean	24.5	25.3	0.3	32.1	25.8	−6.3		
Median	18.3	27.5	−0.9	27.5	18.7	−9.1		
Std. Dev.	17.26	16.19	12.55	18.76	18.64	6.77		
Min., Max.	10.1, 61.4	3.0, 52.9	−16.7, 18.1	10.9, 78.9	9.8, 69.8	−13.6, 2.4		

* Difference in adjusted mean changes calculated using the ANOVA model.

These data show that rhIDU treatment can reduce sleep apnea in MPS I patients affected at baseline (p = 0.037) and that these effects are clinically meaningful.

6.1.7.1.2 AHI in the Phase 3 Open-Label Extension Study

When the total ITT population of patients with and without clinically significant sleep apnea was analyzed, relatively small changes were observed in the rhIDU/rhIDU group and the placebo/rhIDU group from entry to Week 24.

As in the Phase 3 Double-Blind Study, a separate analysis was performed in patients with sleep apnea at baseline, defined as AHI ≥10 for children and ≥15 for adults. Eleven and 9 patients were identified in the rhIDU/rhIDU group and placebo/rhIDU group, respectively. One patient in the rhIDU/rhIDU group had unusually severe sleep apnea, with AHI scores ranging from 60 to 100. According to the independent expert, variations in AHI scores are not clinically meaningful within the range of 60 to 100 events per hour and are an artifact of the mechanics of the instrument recording of this high number of events. Because wide swings in AHI numbers in this range can have a disproportionate and inappropriate confounding effect on the data, analyses on AHI were run after excluding this patient's data. The results of this analysis are summarized in Table 16.

Table 16: Changes in AHI through Week 24 - Patients with Baseline* Values ≥10 for Pediatric Patients and ≥15 for Adult Patients (ITT Population Excluding Patient 030806) (Phase 3 Open–Label Extension Study: 24–Week Data)

Summary Statistic	Baseline*	Entry**	Week 24	Change from Entry** to Week 24	Change from Baseline* to Week 24
Placebo/rhIDU Patients					
n	9	8	9	8	9
Mean	20.4	22.9	13.7	−9.2	−6.7
Median	17.6	24.8	10.3	−10.8	−5.8
Std. Dev	12.07	15.47	9.22	8.37	10.20
Min., Max	10.1, 41.6	3.0, 52.9	3.6, 34.5	−18.9, 0.6	−31.3, 3.5
rhIDU/rhIDU Patients					
n	10	10	10	10	10
Mean	27.4	21.4	21.9	0.5	−5.5
Median	27.1	18.3	26.2	3.8	−8.7
Std. Dev	11.09	12.23	10.20	11.07	10.32
Min., Max	10.9, 51.7	9.8, 52.7	7.5, 34.4	−18.3, 14.4	−17.3, 16.8

* Last measurement prior to randomization in the Phase 3 Double-Blind Study.

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

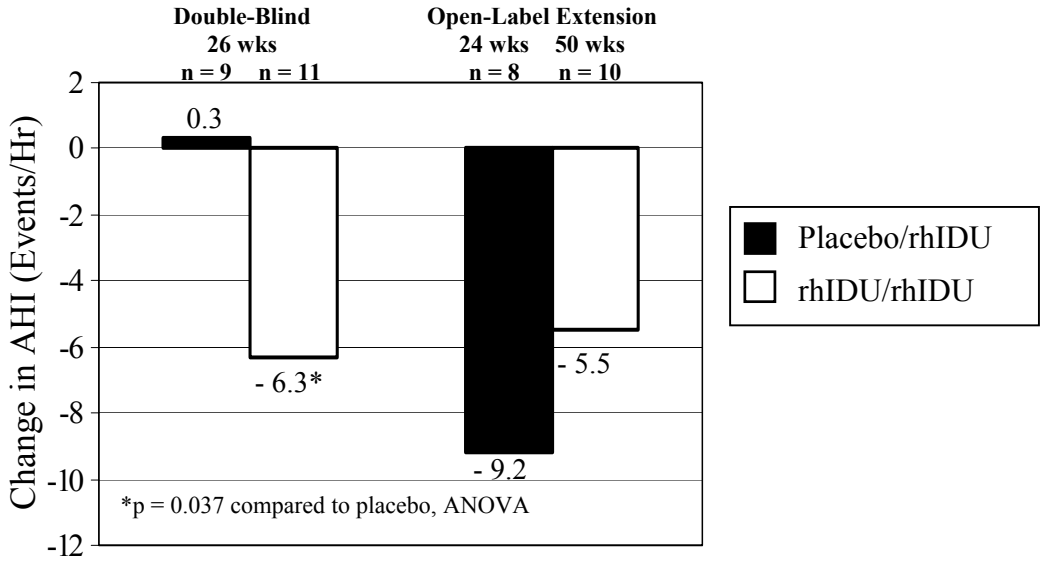
Note: One patient did not have a Week 26 AHI value in Phase 3 Double-Blind Study; another patient did not have a Week 24 value in the Phase 3 Open-Label Extension Study.

Note: Numbers of patients are displayed according to the number of patients with baseline, entry, and Week 24 values in the Phase 3 Open-Label Extension Study, except the Change from Baseline to Entry Column, in which the number of patients with baseline and Week 26 data in the Phase 3 Double-Blind Study are presented.

From Baseline to Week 24, the rhIDU/rhIDU patients maintained the improvement observed during the first 26 weeks of therapy. After 50 weeks of rhIDU treatment, there was a mean decrease in AHI of 5.5 events per hour, a 20% decrease from baseline. Similarly, after receiving rhIDU for 24 weeks, the placebo/rhIDU patients showed a mean decrease in AHI of 9.2 events

per hour, a 40% decrease from Entry (Figure 10). The mean AHI score decreased from 22.9 to 13.7, a level below the clinical cutoff of 15 for CPAP initiation according to USA Medicare guidelines (Tunis, 2001, Centers for Medicare and Medicaid Services Admin File).

Figure 10: rhIDU Reduces AHI



6.1.7.2 Liver Organ Volume (Hepatomegaly) in the Phase 3 Studies

6.1.7.2.1 Hepatomegaly in the Phase 3 Double-Blind Study

Between-treatment group comparisons of the mean changes in liver volume from baseline to Week 26 were evaluated (Table 17).

Table 17: Percent Change from Baseline to Week 26 for Liver Organ Volume (cc) (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo* (%)	p-Value
	Baseline	Week 26	% Change*	Baseline	Week 26	% Change*		
n	22	22	22	22	22	22	−20.0	0.001
Mean	1368.1	1366.5	1.3	1212.2	979.8	−18.9		
Median	1288.2	1323.2	1.1	1222.4	1011.2	−24.7		
Std. Dev.	314.88	316.94	19.22	283.36	321.45	19.44		
Min., Max.	875, 2214	802, 2080	−40, 64	719, 1702	582, 1989	−36, 44		

* Difference in adjusted mean changes calculated using the ANOVA model.

The percent change from baseline to Week 26 in mean liver organ volume was clinically and statistically significant in favor of the rhIDU group, with a mean decrease of 18.9% in the rhIDU group compared to an increase of 1.3% in the placebo treatment group (p=0.001).

Shifts in Abnormal/Normal from Baseline to Week 26: The shifts in abnormal/normal liver organ volume (hepatomegaly) from baseline to Week 26 are tabulated in Table 18.

Table 18: Shift in Abnormal/Normal Liver Organ Volume (Hepatomegaly) from Baseline to Week 26 (ITT Population) (Phase 3 Double-Blind Study)

Baseline	Placebo		rhIDU	
	Week 26 Abnormal (n)	Week 26 Normal (n)	Week 26 Abnormal (n)	Week 26 Normal (n)
Abnormal	11 (79%)	3 (21%)	5 (28%)	13 (72%)
Normal	1	7	0	4

Of the 14 patients in the placebo group who were classified as having abnormal baseline liver organ volumes, 3 patients (21%) were considered normal at Week 26. Of the 18 patients who were classified as having abnormal liver organ volumes at baseline in the rhIDU group, 13 patients (72%) were considered normal at Week 26.

The mean percent change in liver organ volume from baseline to Week 26 favored rhIDU-treated patients at each of the study centers. In parallel, variable increases were observed at 4 of the study centers among placebo-treated patients.

6.1.7.2.2 Hepatomegaly in the Phase 3 Open–Label Extension Study

The mean percentage changes in liver volume from baseline and entry to Week 24 were evaluated and are summarized in Table 19.

Table 19: Percentage Changes in Liver Organ Volume through Week 24 (ITT Population)(Phase 3 Open–Label Extension Study: 24-Week Data)

Summary Statistic	Baseline* (cc)	Entry** (cc)	Week 24 (cc)	% Change from Baseline* to Entry**	% Change from Entry** to Week 24	% Change from Baseline* to Week 24
Placebo/rhIDU Patients						
n	18	18	18	22	18	18
Mean	1358.0	1300.6	1114.1	1.3	– 12.6	– 16.5
Median	1282.5	1271.5	1073.5	1.1	– 18.3	– 21.8
Std. Dev	301.44	278.32	256.51	19.22	19.73	19.11
Min., Max	991.3, 2214.2	802.1, 1769.1	771.8, 1723.9	– 40, 64	– 34.7, 38.3	– 32.8, 36.1
rhIDU/rhIDU Patients						
n	20	20	20	22	20	20
Mean	1211.2	998.8	945.9	– 18.9	– 3.6	– 21.7
Median	1216.5	1012.4	961.1	– 24.7	1.9	– 25.1
Std. Dev	297.65	331.50	286.42	19.44	16.37	17.06
Min, Max	718.6, 1702.1	581.6, 1988.9	439.0, 1493.3	– 36, 44	– 52.2, 17.9	– 52.6, 33.5

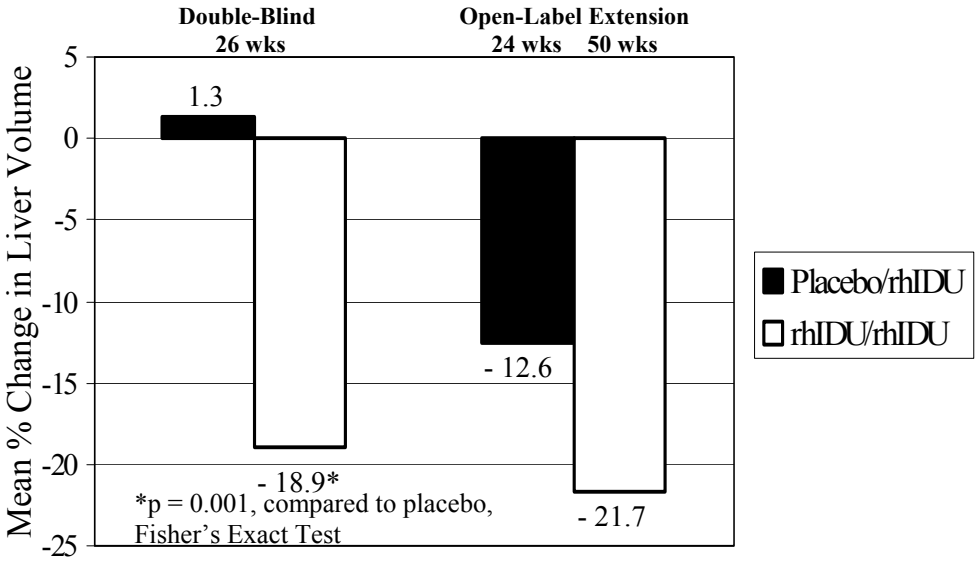
* Last measurement prior to randomization in the Phase 3 Double-Blind Study.

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

Note: Numbers of patients with data varied between time points because Week 24 MRI data was not sent in to the central reader in time to make the 24-week snapshot of the database, and summary statistics for baseline, entry, and changes from baseline and entry to Week 24 are only calculated for patients with complete Phase 3 Open-Label Extension Study data.

In the rhIDU/rhIDU group, liver organ volume decreased by a mean of 3.6% from entry to Week 24. During the entire 50 weeks of rhIDU treatment (from baseline to Week 24), liver organ volume decreased by a mean of 21.7% for this treatment group. In the placebo/rhIDU group, liver organ volume decreased by a mean of 12.6% from entry to Week 24 (Figure 11).

Figure 11: rhIDU Decreases Hepatomegaly



Shifts in Abnormal/Normal from Baseline and Entry to Week 24.

The shifts in abnormal/normal liver organ volume from baseline and entry to Week 24 were recorded and are tabulated in Table 20.

Table 20: Shifts in Abnormal/Normal Liver Organ Volume (Hepatomegaly) from Baseline* and Entry to Week 24 (ITT Population) (Phase 3 Open-Label Extension Study: 24-Week Data)**

	Placebo/rhIDU Patients		rhIDU/rhIDU Patients	
	Week 24 Abnormal (n)	**Week 24 Normal (n)**	**Week 24 Abnormal (n)**	**Week 24 Normal (n)**
Baseline*				
Abnormal	6	6	3	12
Normal	0	4	0	3
Entry**				
Abnormal	5	5	3	2
Normal	1	5	0	13

* Last measurement prior to randomization in the Phase 3 Double-Blind Study.

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

Note: MRI and weight data was not available for all patients at all timepoints.

After 50 weeks of treatment with rhIDU, 12/15 (80%) evaluable patients who had abnormal liver volumes at baseline had values in the normal range at Week 24. In the placebo/rhIDU group, 5/10 (50%) evaluable patients who had abnormal liver volumes at entry had values in the normal range at Week 24.

6.1.7.3 Disability Index (CHAQ and HAQ) in the Phase 3 Studies

6.1.7.3.1 Disability Index (CHAQ and HAQ) in the Phase 3 Double–Blind Study

The CHAQ/HAQ Disability Index evaluates the extent of disability using a scale of 0 to 3, with 3 being the worst score. Patients in this study had mean baseline scores of 1.9 and 2.0 in the placebo/ rhIDU and rhIDU/ rhIDU groups, respectively. No statistically significant difference between the rhIDU treatment and placebo groups was observed for the mean change in Disability Index score after the 26 week treatment period ($p=0.815$). Patients in the placebo group showed a decrease in the index of 0.1 and the rhIDU patients showed a decrease of 0.2. The lack of improvement in the rhIDU group was most likely due to the lack of sensitivity and specificity of this generic instrument to detect change in MPS I disease over a short time period.

6.1.7.3.2 Disability Index (CHAQ and HAQ) in the Phase 3 Open–Label Extension Study

Changes in the score from baseline and entry to Week 24 were small for both groups, but they began to approach clinical significance for the rhIDU/rhIDU group after 50 weeks of treatment. The rhIDU/rhIDU patients had an overall reduction of 0.3 from baseline to Week 24, corresponding to a 10% change on a 3-point scale, while the placebo/rhIDU patients had a 0.2 decrease from entry to Week 24. A change of 10% is approaching clinical significance.

6.1.7.4 Shoulder Flexion ROM in the Phase 3 Studies

6.1.7.4.1 Shoulder Flexion ROM in the Phase 3 Double-Blind Study

The between treatment group comparison of the mean change from baseline to Week 26 in the active shoulder flexion variable, defined as the mean of right and left shoulder flexion, was part of the joint ROM tests (Table 21).

Table 21: Changes from Baseline to Week 26 for Shoulder Flexion Degrees (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo*	p-Value
	Baseline	Week 26	Change*	Baseline	Week 26	Change*		
N	23	23	23	19	22	19	−0.1	0.987
Mean	89.8	84.9	−4.9	96.1	88.5	−1.5		
Median	88.5	91.5	4.0	97.5	90.0	3.5		
Std. Dev.	23.99	33.11	27.65	30.25	38.25	30.39		
Min., Max.	46, 135	31, 149	−104, 25	34, 173	34, 150	−85, 47		

* Difference in adjusted mean changes calculated using the ANOVA model.

When looking at the overall population for shoulder flexion changes from baseline to Week 26, the placebo group decreased by a mean of 4.9 degrees compared to a mean decrease of 1.5 degrees in the rhIDU group, but the difference was not significant (p=0.987).

As can be seen in Table 21, there was large variability in the baseline values of patients in both treatment groups. Therefore, because patients with less joint restriction may create a ceiling effect, further analyses of patients with baseline values less than or equal to or greater than the overall median score at baseline (overall median of 90.5 degrees at baseline) were conducted. Table 22 summarizes the mean change ± standard deviation from baseline to Week 26 in shoulder flexion by baseline severity.

Table 22: Mean Shoulder Flexion Change from Baseline by Baseline Severity (ITT Population) (Phase 3 Double-Blind Study)

Baseline ROM Severity	Placebo		rhIDU	
	Baseline	Change*	Baseline	Change*
≥ Median	n=10 106.7±14.61	4.9±12.65	n=11 111.9±23.95	−1.0±24.27
< Median	n=12 72.0±13.88	−4.8±20.46	n=7 68.0±18.01	9.6±21.96

* Difference in adjusted mean changes calculated using the ANOVA model.

The numbers in this subset of patients with less than the median flexion, representing the patients with more restriction at baseline, are too small to lead to statistical significance, but there was a trend seen in the rhIDU group towards an almost 10 degree increase, while the placebo group decreased by almost 5 degrees.

6.1.7.4.2 Shoulder Flexion ROM in the Phase 3 Open-Label Extension Study

In the overall population, patients in both groups demonstrated mean improvements in shoulder flexion ROM at Week 24 compared to entry. A further analysis was performed on those patients

with more severe shoulder flexion restriction at baseline; i.e., those patients with baseline joint ROM scores at or above and below the median score at baseline (overall median of 90.5 degrees at baseline). Results of this analysis are summarized in Table 23.

Table 23: Changes(Degrees) in Joint ROM Through Week 24 – Shoulder Flexion for Patients Below the Median (ITT Population) (Phase 3 Open–Label Extension Study: 24-Week Data)

Summary Statistic	Baseline*	Entry**	Week 24	Change from Baseline* to Entry**	Change from Entry** to Week 24	Change from Baseline* to Week 24
Placebo/rhIDU Patients						
n	12	12	12	12	12	12
Mean	72.0	67.7	82.9	−4.8	15.2	10.9
Median	74.0	59.0	85.3	−1.0	8.5	14.3
Std. Dev	13.88	21.53	15.14	20.46	20.06	11.51
Min., Max	45.5, 88.5	44.5, 101.5	62.5, 107.5	−38, 25	−8.0, 52.5	−18.5, 21.0
rhIDU/rhIDU Patients						
n	9	9	9	7	9	9
Mean	72.9	75.0	81.6	9.6	6.6	8.7
Median	74.5	65.0	87.5	8.0	5.0	12.0
Std. Dev	18.37	29.12	18.35	21.96	19.37	16.50
Min., Max	33.5, 90.0	41.5, 131.0	45.5, 101.0	−23, 47	−30.0, 28.5	−28.5, 25.0

* Last measurement prior to randomization in the Phase 3 Double-Blind Study.

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study.

Note: Numbers of patients are displayed according to the number of patients with baseline, entry, and Week 24 values in the Phase 3 Open-Label Extension Study, except the Change from Baseline to Entry Column, in which the number of patients with baseline and Week 26 data in the Phase 3 Double-Blind Study are presented.

In patients with more severely restricted shoulder flexion, the rhIDU/rhIDU group showed a mean increase in shoulder flexion of 6.6 degrees from entry to Week 24, and a mean increase of 8.7 degrees from baseline to Week 24. The placebo/rhIDU group showed a mean increase of 15.2 degrees from entry to Week 24.

6.1.8 Tertiary Efficacy Results of the Phase 3 Studies

6.1.8.1 Urinary GAG Levels in the Phase 3 Studies

6.1.8.1.1 Urinary GAG Levels in the Phase 3 Double-Blind Study

The difference between treatment groups in mean percent change from baseline to Week 26 was evaluated for urinary GAG levels (Table 24).

Table 24: Percent Changes from Baseline to Week 26 for Urinary GAG Levels (µg/mg Creatinine) (ITT Population) (Phase 3 Double-Blind Study)

Summary Statistic	Placebo			rhIDU			Difference From Placebo* (%)	p-value
	Baseline	Week 26	% Change*	Baseline	Week 26	% Change*		
n	22	23	22	21	22	21		
Mean	183.3	250.2	47.3	188.9	81.3	−54.1		
Median	171.4	245.8	32.4	185.3	82.3	−56.8	−101	<0.001
Std. Dev.	72.05	105.09	59.34	60.93	26.36	19.49		
Min., Max.	46, 303	74, 482	−50, 231	74, 298	25, 135	−85, −5		

* Difference in adjusted mean changes calculated using the ANOVA model.

The mean urinary GAG levels increased by 47.3% for patients in the placebo group and decreased by 54.1% for patients in the rhIDU group, for a between-group difference of 101% ($p < 0.001$).

Mean urinary GAG levels for each treatment group by patient visit are summarized graphically in Figure 12, along with data from the Phase 3 Open-Label Extension Study.

The decrease in urinary GAG levels observed in the rhIDU group was evident by Week 4 of the study period and was maintained through Week 26.

Shifts in Normal/Abnormal from Baseline to Week 26: All patients in both groups had abnormal urinary GAG levels at baseline. Although all patients in the rhIDU group showed reductions that approached the upper limit of normal, none achieved a normal level by Week 26.

6.1.8.1.2 Urinary GAG Levels in the Phase 3 Open-Label Extension Study

The mean percentage changes from baseline and entry to Week 24 in urinary GAG levels are summarized in Table 25.

Table 25: Percentage Changes in Urinary GAG Levels through Week 24 (ITT Population) (Phase 3 Open-Label Extension Study: 24–Week Data)

Summary Statistic	Baseline* (Unit)	Entry**	Week 24	% Change from Baseline* to Entry**	% Change from Entry** to Week 24	% Change from Baseline* to Week 24
Placebo/rhIDU Patients						
n	23	23	23	22	23	23
Mean	185.3	250.2	74.3	47.3	−68.9	−56.3
Median	171.5	245.8	74.4	32.4	-68.5	−55.8
Std. Dev	71.03	105.09	30.78	59.34	11.56	16.70
Min., Max	46.3, 303.1	74.2, 482.1	0.0, 128.3	−50, 231	−100.0, −47.0	−100.0, −14.1
rhIDU/rhIDU Patients						
n	22	22	22	21	22	22
Mean	190.2	81.3	64.9	−54.1	−20.2	−64.8
Median	189.4	82.3	62.3	−56.8	−18.0	-64.6
Std. Dev	59.81	26.36	30.48	19.49	26.47	19.15
Min., Max	73.9, 298.3	24.5, 134.7	0.0, 117.8	−85, −5	−100.0, 27.5	−100.0, −13.5

* Last measurement prior to randomization in the Phase 3 Double-Blind Study

** Last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study

Note: Normal urinary GAG levels are (in µg/mg creatinine) 24.6 to 71.0 for patients aged 5 to 12 years, 7.0 to 38.5 for patients aged 13 to 18 years, and 4.2 to 16.9 for adults .

Note: Numbers of patients are displayed according to the number of patients with baseline, entry, and Week 24 values in the Phase 3 Open-Label Extension Study, except the Change from Baseline to Entry Column, in which the number of patients with baseline and Week 26 data in the Phase 3 Double-Blind Study are presented.

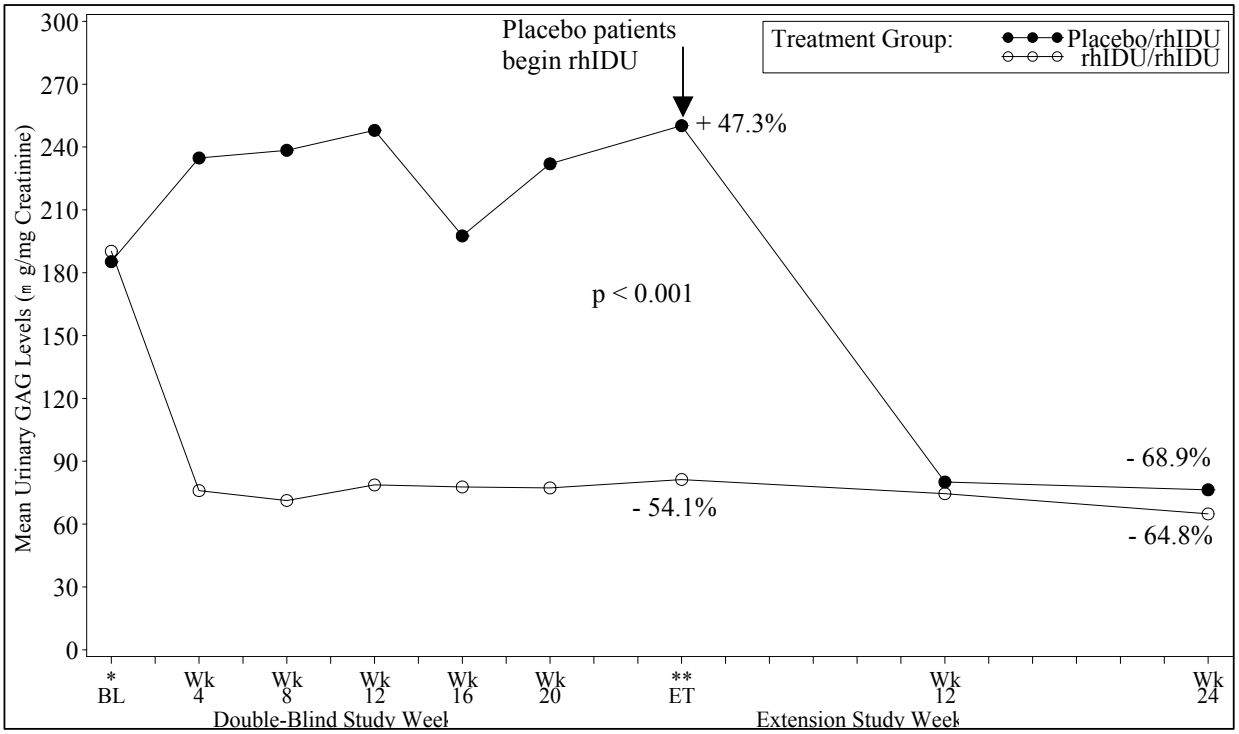
The mean percentage decrease from entry to Week 24 of the Phase 3 Open-Label Extension Study in the rhIDU/rhIDU group was 20.2%. The total percent decrease over the 50 weeks of treatment in the rhIDU/rhIDU group was 64.8%.

In the placebo/rhIDU group, the mean decrease in urinary GAG levels from entry to Week 24 of the Phase 3 Open-Label Extension Study was 68.9%, similar to the reduction seen in the rhIDU/rhIDU group.

The absolute levels of urinary GAG at Week 24 decreased to near-normal levels for both treatment groups.

Mean urinary GAG levels for each of the treatment groups by patient visit are presented in Figure 12.

Figure 12: Changes in Urinary GAG Levels (µg/mg Creatinine) through Week 24 (ITT Population) (Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study: 24-Week Data)



* BL = baseline, last measurement prior to randomization in the Phase 3 Double-Blind Study

** ET = entry, last measurement in the Phase 3 Double-Blind Study prior to enrollment in the Phase 3 Open-Label Extension Study

Shifts in Normal/Abnormal from Baseline and Entry to Week 24. By Week 24, 6/22 (27.3%) rhIDU/rhIDU patients and 3/23 (13.0%) placebo/rhIDU patients with abnormal urinary GAG levels at Baseline had normal urinary GAG levels.

6.1.8.2 Summary of Other Tertiary Endpoints

Several other tertiary endpoints were evaluated, including Total Respiratory Event Index, CHAQ/HAQ Pain Scale, Other Joint ROM, CHQ and SF-36 Quality of Life Assessments, Height in Pre-Pubertal Patients, Ophthalmology Measures (Examination, Visual Acuity, Tonometry), Cardiac Parameters (Electrocardiograms, Echocardiography), Physician Global Assessment, Other Pulmonary Function Tests (FEV_1, TLC, D_L), and post-6 Minute Walk Test Vital signs (Heart Rate, Respiratory Rate, O_2 Saturation). In general, changes were small and not clinically significant with a few exceptions. Positive trends were observed in patients receiving rhIDU compared to placebo in joint range of motion involving shoulder extension, knee flexion, and knee extension, especially in patients whose range of motion was below the median. The changes in joint range of motion observed in rhIDU/rhIDU were maintained or improved upon in the Phase 3 Open-Label Extension Study, and placebo/rhIDU patients began to show positive trends in the Phase 3 Open-Label

Extension Study. In the Phase 3 Double-Blind Study, a 2-line improvement in visual acuity was observed in 5/22 rhIDU patients compared to none of the placebo patients. In the Phase 3 Open-Label Extension Study, a 2-line improvement in visual acuity was observed in 3/22 rhIDU/rhIDU patients and in none of the placebo/rhIDU patients.

In the Parent or Caregiver CHQ-PF-50 Assessment, improved scores were seen in the placebo/rhIDU and rhIDU /rhIDU groups after 26 and 50 weeks of rhIDU treatment, respectively. In the Patient CHQ-CF-87 Assessment, improvements in all domains were seen in the rhIDU/rhIDU group after 50 weeks of treatment, particularly in several physical and general health domains. Smaller improvements were seen in placebo/rhIDU patients between entry and Week 24. In the Patient SF-36 Assessment, there was a positive trend in the physical health score of rhIDU/rhIDU patients after 50 weeks of treatment. Like the CHAQ/HAQ instruments, the SF 36 and CHQ are generic meausres that may not be sensitive or specific enough to detect significant change in MPS I patients in a short timeframe.

6.1.9 Effect of the Immune Response on Efficacy

Because nearly all patients developed anti-rhIDU IgG antibodies (20/22 rhIDU patients in the Phase 3 Double-Blind Study (Section 7.2.10.4) and 21/23 placebo/rhIDU patients in the Phase 3 Open-Label Extension Study (Section 7.3.10.4)), it is not possible to compare efficacy results between seropositive and seronegative patients in a meaningful way. However, patients did develop different levels of IgG antibodies as reflected by the ELISA assay, and hence two types of analyses were performed.

In the first series of analyses, scatterplots were generated to compare the ELISA OD_{450} values versus changes in the 2 co-primary efficacy variables (percent of predicted FVC and the 6-Minute Walk Test) and versus percentage changes in the two surrogate markers (liver volume and urinary GAG level). Values were plotted after 6 and 12 months of treatment and across all patients in the study. The scatter plots revealed no correlation between antibody level and changes in percent of predicted FVC, 6-Minute Walk Test distance, or liver volume following 6 and 12 months of rhIDU treatment in both groups of patients. Patients with the higher antibody titers tended to have less reduction in urinary GAG levels, although reductions in urinary GAG levels were still marked in these patients. In the Phase 3 Open-Label Extension Study, this apparent association seen between antibody titer and percentage change in urinary GAG levels was diminished.

In the second series of analyses, individual patient data plots of percent of predicted FVC and the 6-Minute Walk Test distance were generated for various timepoints in the Phase 3 Double-Blind Study. No consistent trends were observed with respect to efficacy before or after the development of IgG antibodies.

These results suggest that development of an immune response does not affect the efficacy of rhIDU. There was also no association between the level of inhibitory activity and changes in efficacy variables.

6.1.10 A Responder Analysis Based on a Composite Endpoint Approach

6.1.10.1 Development of the Composite Endpoint

The use of mean or median group changes in statistical analyses may underestimate true treatment effects when significant patient-to-patient heterogeneity is present. Therefore, a post-hoc composite endpoint approach and responder analysis was developed to monitor change on a patient-by-patient basis across several domains, simultaneously. Analysis of individual patient data for several efficacy endpoints in the Phase 3 Double-Blind Study showed treatment effects in FVC, the 6-Minute Walk Test, AHI, shoulder flexion, and visual acuity. In general, the patients who tended to respond the best for each assessment were the ones who received rhIDU, whereas those who tended to decline the most were the ones who received placebo. Given that the disease is heterogeneous in its symptoms, that the patients span a wide age range (6 to 43 years old), and that each individual has a unique rate of disease progression, different degrees of reversible and irreversible components to a patient's disease symptoms are to be expected.

Recognizing that a treatment effect might be better captured as change across several endpoints in individual patients rather than as change in group means of individual endpoints, a composite clinical endpoint approach was developed in conjunction with MPS I experts and other subspecialists. For a composite endpoint to be valid, the domains should reflect important clinical aspects of MPS I, the assessments should be appropriate and reliable measures of change, and the thresholds of change should be considered to be clinically significant by experts. Within each domain, changes beyond thresholds of opposite magnitude reflect clinical improvement or decline, while changes below a threshold are not clinically significant. Equal weight is given to the domains because they reflect important and different types of functional impairment in patients with MPS I disease. The 5 domains and their thresholds for clinically signficant change are as follows:

- FVC, ≥ 11% change from baseline
- 6MWT, ≥ 54 m change from baseline
- AHI, ≥ 10 events per hour in patients ≤15 years old with AHI 10-60 events per hour and AHI ≥ 15 events per hour in patients >15 years old with AHI 15-60 events per hour
- Shoulder flexion, ≥ 20 degrees
- Visual acuity, ≥ 2-line change on an acuity chart

A complete description and the rationale for the domains of the composite endpoint can be found in Appendix I.

6.1.10.2 Examination of the Phase 3 Study Data using a Composite Endpoint Approach: Clinically Significant Change on a Per-Patient Basis

The results of the responder analysis of the Phase 3 Double-Blind study, as defined in Section 6.1.10.1, are shown in Table 26. This table shows the clinically significant changes in 5 domain assessments (FVC, 6 Minute Walk Test, shoulder flexion, AHI, and visual acuity) on a patient-by-patient basis. Improvements are labeled with an "X" and are color-coded green, while declines are labeled with an "O" and color-coded yellow. Empty boxes indicate no change based on the above thresholds, and "NA" means that the patient did not have data. Overall, placebo patients showed more declines than improvements (18 versus 9), whereas rhIDU patients showed more improvements than declines (32 versus 10).

Table 26: Composite Endpoint Analysis in Phase 3 Double-Blind Study

Placebo Patients						rhIDU Patients					
	Primary Efficacy		Secondary Efficacy				Primary Efficacy		Secondary Efficacy		
Pt. No.	FVC	6-Minute Walk Test	Shoulder Flexion	AHI	Acuity	Pt. No	FVC	6-Minute Walk Test	Shoulder Flexion	AHI	Acuity
010202			O	NA		010101	X		O		
010303						010404	X	X			X
010505		O				010606		O			
010707	O		X			010808		O			
010909		O				011010		X	X		X
011312		O	X	O		011211				X	
030101		X				030404	O	X	X	NA	X
030203				NA		030608	X	X	X		
030309	X			X		030806	X				X
030502	O			NA		030910		X	X		
030705				X		040101		X	O		
040202		O				040404	X	X	X		X
040303		O				040606	X	X			
040505		X				050101			NA	X	
050202	O		O			050504*	X		O		
050403		X				050706	X	X	O	X	
050605*			O	O		060101		O	O		
050807			O			060404					
060202			O			060506			NA	NA	
060303		O				060908		O			
060607	X			O		061010	X		NA		
060705						061111				X	
060809			O								

*Myelopathy.

X = Improvement; O = Decline, NA = Not Available.

Note: Clinically Significant Changes from Baseline to Week 26 are defined as: FVC ≥ 11%; 6MWT ≥ 54 m; Shoulder Flexion ≥ 20 degrees; AHI ≥ 10 events/hour; Visual Acuity ≥ 2 lines.

Table 27 lists the contributions of the different efficacy variables in distinguishing a treatment effect between patients treated with rhIDU and placebo. For each assessment, the contribution favored the rhIDU treatment group. The differences between groups were highest for FVC and

6MWT, while lower but similar changes were observed for shoulder flexion ROM, AHI, and visual acuity. Although there was no net improvement in shoulder flexion ROM for rhIDU patients, there was a net decline of 4 patients in the placebo group. The total difference in net change per patient between groups was +31 in favor of the rhIDU treatment group.

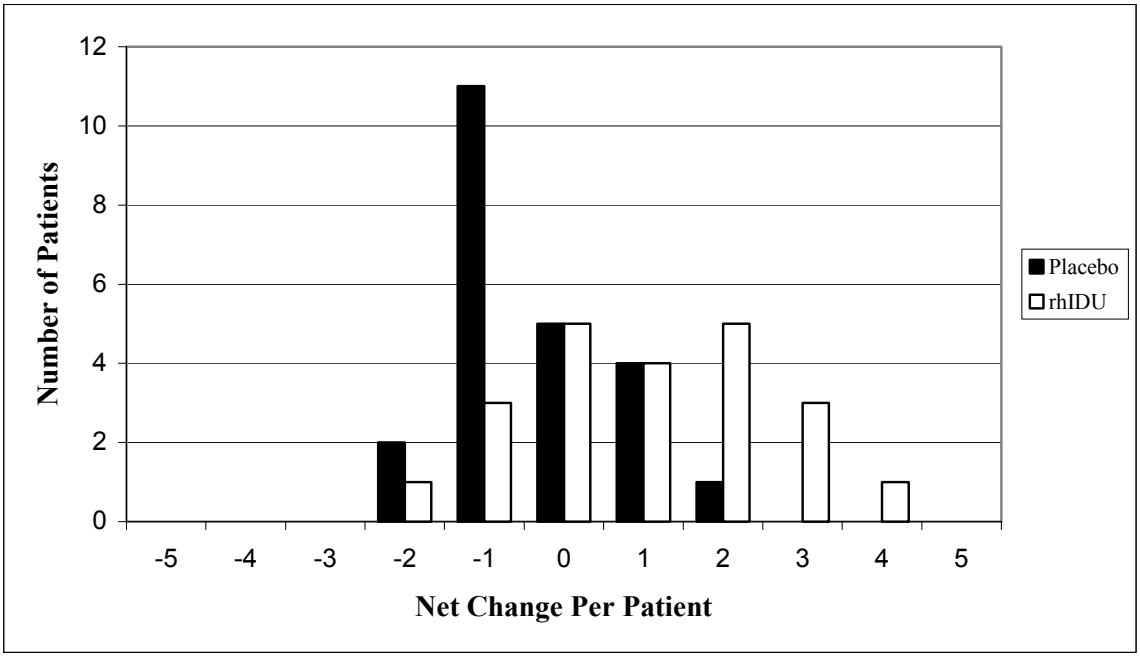
Table 27: Net Change by Domain in the Phase 3 Double-Blind Study

Efficacy Variable	rhIDU Patients (n = 22)		Placebo Patients (n = 23)		Difference Between Groups
	Improve/ Decline	Net Change	Improve/ Decline	Net Change	
FVC	9/1	+8	2/3	−1	+9
6MWT	9/4	+5	3/6	−3	+8
Shoulder Flexion-	5/5	0	2/6	−4	+4
AHI	4/0	+4	2/3	−1	+5
Visual Acuity	5/0	+5	0/0	0	+5
Total	32/10	+22	9/18	−9	+31

6.1.10.2.1 Net Improvement Across Domains

Figure 13 is a histogram showing the distribution of patients according to net change in domains (improvements minus declines). Values above 0 indicate net improvement, and values below 0 indicate net decline. There is a clear shift to the right towards net improvement in rhIDU-treated patients, and a clear shift to the left towards net decline in placebo patients. Overall, total net change was positive in the rhIDU group (+22 domains) and negative in the placebo group (−9 domains). Mean net change per patient also was higher in rhIDU-treated patients (+1.00 domains) compared to placebo patients (−0.39 domains) for a between-group difference of 1.39 domains of net improvement in favor of the rhIDU group.

Figure 13: Net Change Per Patient in the Phase 3 Double-Blind Study



Most of the rhIDU-treated patients, 59% (13/22) showed net improvement and were defined as responders, compared to only 22% (5/23) of the placebo patients. The majority of responders in the rhIDU treatment group, 69% (9/13) showed net improvement in at least 2 domains, and 31% (4/13) showed net improvement in 3 to 4 domains. Conversely, no placebo patient showed net improvement in more than 2 domains.

Most of the patients who showed net decline were in the placebo group, 76% (13/17). Only 18% (4/22) of patients in the rhIDU group showed net decline compared to 56% (13/23) of placebo patients.

In summary, most of the net improvements occurred in rhIDU-treated patients, most of the net declines occurred in placebo patients, and the proportion of responders was much higher in the rhIDU-treatment group than in the placebo group.

6.1.10.2.2 Confirmation of the Composite Endpoint Analysis

The purpose of this analysis was to confirm the results of the composite endpoint analysis in a second set of patients, i.e., the placebo/rhIDU patients crossing over from placebo to rhIDU in the Phase 3 Open-Label Extension Study. It was expected that these patients would show overall net improvement similar to the rhIDU patients during the Phase 3 Double-Blind Study. For the purpose of these analyses, the placebo/rhIDU patient who died at Week 16 of the Phase 3 Open-Label Extension Study was classified as a non-completer in the domain analysis and a non-responder in the responder analysis.

In contrast to their net decline of −9 domains in the Phase 3 Double-Blind Study, placebo/rhIDU patients showed net improvement of +14 domains in the Phase 3 Open-Label Extension Study. Placebo/rhIDU patients improved in 17 domains and declined in 3 domains. Mean net improvement was +0.64 domain per patient, approximately half of what rhIDU patients achieved in the Phase 3 Double-Blind Study (Figure 14). In the Phase 3 Open-Label Extension Study, 39% (9/23) of placebo/rhIDU patients were responders (Figure 15). When compared to the results of the Phase 3 Double-Blind Study, this percentage is less than the 59% of responders who received rhIDU but nearly twice the 22% of responders who received placebo. The lower number of net domains of improvement and smaller proportion of responders seen in the placebo/rhIDU group may have been due to an overall decline in functional status occurring during the Phase 3 Double-Blind Study and/or the fewer number of assessments completed by patients at Week 24 of the Phase 3 Open-Label Extension Study.

Figure 14: Mean Net Change in Domains

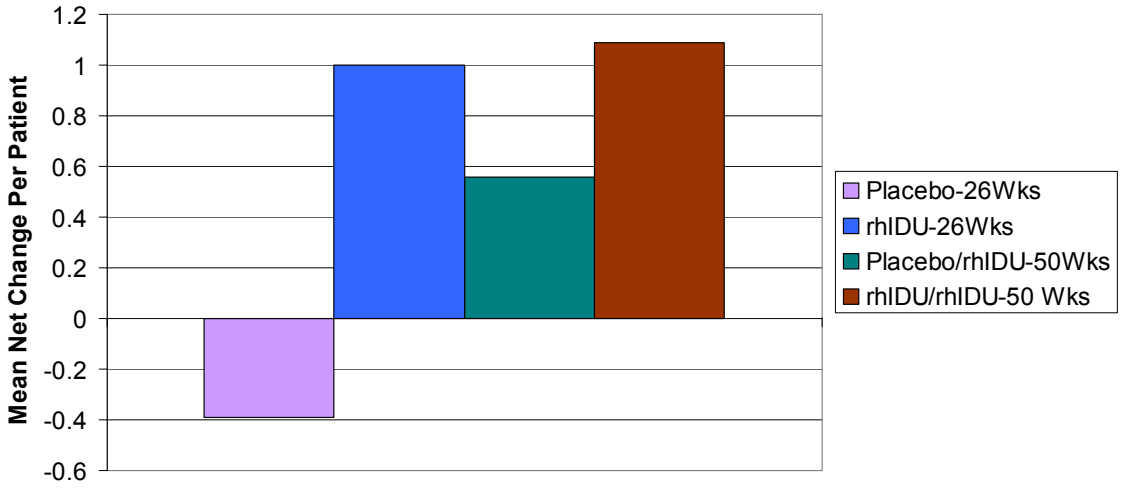
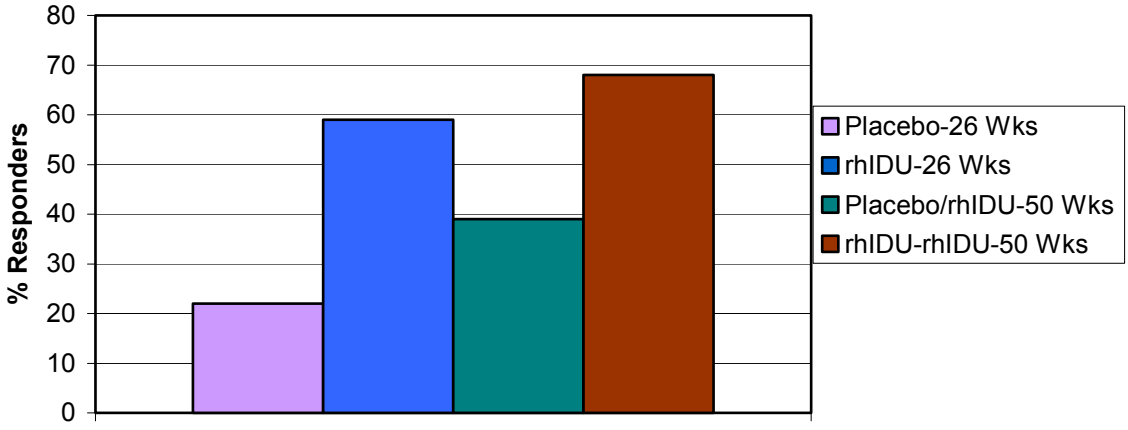


Figure 15: Proportion of Responders Per Treatment Group



6.1.10.2.3 Concordance of the Treatment Response in the Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study

The purpose of this analysis was to determine the concordance of the treatment response between patients treated with rhIDU in the Phase 3 Double-Blind and Open-Label Extension Studies. Net improvement in rhIDU patients increased from + 22 domains in the Phase 3 Double-Blind Study to +23 domains in the Phase 3 Open-Label Extension Study. Mean net improvement increased from 1.00 to 1.05 domains per rhIDU patient. The proportion of rhIDU responders was the same at Week 50, 59% (13/22) as at Week 26. Five patients converted from being non-responders at Week 26 to responders at Week 50, and 5 patients who had been responders became non-responders. Of the 13 patients who were responders at Week 26, 62% (8/13) remained responders at Week 50. Thus, there was high concordance among rhIDU patients treated for 26 and 50 weeks, indicating a robust treatment effect.

6.1.10.3 Summary of the Responder Analysis Based on Change in Individual Patients

Post-hoc analysis of the Phase 3 Double-Blind Study data using a composite clinical endpoint and responder approach at the level of the individual patient lends independent support for a rhIDU treatment effect. The composite endpoint consists of clinically significant changes in FVC, 6-Minute Walk Test, AHI, shoulder flexion, and liver volume. A responder is defined as a patient who shows net improvement. Specifically, there were 59% (13/22) responders in the rhIDU group compared to 22% (5/23) in the placebo group ($p = 0.016$). Most rhIDU-treated patients improved in more than 1 domain and showed net overall improvement, whereas most placebo patients showed little improvement with an average decline in 1 domain and a slight net decline overall. The assessments that most clearly distinguished patients in the 2 groups in terms of a rhIDU treatment effect were FVC and the 6-Minute Walk Test.

The responder analysis was further validated by finding (1) nearly twice the number of responders in the placebo/rhIDU group in the Phase 3 Open-Label Extension Study as compared to the Phase 3 Double-Blind Study (39% vs. 22%); and (2) a high concordance of responders who received rhIDU treatment for 26 weeks versus 50 weeks.

6.2 Results of the Phase 1/2 Study

6.2.1 Patient Disposition in the Phase 1/2 Study

Ten patients were enrolled into this study. All 10 patients successfully completed the first 52 weeks of the study, and 8 patients were active at Week 152. One patient died of apnea (respiratory arrest) 4 days after the Week 103 infusion, following a viral illness. Another patient died of complications following spinal fusion surgery for worsening of scoliosis 19 days after the patient's last study drug infusion at Week 137.

6.2.2 Patient Demographics in the Phase 1/2 Study

Patient demographics at baseline are listed in Table 28.

Table 28: Listing of Demographic and Pretreatment Characteristics (Phase 1/2 Study)

Patient No.	Age (years)	Height (cm)	Weight (kg)	Sex	Race	Clinical Status*
001	17	132.5	38.1	M	White	MPS IH/S
002	10	121.0	22.6	F	White	MPS IH/S
003	9	122.5	27.0	M	White	MPS IH/S
004	8	125.0	34.6	M	White	MPS IH/S
005	12	127.0	24.4	M	White	MPS IH/S
006	22	152.7	64.5	M	White	MPS IH/S
007	17	160.0	57.2	F	White	MPS IS
008	5	87.0	14.8	F	White	MPS IH
009	9	118.5	24.2	F	White	MPS IH/S
010	14	160.0	54.6	M	White	MPS IH/S
Mean (SD)	12.3 (5.2)	130.62 (22.29)	36.20 (16.99)			

* Clinical Status: MPS IH=Hurler; MPS IH/S=Hurler-Scheie; MPS IS=Scheie.
Note: Data on clinical status on file at BioMarin Pharmaceutical Inc.

6.2.3 Extent of Exposure in the Phase 1/2 Study

Over 1100 weekly study-drug infusions of 100 U/kg (0.58 mg/kg) were administered to the 10 patients enrolled in the study. The first infusion was given on 19 December 1997, and the last infusion for this report was given on 29 March 2001. All patients completed the first 52 weeks of the study, 9 patients completed 104 weeks, and 8 patients completed 152 weeks. The mean number of administered infusions per patient was 115.0 (std dev 17.5, range 82 to 135). The mean number of missed infusions was 36.2 (std dev 17.0, range 22 to 80).

Missed infusions were examined by study period—Weeks 1 to 52, Weeks 53 to 104, and Week 105 through 30 March 2001. For most patients, the majority of missed infusions (66%) were due to unavailability of the study drug. The period of greatest study-drug unavailability was Weeks 53 to 104 for the first patients enrolled, and Weeks 26 to 88 for the last patients enrolled. No infusions were missed because of drug unavailability from Week 105 to the end of the study period.

Most of the other infusions were missed because of patient illnesses or surgeries, parents' illnesses, logistical problems in getting to the clinic, vacations, or decisions on the part of the patient or parents to receive infusions less frequently than once a week.

6.2.4 Primary Efficacy Results of the Phase 1/2 Study

6.2.4.1 Hepatomegaly (Liver Volume) in the Phase 1/2 Study

The MRI results are shown in Table 29. The mean reduction in liver size was statistically significant ($p < 0.001$) for all time points through Week 52 when compared with pretreatment values. Patients reported increased appetite, easier breathing, greater endurance and less fatigue as liver size decreased.

Table 29: Mean Normalized Liver Volume as a Percentage of Pretreatment: MRI Readings Through Week 104 (Phase 1/2 Study)

Time	Mean	SD	Min	Max	n	# Pts. w/ ≥ 20% Decrease	# Pts. in Normal Range*	p-value*** for Comparison with Pretreatment
Pretreatment	100	0	100.0	100.0	10	N/A	0	—
Week 6	77.76	7.12	67.8	93.8	10	7	8	< 0.001
Week 12	76.94	3.75	71.1	83.5	10	8	8	< 0.001
Week 26	76.86	9.99	65.8	101.7	10	8	8	< 0.001
Week 52	74.02	7.59	63.4	86.9	10	7	9	< 0.001
Week 104	76.03	5.92	66.8	87.0	9	7	8	ND**

* Below the upper 95% confidence interval of the normal range.
** Not Done as per protocol.
*** Using Student's t-test.

Liver size reduced rapidly in the first 6 weeks of enzyme therapy as 8 of 10 patients had a normal liver size. Seven of 10 and 7 of 9 patients had ≥ 20% reduction at Weeks 52 and 104, respectively. Three patients who did not achieve the ≥ 20% reduction in liver size after 52 weeks of treatment did shift from abnormal to normal liver size for age at Week 52 and remained in the normal range at Week 104.

Only 1 patient, who had the largest liver volume at pretreatment, did not reach normal size by Week 52, although the liver size decreased substantially from baseline (31.3% and 31.4%, respectively, at Weeks 26 and 52). Pre-existing liver disease unrelated to MPS I may also have limited the patient's liver volume response. At Week 104, liver size was reduced by 33.2%, but it was still above the normal limit for age.

6.2.4.2 Splenomegaly (Spleen Volume) in the Phase 1/2 Study

The MRI results demonstrated a ≥20% reduction in spleen volume in 6 of 10 patients at Week 6 (Table 30). By Week 52, mean spleen volume reduction in all patients was 20.79%. The reduction in spleen size was statistically significant at all time points except for Week 26. The unblinded MRI results show that the reductions seen at Week 52 were sustained at Week 104.

Spleen size was reduced substantially in some patients, and 2 patients showed reduction to normal size for the appropriate age group at Week 52.

Table 30: Mean Normalized Spleen Volume as a Percentage of Pretreatment: MRI Readings Through Week 104 (Phase 1/2 Study)

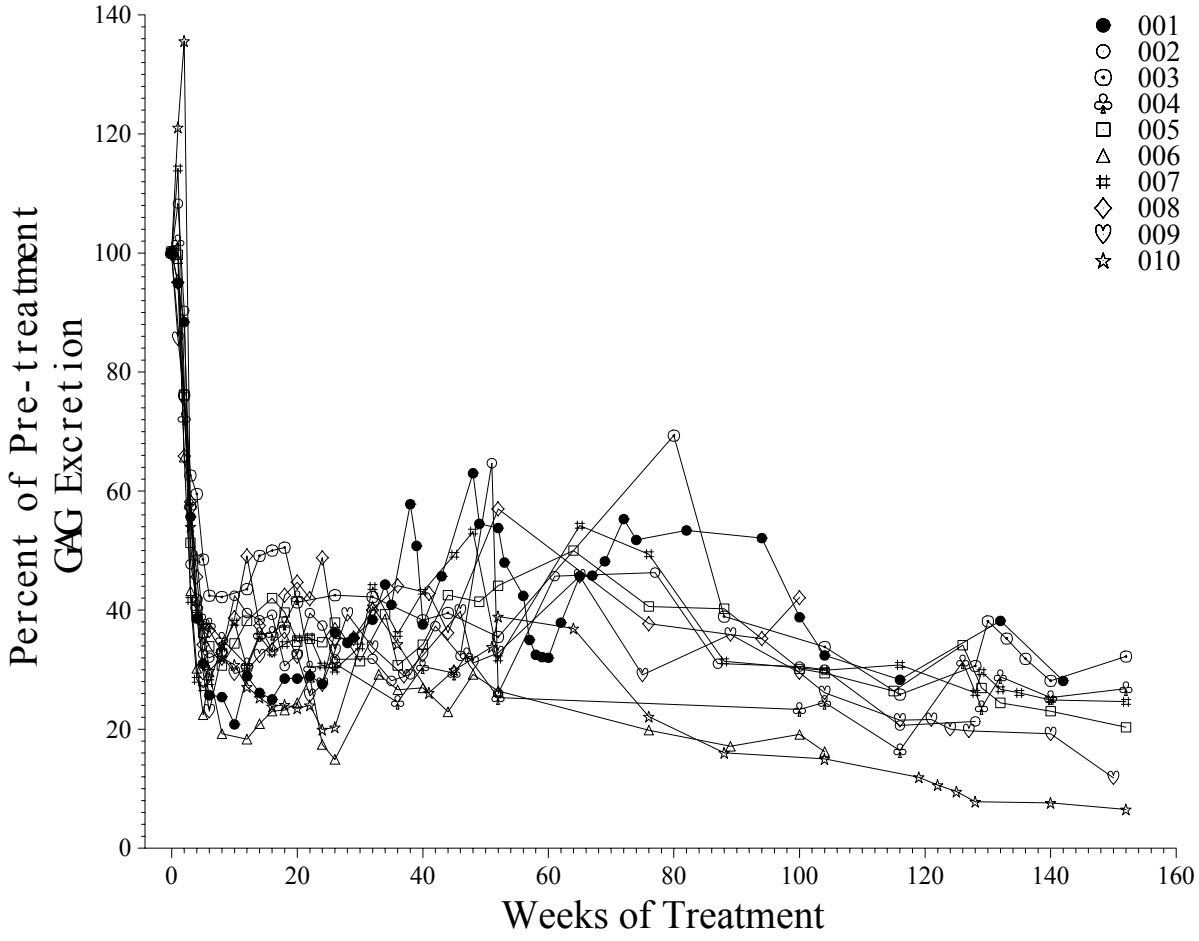
Time	Mean	SD	Min	Max	n	# Pts. w/ ≥20% Decrease	# Pts. in Normal Range*	p-value*** for Comparison with Pretreatment
Pretreatment	100	0	100.0	100.0	10	N/A	0	—
Week 6	74.48	12.33	56.2	94.7	10	6	3	0.007
Week 12	79.50	10.73	64.9	97.1	10	6	2	0.027
Week 26	94.29	41.64	63.6	204.4	10	4	1	0.524
Week 52	79.21	10.31	62.8	95.4	10	6	2	0.025
Week 104	77.94	14.39	59.1	101.1	9	4	1	ND**

* Below the upper 95% confidence interval of the normal range.
** Not Done as per protocol.
*** Using Student's t-test.

6.2.4.3 Urinary GAG Excretion in the Phase 1/2 Study

After 1 to 2 doses of enzyme, urinary GAG dropped steeply. After 5 to 6 doses, urinary GAG levels appeared to reach a plateau that was approximately 30% of the pretreatment level. There was a further gradual decline from Week 80 to the end of the study period (Figure 16). This decline in urinary GAG was consistent for all patients.

Figure 16: Urinary GAG Excretion during rhIDU Treatment (Phase 1/2 Study)



When urinary GAG levels were normalized to pretreatment levels (i.e., 100%), the mean urinary GAG level had declined to 31.28% at Week 26, to 37.17% at Week 52, and to 26.37% at Week 104. The 7 patients with values at Week 152 showed a mean reduction to 21.47% (Table 31). Statistical analysis demonstrated that at Weeks 6, 12, 26, and 52, the reduction in urinary GAG was statistically significant ($p < 0.001$).

Table 31: Mean Reduction in Urinary GAG at Assessment Weeks Compared with Pretreatment (Phase 1/2 Study)

Time	Mean	SD	Min	Max	N	# of Pts. with ≥50% Decrease	p-values[7] Relative to Pretreatment
Pretreatment	100	0	100	100	10	N/A	—
Week 6	31.84	5.88	23.0	42.4	10	10	<0.001
Week 12	33.56	8.98	18.3	49.1	10	10	<0.001
Week 26	31.28	8.19	14.9	42.5	10	10	<0.001
Week 52[1]	37.17	11.31	25.3	57.0	10	8	<0.001
Week 104[2]	26.37	6.73	15.0	33.8	9[4]	9	ND[6]
Week 152[3]	21.47	9.28	6.5	32.2	7[5]	7	ND[6]

[1] Data collected during a single visit per patient between Weeks 49 and 52.
[2] Data collected during a single visit per patient between Weeks 101 and 104.
[3] Data collected during a single visit per patient between Weeks 141–152.
[4] Patient 008 died between Weeks 103 and 104.
[5] Patient 002's last infusion was at Week 137 and death occurred 19 days later; urinary GAG results could not be obtained for Patient 006 from Week 116 through Week 152 because the urine was too dilute.
[6] ND=Not done as per protocol.
[7] Using Student's t-test.

The primary endpoint of a ≥50% reduction of urinary GAG in two-thirds of the patients was met, with 8 of the 10 patients achieving this reduction at Week 52, and all patients achieving this response at Weeks 100 to 104.

6.2.5 Secondary Efficacy Results of the Phase 1/2 Study

6.2.5.1 Joint ROM in the Phase 1/2 Study

Patients were evaluated for shoulder flexion and extension, knee flexion and extension, and elbow extension. Results were analyzed for changes in ROM and changes in degrees of restriction of ROM (mean degrees of movement in an age-adjusted normal population minus the degrees of movement in the MPS I patients).

By Week 26, the majority of patients showed some improvement in ROM in 1 or more joints, although interpatient variability was large. By Week 26, right and left shoulder flexion improved by 10.75 and 8.25 degrees, respectively. The movements that showed the most improvements at Week 52 were shoulder flexion, right knee extension, and elbow extension. Right and left shoulder flexion increased by 28.13 degrees ($p<0.001$) and 26.12 degrees ($p=0.002$), respectively, at Week 52. The improvements in shoulder flexion were sustained at Week 104. Right and left knee extension increased by 3.52 degrees and 2.78 degrees, respectively at Week 52 (these changes were not statistically significant), but the test for linear trend from pretreatment to Week 52 was statistically significant ($p=0.025$). The degrees of extension in both knees increased further at Week 104. Right and left elbow extension showed statistically

significant improvements of 7.02 degrees (p=0.031) and 7.10 degrees (p=0.007), respectively, at Week 52, but the improvement in the right elbow was not fully sustained at Week 104.

Mean right and left shoulder extension increased from pretreatment by 5.07 degrees and 7.60 degrees, respectively, at Week 52 and by 15.91 degrees and 14.66 degrees, respectively, at Week 104. The changes at Week 52 were not statistically significant.

Mean right knee flexion improved significantly from 126.56 degrees at pretreatment to 131.26 degrees at Week 52 (p=0.016). Left knee flexion improved from 126.56 degrees at pretreatment to 130.14 degrees at Week 52, but the change was not statistically significant. Some of the improvement seen in the right knee flexion had decreased at Week 104, but the mean ROM was still better than at pretreatment. Mean left knee flexion continued to improve at Week 104.

The improvements in joint ROM were reflected in patient self-reports of improved hand dexterity and grip, being able to walk more easily, and being able to engage in activities, such as sports, that require arm and shoulder movements.

6.2.5.2 NYHA Scores in the Phase 1/2 Study

NYHA Scores. All 10 patients were rated by a pediatric cardiologist at pretreatment and all improved by 1 or 2 NYHA classes by Week 52 of rhIDU treatment. At pretreatment, no patient had NYHA Class I functional capacity (Table 32), but by Week 52, 50% of patients (5/10) had improved to Class I, and by Week 104, 67% of patients (6/9) had improved to Class I.

The mean change in NYHA classification was statistically significant at Week 26 (p=0.008) and at Week 52 (p=0.002), and these changes were sustained at Week 104 (Table 32). Improvement in joint function and airway function likely contributed to improved NYHA classification.

Table 32: NYHA Scores (Phase 1/2 Study)

Time	n	NYHA Class (number in each class)				Min Class	Max Class	p-Value*
		I	II	III	IV			
Pretreatment	10	0	3	6	1	II	IV	—
Week 12	10	2	4	3	1	I	IV	0.063
Week 26	10	3	6	0	1	I	IV	0.008
Week 52	10	5	4	1	0	I	III	0.002
Week 104	9	6	2	1	0	I	III	ND**

* Using Wilcoxon signed rank test compared with pretreatment.

** ND=not done as per protocol.

6.2.5.3 Sleep Apnea and Airway Obstruction in the Phase 1/2 Study

Note that in the Phase 1/2 Study, the methodology used to determine apneic and hypopneic events was different from that used in the Phase 3 Double-Blind Study and Open-Label

Extension Study. Nasal thermisters were used in the Phase 1/2 Study and nasal cannulae were used in the Phase 3 Studies. Therefore, the sets of measurements cannot be directly compared.

Polysomnography. Polysomnography results are presented in Table 33. The number of apneas per night decreased at Week 26 in all 6 patients who had apnea at pretreatment. One patient had apnea at Week 26 but none at pretreatment. According to the ATS (ATS, 1996, Am J Respir Crit Care Med), obstructive apnea of any duration exceeding 1 apnea per hour is considered abnormal. Nine patients had hypopneas at pretreatment; 5 patients had a decreased number per night at Week 26, 2 patients were unchanged, with 1 hypopneic event at both pretreatment and at Week 26, and 2 patients had an increased number of events at Week 26. Minutes of hypoxia per night decreased substantially in the 2 patients with hypoxic events at pretreatment. Two patients had no hypoxia at pretreatment but each had 6 minutes of hypoxia per night at Week 26. The AHI decreased in 7 out of 10 patients. Mean AHI decreased from 2.08 at pretreatment to a mean of 0.97 at Week 26, a 53% reduction.

Table 33: Polysomnography Results at Pretreatment and at Week 26 of rhIDU Treatment (Phase 1/2 Study)

	Apneas		Hypopneas		Hypoxic Events (min. below 90% O_2)		Apnea/Hypopnea Index	
Patient	Pre-	26	Pre-	26	Pre-	26	Pre-	26
001	0	0	1	1	0	0	0.14	0.14
002	7	2	27	1	48	1	4.45	0.39
003	2	0	13	2	0	6	2.23	0.36
004	3	0	1	1	0	M*	0.63	0.16
005	2	0	5	2	0	0	0.92	0.29
006	0	0	12	6	61	28	1.96	0.93
007	4	0	0	0	0	0	0.57	0.00
008	0	5	1	17	0	0	0.13	3.11
009	48	4	28	17	0	6	9.48	3.96
010	0	0	1	2	0	0	0.27	0.35
MEAN	—	—	—	—	—	—	**2.08**	**0.97**

* M=missing value. Mean values for apneas, hypopneas, and hypoxia not presented because of sparsity of events in some columns, particularly at Week 26.

The 3 patients with the largest number of apneas, hypopneas, or hypoxic events per night (Patients 002, 006, 009) at pretreatment improved during treatment.

Patient 008 had no apneas or hypoxic events and only 1 hypopneic event at pretreatment, but had an increased number of obstructive apneic events and hypopneic events at Weeks 26. At that time, the increase was felt to be attributable to an upper respiratory infection. Because of these results, a repeat study was requested at Week 52, at which time the patient demonstrated a further

increase in apneic events and also had hypoxic events. At Week 52, this patient also showed developmental regression, possibly due to increased intracranial pressure as demonstrated by increased ventriculomegaly on MRI scans of the brain. High-pressure hydrocephalus can impact CNS function and increase apneic events by decreasing pharyngeal tone. The patient had undergone ventriculoperitoneal (VP) shunt at Week 61.

6.2.5.4 Eye Disease in the Phase 1/2 Study

Visual Acuity. Four patients did not have significant visual impairment at baseline. The 3 patients with the worst visual acuity at pretreatment all showed improvement in at least 1 eye .

Patient 001 had improvement from only being able to count fingers at a distance of 2 to 3 feet (0.61 to 0.91 meters) using the left eye to 20/800 vision at Week 52. The patient had a corneal transplant prior to Week 104, which improved vision in this eye to 20/300.

Patient 002's acuity increased in the right eye from 20/400 at pretreatment to 20/60 at Week 104 and from 20/1000 at pretreatment to 20/200 at Week 104 in the left eye.

Patient 009's acuity improved in the right eye from 20/300 at pretreatment to 20/80 at Week 104.

Glaucoma and Intraocular Pressure. No significant disease was present at pretreatment for which to assess therapeutic efficacy. No consistent changes were noted and no patients had intraocular pressure outside the normal range at any timepoint.

Corneal Clouding. During the study, no patient had an obvious change in corneal clouding by either ophthalmological exam or corneal photographs.

6.3 Efficacy Conclusions

The consolidated and individually summarized efficacy data presented in this report demonstrate that treatment with rhIDU provides clinical benefit to patients with MPS I. The efficacy endpoints of the 3 studies were prospectively defined as either the change between the rhIDU-treatment and placebo groups (Phase 3 Double-Blind Study) or as the change from baseline within the rhIDU treatment group (Phase 3 Open-Label Extension Study and Phase 1/2 Study). In the Phase 3 Double-Blind Study, treatment with rhIDU led to a statistically significant and clinically meaningful improvement in FVC in the primary ITT analysis and a statistically significant and clinically meaningful improvement in the 6-Minute Walk test by ANCOVA. FVC and the 6-Minute Walk Test are measures of pulmonary function and functional capacity, which are prominent medical problems and major contributors to the morbidity and mortality in patients with MPS I. While hepatomegaly and urinary GAG excretion showed significant changes across all patients in the two groups, for other efficacy variables, statistically significant differences or trends were observed in the subgroups of patients with more severe symptoms. A responder analysis based on change in a composite clinical endpoint was developed to accommodate this patient-to-patient heterogeneity. This independent and complementary analysis revealed a high

proportion of responders in patients treated with rhIDU compared to placebo, providing additional evidence for a rhIDU treatment effect. There was no apparent impact of antibody formation on the efficacy of rhIDU. In summary, the totality of the data show that treatment with rhIDU is efficacious in patients with MPS I.

7. SAFETY

7.1 Overall Safety Summary

The evaluation of safety variables monitored in patients treated with rhIDU in this clinical development program, including adverse event (AE) reporting, physical examination findings, vital signs, electrocardiography (ECG), echocardiography (ECHO), and standard clinical laboratory and immunogenicity testing, indicates that rhIDU has an acceptable safety profile in patients receiving both short-term and long-term treatment.

Almost all of the patients enrolled in the 3 clinical studies experienced at least 1 AE, including patients receiving placebo treatment in the Phase 3 Double-Blind Study. This is not unexpected given the nature of the disease under study, which affects multiple organ systems by lysosomal storage of GAGs. In the Phase 3 Double-Blind study, the overall patient incidence and types of adverse events were similar between the placebo and rhIDU treated patient. In the Phase 3 Open-Label Extension Study, the overall patient incidence and types of adverse events observed for both treatment groups were similar to those seen in the Phase 3 Double-Blind Study, even with the approximately 50% greater exposure time in the latter group.

In the Phase 3 Studies, infusion-associated reactions (IARs) were defined as those AEs reported by the investigator as related to study drug that occurred on the day of infusion, excluding those AEs identified by protocol-required assessments that were performed prior to drug infusion. IARs were reported in one-third to one-half of patients in both Phase 3 Studies, regardless of treatment group. The vast majority of these were mild and did not require intervention. The incidence of patients experiencing IARs, as well as the type and number of IARs reported, was similar between treatment groups in both Phase 3 Studies. Over time, the number of patients experiencing IARs remained the same, while the number of IARs reported decreased.

Almost all of the patients in the Phase 3 Studies developed measurable levels of antibody to rhIDU. When comparing results of the Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study, the presence of IgG antibodies to rhIDU does not appear to have an effect on overall safety. The lack of significant proteinuria in patients further suggests that there has been no significant clinical manifestation of immune complex disease. Given that rhIDU and placebo were similarly well tolerated, it seems unlikely that the development of IgG antibodies had any clinically significant effect on overall safety. Finally, none of the patients who were tested for immunoglobulin E (IgE) antibodies to rhIDU was found to test IgE-positive.

Assessment of neutralizing antibody titers at Week 24 of the Phase 3 Open-Label Extension Study revealed that a majority of patients do not show a significant rise in inhibitory activity from the start of rhIDU treatment through Week 24. There was no discernible association between patients experiencing IARs and inhibitory activity.

The majority of the AEs experienced by the patients in the Phase 3 Studies occurred on non-infusion days and were judged by the investigators to be unrelated to study treatment. Each of the AEs experienced on non-infusion days that were reported to be treatment-related by the investigator, occurred in a single patient, in almost all instances.

In the Phase 1/2 Study, all patients experienced at least 1 AE. Urticarial rashes on the day of infusion was noted more commonly in the Phase 1/2 Study, but were infrequently seen in the Phase 3 Studies. Angioedema symptoms occurred infrequently and in general, were manageable using increased premedication and slowed infusion rate. The difference in frequency of urticaria and related symptoms may be due to the difference between the drug product administered during the majority of the Phase 1/2 Study and the product of increased purity administered in the later studies. Forty percent of the patients in the Phase 1/2 Study developed IgG antibodies that were specific to rhIDU based on Western blot analysis, although no consistent relationship between these findings and the treatment-related AEs on the day of infusion was seen.

Among the 55 patients who have received rhIDU treatment in clinical studies, there have been 4 reported deaths—1 in the Phase 3 Open-Label Extension Study (Week 16), and 3 in the Phase 1/2 Study (Weeks 103, 139, and 234). All deaths were reported by the investigators to be unrelated to rhIDU treatment. There have been 2 deaths, reported as unrelated to rhIDU treatment, among the 16 patients who have received rhIDU in the Expanded Access Program.

There were no discontinuations due to adverse events, other than patients who died.

In both Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study (up to Week 24), all serious adverse events (SAEs) were reported by the investigator to be unrelated to rhIDU treatment and consistent with complications of the underlying disease. A total of 12 patients experienced 21 SAEs during the Phase 3 Double-Blind and Open-Label Extension Studies, including 1 patient who experienced SAEs in both studies. Three rhIDU-treated patients experienced 7 SAEs in the Phase 3 Double-Blind Study, while in the Phase 3 Open-Label Extension Study, 6 patients formerly treated with placebo experienced 11 SAEs and 3 patients formerly treated with rhIDU experienced 3 SAEs. Of the 9 SAEs experienced by 5 patients during the update period, all were unrelated except for an expected event of dyspnoea that was reported by the investigator as possibly related.

In the Phase 1/2 Study, 8 patients experienced 32 SAEs over a 3-year period of treatment. A majority of these SAEs (23) were judged by the investigator to be unrelated to rhIDU treatment. Nine SAEs were reported to be related to rhIDU treatment, and all but 1 were considered allergic reactions. None of the three SAEs experienced by 2 patients during the Update period were related to study drug treatment.

No new trends were noted in safety variables monitored in patients treated with rhIDU in the update period, including AE reporting, physical exam findings, vital signs, ECG, ECHO, and standard clinical laboratory and immunogenicity testing.

Following the evaluation of safety data collected in this clinical development program, short-term and long-term rhIDU treatment in patients with MPS I disease has an acceptable safety profile.

7.2 Phase 3 Double-Blind Study

7.2.1 Summary

AEs during double-blind treatment were defined as any AE that occurred from Day 1 of study drug infusion up to and including 2 weeks after completion of the study. All of the placebo patients and 21 (95%) of the rhIDU-treated patients experienced 1 or more AEs during double-blind treatment. Drug-related AEs (defined as those AEs judged by the investigator to be possibly, probably or definitely related to study medication) were reported in 16 (70%) of the patients in the placebo group and 12 (55%) in the rhIDU-treated group. None of the patients in the placebo group and 3 in the rhIDU-treated group experienced SAEs. IARs were defined as all drug-related AEs occurring on the day of infusion excluding those AEs identified by protocol-required assessments performed on that day (i.e., laboratory and physical examination abnormalities) assessed prior to drug infusion. IARs occurred in 11 (48%) of the 23 placebo patients and 7 (32%) of the 22 rhIDU-treated patients. None of the patients discontinued from the study due to AEs and there were no reported deaths. A summary of AEs during double-blind treatment is provided in Table 34.

Table 34: Safety Summary during Double-Blind Treatment (Phase 3 Double-Blind Study)

Category	Summary Statistic	Placebo n = 23	rhIDU n = 22
Having AEs	n (%)	23 (100)	21 (95)
Deaths	n (%)	0 (0)	0 (0)
Discontinuations Due to AEs	n (%)	0 (0)	0 (0)
Having Drug-Related AEs	n (%)	16 (70)	12 (55)
Having Serious AEs (SAEs)	n (%)	(0)	3 (14)
Having Severe AEs	n (%)	2 (9)	6 (27)
Having Infusion-Associated Reactions	n (%)	11 (48)	7 (32)

All AEs occurring with an incidence of ≥ 30% in either treatment group during double-blind treatment are listed in Table 35. The most commonly reported AEs in both the placebo and rhIDU-treated groups during double-blind treatment were: headache (placebo, 70% and rhIDU, 50%), fever (placebo, 61% and rhIDU, 45%) and rhinitis (placebo, 43% and rhIDU, 36%).

Table 35: Summary of Most Commonly Occurring AEs during Double-Blind Treatment (≥ 30% of Patients) (Phase 3 Double-Blind Study)

WHO-ART Body System	WHO-ART Preferred Term*	Placebo n = 23 n (%)	rhIDU n = 22 n (%)
Any AE	N/A	23 (100)	21 (95)
Cent./Periph. Nervous System Disorders	Headache	16 (70)	11 (50)
Body as a Whole General Disorders	Fever	14 (61)	10 (45)
	Pain	7 (30)	5 (23)
Respiratory System Disorders	Rhinitis	10 (43)	8 (36)
	Coughing	6 (26)	7 (32)
	URTI	4 (17)	7 (32)
Skin and Appendages Disorders	Rash	5 (22)	8 (36)
Gastrointestinal System Disorders	Diarrhea	8 (35)	7 (32)
	Vomiting	9 (39)	5 (23)
Hearing and Vestibular Disorders	Earache	8 (35)	1 (5)

* A patient experiencing more than 1 AE within a preferred term is counted once within that preferred term.
NA = Not Applicable; URTI = Upper Respiratory Tract Infection; Cent./Periph. = Central & Peripheral.

7.2.2 Summary of Adverse Events by Relatedness

Overall, there was a greater incidence of related (termed possibly, probably, or definitely related to treatment by the investigator) AEs in the placebo-treated group (70%) relative to the rhIDU-treated group (55%). The most commonly occurring related AEs (> 10% of patients) in rhIDU treatment group were flushing (23%) and rash (14%) and in the placebo group were headache (26%), flushing (17%), arthropathy (17%), and fever (13%).

7.2.3 Infusion-Associated Reactions (Drug-related AEs on Day of Infusion)

IARs were defined to encompass AEs that began either during the infusion or after completion of the infusion, but before the end of the day of infusion. Any AE occurring on the day of infusion that was reported as possibly, probably or definitely related to study drug and were not revealed by a protocol-required assessment performed on that day (i.e., laboratory and physical examination abnormalities performed prior to study drug administration) was considered to be IARs.

IARs occurred in both treatment groups with 11 (48%) placebo patients experiencing 82 IARs and 7 (32%) rhIDU patients experiencing 66 IARs. The most frequently reported IARs in the placebo and rhIDU groups were: flushing (17% and 23%), fever (13% and 5%), headache (9% and 9%), and rash (9% and 5%), respectively. The majority of IARs were of mild intensity and none were reported as severe. IARs occurring during double-blind treatment are provided in Table 36.

Table 36: Summary of Infusion-Associated Reactions (Phase 3 Double-Blind Study)

WHO-ART Preferred Term**	Placebo (n = 23)		rhIDU (n = 22)	
	No. Pts. (%)*	No. Events	No. Pts. (%)*	No. Events
Any IAR	11 (48)	82	7 (32)	66
Flushing	4 (17)	47	5 (23)	48
Fever	3 (13)	8	1 (5)	1
Headache	2 (9)	3	2 (9)	4
Rash	2 (9)	2	1 (5)	1
Back Pain	1 (4)	1	1 (5)	2
Sweating Increased	1 (4)	1	1 (5)	1
Temp. Change Sensation	1 (4)	1	1 (5)	2
Vomiting	1 (4)	1	1 (5)	1
Coughing	0	0	1 (5)	1
Face Edema	0	0	1 (5)	1
Hypotension	0	0	1 (5)	1
Paresthesia	0	0	1 (5)	2
Tachycardia	0	0	1 (5)	1
Abdominal Pain	1 (4)	1	0	0
Diarrhoea	1 (4)	1	0	0
Edema	1 (4)	1	0	0
Edema Peripheral	1 (4)	2	0	0
Flatulence	1 (4)	1	0	0
Hot Flushes	1 (4)	1	0	0
Hypertension	1 (4)	1	0	0
Nausea	1 (4)	1	0	0
Pain	1 (4)	2	0	0
Psoriasis	1 (4)	5	0	0
Rigors	1 (4)	1	0	0
Skin Disorder	1 (4)	1	0	0

* Percentages for number of patients are based on the total number of patients in each treatment group.
** A patient experiencing more than 1 AE within a preferred term is counted once within that term.

Five placebo patients and 3 rhIDU patients required either study drug infusion modification (infusion rate decrease or infusion interruption) and/or medication (antipyretics and/or antihistamines) to treat the IAR. None of the patients required steroid treatment.

7.2.4 IgE, Complement Activation, and Skin Testing

During the study, patients who experienced moderate or severe IARs were tested for the formation of rhIDU-specific IgE antibodies as well as complement activation. If IgE testing was

positive, skin testing was considered. A total of 3 patients were tested due to moderate IARs (1 in the placebo and 2 in the rhIDU group). All patients tested negative for both IgE and complement activation, and skin testing was not considered.

7.2.5 Adverse Events on Non-infusion Days

All placebo patients and 21 (95%) of the rhIDU patients experienced 1 or more AEs on the non-infusion days. The most frequently reported AEs experienced by placebo patients on non-infusion days, regardless of relationship, were: headache (57%), fever (43%), rhinitis (39%), and diarrhea (35%). The most frequently reported AEs experienced by rhIDU patients on non-infusion days were: headache (45%), fever (36%), rhinitis (36%), rash (32%), coughing (32%), and upper respiratory tract infection (URTI; 32%). Few of the AEs experienced non-infusion days were reported as related to study drug. Placebo patients experienced drug-related AEs of headache (17%), alopecia (4%) and arthralgia (4%), while the most frequent AE in the rhIDU patients was rash (9%).

Four patients experienced severe AEs on non-infusion days, 1 patient in the placebo group (arthropathy) and 3 rhIDU patients. One of the rhIDU patients developed multiple severe unrelated AEs during a single, lengthy hospitalization that included pneumonia, respiratory insufficiency, sepsis, acute renal failure and cardiac arrest. This patient's medical history was remarkable for severe aortic and mitral valve stenosis, angina pectoris and possible coronary heart disease at baseline. The patient underwent valvuloplasty and commissurotomy, fully recovered and resumed rhIDU infusions. The second patient was hospitalized due to headache, vomiting and dehydration in relation to intracranial hypertension, which was assessed as unlikely related to rhIDU. Following revision of the patient's ventricular shunt, the patient recovered without sequelae and continued rhIDU infusions. The third rhIDU patient was reported to have experienced a non-serious but severe AE of hepatomegaly. This patient's liver size was abnormal at baseline (12 cm below right costal margin) and increased at Week 4 to 15 cm. By Week 12, liver size had decreased to 11 cm.

7.2.6 Deaths

There were no deaths reported in either the placebo or the rhIDU treatment groups during the conduct of the Phase 3 Double-Blind Study.

7.2.7 Serious Adverse Events

During double-blind treatment, 3 patients in the rhIDU treatment group experienced 7 SAEs. All SAEs were reported as unrelated to study drug treatment and all patients recovered. One patient experienced constipation, the second aortic stenosis, cardiac arrest, pneumonia, sepsis, and acute renal failure and the third patient experienced intracranial hypertension.

7.2.8 Adverse Events Resulting in Patient Discontinuation

There were no reported discontinuations due to AEs during the study.

7.2.9 Clinical Laboratory Values

Laboratory assessments that included serum chemistry, hematology, and urinalysis were performed at baseline, and Weeks 4, 12, and 26 of the double-blind treatment period and were tested at a central laboratory. All laboratory samples were obtained prior to administration of the scheduled infusion of study medication. Mean changes from baseline were determined using the last observation that was available for each patient and reviewed. No clinically relevant changes were observed for any of the parameters over time.

Overall, there were few patients in either treatment group who presented with clinically significant laboratory values at baseline or during the double-blind treatment. No trend toward a greater incidence of clinically relevant values for any serum chemistry, hematological or urinary parameter was observed. Shifts from normal at baseline to abnormal (above or below the normal range) at the last available observation were similar in both treatment groups for those chemistry parameters that were noted to have shift changes. Shifts from normal at baseline to abnormal at the last available observation were also similar for both treatment groups regarding hematology and urinalysis parameters.

7.2.10 Other Observations Related to Safety

7.2.10.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures, heart rate, respiratory rate and temperature were recorded once during the baseline phase and just prior to the start and immediately after every study-solution infusion.

Mean changes from baseline and the last available observation taken during the double-blind treatment period for temperature, respiratory rate, systolic and diastolic blood pressures were similar between treatment groups.

7.2.10.2 Physical Examination Findings

A physical examination was performed once during the baseline phase and at Weeks 4, 12, and 26 for all patients. A majority of the patients in both treatment groups had abnormal findings on physical examination at baseline. This is not unexpected given the disease under study for this population. For those patients who were evaluated as normal at baseline, across the various parameters, very few shifted to abnormal in either treatment group.

7.2.10.3 Brain/Cranio-Cervical Junction MRI

Each patient had a MRI of the brain and cranio-cervical junction performed once during the baseline phase to provide reference information, if needed. An additional MRI of the brain

and/or cranio-cervical junction was performed at Week 26 at the discretion of the Investigator. Nine placebo-treated patients and 6 patients treated with rhIDU had discretionary brain/cranio-cervical junction MRI evaluations performed at Week 26. For all patients, regardless of treatment group, baseline MRI evaluations were abnormal. For all 9 placebo-treated patients, Week 26 MRI evaluations remained unchanged (abnormal) while 1 of the 6 rhIDU-treated patients, abnormal at baseline, had a normal MRI evaluation at Week 26.

7.2.10.4 Immunology: IgG Testing

IgG antibody testing was performed at a central laboratory for all patients at baseline and at Weeks 4, 8, 12, 16, 20 and 26. IgG screening was performed using enzyme-linked immunosorbent assay (ELISA) and confirmed by radioimmunoprecipitation (RIP) testing in order to further investigate potential immunogenicity. Confirmatory RIP data are presented in Table 37. All patients were evaluated for the development of IgG antibodies by using an ELISA screening assay and, when possible, all samples from the rhIDU and placebo patients positive by ELISA were confirmed by RIP.

Table 37: Summary of IgG Testing for rhIDU-Treated Patients–RIP Confirmation (Phase 3 Double-Blind Study)

Category	Summary Statistic	RhIDU
Number of Patients Received Drug	n (%)	22 (100)
Number of Patients Confirmed RIP Positive	n (%)	20 (91)
Time to RIP positive testing (Days from First Infusion)	n	20
	Mean	52.6
	Median	50.0
	Standard Deviation	24.1
	Minimum, Maximum	20, 106

Twenty of 22 patients who received rhIDU treatment and 1 patient who received placebo tested positive for IgG antibodies by RIP (seroconverted). The placebo patient tested positive at a single, mid-study time point, which was most likely due to a compromised sample.

7.3 Phase 3 Open-Label Extension Study: 24-Week Data

7.3.1 Summary

In the Phase 3 Open-Label Extension Study, AEs were defined as any AE that began from the time of enrollment in the Phase 3 Open-Label Extension Study through Week 24, or that began in the Phase 3 Double-Blind Study and worsened from the time of enrollment in the Phase 3 Open-Label Extension Study through Week 24.

Table 38 summarizes the overall incidence and important classifications of AEs. All patients experienced at least 1 AE. There was 1 death, attributed to an upper respiratory infection and

assessed as related to complications of underlying MPS I disease and unrelated to rhIDU treatment. This placebo/rhIDU patient was considered to have discontinued due to an AE. Drug-related AEs were reported in 11(48%) of the patients in the placebo/rhIDU group and 10 (45%) in the rhIDU/rhIDU group. Six patients in the placebo/rhIDU group and 3 patients in the rhIDU/rhIDU group experienced SAEs. Severe AEs were experienced by 3 (13%) and 1 (5%) of the placebo/rhIDU and rhIDU/rhIDU patients, respectively. IARs consisted of all drug-related AEs occurring on the day of infusion, excluding those AEs identified by protocol-required assessments performed that day prior to drug infusion (e.g., laboratory and physical examination abnormalities). IARs occurred in 7 (30%) of the placebo/rhIDU patients and 8 (36%) of the rhIDU/rhIDU patients.

Table 38: Incidence of AEs from Entry* through Week 24 (Phase 3 Open-Label Extension Study)

Category	Summary Statistic	Placebo/rhIDU n = 23	rhIDU/rhIDU n = 22
Patients With Any AEs	n (%)	23 (100)	22 (100)
Deaths	n (%)	1 (4)	0 (0)
Discontinuations Due to AEs	n (%)	1 (4)	0 (0)
Patients With Serious AEs (SAEs)	n (%)	6 (26)	3 (14)
Patients With Drug-Related AEs	n (%)	11 (48)	10 (45)
Patients With Severe AEs	n (%)	3 (13)	1 (5)
Patients With IARs	n (%)	7 (30)	8 (36)

* Last measurement in the Phase 3 Double-Blind Study (ALID-003-99) prior to enrollment into the Phase 3 Open-Label Extension Study (ALID-006-01).

All AEs occurring with an incidence of ≥ 30% in either treatment group during the first 24 weeks of this study are presented in Table 39 by WHO-ART Body System and Preferred Term. The most commonly reported AEs in the placebo/rhIDU and rhIDU/rhIDU groups, respectively, were headache (57% and 45%) and rhinitis (43% and 41%). Other common AEs included coughing, pharyngitis, diarrhea, vomiting, and nausea. The commonly occurring AEs were noted to be of similar incidence in both the placebo/rhIDU patients, who had received a total of 24 weeks of rhIDU treatment, and the rhIDU/rhIDU patients, who had received a total of 50 weeks of rhIDU treatment, with the exception of diarrhea, nausea, and vomiting, which were found to be higher in the placebo/rhIDU group during the 24 Week extension period. The majority of these gastrointestinal events were reported as unrelated to rhIDU treatment and occurred on non-infusion days. In addition, these gastrointestinal events were noted to be of similar patient incidence rates when comparing the placebo and rhIDU groups from the Phase 3 Double-Blind study, as well as when comparing the placebo/rhIDU group from the Open-Label Extension Study with the rhIDU group from the Double-Blind study.

Table 39: Summary of Most Commonly Occurring AEs (≥ 30% of Patients in Either Group) from Entry* through Week 24 (Phase 3 Open-Label Extension Study)

WHO-ART Body System	WHO-ART Preferred Term**	Placebo/rhIDU n = 23 n (%)	rhIDU/rhIDU n = 22 n (%)
Any AE	N/A	**23 (100)**	**22 (100)**
Central and Peripheral Nervous System Disorders		**15 (65)**	**12 (55)**
	Headache	13 (57)	10 (45)
Respiratory System Disorders		**17 (74)**	**15 (68)**
	Rhinitis	10 (43)	9 (41)
	Coughing	7 (30)	8 (36)
	Pharyngitis	7 (30)	6 (27)
Gastrointestinal System Disorders		**16 (70)**	**10 (45)**
	Nausea	7 (30)	0
	Diarrhea	8 (35)	3 (14)
	Vomiting	7 (30)	4 (18)

* Last measurement in the Phase 3 Double-Blind Study (ALID-003-99) prior to enrollment into the Phase 3 Open-Label Extension Study (ALID-006-01).

** A patient experiencing more than 1 AE within a preferred term is counted once within that preferred term.

7.3.2 Summary of Adverse Events during the First 24 Weeks by Relatedness

Overall, the incidence of related AEs was similar in the placebo/rhIDU (48%) and rhIDU/rhIDU (45%) groups. The most common of these AEs (> 1 patient) in the placebo/rhIDU group were arthralgia (9%, 2 patients) and leg pain (9%, 2 patients) while the most common (> 1 patient) in the rhIDU/rhIDU group were arthropathy (14%, 3 patients) and flushing (14%, 3 patients). Overall, there were few AEs related to study drug reported in either treatment group.

7.3.3 Infusion-Associated Reactions (Drug-Related AEs on Day of Infusion)

IARs were defined as those AEs that occurred on the day of infusion, and began either during or after the infusion. As previously defined, AEs occurring on the day of infusion that were reported as possibly, probably or definitely related to study drug, that were not revealed by a protocol-required assessment (i.e., laboratory and physical examination abnormalities performed prior to study drug administration), were considered to be IARs.

IARs occurred in both treatment groups with 7 (30%) placebo/rhIDU patients experiencing 16 IARs and 8 (36%) rhIDU/rhIDU patients experiencing 16 IARs. In both treatment groups, the most commonly occurring AE was flushing. The majority of IARs were of mild intensity and none were reported as severe. A listing of all AEs considered to be possibly, probably, or definitely related to treatment that occurred on the day of infusion is summarized below in Table 40.

Table 40: Summary of AEs Reported as Infusion-Associated Reactions from Entry* through Week 24 (Phase 3 Open-Label Extension Study)

WHO-ART Preferred Term***	Placebo/rhIDU (n= 23)		rhIDU/rhIDU (n = 22)	
	No. Pts. (%)**	No. Events	No. Pts. (%)**	No. Events
Any IAR	7 (30)	16	8 (36)	16
Flushing	1 (4)	3	3 (14)	9
Rash	0	0	1 (5)	2
Abdominal Pain	1 (4)	1	1 (5)	1
Diarrhoea	1 (4)	1	1 (5)	1
Arthropathy	0	0	1 (5)	1
Fatigue	0	0	1 (5)	1
Headache	0	0	1 (5)	1
Agitation	1 (4)	2	0	0
Arthralgia	1 (4)	2	0	0
Fever	1 (4)	1	0	0
Hypotension	1 (4)	1	0	0
Leg Pain	1 (4)	1	0	0
Nausea	1 (4)	1	0	0
Pain	1 (4)	1	0	0
Rash Maculo-Papular	1 (4)	1	0	0
Skeletal Pain	1 (4)	1	0	0

* Last measurement in the Phase 3 double-blind study (ALID-003-99) prior to enrollment into the open-label extension study (ALID-006-01).
** Percentages for number of patients are based on the total number of patients in each treatment group.
*** A patient experiencing more than 1 AE within a preferred term is counted once within that term.

Three patients in the placebo/rhIDU group and 2 patients in the rhIDU/rhIDU group received medication to treat an IAR. None of the IARs was severe in intensity, none of the patients required rhIDU-treatment interruption or adjustment, and none required steroid treatment. Overall, there were few patients who experienced IARs; the majority of the reactions were mild (12 of 16 in the placebo group, 16 of 16 in the rhIDU group) and did not require medication (12 of 13 in the placebo group, 14 of 16 in the rhIDU group).

7.3.4 IgE, Complement Activation and Skin Testing

Three patients experienced IARs of moderate intensity although samples for IgE and complement activation were not drawn per decision of the Investigator.

7.3.5 Adverse Events on Non-Infusion Days

All 23 (100%) placebo/rhIDU patients and 21 of 22 (95%) rhIDU/rhIDU patients experienced 1 or more AEs on non-infusion days regardless of relationship to study drug. In both groups, the

most commonly reported AEs were headache, rhinitis, and coughing. The incidence and type of AEs reported on non-infusion days were similar in both groups, except for nausea, which occurred in 4 (17%) of the placebo/rhIDU group and in none of the patients in the rhIDU/rhIDU group.

Seven (30%) placebo/rhIDU patients and 4 (18%) rhIDU/rhIDU patients experienced AEs on non-infusion days that were judged by the investigator to be related to study drug. Few related AEs occurred on non-infusion days.

Two patients in the placebo/rhIDU group were reported as having 4 severe AEs. One patient experienced an episode of choking on hard candy, which resolved in 5 minutes and was assessed as unrelated to study drug treatment. The second patient, previously described as discontinuing due to an AE, died secondary to a severe upper respiratory infection. Autopsy results also revealed severe tracheitis, bronchitis and myocarditis all of which were assessed as unrelated to study drug therapy. One patient in the rhIDU/rhIDU group experienced decreased visual acuity, which was assessed as non-serious, severe and unrelated to study drug treatment.

7.3.6 Deaths

One patient in the placebo/rhIDU group of the Phase 3 Open-Label Extension Study, died at Week 16 due to complications of an upper respiratory tract infection. The event and the patient's death were assessed by the Investigator as unrelated to rhIDU therapy.

7.3.7 Serious Adverse Events

Nine patients (6 placebo/rhIDU, 3 rhIDU/rhIDU) experienced 14 SAEs (11 placebo/rhIDU, 3 rhIDU/rhIDU) during the first 24 weeks of the Phase 3 Open-Label Extension Study. All SAEs were assessed by the Investigator as unrelated to study drug. SAEs experienced by patients in the placebo/rhIDU group consisted of: vein disorder, abdominal pain, dyspnea, transplant rejection, respiratory disorder, upper respiratory tract infection, tracheitis, bronchitis and choking. The SAEs experienced by the rhIDU/rhIDU patients included: otitis media, palpitation, and vein disorder.

7.3.8 Adverse Events Resulting in Patient Discontinuation

One patient discontinued from the study due to an AE that resulted in death (Section 7.3.6) and was assessed as unrelated to the study drug.

7.3.9 Clinical Laboratory Values

No clinically relevant mean changes from baseline to Week 24 and from entry to Week 24 or clinically relevant shifts were observed in serum chemistry parameters. No clinically relevant mean changes were observed over time for any of the hematological parameters except for an increase in platelet count from baseline and entry to Week 24 that remained within normal range.

No clinically relevant shifts were observed for any of the hematological parameters at Week 24. No clinically relevant changes were observed for any urinalysis parameters over time.

7.3.10 Other Observations Related to Safety

7.3.10.1 Vital Signs

Mean changes from baseline and entry to Week 24 in temperature, respiratory rate, systolic and diastolic blood pressures were similar between treatment groups. Mean vital sign values remained within normal limits and observed changes were unremarkable.

7.3.10.2 Physical Examination Findings

Physical examinations were performed throughout the Phase 3 Open-Label Extension Study. A majority of the patients in both groups had abnormal findings on physical examination at baseline or at entry. For those patients who were evaluated as normal at baseline and entry in the various parameters, very few in either group shifted to abnormal at Week 24.

7.3.10.3 Brain/Cranio-Cervical Junction

Brain/Cranio-Cervical Junction MRIs were not performed in this study.

7.3.10.4 Immunology: IgG Testing, AEs by IgG Status, and Neutralizing Antibody Data

IgG Testing

All patients were screened for the development of IgG antibodies by ELISA assay and when available, samples were confirmed by RIP assay. Confirmatory RIP d ata are presented in Table 41.

Table 41: Summary of IgG Testing Confirmed by RIP from Baseline to Week 24 of the Phase 3 Open-Label Extension Study

Category	Summary Statistic	Placebo/rhIDU n (%)	rhIDU/rhIDU n (%)
Number of Patients Who Received Drug	n (%)	23 (100)	22 (100)
Number of IgG Positive Patients (RIP)	n (%)	21 (91)	19 (86)
Time to RIP positive testing* (Days from First Infusion)	n	21	19
	Mean	42.4	62.1
	Median	50.0	50.0
	Standard Deviation	22.1	53.3
	Minimum, Maximum	20, 106	20, 259
Mean Time From First Positive in the Double-Blind to First Negative in the Extension Studies (days)	Mean		140.5 (n = 2)

* For the placebo/rhIDU group the time to RIP positive is from first infusion in the Phase 3 Open-Label Extension Study. For rhIDU/rhIDU group the time to RIP positive is from first infusion in the Phase 3 Double-Blind Study.

A total of 21 placebo/rhIDU patients seroconverted by Week 24 of the Phase 3 Open-Label Extension Study. Two patients in the placebo/rhIDU group remained IgG-negative at Week 24 of the Phase 3 Open-Label Extension Study.

During the Phase 3 Double-Blind Study, 20 of the 22 rhIDU patients seroconverted by RIP assay by Week 26 with a mean of 52.6 days. Two patients did not seroconvert. During the Phase 3 Open-Label Extension Study, one of the 2 patients who did not seroconvert during the Double-Blind Study remained IgG-negative by RIP assay, while the other patient eventually seroconverted. Therefore, 21 of the 22 rhIDU/rhIDU-treated patients seroconverted. Additionally, during the Phase 3 Open-Label Extension Study 2 rhIDU/rhIDU patients tolerized to study drug as evidenced by lack of IgG-positive testing (RIP negative) through Week 24 of the Phase 3 Open-Label Extension Study. As a result, a total of 19 rhIDU/rhIDU patients were reported as being IgG-positive by RIP assay at Week 24 of the Phase 3 Open-Label Extension Study.

Adverse Events by IgG Status: Phase 3 Double-Blind Study and Phase 3 Open-Label Extension Study

Overall, 40 (89%) of the 45 patients treated with rhIDU in the Phase 3 Open-Label Extension Study were noted to have seroconverted to IgG-positive status by RIP assay testing. Given the few number of placebo/rhIDU patients (2 or 9%) and rhIDU/rhIDU patients (3 or 14%) who did

not seroconvert, the incidence of IARs with respect to IgG status would be similar to the incidence of IARs for each treatment group regardless of IgG status.

A total of 7 placebo/rhIDU patients who were IgG-positive during the Phase 3 Open-Label Extension Study experienced IARs. Four of these 7 patients also experienced IARs during the Phase 3 Double-Blind Study. There was an overall decreased incidence by number of patients and number of events of IARs by the IgG-positive placebo/rhIDU patients in the Phase 3 Open-Label Extension Study relative to those patients who were IgG-negative in the Phase 3 Double-Blind Study.

A total of 8 (42%) IgG-positive patients in the rhIDU/rhIDU group experienced IARs during the Phase 3 Open-Label Extension Study. A similar number of IgG-positive patients in the rhIDU group (7 or 35%) experienced IARs during the Phase 3 Double-Blind Study. Overall, the number of IARs experienced by the IgG-positive patients during the first 24 weeks of Phase 3 Open-Label Extension Study rhIDU treatment (rhIDU/rhIDU group) was approximately 25% of the number of IARs experienced by the IgG-positive patients during the 26-week Phase 3 Double-Blind Study (rhIDU group).

Neutralizing Antibody Data

Neutralizing antibody titers were determined using a validated assay for the inhibition of enzyme activity in the presence of patient serum. Assessment of neutralizing antibody titers at Week 24 of the Phase 3 Open-Label Extension Study revealed that a majority of patients do not show a significant rise in inhibitory activity from the start of rhIDU treatment through Week 24. In 8 patients, there was an increase in inhibitory signal level to 6% inhibition or more over the background level of 6%. In 3 of these patients the increase in inhibition was 30.0%, 19.2 % and 11.3%. There was no discernible association between patients experiencing IARs and inhibitory activity.

7.4 Phase 3 Open-Label Extension Study: Updated Safety Information for Weeks 25 – 36

AEs during this update period were defined as any AEs that began at Week 25 up to and including Week 36, or began prior to Week 25 during the Phase 3 Open-Label Extension Study and increased in intensity or frequency at any time from Week 25 to Week 36.

7.4.1 Most Commonly Occurring AEs

All patients experienced at least one AE during the update period. The most commonly reported AEs in the placebo/rhIDU and rhIDU/rhIDU groups, respectively were headache [13 patients (62%) and 9 patients (41%)] and rhinitis [9 patients (43%) and 7 patients (32%)]. The types and incidence of AEs during this update period were similar (with the exception of pharyngitis) in

both the placebo/rhIDU patients who had received a maximum of 36 weeks of rhIDU treatment, and the rhIDU/rhIDU patients, who had received a maximum of 62 weeks of rhIDU treatment.

Overall, few patients in either treatment group experienced AEs related to study drug. The overall incidence of related AEs was higher in the placebo/rhIDU group (38%) than in the rhIDU/rhIDU (14%) group. The most common of these AEs (reported in > 1 patient) in the placebo/rhIDU group were rash [2 patients (10%)], arthralgia [2 patients (10%)] and headache [2 patients (10%)]. There were no AEs which occurred in >1 patient in the rhIDU/rhIDU group.

7.4.2 Infusion-Associated Reactions

During this update period, IARs occurred in both treatment groups with 5 (24%) placebo/rhIDU patients experiencing 14 IARs and 2 (9%) rhIDU/rhIDU patients experiencing 10 IARs. The most commonly reported IAR was flushing (5 events), which was reported in 1 (5%) of the placebo/rhIDU patients and pruritus (3 events), which was also reported in 1(5%) of the rhIDU/rhIDU patients. Overall, few patients experienced IARs during this reporting period. The majority were of mild intensity and did not require treatment with medication or adjustment of study drug administration.

7.4.3 IgE, Complement Activation Testing and Skin Testing

Two patients experienced moderate IARs resulting in IgE and Complement Activation testing, per protocol. One patient in the rhIDU/rhIDU group experienced recurrent rash, pruritus and urticaria and tested negative for both serum IgE and complement activation; this patient was not skin tested. The other patient in the placebo/rhIDU group experienced dyspnea and tested positive for both serum IgE and complement activation. The patient was skin tested, due to the positive serum IgE testing results, and was reported as negative. Skin testing consisted of scarification followed by intradermal testing with a 1:20 dilution of study drug. Control panel testing was not possible due to patient uncooperativeness.

7.4.4 AEs on Non-Infusion Days

In both treatment groups, the most commonly reported AEs occurring on non-infusion days were headache and rhinitis. The incidence and type of AEs reported on non-infusion days were similar in both groups, except for pharyngitis, which occurred in 5 (24%) of the placebo/rhIDU group and in none of the patients in the rhIDU/rhIDU group.

7.4.5 Deaths and Discontinuations Due to Adverse Events

There were no deaths or discontinuations due to AEs from Week 25 up to and including Week 36.

7.4.6 Serious Adverse Events

Ten SAEs were reported in 4 patients: 2 SAEs in 1 patient in the placebo/rhIDU group and 8 SAEs in 4 patients in the rhIDU/rhIDU group. All SAEs were reported as being unrelated to

study drug with the exception of one patient from the placebo/rhIDU group who experienced dyspnea which was reported as possibly related. This patient also experienced confusion which was reported as not related. The SAEs experienced by the rhIDU/rhIDU patients consisted of convulsions, EEG abnormal, apnea, line infection, vein disorder, gastroenteritis, and infection bacterial.

7.4.7 Post Data Cut-Off Serious Adverse Event Information (> 36 Weeks)

Significant safety information was received after the cut-off date regarding a placebo/rhIDU patient. This patient's medical history was remarkable for restrictive lung disease with a severely compromised airway and limited ventilatory reserve, sleep apnea and a generalized anxiety disorder. This patient's rhIDU infusions were complicated by several IARs of varying intensities, including anxiety, respiratory distress and decreased oxygen saturation, which were most often managed with oxygen and anxiolytics. BiPAP was inconsistently utilized during infusion administration due to patient lack of compliance. After an episode of severe dyspnoea at Week 34, the patient tested positive for both serum IgE and complement activation, with a subsequent negative skin test prior to re-introduction of rhIDU therapy (Section 7.4.3). After rhIDU re-introduction, the patient experience IARs but not during every infusion. At Week 62 (infusion #44), the patient experienced an IAR approximately 3.5 hours after the start of the infusion consisting of a progressive rash with urticaria and angioedema, as well as acute respiratory arrest, which the investigator reported as an anaphylactic reaction. The patient underwent emergency tracheostomy and was mechanically ventilated. The patient stabilized with no signs of neurological deficit, and was discharged to home on ventilatory support. At the time of this report the patient remains ventilator-dependent and, according to the investigator, in light of the patient's long-standing respiratory instability the tracheostomy will remain in place indefinitely.

In the opinion of the Sponsor, the development of angioedema in this patient with a markedly restricted airway may have contributed significantly to the acute respiratory event. The respiratory event occurred well after infusion initiation and did not manifest with wheezing or decreased blood pressure as is typically seen with anaphylactoid reactions. Therapy with rhIDU has been temporarily interrupted pending further evaluation.

7.4.8 Clinical Laboratory Values

There were no trends observed in any of the chemistry, hematological or urinalysis testing results.

7.4.9 Physical Examination and Vital Signs

There were no trends noted in physical examination or vital signs findings.

7.4.10 IgG Testing

There were no changes to IgG seroconversion status during the updated reporting period from Week 25 to 36.

7.5 Phase 1/2 Study

7.5.1 Introduction

During the Phase 1/2 Study, rhIDU was initially manufactured using a small-scale process. With the advent of a revised commercial-scale production process that allowed for improved capacity and product purity, the drug manufacturing process was transferred to another facility. The cross-over to the new product occurred between study weeks 119 and 130 for patients in the Phase 1/2 Study. Ongoing treatment in that study as well as all studies started after the Phase 1/2 Study received rhIDU with the newer product.

During the Phase 1/2 Study there was also a period of drug unavailability, which resulted in patients missing several infusions. Drug availability was sporadic from December 1998 through December 1999. The period of greatest drug unavailability was Week 53 to 104 for the first patients enrolled and Weeks 26 to 88 for the last patients enrolled. No infusions were missed because of drug unavailability after Week 105.

7.5.2 Summary

This summary contains all AEs reported through 30 March 2001, including study data up to Week 171. All 10 patients experienced at least 1 AE, and all 10 patients had at least 1 AE that was judged to be study drug-related. There were 960 AEs reported during the approximately 3 year study period. Eight patients experienced a total of 32 SAEs, including 2 that resulted in death. Seven patients had a total of 33 AEs that were reported as severe. These results are summarized in Table 42.

Table 42: Summary of Patients Experiencing Adverse Events during Treatment (Phase 1/2 Study)

Category	Number of Patients (Percent) (N = 10)
Patients Experiencing Adverse Events	10 (100%)
Discontinuations Due to Adverse Events	2 (20%)
Patients with Study Drug-Related Adverse Events	10 (100%)
Patients with Serious Adverse Events	8 (80%)
Patients with Severe Adverse Events	7 (70%)
Patients with Adverse Events on the Day of Infusion*	9 (90%)

* Defined as any AE occurring on the day of infusion and related or having an unknown relationship to study drug. AEs known to occur prior to the start of study drug infusion were excluded. Six of the nine patients experienced events considered to be the typical signs and symptoms of hypersensitivity-type reactions.

The overall incidence of AEs reported by 30% or more of the patients is presented in Table 43. The most commonly reported terms were rhinitis (10 patients), pain, asthenia, and fever (9 patients each), and increased cough, abdominal pain, vascular disorder, and rash (8 patients each).

Table 43: Incidence of AEs Reported by ≥ 30% of Study Patients by Body System and Preferred Term (Phase 1/2 Study)

COSTART Body System and Preferred Term	Number of Patients
Respiratory System	**10**
Rhinitis	10
Cough Increased	8
Sinusitis	7
Respiratory Disorder	7
Dyspnea	6
Bronchitis	5
Pneumonia	5
Apnea	3
Asthma	3
Pharyngitis	3
Body as a Whole	**10**
Pain	9
Asthenia	9
Fever	9
Abdominal Pain	8
Headache	7
Allergic Reaction	6
Accidental Injury	6
Back Pain	6
Injection Site Reaction	5
Infection	4
Injection Site Pain	3
Cardiovascular System	**10**
Vascular Disorder	8
Cardiovascular Disorder	6
Cardiomegaly	3
Hypotension	3

COSTART Body System and Preferred Term	Number of Patients
Musculoskeletal System	**10**
Joint Disorder	6
Bone Disorder	5
Myalgia	3
Generalized Spasm	3
Digestive System	**9**
Vomiting	7
Nausea	5
Constipation	3
Dyspepsia	3
Tooth Disorder	3
Special Senses	**9**
Ear Disorder	4
Otitis Media	4
Ear Pain	3
Nervous System	**9**
Dizziness	3
Abnormal Gait	3
Somnolence	3
Thinking Abnormal	3
Tremor	3
Skin and Appendages	**8**
Rash	8
Urticaria	6
Skin Disorder	4
Angioedema	3
Metabolic and Nutritional Disorders	**6**
Edema	3
Peripheral Edema	3

The most frequently reported AEs during Weeks 1 to 52 were pain (8 patients), rhinitis, headache and vomiting (7 patients each), rash, and respiratory disorder (6 patients each), and asthenia, fever, abdominal pain, sinusitis, allergic reaction, cardiovascular disorder, and urticaria (5 patients each). The most frequently reported AEs during Weeks 53 to 104 were asthenia (8 patients), pain (7 patients), fever (6 patients), and rhinitis, abdominal pain, headache, and sinusitis (5 patients each). The most frequently reported AEs during Weeks 105 to March 30, 2001, i.e., up to Week 171, were fever and headache (6 patients each), and pain, abdominal pain, cough increased, rash, and urticaria, (5 patients each).

7.5.3 Severe Adverse Events

Seven of the 10 patients experienced 33 AEs reported by the investigator as being severe. These 33 AEs represented 3.4% of the total number of AEs reported (960).

The most frequently reported severe AEs were bone disorder (4 patients with 5 AEs), apnea and vascular disorder (3 patients with 3 AEs each), and allergic reaction, and headache (2 patients with 2 AEs each).

Ten of the 33 severe AEs (30%) were judged to be definitely or possibly related to study drug, 4 (12%) had an unknown relationship to study drug, and 19 (58%) were judged unrelated to study drug. Fourteen of the 33 severe AEs were SAEs. (Refer to Section 7.5.9.)

7.5.4 Adverse Events by Relationship and Severity to Study Drug

All 10 patients experienced at least 1 AE that was judged by the investigator to be causally related (or had an unknown relationship) to study drug. The most frequently reported AEs related to the study drug (defined as definitely or possibly related or with an unknown relationship) were rash (6 patients), urticaria and headache (5 patients each), allergic reaction, pain, asthenia, and dyspnea (4 patients each) and fever, injection site reaction, abdominal pain, angioedema, and myalgia (3 patients each). The majority of the AEs were mild or moderate in severity.

Ten study drug-related AEs were assessed as severe but were reported by fewer than 30% of the patients. The AEs reported as severe were bone disorder (cord compression experienced by 2 patients), edema and brain edema (1 patient with both), neck pain (1 patient), tachycardia, peripheral vascular disorder, thinking abnormal, tremor, and hypertension (all experienced by 1 patient during 1 study drug infusion), and apnea (1 patient).

7.5.5 Drug-Related AEs on Day of Infusion

AEs that occurred during the Phase 1/2 study were also evaluated according to whether they occurred on the day of infusion in order to determine the AEs that could possibly represent hypersensitivity-type reactions. AEs occurring on the day of infusion and that were considered related to drug or that had an unknown relationship to study drug, are presented by study period in Table 44. AEs that were known to occur prior to the start of study drug infusion are excluded.

Table 44: Drug-Related Adverse Events on Day of Infusion: Phase 1/2 Study

COSTART Body System and Preferred Term	Weeks 1 to 52* No. Pts. (No. AEs)	Weeks 53 to 104* No. Pts. (No. AEs)	Weeks 105** to data lock*** No. Pts. (No. AEs)	Total No. Patients No. Pts. (No. AEs)
Skin & Appendages	6 (40)	3 (54)	5 (46)	6 (140)
Rash	3 (7)	3 (4)	4 (5)	6 (16)
Urticaria	5 (29)	3 (47)	4 (21)	5 (97)
Angioedema	2 (3)	1 (1)	2 (11)	3 (15)
Pruritus	0	1 (1)	2 (6)	2 (7)
Skin Discolor	0	0	2 (3)	2 (3)
Skin Nodule	1 (1)	1 (1)	0	1 (2)
Body as a Whole	5 (22)	4 (10)	5 (13)	8 (45)
Allergic Reaction	3 (5)	1 (2)	1 (1)	4 (8)
Headache	3 (7)	1 (1)	1 (1)	4 (9)
Fever	1 (3)	1 (1)	1 (2)	3 (6)
Injection Site Reaction	0	2(2)	2 (2)	3 (4)
Chills	2 (2)	0	1 (3)	2 (5)
Pain	1 (1)	1 (3)	1 (1)	2 (5)
Abdominal Pain	2 (3)	0	1 (1)	2 (4)
Hypersensitive Injection Site	1 (1)	0	0	1 (1)
Neck pain	0	1 (1)	0	1 (1)
Generalized Edema	0	0	1 (2)	1 (2)
Respiratory System	2 (2)	0	1 (1)	3 (3)
Dyspnea	2 (2)	0	1 (1)	3 (3)
Cardiovascular System	3 (9)	1 (1)	1 (3)	4 (13)
Hypotension	1 (1)	1 (1)	1 (2)	2 (4)
Vasodilation	2 (5)	0	0	2 (5)
Bradycardia	0	0	1 (1)	1 (1)
Hypertension	1 (1)	0	0	1 (1)
Tachycardia	1 (1)	0	0	1 (1)
Peripheral Vascular Disorder	1 (1)	0	0	1 (1)

Table 44: Drug-Related Adverse Events on Day of Infusion: Phase 1/2 Study (cont'd)

COSTART Body System and Preferred Term	Weeks 1 to 52* No. Pts. (No. AEs)	Weeks 53 to 104* No. Pts. (No. AEs)	Weeks 105** to data lock*** No. Pts. (No. AEs)	Total No. Patients No. Pts. (No. AEs)
Musculoskeletal System	2 (4)	0	2 (2)	3 (6)
Myalgia	2 (2)	0	0	2 (2)
Joint Disorder	1 (2)	0	1 (1)	2 (3)
Leg Cramps	0	0	1 (1)	1 (1)
Nervous System	3 (5)	1 (1)	1 (9)	3 (15)
Reflexes Increased	0	0	1 (8)	1 (8)
Tremor	1 (1)	0	0	1 (1)
Anxiety	1 (1)	0	0	1 (1)
Depression	1 (1)	0	0	1 (1)
Neuralgia	1 (1)	0	0	1 (1)
Nervousness	0	0	1 (1)	1 (1)
Thinking Abnormal	1 (1)	0	0	1 (1)
Somnolence	0	0	0	1 (1)
Digestive System	1 (2)	1 (1)	1 (1)	2 (3)
Vomiting	1 (2)	0	0	1 (2)
Nausea	0	0	1 (1)	1 (1)
Metabolic & Nutritional	1 (1)	0	1 (6)	2 (7)
Edema	0	0	1 (4)	1 (4)
Peripheral Edema	0	0	1 (2)	1 (2)
Weight Gain	1 (1)	0	0	1 (1)

* Ten patients reporting; one patient died between Weeks 103 and 104.
** Nine patients reporting; one patient died at Week 139.
*** At the time of data lock on March 30, 2001, patients had received treatment for 152 to 171 weeks.

Six patients experienced repeated signs and symptoms of hypersensitivity during enzyme infusion at some point during their treatment with rhIDU. The most common manifestations of a hypersensitivity reaction were rash (6 patients), urticaria (5 patients), and allergic reaction and headache (4 patients each). The severity of these reactions varied by patient but no patient discontinued from the study due to these reactions.

All patients were pre-medicated with diphenhydramine IV and, in some cases, corticosteroids and nonsteroidal anti-inflammatory drugs. If a reaction occurred during infusion, the rate of infusion was temporarily stopped, the dosage was temporarily reduced, additional doses of diphenhydramine and/or corticosteroids (e.g., methylprednisolone, hydrocortisone) were administered, or other clinical interventions were performed.

Four of the six patients experienced hypersensitivity-type reactions that were described as allergic reactions and reported as SAEs by the investigator (refer to Section 7.5.9).

7.5.6 IgE, Complement Activation Testing and Skin Testing

IgE testing for Phase 1/2 Study patients was not performed due to the unavailability of the test at the time. See Section 7.5.13.1 for Complement Activation testing results. Patients in the Phase 1/2 Study were skin tested; however, the results did not correlate with clinical manifestations. All patients were able to continue with treatment.

7.5.7 Adverse Events on Non-Infusion Days

The most commonly AEs reported on non-infusion days were rhinitis (10 patients), pain (9 patients), asthenia and cough increased (8 patients each), abdominal pain, fever, headache, vomiting, and sinusitis (7 patients each), accidental injury, cardiovascular disorder, respiratory disorder, and rash (6 patients each), and back pain, vascular disorder, nausea, and bone disorder (5 patients each).

7.5.8 Deaths

There were 2 deaths that occurred during the reporting period through Week 171. Neither death was associated with an infusion.

One patient died at Week 104 due to respiratory arrest, which was assessed as unlikely related to study drug. The patient's autopsy report indicated that death was due to a systemic viral infection associated with significant pulmonary and cardiac infection that in combination with the increased altitude while on an airplane and decreased oxygenation led to respiratory arrest. The second patient died at Week 139 due to apnea/respiratory failure, which was assessed as unrelated to study drug.

7.5.9 Serious Adverse Events

Of the 32 SAEs experienced by 8 patients in the Phase 1/2 Study, 9 were considered definitely or possibly related to study drug by the Investigator. Eight of these 9 events, experienced by 4 patients, were allergic reactions that occurred during drug infusion which all resolved, usually within hours of the event. Six of the 8 allergic reactions were reported as of mild or moderate intensity. The ninth related event was cervical cord compression, which was considered to be possibly related to study drug. Cervical cord compression was present at pretreatment in this patient.

Twenty-three SAEs experienced by 6 patients were assessed as unrelated to study drug. The unrelated SAEs were associated with underlying MPS I disease and most were related to the respiratory system. Twelve of the 22 unrelated SAEs involved the respiratory system, were experienced by 5 patients, and included respiratory infection, pneumonia, pulmonary edema, respiratory failure, and pharyngitis. Four of the unrelated SAEs were bone and/or tendon

disorders, experienced by 3 patients, and included carpal tunnel syndrome, worsening scoliosis, worsening lumbosacral spondylolisthesis, and progressive kyphoscoliotic deformity. The other unrelated SAEs involved worsening of eye disease, cardiac disease, paralysis, hydrocephalus, and umbilical hernia strangulation. All of the unrelated SAEs resolved.

Thirteen SAEs in 6 patients occurred during the first 52 study weeks; 10 SAEs in 5 patients, including 1 event that led to death, occurred between Weeks 53 and 104; and 9 SAEs in 4 patients, including 1 event that led to death, occurred between Weeks 105 and 152.

7.5.10 Adverse Events Resulting in Patient Discontinuation

Two patients discontinued from the study due to AEs that resulted in death and were assessed as unrelated to study drug.

7.5.11 Clinical Laboratory Values

Complete sets of clinical laboratory evaluations were obtained on patients before and during the study. Complete blood counts, liver enzymes, renal labs, electrolytes, urinalysis with microscopic analysis, and 24-hour creatinine clearance did not show any consistent changes.

7.5.12 Other Observations Related to Safety

7.5.12.1 Vital Signs

Systolic and diastolic blood pressure (BP), pulse, and respiratory rate were measured at weekly intervals throughout the 152-week study period. Changes in these values were variable among patients and were probably related to MPS I disease status

7.5.12.2 Physical Examination Findings

Physical examinations were performed throughout the Phase 1/2 Study. Findings were consistent with patients' underlying disease.

7.5.12.3 Brain/Cranio-Cervical Junction MRI

These studies were designed to evaluate the presence of cord compression and injury to the cervical cord based on increased T2-weighted signals within the substance of the cord. Evaluations at baseline showed spinal stenosis due to bony abnormalities and significant thickening of the meninges. Evaluations with T2 weighting showed an absence of fluid around the cervical cord in these patients, suggesting that the thickening of the meninges and the spinal canal stenosis lead to a tight fit of the meninges on the cord, without room for movement. Cord compression was present at baseline in two patients. No MRI changes in cord compression were seen through Week 104 for these patients. However, 1 of these patients had cord compression AEs starting at Week 29 due to subluxation of C3–C4 in the cervical spine and subsequently underwent cervical fusion surgery. Cord compression was observed at Week 104 in a third patient in which no cord compression had been noted at baseline through Week 52.

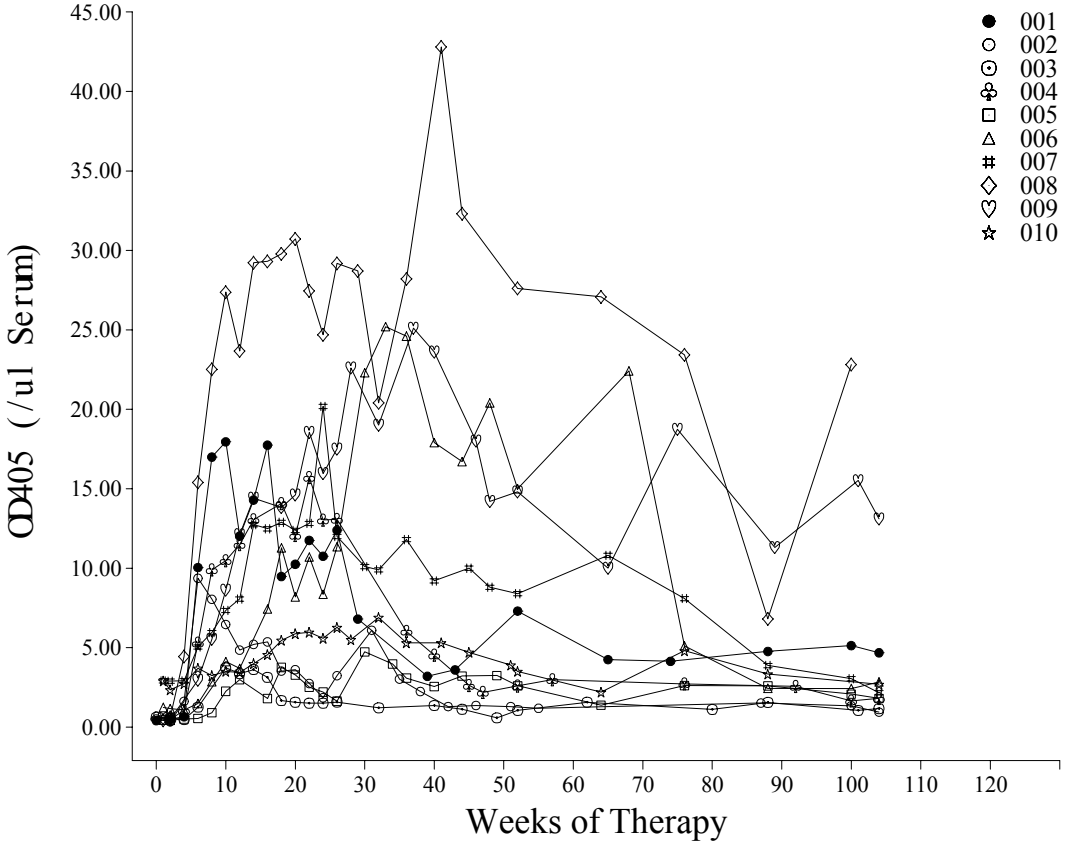
7.5.13 Immunology

7.5.13.1 IgG Testing

An ELISA assay was developed using rhIDU product to screen for presence of IgG antibodies in patients; however, the assay did not provide information about the possible target of such IgG (i.e., contaminants or iduronidase).

ELISA assays using rhIDU product demonstrated the presence of IgG antibodies in all patients by Weeks 6 to 12 of treatment (Figure 17). The titers, expressed as OD_{405} units per mL of serum, showed different patterns over time, but titers in all patients decreased over time, suggesting tolerization to treatment with rhIDU. After a decrease in titer between Weeks 40 and 90, one patient had an increase at Week 100. The equivalent titer for most patients was less than 1:1000 for dilutions producing a signal of 3x background with the exception of one patient who had an equivalent titer of 1:25,000.

Figure 17: IgG Antibody ELISA Results (1:1000 Dilution) IgG Antibody ELISA Results (1:1000 Dilution) (Phase 1/2 Study)



A confirmation of antibody specificity conducted using a standard Western blot technique showed that all patients developed IgG antibodies to protein impurities. The response was primarily directed at a 60 kDa protein, which was not observed on Coomassie Blue and silver

stained gels. It was present in the supernatant from the parent cell line transfected with a blank expression construct.

Specific immune responses to rhIDU were seen in 4 of 10 patients as determined by Western blot. One patient had IDU-specific antibodies transiently around Weeks 10 to 14, 2 patients had a significant IDU-specific antibody response, and the fourth patient had relatively few specific anti-IDU antibodies. All IDU-specific antibodies declined with time in these 4 patients, as observed by Western blot. The 2 patients with transient or few antibodies had few or no IDU-specific antibodies by Week 26.

There was no consistent relationship between the presence of IgG antibodies (whether specific to IDU or not) and hypersensitivity-type reactions. All 10 patients developed IgG antibodies to rhIDU product, but only 6 patients had hypersensitivity-type reactions and only 2 patients developed IDU-specific antibodies. Four of the six patients experienced events captured as allergic reactions, which consisted of a combination of events including angioedema (3 patients), fever and chills (2 patients), fever alone (1 patient) and pruritus (2 patients). Five of the six patients experienced study drug-related urticaria.

IgG titer did not correlate with hypersensitivity-type reactions in these patients. For example, 2 patients had relatively low antibody titers but had significant periods of recurrent urticarial reactions. In addition, titers in these 2 patients had declined rather than risen during the periods of hypersensitivity reactions. Conversely, one patient had no hypersensitivity-type reactions but relatively high antibody titers to rhIDU product.

The 4 patients with IDU-specific antibodies also showed evidence of complement activation. Complement activation, as measured by the difference between the pre-and post-dose levels of CH50 and either C3 or C4, was highest for two patients, and highest at Week 12 for the other 2 patients. Complement activation was greatly reduced or resolved by Week 26 and no apparent complement activation was seen at Week 52 in any patient.

There was no relationship between complement activation and steroid use. Of the 6 patients who were prescribed glucocorticoids as a pre-medication for at least one infusion or who received them during infusions to manage hypersensitivity-type reactions, 4 patients did not have complement activation. Of the patients who tested positive complement activation, 2 patients were not prescribed glucocorticoids and 1 patient received them on only 1 occasion.

The fourth patient, who received glucocorticoids at virtually all study infusions starting at Week 8, showed complement activation at Week 6, prior to administration of glucocorticoids, and had no complement activation by Week 52, while still receiving weekly glucocorticoids. Therefore, the initiation and resolution of complement activation was not related to steroid use in this patient.

7.5.13.2 Evaluation of Immune Complex Disease

There were no apparent effects of the immune responses on development of immune complex disease or on glomerulonephritis based on urinalysis and GFR results. Urine protein was rarely positive and GFR had not declined from pretreatment at the last study determination (Week 26 or 52) in any of the 10 patients, and had improved in some patients. BUN, serum creatinine, and the BUN/creatinine ratio did not increase over time, also indicating no renal impairment.

7.6 Phase 1/2 Study: Safety Information from 31 March 2001 to 30 June 2002

Safety information was collected from 31 March 2001 to 30 June 2002 and are presented below.

7.6.1 Most Commonly Occurring Adverse Events

All patients experienced at least one AE and the most commonly reported AEs were headache (6 patients), rhinitis, respiratory disorder and cough increased (5 patients each) and rash, pain, and vomiting (4 patients). Three patients experienced 6 severe AEs of which none were reported as being related to study drug.

7.6.2 Incidence of Study Drug-Related Adverse Events on the Day of Infusion

During the updated period, 4 patients experienced a total of 85 drug-related AEs on the day of infusion. The most common AEs were urticaria in 2 patients (33 events), angioedema in 3 patients (11 events) and pruritus in 2 patients (3 events). Two patients experienced 1 episode each of angioedema that were reported as moderate and mild in intensity. The third patient experienced 9 of the 11 reported episodes of angioedema, 3 of which were reported as moderate and 6 as mild. This patient also experienced four episodes of mild facial edema.

7.6.3 Deaths and Discontinuations Due to Adverse Events

There were no deaths or discontinuations due to AEs during this updated period.

7.6.4 Serious Adverse Events

Two patients experienced 3 SAEs. All SAEs were reported as not related. One patient experienced increased left foot pain related to a bunion and the other experienced increased umbilical hernia pain and cholecystitis.

7.6.5 Clinical Laboratory Values

There were no trends observed in review of the data for chemistry, hematology or urinalysis data.

7.6.6 Physical Examination and Vital Signs

There were no trends observed in review of the data for physical examination and vital signs.

7.6.7 IgG Testing

During the updated period, IgG antibody titers remained relatively stable or decreased in 6 of the 8 patients. Two patients had increases in IgG titer levels. One patient had an increase in the

frequency of hypersensitivity-type reactions, and the other patient did not experience any hypersensitivity-type reactions. For the remainder of the patients, there was no consistent relationship between IgG antibody level and hypersensitivity-type reactions.

7.6.8 Serious Adverse Event Information After 30 June 2002

One unrelated patient death due to cardiopulmonary arrest following mitral valve replacement surgery occurred on 06 November 2002 (Week 235).

7.7 Expanded Access Program

In the Expanded Access Program (EAP), SAEs (including deaths) and IARs were required to be reported. A total of the 4 patients were treated under the EAP during the reporting period up to and including 29 April 2002.

7.7.1 Infusion-Associated Reactions (Drug-related AEs on Day of Infusion)

One patient experienced an IAR consisting of dyspnea and headache during the rhIDU infusion, which was reported as non-serious.

7.7.2 Deaths

There was 1 death in the Expanded Access Program, as of 29 April 2002. The single patient enrolled in the ALID-007-01 protocol died after 28 weeks of treatment. The SAEs (cardiac failure and sepsis) and the patient's death were assessed by the physician as unrelated to rhIDU therapy.

7.7.3 Serious Adverse Events

In the Expanded Access Program, up to and including 29 April 2002, there have been 2 patients who have experienced SAEs. One of these patients experienced 15 SAEs, 2 of which (cardiac failure and sepsis) resulted in death. The other patient experienced 2 SAEs (cardiac failure and heart valve disorder) which were assessed by the Investigator as unrelated to study drug.

7.7.4 Adverse Events Resulting in Patient Discontinuation

One patient, who was being treated in the Expanded Access Program under Protocol ALID-007-01, discontinued from the study due to death.

7.8 Expanded Access Program: Safety Information from 30 April 2002 through 30 September 2002

The safety data for the EAP includes SAEs and IARs from 30 April 2002 up to and including 30 September 2002. Twelve new patients enrolled and began receiving rhIDU during this update period.

7.8.1 Infusion-Associated Reactions

There was 1 patient who experienced an IAR during the update period that was described as dyspnea, rigors and pallor. The IAR was reported as non-serious.

7.8.2 Deaths and Discontinuations Due to Adverse Events

There was 1 patient death reported among the 12 new patients. One patient experienced a single SAE of cardiac failure, which resulted in death, which was reported as unrelated to rhIDU treatment. The patient death was also considered to have been a discontinuation due to an adverse event.

7.8.3 Serious Adverse Events

There were 2 patients who experienced a total of 5 new SAEs during the update period. One patient experienced cardiac failure that resulted in death and was reported as unrelated. The remaining 4 SAEs occurred to the other patient who underwent cardiac valve surgery during the previous reporting period and subsequently experienced post-operative complications during the update period, which were reported as SAEs (chest pain, cardiac arrest, acute renal failure and sepsis) during the update reporting period. All SAEs were reported as unrelated to rhIDU treatment.

7.9 Safety Conclusion

Given the nature of MPS I, in which multiple organ systems are affected by lysosomal storage of GAGs, it is not surprising that almost all of the patients enrolled in the 3 clinical studies experienced at least 1 AE, including patients receiving placebo treatment in the Phase 3 Double-Blind Study. Overall, rhIDU and placebo infusions were similarly tolerated; therefore it seems unlikely that the development of IgG antibodies had any clinically significant effect on overall safety. Following the evaluation of safety data collected in this clinical development program, short term and long term rhIDU treatment appears to have an acceptable safety profile in MPS I disease which is progressive and life-threatening.

8. BENEFITS AND RISKS ASSESSMENT

An assessment of the benefits and risks of the treatment with rhIDU in MPS I patients is provided in this section.

8.1 Scientific Rationale for the Benefits of rhIDU Treatment

The benefits of rhIDU treatment are based on the fundamental biology of lysosomal enzymes derived from scientific research of the last 30 years. The scientific and animal studies have demonstrated the rational biologic basis for enzyme replacement therapy in MPS I and verified that the mechanisms of enzyme replacement described in vitro 30 years ago do function in animal models of MPS disease. The advent of adequate production systems of high-uptake rhIDU has afforded the opportunity to study enzyme replacement treatment in MPS I patients.

8.2 Physiologic Activity: Reduction in Lysosomal Storage

Reduction in hepatomegaly by liver MRI and decrease in urinary GAG excretion were assessed in all 3 studies.

Disease Relevance. Hepatomegaly and elevated urinary GAG excretion are relatively consistent features of MPS I that reflect excessive accumulation of GAG in the body. At baseline, 73% (32/44) of patients in the Phase 3 Double-Blind Study had hepatomegaly and all patients showed elevated urinary GAG levels. Reductions in these surrogate markers indicate that rhIDU is being taken up by tissues and that GAG is being cleared from the body.

Consolidated Findings. In the Phase 1/2 Study, treatment with rhIDU began to clear GAG from the liver as early as Week 2 by physical examination and as early as Week 6 by MRI. In the Phase 3 Double-Blind Study, patients treated with rhIDU showed an 18.9% reduction in liver volume after 26 weeks, followed by a 3.6 % reduction over the next 24 weeks, for a total reduction of 21.7% after weeks 50 weeks. The difference between the rhIDU and placebo treatment groups for percent change in liver volume after 26 weeks was statistically significant ($p=0.001$), favoring the rhIDU group. In the Phase 3 Open-Label Extension Study, the placebo/rhIDU patients showed a 12.6% reduction in liver volume, similar to but not quite as high as the rhIDU patients in the Phase 3 Double-Blind Study. The smaller reduction in size may be due to missed infusions or smaller normalized liver volumes in the placebo patients relative to rhIDU patients.

In the Phase 3 Double-Blind Study, there was a shift in liver volume from abnormal at baseline to normal at Week 26 in 72% (13/18) of rhIDU patients compared to 21% (3/14) of placebo patients, again providing evidence for an active treatment effect. In the Phase 3 Open-Label Extension Study, an additional 2 of 5 rhIDU/rhIDU patients shifted from abnormal to normal, such that after a total of 50 weeks of treatment, 80% of rhIDU/rhIDU patients (15/18) had shifted from abnormal to normal. In the placebo/rhIDU group entering the Phase 3 Open-Label

Extension Study, 10 patients had abnormal liver volumes at entry and 50% normalized by Week 24. In all, 64% (18/28) of patients normalized their liver volumes within 6 months of starting rhIDU treatment.

In the Phase 1/2 study, approximately 90% of patients normalized their liver volumes by Week 52 (9/10) and Week 104 (8/9) of treatment. This study met its primary endpoint of two-thirds of patients showing a ≥20% reduction in liver or spleen volume after 52 weeks of treatment. By Week 26, 80% (8/10) of patients had reduced their liver volumes by ≥20% and by 52 weeks the number was 70% (7/10). Spleen volumes also decreased, with 50% (5/10) of patients showing ≥20% reduction in spleen size at Weeks 26 and 52.

In the Phase 1/2 and Phase 3 Double-Blind Studies, a rapid and precipitous decline in urinary GAG excretion was observed by Week 4, with slow further reduction over several months to near normal age-specific levels. The decreases in urinary GAG levels from baseline were similar (approximately -60%) between patient groups following 6 to 12 months of rhIDU treatment. By the end of the Phase 3 Open-Label Extension Study, 6 patients in the rhIDU/rhIDU group and 3 patients in the placebo/rhIDU had achieved a normal GAG level. In the Phase 1/2 Study, 80% (8/10) patients had a ≥50% reduction in urinary GAG excretion, and 100% (9/9) of patients had a ≥50% reduction at Week 104.

Clinical Significance. Overall, large reductions in mean liver volume and urinary GAG level were observed for patients in all 3 clinical studies. Although hepatomegaly is considered a surrogate marker of disease, reduction in liver size may have several clinical benefits, including improved diaphragm excursion, ability to bend over, satiety, physical appearance (decreased clothing size), discomfort, and self-esteem. Patients in all 3 clinical studies reported that the reduction in organ size improved their comfort and ability to breathe and eat. The clinical benefit associated with a reduction in organ size was important to these patients.

The high percentage of patients who normalized their liver volumes and had near normal urinary GAG levels after 52 weeks of treatment suggests that the rhIDU dose regimen is effective in removing accumulated GAG from accessible tissues.

The test-retest accuracy of liver volume measured by MRI in the Phase 3 Double-Blind Study is approximately 10% (Bio-Imaging Technologies, Inc., Newtown, PA, USA), which would correspond to the minimal detectable treatment effect. In the Phase 3 Double-Blind Study, 82% (18/22) of rhIDU patients achieved a ≥10% reduction in liver volume versus 17% (4/23) of placebo patients. Conversely, 13% (3/22) of rhIDU patients showed ≥10% enlargement versus 22% (5/23) of placebo patients. Overall, there was a net improvement in liver volume in 68% (15/22) of rhIDU patients compared to a net decline in 4% (1/23) of placebo patients.

8.2.1 Benefit: Improvement in Respiratory Function

An improvement in respiratory function following treatment with rhIDU was demonstrated by the results of forced vital capacity (FVC) testing (co-primary endpoint in the Phase 3 Studies). Supportive data are available from the results of apnea/hypopnea testing (a secondary endpoint in both the Phase 3 and Phase 1/2 clinical studies) in more severely affected patients.

8.2.2 Percent Predicted Normal Forced Vital Capacity

Disease Relevance. Respiratory insufficiency is an important aspect of MPS I disease and is a major cause of morbidity and mortality. Patients exhibit reduced lung capacity that manifests functionally as a restrictive-type abnormality and clinically as hypoventilation syndrome, leading to atelectasis, pulmonary infections, and impaired gas exchange. In conjunction with airway obstruction, reduced lung capacity can lead to sleep apnea and hypoxemia. In the Phase 3 Double-Blind Study, 31% of patients had a history of lower respiratory tract infections and 24% a history of asthma/reactive airways disease. In addition, 9% reported the use of CPAP and 7% the use of nebulizers.

Thus, percent predicted FVC was selected as a clinical measure of restrictive lung disease and lung capacity. All patients enrolled in the study were required to have ≤ 80% of predicted FVC at baseline. The mean baseline FVC value, 51.4%, reflects loss of nearly half of vital lung volume and constitutes a moderate-to-severe restriction-type abnormality (ATS, 1991, Am Rev Respir Dis). Reduction in FVC is likely to be caused by several features of MPS I, including limitation of diaphragmatic excursion by hepatosplenomegaly, chest wall rigidity, spinal deformity, infiltration of the lung parenchyma with GAG, and premature closure of the glottis by redundant tissue during exhalation.

Consolidated Findings. Percent of predicted FVC was used as a measure of pulmonary function in both the Phase 3 Double-Blind and the Phase 3 Open-Label Extension Studies where it was 1 of 2 co-primary efficacy variables.

In the Phase 3 Double-Blind Study, the rhIDU group showed a 5.6 percentage point difference from placebo in percent of predicted FVC (median difference from placebo was 3.0 percentage points, $p = 0.009$). Following an additional 36 weeks of treatment, the rhIDU/rhIDU group maintained its prior improvement in FVC with a statistically significant 5.4 percentage point increase from baseline ($p = 0.001$). After 36 weeks of receiving Aldurazyme, the placebo/rhIDU patients showed a 2.6 percentage point increase in FVC compared to a –0.7 percentage point decrease in the placebo phase of the study. The smaller and delayed treatment response in placebo/rhIDU patients may be related to their relatively less pulmonary restriction (higher FVC) at baseline or other factors such as seasonal effects (assessments were done during winter), missed infusions, or values carried forward in the extension study.

An 11% relative change from baseline FVC was set as a threshold for a clinically significant change in individual patients according to ATS guidelines. In the Phase 3 Double-Blind Study, 41% (9/22) of rhIDU patients achieved this degree of improvement compared to only 9% (2/23) of placebo patients. Conversely, 4% (1/22) of rhIDU patients showed a decline in FVC by this degree compared to 13% (3/23) of placebo patients. Overall, there was a net improvement in FVC in 36% (8/22) of rhIDU patients versus a net decline in 4% (1/23) of placebo patients. On an individual patient basis, the majority of patients who showed a clinically significant improvement in FVC received rhIDU, while the majority of patients who showed a clinically significant decline in FVC received placebo.

Clinical Significance. The mean increase in percent of predicted FVC corresponds to a 10% relative improvement over baseline FVC of 48.4%, which is close to the 11% change considered by the American Thoracic Society (ATS) to be a clinically significant change and not due to week-to-week variability. (ATS, 1991, Am Rev Respir Dis) This improvement is even more meaningful given that MPS I is a progressive disorder and most patients in this study had moderate or severe restrictive lung disease. Much of the restriction in these MPS I patients is due to skeletal deformity that would probably not respond to treatment. Even so, the magnitude of change in lung function observed in this study is similar to changes in pulmonary function test measurements used to support the efficacy claims of approved drugs to treat asthma and cystic fibrosis [Flovent® Rotadisk® (fluticasone propionate inhalation powder), Serevent® Diskus® (salmeterol xinafoate inhalation powder), Singulair® (montelukast sodium), and Pulmozyme® (dornase alfa)].

8.2.3 Obstructive Sleep Apnea (AHI)

Disease Context. Upper airway obstruction is a significant contributor to morbidity and mortality in MPS I patients. The most important clinical manifestations are obstructive sleep apnea, which can lead to numerous medical and behavioral problems, and difficulty with intubation, which makes these patients high anesthesia risks. Sleep apnea may have several consequences, including excessive sleepiness, poor endurance, morning headaches, and, in children, neurobehavioral changes such as learning disabilities, attention deficit, and hyperactivity (American Academy Pediatrics, 2002). Systemic hypertension (Nieto, 2000, JAMA) as well as pulmonary hypertension with right-heart failure, are medical complications that correlate with AHI level.

Patients in the Phase 3 Double-Blind Study reported a prior history of, on average, 3 surgical procedures requiring sedation or general anesthesia, which poses a significant risk for these compromised patients At baseline, approximately half of the patients had AHI values suggestive of sleep apnea but only 9% were being treated with nasal CPAP. While under-diagnosis is the most likely explanation, a poorly fitting mask or an inability to tolerate CPAP are other

possibilities. Although most patients with MPS I do undergo tonsillectomy and adenoidectomy, which is the treatment of choice for sleep apnea in otherwise healthy children, patients are not rendered symptom-free long-term because of other obstructive airway components.

Consolidated Findings. Improvement in obstructive sleep apnea following treatment with rhIDU was demonstrated in all 3 studies.

The patients who showed the largest treatment effect were those who had an abnormal AHI at baseline (≥10 AHI for children, ≥15 AHI for adults). This subgroup of patients treated with rhIDU showed a mean decrease of 6.3 events per hour over the first 26 weeks of treatment, which is an improvement that was maintained through 50 weeks of treatment. The placebo/rhIDU patient subgroup showed a similar improvement with a mean decrease of 9.2 events per hour during the Phase 3 Open-Label Extension Study. The latter represents a 40% decrease, and a change in the mean AHI value to below 15, the Medicare threshold for initiation of CPAP (Tunis, 2001, Centers for Medicare and Medicaid Services Admin File).

In the Phase 1/2 Study, the methodology used to measure obstructive events was different than that used in the Phase 3 Studies, resulting in a different scoring system (normal AHI <1). Nevertheless, mean AHI decreased from 2.08 at pretreatment to a mean of 0.97 at Week 26, a 53% reduction, and 3 patients with clinically significant sleep apnea all improved.

Clinical Significance. The improvements in AHI seen in MPS I patients with sleep apnea who were treated with rhIDU are most likely due to a reduction in GAG substrates from the tissues surrounding the upper airway, thereby relieving airway obstruction. Although not formally assessed in the Phase 3 Studies, reduction in GAG in the tongue, pharynx, and trachea is expected to make the airway easier to intubate, thereby decreasing the risk of complications with anesthesia.

The minimum clinically significant change in AHI has not been established. A change in AHI of at least 10 events per hour is reasonable as it is above the test-retest variability of placebo-treated patients, similar in magnitude to the upper range of normal for children (10 events per hour) and adults (15 events per hour), and approximately 20% of the evaluable range for sleep apnea (10 to 60). In the Phase 3 Double-Blind Study, 44% (20/45) of patients had AHI scores suggestive of sleep apnea at baseline based upon an AHI ≥10 for pediatric patients and AHI ≥ 15 for adult patients. Using a threshold of change of at least 10 events per hour, 20% (4/20) of rhIDU patients improved compared to 10% (2/21) of placebo patients. Conversely, no rhIDU patient deteriorated compared to 14% (3/21) of placebo patients. Overall, there was net improvement in 20% (4/20) of rhIDU patients versus a net decline in 5% (1/21) of placebo patients.

8.3 Benefit: Improvement in Functional Capacity

An improvement in functional capacity following treatment with rhIDU was demonstrated by the results of the 6-Minute Walk Test (co-primary endpoint in the Phase 3 Studies) and the joint range of motion (ROM) testing (secondary and tertiary endpoints in the Phase 3 Studies and a secondary endpoint in the Phase 1/2 Study) in patients with more severe baseline disease. The results of the New York Heart Association (NYHA) classifications (secondary endpoint in the Phase 1/2 study) provide further evidence of improvements in functional capacity.

8.3.1 6-Minute Walk Test and NYHA Classification

Disease Relevance. Impaired mobility and ambulation is a prevalent and significant disability for patients with MPS I. As is the case for FVC, the ability to walk is likely affected by the varied symptoms of MPS I, including cardiorespiratory disease, hepatomegaly, musculoskeletal disease (bony deformities and joint contractures, stiffness, and pain), and spinal cord compression with myelopathy. Even though the Phase 3 Double-Blind Study patients predominantly had the intermediate form of MPS I disease, 31% (14/45) of patients used a wheelchair, 7% (3/45) used a walker, and 2% (1/45) used a cane. One-third of patients (15/45) were unable to walk more than 330 m in 6 minutes. Although no normative data exist in children, this 6-Minute Walk Test distance approximates the lower limit of normal for healthy adult women (310 m) (Enright, 1998, Respir Crit Care Med) and the lower limit of normal for "community ambulation" (332 m). (Robinett,1988, Phys Ther) (Menard-Rothe, 1997, J.Cardiopulm.Rehabil.). Independent community ambulation, defined as the ability to walk at a near normal speed of 80 m/min for 332 m, is considered to be functionally important for activities such as crossing a street or performing an errand in the neighborhood. In the Phase 3 Double-Blind Study, patients walked at a mean speed of 57 m/min at baseline. In the Phase 1/2 Study, patients also showed clinically significant functional limitations, with none of the 10 patients identified as Class I (no symptoms) in the NYHA Classification at baseline.

Consolidated Findings. The 6-Minute Walk Test was used as a measure of functional capacity in the Phase 3 Double-Blind and Phase 3 Open-Label Extension Studies, and the NYHA Classification was used as a measure in the Phase 1/2 Study. Patients showed increased functional capacity and endurance following 6 to 12 months of treatment with rhIDU.

Improvements in the 6-Minute Walk Test were consistent after initiation of rhIDU treatment in the Phase 3 Double-Blind and Open-Label Extension Studies. Patients treated with rhIDU in the double-blind study showed a 19.7 m mean increase after 26 weeks (median difference from placebo of 38.5 m, $p=0.066$ versus placebo). While this difference from placebo did not reach statistical significance in the primary analysis, statistical significance was reached in a pre-specified ANCOVA ($p=0.039$) that accounted for baseline differences between groups that might affect outcome, including center, baseline 6-Minute Walk Test, gender, height, and liver

volume. This treatment group showed an additional 20.3 m mean increase (p=0.146 versus entry value) after 36 more weeks of treatment, for a total mean increase of 40.0 m (p=0.005 versus baseline value) over 62 weeks. The placebo/rhIDU patients showed a 18.4 m mean decrease in the placebo phase followed by a 32.4 m mean increase in the 36-week rhIDU treatment phase (p = 0.023 versus entry value). The magnitude of change in placebo/rhIDU patients in the extension study is consistent with the treatment response of rhIDU patients in the Phase 3 Double-Blind Study.

In the Phase 1/2 study, the NYHA Classification improved in all patients after 52 weeks (n=10) and 104 weeks (n=9) of treatment. The mean change in NYHA Classification from baseline was statistically significant at Week 52 (p = 0.002) and was maintained through Week 104. With treatment, 50% of patients (5/10) improved to Class I after 52 weeks and 67% of patients (6/9) improved to Class I by 104 weeks.

Clinical Significance. The 38.1-m difference between groups after 26 weeks and the 42.9-m change within the rhIDU/rhIDU group after 50 weeks of rhIDU treatment in the Phase 3 studies are comparable to the 54-m difference (95% CI, 37 to 71 m) that is frequently cited in the literature as the minimal clinically significant difference perceived by individuals in the 6-Minute Walk Test. (Redelmeier, 1997, Am J Respir Crit Care Med). This distance was based on the testing of elderly adults with chronic obstructive pulmonary disease, as opposed to children with MPS I, and may overestimate the change needed to be perceived as clinically significant because of the shorter stride length in the younger and shorter MPS I patients who participated in these Phase 3 studies. This 54-meter difference is also considerably higher than the training effect observed during the 3 successive baseline evaluations of patients in the Phase 3 Double-Blind Study.

Using the 54-m threshold, a clinically significant improvement was seen in 41% (9/22) of rhIDU patients versus 13% (3/23) of placebo patients, whereas a ≥54 m decline was seen in 18% (4/22) of rhIDU patients versus 26% (6/23) of placebo patients. Overall, there was a net improvement in the 6-Minute Walk Test in 23% (5/22) of rhIDU patients versus a net decline in 13% (3/23) of placebo patients.

The 6-Minute Walk Test is among the most widely used sub-maximal exercise tolerance tests for patients with cardiovascular and pulmonary disease. The distance walked in 6 minutes is a strong independent predictor of morbidity and mortality in patients with congestive heart failure (Bittner, 1993, JAMA)(Shah, 2001, Am J Card) and with primary pulmonary hypertension (Miyamoto, 2000, Am J Respir Crit Care). Two pulmonary hypertension (HTN) medications [Tracleer™ (bosentan) and Flolan® (epoprostenol sodium)] have been approved with the 6-Minute Walk Test as the primary endpoint, with improvements similar to the mean change occurring in the Phase 3 Double-Blind Study. The 6-Minute Walk Test also has proved useful

for determining the appropriate time for lung transplantation in patients with a variety of pulmonary diseases (Kadikar, 1997, J.Heart Lung Transplant.) and correlates with the functional and hemodynamic severity of patients with peripheral arterial occlusive disease (Montgomery, 1998, Am J Geri Soc).

The improvements in the NYHA score were statistically significant and are intrinsically clinically meaningful based on the clinical status categories that the NYHA score represents.

8.3.2 Shoulder Flexion and other Joint Range of Motion

Disease Relevance Joint stiffness and pain is a prevalent feature of MPS I disease that limits activities of daily living and mobility. Reduced joint ROM is a physiologic consequence of accumulation of GAG in the synovium, periarticular connective tissues as well as secondary bony changes. At baseline in the Phase 3 Double-Blind Study, 78% of patients complained of joint stiffness, 53% of joint contractures, and 31% of joint pain. Mean shoulder flexion was 92.7 degrees, which approximate the horizontal and reflect significant limitation. Using 150 degrees as the lower limit of the normal range for shoulder flexion (Norkin C.C, 1995, Allied Health: Jean-Francois Vilain), 98% (44/45) of patients showed reduced flexion, and 60% (27/45) had flexion less than 100 degrees.

Consolidated Findings. Increased shoulder flexion and other joint ROM were observed in all 3 studies and treatment over longer period of times in the Phase 1/2 patients showed more improvement than treatment after shorter periods of time.

In the Phase 3 Double-Blind Study, when shoulder flexion was evaluated in all patients, or in all patients except for two with symptomatic cervical cord compression, there was a modest mean treatment effect in favor of rhIDU-treated patients but the primary analysis was not statistically significant. Based on the earlier results from the Phase 1/2 Study in which more severely restricted patients showed greater improvement, patients with greater shoulder restriction at baseline of the Phase 3 Double-Blind study (below the median subset) were analyzed and showed an almost 10-degree mean increase in the rhIDU group compared to a 5-degree decrease in the placebo group. The change was still not statistically significant. In the Phase 3 Open-Label Extension Study, patients with more severely restricted shoulder flexion in the rhIDU/rhIDU group showed a mean increase in shoulder flexion of 6.6 degrees from Week 24 to Week 50, for a total mean increase of 8.7 degrees after 50 weeks. The placebo/rhIDU group showed a mean increase of 15.2 degrees from entry to Week 24.

In the Phase 1/2 Study, right and left shoulder flexion improved by 10.75 and 8.25 degrees, respectively, after 26 weeks and by 28.13 ($p<0.001$) and 26.12 degrees ($p<0.002$), respectively, by Week 52. In both the Phase 3 and Phase 1/2 Studies, rhIDU-treated patients also demonstrated trends or significant improvements in other joint ROM measures (shoulder

extension, knee flexion/extension, and elbow extension) with patients showing severe joint restriction at baseline demonstrating larger improvements.

Clinical Significance. Shoulder function is necessary for self-care skills and functional independence and, for patients with significant shoulder restriction, increased active joint ROM is prerequisite for improved shoulder function. Joint function is also an important component of walking and functional capacity. The combination of improvements observed in joint range of motion suggest that patient mobility is overall improved with rhIDU. Based on the results of long-term treatment with rhIDU in the Phase 1/2 study, joint range of motion is expected to continue to improve with time.

8.4 Supporting Measures of Benefit

In addition to effects on lysosomal storage, respiratory function, and functional capacity, individual patients showed improvement in a number of other important parameters of the disease. Results from the following secondary and tertiary efficacy endpoints in the 3 clinical studies support the ability of treatment with rhIDU to limit or reverse the progressive nature of the disease.

Quality of Life (QoL) Assessments. Changes in the CHAQ/HAQ disability index were not significant after 24 or 26 weeks or rhIDU treatment. After 50 weeks, however, rhIDU/rhIDU patients showed a decrease of 0.3 points on a 3-interval scale. This 10% decrease approximates the minimal clinically important difference. Similarly, in the patients treated with rhIDU for 50 weeks during the Phase 3 Open-Label Extension Study, there were several physical and general health domains in the patient Childhood Health Questionnaire (CHQ)-CF-87 assessment that showed improvements. Patients treated for 26 weeks in the Phase 3 Double-Blind Study or for 24 weeks in the Open-Label Extension Study did not show clinically significant changes in either the parent CHQ-PF-50 or the patient CHQ-CF-87, suggesting that these improvements take time and are not a placebo effect. Although no formal measures of QoL were assessed, the patients in the Phase 1/2 Study reported improvements in daily activity levels.

Visual Acuity. In the Phase 3 Double-Blind Study, a 2-line improvement in visual acuity was observed in 5/22 rhIDU patients compared to none of the placebo patients. In the Phase 3 Open-Label Extension Study, a 2-line improvement in visual acuity was observed in 3/22 rhIDU/rhIDU patients and in none of the placebo/rhIDU patients.

In the Phase 1/2 Study, four patients did not have significant visual impairment at baseline. The 3 patients with the worst visual acuity at pretreatment all showed improvement in at least 1 eye .

A Responder Analysis Based on a Composite Endpoint Approach. The variation in disease manifestations and severity in this population makes the evaluation of these clinical data more challenging. At baseline, patients had different levels of disease severity, making it difficult to

study all endpoints in the same group of patients. To address this patient-to-patient heterogeneity and to evaluate clinical efficacy at the level of the individual patient, a composite endpoint was developed and a responder analysis was applied to the Phase 3 Double-Blind Study and the Phase 3 Open-Label Extension Study data. This analysis evaluated individual patient improvements above a clinically meaningful threshold in 5 different domains: pulmonary function (FVC), functional capacity (6-Minute Walk Test), obstructive sleep apnea (AHI), joint range of motion (shoulder flexion), and visual function (acuity). A responder is defined as a patient who shows net improvement. The analysis allowed patients to be assessed on the basis of their unique constellation of symptoms and provided an independent and complementary analysis of the efficacy data.

Specifically, there were 59% (13/22) responders in the rhIDU group compared to 22% (5/23) in the placebo group ($p = 0.016$). Most rhIDU-treated patients improved in more than 1 domain and showed net overall improvement (1.00 domains per patient), whereas most placebo patients showed little improvement with an average decline in 1 domain and a slight net decline overall (-0.39 domains per patient). The assessments that most clearly distinguished patients in the 2 groups in terms of a rhIDU treatment effect were FVC and the 6-Minute Walk Test.

The responder analysis was further validated by finding (1) nearly twice the number of responders in the placebo/rhIDU group in the Phase 3 Open-Label Extension Study as compared to the Phase 3 Double-Blind Study (39% vs. 22%); and (2) a high concordance of responders who received rhIDU treatment for 26 weeks versus 50 weeks.

8.5 Risks of Recombinant Human α-L-Iduronidase Treatment

The potential risks associated with the use of rhIDU treatment are consistent with those risks seen with the administration of proteins, in general, and are primarily immunological in nature. In general, infusion-associated reactions (IAR) in the rhIDU studies were mild in nature and, when necessary, were managed with rate reduction/temporary discontinuation and medicinal treatment either during the reaction or prior to subsequent infusions.

Adverse events on non-infusion days were generally related to the underlying disease and did not reveal any specific rhIDU-related risks. None of the patients in the clinical studies experienced classical IgE-mediated reactions which commonly manifest acutely at the onset of an infusion as severe respiratory compromise, hypotension and other systemic symptoms.

One patient in the Phase 3 Open-Label Extension study with a history of a compromised airway developed an immune response that presented primarily as angioedema, which resulted in an acute respiratory arrest necessitating placement of a tracheostomy. This reaction occurred 3.5 hours after initiation of the infusion and was not consistent with an IgE-mediated immune response. Although the angioedema was most likely triggered by rhIDU treatment via IgG

antibodies, the compromised airway in this patient was a significant factor in the patient's respiratory event.

The safety findings noted in the rhIDU clinical program indicate that the primary risk associated with rhIDU treatment is the occurrence of IARs during administration of the infusion. IARs are manageable with rate modifications and/or medicinal treatment/pre-treatment. Care must be taken to intermittently assess underlying medical conditions prior to infusion administration, in particularly the patient's respiratory status, to ensure that otherwise non-serious IARs do not exacerbate the underlying medical condition and contribute to serious clinical outcomes.

8.6 Risk/Benefit Conclusions

rhIDU reduces lysosomal storage and provides significant clinical benefit to MPS I patients. The in vitro and canine MPS I model data demonstrate the potency and efficiency of the uptake of rhIDU and its effects on reduction of lysosomal storage. Clinical studies have demonstrated a parallel effect in reducing lysosomal storage in patients, with a rapid reduction and normalization of liver enlargement and a reduction in urinary GAG excretion. Consistent with these reductions in lysosomal storage, the studies demonstrate clinical benefit in a variety of endpoints. Improvements were observed in respiratory function (FVC and sleep apnea), functional capacity (6-Minute Walk Test, NYHA classification, and joint ROM), and a variety of less common problems. Given the progressive nature of the disease, the heterogeneity of patients in terms of disease manifestation and age, and the challenges in reversing the chronic effects caused by years of lysosomal storage, these improvements represent important clinical benefit to MPS I patients. The risks of the treatment primarily relate to infusion-associated reactions that were manageable and not life-threatening.

MPS I disease represents an unmet medical need because the currently available treatments are not satisfactory for the majority of patients with MPS I. The data show that enzyme replacement therapy with rhIDU improves many clinical aspects of the disease and reduces lysosomal storage as well. The safety and efficacy data provided in this application combine to support a positive risk-benefit profile for rhIDU.

9. REFERENCES

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APPENDIX I

Rationale for the Composite Endpoint

To address the high degree of variability in the presenting symptoms of study patients at baseline, a composite clinical efficacy endpoint has been developed to evaluate the treatment effect of rhIDU in individual MPS I patients. A composite clinical efficacy endpoint has the potential to overcome many of the challenges of traditional study designs involving between-group differences in single endpoints. This approach differs from the traditional analysis employed in the Phase 3 Double-Blind Study (single endpoints for single clinical measures) by capturing clinical benefit across multiple domains simultaneously. Following treatment, each patient is assessed for the ability to achieve a threshold of clinically significant change in several domains of equal weight, and the net change is defined as the overall treatment effect. Clinically significant increases (improvement) and decreases (decline) in functional status are both important determinants of clinical benefit.

Two complementary outcome variables of a composite endpoint analysis are the net change per patient and the proportion of responders. Net change per patient captures the breadth of the treatment effect across multiple domains, whereas the responder analysis captures the breadth of the treatment effect across patients. A responder is defined as a patient who shows net improvement, such that the number of domains with clinically significant improvement is greater than the number of domains with clinically significant decline. Conversely, a non-responder is a patient who shows no net improvement, such that the number of domains with clinically significant improvement is less than or equal to the number of domains with clinically significant decline.

Description and Rationale for the Domains of the Composite Endpoint

Pulmonary Function

Threshold: The threshold for a clinically significant change was ≥11% in FVC.

Domain Validity: Respiratory insufficiency was an important aspect of MPS I disease and was a major cause of morbidity and mortality. Patients exhibit reduced lung capacity that manifests functionally as a restrictive-type abnormality and clinically as hypoventilation syndrome, leading to atelectasis, pulmonary infections, and impaired gas exchange. In conjunction with airway obstruction, reduced lung capacity can lead to sleep apnea and hypoxemia. Patients with significant respiratory insufficiency may require supplemental oxygen or assisted ventilation. In the Phase 3 Double-Blind Study, 31% of patients had a history of lower respiratory tract infections and 24% a history of asthma/reactive airways disease. In addition, 9% reported the use of continuous positive airway pressure (CPAP) and 7% the use of nebulizers. Thus, FVC was selected as a clinical measure of restrictive lung disease and lung capacity. All patients enrolled

in the study were required to have ≤80% of predicted FVC at baseline. The mean baseline FVC value, 51.4%, reflects loss of nearly half of vital lung volume and constitutes a moderate-to-severe restriction-type abnormality (American Thoracic Society, 1991, Am Rev Respir Dis). Reduction in FVC is likely to be caused by several features of MPS I, including limitation of diaphragmatic excursion by hepatosplenomegaly, chest wall rigidity, spinal deformity, infiltration of the lung parenchyma with glycosaminoglycans (GAGs), and premature closure of the glottis by redundant tissue during exhalation.

Review of the cross-sectional baseline data from the 45 MPS I patients enrolled in the Phase 3 Double-Blind Study shows that FVC increases during childhood and adolescence at a much slower rate than normal, leading to a decline in the percent of predicted FVC with age (Figure 18 and Figure 19). For these patients, the rate of increase in raw FVC was approximately 100 cc per year, or approximately 40% of the normal rate of 250 cc per year (calculated from (Hankinson, 1999, Am J Respir Crit Care Med). The percent of predicted normal FVC declined by approximately 4 percentage points per year instead of remaining at the same level. Patients described as having intermediate MPS I disease (Hurler-Scheie syndrome) were all less than 25 years old, and death in this group of patients typically occurs by adolescence or early adulthood. The few patients over the age of 25 years who participated in the Phase 3 Double-Blind Study carried the diagnosis of Scheie syndrome, the milder disease manifestations of which accounts for their higher percent of predicted normal FVC.

Figure 18: Baseline FVC Versus Age in MPS I Patients

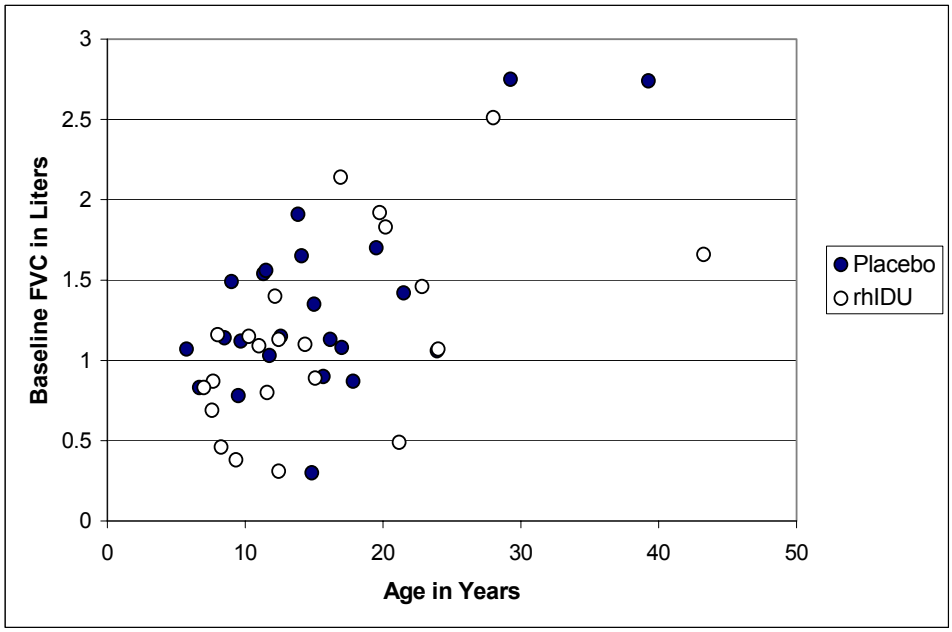
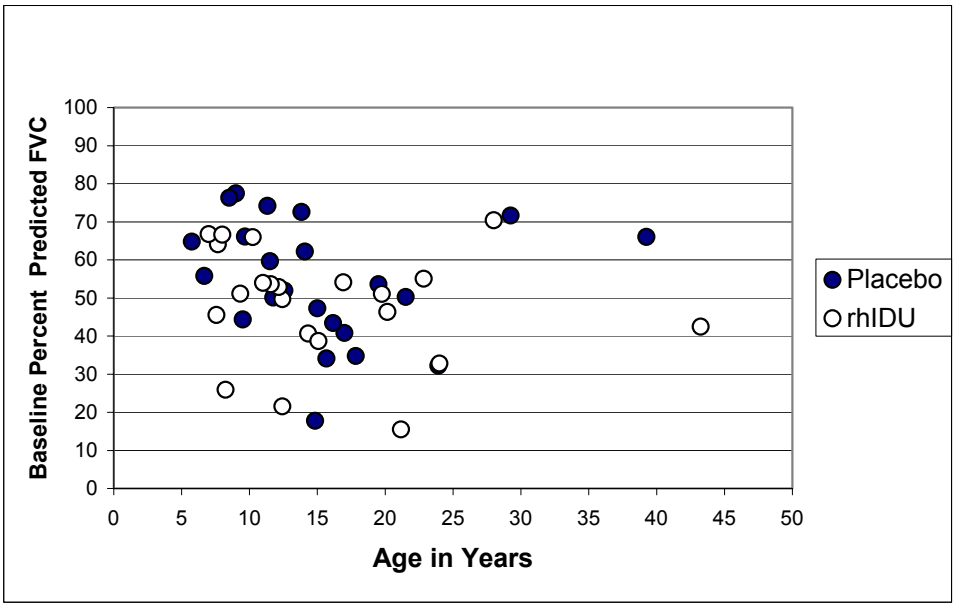


Figure 19: Baseline Percent of Predicted FVC Versus Age in MPS I Patients



Assessment Validity: FVC can be reliably measured by spirometry according to ATS guidelines (American Thoracic Society, 1995, Am J Respir Crit Care Med). The best of the 3 highest values within 5% of each other is recorded. Longitudinal assessments are repeated during the same time of day to minimize intraday variability. The percent of predicted FVC is calculated using published regression equations that take into account age, gender, race, and standing height (Polgar G, 1971, WB Saunders)(Hankinson, 1999, Am J Respir Crit Care Med). Because no regression equation spans the entire age range of affected patients, Polgar was used from ages 5 to 7, and Hankinson was used from age 8 and above. Changes in FVC of a magnitude similar to that observed in the Phase 3 Double-Blind Study have been used to support the efficacy claims of approved drugs to treat asthma and cystic fibrosis (Flovent® Rotadisk® [fluticasone propionate inhalation powder], Serevent® Diskus® [salmeterol xinafoate inhalation powder], Singulair® [montelukast sodium], and Pulmozyme® [dornase alfa]).

Threshold Validity: The FVC threshold was a modification of the ATS guidelines for normal adults, which uses an 11% change in raw FVC with a minimum change of 200 cc as a clinically significant change over several weeks to months (American Thoracic Society, 1991, Am Rev Respir Dis). For the composite endpoint study, the minimum change of 200 cc FVC volume was removed from the threshold criteria because this absolute change was intended for normal adults who have much larger lung volumes, and it is not appropriate for a predominantly pediatric study population of patients who have a syndrome that causes short-trunk dwarfism.

6-Minute Walk Test

Threshold: The threshold for a clinically significant change was ≥54 m in the 6MWT.

Domain Validity: Impaired mobility and ambulation was a prevalent and significant disability for patients with MPS I. As is the case for FVC, the ability to walk was likely affected by the varied symptoms of MPS I, including cardiorespiratory disease, hepatomegaly, musculoskeletal disease (bony deformities and joint contractures, stiffness, and pain), and spinal cord compression with myelopathy. Even though the Phase 3 Double-Blind Study patients predominantly had the intermediate form of MPS I disease, 31% (14/45) of patients used a wheelchair, 7% (3/45) used a walker, and 2% (1/45) used a cane. One-third of patients (15/45) were unable to walk more than 330 m in 6 minutes. Although no normative data exist in children, this 6MWT distance approximates the 310 m lower limit of normal for healthy adult women (Enright, 1998, Am J Respir Crit Care Med) and the 332 m lower limit of normal for "community ambulation" (Robinett, 1988, Phys Ther)(Menard-Rothe, 1997, J Cardiopulm Rehabil). Independent community ambulation, defined as the ability to walk at a near normal speed of 80 m/min for 332 m, is considered to be functionally important for activities such as crossing a street or performing an errand in the neighborhood. In the Phase 3 Double-Blind Study, patients walked at a mean speed of 57 m/min at baseline.

Assessment Validity: The 6MWT can be performed in a standardized manner and is among the most widely used submaximal exercise tolerance tests for patients with cardiovascular and pulmonary disease (Enright, 1998, Am J Respir Crit Care Med). The distance walked in 6 minutes is a strong independent predictor of morbidity and mortality in patients with congestive heart failure (Bittner, 1993, JAMA)(Shah, 2001, Am J Cardiol) and with primary pulmonary hypertension (Miyamoto, 2000, Am J Respir Crit Care Med). Two pulmonary hypertension (HTN) medications (Tracleer™ [bosentan] and Flolan® [epoprostenol sodium]) have been approved with the 6MWT as the primary endpoint, with improvements similar to the mean change occurring in the Phase 3 Double-Blind Study. The 6MWT also has proved useful for determining the appropriate time for lung transplantation in patients with a variety of pulmonary diseases (Kadikar, 1997, J Heart Lung Transplant) and correlates with the functional and hemodynamic severity of patients with peripheral arterial occlusive disease (Montgomery, 1998, J Am Geriatr Soc).

Threshold Validity: In the literature, a 54-m change (95% confidence interval: 37 to 71 m) in the 6MWT was the minimum noticeable change in a pulmonary rehabilitation study of adults with chronic pulmonary obstructive disease (COPD) who were able to walk between 100 and 300 m at baseline (Redelmeier, 1997, Am J Respir Crit Care Med). In discussion with experts, the 54-m change was felt to be a valid change for children as well as patients with baseline

distances outside of the 100 to 300 m range. The 54-m threshold is much higher than the observed 15 to 20 m training effect observed at baseline in the Phase 3 Study.

Shoulder Flexion Range of Motion

Threshold: The threshold for a clinically significant change was ≥20 degrees in mean shoulder flexion ROM.

Domain Validity: Joint symptomatology was a prevalent feature of MPS I disease that limits activities of daily living and mobility. Reduced joint ROM was a physiologic consequence of accumulation of GAG in the synovium as well as secondary bony changes. At baseline in the Phase 3 Double-Blind Study, 78% of patients complained of joint stiffness, 53% of joint contractures, and 31% of joint pain. Mean baseline shoulder flexion was 92.7 degrees, which approximates the horizontal and reflect significant limitation. Using 150 degrees as the upper limit of the normal range for shoulder flexion (Norkin, 1995, Allied Health: Jean-Francois Vilain), 98% (44/45) of patients showed reduced flexion, and 60% (27/45) had flexion less than 100 degrees. Nevertheless, there was a wide range of variability in shoulder flexion at baseline, and a positive trend in treatment effect was observed only in patients with more severe restriction at baseline, i.e., below the median.

Assessment Validity: Goniometry is the most commonly used method to accurately measure joint ROM. Unlike passive ROM measurements in which the examiner manipulates the shoulder through the full ROM, active ROM depends on the effort of the patient and reflects the patient's own ability to move his/her shoulder. The test-retest accuracy of goniometric shoulder measurements is considered to be 5 to 10 degrees (Marx, 1999, J Hand Surg), whereas in the Phase 3 study it was approximately 15 degrees. As the same examiner performed all ROM assessments on the same patient, the higher variability is likely due to difficulty in the positioning of or changes in effort by chronically ill patients.

Shoulder ROM is one of the main components of several widely used scoring systems to assess shoulder function, e.g., the Constant score (Constant, 1987, Clin Orthop) and the American Shoulder and Elbow Surgeons scale (Richards, 1994, J Shoulder and Elbow Surg). In these 2 scoring systems, points are awarded when patients are able to cross over predefined 30-degree category increments of shoulder flexion. These scales are commonly used for monitoring the success of surgical intervention in which a large functional change is expected in a relatively short time period. The degree of change in joint ROM following surgery is expected to occur faster than with enzyme replacement therapy. Because the overall scores of these scales also takes into account changes in strength, pain, and patient well being, they are not expected to be as sensitive to change in patients with MPS I, in whom restriction of joint ROM is the predominant impairment.

Threshold Validity: A change of ≥20 degrees in shoulder ROM is proposed as the minimal clinically significant change in MPS I patients. This amount of change is greater than the variability of the assessment.

Apnea-Hypopnea Index

Threshold: The threshold for a clinically significant change was ≥10 events/hour within age-appropriate evaluable ranges.

Domain Validity: Sleep apnea in MPS I primarily resulted from airway obstruction, which was an important contributor to MPS I morbidity and mortality. Accumulation of GAGs leads to an enlarged tongue, tonsils, and adenoids, and importantly narrowing of the trachea. Intubation is particularly difficult because of the redundant tissue, and several patients have died as a result of failed intubation. In the Phase 3 study, 44% (20/45) of patients had AHI scores suggestive of sleep apnea at baseline using the recommended thresholds of AHI≥10 for children and AHI≥15 for adults.

Assessment Validity: Discussion with sleep study experts led to the choice of the sleep study parameter AHI as the most objective measure of obstructive sleep apnea. Sleep studies may be reliably performed and the test-retest variability is low in both adults and children. Apnea and hypopnea have been defined for children and adults, and sleep study experts indicated that abnormal ranges would be an AHI score ≥10 for patients ≤15 years and an AHI score ≥15 for patients >15 years, based on recently published guidelines for evaluating obstructive sleep apnea-hypopnea syndrome (Goodwin, 2001, Sleep)(Tunis, 2001, Centers for Medicare and Medicaid Services Admin File). Medicaid guidelines reimburse for nasal CPAP in adults with sleep study AHI≥15 (Tunis, 2001, Centers for Medicare and Medicaid Services Admin File). A recent position paper from American Academy of Pediatrics advises pediatricians to screen for sleep apnea if a child snores and to consider intervention if the AI>1 (American Academy of Pediatrics, 2002, Pediatrics). In adults, obstructive sleep apnea leads to a variety of symptoms, the most common of which are excessive daytime sleepiness, poor concentration, and morning headaches. In children, obstructive sleep apnea may manifest clinically as hyperactivity, attention deficit disorder, and learning difficulties. Medical sequelae that may result from sleep apnea include hypertension and cor pulmonale.

Threshold Validity: A successful response rate for surgery in relieving sleep-disordered breathing is considered to be a 50% reduction in AHI with a post-surgical AHI <20 (Sher, 1996, Sleep). This threshold is more empiric than evidence-based and is more appropriate for a one-time surgical intervention to remove local areas of obstruction e.g., enlarged tonsils. A change in AHI of at least 10 events per hour is reasonable as it is above the test-retest variability of placebo-treated patients, similar in magnitude to the upper range of normal for children (10 events per hour) and adults (15 events per hour), and approximately 20% of the evaluable

range for sleep apnea (10 to 60). Instead, after discussion with sleep study experts, a minimum change of 10 events/hr with a 25% reduction in AHI wasproposed as reflecting clinical significant change within age-appropriate evaluable ranges. The evaluable range for patients ≤15 years old is10 to 60 events/hr, and the evaluable range for patients >15 years old is 15 to 60 events/hr. Changes that cross the lower and upper limits also are considered to be evaluable using the same threshold for change, but changes that fall entirely outside of these ranges are not considered to be clinically significant.

Visual Acuity

Threshold: The threshold for a clinically significant change was ≥2 lines on a standardized visual acuity chart.

Domain Validity: Decreased visual acuity is commonly found in patients with MPS I and can 7be exacerbated by other problems such as corneal clouding, retinal dysfunction, and glaucoma. Vision is considered to be one of the basic senses and is important for reading, driving, and other daily activities. In the Phase 3 study, a significant proportion of patients had visual impairment, which despite correction with glasses, remained below normal. Following treatment for 26 weeks, visual acuity improved significantly in both eyes of 5/22 patients who received rhIDU versus 0/23 who received placebo.

Assessment Validity: Visual impairment has been associated with decreased quality of life and is considered to be a disability (Cochiarella and Andersson, 2001, Guides to the Evaluation of Permanent Impairment). Best-corrected visual acuity testing in patients with impaired vision can be reliably performed using standardized acuity charts.

Threshold Validity: A change of at least 2 lines in visual acuity is considered to be clinically significant (Ferris, III, 1982, Am J Ophthalmol)(Lovie-Kitchin, 1988, Ophthalmic Physiol Opt.)(Reeves, 1993, Ophthalmic Physiol Opt.). Since enzyme replacement therapy is a systemic treatment that should affect both eyes equally, the threshold for change is a 2-line change in visual acuity for both eyes. A 2-line change in 1 eye with less than a 2-line change in the other eye, or, 2-line changes of opposite magnitude in different eyes of the same patient are more difficult to interpret, and thus, are recorded as no significant change.