Protocol BIO7500-001: Enzyme Replacement Therapy in the Treatment of Mucopolysaccharidosis I.

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Investigators and Study Center(s)

Initially, patients were treated at a single center in the United States. Subsequently patients were allowed to be treated at 11 regional centers near their homes. Patients returned to the initial center for efficacy evaluations.

Studied Period

First Patient Enrolled 28 November 1997
Last Patient Completed 29 March 2001
Study Duration: Ongoing
Report Period: 152 weeks

Phase of Development

Phase 1/2

Objectives

To demonstrate the safety and efficacy of recombinant human α-l-iduronidase (laronidase) in the reduction of lysosomal storage in the human genetic disease mucopolysaccharidosis I (MPS I).

Methodology

This study was conducted as an open-label study with patients serving as their own controls. Up to 10 patients could be enrolled to ensure that at least 6 evaluable patients completed the initial 26 weeks of treatment. Patients underwent baseline studies of their disease status. These studies included MRI evaluations of liver and spleen volume, urinary glycosaminoglycan (GAG) excretion, assessments of joint movement, cardiac, and airway function, visual acuity, CNS abnormalities, bone disease, and height and weight. Recombinant human α-L-iduronidase (laronidase) in doses of 100 U/kg (0.58 mg/kg) was administered by slow intravenous infusion once weekly. After 6 weeks of treatment at the initial center and barring any safety concerns, the patients were allowed to return home. A coordinating principal investigator near the patient's home continued weekly enzyme administration for the subsequent weeks. At Weeks 12, 26, 52, and 104, the patients returned for efficacy assessments at the initial center.. Safety monitoring and urinary GAG excretion determinations were performed throughout the study period.

Number of Patients (Planned and Analyzed)

10 patients planned, 10 patients enrolled and treated. At week 152, 8 patients on study. All 10 patients evaluated for efficacy, safety and pharmacokinetics.

Diagnosis and Main Criteria for Inclusion

Male and female patients, aged 5 years and over, with a diagnosis of mucopolysaccharidosis I (MPS I) confirmed by clinical and enzymatic assessments. Patients must have had significant physical disease indicative of the disorder, including enlarged liver or spleen size based on expected size normalized for body weight, and elevated urinary GAG levels

Test Product, Dose, and Mode of Administration

Laronidase 100 U/kg (0.58 mg/kg) was infused intravenously over a 3- to 4-hour period.

Duration of Treatment

One 3- to 4-hour infusion per week for 152 weeks

Reference Therapy, Dose and Mode of Administration

None.

Criteria for Evaluation
Efficacy

Primary Efficacy Endpoints The primary efficacy endpoint was a reduction in lysosomal storage at Week 52 as observed by a change in liver or spleen volume (measured through Week 104 only) and by measurement of urinary GAG levels (through Week 152).

Hepatosplenomegaly Hepatosplenomegaly in each patient was considered significantly reduced if the total size of either the liver or the spleen or both was reduced from pretreatment by 20% at Week 52. The treatment was considered effective if at least two-thirds of the patients showed a 20% reduction in liver and/or spleen size by Week 52. Assessments were made at pretreatment and Weeks 6, 12, 26, 52 and 104.

Urinary GAG excretion Urinary GAG in each patient was considered significantly reduced if the level decreased from pretreatment by at least 50% at Week 52. The percent reduction in urinary GAG excretion was calculated by comparing the average of the pretreatment urinary GAG samples with the average of urinary GAG measurements from the measurements taken in the 6 weeks prior to Week 52. The treatment was considered effective if at least two-thirds of the patients completing the study showed a 50% reduction in urinary GAG at Week 52. Urinary GAG assessments were performed at pretreatment and weekly through Week 6, every 2 weeks through Week 26, every 4 weeks through Week 52, and at least every 12 weeks through Week 152.

Secondary Efficacy Endpoints The secondary measures of efficacy evaluated during the study included joint range of motion (ROM) (goniometry), cardiac function (New York Heart Association (NYHA) class, cardiac physical examination, chest X-ray, ECG, echocardiogram), airway obstruction, and eye disease. Secondary endpoint assessments were performed at pretreatment and at Weeks 12, 26, 52, and 104, except for sleep studies, which were performed at pretreatment and Week 26, and, if still abnormal, at Week 52 and Week 104. Additional measures of efficacy determined to be of importance to MPS I patients included CNS abnormalities (MRI, opening pressure during lumbar puncture), bone evaluations, and height and weight growth in prepubertal patients. Brain MRI and bone evaluations were performed at pretreatment and at Weeks 12, 26, 52, and 104. Lumbar puncture, when not contraindicated, was performed at pretreatment and Week 26. Height and weight were measured at pretreatment, Weeks 6, 12, 26, 52, and 104 at Harbor-UCLA and throughout the study period at the local investigator sites. Historical data on height and weight were collected to establish a pretreatment growth rate for prepubertal patients.

Safety

Adverse events were monitored throughout the study. Complete blood counts, chemistry panels, urinalysis (including microscopic UA) were performed at pretreatment and weekly through Week 6, every 2 weeks through Week 26, every 4 weeks through Week 104, and every 12 weeks through Week 152. ECG monitoring and pulse oximetry were performed during enzyme infusions for the first 26 weeks. From Week 27 to 104, only pulse oximetry was performed unless an ECG was clinically indicated. After Week 104, pulse oximetry was not required unless an adverse event related to study drug occurred. Pulse oximetry was then required for 12 weeks following the AE. Blood was collected for determination of serum IgG antibodies to laronidase product prior to the first 3 infusions, every 2 weeks through Week 26, every 4 weeks through Week 52, and every 12 weeks through Week 152. Complement studies were performed at pretreatment, Weeks 4, 6, 12, 26, 52, and 104.

Pharmacokinetics

Standard measurements of pharmacokinetics of α I-iduronidase (IDU) were assessed, including $Cmax_{(obs)}$, $Tmax_{(obs)}$, $AUC_{(0-t)}$, $AUC_{(0-\infty,)}$, CL, V_{ss}, $t_{1/2}$, and MRT, at pretreatment and Weeks 1, 2, 6 (2 patients), 12, and 26.

Tissue Uptake

Buccal IDU measurements were made weekly through Week 6, every 2 weeks through Week 26, every 4 weeks through Week 52, and every 12 weeks or as indicated by an abnormality, through Week 104. Leukocyte IDU measurements were made at pretreatment and at Weeks 2, 6, 12, and 26.

Statistical Methods

Inferential tests were performed on primary and secondary efficacy variables through Week 52. Descriptive statistics only are provided for assessments at Week 104 (and Week 152 for urinary GAG)

Efficacy
Primary Efficacy Variables

Hepatosplenomegaly and Urinary GAG The following statistical analyses were performed on the primary measures of efficacy. A repeated measures analysis of variance (ANOVA) was performed on each of the normalized assessments separately (ie, liver volume, spleen volume, and urinary GAG assessment), including terms for patient and week (ie, pretreatment, Weeks 6, 12, 26, 52). Liver and spleen volumes and urinary GAG levels are described at Weeks 104 and 152.

Secondary Efficacy Variables

Joint ROM The patients were measured at full extension of the left and right elbow, shoulder, and knee joints at pretreatment and Weeks 6, 12, 26, 52, and 104. Measurements were also taken at full flexion for the right and left shoulder and knee joints. A repeated measures ANOVA was performed at Weeks 12, 26, and 52, including a linear trend over time. The measurements, the degrees of restriction, and percentage restriction were separately summarized for the left and right sides, including changes from pretreatment (mean, median, sd, minimum, maximum, n) by week, through Week 104.

Cardiac Function A scoring system for cardiac function was developed that combined cardiac physical exam, CXR, ECG, NYHA score, and ECHO findings to determine a severity score. The scoring system was applied to each patient at pretreatment and Weeks 12, 26, 52, and 104. A repeated measures ANOVA was performed for total cardiac function score, pulmonary hypertension score, and valvular regurgitation score for Weeks 12, 26, and 52. The cardiac function, pulmonary hypertension, valvular regurgitation, and NYHA class scores were summarized, including changes from pretreatment (mean, median, sd, maximum, minimum, n) by week, through Week 104. Changes in NYHA class scores from baseline were subjected to a Wilcoxon paired signed rank test at each assessment separately, through Week 52.

Airway Obstruction Sleep studies were performed at pretreatment and at Week 26. Week 52 and 104 assessments were made only if the previous assessment was abnormal. The number of apneas, hypopneas, hypoxic events, and the apnea-hypopnea indices (AHI) during sleep studies were summarized. Tongue diameter and airway index were recorded and summarized from MRIs performed at pretreatment and Weeks 6, 12, 26, 52, and 104.

Eye Disease Visual acuity testing and complete ophthalmology examinations were performed at pretreatment and Weeks 12, 26, 52, and 104. Data were summarized for each visit.

Safety

Additional Measures Data for CNS abnormalities and bone evaluations were summarized. Height and weight were recorded at least every 4 weeks to Week 104 and at least every 12 weeks between Week 105 and Week 152. However, for consistency in methodology of measurement, only measurements taken at Harbor-UCLA, where a standardized procedure was used, are included in the comparisons to the pretreatment measurements. For each prepubertal patient, pre- and posttreatment height growth rates were calculated using linear regression and compared using a paired t-test. A similar method was used to assess the weight growth rates. Historical heights and weights were collected at pretreatment.

Summary – Conclusions
Patient Population

There were 6 males and 4 females in this study. At enrollment, patients ranged in age from 5 to 22 years, with a mean of 12.3 (sd: $\pm$ 5.2 years). They had a mean height of 130.62 cm (sd: $\pm$ 22.29; range 87.0-160.0 cm) and mean weight of 36.20 kg (sd: $\pm$ 16.99; range 14.8-64.5 kg). All 10 patients were white (Caucasian).

Additional Analyses

CNS Abnormalities The patient who had the most severe developmental regression at pretreatment showed improvement initially, but worsened by Week 26. The patient's MRI suggested increased ventriculomegaly and hydrocephalus. MRIs of the brain and cervical cord showed no significant changes for the other 9 patients. CSF GAG levels fell to normal or close to normal in 3 of 4 patients with abnormally high levels of GAG at pre-treatment. There were no consistent changes in opening pressure on lumbar puncture between pre-treatment and week 26.

Bone Evaluation Review of genetic skeletal surveys indicated no significant changes in bone disease during the study. However, one patient had worsening cord compression due to increased subluxation of cervical vertebrae that required spinal fusion surgery.

Height and Weight In the 6 prepubertal patients, mean height increased from pretreatment by 6.0 cm (5.13%) at Week 52, and by 10.0 cm (8.39%) at Week 104. Mean weight increased by 4.2 kg (15.83%) at Week 52, and by 7.9 kg (29.72%) at Week 104. Three of the 5 prepubertal patients remaining in the study at Week 104 had a normal height growth rate and 4 had a normal weight growth rate. None had normal growth rates at pretreatment.

Extent of Exposure

Ten patients completed 52 weeks of treatment with laronidase, 9 patients completed 104 weeks, and 8 patients completed 152 weeks and were on laronidase treatment as of March 30, 2001.

Pharmacokinetics (PK)

Infusions of laronidase resulted in elevated circulating plasma IDU activity levels for periods of 3 hours or more. The circulating levels achieved peak at 100-200 U/ml in the majority of infusions, approximately 10 times the half-maximal uptake of the enzyme in vitro. The circulating half-life ($t_{1/2}$) of IDU was approximately 1.8 to 1.9 hours during Weeks 1 and 2 and decreased to 1.2 to 1.3 hours at Weeks 12 and 26. As treatment progressed, intra-patient physiological variations in half-life and plasma clearance occurred. Variations in PK parameters did not significantly impact efficacy in terms of urinary GAG excretion.

Tissue Uptake

IDU activity level in buccal brushings had a trough level of 1% of normal during treatment, a level expected to reduce GAG storage. IDU activity levels in leukocytes reached 35% of normal by Week 104, a level comparable to that seen in asymptomatic carriers.

Efficacy
Primary Efficacy Endpoints

Hepatosplenomegaly The primary endpoint of a $\geq$ 20% reduction in liver and/or spleen size in two-thirds of the patients, using blinded MRI readings, was met at Weeks 26 and 52. Eight of 10 patients had a $\geq$ 20% reduction in liver size at Week 26 and 7 of 10 had a $\geq$ 20% reduction at Week 52. Five of 10 patients had a $\geq$ 20% reduction in spleen size at Weeks 26 and 52. At Weeks 52 and 104, 9 of 10 and 8 of 9 patients, respectively had normalized liver sizes when expressed as a percent of body weight. Two of 10 and 1 of 9 patients, respectively, had normalized spleen sizes when expressed as a percentage of body weight at Weeks 52 and 104.

Urinary Glycosaminoglycans (GAGs) The primary endpoint of a $\geq$ 50% reduction in urinary glycosaminoglycan (GAG) levels in two-thirds of the patients was met at Weeks 26 and 52. Ten of 10 patients had a $\geq$ 50% reduction at Weeks 6, 12, and 26, and 8 of 10 patients had a $\geq$ 50% reduction at Week 52. When mean GAG levels of Weeks 27-52 were compared with pretreatment levels, all 10 patients showed a $\geq$ 50% reduction. At Weeks 104 and 152, 9 of 9 patients and 7 of 7 patients, respectively, showed a $\geq$ 50% reduction in urinary GAG. By Week 152, mean GAG levels were within the range of urinary GAG excretion in a normal population.

Secondary Efficacy Endpoints

ROM Improvements were seen in the majority of patients for each joint ROM assessment at Week 26. At Week 52, right and left shoulder flexion ROM increased 28.13° (p < 0.001) and 26.12° (p = 0.002), respectively, with improvement in 7 of 8 patients. Mean elbow extension ROM also showed statistically significant improvements of approximately 7° bilaterally (p = 0.031 for the right elbow and p = 0.007 for the left elbow) at Week 52. Improved knee extension was seen overall, with large gains in the 2 patients with significant restriction at pretreatment; the test for linear trend of mean ROM was significant for the right knee (p = 0.025) but not for the left knee at Week 52. Improvements in shoulder ROM were sustained or increased at Week 104. Improvements in knee ROM were maintained at Week 104, but elbow ROM decreased from Week 52 to Week 104.

Cardiac Function New York Heart Association scores of functional ability improved by one class or more in all 10 patients at Week 26 (p = 0.008), Week 52 (p = 0.002), and Week 104. Improvements in joint and pulmonary function probably contributed to the increase in the patients' functional ability. Mean cardiac function scores improved from 15.40 at

pretreatment to 14.25 at Week 26, and to 12.15, which was statistically significant at p = 0.008, at Week 52. The mean score improved further to 11.00 at Week 104. Echocardiographic studies showed a modest improvement in tricuspid regurgitation in 6 of 10 patients, but one patient had significant worsening of mitral valve regurgitation. A pretreatment abnormal heart rhythm (predominantly atrial flutter and 2:1 block with other intermittent abnormalities) resolved to a normal sinus rhythm with first-degree block in the patient who had the worst cardiac disease in the study at pretreatment. Signs of congestive heart failure, such as 2-3+ pedal edema and dyspnea at rest, resolved by 12-26 weeks in this patient.

Airway Obstruction The AHI decreased from 2.08 at pretreatment to 0.97 at Week 26, indicating a decrease in airway obstruction during sleep. All 6 patients with apnea at pretreatment and 5 of 9 patients with hypopnea at pretreatment had decreases at Week 26. Two patients had an increased number of events at Week 26. One of these patients had a decreased number of events at Week 52; the other had an increased number of events at Week 52. Airway index showed a trend towards improvement; tongue diameter did not show consistent changes.

Eye Disease Visual acuity improved substantially in the 3 of 10 patients with the most severe baseline disease. There were no apparent changes in corneal clouding over the 104-weeks evaluation period.

Safety Results

Eight patients had a total of 32 serious adverse events (SAE) during the study. Nine of the SAEs were definitely related or possibly related to treatment with laronidase and included bone disorders and allergic reactions. One SAE had an unlikely relationship to study drug; 22 were not related to study drug. Two patients died. The adverse event (AE) resulting in one death was judged to have an unlikely relationship to study drug and the second AE resulting in death was judged to be unrelated to study drug.

The most frequently reported study drug-related AEs (in terms of the numbers of patients with the event) were rash (6 patients), headache and urticaria (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). All 10 patients developed measurable levels of antibody to the study drug product by Week 12, and 4 patients had IDU-specific antibodies; these 4 patients also showed complement activation. There were no apparent effects of the immune responses on development of immune complex disease or on glomerulonephritis based on urinalysis and GFR results.

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