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Original Submission

BioMarin Pharmaceuticals, Incorporated

ALDURAZYME™

Laronidase

For the Treatment of Mucopolysaccharidosis I

Clinical Review

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Introduction

This document is the medical officer's review of the clinical data submitted with the Biologics License Application (BLA) Submission Tracking Number 125058. This application is for Laronidase (ALDURAZYME), a recombinant enzyme product which is proposed for usage as enzyme replacement therapy for patients with Mucopolysaccharidosis I.

Proposed indication and dose

BioMarin proposes that Laronidase is indicated as long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I) to treat the non- central nervous system manifestations of the disease. The proposed dosage regimen of Laronidase is 100 U / kg (0.58 mg / kg) administered once weekly intravenously.

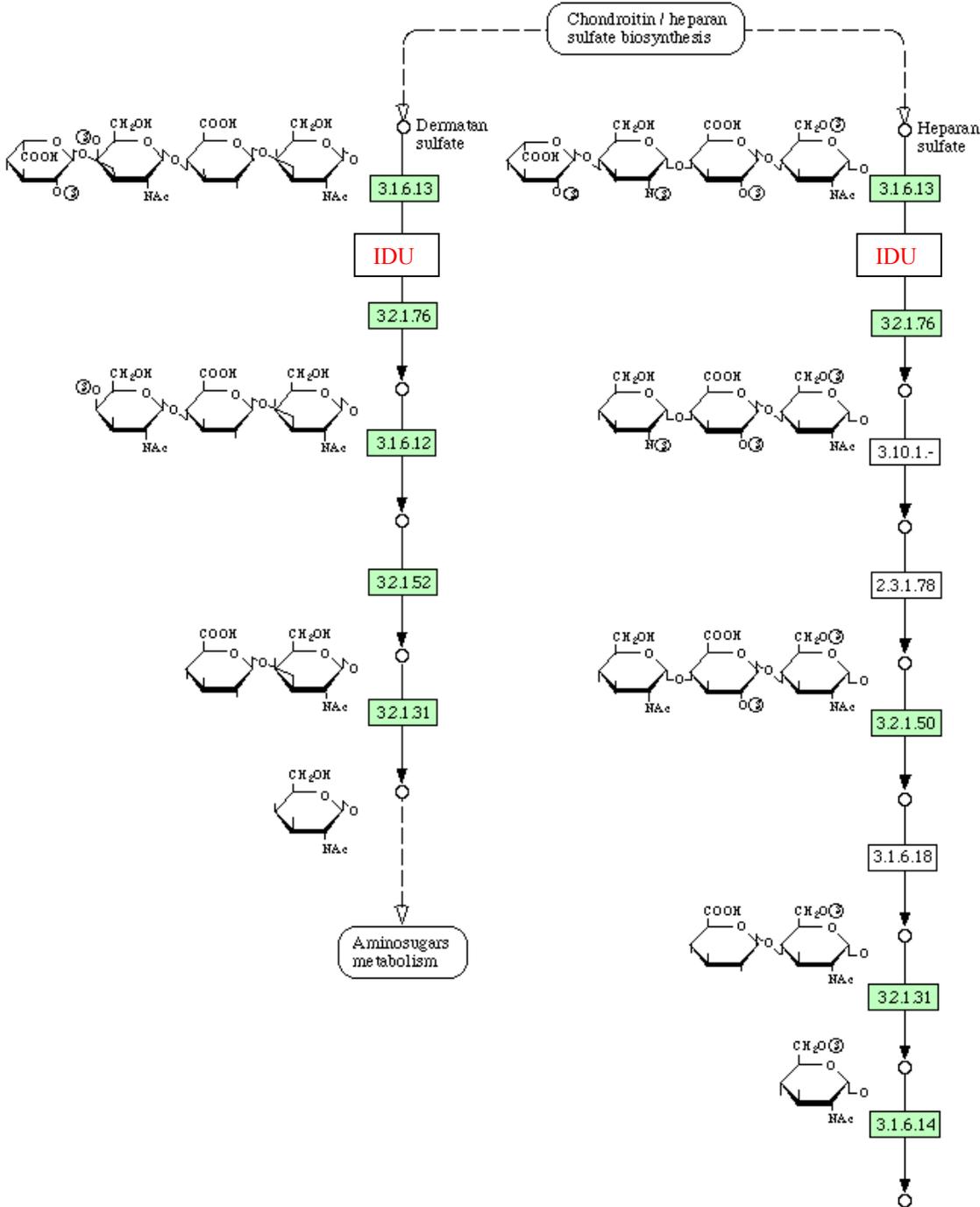
Reviewer's comment: This disorder, as for all forms of lysosomal storage diseases, has complex and multiple organ and tissue manifestations. There are variable phenotypes and a broad spectrum of severity. Evidence-based determination of a treatment effect on specific endpoints should be required to support a claim of benefit for these endpoints. A claim of general benefit in the management of the disease as a whole may be inappropriate.

Biochemical and Clinical Background

Lysosomal storage disorders result from a genetic defect that causes deficient production or function of one or more of the lysosomal enzymes. The enzymatic deficiency results in an abnormal accumulation of metabolites within a lysosome and ultimately disruption of the normal cell function and cell death. Lysosomal storage disorders are usually classified according to the nature of the macromolecule that is abnormally catabolized and consequently accumulates within the lysosome. Sphingolipidoses (including gangliosidoses) are associated with the accumulation of complex lipids, the basic structure of which is a sphingosine, a long chain amino-alcohol. Oligosaccharidoses or mucopolipidoses are associated with the storage of complex glycoproteins. Mucopolysaccharidoses are caused by deficiencies of enzymes needed to degrade glycosaminoglycans (also known as mucopolysaccharides). Glycosaminoglycans themselves are lysosomal degradation products derived by proteolytic removal of the protein core of proteoglycans (macromolecules occurring in the cell membrane and extracellular matrix). Mucopolysaccharidosis I is the subject of this license application, and will be described here briefly.

Mucopolysaccharidosis I (MPS I) is characterized biochemically by the deficiency of the lysosomal enzyme α -L-iduronidase (IDU). This enzyme cleaves the terminal iduronic acid residues of dermatan sulfate and heparan sulfate (Figure 1).

Figure 1. Catabolism of glycosaminoglycans highlighting role of IDU



00531 1/30/02

Source: www.genome.ad.jp/dbget-bin/get_pathway?org_name=hsa&mapno=00531
 assessed on October 16, 2002

Experiments in cultured fibroblasts show that the enzyme is made in a precursor form, cleaved intracellularly to a 628 amino acid protein and incorporated with mannose 6-phosphate markers for targeting to lysosomes. The gene encoding IDU is located in the short arm of chromosome 4 (locus 4p16.3) and MPS I is inherited with autosomal recessive transmission. Homozygosity or compound heterozygosity for the W402X (stop codon) and Q70X mutations are the common causes of MPS I with a severe form in affected Caucasian individuals. Japanese patients with MPS-I have other predominant IDU gene mutations.

Historically, MPS I patients have been broadly categorized into three clinical syndromes: Hurler, Hurler-Scheie, and Scheie, representing severe, intermediate, and mild clinical phenotypes, respectively. These classifications are arbitrary categorizations of points on a continuous spectrum of patient phenotypes. Biochemically, patients with the milder disease form retain trace residual amounts of IDU that are sufficient to ameliorate the phenotype to varying degrees. However there is considerable heterogeneity in the severity and symptoms within each phenotype and substantial overlap of the three syndromes. The true incidence of MPS I is unknown, with estimates in the range of 1/76,000 for MPS IH, 1/280,000 for MPS IH-S, and less than 1 in 840,000 live births for MPS IS in Northern Ireland. Semi quantitative analysis of spot urinary glycosaminoglycans can be used for screening, but is subject to both false negative and false positive results. Definitive diagnosis is established by lysosomal enzymes assays in leukocytes, cultured skin fibroblasts or serum. Pre-natal diagnosis is established by IDU assays in cultured cells from amniotic fluid or chorionic villus biopsies. Carrier testing is currently performed with analysis of enzyme activity in family members, but may be superseded by molecular analysis of specific family mutations in the enzyme gene.

Hurler syndrome (MPS IH) is a progressive disorder that affects multiple organs and tissues and leads to death during childhood. The symptoms of MPS IH present between 6 months and 2 years of age. They include inguinal or umbilical hernias, hepatosplenomegaly, coarse facies, deafness, recurrent ear and sinus infections, macroglossia, noisy breathing, obstructive airway disease and sleep apnea, communicating hydrocephalus with increased intracranial pressure, prominent forehead, developmental delay, skeletal deformities (dysostosis multiplex), corneal clouding, joint stiffness, acute cardiomyopathy associated with endocardial fibroelastosis, valvular heart disease and pulmonary hypertension. The most frequent causes of death are related to obstructive airway disease, respiratory infections and cardiac complications.

Symptoms of Hurler-Scheie Syndrome (MPS IH-S) include dysostosis multiplex, corneal clouding, joint stiffness, short stature, deafness, and obstructive airway disease with little or no intellectual dysfunction. The onset of these symptoms is observed between ages 3 and 8 years of age, and death usually occurs in the second or third decade of life, usually from the same complications described in the Hurler patients.

Patients with Scheie Syndrome (MPS IS) have variable amounts of joint stiffness, aortic valve disease, mild hepatosplenomegaly, and corneal clouding, usually without

neurologic involvement. Symptoms start in children older than 5 years and the diagnosis is usually made between 10 and 20 years of age. Patients achieve normal stature and normal lifespan.

Current management of patients with MPS I is restricted to supportive care and treatment of specific complications. Ventriculoperitoneal shunting in moderate to severe hydrocephalus, ventilating tubes and hearing aids, range of motion exercises, tracheostomy and high pressure nasal continuous positive airway pressure, mitral or aortic valve replacement can improve symptoms.

A treatment that can replace the defective enzyme by supplying either cells capable of normal IDU secretion or functional IDU can potentially improve the clinical manifestations of MPS I. Cell culture and animal model experiments have demonstrated feasibility and raised optimism. Despite numerous trials using different enzyme sources, the only significant advance has been transplantation of allogeneic bone marrow in patients with MPS IH, particularly if instituted before the age of 2 years. With stable bone marrow engraftment the biochemical and somatic features revert, and long-term survival is possible. Neuropsychological function and some skeletal abnormalities are not reversed in patients that undergo bone marrow transplantation after age 2. However, limitations in the appropriate donor pool, and the high risks of significant morbidity and mortality make this therapeutic option restricted to a few affected individuals.

With the cloning of complementary DNA for IDU, large scale production of the recombinant human α - L – IDU became possible, with the mannose 6 phosphate sites necessary for targeting lysosomes.

Product Background

Recombinant human α -L-iduronidase (rhIDU) is a 628 amino acid lysosomal hydrolase. The enzyme is a single polypeptide chain of molecular mass 70.1 kilodaltons (from translated cDNA sequence). rhIDU contains six N-linked glycosylation sites, two of which carry the bis mannose-6-phosphate oligomannose⁷ oligosaccharide that binds the target cell surface receptor. The apparent molecular mass of full-length rhIDU is approximately 83 kilodaltons, suggesting that posttranslational modifications of rhIDU contribute approximately 13 kilodaltons to the molecular mass.

----- . The ----- formulated drug product is supplied as a sterile solution at a concentration of 0.58 mg/mL (100 U/mL) in a sodium chloride and sodium phosphate buffer. Each vial of drug product contains 2.90 mg of Aldurazyme™ and is intended for single use.

The product used in the pre-clinical studies and the Phase 1 clinical study was originally defined with an activity of 125,000 U/mL and a protein concentration of 0.5 mg/mL. These characteristics of laronidase were subsequently redefined (due to changes in assay procedures) as 100 U /mL activity and 0.58 mg/mL protein concentration. These redefinitions do not represent any changes in actual enzyme activity or concentration, rather reflecting changes in assay methodology. However, terminology used in the Phase 1 study and in preclinical study reports are based upon the prior assay process.

Regulatory History

Development of laronidase was conducted under IND 7334, initially submitted September 19, 1997 proposing a Phase 1 clinical study. Subsequently, a single Phase 3 study was conducted.

Pre-clinical studies

Reviewer's comment: It is important to note that the assay for α -L-iduronidase activity was changed during the drug development to make it more reproducible and robust. A change in the definition of activity unit to be more conventional occurred as a consequence. The dose used in the Phase 1 study was reported as 125,000 U, which was determined to be equivalent to 100 U under the revised activity definition. The method for determination of protein concentration was also changed, resulting in a small apparent mass increase, such that the 0.5 mg / ml formulation of rhIDU now measured 0.58 mg / ml in the new assay.

Dosing in all the pharmacodynamic studies was reported on an enzymatic activity basis (U / kg) using the old activity unit and protein assay. Dosing in the toxicity studies was reported only on a weight basis using the older protein assay. Most of the pre-clinical study reports present the dose used in a mg / kg basis, except for the pharmacodynamic studies, which also present data in the original activity units for comparison to the published literature.

Toxicology studies

Placebo and dose-controlled acute toxicity studies using single doses of laronidase were conducted in rats and dogs with a dose range of 0.29 to 5.8 mg kg in rats and 0.116 to 11.6 mg/kg in dogs. No treatment related toxicities were found, although dogs had low incidence of emesis and mucoid liquid stools following treatment with laronidase, unrelated to dose. Female rats developed small foci of hepatocellular necrosis of unclear relationship to the treatment and unclear significance.

An intravenous laronidase study in cynomolgus monkeys showed a slight increase in lymphocytes and eosinophils when the highest dose (16.6 mg/kg) was infused weekly for 26 weeks.

Pharmacodynamic studies

In vitro studies were carried out to explore the uptake of laronidase by MPS I patient fibroblasts, its effect on GAG storage and its cell half-life. These studies demonstrated

effective laronidase endocytosis by the fibroblasts via a mannose-6-phosphate dependent receptor with a half-maximal uptake at approximately 0.7 nM enzyme. Laronidase reduced GAG storage in MPS I patient fibroblasts with half-maximal reduction at approximately 0.7 pM. The half-life of the enzyme in the fibroblasts was estimated at 5 days.

Reviewer's comment: The sponsor claims this result supports a once weekly dosing regimen, but no in-vivo studies were performed to examine the tissue half-life of the enzyme.

Subsequent studies in the canine model using laronidase at 125,000 versus 500,000 U/kg/week (0.5 or 2.0 mg/kg/week) showed superiority of 9-hour weekly infusions over continuous infusions in raising tissue enzyme levels and decreasing tissue GAG accumulation. More importantly, this study also demonstrated that at the 2.0 mg/kg/week dose, the 9-hour infusion was more effective than continuous infusion at lowering GAG levels in cornea, kidney cortex, liver, myocardium, pancreas, synovium, cerebral cortex, and medulla. There were no significant differences in GAG accumulation within denser connective tissues (i.e. ligaments, cartilage, cornea, atrioventricular valve leaflets).

Preclinical Safety

Infusion related anaphylactoid reactions were observed in dogs and cats and managed by stopping the infusion, intravenous fluid administration and, if necessary, oxygen supplementation. The most likely cause of these reactions is IgG-mediated complement activation. Anti-histamines treatment prior to the infusions was effective in eliminating or decreasing these reactions. Lowering the infusion rate and the addition of canine serum albumin also mitigated these reactions in long term laronidase administration. BioMarin notes that the clinical grade product is more pure than the one used in the pre-clinical studies, and polysorbate 80 added as a detergent in the clinical grade product can potentially decrease microaggregation. Anaphylactoid reactions were not seen in monkeys or dogs treated with the clinical grade product, even without pre-treatment with antihistamines.

Overview of Clinical Studies

This application contains data from a total of 59 patients with various forms of MPS I. The initial open label study of laronidase has been extended as a single arm, uncontrolled trial. Study ALID-003 enrolled 45 subjects into the single randomized, placebo controlled, double blind trial reported with this application. At the end of the study all subjects were offered participation in an open label single arm laronidase protocol. Subjects previously randomized to placebo were converted to laronidase treatment.

There is also a small ongoing Open Label Study 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 29 April 2002, 4 patients had received laronidase treatment in this program.

The sponsor has conducted 3 clinical studies during the clinical development of laronidase (Table 1)

Table 1. Clinical Studies Included in this Submission

Protocol	Study Design	Completion Status / Study Dates	Location/ Number of Centers	Duration of treatment (weeks)	n
ALID-003	Phase 3 Double Blind, Placebo Controlled Randomized	Completed 12/28/00 to 9/6/01	USA:2 Canada: 1 UK: 1 Germany: 1	26	45
ALID-006	Phase 3 Open Label , non-randomized Extension	Ongoing	USA: 13 Canada: 2 UK: 1 Germany: 2	24	45
BIO7500	Phase 1 / 2 Open Label, non-randomized	Ongoing Started 11/28/97	USA: 13	171 (safety)	10
Special Access & ALID-007	Uncontrolled administration	Ongoing	Australia: 3	35	3
	Single patient	Completed (subject died)	USA: 1	28	1

A multicenter observational study (ALID-004) was also conducted in 2000 to collect normative data in patients with MPS I. The single session survey included 5 centers in the USA and Europe and enrolled 45 patients. The objective was to determine median values for the six minute walk distance test (6MWD) and the forced vital capacity (FVC) in patients with MPS I intended to participate in the Phase 3 clinical trial. Information from this study was used to partly guide design of Study ALID-003. A notable finding was the higher than expected distances on the six minute walk test. This relatively mild degree of impairment might have suggested that there would be difficulty in demonstrating a clinically meaningful difference in a randomized study.

Study BIO7500

“Phase 1 / 2, Open-Label Study of Recombinant Human α - L – Iduronidase as Enzyme Replacement Treatment for Mucopolysaccharidosis I (MPS I)”.

Overview

This study was conducted under IND 7334 according to Protocol BIO7500-001. The study started on November 28, 1997 and is still ongoing.

The submitted study report contains safety and clinical outcome data derived from a 152 week period. The original protocol submitted proposed a 26 week study and was subsequently modified to extend the treatment duration. A change in product manufacture method and formulation occurred during the study. Crossover comparisons of pharmacokinetic and pharmacodynamic parameters were done.

The reported results demonstrate that the newer product had a comparable safety profile to the older product in the seven subjects that participated in the crossover study. An apparent increase in plasma enzyme activity 20 minutes after completion of infusion was observed with newer as compared to the older product.

Protocol

Title: “Phase 1 / 2, Open-Label Study of Recombinant Human α - L – Iduronidase as Enzyme Replacement Treatment for Mucopolysaccharidosis I (MPS I)”. Protocol BIO7500-001.

The study was initiated on November 28, 1997 and the reporting period included in the corresponding study report included in this submission ended on March 30, 2001. Six protocol amendments occurred after initiation of the study. These served largely to clarify certain study criteria or procedures, or to extend the study duration, and are incorporated in the following description.

Design

Open label non-randomized, single dose, multicenter, phase 1 study in 10 subjects with MPS I. Effect of laronidase treatment was compared to pre-treatment levels. The study drug was to be administered intravenously on a weekly basis initially for a period of 26 weeks. Subsequent amendments to the protocol extended the study period to 152 weeks.

Reviewer’s comment: the sponsor classified this design as “patients serving as their own control” but this is in reality an uncontrolled study.

Reviewer’s comment: this study is classified as a multicenter study, but the design is such that all eligible subjects receive the first 6 weeks of product administration at one

site (Harbor-UCLA Clinical Research Center) and would have to return to this site for efficacy assessments at 12, 26, 52 and 104 weeks of treatment.

Objectives

- Assess the safety of repeated infusions of laronidase
- Assess the effect of repeated infusions of laronidase in the reduction of lysosomal storage as assessed by liver and spleen size and urinary GAG excretion and in clinical conditions caused by MPS I, including joint disease, cardiac disease, sleep apnea/airway obstruction, and eye disease

Eligibility Criteria

Inclusion criteria:

- Male and female patients with a clinical and enzymatic diagnosis of MPS I, as confirmed by clinical and enzymatic assessments by the Study Investigators.
- Patients at least 5 years of age.
- Patients with 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).

Exclusion Criteria:

- Patients who were critically ill. Critical health conditions included congestive heart failure, serious respiratory compromise with chronic hypoxia or pulmonary hypertension, serious spinal cord compression with evidence of substantial neurologic compromise, or any other conditions which could have prevented the child from cooperating and tolerating the experimental protocol or might be expected to lead to death or incapacitation within the study period.
- Patients who had previously undergone bone marrow transplant.
- Patients who received an investigational drug or procedure within 30 days of study enrollment.

Treatment assignment / randomization

In this non-randomized study all subjects were assigned to active treatment.

Product information and administration

Laronidase was diluted in normal saline with 0.1% (1.0 mg/mL) human serum albumin. The total laronidase dose was 125,000 U/kg (100 U/kg by redefined units), infused over a 3-4 hour period. Intravenous diphenidramine pre-medication was given 10-30 minutes prior to enzyme infusion. During the first hour, the enzyme was infused at a rate

of 50 U/kg/min equivalent to 3,000 U/kg/hr. During the second and third hours, the rest of the dose was administered at a maximum rate of 61,000 U/kg/hr.

Evaluations

(except as noted, at baseline, weeks 6, 12, 26, 52, 104)

- a. Liver and spleen volume were assessed by MRI. Organ density assumed 1g/ml to enable calculation of organ weight as a percentage of body weight. An unblinded radiologist evaluated the MRI in real time. At study end a second radiologist blinded to subject identity and MRI timepoint analyzed organ volumes in a randomized fashion. These data were compared to healthy children and adolescents liver and spleen weights in proportion to the average weight for their age. Liver and spleen volume data is reported through week 104 in the unblinded extension study.
- b. Urinary GAG was collected at pre-treatment and weekly for the first 6 weeks, and at decreasing frequency thereafter. All determinations were made at Harbor-UCLA by a validated method using Alcyan blue dye and quantification by spectrophotometer. The values were corrected by urine creatinine concentration and expressed as micrograms of GAG per mg of creatinine.
- c. Joint range of motion (ROM) of shoulder, knee and elbow. Measurements obtained by a single physical therapist using a goniometer. 5 independent measurements for each joint and for each visit were obtained and averaged.
- d. Cardiac function was assessed in a prospectively defined but unvalidated “cardiac scoring system” which is a composite score of EKG (weight 3), echocardiogram (weight 5), history (weight 4), physical examination (weight 4), and radiological findings (weight 4). The subject was also assessed according to the New York Heart Association functional classification.
- e. Airway obstruction was assessed by a variety of parameters measured during polysomnography to investigate the frequency of apnea (cessation of airflow for 10 or more seconds), hypopnea (50% decrease in airflow per breath accompanied by arousal or desaturation), as well as minutes of hypoxia (oxygen saturation below 90%). Sleep studies were performed at pre-treatment, week 26, and if previously abnormal, at weeks 52 and 104. MRI assessments of the tongue and measurement of the airway index (ratio of mid-sagittal anterior-posterior width of the pharyngeal and tracheal airway to total width of the pharynx) were performed by an unblinded radiologist at pre-treatment and at weeks 6, 12, 26, 52 and 104.
- f. Eye disease was assessed by a combination of visual acuity testing, complete ophthalmologic exam, intraocular pressure measurements, corneal photographs.
- g. Central nervous system abnormalities were assessed by brain and cervical cord MRI, by lumbar puncture if there were no contraindications for the procedure, and by a pediatric neurologist examination. In addition the Wechsler Intelligence Scale was administered
- h. Genetic skeletal surveys .

- i. Height and weight were assessed from health records obtained from the 2 years prior to study to establish baseline growth rates, and every 4 weeks to week 52, and every 12 weeks to week 152 during treatment with rhIDU in pre-pubertal subjects (age 5 to 12). Only those assessments performed at Harbor-UCLA were used in the analysis of the results.
- j. Clinical Laboratory Safety assessments were performed periodically during the study. 24 hour creatinine clearance was performed at pre-treatment and weeks 12, 26, 52 and 104. Complement testing (CH50, C3 and C4) was done pre- and post-infusion, at pre-treatment and weeks 4, 6, 12, 26, 52, and 104. ELISA assessments for IgG serum antibodies against rhIDU with Western blot specificity confirmation were performed at pre-treatment and weeks 1, every other week to week 26, every 4 weeks to week 52, and every 12 weeks to week 152.
- k. Enzyme activity was assessed in buccal brushings. Enzyme activity was also assessed in leukocytes.
- l. Pharmacokinetic studies were performed at pre-treatment, and weeks 1, 2, 12 and 26. Pharmacokinetic studies were also performed on Week 6 for subjects 001 and 002, in addition to the other timepoints.

Safety Monitoring

A study monitor designated by BioMarin would monitor both safety and study conduct at the study sites.

Endpoints

Primary endpoints: The primary endpoints cited in the original protocol were:

1. Proportion of subjects with 20 % reduction of the excess size of either liver or spleen or both. In order to calculate the excess organ size the sponsor proposed to subtract the normal organ size, which in the original protocol was estimated as 2.5 % of body weight for the liver and 0.2 % of body weight for the spleen.

Reviewer's comment: This endpoint has changed substantially in subsequent amendments of the protocol. Amendment 1 of 3/3/98 revised the definition of a significant reduction in organomegaly to a 20 % reduction in the total size of either the liver or the spleen or both. The 20% criterion was selected by reference to experience in Gaucher's disease. However, it is unclear how to extrapolate the clinical meaning of hepatomegaly in one disorder to a different disorder.

2. Percentage reduction in urinary GAG excretion as calculated by taking the average of the pretreatment samples compared with the average of samples from the last 6 weeks of therapy.

Reviewer's comment: The definition of endpoint for analysis was very vague in the original protocol. Amendment 2 (9/13/98) revised the definition in the statistical analytical plan as "the four pre-treatment values will be averaged and compared with the

last six specimens taken through week 26". As the study duration was extended, the timepoint for endpoint comparison has been modified.

A general comment related to the analysis of "efficacy" endpoints is that this study is uncontrolled, and variations in these endpoints would demonstrate, at best, bioactivity to guide more definitive studies.

Secondary endpoints:

1. Cardiac ejection fraction, valvular regurgitation, pulmonary hypertension as assessed by the cardiac scoring system, and NYHA classification
2. Corneal clouding, and visual acuity
3. Joint stiffness / range of motion, based on goniometer, subjective reports of stiffness or pain, as well as video examinations of standard motions.

Statistical analysis

The revised analytic plan provided for specific analysis procedures which were not detailed in the original protocol.

Reviewer's comments: In this uncontrolled study, pre- and post-treatment comparisons are not meaningful in support of laronidase efficacy.

Study Conduct

Study Conduct was monitored by 2 contract research organizations (CRO's) during the study period: from 11/28/97 until 6/12/2000 Inveresk Research was charged with study monitoring and from 6/12/00 until the end of the study period Abt Associates Clinical Trials monitored study conduct.

This study report includes data collected through March 30, 2001. As of this date, the first patient enrolled had completed Week 171 and the last patient enrolled had completed Week 152.

Protocol Violations

The most common deviations involved variations from protocol-specified collection times for safety and efficacy assessments, particularly laboratory evaluations (urinalysis, urinalysis with microscopy, CBC, and blood chemistries) and urinary GAG measurements. Most variations resulted from missed study visits. Together the 10 subjects missed a mean of 19.8 infusions due to frequent unavailability of study drug from December 1998 through December 1999.

Reviewer's comment: The sponsor does not explain the unavailability of laronidase during the study period. The sponsor states that 66% of missed infusions are due to laronidase unavailability, but this figure is inconsistent with the Appendix that lists protocol violations.

FDA site inspection findings

No site inspections have been performed for this study.

Results

Subject disposition

Ten subjects were enrolled into this study. The first subject signed the consent form and was enrolled on November 28, 1997, the first study dose was given on December 19, 1997, and the last subject completed the 152-week timepoint on March 29, 2001. All 10 subjects successfully completed the first 52 weeks of the study, and 8 subjects were active at Week 152. Subject 008 died between Weeks 103 and Week 104 of a viral illness. Subject 002 died 19 days after the patient's last study drug infusion at Week 137 of complications following spinal fusion surgery for worsening of scoliosis.

Baseline characteristics

Table 2 shows the demographic and relevant baseline characteristics of the subjects enrolled in this study.

Table 2. Demographic and baseline characteristics

Subject	Age (yrs)	Height (cm)	Weight (kg)	Gender	Race	Clinical Status
001	17	132.5	38.1	M	White	MPS IH-S
002	10	121	22.6	F	White	MPS IH-S
003	9	122.5	27	M	White	MPS IH-S
004	8	125	34.6	M	White	MPS IH-S
005	12	127	24.4	M	White	MPS IH-S
006	22	152.7	64.5	M	White	MPS IH-S
007	17	160	57.2	F	White	MPS IS
008	5	87	14.8	F	White	MPS IH
009	9	118.5	24.2	F	White	MPS IH-S
010	14	160	54.6	M	White	MPS IH-S

There were 6 pre-pubertal subjects in the study. These subjects covered a broad spectrum of clinical presentation. The Principal Investigator / Medical Monitor used a protocol classification of MPS I phenotypes to describe the subjects disorder severity at the time of enrollment. Under this classification one subject had mild disease (MPS IS, Scheie), 8 subjects had moderate disease (MPS IH-S, Hurler-Scheie) and one subject had severe disease (MPS IH, Hurler). All subjects had in common the wide spectrum of

MPS I impairments, with unknown and variable intensity in each affected organ, tissue or functional system. Most of the concomitant medications used by these subjects at the time of entry were analgesics or anti-inflammatory agents for relief of headaches or other pains.

Reviewer's comment: It is important to note that the phenotype classification is based on a subjective impression of the overall degree of organ or tissue impairment seen at a specific age range.

Study drug exposure

Ten subjects participated in this uncontrolled, open label study and have received by the time of the study report weekly intravenous infusions of rhIDU for an average 151 weeks (range 103 – 171).

The mean (\pm SD) number of administered infusions per subject was 115.0 (\pm 17.5, range 82 to 135). As mentioned under Protocol Violations, the majority of missed infusions were due to unavailability of the study drug. 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 subject or parents to receive infusions less frequently than once a week.

Primary endpoints

Hepatomegaly

Results of the blinded review of liver volumes are reported in Table 3. Due to the wide variation in liver volumes at baseline, these results were normalized as percent reduction from baseline for each subject and averaged.

Table 3. Mean normalized liver volume as a percentage of pre-treatment

Time	Mean	SD	# Subjects with \geq 20 % decrease
Pre-treatment	100	0	N/A
Week 6	79.9	6.5	5
Week 12	78.2	6.1	6
Week 26	76.6	10.2	8
Week 52	75.0	9.2	7

The 3 subjects that did not achieve the stated endpoint of 20 % reduction had liver volumes in the normal range for their ages by week 52, and achieved the 20% or greater reduction in liver volume in the unblinded readings at week 104.

Splenomegaly

Results of MRI blinded review of the spleen volumes paralleled those obtained for liver volumes. 7 of the 10 subjects demonstrated a \geq 20% reduction at week 6. Subject 009 developed clarithromycin-induced hepatitis just prior to the Week 26 imaging timepoint, with a sharp increase in liver and particularly spleen size to twice her baseline volume.

As her serum liver enzymes normalized by week 46, both the liver and spleen volumes returned to normal.

In conclusion, using blinded MRI readings, 7 of 10 subjects had a greater than 20% reduction in liver volumes at Week 52, and 5 of the 10 subjects had a 20% reduction in spleen volume at Weeks 26 and 52. Using unblinded MRI readings, 9 of the 10 subjects had normalized liver size by week 52 (8 / 9 by week 104) and 2 of the ten subjects had normalized spleen volumes by weeks 52 (1 / 9 by week 104).

BioMarin believes (-----) that the reduction in liver and spleen sizes caused improvements in comfort and edurance and the ability to eat and breathe.

Reviewer's comment: It is important to note that even though the reduction in liver and spleen volumes was clearly demonstrated, its impact on general well being of the subjects may have been overstated by other factors, including the fact that this is an open label, uncontrolled study.

Urinary Glycosaminoglycans

All subjects had elevated urinary GAG levels prior to treatment that were generally proportional to the severity of disease in this limited sample of MPS I subjects. For example, the most severely affected subject (008) had urinary GAG exceeding 500 µg GAG/mg creatinine, whereas the subjects with the mildest disease (003 and 007) had levels of 63.25–112.8 µg GAG/mg creatinine. Table 4 shows the mean normalized urinary GAG level reported as percentage of baseline from pre-treatment to week 152. By week 152 mean GAG levels were within the normal range.

Table 4. Mean normalized urinary GAG as a percentage of pre-treatment

Time	Mean	SD	n	# Subjects with ≥ 50 % decrease
Pre-treatment	100	0	10	N/A
Week 6	31.8	5.9	10	10
Week 12	33.6	9.0	10	10
Week 26	31.3	8.2	10	10
Week 52	37.2	11.3	10	8
Week 104	26.4	6.7	9*	9
Week 152	21.5	9.3	7**	7

* Subject 008 died before week 104

** Subject 002 died before week 152

For comparison, mean (± SD) urinary GAG in 68 healthy subjects is as follows: 32.4 ± 6.9 µg GAG/ mg creatinine for ages 3 – 12 (n=42), 14.9 ± 3.4 µg GAG/mg creatinine for ages 13-18 (n=12), and 8.5 ± 1.8 µg GAG/mg creatinine for ages 19-52.

Reviewer's comment: This study provides indication of laronidase activity through the substantial but incomplete reduction in urinary GAG levels. The sites of enzyme action

and the extent of tissue and organ function recovery cannot be inferred from these data. Similarly, the clinical significance of this finding remains unclear.

Secondary endpoints

Joint ROM

Subjects were evaluated for shoulder flexion and extension, knee flexion and extension, and elbow extension. Results were analyzed for changes in ROM (the angle of a limb relative to the body at maximal flexion or extension) 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 subjects).

By Week 26, the majority of subjects showed some improvement in ROM in one or more joints, although inter-subject variability was large. The movements that showed the most improvements at Week 52 were shoulder flexion, knee extension, and elbow extension (Table 5)

Table 5. Mean (\pm SD) Joint ROM and changes from pre-treatment

Joint	Time	Mean \pm SD (angle)	Mean (\pm SD) change from pre-treatment
R Shoulder flexion	Pre-treatment	100.6 \pm 17.5	28.1 \pm 21.5
	Week 52	128.7 \pm 16.2	
L Shoulder flexion	Pre-treatment	101.2 \pm 18.5	26.1 \pm 26.8
	Week 52	127.4 \pm 17.6	
R Shoulder extension	Pre-treatment	32.1 \pm 14.0	5.1 \pm 19.1
	Week 52	37.2 \pm 7.1	
L Shoulder extension	Pre-treatment	26.8 \pm 6.9	7.6 \pm 12.8
	Week 52	34.4 \pm 7.5	
R Elbow extension	Pre-treatment	156.7 \pm 13.4	7.0 \pm 6.3
	Week 52	163.7 \pm 13.6	
L Elbow extension	Pre-treatment	156.1 \pm 19.1	7.1 \pm 9.0
	Week 52	163.2 \pm 16.7	
R Knee flexion	Pre-treatment	126.6 \pm 14.1	4.7 \pm 5.0
	Week 52	131.3 \pm 14.4	
L Knee flexion	Pre-treatment	126.6 \pm 19.7	3.6 \pm 8.8
	Week 52	130.1 \pm 13.7	
R Knee extension	Pre-treatment	172.0 \pm 11.0	3.5 \pm 10.4
	Week 52	175.5 \pm 5.6	
L Knee extension	Pre-treatment	171.3 \pm 11.0	2.8 \pm 6.4
	Week 52	174.1 \pm 6.3	

Reviewer's comment: The increase in ROM for some joints was modest, although the mean changes seem to be favorable to the laronidase treatment. Caution should be exercised in the interpretation of this unblinded uncontrolled study in correlating the modest ROM changes to improvements seen in daily activities.

Cardiac Function

The subjects in this study exhibited typical MPS I cardiac disease, including valvular insufficiency, pulmonary hypertension, and congestive heart failure, although only Subject 006 was in serious heart failure at the start of the study.

At Week 26, 3 of 10 subjects had improvements in NYHA scores. After 52 and 104 weeks of treatment, NYHA scores improved in 10 of 10 and 9 of 9 subjects, respectively, with 6 subjects achieving normal scores of Class I. No subject was in Class I at pretreatment.

Tricuspid regurgitation also modestly improved some subjects.

Reviewer's comment: The data suggest inconsistent echocardiographic improvement in a few subjects with underlying cardiac disorders in this small uncontrolled study. In contrast the improvement seen using the NYHA scores is more open to the bias inherent in open label studies. These findings may not be surprising in view of the lack of effect of laronidase on GAG accumulation in heart valve and myocardium in the canine model of MPS I.

Polysomnography and airway evaluations

Six subjects who had sleep apnea at pre-treatment demonstrated improvement in the number of apnea episodes by week 26. Five of the 9 subjects with pre-treatment hypopneas showed improvement in the number of hypopneas per night by week 26. The apnea hypopnea index (AHI) improved in 7 out of 10 subjects, and the mean AHI decreased from 2.08 to 0.97 (53% reduction) at week 26. However, some subjects had worsening of some parameters.

Other measures of airway function (airway index and tongue diameter) showed inconclusive results, in part due to technical difficulties

Eye disease

Three subjects had improvement in visual acuity by week 52, and with additional favorable changes noted at week 104. No changes were observed in intra-ocular pressure or in corneal clouding.

CNS abnormalities

MRI studies of the brain and cervical cord pretreatment demonstrated the substantial pathology expected in MPS I patients. This included perivascular storage, meningeal thickening and spinal cord compression or restriction, and miscellaneous other findings. There were no substantial changes seen on MRI during the 104-week course of laronidase treatment.

Reviewer's comment: These findings are consistent with the lack of enzyme activity in the central nervous system. They are also similar to those pre-clinical studies showing absence of CNS effects in dogs affected by MPS I.

Bone evaluations

No significant changes were observed in the genetic skeletal surveys performed during the study. All subjects had radiologic evidence of odontoid dysplasia and dysostosis multiplex, commonly seen in patients with MPS I.

Height and weight

In 6 pre-pubertal subjects, height increased by a mean of 6.0 cm at Week 52 and a mean of 10.0 cm at Week 104. Weight increased by a mean of 4.2 kg at Week 52 and a mean of 7.9 kg at Week 104 in these subjects.

Height growth rate normalized for 3 of 6 pre-pubertal subjects at Week 52. Weight growth rate normalized for 2 of the 6 pre-pubertal subjects at Week 52.

Pharmacokinetics

Intravenous administration of laronidase (125,000 U/kg) resulted in significant circulating plasma IDU activity levels of IDU for periods of 3 hours or more.

The circulating levels of IDU achieved peak at 100-200 U/ml for the majority of infusions, which was approximately 10 times the half-maximal uptake of the enzyme in vitro.

The mean circulating half-life ($t_{1/2}$) of IDU was approximately 1.8 to 1.9 hours at Weeks 1 and 2 and decreased to 1.2 to 1.4 hours at Weeks 12 and 26 in 7 of the 10 subjects.

Differences in pharmacokinetic parameters did not correspond to differences in urinary GAG excretion.

In examining the question of factors responsible for variations in pharmacokinetic parameters, the sponsor found that presence of antibodies to laronidase did not correlate with a decrease in terminal half-lives by linear regression analysis. The 3 subjects with consistent IDU-specific antibodies did not have consistent and clear changes—either increased or decreased half-life—compared to patients without IDU-specific antibodies.

In addition, no relationship was found between urinary GAG levels, enzyme activity in buccal mucosa brushings and pharmacokinetic parameters.

Enzyme uptake into buccal mucosa and leukocytes

Prior to treatment all subjects had very little or undetectable α - L -iduronidase in their buccal mucosa or peripheral leukocytes.

By the Week 2 pre-infusion assessment, enzyme was detectable in the buccal mucosa, reaching an average of about 1% of normal in all patients. Leukocyte enzyme levels have also shown persistently higher levels during treatment (mean of 18%, 12% and 35% of normal at weeks 26, 52 and 104 respectively).

Safety

Adverse events

All 10 subjects had at least 1 adverse event, and at least one deemed to be study drug-related. There were a total of 960 adverse events reported. Eight subjects experienced 32 serious adverse events, including 2 that resulted in death. Seven subjects had 33 adverse events reported as severe.

The most common adverse events reported during the study were: rhinitis (10 subjects), pain, asthenia and fever (9 subjects each), and increased cough, abdominal pain, vascular disorder, and rash (8 subjects each).

The most common of the 33 severe adverse events reported during the study were: bone disorder (including cervical cord compression and spinal deformities), apnea and vascular disorders, allergic reactions and headaches. Ten of these 33 severe events were judged to be definitely or possibly related to the study drug. Fourteen of these 33 severe adverse events were also serious adverse events.

Adverse events were also classified by having occurred on an infusion date after the start of the infusion or as having occurred in non-infusion days. The infusion day adverse events reported by most subjects were: rash, urticaria, allergic reactions and headaches and adverse events with the greatest occurrences were: urticaria (97 events), rash, and angioedema.

All subjects were pre-medicated with diphenidramine intravenously before the laronidase infusion, and some subjects also received corticosteroids and nonsteroidal anti-inflammatory drugs. If a reaction occurred during an infusion, the rate of infusion was slowed or temporarily stopped, the dosage could temporarily be reduced, additional doses of diphenidramine or corticosteroids could be administered or other interventions could be performed.

Reviewer's comment: Approaches to prevent or treat an infusion reaction were so varied that guidelines for a label would be problematic.

Deaths

There were 2 deaths that occurred during the 152-week portion of the study.

Subject 008, age 7, died 4 days after the Week 103 infusion, of apnea (respiratory arrest). Respiratory distress occurred during a flight for the Week 104 assessment, followed by respiratory arrest, without response to intubation and full CPR efforts.. Autopsy findings indicated an apparent systemic viral illness with histologic evidence of an active lymphocytic myocarditis and patchy bronchiolitis. Subject 008 had a high antibody titer, including IgG specifically to laronidase, which persisted until the last assessment at week 100. Complement activation was seen at weeks 6 and 12, but not subsequently. Autopsy findings included mild immune complex deposits in glomerular basement membranes, and mild focal deposition of IgM in lung capillaries with minimal C3, but without any pathologic change by light or electron microscopy in either organ to suggest a functional effect. The subject's residual underlying MPS I disease and/or viral illness may have contributed to death. This subject had received weekly infusion premedication with methylprednisolone starting at Week 8 and continuing throughout the study due to hypersensitivity-type reactions. Study drug did not appear to be directly implicated based on history and autopsy findings.

Reviewer's comment: This death is likely related to acute complications of a viral illness in a subject with severe manifestations of the disorder. The use of systemic steroids as pretreatment for the enzyme infusions may have also contributed.

Subject 002, age 13, died 19 days after the subject's last study infusion at Week 137, of cardiac and respiratory arrest. This subject had a significant medical history of musculoskeletal disease at study enrollment, including scoliosis. The subject was admitted to the hospital for posterior spinal fusion for worsening of her scoliosis from T5 to L4. Postoperatively, the subject was unable to move the lower extremities, and through additional testing and procedures, was diagnosed with spinal cord injury and ascending quadriplegia which progressed to respiratory failure. The subject and family requested discontinuation of the ventilation leading to the subject's death.

Laboratory Abnormalities

Serum Chemistries: Most subjects had elevated serum levels of alkaline phosphatase at screening and pre-treatment. These levels generally decreased by week 8, although for some subjects levels declined and remained above normal for the study period. One subject had an elevated serum LDH level at week 8, which returned to normal by week 10. One subject had an episode of presumed macrolide hepatotoxicity from week 26 until week 30.

Hematology: Several subjects had chronic anemia at pre-treatment and the indices related to red blood cell remained stable throughout the study period.

Antibody development

All subjects developed IgG antibodies to the laronidase product as detected by ELISA by week 6 or 12 of treatment. Serum antibody levels generally declined over time. Using a Western blot technique, the sponsor determined that the initial antibodies detected were directed against a 60 KD protein impurity. Specific immune responses to rhIDU were seen in 4 subjects by Western Blot which were either transient or declined with time.

IgG titer did not correlate with hypersensitivity-type reactions in these patients.

There was no apparent correlation between IgG antibody titer to laronidase product and reductions in excess urinary GAG levels, liver or spleen size. These antibodies did not neutralize enzyme activity.

Complement activation, as measured by the difference between the pre-and postdose levels of CH50 and either C3 or C4, was highest at Week 6 or 12 in 4 subjects, but was greatly reduced or resolved by Week 26 and absent at Week 52. There was no correlation between complement activation and need to receive glucocorticoids as pre-medications for infusion or to manage hypersensitivity-type reactions during infusions. There were no apparent effects of the immune responses on development of immune complex disease or on glomerulonephritis based on urinalysis and GFR results.

Summary

This uncontrolled Phase 1 study of laronidase in 10 subjects with MPS I was able to demonstrate bioactivity in clinical areas that correspond to large accumulation of GAG's such as the reticulo-endothelial system and the kidneys, resulting in substantial reductions of hepatosplenomegaly and excretion of urinary GAG's. An effect on other endpoints, particularly of clinical significance, was not demonstrated in this study. Some data suggested a favorable trend, but it is imperative to note that these data obtained from an open label uncontrolled study cannot provide support for laronidase efficacy in MPS I.

All subjects had infusion associated reactions, which were mild or moderate. All subjects had antibodies to laronidase as assessed by ELISA, but specific anti-IDU antibodies were confirmed in 4 subjects. 2 deaths occurred during this study, but these seem to be unrelated to the study drug, and consistent with the natural history of the severe presentation of MPS I.

Study ALID-003

Overview

This is the only Phase 3, double blind, placebo-controlled, randomized clinical trial conducted for this product to support a claim of efficacy and safety in the treatment of patients with MPS I. The study started on December 28, 2000 and was completed on September 6, 2001.

At the end of the 26-week study period, all subjects were offered participation in an open label extension study (ALID-006).

Protocol

Title: “A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Multinational, Clinical Study of Recombinant Human Alpha-L-Iduronidase in Patients with Mucopolysaccharidosis Type I”. Protocol ALID-003-99.

Design

This was a randomized, double-blind, placebo-controlled, multicenter, multinational study. The study was divided into 2 consecutive phases: a 2-week period to assess eligibility and obtain baseline parameters, and a 26-week treatment phase in which subjects are randomized to receive weekly laronidase or placebo.

Objectives

- **Primary:** assess treatment-related changes in parameters of physiological and functional importance to subjects with MPS I to support a claim of efficacy of laronidase in the treatment of these various conditions.
- **Additional objective:** pharmacokinetic assessment in a subset of study subjects and exploring changes in pharmacokinetic parameters over time.
- **Safety:** assess the incidence of adverse events, including laboratory parameters, vital signs, physical examination, cardiac parameters and immunogenicity.

Eligibility Criteria

Inclusion criteria:

- Male or female, and aged five years or older.
- 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.

- Negative pregnancy test (urine β -hCG) for female subjects of childbearing potential at baseline and use effective contraception throughout the study. Sexually mature males also must use effective contraception.
- Capable of standing independently a minimum of six minutes and walking a minimum of five meters within six minutes.
- Capable of performing a reproducible FVC maneuver.
- Baseline FVC value that is less than or equal to 80% of his/her predicted normal FVC value based on Polgar predicted values for standing height for children five through seven years of age and the Hankinson predicted values for patients aged 8 and above.

Exclusion criteria:

- Prior tracheostomy.
- Prior bone marrow transplantation.
- Pregnant or lactating.
- Use of an investigational drug within 30 days prior to study enrollment.
- Medical condition, serious intercurrent illness, or extenuating circumstance that may significantly interfere with study compliance.
- Known hypersensitivity to laronidase or to components of the active or placebo test solutions.

Treatment assignment / Randomization

Eligible subjects were randomized to the laronidase or placebo group according to a central randomization scheme blocked by site. All subjects, investigators, site personnel, and members of the sponsor's staff were masked to the treatment assignment. The computer-generated randomization codes were held by Genzyme Corporation.

Product information and administration

Subjects randomized to the treatment group received laronidase at a dose of 100 U / kg intravenously weekly during the treatment phase for 26 weeks. Placebo subjects received a pH-adjusted, phosphate-buffered solution. Study solutions were infused weekly, with a minimum interval between consecutive infusions being 4 days.

For administration to subjects, the laronidase or placebo were diluted with between 100 mL to 250 mL (depending on the subject's weight) of 0.1% human serum albumin in saline.

All subjects were pretreated 30 minutes to one hour prior to infusion with an antipyretic regimen (acetaminophen or ibuprofen) and an antihistamine regimen (diphenhydramine, hydroxyzine, chlorpheniramine, cetirizine, fexofenadine or loratadine).

The initial infusion rate of 0.01 mg/kg (2 U/kg) of body weight per hour for 15 minutes was incrementally increased if well tolerated to a maximum of 0.25 mg/kg (43 U/kg) of body weight per hour to deliver the total volume of the infusion over approximately 4 hours. The total infusion volume for subjects weighing between 5 and 20 kg was 100 mL and for subjects weighing between 21 and 100 kg was 250 mL.

If a patient was unable to receive a scheduled treatment infusion within the 10-day maximum period allowed following the last scheduled infusion, that patient received a treatment infusion at the earliest possible date. After such an out-of-schedule treatment infusion, the next infusion was given within 7 ± 3 days. Subsequent treatment infusions were given according to the original weekly treatment infusion schedule.

Evaluations

(baseline and Weeks 4, 8, 12, 16, 20, 26 except as noted)

- a. Forced Vital Capacity (FVC)
- b. Six-minute walk distance, reported in meters walked. Baseline exam repeated 3 times for training, and third trial used as baseline.
- c. Children's Health Assessment Questionnaire (CHAQ) for subjects 5 –18 years of age or Health Assessment Questionnaire (HAQ) for subjects 19 years of age or older. (assessed at baseline, weeks 4, 12, and 26)
- d. Sleep study (to measure apnea/ hypopnea events and oxygen desaturation) are assessed at baseline, and weeks 4, 12, and 26
- e. Liver volume by MRI at baseline and week 26
- f. Urinary Glycosaminoglycans (GAG)
- g. Joint Range of Motion at baseline and weeks 12 and 26
- h. Child Health Questionnaire or SF-36 at baseline and weeks 12 and 26
- i. Resource utilization
- j. Standing heights for measurement of growth velocity
- k. Investigator global assessment at week 26
- l. Visual acuity by standard eye chart testing, ocular pressure, corneal clouding, and retina / optic nerve exam at baseline and week 26
- m. EKG and echocardiogram at baseline and week 26
- n. FEV₁, total lung capacity and diffusing capacity at baseline and week 26
- o. Parent/caregiver quality of life at baseline and week 26

- p. Pharmacokinetic assessments at 2 selected sites for all enrolled subjects at those sites at week 1, 12 and 26, with samples collected at pre-dose, 15, 45, 90 minutes of infusion, 3 and 4 hours of infusion, 10, 30, 45, 60 minutes post-infusion, 2, 3, 4 and 6 hours post-infusion.
- q. Medical history, VS, and physical examination
- r. Brain / cranio-cervical junction MRI at baseline (all subjects) and at the investigator's discretion at week 26
- s. Laboratory evaluations at baseline and weeks 4, 12 and 26, including clinical chemistry, hematology and urinalysis. Urine pregnancy test for females of childbearing potential at baseline and every 4 weeks.
- t. Antibody testing at baseline and every 4 weeks. Complement activation (CH100 or CH50 and C3 or C4 components) was measured if symptoms of a hypersensitivity reaction are noted.
- u. Adverse events

Safety Monitoring

An independent Allergic Reaction Review Board (ARRB) was created to review signs of moderate or severe hypersensitivity and provide guidance on management of these reactions. The ARRB interacted with the Genzyme Pharmacovigilance group and infrequently directly with investigators.

Endpoints

- Primary efficacy (co-primary endpoints):
 - a. Mean change from baseline to week 26 in the percent predicted FVC value based on standing height
 - b. Mean absolute change from baseline to week 26 in the 6 minute walk (in meters)
- Secondary efficacy:
 - a. Apnea / Hypopnea Index
 - b. Hepatomegaly
 - c. Children's Health Assessment Questionnaire (CHAQ) / Health Assessment Questionnaire (HAQ)
 - d. Urinary GAG's
- Tertiary Efficacy:
 - a. Global status Child Health Questionnaire given to children 5 to 18 years old or the Short Form – 36 given to adult subjects
 - b. Growth Velocity for pre-pubertal subjects
 - c. Visual Acuity
 - d. Cardiac Function Testing by electrocardiogram and echocardiogram parameters

- e. Investigator Global Assessment
- f. Forced Expiratory Volume in One second (FEV1)
- g. Total Lung Capacity
- h. Diffusing Capacity
- i. Parent / Primary Caregiver QoL
- j. Resource Utilization

Reviewer's comment: The primary efficacy endpoint of percent predicted FVC was modified to include different formulas to calculate the variable according to age categories (Polgar for ages 5 – 7 years and Hankinson for subjects 8 years of age or older at baseline). The percent predicted FVC was again revised at the study conclusion to be calculated with reference to baseline height, instead of the current height at the time of spirometry assessment at week 26. Secondary and tertiary endpoints were modified as follows:

The sleep study endpoint was clarified further to include measures of electroencephalogram, electromyogram, nasal and oral airflow, chest and abdominal movement, oxygen saturation, and rapid eye movement. The data would be transferred to a core laboratory at New York University and interpreted in a blinded fashion. During the course of the blinded reading, the independent expert noted a substantial proportion of subjects with normal AHI scores at baseline and recommended a subset analysis of the most severely affected subjects (AHI scores ≥ 10 for children younger than 15 years and AHI scores ≥ 15 for subjects older than 15 years) and for all subjects with AHI ≥ 20 , in whom clinical intervention may be warranted.

Active shoulder flexion was added as a secondary endpoint, whereas shoulder extension, knee flexion and extension were added as tertiary endpoints.

The secondary endpoint of CHAQ / HAQ was further defined as the Disability Index derived from the questionnaires, as a summary score of activities of daily living. Another component of the CHAQ / HAQ was made into a tertiary efficacy endpoint as an assessment of the subject's pain, plotted in a visual analog scale.

Urinary GAG's measurements became tertiary endpoints.

Visual Acuity was further expanded to included assessments of tonometry, funduscopy and slit lamp examinations.

Statistical Analysis

Sample size was estimated based on the cross-sectional, non-interventional survey study ALID-004 data in MPS I subjects. A total sample of 42 subjects (21 per treatment group) provided 80% power to detect an absolute difference of 15% from a value of 55% in mean percent predicted FVC from baseline to week 26, assuming a standard deviation of 15% and a dropout rate of 20% and maintaining a Type I error at 5%. The same total sample size provided 80% power to detect a difference of 125 meters in the

mean distance walked comparing baseline to week 26, assuming a standard deviation of 15% and a dropout rate of 20% and maintaining a Type I error at 5%.

The final statistical analysis plan was submitted on 9/19/01, 13 days after conclusion of the study. Genzyme was responsible for data entry and editing, review of information in the CRF's, statistical analysis and generation of the clinical study reports.

Primary efficacy endpoints are analyzed for both the Intent to Treat (ITT) population and the Per Protocol (PP) population. ITT population includes all randomized subjects and is the basis for the efficacy determination. Per Protocol population is defined as all subjects who received at least one infusion and had no major protocol violations, e. g. missing more than 5 of the 26 total infusions. Hypothesis testing is done using Wilcoxon rank-sum test on the change from baseline to week 26 in the 2 treatment groups for both primary endpoints. Baseline is defined as the third or final evaluation during the baseline phase just prior to randomization. This is due to a potential training effect of performing 3 assessments for FVC and 6 minutes walk distance in a 2-week period.

The study used co-primary endpoints and was to be considered statistically significant only if both primary endpoints meet or exceed the critical p-value of 0.05.

Secondary and tertiary endpoints are tested for the ITT population using ANOVA, with treatment group and study site as independent variables and mean change from baseline for each continuous secondary and tertiary endpoint as the dependent variable, except for the Investigator Global Assessment, which is intrinsically a categorical comparison to baseline. In addition, descriptive statistics are used for the ITT population to present changes from baseline to all timepoints in the study, by treatment group. Categorical tertiary endpoints are analyzed with Fisher's Exact test.

Missing data for subjects who missed study visits or terminated the study early are imputed by the last observation carried forward method, except for safety data or resource utilization data, which are not imputed.

Study Conduct

The study was conducted under IND 7334. Study sites were audited by representatives of Genzyme Corporation or Genzyme Europe for North America or European sites, respectively.

Study conduct changes:

- Antibody confirmation after screening ELISA was changed to a radioimmunoprecipitation assay.
- Amendment 3 submitted on 3/27/01 (3 months into the study) revises and expands on the allowed antihistamines and antipyretics to be used prior to infusion.
- Amendment 3 also revises the method to determine the predicted FVC values according to the age of the affected subject: Polgar predicted values for children 5 to 7 years old and Hankinson predicted values for subjects 8 years and older.

Reviewer's comment: This last change has no effect in the data collection of FVC, as the calculation of the predicted FVC value for the purpose of the analysis is not performed at the time of the assessment.

- The 6-minute walk test has been developed and validated based on a 30m long walking path, with subjects making turns each time the full length is reached. However, not all centers in this study were able to employ a 30m length, and a 15 m length was necessary. In order to ensure consistency, all centers were instructed to use the 15m length.

Reviewer's comment: This change ensured that the results would be fair for comparisons between centers and pooling of the centers. However, this is not exactly the validated testing tool. Comparison to prior uses of this evaluation tool, and to standardized normal values may not be valid. This modification was retained through the extension study as well.

Database Integrity

Representatives of BioMarin/ Genzyme LLC monitored the study progress in all sites according to ICH-GCP guidelines.

After completing the final study report for ALID-003 on February 17, 2002, it was ascertained that the joint range of motion data had been incorrectly recorded at several sites. To maintain the integrity of the database, the joint range of motion measurements were corrected in the database. A revised study report was reissued.

Protocol violations

Protocol violations were prospectively defined prior to locking the database as follows:

- a. subject missing more than 5 of the 26 infusions
- b. occurrence of a treatment dispensing error with the subject receiving the incorrect drug assignment
- c. tracheostomy performed in a subject during the study
- d. bone marrow transplantation performed in a subject during the study
- e. occurrence of infusion associated reaction classified as severe by the investigator

There were numerous protocol deviations in all clinical sites. However, these deviations did not impact the overall study interpretation. The majority of the deviations were related to small divergences in timing of infusion or assessments, or incomplete performance of the required assessments at a given timepoint. Deviations occurring in 2 subjects were considered major protocol violations that could impact in the efficacy analyses; these subjects were excluded from the PP analysis. The violations were: presence of a significant medical condition (prior heart transplant and pacemaker implant) in a subject randomized to placebo and missing 7 of the 26 infusions in a subject randomized to laronidase. These subjects were included in the ITT analyses, but do not impair forming conclusions based upon these analyses.

FDA site inspection findings

The FDA inspector for the Canadian and United Kingdom sites noted that either the Polgar normative method (irrespective of the subject's age) or a non-specified method were used in on-site calculations of the percent of predicted Forced Vital Capacity (FVC). Since the only % FVC values generated at the clinical sites were those used in the determination of eligibility to the study, this does not impact outcome evaluation.

In addition, the FDA site inspector for the University of North Carolina uncovered discrepant information for 5 subjects related to assessment of FVC (in liters) in the pediatric pulmonary lab and the data recorded in the CRF for the week 26 visit. The sponsor explained that all values for the pulmonary testing to be recorded in the CRF were supposed to originate from the testing performed at the pediatric pulmonary lab. In the North Carolina site, however, the diffusing capacity and total lung capacity data had to be obtained in the adult pulmonary laboratory, which also generated redundant data related to FVC and FEV1. The five subjects had the FEV1 and FVC data obtained in the adult pulmonary laboratory entered in the CRF erroneously and unknown to study monitors. These data were used in the sponsor's analyses.

The sponsor will generate an Erratum containing the FEV1 and FVC values from the pediatric pulmonary laboratory and will re-analyze the FVC endpoints in the study. Corrected analyses and data files have not been submitted to FDA as of the date of this document. All analyses in this document are based on the datasets with the erroneous data included. However, the preliminary assessment is that these changes are minor, and will not change any study conclusions

Results

Subject disposition

The study started on December 28, 2000 and completed September 6, 2001. 47 subjects with MPS I enrolled into the study for screening, of whom 2 failed to have reproducible FVC measurements and were excluded. The 45 subjects were randomized, 22 to laronidase and 23 to placebo. All 45 subjects completed the study. The 45 subjects were enrolled in 5 centers in North America and Europe, with 6 to 12 subjects at each center.

Baseline characteristics

Table 6. Study subject baseline characteristics for selected parameters

Baseline Characteristic	Category	Placebo n = 23	Laronidase n = 22
Gender	Male	11	11
	Female	12	11
Race	Caucasian	21	16
	Black	0	0
	Hispanic	0	4
	Asian	1	1
	Other	1	1
Age Group	≤ 12 years	10	12
	13 to ≤ 18 years	8	3
	19 to ≤ 65 years	5	7
Syndrome	Hurler	1	0
	Hurler-Scheie	19	18
	Scheie	3	4
Years since onset of symptoms	Mean ± SD	12.7 ± 7.7	12.7 ± 8.5
Years since initial diagnosis	Mean ± SD	8.7 ± 6.1	9.4 ± 6.6
Enzyme activity (% lower normal range)*	Mean ± SD	1.9 ± 3.2	1.2 ± 2.1
Weight (kg)	Mean ± SD	40.3 ± 13.0	35.3 ± 12.4
Height (cm)	Mean ± SD	137.2 ± 12.1	133.5 ± 16.1

* Enzyme activity as assessed in skin fibroblasts or leukocytes

Table 7 shows the baseline characteristics for the 2 % FVC and 6 minute walk distance.

Baseline Characteristics	Placebo n = 23	Laronidase N = 22
Mean % Predicted FVC	54.2 ± 16.0	48.4 ± 14.8
Mean 6 min. walk distance (m)	366.7 ± 113.7	319.0 ± 131.4

Study drug exposure

All 45 randomized subjects completed 26 weeks of the study. The mean (± SD) number of study drug infusions for the placebo group was 25.4 ± 0.9 whereas for the laronidase-treated group was 25.3 ± 1.6 infusions. One subject in the laronidase group missed 7 infusions, but 6 of these were due to a hospitalization for aortic stenosis. The most common reasons for missing infusions were similar for placebo and laronidase and related to problems in travel arrangements or illness.

Primary endpoints

Percent Predicted Forced Vital Capacity (% FVC)

Primary analysis

Lung volumes (measured in Liters) vary greatly among individuals due to extra-pulmonary factors, such as age, height, race and gender. In order to account for these variations and increase interpretability of the data, the sponsor proposed the use of % FVC. % FVC is usually calculated based on the subject's height at the time of assessment of the pulmonary function.

After the breaking of the blind, the issue of appropriateness of adjustment of respiratory volume by the current height was reconsidered. Factors in favor of using baseline height in the calculation of % FVC were:

- Height is difficult to measure in subjects with MPS I due to skeletal and joint disease leading to abnormal posture, with intra-subject variability
- If true changes in joint stiffness and posture were to occur, there would be a change in %FVC even without any change in respiratory function. If this were a systematic change in posture, such as a lessening of postural abnormalities in the laronidase group, there would be a systematic effect to decrease % FVC.
- Conversely, it was seen that the placebo-treated subjects had an apparent 2.7 % decrease in the % FVC without any actual change in lung volumes. The actual change in respiratory function (i.e., none on average) is better reflected in the % FVC as calculated using baseline height.

Assessments for all subjects at baseline and week 26 were completed. Therefore no imputation for missing data was necessary. Table 8 shows the changes from baseline to week 26 in median and mean % FVC, as calculated using both the current height at the time of assessment or using the baseline height, for both treatment groups.

Table 8. Changes from Baseline (\pm SD) to Week 26 in median and mean % FVC

% FVC	Laronidase	Placebo	p value
Mean Baseline	48.4 \pm 14.8	54.2 \pm 16.0	
Mean Week 26 (Baseline Height)	53.7 \pm 18.6	53.3 \pm 14.2	
Mean Change (Baseline Height)	5.3	- 0.6	
Mean Difference between groups	5.9		
Median Change (Baseline Height)	3.0	0.0	0.016 *
Mean Week 26 (Current Height)	50.2 \pm 17.1	51.5 \pm 13.1	
Mean Change (Current Height)	1.8	- 2.7	
Mean Difference between groups	4.5		
Median Change (Current Height)	1.0	- 1.1	0.028 *

*Wilcoxon test

Reviewer's comment: As discussed above regarding the use of current height at week 26 or baseline height in the computation of % FVC, the data on height for the placebo-treated group shows only a modest increase from a mean (\pm SD) of 137.2 (\pm 12.5) cm to 139.0 \pm 11.6, a mean change of 1.8 cm in 26 weeks of study. In contrast, the mean laronidase-treated group increased the mean height from 133.5 \pm 16.1 to 136.5 \pm 15.4 cm, a mean change of 3 cm in the 26 weeks of the study.

In addition to the statistical significance for the treatment effect between the 2 groups, the sponsor also notes this is an 11% relative improvement from baseline for the laronidase group (5.3 % / 48.4 %). The sponsor proposes that this is a clinically significant improvement according to the American Thoracic Society.

Reviewer's comment: Even as the analysis shows a statistically significant treatment effect for laronidase, the clinical significance of the effect size is unclear. Forced Vital capacity has been chosen as a surrogate for the restrictive component of the pulmonary impairment, but may not reflect the entire spectrum of impairment seen in other areas of lung and upper airway function. The fact that eligibility for this trial was restricted to subjects with impaired lung function (less than 80% of predicted normal FVC) would be expected to improve the chances of demonstrating a larger clinical effect, as compared to a lessened treatment effect that might be seen if subjects with healthier FVC's were also enrolled.

Exploratory Analysis

Prospectively Defined Exploratory Analysis

Analysis of covariance was performed and has shown the retention of the treatment effect when covariates such as clinical site, baseline FVC, baseline Apnea Hypopnea Index, baseline Total Lung Capacity, baseline liver volume, and baseline GAG level are

taken into account ($p= 0.04$). The ANCOVA was performed using the % FVC as calculated using the current height.

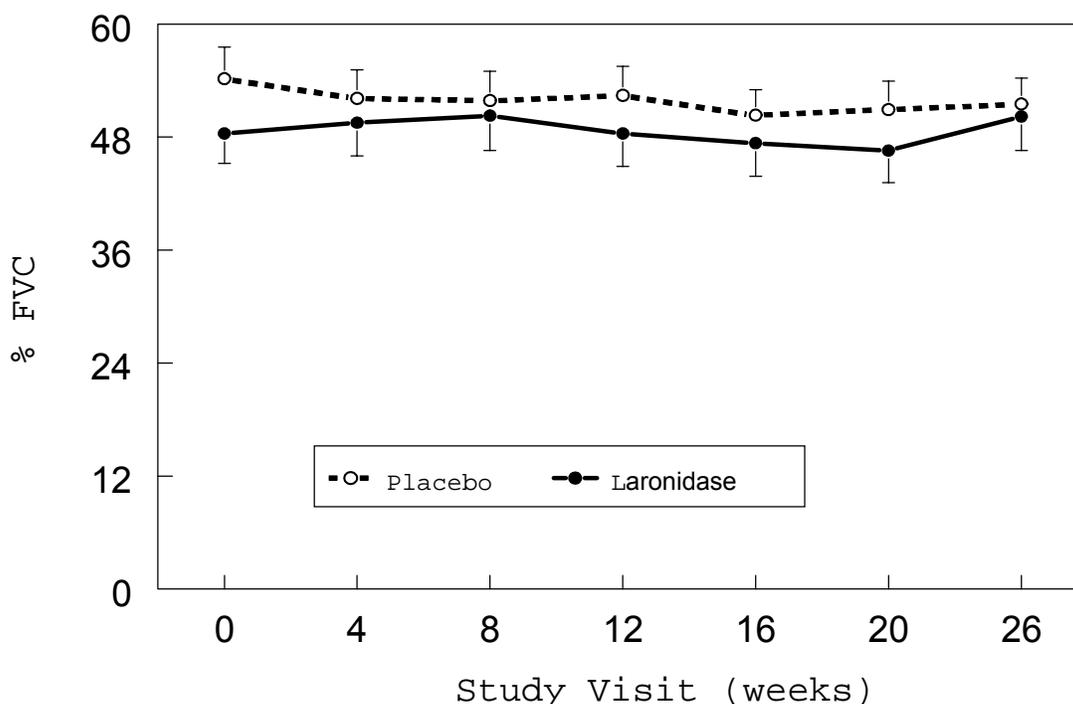
Post-hoc Exploratory Analysis

Analysis of Forced Vital Capacity, in absolute volume

The laronidase-treated group had a mean (\pm SD) increase in forced vital capacity of 0.11 (\pm 0.14) L, whereas the placebo-treated group had no change in the mean forced vital capacity ($- 0.02 \pm 0.13$ L; $p < 0.01$, Wilcoxon test). When analyzing the relative change in liters of forced vital capacity from baseline to week 26, the laronidase-treated group had a mean (\pm SD) increase of 12.2 (\pm 21.9) % increase, whereas the placebo-treated group had a mean increase of 1.8 (\pm 18.4) % in forced vital capacity ($p = 0.02$, by Wilcoxon test). (Note: Data include the described incorrect data for the 5 subjects at Site 4. Preliminary revised analyses do not appear to alter any conclusions)

Analysis by Study Visit:

Figure 2 demonstrates the effect of laronidase treatment on the % FVC (calculated with current heights) across the study period, as compared to control.



Note: 4 missing values for Week 4 were imputed by LOCF.

Mean % FVC was lower in the laronidase-treated group than the placebo group at baseline. From baseline to week 4 a tendency to converge the lines for the 2 treatment groups is seen. This is due to a small increase in %FVC in the laronidase group, but a larger acute decline in %FVC in the placebo group. While the placebo-treated subjects

had a relatively constant mean % FVC for the remainder of the study, laronidase-treated subjects had a small decline in mean % FVC from week 8 to week 20. There was a tendency for the 2 curves to converge by the end of the 26 week study period, primarily because of a rise of % FVC in the laronidase-treated group between weeks 20 and 26.

Reviewer's comment: The sponsor explains the drop in % FVC seen between weeks 8 and 20 in the laronidase-treated group as possibly related to a combination of various factors, including intercurrent illness, assessment following an infusion, seasonal effects or subject fatigue from repeat study visits. However, given the size of the sample and the homogeneous distribution of disease severity in the 2 treatment groups, one would expect to observe the same factors playing a role in the control arm, which did not show a decline in FVC. Two subjects in the laronidase-treated group had significant worsening in the %FVC between weeks 12 and 20, not explained by a correlation with AE's or use of concomitant medications.

The rise in % FVC between week 20 and week 26 in the laronidase-treated group is notable. Three laronidase-treated subjects had a substantial rise in % FVC in that time period. Subject 30608 manifested an increase from 59.4 % to 80.6 % of the normal predicted FVC, without an obvious explanation; Subject 30806 increased % FVC from 40 % to 53.7 %, which could be explained on the basis of recovery from a series of SAE's, starting with severe CHF diagnosed at week 12, secondary to severe aortic stenosis, complications of aortic valvuloplasty, with cardiac arrest, pneumonia and sepsis; and Subject 61010 also had an unexplained significant rise in % FVC from 17 to 30.9 %.

On the other hand, the placebo-treated group had a remarkable but unexplained drop in the % FVC from Baseline to week 4, with subsequent stabilization of %FVC's until week 26. The drop cannot be attributed to a training effect during the 3 baseline assessments made because it was not observed in the laronidase group. Placebo-treated Subject 60603 had a substantial drop from baseline to week 4 in the order of 23 points in the %FVC (clearly an outlier for both groups in the magnitude of drop). A sensitivity analysis excluding this subject maintains the treatment effect seen (6.4 %) with a $p = 0.04$.

However, the importance of this initial, but not continuing, decline in %FVC to the analysis is illustrated by the sensitivity analysis of comparing the change from baseline to week 26 in the laronidase-treated group and the change from week 4 to week 26 in the placebo-treated group (in other words, considering week 4 as the "baseline" for the placebo-treated group) would eliminate the treatment effect observed in the ITT population, with a difference from placebo of 2.5 % ($p=0.22$).

Analysis by Study Center: There was general consistency in study outcomes for this endpoint. In 4 of the 5 clinical sites, placebo-treated subjects experienced worsening of the % FVC and rhIDU-treated subjects showed improvement in this primary endpoint. In one center (Canada), the laronidase-treated subjects did not show improvement of % FVC, whereas placebo-treated subjects did.

Analysis by Gender: Table 9 shows the mean (\pm SD) baseline and changes from baseline to week 26 in % FVC (as calculated from current heights) by gender.

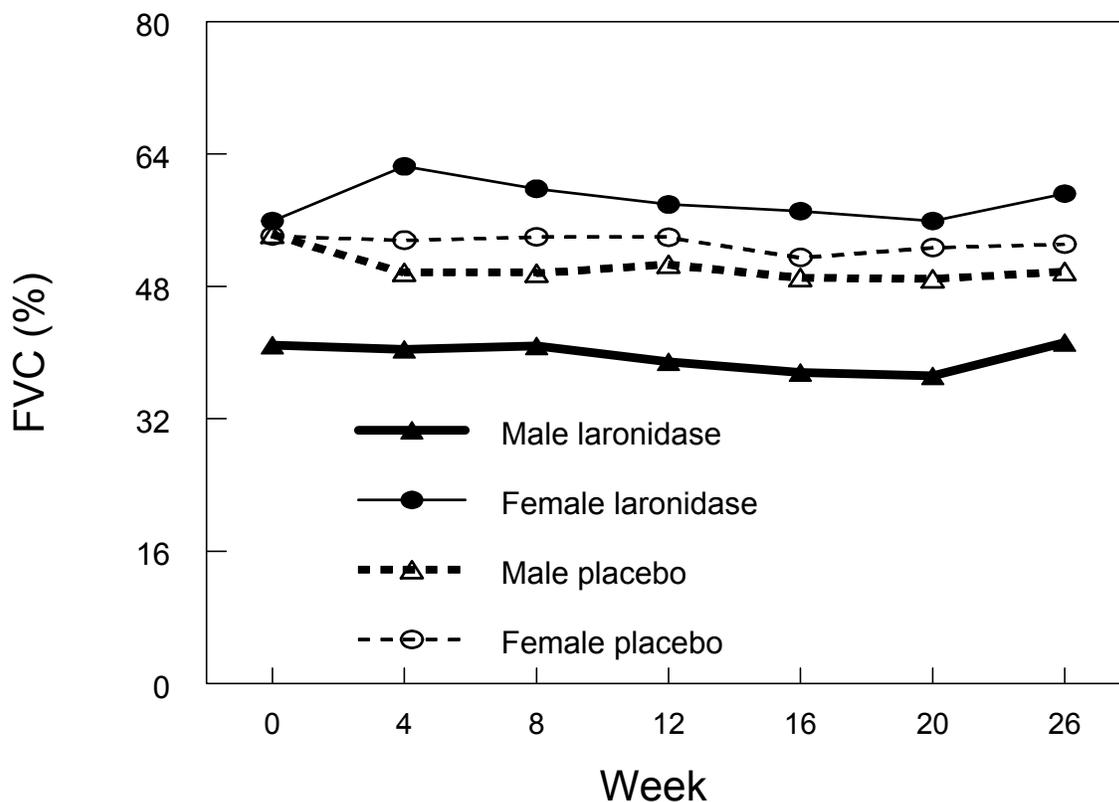
Table 9. Mean % FVC baseline and changes from baseline to week 26 according to gender

Gender	Placebo				Laronidase			
	n	Baseline	Week 26	Change	n	Baseline	Week 26	Change
Female	12	54.1 ± 13.1	53.1 ± 11.8	- 1.0	11	55.9 ± 9.9	59.2 ± 15.4	3.3
Male	11	54.4 ± 19.4	49.8 ± 14.8	- 4.6	11	40.9 ± 15.5	41.2 ± 14.1	0.3

(Note: Data include the described incorrect data for the 5 subjects at Site 4. Preliminary revised analyses do not appear to alter any conclusions)

Reviewer's comment: The treatment-associated difference in change from baseline was similar for both males and females, but males fared worse than females within each treatment groups. Most of the overall between groups difference in the %FVC comes from FVC increase in laronidase-treated females with FVC decline in placebo-treated males. It is also notable from data shown in Table 9 that laronidase-treated males had substantially worse mean % FVC at baseline and at week 26 compared to females or placebo treated males. Both of these observations are illustrated in Figure 3.

Figure 3. Mean % FVC (calculated using current heights) across the study visits plotted by gender and treatment groups



Analysis by Age Category: Table 10 shows the mean % FVC at baseline and change from baseline to week 26 in the 2 treatment groups subdivided by age category tertiles.

Table 10. Mean % FVC baseline and changes from baseline to week 26 according to age category.

Age category	Placebo				Laronidase			
	n	Baseline	Week 26	Change	n	Baseline	Week 26	Change
≤ 12	10	62.1 ± 11.6	56.1 ± 10.3	-6.0	12	51.5 ± 14.9	53.5 ± 18.8	+2.0
13 – 18	8	44.1 ± 17.1	45.6 ± 15.0	+1.5	3	44.5 ± 8.4	44.3 ± 5.8	-0.2
19 – 65	5	54.8 ± 15.3	51.9 ± 14.0	-2.9	7	44.8 ± 17.4	47.1 ± 17.7	+2.3

(Note: Data include the described incorrect data for the 5 subjects at Site 4. Preliminary revised analyses do not appear to alter any conclusions)

Reviewer's comment: Approximately half of the subjects were younger than 12 years, limiting the ability to form comparisons between age subset. No clear pattern of differential in between group differences was apparent.

Analysis by Race / Ethnicity: The great majority of subjects were Caucasian, and no meaningful comparisons were possible among the races to examine the treatment effect.

Analysis by severity of FVC impairment at baseline: Biomarin performed an analysis dividing the treatment groups roughly in half based on the study-aggregate median baseline %FVC. Biomarin observed that subjects with milder pulmonary disease at baseline did better than subjects with lower FVC at baseline ($p=0.04$) with an 8.6 % difference between groups in the milder pulmonary severity subset compared to – 0.3 % difference in the more severely affected individuals at baseline.

Reviewer's comment: This observation suggests that the laronidase effects may be more easily distinguished from that of the control arm when irreversible structural changes did not take place yet.

One needs to keep in mind that % FVC is mostly an index of pulmonary function, but other parameters, such as liver volume could possibly have impact on the amount of restriction being assessed. Hepatosplenomegaly, as seen in both the Phase 1 study as well as in the present study (see below) is reduced in the laronidase-treated group.

Table 11 shows the mean changes from baseline to week 26 in the % predicted FVC among the 4 quartiles of baseline severity in % FVC.

Table 11. Mean changes (\pm SD) from baseline to week 26 in % FVC by the quartiles of severity at baseline

Severity level	range % FVC	Laronidase	N	Placebo	n
least	77.4 – 65.4	10.3 \pm 8.6	4	-2.5 \pm 3.9	7
	65.4 – 51.9	6.1 \pm 8.6	6	-3.2 \pm 8.9	6
	51.9 – 41.6	2.2 \pm 12.3	6	0.9 \pm 6.0	5
most	41.6 – 15.5	4.2 \pm 6.5	6	3.9 \pm 5.3	5

(Note: Data include the described incorrect data for the 5 subjects at Site 4. Preliminary revised analyses do not appear to alter any conclusions)

Reviewer's comment: In the laronidase-treated group, there is a suggestion of greater improvement in % FVC among the less severely affected subjects, However the placebo group suggests a trend towards less decline of FVC with increasing severity. The consistent gradual lessening of the treatment associated difference as severity increases suggests the possibility that laronidase has less benefit in subjects with more advanced pulmonary restriction.

Analysis of subject distribution according to gender, age category, treatment assignment and severity of % FVC at baseline

As seen from the exploratory analyses of the FVC data changes in the two treatment groups by subsets in gender and severity, these demographic factors may have influenced the observed treatment effect. The total subject number is highly limited in this study, and there is potential that imbalances of subject distribution in one of these factors could have an effect on a subset analysis intended to examine a different factor.

The gender and baseline severity factors appear to have a potential interaction with treatment effect. While within the placebo group there is a uniform distribution of each gender across the severity categories, the laronidase group is problematic. Somewhat more female laronidase subjects are in the lower two severity categories (7:4) while somewhat more male laronidase subjects are in the two more severe categories (3:8). This inverse imbalance leads to the problem that within the laronidase group, it is difficult to distinguish between a gender related factor (i.e., female patients did better on laronidase than male) versus a severity related factor (i.e., less severe patients on laronidase did better than more severe). Thus, conclusions regarding the previous subset explorations may be difficult.

Immunogenicity: The ELISA assay provided was somewhat non-specific to laronidase, probably because of cross reactivity with a 60 kD protein impurity present in the final product. By the ELISA assay, all laronidase-treated subjects became seropositive while 5 placebo-treated subjects were also ELISA positive. The anti-laronidase antibody became detectable early in the study, between weeks 4 and 8. There was no correlation between the ELISA determined antibody levels and the % FVC change from baseline at week 26.

Radioimmunoprecipitation (RIP) was used as a confirmatory assay for the ELISA. While highly specific to laronidase as a substrate, RIP is a qualitative assay only. 20 of 22 laronidase-treated subjects developed RIP-based anti-laronidase antibodies.

Reviewer's comment: Nearly all laronidase subjects became antibody positive. Comparisons between seropositive and seronegative laronidase-treated subjects are not informative.

Analysis by baseline enzyme level: There was no correlation between the baseline enzyme levels and the baseline %FVC or the change in % FVC at week 26 from baseline in the group as a whole or the 2 treatment groups.

Analysis by change in height: No discernible trends were seen in comparing the change in subjects heights during the 26 weeks of study with their change in FVC.

Six minute walk distance (meters)

Primary analysis

After 26 weeks of the study, subjects in the laronidase group had a median increase of 27.5 meters in the 6 minute walk distance, while subjects in the placebo group showed a median decrease of 11.0 meters walked in the 6 minute interval. The overall difference, as analyzed by the Wilcoxon rank sum test, did not reach statistical

significance between the treatment groups (Table 14). Assessments for all subjects at baseline and week 26 were completed and no missing values were present.

Table 12. Changes from Baseline to Week 26 in 6 minute walk distance (in meters)

	Laronidase (n=22)	Placebo (n=23)	p value
Mean Baseline (m)	319.1 ± 131.4	366.7 ± 113.7	
Mean Week 26 (m)	338.8 ± 127.1	348.3 ± 128.8	
Mean Change (m)	19.7	- 18.4	
Difference between groups	38.1		
Median Change	27.5	-11.0	0.07 *

*Wilcoxon test

Reviewer's comment: The trend was favorable to laronidase effect, but statistical significance was not reached. The clinical significance of this difference is also unclear. This endpoint was selected because the distance walked in the 6 minute walk test is an assessment of overall function and has the opportunity to demonstrate a clinically meaningful effect. Walk distance probably indicates a measure of heart function, lung function, joint and neuromuscular function, all of these affected in subjects with MPS I, to a greater or smaller extent.

Unlike %FVC, there was no effort to limit enrollment to subjects substantially affected in their capacity to walk, which may have limited the ability to observe a clinical effect and contributed to lack of statistical significance. However, a sensitivity analysis conducted post-hoc comparing the effect of laronidase treatment to placebo in subjects above and below the median failed to demonstrate an effect of the test drug in the more severely affected subjects. Please refer to this and other sensitivity analyses described below.

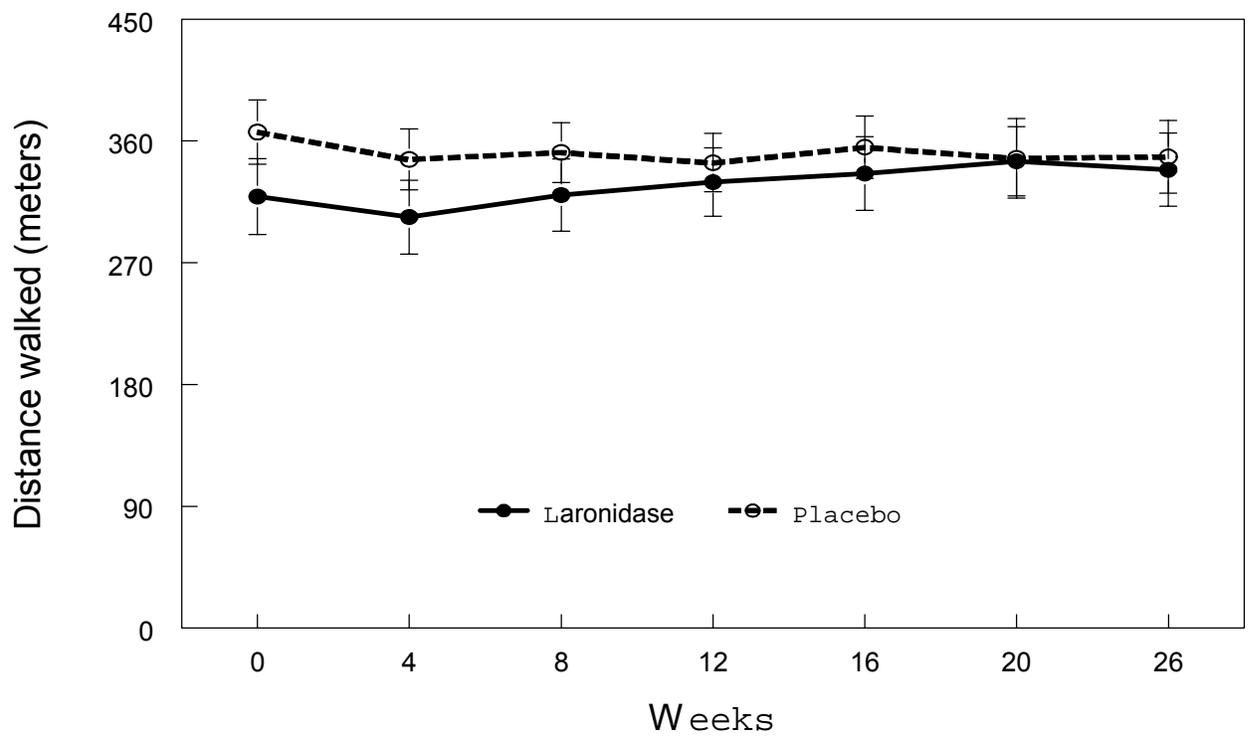
Exploratory Analysis

Prospectively Defined Exploratory Analysis

Analysis of covariance was performed with center, baseline 6 minute walk distance, gender, baseline standing height, and baseline liver volume used as covariates. In this model, the treatment effect p-value achieved statistical significance ($p=0.04$). This treatment effect was seen in the ANCOVA after controlling for the significant covariates of gender ($p=0.02$) and baseline 6 minute walk distance ($p < 0.001$).

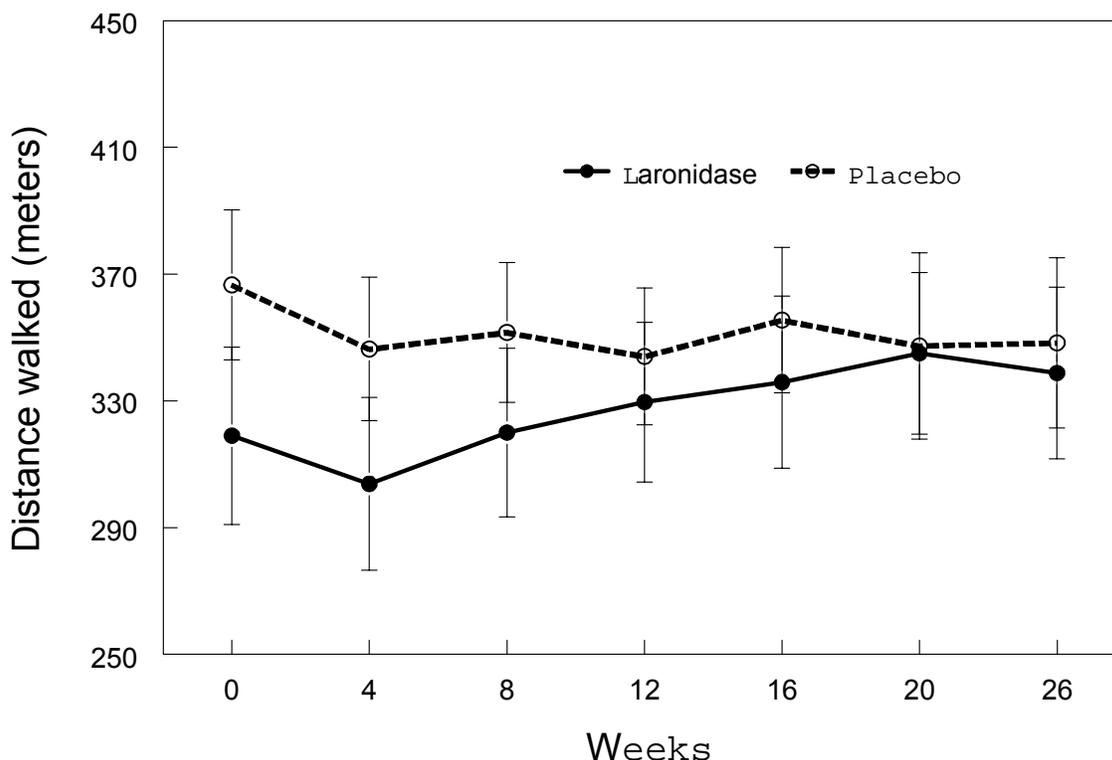
Analysis by Study Visit: Figure 4 and Figure 5 demonstrate the effect of laronidase treatment on the 6 minute walk distance across the study period, as compared to control.

Figure 4. Mean (\pm SD) distances during Study 003 by treatment group



Reviewer's comment: Because the 2 lines seem almost superimposed, the following figure amplifies the range 250 to 450 meters where the subtle changes in distance walked were observed

Figure 5. Mean (\pm SD) distances walked across the 26 weeks of Study 003 by treatment group, plotted in the range where the changes occurred



Reviewer's comments: The drop observed for both treatment groups between baseline and Week 4 is attributed to the training effect obtained by selecting the third measurement of this test in a period of approximately 7 days for determination of baseline. There is a small but consistent increment in distance between the first and the third of these assessments. The effect of training is likely lost after a 4 week interval. Three trials were not used for the subsequent assessments. The same training effect was not observed in the analysis among the 3 baseline measures of % FVC for determination of the baseline value for that endpoint.

The two groups were not identical in walking capacity at baseline, with the laronidase group walking lesser distances. However, unlike the data shown for the % FVC, here there is small but consistent improvement in the distance walked in 6 minutes in the laronidase-treated group, even if with unclear clinical significance. Unlike the graphic shown for the % FVC by study visit, the laronidase-treated group does not show a difficult to interpret mean increase in the Week 20 to Week 26 interval.

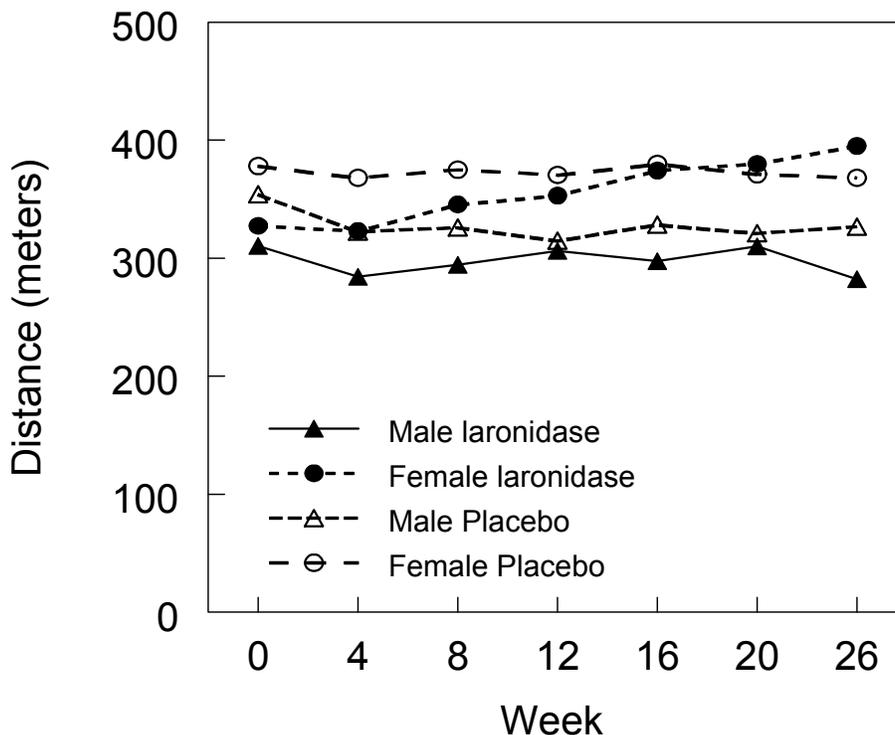
Analysis by Gender

Reviewer’s comment: Further analysis into the covariates that drove the statistical significance in this ANCOVA has demonstrated that the trend to favorable treatment – associated difference is largely from female subjects, as shown in Table 13 and Figure 6. These findings are similar to those related to laronidase effects on % FVC by gender; where only laronidase-treated females showed improvement. Unlike the % FVC data, there was no difference between groups in the change from baseline for males.

Table 13. Baseline, Week 26 mean (± SD) distances walked and mean changes in the 6 minute walk distance from baseline to Week 26 by Gender

	Timepoint	Laronidase	n	Placebo	n
Female	Baseline	327.6 ± 107.7	11	378.1 ± 104.4	12
	Week 26	395.2 ± 82.8		368.1 ± 121.1	
	Change	67.5		- 10.0	
Male	Baseline	310.5 ± 157.0	11	354.2 ± 126.9	11
	Week 26	282.4 ± 141.6		326.7 ± 139.3	
	Change	- 28.1		-27.5	

Figure 6. Mean distance walked in 6 minutes across the study visits plotted by gender and treatment groups



Reviewer's comment: Similar to %FVC examined by study visit and gender, the laronidase-treated males had a lower baseline distance compared to the other 3 groups. Both the figure and the table clearly show only the laronidase-treated females contribute to the marginal treatment effect seen.

Analysis by Severity: BioMarin performed the prospectively planned analysis by severity at baseline of dividing the treatment groups into a mild subset and more impaired subsets by subdividing based on baseline walking distance and baseline aggregate median (358 m). This analysis did not yield any significant differences in the pattern compared to the study overall.

Reviewer's comment: A more informative analysis of the mean changes in the 6 minute walk distance by severity, as seen in Table 14, divides the 45 participating subjects into 4 quartiles by severity at baseline.

Table 14 . Mean changes from baseline to week 26 in the 6 minute walk distance by the quartiles of severity at baseline

Severity level	Baseline Distance range	Laronidase	n	Placebo	n
least	411 – 591	-5.3 ± 74.0	3	-19.6 ± 61.4	8
	358 – 411	31.1 ± 64.7	7	-7.7 ± 95.1	4
	276.5 – 358	-8.4 ± 60.9	5	-28.1 ± 83.6	7
most	14 – 276.5	39.1 ± 80.1	7	-9.2 ± 33.1	4

No trend related to severity at baseline can be distinguished. This is unlike the comparable exploratory analysis for FVC.

Unlike the examination of distribution of subjects in cross categories of gender and FVC severity, the distribution of subjects by dual categorization of gender and Walk distance severity shows less imbalance in the distribution of numbers of subjects. Thus factors of gender and severity could be better distinguished on this endpoint. Thus, it is interesting to note that for this endpoint, gender is still suggested to have an impact on treatment associated difference, but baseline severity is not.

Post-hoc Exploratory Analysis

Some effect of the age categories contributed to differences between the treatment groups, as shown in Table 15.

Table 15. Baseline and Week 26 mean (\pm SD) 6 minute walk distances and difference between placebo and laronidase changes by Age Category

Age category	Placebo			Laronidase		
	n	Baseline	Week 26	n	Baseline	Week 26
≤ 12	10	410.4 \pm 119.3	382.9 \pm 120.6	12	321.8 \pm 121.0	353.6 \pm 127.7
		Difference between groups: 59.3 meters				
13 – \leq 18	8	308.8 \pm 112.9	274.6 \pm 142.6	3	482.3 \pm 111.6	480.7 \pm 33.2
		Difference between groups: 32.5 meters				
19 – \leq 65	5	371.8 \pm 72.3	397.0 \pm 78.2	7	244.3 \pm 97.8	252.6 \pm 84.0
		Difference between groups: - 16.9 meters				

Reviewer's comment: A comparison of the baseline data among the 2 treatment groups in the different age categories reveals more imbalances between treatment groups within age category than overall for the study. Although there are few subjects in the older age categories, these data suggest the possibility that intervention at an earlier age may be more favorable than at an older age. It is possible, but not proven, that reduction of accumulated GAG's in heart, lungs and joints be less resistant to therapy. These data do not suggest even a trend to benefit in older patients.

However, the baseline imbalances for these subsets may preclude drawing any firm conclusions from this post-hoc exploratory analysis.

Analysis by Study Center: Study outcomes were examined by center. Overall, placebo treated subjects improved in 2 / 5 centers, whereas laronidase-treated subjects improved in 4 / 5 centers. However, the numbers are too small to permit drawing any conclusions regarding center related interactions.

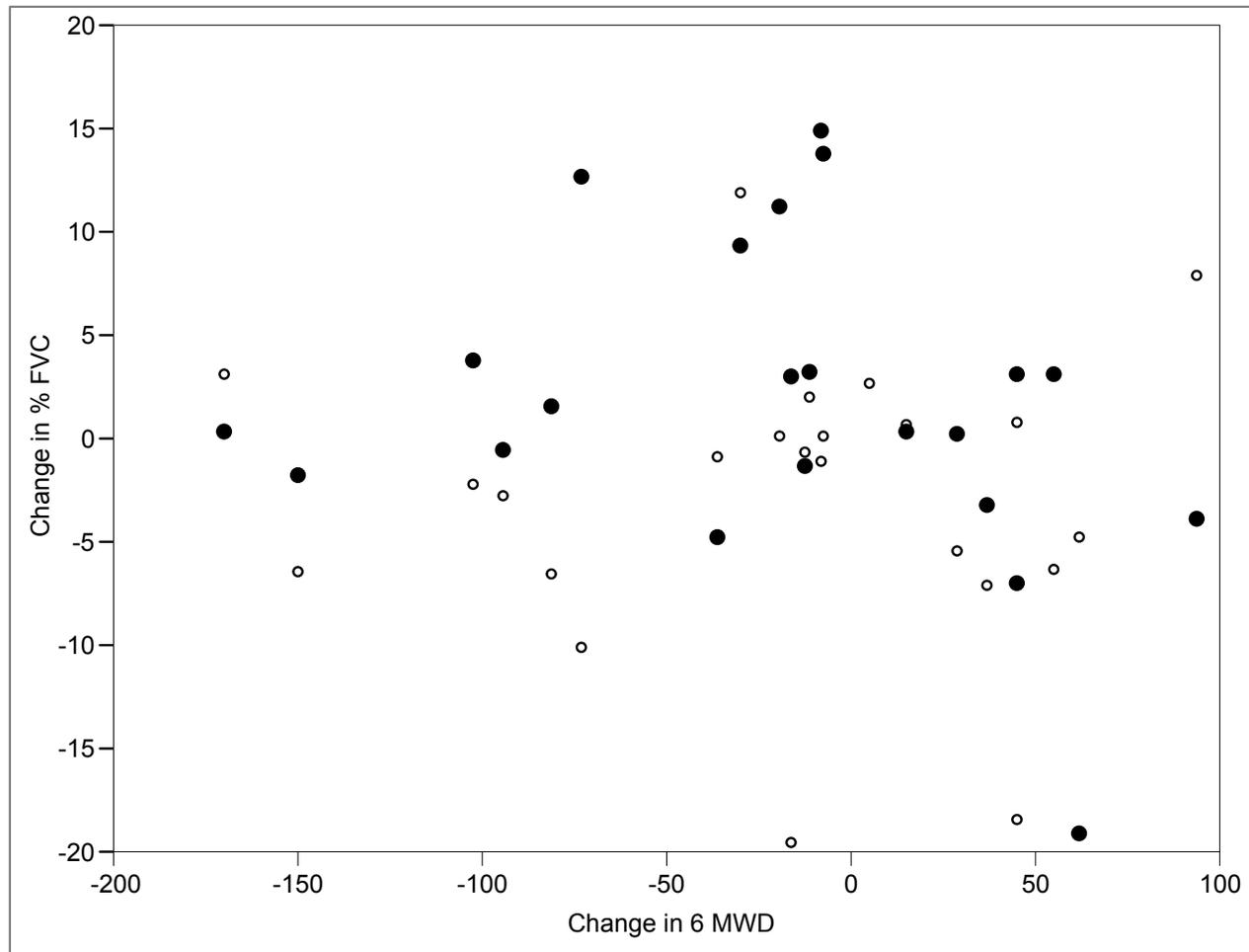
Analysis of effect of anti-laronidase antibodies: The anti-laronidase antibody became detectable, using the ELISA assay, between weeks 4 and 8 for most laronidase-treated subjects (20/22). Therefore, comparisons between seropositive and seronegative subjects regarding the change in the 6 minute walk distance were not informative. There was no correlation between anti-laronidase IgG antibody levels, as determined by ELISA and the 6 minute walk distance change from baseline at week 26.

Analysis by baseline enzyme level: There was no correlation between the baseline enzyme levels and the baseline 6 minute walk distance or the change in 6 minute walk distance at week 26 from baseline in the study as a whole or the 2 treatment groups.

Analysis by treatment effect in the change of % FVC from baseline: There is no correlation between the direction and magnitude of change from baseline to week 26 in

% FVC and the 6 minute walk distance, as seen in figure 7. Subjects who demonstrated improvement in one of the endpoints cannot be predicted to have demonstrated improvement in the other. This can be interpreted as indicating the observed changes in % FVC in the study are not large enough to have notable impact upon the distance walked in 6 minutes for these subjects, thus raising uncertainty as to the clinical meaning of %FVC changes of the size observed in the study.

Figure 7. Baseline to week 26 changes in the % FVC plotted against the changes in the 6 minute walk distance in individual subjects



Legend: Points shown as filled circles represent laronidase-treated subjects and points represented as empty circles represent placebo-treated subjects.

Secondary endpoints

Apnea / Hypopnea Index (AHI) of the sleep study

Primary Analysis

The endpoint used for the analysis of efficacy was the mean AHI change from baseline to week 26 comparison between the treatment groups by ANOVA. The AHI is defined as the number of apnea (cessation of airflow for 10 or more seconds) and hypopnea (50% decrease in airflow per breath accompanied by arousal or desaturation) events divided by the hours of sleep, reported as events per hour. Therefore a decrease in the index is a favorable event. The laronidase-treated subjects experienced an AHI decrease of 2.9, whereas the placebo-treated subjects had a 0.4 increase in the AHI. The difference between groups of -3.6 events per hour was favorable to laronidase but did not reach statistical significance ($p=0.14$). The clinical significance of this finding is questionable.

Exploratory Analysis

The independent expert who performed the blinded readings of the sleep studies had noted that a significant number of subjects (18 / 21 placebo-treated and 11 / 20 rhIDU-treated) had normal AHI at baseline (< 20), which could have obscured the treatment effect in those with sleep apnea. He recommended an analysis of the results from subjects younger than 15 years with AHI scores ≥ 10 and adults with AHI scores ≥ 15 , based on recently published guidelines (American Academy of Sleep Medicine Report: Sleep-Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. *Sleep* 1999, 22(5):667-689. and American Academy of Pediatrics, Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. *Pediatrics* 2002 Vol. 109(4):704-714).

Table 16 shows the data and comparative analysis in the subjects with clinical sleep apnea/hypopnea at baseline.

Table 16. Baseline and Week 26 mean (\pm SD) changes in Apnea/Hypopnea Index (AHI) in Pediatric Subjects with baseline AHI ≥ 10 and Adult Subjects with baseline AHI ≥ 15

	Statistic	Laronidase (n=11)	Placebo (n=8)
More severe AHI	Mean Baseline	32.1 \pm 18.7	26.8 \pm 17.6
	Mean Week 26	25.8 \pm 18.6	25.8 \pm 17.2
	Mean Change	- 6.3	- 1.1
	Mean Difference	- 5.2	
	Statistic	Laronidase (n=9)	Placebo (n=11)
Less severe AHI	Mean Baseline	6.2 \pm 2.7	6.5 \pm 3.6
	Mean Week 26	7.6 \pm 5.1	8.0 \pm 6.8
	Mean Change	1.3	1.5
	Mean Difference	0.2	

Reviewer comment: There is a favorable trend in the decrease of the number of events during sleep studies among those subjects more severely affected by sleep apnea / hypopnea that were treated with laronidase during Study 003. However, this is a small exploratory subset analysis which does not permit reaching conclusions on the clinical or the statistical significance of these data. No difference was observed between treatment groups in the AHI for the subjects with few apnea / hypopnea events.

BioMarin analyzed these subset data with adjusted mean changes using ANOVA with a change from baseline to week 26 in the placebo-treated group of 0.3 (n=9) and a

change in the laronidase-treated group (n=11) of – 6.3, and a difference between groups of – 9.1 (p= 0.04)

The expert also recommended analyzing results from all subjects with AHI \geq 20, a criterion that may warrant nasal CPAP intervention when apnea-related symptoms are present. The fact that only 3 subjects allocated to placebo had an AHI \geq 20 did not allow a meaningful between-groups subset analysis. However, the 9 laronidase-treated subjects who had AHI \geq 20 at baseline demonstrated a decrease of 7.4 events / hour. Among these laronidase-treated subjects 4 reduced the AHI from \geq 20 to $<$ 20.

Reviewer's comment: It is clinically meaningful to make a comparison among the subjects that are more severely affected, particularly the subjects considered for medical intervention. However, due to too few subjects, no between groups analysis is possible so that no conclusions can be drawn regarding this subset comparison.

Liver volume

Primary analysis

The endpoint used for the analysis of efficacy was the mean liver volume change from baseline to week 26 ANOVA comparison between the treatment groups. A statistically significant change occurred favoring the laronidase-treated group, with a mean 18.9 % decrease (n=22) as compared to a 1.3 % liver volume increase in the placebo-treated subjects (n=22) (p=0.001).

Prospectively Defined Exploratory Analysis

Of the 14 placebo-treated subjects with hepatomegaly at baseline, 3 subjects (21%) were considered to have reached normal liver volume at week 26. Of the 18 subjects with hepatomegaly at baseline in the laronidase-treated group, 13 (72%) had liver volume normalized by week 26.

All clinical sites had shown substantial reductions in liver volume for their laronidase-treated subjects, and only the University of North Carolina site had shown a reduction in liver volume among placebo-treated subjects.

Reviewer's comment: These results replicate the findings of the Phase 1 study, now in a randomized controlled trial. The findings provide strong evidence of bioactivity of the enzyme in that it facilitates the clearance of liver-accumulated heparan and dermatan sulfate. This could be considered a marker of the activity in MPS I, but the role as a surrogate for clinically meaningful endpoints is not established. It is important to notice that liver function is normal in these individuals with hepatomegaly, and the main negative effect of hepatomegaly, if any, might relate to the volume burden in respiratory restriction and discomfort. On the other hand, GAG-related hepatomegaly in MPS I may carry no clinical implications. There is no correlation between the laronidase-treated subjects liver volume at baseline and the magnitude of reduction achieved during the 26 weeks of laronidase treatment.

Disability Index from the CHAQ or HAQ

Primary Analysis

The Disability Index was derived from the Children's Health Assessment Questionnaire (subjects aged 5 –18 years) and the Health Assessment Questionnaire (subjects aged 19 years and older) and is an overall summary score from 8 different categories that address dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The extent of disability is evaluated using a scale of 0 to 3, with 3 being the worst score. However, these assessment tools have not been validated in this disease.

The endpoint used for the analysis of efficacy was the mean change from baseline to week 26 ANOVA comparison of the Disability Index between the treatment groups. The mean Index for placebo subjects was 1.9 at baseline and 1.8 at week 26, whereas the mean score for laronidase-treated subjects was 2.0 at baseline and 1.9 at week 26. Neither group showed any changes from baseline using these tools.

Prospectively Defined Exploratory Analysis

Comparisons of subsets based on severity (above and below the baseline median value) were inconclusive. There were no significant variations on these findings among different study centers.

Shoulder Flexion

Primary analysis

The shoulder flexion variable for this analysis was defined as the mean of right and left shoulder flexion. The endpoint for the statistical comparison using ANOVA was the change in flexion degrees from baseline to week 26 between treatment groups.

The difference between the groups was not statistically significant ($p=0.99$), with a mean decrease of 4.6 degrees in the placebo-treated subjects and a mean decrease of 1.2 degrees in laronidase-treated subjects.

Prospectively Defined Exploratory Analysis

Exclusion of 2 subjects with baseline cervical cord compression did not change the overall between-groups difference. Analysis subdivided by baseline joint severity also did not yield any informative results.

Reviewer's comment: The choice of shoulder flexion as a secondary endpoint is based on the empiric findings from the Phase 1 study where a larger change from baseline for this joint than others was observed. There is no particular medical basis for favoring the shoulder joint. No conclusion can be drawn from these data on the effect of laronidase treatment in the shoulder flexion ROM.

Tertiary Endpoints

Urinary GAG levels

The endpoint for the statistical comparison using ANOVA was the mean %change in urinary GAG levels (expressed as $\mu\text{g} / \text{mg}$ creatinine) from baseline to week 26 between the treatment groups. The mean (\pm SD) urinary GAG levels increased from 183.3 ± 72.0 at baseline to 250.2 ± 105.1 at week 26 among the placebo-treated subjects, whereas the mean urinary GAG levels decreased from 188.9 ± 60.9 at baseline to 81.3 ± 26.4 at week 26 among the laronidase-treated subjects. The difference from placebo in mean % change from baseline to week 26 urinary GAG was 101% ($p < 0.001$). All laronidase-treated subjects had reductions of their urinary GAG levels, with substantial decreases seen as early as at week 4 and maintained through week 26. Despite the substantial reduction in the laronidase group, no subjects in that group reached the normal range for urinary GAG levels. These results were consistent across study centers.

Reviewer's comments: Studies in the canine model of MPS I revealed decreased vacuolation in glomerular mesangial cells and distal cortical tubules following treatment with laronidase as a histologic evidence of GAG clearance. However, patients with MPS I have no demonstrable impairment in renal function, and therapy with laronidase would therefore not be expected to affect the kidney function. Therefore, reduction of urinary GAG levels is a marker of bioactivity, rather than demonstration of direct clinical benefit, similar to the interpretation of the reduction in liver volume.

Other Tertiary Endpoints

Other tertiary endpoints of this study provided largely inconclusive results. No support for a finding of efficacy associated with laronidase can be drawn from these endpoints. These endpoints are described in detail in Appendix A.

Pharmacokinetic Studies

All subjects randomized at the United Kingdom and the Canadian clinical sites participated in the pharmacokinetic studies. A total of 23 subjects (12 randomized to laronidase and 11 to placebo) took part and completed the study. Infusions at weeks 1, 12 and 26 were selected for the pharmacokinetic studies. Due to the short $t_{1/2}$ observed in the study relative to the weekly dosing frequency, each infusion was treated as a single dose for the purpose of pharmacokinetic analysis.

Table 17 shows selected pharmacokinetic parameters assessed in the 12 laronidase-treated subjects for Infusions 1, 12, and 26 representing the beginning, the middle and the end of the double blind period.

Table 17. Selected pharmacokinetic parameters associated with rhIDU infusions

Parameter	Infusion 1		Infusion 12		Infusion 26	
	n		n		N	
Dose (U/Kg)	12	105 ± 5	12	104 ± 3.3	12	103 ± 3.2
Infusion time (h)	12	3.98	12	4.00	12	3.96
C _{max} (U/mL)	12	0.197 ± 0.05	11	0.210 ± 0.08	12	0.302 ± 0.09
T _{max} (h)	12	3.93	11	3.83	12	3.92
AUC _∞ (h·U/mL)	10	0.93 ± 0.21	6	0.91 ± 0.44	10	1.19 ± 0.45
CL (ml/min/kg)	10	1.96 ± 0.49	6	2.31 ± 1.13	10	1.68 ± 0.76
V _z (L/Kg)	10	0.60 ± 0.17	6	0.31 ± 0.14	10	0.24 ± 0.13
V _{ss} (L/Kg)	10	0.44 ± 0.12	6	0.25 ± 0.08	10	0.22 ± 0.08
λ _z (h ⁻¹)	10	0.20 ± 0.05	6	0.77 ± 1.01	10	0.60 ± 0.52
t _{1/2} (h)	10	3.61 ± 0.89	6	2.02 ± 1.26	10	1.94 ± 1.09
MRT (h)	10	3.84 ± 1.04	6	2.23 ± 1.21	10	2.36 ± 0.83

C_{max}=maximum plasma concentration; T_{max}= time to maximum plasma concentration; AUC_∞=area under the plasma concentration – time curve to infinity; CL= total plasma clearance; V_z= mean volume of distribution; V_{ss}= mean volume of distribution at steady state; λ_z=terminal elimination rate constant; t_{1/2}=mean elimination half life; MRT=mean residence time.

Observations and conclusions derived from these studies:

- differences among the 3 infusions for C_{max}, V_z and V_{ss} were statistically significant, using Friedman's test (p ≤ 0.015)
- there was a trend toward an increase in C_{max} over the 26 week study
- CL does not appear to be affected by administration of rhIDU for 26 weeks
- there was a 50 % decrease in the V_z and V_{ss} between Infusions 1 and 12 which remained constant until week 26
- therefore, increases in C_{max} were related to decreases in V_z
- decrease in V_z without changes in CL resulted in decrease in t_{1/2} between Infusions 1 and 12, not statistically significant
- decrease in V_z may be related to antibody formation between Infusion 1 and subsequent pharmacokinetic studies. An inverse relationship between V_z and antibody levels was seen, causing the speculation that antibody-bound laronidase differs from unbound enzyme in its distribution, increasing the total body load in plasma and reducing the V_z
- following the infusion the plasma concentration of laronidase remained above the concentration for half-maximal saturation of uptake into cells, 0.7 nM (0.01 U /mL) for approximately 3 – 4 hours.

Reviewer's comment: These findings were similar to those observed in canine studies, in which anti-laronidase antibodies resulted in decreased clearance and decreased tissue uptake of the enzyme. With a somewhat shorter half life after the first infusions,

and a decrease of enzyme transfer to lysosomes in affected tissues, a concentration to achieve half maximal saturation of uptake may be sufficient to result in biologic effects in certain organs and tissues, as seen in liver and kidney in this study, but not at other organs or tissues, such as central nervous system, heart, airways and joints. Antibody formation may alter the uptake distribution of enzyme. Even if the enzyme is not directly neutralizing, it may still limit activity in some tissues if antibody-bound enzyme is not distributed into certain tissues. Note that the data on concentration for half maximal saturation of uptake into cells is derived not from binding studies in histologic specimens but from fibroblasts in culture, possibly with different binding affinities.

Safety

AE's

The Safety population consists of the 45 subjects randomized to treatment, of which 22 received laronidase. AE's were recorded from the time of signing the consent form until 2 weeks after completion of the final study procedures. None of the subjects were discontinued from the study. 6 / 23 subjects in the placebo group and 10 / 22 subjects in the laronidase group had mild or moderate AE's during the baseline (pre-randomization) period. During the double blind period all placebo subjects and 21 / 22 laronidase subjects had ≥ 1 AE's. Drug-related AE's were reported in 16 / 23 placebo subjects and in 12 / 22 laronidase subjects. Among the latter, infusion associated reactions (IAR's) occurred in 11 / 23 placebo subjects and in 7 of 22 laronidase-treated subjects. IAR's were defined as all drug-related AE's occurring on the day of infusion, except for those identified by protocol required assessments prior to the infusion.

All AE's with incidence higher than 30 % in either treatment group during the double-blind period were summarized as organized by the World Health Organization Adverse Reaction terminology (WHO-ART) and identified by the Preferred Term. Headaches, fever and rhinitis were the most common AE's reported, and these were all more common in the placebo-treated group (Table 18).

Table 18. Summary of AE's with frequency $\geq 30\%$ during the double blind period

WHO-ART Body System	Preferred Term	Placebo		Laronidase	
		n	%	n	%
Central/Peripheral CNS Disorders	Headache	16	70	11	50
Body as 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
Gastro-Intestinal System Disorders	Diarrhea	8	35	7	32
	Vomiting	9	39	5	23
Hearing and Vestibular Disorders	Earache	8	35	1	5

Of the less common AE's (those occurring in ≥ 1 subject), arthropathy was present in 4 placebo- and 2 laronidase-treated subjects, back pain in 1 placebo- and 2 laronidase-treated subjects, and fever was reported in 3 placebo- and one laronidase subject. Two placebo subjects had diarrhea and abnormal gait, which none of the laronidase-treated subjects had.

AE's that were possibly, probably or definitely related to study treatment were reported more often in the placebo-treated group (16 / 23) than in the laronidase-treated group (12 / 22). From these, the most common were in the laronidase-treated group were flushing (5 / 22) and rash (3/ 22) whereas headache (6/ 23), flushing (4 / 23), arthropathy (4 / 23) and fever (3 / 23) were the most commonly reported study treatment – related AE's in the placebo group. The number of these study treatment related AE's was small, and the data showed no trend for any cluster of AE's in any body system associated with a specific treatment group.

Two placebo-treated subjects had severe AE's. Subject 50605 had worsening of the ankle flexion deformity, and subject 60809 had worsening of psoriatic lesions and increased hepatosplenomegaly. Six laronidase-treated subjects had severe AE's. Subject 30608 had worsening of otitis media, subject 60404 had worsening of arthropathy, subject 60908 had increased hepatosplenomegaly, and subjects 61010 and 61111 both had hepatomegaly. Laronidase-treated subjects 30806 and 40606 had severe AE's that are described below under SAE's.

Eleven of 23 placebo-treated subjects experienced 82 IAR's, whereas 7 / 22 laronidase-treated subjects had 66 IAR's. The most frequently reported IAR's in the placebo and laronidase treated groups were: flushing (4 / 23 and 5 / 22), fever (3 / 23 and 1 / 22), headache (2 / 23 and 2 / 22) and rash (2 / 23 and 1/ 22) respectively. The majority of

these IAR's were reported as mild. 5 / 23 placebo-treated subjects and 3 / 22 laronidase-treated subjects with IAR's required study drug infusion rate decrease or interruption, or medication with antipyretics and / or antihistamines.

The protocol called for IgE testing in subjects experiencing moderate or severe IAR's. 3 subjects with moderate IAR's were tested, being 2 in the laronidase group and one in the placebo group. The 3 tested negative for laronidase-specific IgE antibodies.

Data from AE's related to study drug occurring in non-infusion days was inconclusive.

Deaths and SAE's

There were no deaths during the study. One subject had a SAE during the baseline period of admission to the hospital due to worsening otitis media. She was later randomized to the laronidase-treated group.

During the double blind period, 3 laronidase-treated subjects had SAE's, as follows:

- Subject 10101, a 7 year old female with MPS I H-S, was admitted to the hospital with mild abdominal pain after the fourth infusion due to constipation that resolved with treatment.
- Subject 30806, a 43 year old male with MPS I S, had a past medical history significant for coronary artery disease with a prior myocardial infarction and had cardiac valvular disease at baseline. His valvular disease worsened, requiring surgical repair after the 12th infusion. Post operative course included a cardiac arrest due and subsequent pneumonia with sepsis and renal failure. The subject was treated with and fully recovered, being discharged from the hospital 76 days after his admission.
- Subject 40606, a 7 year old female with MPS I H-S was hospitalized for dehydration after completing 8 infusions. She was diagnosed with a partial obstruction of a ventricular shunt, and underwent a shunt revision.

Clinical Laboratory Evaluations

There were no notable abnormalities in clinical chemistries.

One subject randomized to laronidase had a baseline platelet count of 210,000 / μL and at week 4 108,000 / μL . The platelet count normalized at Visits 12 and 26.

No other subjects had significant platelet decreases. For the groups overall, the mean platelet counts in the laronidase group increased from a baseline of $218 \times 10^3/\mu\text{L}$ to $253 \times 10^3/\mu\text{L}$ (n=22) on study, whereas in the placebo-treated group the platelet count decreased from a baseline of $236 \times 10^3/\mu\text{L}$ to $212 \times 10^3/\mu\text{L}$ (n=21) at week 26.

No relevant changes in urinalysis were noted in either treatment group.

Vitals signs and physical findings

The vital signs assessed at baseline and just prior to the start and immediately after every infusion were systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. No clinically significant changes were observed.

Data available on changes in physical examinations compared to the baseline exam do not demonstrate any trends.

Other findings

No clinically significant electro- or echocardiographic changes from baseline were seen in either treatment group.

All subjects underwent brain and cranio-cervical junction MRI at baseline. All subjects were found to have abnormal findings in the MRI. The protocol called for a repeat MRI at the end of the study at the investigator's discretion. 9 placebo-treated subjects and 6 laronidase-treated subjects had a repeat MRI at week 26. From these, the MRI evaluations of the placebo-treated subjects remained unchanged, while the 1 /6 laronidase-treated subjects had a shift to a normal MRI at Week 26.

Given the near universal antibody formation in the laronidase-treated group, any correlation between serum anti-laronidase IgG antibodies and adverse events cannot be evaluated in a meaningful way. The effect of these antibodies on the 2 primary efficacy endpoints, in a qualitative analysis (i.e. presence or absence of antibodies) was equally inconclusive.

Reviewer's comment: An attempt to analyze levels of IgG antibodies as measured in OD units from the RIP assay with the primary efficacy outcomes across the 26 weeks of the study among laronidase-treated subjects failed to demonstrate a significant correlation.

Complement testing was performed in 3 subjects with moderate IAR's (1 placebo-treated and 2 laronidase-treated subjects) within one hour of the onset of the IAR. All 3 subjects had negative complement activation testing.

Summary

Study ALID-003 was able to demonstrate a statistically significant change in the % FVC for the overall laronidase-treated group compared to placebo, over the 26 weeks of the study. The data, however, does not demonstrate a progressive improvement in this %FVC over the course of the study. Rather, the benefit is related to an abrupt improvement from week 20 to week 26 in the laronidase group, and an abrupt early decrease in % FVC in the placebo group. The effect is also not uniform across the enrolled patient population. The treatment effect is driven by an improvement seen in laronidase-treated females and is more prominent in the younger subjects. The clinical significance of the observed increase in %FVC over the study period (5.9%) is marginal, with an absolute volume mean increase in FVC of 110 mL in the laronidase-treated group, compared to a 20 mL decrease in the placebo group.

The study has not shown a statistically significant difference in the other primary endpoint, the 6 minute walk test. Similar to the findings of subset analyses for the %FVC, a favorable trend is seen, mostly in females and the younger subjects in the laronidase-treated group.

The clinical significance of these findings is unclear, and interpretation of these data to support to a claim of efficacy for a broad range of patients is further confounded by the subset analyses suggesting non-uniform treatment-associated effects.

This study suggests the possibility that younger and / or patients with less advanced disease may have some benefits from laronidase treatment, but this is not conclusively proven. Furthermore, older patients or subjects with more advanced disease have little evidence of benefit. The differential effects in the two genders, with the observed better outcome for both co-primary endpoints in females, cannot be explained on the basis of known pathophysiology. Females in some clinical trials show a greater degree of compliance with the treatment and adherence to study visits, but these potential gender-related effects were not a factor in this study.

Safety results do not reveal any specific serious or severe adverse events clearly associated with laronidase. Infusion reactions are frequent, but were more frequent with the placebo infusion. Infusion reactions were largely mild and did not pose a difficulty to receiving laronidase.

Antibody formation against laronidase is nearly universal, when assessed both by the quantitative but less specific ELISA assay or the specific but qualitative RIP assay. Antibody response appears within the first 2 months of treatment. Pharmacokinetic parameters were altered by antibody formation. The longer term consequences of antibody formation could not be evaluated in this 6 month study.

Study ALID-006

“A Multicenter, Multinational, Open-Label Extension Study of the Safety and efficacy of recombinant Human Alpha- L-Iduronidase in Patients with Mucopolysaccharidosis I”.

Overview

This ongoing study is being conducted under IND 7334. This is an open label extension of the double blind study ALID-003 reported above solely for subjects who participated in study ALID-003, and is intended to provide additional longer term safety and clinical outcome information. The study period is planned to span 72 weeks or until market approval of laronidase. The study report included in this review includes 24 weeks of data on this open label extension study.

Protocol

Title: “A Multicenter, Multinational, Open-Label Extension Study of the Safety and efficacy of recombinant Human Alpha- L-Iduronidase in Patients with Mucopolysaccharidosis I”. Protocol ALID-006-01.

The original protocol was submitted on April 6, 2001

Design

This was a multicenter, multinational open label extension study of subjects with MPS I who had previously participated in the Study ALID-003 (double-blind 26 week study), for either 72 weeks or until laronidase obtains marketing approval.

All subjects previously allocated to placebo treatment under ALID-003 were treated with laronidase for this study. The 5 Centers that participated in Study ALID 003 continued to treat and follow subjects for all clinical evaluations. However the weekly infusions of laronidase and safety evaluations could be performed at one of 13 regional investigational sites closer to the subjects’ homes. The principal investigator for the 5 major sites would still be responsible for the full evaluation of the subject’s medical condition and for all relevant safety issues, along with the Sponsor Medical Monitor.

Objectives

The objective is collection of additional long-term safety data and clinical status of subjects with laronidase treatment. The interim study report described here includes safety and clinical status data for the first 24 weeks of this ongoing study.

Eligibility Criteria

Inclusion criteria:

- Must have completed Study ALID-003 and have received at least 21 of the 26 consecutive weekly infusions under that study
- No safety issues that contraindicate participating in this study
- Females of childbearing potential must have a negative pregnancy test at study entry and use adequate contraception during the study.

- Sexually mature male subjects are advised to use a medically acceptable method of contraception during the study

Exclusion criteria:

- Pregnancy or lactation
- Use of investigational drugs other than those used in Study ALID-003 within 30 days prior to study enrollment
- Medical condition, serious intercurrent illness or other circumstances affecting compliance with laronidase treatment and study evaluations and follow ups.

Treatment assignment / Randomization

In this non-randomized study all eligible subjects were assigned to active treatment (laronidase).

Product Information and Administration

All subjects received laronidase at a dose of 100 U / kg intravenously weekly. As in Study 003, laronidase was diluted with between 100 mL to 250 mL of 0.1% human serum albumin in saline through week 24. Infusions of laronidase after week 24 were prepared without human serum albumin.

Details of the infusion regimen, including pre-treatment, were as done in Study ALID-003 (see prior study review for details).

Amendment 1 was submitted on February 25, 2002 to remove the 0.1 % human serum albumin from the product formulation after week 24 of each subjects participation, due to potential safety concerns related to use of a human derived product.

Evaluations

In general, evaluations were of a similar type as performed in ALID-003. Evaluations were at study entry (which was also the final study visit of Study ALID-003) and except as noted, every 12 weeks during this study.

- Forced Vital Capacity (FVC)
- Six-minute walk distance (in meters)
- Children's Health Assessment Questionnaire (CHAQ) / Health Assessment Questionnaire (HAQ) (age appropriate tool used)
- Sleep study (apnea/ hypopnea events and oxygen desaturation) [Wk 24, 72]
- Liver volume by MRI at Weeks 24 and 72.
- Urinary Glycosaminoglycans (GAG) .
- Joint Range of Motion
- Child Health Questionnaire or SF-36 at Weeks 24, 48 and 72.
- Resource utilization
- Standing heights for measurement of growth velocity
- Visual acuity by standard eye chart testing, ocular pressure, corneal clouding, and retina / optic nerve exam at Weeks 24 and 72.

- EKG and echocardiogram at Weeks 24, 48, and 72.
- FEV₁, total lung capacity and diffusing capacity
- Medical history, VS, and physical examination
- Clinical Laboratory evaluations
- Antibody testing at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60 and 72. IgE and complement activation (CH100 or CH50 and C3 or C4 components) were measured if symptoms of a moderate or severe infusion associated reaction are noted.
- Adverse events

Safety Monitoring

An independent Allergic Reaction Review Board (ARRB) was created to review signs of moderate or severe hypersensitivity and provide guidance on management of these reactions. The ARRB interacted with the Genzyme Pharmacovigilance group and infrequently directly with investigators.

Endpoints

- Primary:
 - a. Percent predicted FVC:
 - b. 6 minute walk:
- Secondary:
 - a. Sleep study – Apnea Hypopnea Index:
 - b. Liver volume:
 - c. Shoulder flexion:
 - d. Disability Index:
- Tertiary:
 - a. Urinary GAG's
 - b. Total respiratory event index and total sleep time O₂ saturation less than 90 % and less than 80 % (derived from the sleep study)
 - c. Pain scale (derived from the Children's Health Assessment Questionnaire [CHAQ] / Health Assessment Questionnaire [HAQ])
 - d. Joint Range of Motion
 - e. Global assessment based on Child Health Questionnaire or SF– 36
 - f. Growth Velocity for pre-pubertal subjects
 - g. Visual Acuity, Ophthalmologic exam, tonometry, fundoscopy and slit lamp exam
 - h. Cardiac Function Testing by electrocardiogram and echocardiogram parameters
 - i. Forced Expiratory Volume in One second (FEV₁)
 - j. Total Lung Capacity
 - k. Diffusing Capacity
 - l. Heart rate, respiratory rate and O₂ saturation

Statistical Analysis

The ITT population was used for data analysis. The 2 treatment groups represented in the report are:

- laronidase / laronidase group which received laronidase infusions for 26 weeks in Study ALID-003 followed by laronidase infusions for 24 weeks in the present study
- placebo / laronidase group which received placebo infusions for 26 weeks in Study ALID-003 followed by laronidase infusions for 24 weeks in the present study

Missing data from missed study visits or early study dropouts were imputed with the LOCF method in the primary analysis, except for safety data, which were not imputed.

Primary efficacy endpoints (% FVC and 6 minute walk distance) were analyzed by descriptive statistics and within group t test. Secondary analyses include the descriptive changes stratified by center, age, gender, seroconversion status and baseline severity.

Secondary endpoints were analyzed by the descriptive changes, without hypothesis testing. Additional analysis of the sleep study – AHI endpoint was performed in those subjects with AHI ≥ 20 at baseline and for pediatric subjects with AHI ≥ 10 or adult subjects with AHI ≥ 15 at baseline. Liver volume changes were also reported in terms of shifts in normal / abnormal rates. The disability index and shoulder flexion were also reported on the basis of baseline severity.

Tertiary endpoints were analyzed by descriptive changes.

Study Conduct

Database Integrity

Genzyme Corporation had responsibility as clinical monitor and as CRO for data collection, completeness and accuracy verification, and analysis. All data editing was complete and data-related decisions finalized made prior to locking the study-interim database.

Protocol Violations

Subject 30309 in the placebo/laronidase group had a heart transplant, violating exclusion criteria; Subject 30806 in the laronidase/laronidase group violated inclusion criteria by failing to receive at least 21 of the 26 infusions in the double blind study. These violations do not impair interpreting the data resulting from this study.

FDA site inspection findings

The findings of site inspections are pending at the time of writing this review.

Results

Subject disposition

The study started on May 29, 2001 and is still ongoing. The same 23 subjects allocated to the placebo treatment arm and the 22 subjects allocated to laronidase treatment are participating in Study ALID-006. The only treatment all subjects received was laronidase at a dose of 100 U / kg IV weekly. The 2 groups referred to in this study report are:

laronidase / laronidase and placebo / laronidase, for the subjects continuing to receive weekly infusions of laronidase and for those switched to laronidase, respectively.

Study entry characteristics

The term “study entry” is used to mean the time of the last infusion in ALID-003. At study entry, the primary clinical characteristics were as shown in the Table 19.

Table 19. Entry characteristics of primary endpoints in the treatment groups

Entry Characteristics	Placebo/laronidase n = 23	Laronidase/laronidase n = 22
% Predicted FVC (mean ± SD)	53.6 ± 14.2	53.7 ± 18.6
6 min. walk distance (m) (mean ± SD)	348.3 ± 128.9	338.8 ± 127.1

Study drug exposure

The mean number of infusions in the placebo/laronidase treatment group was 21.6 and in the laronidase/laronidase group was 21.8, out of a maximum of 24 infusions. The mean number of days in the study was 157.5 days in the placebo/laronidase group and 158.9 days in the laronidase/laronidase group. Subjects 10303, 60809, 30705 and 30806 missed 7, 9, 7 and 8 infusions, respectively.

Primary endpoints

Note: For the purpose of the review of this study report and to keep nomenclature consistent with the sponsor’s designations, baseline is defined as the last measurement prior to randomization in the Study ALID-003 and study entry is defined as the last measurement obtained in study ALID-003.

Percent Predicted Forced Vital Capacity (% FVC)

Primary Analysis

From entry to week 24 the mean change in % FVC for the laronidase/laronidase group was a 0.6 % increase. The placebo/laronidase group had a 0.6 % decrease in % FVC from study entry to week 24.

Table 20 shows the mean (± SD) changes in % FVC from baseline to week 24.

Table 20. Mean (\pm SD) changes in % FVC from baseline to week 24

	Laronidase/laronidase (n=22)	Placebo/laronidase (n=23)
Baseline	48.4 \pm 14.8	54.2 \pm 16.0
Entry	53.7 \pm 18.6	53.6 \pm 14.2
Week 24	54.3 \pm 19.6	53.1 \pm 16.2
Change from baseline to week 26 of Study 003	5.3	- 0.6
Change from entry into Study 006 to week 24	0.6	- 0.6

Reviewer's comment: The response in both treatment groups is notable given the relatively favorable results observed for this endpoint in the double blind controlled study. After an initial improvement in the mean % FVC for the laronidase-treated group in 26 weeks of study ALID-003, no additional improvement was obtained after another 24 weeks with the same treatment.

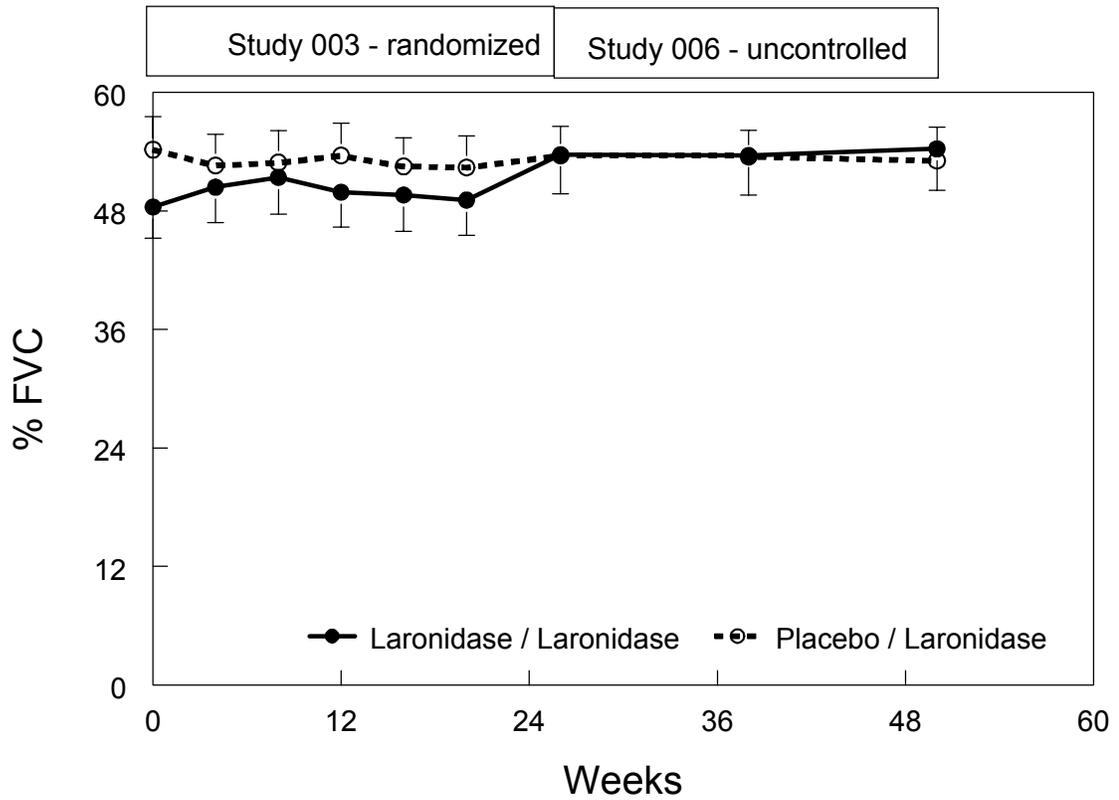
Even more significant is the fact that after receiving 24 weeks of laronidase treatment the prior-placebo subjects had their % FVC unchanged. The sponsor proposed to interpret these data as not creating uncertainty regarding the efficacy of laronidase based on the fact that the placebo group had less severe restriction at baseline, or that missed infusions and seasonal changes contributed to these findings. However Study 003 suggests that subjects with less severe lung restrictions were the ones that had a better chance of improvement under treatment with laronidase, contrary to the sponsor's interpretation of Study 006 data. Furthermore, there are no data to support the proposal that seasonal changes or missed infusions in the placebo-laronidase group contributed to the lack of change of %FVC over the 24 weeks of laronidase treatment in the placebo-laronidase group.

Reviewer's note: The FVC data include results obtained at study entry from 5 subjects in Clinical Site 4 who had incorrect data entered as described for Study ALID-003 (adult pulmonary laboratory assessments instead of the pediatric pulmonary lab). Preliminary assessment of the corrected data are reported to not substantially change the results. This note applies to all FVC analyses for this study.

Exploratory Analysis

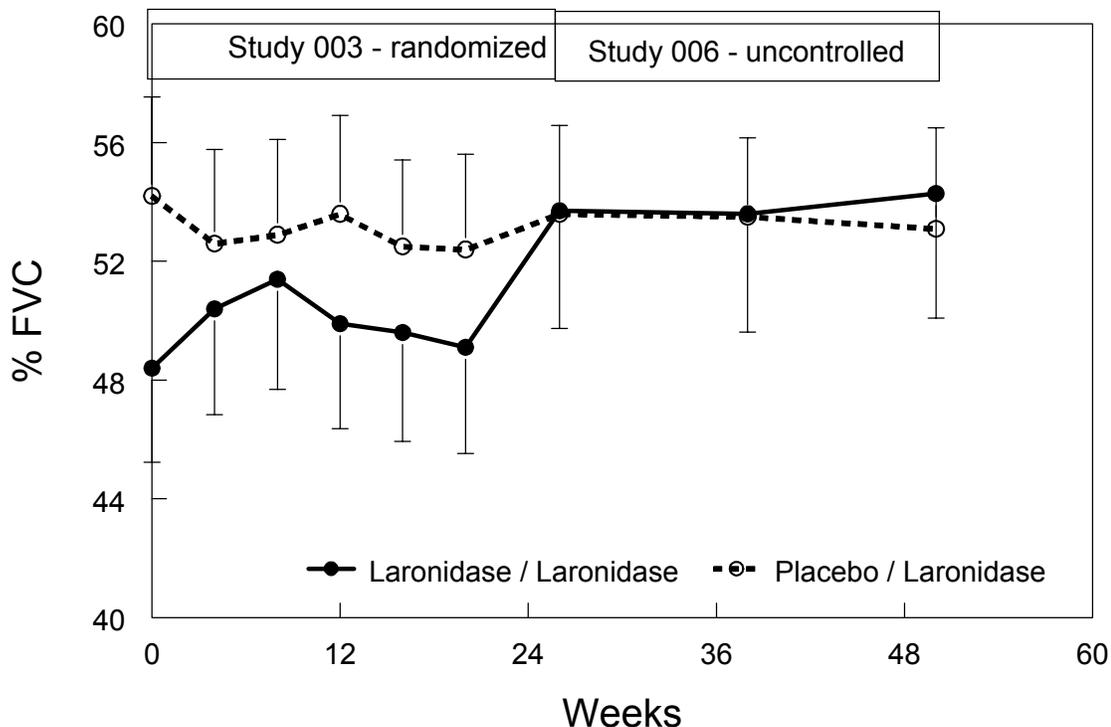
Analysis by Study Visit: Figure 8 shows changes in % FVC from baseline (calculated based on current height at the time of the study visits when the endpoint was assessed) through week 26 in the double blind study ALID-003 and through week 24 of the extension study ALID-006.

Figure 8. % FVC in Study ALID-006.



Reviewer's comment: The figure was amplified in the range 40 to 60 % where the subtle changes in predicted FVC were observed (Figure 9)

Figure 9. Mean % FVC (calculated using baseline height) Study 006



Reviewer's comment: This figure illustrates the absence of % FVC change in the groups during Study 006. The analysis of FVC based as pulmonary volumes (see below) shows no change during ALID-006 as well.

Analysis by Study Center: Mean %FVC change to week 24 within each center ranged from -2.6 to 3.0 in the laronidase/laronidase group, and -4.0 to 1.4 in the placebo/laronidase group. With these small numbers of subjects per site, no conclusions regarding any site-related differences are possible.

Analysis by Gender: Table 21 shows the mean changes for males and females in both treatment groups

Table 21. Mean changes (\pm SD) from entry to week 24 in % FVC in Study ALID-006 by Gender

Gender	Laronidase/laronidase	n	Placebo/laronidase	n
Females	1.7 \pm 9.45	11	-1.6 \pm 3.7	12
Males	-0.5 \pm 7.2	11	0.5 \pm 6.0	11

Reviewer's comment: These changes are relatively small. It is interesting to note that the laronidase-treated females in the double blind study exhibited the largest improvement, there was still a suggestion of a small additional improvement during the additional 24 weeks of laronidase treatment in these same females. On the other hand, placebo-treated females in the double blind study did not realize the same apparent benefit in % FVC when they converted to laronidase treatment in the extension study, and in fact a further, small decline is suggested. Males were largely unchanged in their % FVC during Study 006. Therefore, again the evidence for an improvement following treatment with laronidase in % FVC derives entirely from the 11 females initially assigned to laronidase. Neither the 12 females subsequently treated with laronidase nor either set of males has demonstrated improvement with laronidase.

The stability of % FVC over the Study 006 period is impossible to interpret due to the absence of a control group.

Analysis by Age group: Table 22 shows the changes by age category in the % FVC

Table 22. Mean changes (\pm SD) from entry to week 24 in % FVC in Study ALID-006 by Age Category

Age category	Laronidase/laronidase	n	Placebo/laronidase	n
≤ 12	2.8 \pm 10.5	12	0.5 \pm 5.1	10
13 – 18	0.5 \pm 4.5	3	-2.0 \pm 6.1	8
19 – 65	-3.1 \pm 2.9	7	-0.3 \pm 2.2	5

Reviewer's comment: The effect of laronidase in children younger than 12 years during the double blind study was clearly greater (8%) than that seen in other subset analysis performed on these % FVC data. However, the same finding could not be reproduced in the 10 children initially treated with placebo who were converted to laronidase for a 24 week period (0.5 % increase in mean % FVC). The reasons for this are not apparent. No conclusions regarding any favorable effects can be formed from these data.

Analysis by severity. Table 23 shows the change in % FVC from baseline in Study ALID-003 to week 24 of Study ALID-006 based on quartiles of severity at baseline.

Table 23. Change in % FVC from baseline to week 24 by severity of % FVC at baseline

Severity level	range % FVC	Laronidase/laronidase	n	Placebo/laronidase	n
least ↓	65.4 – 77.4	0.6 ± 2.9	4	0.4 ± 4.4	7
	51.9 – 65.4	2.9 ± 6.0	6	1.3 ± 3.9	6
	41.6 – 51.9	0.7 ± 12.3	6	-3.0 ± 4.1	5
most	15.5 – 41.6	-1.7 ± 9.1	6	-1.7 ± 7.4	5

Reviewer's comment: No conclusion can be formed from the % FVC change according to quartiles of severity at baseline.

Analysis of effect of anti-laronidase antibodies

20 of the 22 laronidase-treated subjects in the double blind study seroconverted as assessed by the RIP assay. An additional laronidase-treated subject seroconverted during the open label extension study. However, 2 of the laronidase-treated subjects became seronegative at different timepoints during the open label study. The vast majority of laronidase-treated subjects that developed anti-laronidase antibodies remained seropositive for the duration of the study. From the 23 placebo-treated subjects in the double blind study, 21 seroconverted during the open label extension study, typically between 4 and 8 weeks of laronidase treatment and remained seropositive for the 24 weeks of Study 006. In view of the high prevalence of anti-laronidase antibody positive subjects in both treatment groups, no meaningful comparisons can be made for the changes in % FVC during the extension study regarding the effects of antibody formation.

Analysis by Forced Vital Capacity as absolute volume: The placebo-laronidase group had a mean (\pm SD) of 1.31 (\pm 0.52) L at Study 006 entry and 1.30 (\pm 0.54) L by week 24. The laronidase-laronidase group had a mean (\pm SD) of 1.26 (\pm 0.59) L at Study 006 entry and 1.25 (\pm 0.57) L by week 24. No change from baseline within each group and no difference between groups could be appreciated.

Reviewer's comment: These data parallel the observed effect of laronidase on the primary endpoint of % predicted FVC for the two treatment groups during the open label extension study (if calculated relative to baseline height). The results reveal the raw pulmonary volume data uninfluenced by factors age and height factors used to calculate the predicted FVC. The absence of improvement with laronidase stand in contrast with the small gains in pulmonary volumes observed during the double blind study 003 by the laronidase-treated group.

6 Minute Walk Distance **Primary Analysis**

From entry to week 24 the mean change in the 6 minute walk distance for the laronidase/laronidase group was an increase of 23.2 meters (Table 24), approximately the same distance gained during the 26 weeks of the double blind study (19.7 meters). The placebo/laronidase group demonstrated a similar change of an increase of 23.8 meters from study entry to week 24. This represents a reversal of the 18.4 meters decrease observed in this group from baseline to week 26 of the double blind study.

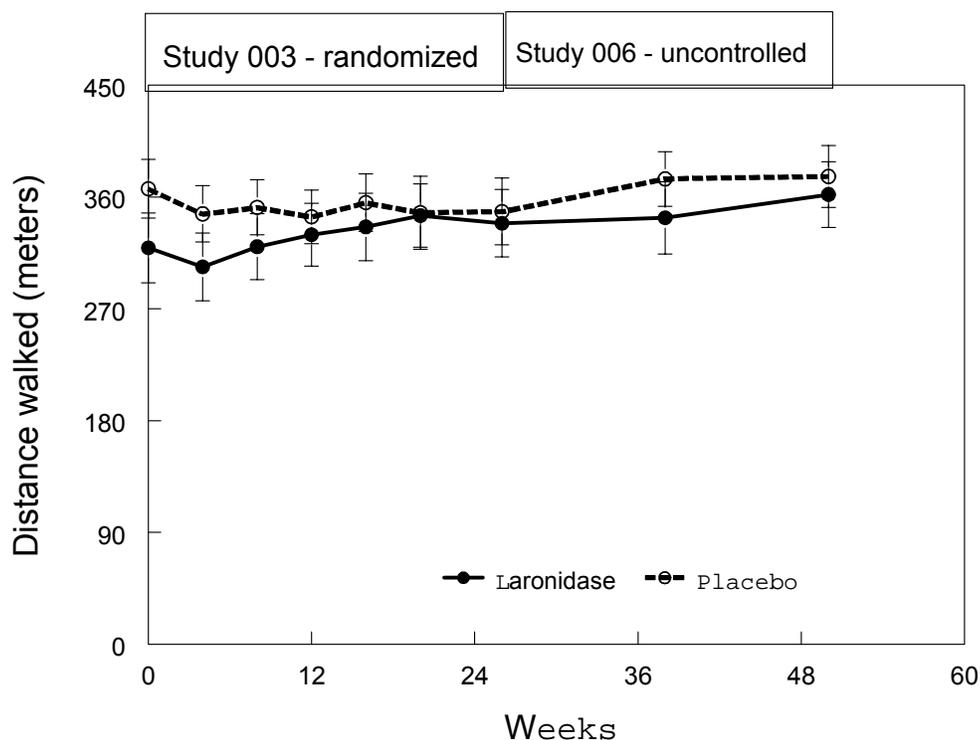
Table 24. Mean (\pm SD) changes in the 6 minute walk distance (meters) from baseline to week 24

	Laronidase/laronidase (n=22)	Placebo/laronidase (n=23)
Baseline	319.0 \pm 131.4	367.6 \pm 116.2
Entry	338.8 \pm 127.1	352.7 \pm 130.1
Week 24	362.0 \pm 124.4	376.5 \pm 116.8
Change from baseline to week 26 of Study 003	19.7	- 18.4
Change from entry into Study 006 to week 24	23.1	23.8

Prospectively defined exploratory analysis

Analysis by Study Visit: Both treatment groups increased their mean distance walked approximately to the same degree, although the placebo/laronidase group appeared to have most of the increase in the first 12 weeks of the extension study and the laronidase/laronidase group had a more substantial increase between weeks 12 and 24 of the extension study (Figure 10)

Figure 10 shows the mean changes (\pm SEM) in the 6 minute walk distance across all timepoints in Study ALID-003 and ALID-006



Analysis by Study Center: Variations among the within center means within treatment group were substantial, ranging from a decline in mean distance by 18 m to an increase in distance by 64 m. No conclusions can be drawn due to the small sample sizes. Most centers observed some increase in distance walked in each group.

Table 25. Mean changes (\pm SD) from entry to week 24 in 6 minute walk distance in Study ALID-006 by Clinical Site

	Laronidase/laronidase	n	Placebo/laronidase	n
1. United Kingdom	17.7 \pm 19.0	6	58.0 \pm 84.5	5
3. Germany	5.3 \pm 11.7	4	18.2 \pm 28.8	5
4. North Carolina	17.7 \pm 44.1	3	-10.0 \pm 34.4	3
5. New York	-17.7 \pm 32.0	3	-14.0 \pm 66.1	4
6. Canada	63.8 \pm 46.0	6	45.6 \pm 46.7	5

Reviewer's comment: It is interesting to note that the 6 subjects originally randomized to Laronidase in the Canadian site had a mean change -17 m in ALID-003 and showed the greatest gain in distance in ALID-006, $+64$ m. The degree to which this illustrates the intra-subject variability over time for this test, the bias related to open label

treatment in ALID-006, or a true 6 month delay in benefit cannot be determined. Of similar note, the apparent decline in walk distance of -18m overall in Study ALID-003 was related to the two large by-site-declines of -54 and -45 m observed in the UK and Canada sites respectively. These declines were almost exactly reversed during ALID-006, by the two largest by-site-improvements in the placebo/laronidase group, so that the placebo/laronidase subjects in these two sites completed ALID-006 with the same walking capacity of 1 year earlier, at the start of ALID-003. Again, there is no ability to distinguish between an illustration of intra-subject variability, bias related to open label treatment, and true treatment effect.

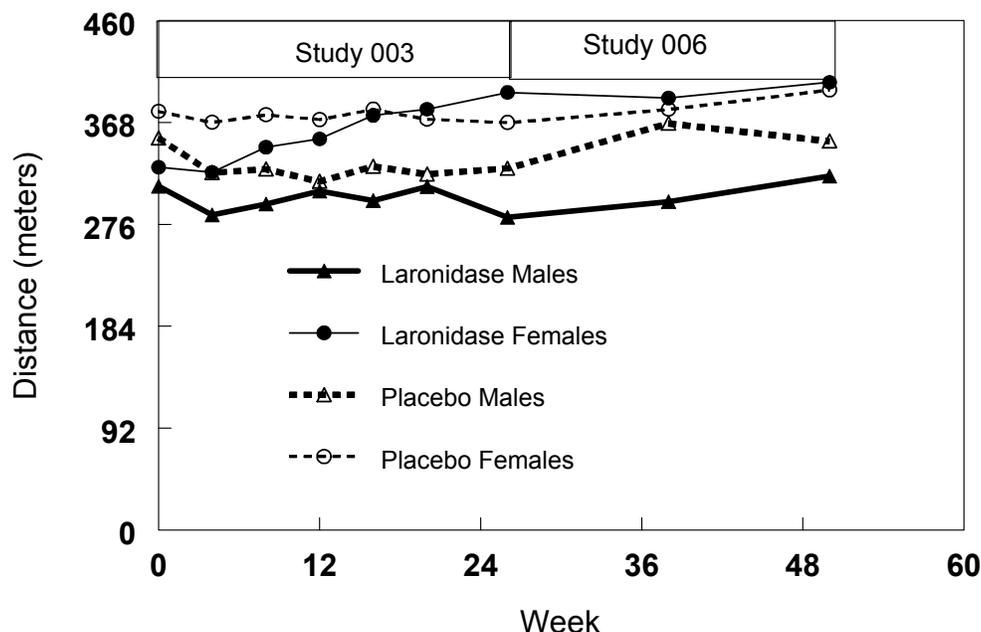
Analysis by Gender: Table 26 shows the mean changes in each site for males and females in both treatment groups

Table 26. Mean changes (\pm SD) from entry to week 24 in the distance walked in 6 minutes in Study ALID-006 by Gender

Gender	Laronidase/laronidase	n	Placebo/laronidase	n
Females	9.2 \pm 25.9	11	29.3 \pm 64.2	12
Males	37.2 \pm 49.2	11	17.1 \pm 55.1	10

Reviewer's comment: The result here is different than that of Study 003, in which males in both treatment groups experienced a decrease of approximately 28 meters, whereas laronidase-treated females had a remarkable mean increase of 67.5 meters. Here there are relatively small increases in distance walked for all groups. The meaning of this observation cannot be determined in the absence of a control group.

Analysis by gender and study visit: Figure 11 shows the variation of the 6 minute walk distance by gender and treatment groups across the study visits.



Reviewer's comment: Unlike the data obtained in the double blind study, in which females treated with laronidase drove the treatment effect, the open label extension study shows no major changes for a particular gender in a particular group.

Analysis by age group

Table 27 shows the effect of 24 weeks of laronidase in the 2 treatment groups of Study ALID-006 by age category.

Table 27. Mean changes (\pm SD) from entry to week 24 in 6 minute walk distance in Study ALID-006 by Age Category

Age category	Laronidase/laronidase	n	Placebo/laronidase	n
≤ 12	28.3 \pm 37.8	12	24.3 \pm 54.9	10
13 – ≤ 18	8.0 \pm 22.3	3	25.7 \pm 83.7	7
19 – ≤ 65	21.0 \pm 53.9	7	20.0 \pm 32.8	5

No conclusion can be drawn from the 6 minute walk distance changes according to age group in Study 006. These results are unlike Study 003, in which a greater effect was seen in the younger subset.

Analysis by severity

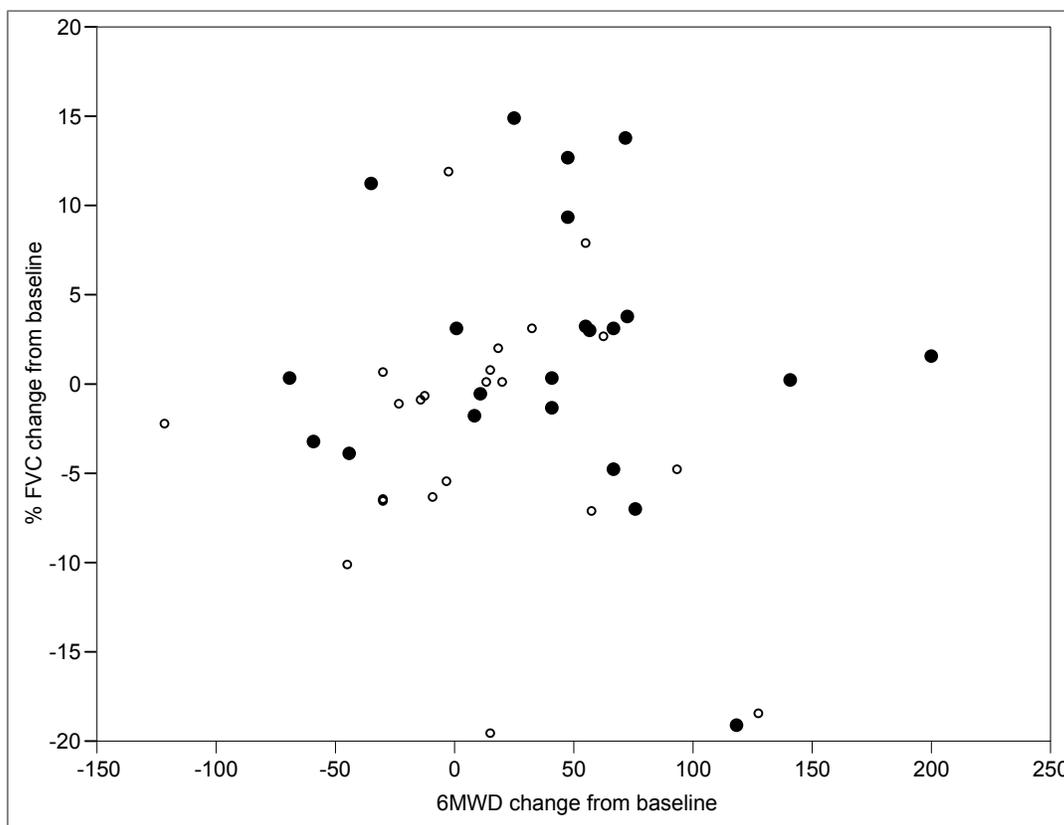
Table 28 shows the mean changes in the 6 minute walk distance for the 2 treatment groups by quartiles of severity at baseline.

Table 28. Mean changes (\pm SD) from entry in Study ALID-006 in the 6 minute walk distance at week 24 by the quartiles of severity at Study ALID-003 baseline

Severity level	Distance range	Laronidase/laronidase	n	Placebo/laronidase	n
least ↓	411 – 591	5.3 \pm 26.8	3	14.5 \pm 40.4	8
	358 – 411	35.0 \pm 47.4	7	35.2 \pm 78.0	4
	276.5 – 358	29.4 \pm 52.8	5	35.0 \pm 89.8	6
most	14 – 276.5	18.9 \pm 34.0	7	27.1 \pm 44.9	4

Reviewer’s comments: No trends are apparent in any category of severity at baseline.

Analysis by treatment effect in the change of % FVC from baseline: There is no correlation between the direction and magnitude of change from baseline to the end of Study ALID-006 between the data observed for % FVC and for the 6 minute walk distance (Figure 12). This again suggests that the changes observed in FVC in these studies are not large enough to be a dominant influence on the walking capacity as tested in the 6 minute walk test.



Legend: Points shown as filled circles represent laronidase-treated subjects and points represented as empty circles represent placebo-treated subjects.

Analysis of effect of anti-laronidase antibodies

Table 29 shows the mean changes from entry into study ALID-006 to week 24 in the 6 minute walk distance for the 2 treatment groups in the anti-laronidase antibody positive groups, and individual values of 6 minute walk distance change in those few subjects that remained or became seronegative by week 24.

Antibody status	Laronidase/laronidase	n	Placebo/laronidase	n
Positive	26.6 ± 43.1	19	22.7 ± 62.1	20
Negative	-5, -2, 11	3	31, 39	2

Duration of anti-laronidase antibodies as measured by RIP in subjects who seroconverted during the double blind study or during the open label extension did not correlate with changes in 6 minute walk distance in those timepoints corresponding to periods of seropositivity or seronegativity. Because most subjects were antibody positive and remained so there is little ability to discern whether or not antibody formation is limiting clinical changes associated with laronidase.

Secondary endpoints

Apnea Hypopnea Index

Primary analysis

Only small changes were observed during ALID-006. During study 006 the placebo/laronidase group experienced a change similar as the laronidase group had experienced in ALID-003. However, the laronidase treated group did not experience any further decline in AHI (Table 30). No statistical or clinical conclusions can be drawn from these data.

Table 30. Mean changes (± SD) in the Apnea/hypopnea Index from baseline of Study 003 through Week 24 of Study 006

	Laronidase/laronidase	n	Placebo/laronidase (n=23)	N
Baseline	21.4 ± 19.1	19	12.8 ± 11.2	19
Entry	18.2 ± 17.0	19	14.3 ± 13.8	17
Week 24	19.4 ± 21.6	19	10.6 ± 7.6	19
Change from baseline to entry	- 2.9		0.4	
Change from entry to week 24	1.2		- 3.5	

Exploratory Analysis

Sleep apnea at baseline: The sponsor prospectively defined an analysis of the subjects who had sleep apnea at baseline, pre-defined as AHI scores ≥ 10 for children under 15

years of age and AHI scores ≥ 15 for adult (older than 15 years of age) subjects. For this analysis, 11 subjects were identified in the laronidase/laronidase group and 9 subjects were identified in the placebo/laronidase group. In addition, the sponsor excluded subject 30806 from this analysis, with the rationale that he had severe sleep apnea with scores ranging from 60 to 100, and variations of the AHI scores within this range are not clinically meaningful, as they likely represent an artifact in the recording of these events.

The data analysis in these subsets showed that subjects in the placebo/laronidase group had a mean reduction of 9.2 events per hour from entry into study 006 to week 24, after the mean increase of 2.5 events / hour during study 003. Subjects in the laronidase/laronidase group had an increase in the mean AHI score of 0.5 from study 006 entry to week 24, generally maintaining the improvement in AHI during study 003 (decrease of 6.3 events per hour). Among the subjects with few apnea/hypopnea events at baseline, no changes from baseline and no differences between the 2 groups were seen.

Reviewer's comment: The rationale of studying the effect of laronidase on the AHI scores of subjects with sleep apnea at baseline is reasonable, and potentially has clinical meaning. However, exclusion of subject 30806 from the 11 subjects in the laronidase/laronidase group may not be as appropriate. While subject 30806 is clearly an outlier, with a baseline index of 78.9, he was included and contributed to the initial drop in the mean AHI score during the double blind study 003 (-9.1 from baseline to week 26 for this subject) and he was not excluded then. His AHI score increased from 69.8 at study 006 entry to 97.2 (a score increase of 27.4, the highest in the group) and is being excluded only for this analysis. Had he been included in the analysis, the laronidase/laronidase group with sleep apnea at baseline would have a mean increase of 2.9, rather than 0.5, events per hour. This would entirely eliminate the group decline in events seen in ALID-003. Consequently, it is further difficult to draw any conclusions regarding effects on AHI based on the results in Study 006.

A separate analysis was conducted to study the effect of laronidase in subjects with baseline AHI ≥ 20 . In the laronidase/laronidase subset with baseline AHI score ≥ 20 , the mean AHI (n=9) increased from 28.8 to 31.2 (or a decrease from 23.6 to 23.0 if subject 30806 is excluded). Only 2 subjects in the placebo / laronidase group had AHI ≥ 20 at baseline, and these 2 subjects had decreases in AHI scores of 18.9 and 18.4 events per hour.

Analysis by gender: Table 31 shows the effect of laronidase (mean \pm SD) on the Apnea / Hypopnea Index in the 2 treatment groups by gender

Treatment Group	Gender	Baseline	n	Entry	n	Week 24	n
Laronidase/laronidase	Male	28.8 \pm 22.2	10	26.3 \pm 19.9	10	25.5 \pm 26.4	11
	Female	12.1 \pm 10.6	10	8.9 \pm 5.4	10	12.9 \pm 11.6	10
Placebo/laronidase	Male	22.7 \pm 20.4	9	23.1 \pm 19.3	8	13.0 \pm 10.4	8
	Female	8.7 \pm 4.9	12	9.9 \pm 7.7	11	8.8 \pm 4.6	11

Reviewer's comment: Males in both treatment groups had worse AHI scores at baseline as compared to females in both groups. The difference between the genders is greater than the suggested possible treatment effect of laronidase. Nonetheless, in study 003, both male and female subjects in the laronidase-treated groups had similar small improvement in AHI scores. In the same study, males and females receiving placebo had similar small degrees of worsening of AHI scores. In the open label extension study 006 most of the improvement seen in the overall placebo/laronidase group is driven by the males in the group with a large decline in AHI out of line with any other subgroup changes seen. These data are difficult to interpret regarding a treatment effect in the absence of a control group.

Liver volume

Primary analysis

During Study 006 the laronidase/laronidase group was essentially unchanged in liver volume, while the placebo/laronidase group had a decline that was not as large that had been observed with the laronidase group of Study 003 (Table 32).

Table 32. Mean (\pm SD) liver volumes (cc) and mean percentage changes (%) in liver volumes during Study 003 and Study 006 by treatment group

Parameter	Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Liver Volume (cc)	Baseline	1211.2 \pm 297.6	20	1358.0 \pm 301.4	18
	Entry	998.8 \pm 331.5	20	1300.6 \pm 278.3	18
	Week 24	945.9 \pm 286.4	20	1114.1 \pm 256.5	18
% Change	Baseline to Entry	- 18.9 \pm 19.4	22	1.3 \pm 19.2	22
	Entry to week 24	- 3.6 \pm 16.4	20	-12.6 \pm 19.7	18

Reviewer's comment: In Study 003, of the 18 laronidase-treated subjects with hepatomegaly at baseline, 13 achieved liver volumes in the normal range during Study 003 (versus 3 of 14 in the placebo group). During study 006, 2 more subjects with hepatomegaly continuing laronidase treatment had normalization of liver volumes. In Study 006, only 5 of the 11 placebo/laronidase subjects with hepatomegaly at study entry had their liver volume normalized.

Similar to the findings of liver volume reduction seen for the Phase 1 study, most of the reduction in volume for the laronidase-treated group took place during the first 6 months of therapy.

Shoulder flexion

Primary analysis

Both treatment groups experienced similar degrees of very mild improvements during the open label extension study 006 (Table 33), although larger than that seen in ALID-003.

Table 33. Mean (\pm SD) shoulder flexion range of motion (degrees) and changes during Study 003 and Study 006 by treatment group

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	96.1 \pm 30.2	19	89.8 \pm 24.0	23
Entry	88.9 \pm 37.7	22	85.2 \pm 32.7	23
Week 24	94.7 \pm 26.1	22	91.5 \pm 24.1	23
Baseline to Entry	- 1.5 \pm 30.4		-4.9 \pm 27.6	
Entry to week 24	5.8 \pm 21.2		6.3 \pm 20.8	

Reviewer's comment: These data do not support a clinically meaningful treatment effect on shoulder flexion range of motion. The impact of unblinding during study 006 may have contributed to the 6 degrees improvement seen in both treatment groups.

Analysis by severity (shoulder flexion range of motion above and below the median for the overall group at baseline of study 003) was also inconclusive.

Disability Index

Primary Analysis

The CHAQ/ HAQ Disability Index evaluates the extent of disability on a scale of 0 to 3, with 3 being the worst score.

Table 34 shows the mean (\pm SD) shoulder flexion range of motion (degrees) and changes during Study 003 and Study 006 by treatment group

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	N
Baseline	2.0 \pm 0.49	21	1.9 \pm 0.6	22
Entry	1.9 \pm 0.58	21	1.8 \pm 0.73	22
Week 24	1.7 \pm 0.54	21	1.6 \pm 0.8	22
Baseline to Entry	- 0.1		- 0.1	
Entry to week 24	-0.2		- 0.2	

These changes through 50 weeks of study (combined Studies 003 and 006) were very small, similar for both treatment groups, and do not support a conclusion of a beneficial treatment effect.

Tertiary endpoints

Urinary GAG's

After the 54 % reduction in urinary GAG concentration noted in the laronidase-treated group during Study 003, an additional 20 % reduction occurred in this group during the open label Study 006. The placebo-treated group had a mean 47 % increase in urinary GAG concentration during Study 003, and had a 68.9% mean reduction when switched to laronidase treatment during the open label extension 006.

At baseline in Study 003 and at entry into Study 006 all subjects in both treatment groups had abnormal urinary GAG concentrations. At week 24 of Study 006 most subjects still had abnormal urinary GAG excretion although, 6 of the 22 subjects in the laronidase/laronidase group had normal GAG levels, and 3 of the 23 subjects in the placebo/laronidase group had normal GAG levels.

Other Tertiary Endpoints

Analyses of other tertiary clinical endpoints do not support any clear conclusions regarding the activity of laronidase treatment in these subjects. Details of these analyses are included in Appendix B.

Safety

AE's

This study report covers the first 24 weeks of the ongoing Study 006. AE's in study 006 are defined as having begun at the time of enrollment in the Open Label Study through Week 24, or that began during the Double Blind Study (003) and worsened during the 24 weeks of Open Label Extension.

All subjects in both treatment groups experienced at least 1 AE during the study. One subject in the placebo/laronidase discontinued treatment due to a SAE, and one subject chose to discontinue treatment at week 24.

Three subjects among the placebo/laronidase group reported severe AE's (one of respiratory distress, one of chronic bronchitis, tracheitis, and myocarditis seen at autopsy and one with choking), and 1 laronidase/laronidase subject reported a severe AE (abnormal vision).

Possibly, probably or definitely drug-related AE's were reported in 11 (48%) placebo/laronidase subjects, and in 10 (45%) laronidase/laronidase subjects. Among these, infusion associated reactions (IAR's) occurred in 7 (30%) placebo/laronidase subjects and in 8 (36%) laronidase/laronidase subjects. IAR's were defined as all drug-related AE's occurring on the day of infusion, except for those identified by protocol required assessments prior to the infusion.

The most frequently reported IAR in both treated groups was flushing (1 / 23 placebo/laronidase subject and 3 / 22 laronidase/laronidase subjects). The majority of these IAR's (flushing, rash) were reported as mild. There were 3 / 23 placebo/laronidase

subjects and 2 / 22 laronidase/laronidase subjects with IAR's that required medication with antipyretics and / or antihistamines. None required drug infusion rate decrease or interruption, or use of steroids.

Among other drug-related AE the most common (defined by the sponsor as 2 or more subjects) in the laronidase/laronidase group were arthropathy (14 %) and flushing (14 %), and in the placebo/laronidase group were arthralgia (9 %) and leg pain (9 %).

All AE's with incidence higher than 30 % in either treatment group during the open label extension Study 006 were reported according to WHO-ART terminology and identified by the Preferred Term. Headache was the most commonly reported AE, with 57% and 45% incidence in the placebo/laronidase and the laronidase/laronidase groups, respectively, followed by rhinitis (43% and 41% in placebo/laronidase and laronidase/laronidase groups, respectively). Coughing and pharyngitis followed with approximately 30 % of subjects reporting these events, with similar frequencies among the 2 treatment groups. Gastrointestinal AE's were more prevalent in the placebo/laronidase group, with 16 subjects (70%) reporting events, contrasted with 10 (45%) reporting in the laronidase/laronidase group. The specific events \geq 30 % were nausea, diarrhea and vomiting.

In comparing the incidence of the AE's with incidence \geq 30% within each treatment group between Studies 003 and 006, the 23 placebo-treated subjects experienced a reduction in these AE's as they were treated with laronidase during the 24 weeks of the open label study. The incidence of these most frequent AE's in the laronidase group during the double blind study remained the same during the open label study.

The protocol called for IgE and complement testing in subjects experiencing moderate or severe IAR's. 3 subjects in the placebo/laronidase group with moderate IAR's were not tested (protocol deviation).

Data from AE's related to study drug occurring in non-infusion days was inconclusive, as most AE's under specific preferred terms were observed in single subjects. GI system symptoms were more common in the placebo/laronidase subjects.

Deaths and SAE's

There was one death on Study 006. Subject (30502) in the placebo/laronidase group died at Week 16 of Study 006 of complications from upper respiratory tract infection and bronchitis. This 7 year old male had a history of central and obstructive sleep apnea. The investigator suggested tracheostomy be considered, and was still under consideration at the time of the event. Six days after infusion 16, the subject was found dead in his bed at home. Autopsy findings revealed marked chronic tracheo-bronchitis with possible acute exacerbation with sepsis. This SAE is classified as unrelated to study drug.

The most notable SAE was:

Subject 60607 (placebo/laronidase) experienced a life-threatening infusion reaction. This is a 15 year old male with history of severe lung restriction, cardiac involvement and anxiety who reported nausea and lightheadedness after the 11th infusion of laronidase, resolving spontaneously. At the 12th infusion, the subject had respiratory distress with hyperventilation and decreased oxygen saturation. The investigator treated the subject for possible atelectasis and anxiety, with improvement. This initial SAE was reported as remotely associated with the study drug. From April 8, 2002 until October 16, 2002 the same subject developed intermittent but progressively worse episodes of urticarial rash and hypoxemia, despite higher doses of anti-histamines and the use of intravenous corticosteroids. His April 2002 plasma complement activation results and IgE were positive, but with a negative skin testing with the enzyme.

On October 16, 2002 (extension week 62), three hours after starting the infusion, the subject developed a rash with "facial flushing" and hypoxemia necessitating biPAP and then oxygen. The infusion was apparently stopped and Solu-Medrol administered. Soon thereafter, intermittent apnea developed and the subjects was transported to an ER where he was noted to be cyanotic with "urticarial lesions extending from the face to the groin area." The subject's airway could not be maintained, attempts at oral intubation were unsuccessful and an emergency cricothyroidotomy was performed. During this time, the subject was bradycardic and epinephrine was administered. Following tracheostomy, initial blood gases showed hypoventilation and hypoxemia. The subject was transported to the ICU where he is reported to be stabilizing. The neurological status is unknown to the sponsor. The investigator reported the events as "definitely related to study medication."

Notably, during the open label extension, obstructive sleep apnea was diagnosed and CPAP was prescribed but the subject was intolerant of it and intermittent nocturnal oxygen was prescribed instead along with periodic use of biPAP.

There were 7 other SAE that do not raise clear concerns regarding drug-relatedness:

Subject 30101 (placebo/laronidase) had repair of a recurrent umbilical hernia, where initial occurrence and repair were several years prior to entry into this study.

Subject 30309 (placebo/laronidase) is a 17 year old male status post heart transplantation where chronic rejection was detected through a heart biopsy, and treated with revised immunosuppressive regimen.

Subject 50807 (placebo/laronidase) is a 14 year old female who experienced a choking episode due to food obstruction of larynx, which resolved with prompt treatment.

Subject 30608 (laronidase/laronidase) is a 7 year old female who was hospitalized for otitis media during the baseline period of Study 003, underwent a tympanoplasty after week 7 on Study 006.

Study 30806 (laronidase/laronidase) is a 44 year old male with a SAE described in Study 003. In summary, patient had complications of aortic valvuloplasty, including cardiac arrest and sepsis, but made full recovery during Study 003. He was hospitalized due to worsening of palpitations after week 21 into the Open Label Extension study. No abnormalities were uncovered despite extensive assessments and the subject was discharged without specific treatment. This SAE is unrelated to study drug.

There were also two subjects with one day hospitalizations for placement of vascular access devices.

Clinical Laboratory Evaluations

No clinically relevant changes were observed for any mean serum chemistry values over the 24 weeks of Study 006.

From the hematologic parameters, platelet counts showed a trend to increase with laronidase treatment. This had been suggested by Study 003 experience as well (Table 35).

Table 35. Mean \pm SD changes in platelet counts from baseline into Study 003 to week 24 of Study 006.

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	218 \pm 52	22	236 \pm 66	21
Entry	253 \pm 72	22	212 \pm 47	21
Week 24	284 \pm 83	22	271 \pm 44	21

Reviewer comment: These changes occurred within the normal range of platelet counts. However, there is a suggestion that laronidase treatment resulted in the increments in platelets. The placebo/laronidase group had a decrease in platelet counts during Study 003, but upon treatment with laronidase had a mean increase of $58.7 \times 10^3/\mu\text{L}$. The laronidase/laronidase group had shown an increase in platelet count during study 003 and this was further slightly increased during study 006. A possible interpretation of these data is that decreases in spleen size (such as those observed during the Phase 1 study) would cause a parallel reduction in platelet removal and destruction. This hypothesis is physiologically plausible, but unproven, particularly given the lack of spleen volume changes in both Studies 003 and 006.

No clinically relevant changes were observed for any mean parameters assessed by urinalysis over the 24 weeks of Study 006.

Vital signs and physical findings

No clinically relevant changes were observed for vital signs and physical examination findings over the 24 weeks of Study 006.

ECG and Echocardiogram findings

Two subjects in the placebo/laronidase group had echocardiographic changes summarized in this review under tertiary endpoints.

Other findings

Forty of the 45 subjects participating in the Open label Extension Study 006 had developed IgG antibodies confirmed by RIP. Nearly all (21 / 23) placebo/laronidase subjects seroconverted during study 006. Twenty of the 22 laronidase-treated subjects

were IgG (+) at study 006 entry. One laronidase-treated subject developed IgG antibodies during the Open label extension. Two laronidase / laronidase subjects became IgG negative after a relatively long period of IgG seropositivity, during study 006. By week 24, 19 laronidase/laronidase treated subjects were IgG (+). No correlation between AE's or IAR's could be established with the IgG antibody status, given the few numbers of IgG (-) subjects in both treatment groups.

Study 006 Summary

Study 006 was conducted as an uncontrolled open label extension trial of laronidase in the 45 subjects that participated in the double blind randomized, placebo-controlled Study 003. The 22 subjects assigned to laronidase and the 23 subjects assigned to placebo weekly intravenous infusions during Study 003 all received the same weekly dose of laronidase (100 U / kg) for a period of 24 weeks, with data included in this BLA submission. This study remains ongoing, with longer term safety data still being collected.

The % FVC showed no changes for both the laronidase/laronidase group and the placebo/laronidase group. This observation is unsupportive of the apparent small but statistically significant improvement in % FVC seen in the laronidase-treated group during Study 003.

The 6MWD test, showed some marginal increments (approximately 20 meters) in the distance walked in 6 minutes, with a similar magnitude for both treatment groups (laronidase/laronidase and placebo/laronidase).

The trend seen during Study 003 of more marked increments in these endpoints in the young, female subset with less severe disease at baseline is not reproduced here. Data from secondary and tertiary endpoints was equally inconclusive and unsupportive, with the exception of the reduction noted in urinary GAG concentrations and in the liver volume.

No conclusions regarding efficacy may be drawn from these data.

Safety events were notable for the life-threatening infusion reaction experienced in one subject in the placebo/laronidase group.

Antibody formation was again seen to occur in nearly all subjects, by both the less specific ELISA and the non-quantitative but more specific RIP assay.

Summary of Efficacy

MPS I is a complex disorder characterized by progressive accumulation of glycosaminoglycans in multiple tissues and organs, at different rates for different individuals. There are multiple clinical aspects of the disease warranting evaluation and for which efficacious treatment would be worthwhile. Based on in vitro binding studies in human MPS I fibroblasts and pre-clinical experience with appropriate canine and feline models of MPS I, a dose of 100 U / kg of laronidase to be given intravenously on a weekly basis was selected for all the clinical development of this product.

An open label, uncontrolled Phase 1 trial of laronidase was conducted in a group of 10 subjects with MPS I, 8 of whom had the Hurler- Scheie form (intermediate severity and progression to death). In this group of subjects, laronidase treatment reduced liver and spleen volumes and significantly reduced urinary GAG's in a matter of a few weeks. The study-observed changes in other endpoints of clinical importance to patients with MPS I were variable and of uncertain clinical significance. Specifically, assessments related to cardiac function, muscle-skeletal, airway and central nervous system function suggested an overall favorable trend. However, these data obtained from an open label uncontrolled study cannot provide strong support for laronidase efficacy in MPS I.

The main support for a Biomarin claim of efficacy comes from a single randomized, placebo-controlled, multicenter trial of laronidase at 100 U / kg weekly vs. placebo in a group of 45 subjects with MPS I for 26 weeks. The two primary endpoints selected were the difference in percent of predicted FVC (% FVC) as change from baseline to week 26 and the difference in the 6 minute walk distance (6MWD) as change from baseline to week 26. In order to explore the effect of laronidase in other important clinical areas affected in MPS I secondary and tertiary endpoints were chosen. Parameters assessing sleep apnea, joint range of motion, liver volume, pain scores, heart function, degree of disability and urinary GAG's were assessed and the data analyzed to provide additional support for the effect in the primary endpoints. Similar to the distribution of subjects in the Phase 1, most were patients with classified as the Hurler-Scheie syndrome.

Twenty two subjects were randomized to laronidase and 23 subjects to placebo. The 2 groups complied with study agent administration and study visits. After 26 weeks the laronidase group had a 5.3 % increase from baseline in the % FVC, whereas the placebo group had a 0.6 % decrease in % FVC, with the % FVC calculated on the basis of the baseline height of the subjects. The difference was statistically significant, but was only marginally meaningful.

In the 6 MWD, the laronidase group walked a mean 19.7 meters more at week 26 than at baseline, whereas the placebo group walked a mean of 18.4 meters less than at baseline. The difference between groups did not reach statistical significance. Subset analysis in both co-primary endpoints revealed a more favorable trend in female subjects, younger subjects, and those with less severe disease. However a firm

conclusion regarding the effect of these factors cannot be drawn from the limited data obtained in this trial.

No general conclusions supportive of efficacy can be drawn from results on the secondary or tertiary endpoints. The data support an active effect to produce reductions in liver volume and urinary GAG's, as seen in the Phase 1 study.

The Phase 3 trial was followed by an Open Label Extension study 006. All 45 subjects that took part in the Phase 3 trial are currently receiving the same laronidase dose used for the laronidase group in the controlled trial, and the study is currently ongoing. Data from the first 24 weeks was collected, analyzed and submitted with this submission. By week 24 of the Open Label Extension study, the mean % FVC has not changed for the 22 subjects continuing on the same laronidase treatment or for the 23 subjects who were switched to laronidase. These data cannot be explained on the basis of individual variations or "seasonal" changes.

In the 6 MWD, the 22 subjects originally assigned to laronidase treatment were able to walk an additional mean of 23.2 meters at week 24 of the extension study, and the placebo/laronidase group was able to walk a mean of 23.8 meters further at week 24. Again, no conclusion can be drawn from these uncontrolled and unblinded data with a small clinical effect.

Secondary and tertiary clinical endpoints were again unsupportive of any conclusion regarding efficacy. Liver volume was reduced by a mean of 12.6 % and urinary GAG levels by a mean of 69 % in the placebo/laronidase subjects.

Antibodies against laronidase formed in most subjects, and no conclusion regarding the impact of these antibodies on efficacy can be formed.

Summary of Safety

Any safety analysis of a product studied in MPS I must be performed in light of the background of significant morbidity that is associated with the enzyme deficiency. Almost all subjects that participated in the Phase 1 or the Phase 3 studies had experienced at least one adverse event (AE). The safety database is 59 subjects exposed to laronidase for variable periods of time, with a minimum of 24 weeks for the placebo subjects switched to laronidase in the Open Label Extension to more than 3 years for the subjects that are still being treated with laronidase infusions under the Phase 1 protocol.

The safety of laronidase treatment can be best assessed by looking at the study 003 controlled data. In that study the overall rate of AE's was very similar between the 2 treatment groups. Infusion associated reactions (mostly flushing and rash) were equally similar in the 2 groups, despite the fact that almost all laronidase-treated subjects developed antibodies against the enzyme. Anti-laronidase antibodies did not generally

appear to be associated with specific adverse events. Two notable exceptions to the lack of correlation are subject 008 that participated in the Phase 1 study and subject 60607 in the Phase 3 study. The former died from a possible viral illness that led to respiratory distress and respiratory arrest. In that subject anti-laronidase IgG antibody titers were high, and there was evidence of immune complex deposition in glomerular capillaries without any histopathological changes. A link between this finding and the worsening of the subject's severe pulmonary involvement cannot be ruled out. The latter subject (60607) developed progressively worse episodes of hypoxemia and rash a few weeks after being switched from placebo to laronidase treatment during the Open Label Extension study. These events occurred in the face of positive anti-laronidase IgE levels and plasma complement activation, and 5 months after the initiation of laronidase culminated with an anaphylactic reaction necessitating an emergency cricothyroidotomy. This particular subject also had a response lower than the group mean in both primary endpoints, as well as 9 % reduction in liver volume and an 11 % reduction in urinary GAG. The event also raises for consideration the value of developing a reproducible and reliable anti-laronidase IgE test to be used in conjunction with laronidase treatment.

Another death in the Phase 1 study and a death occurring in the Open Label Extension are regarded as unrelated to laronidase treatment. Subject 002 died as a result of spinal cord injury after spinal fusion surgery after more than 2 years in the study. Subject 30502 in the placebo/laronidase group died at Week 16 of Study 006 of complications from upper respiratory tract infection, bronchitis and sepsis. All other SAE's reported were related to the morbidity of MPS I and not to laronidase treatment.

Conclusions and Recommendations

The studies presented in the submission provide a suggestion of efficacy of laronidase in the treatment of patients with MPS I. However these data are limited in both statistical strength and in clinical significance. The weight of this conclusion derives from the Phase 3 double blind study 003, which shows a statistically, but not clinically, significant change in % FVC in the laronidase group as compared to placebo control. The other co-primary endpoint, the 6 minute walk test did not reach statistical significance for a treatment-associated difference.

Exploratory analyses of the data suggest that the benefit of the treatment, if any, may not be homogeneous across the MPS I subjects. A subset of females and/or younger subjects and/or those with less severe disease may be more prone to benefit. However in addition to being post-hoc exploratory analyses, there are few subjects in these studies, and these factors cannot be readily isolated for examination. Consequently, firm conclusions regarding subsets more or less appropriate for treatment with this dose and regimen may be infeasible.

Two markers of in vivo enzyme activity were associated with significant reductions during the 26 weeks of Study 003: liver size reductions and urinary GAG concentration. The response of these markers to laronidase has been consistently shown also in the pre-clinical experiments and in the Phase 1 clinical trial, as well as in the placebo-treated subjects switched to laronidase treatment during the Open label Extension.

However, these markers cannot be viewed as surrogates for improving clinical endpoints that contribute to the morbidity and untimely mortality of MPS I.

Possible reasons for non-robust indications of clinical benefit (besides the possibility that the treatment is ineffective) may include inadequate knowledge regarding dose-regimen-response so that an optimal dose and regimen was not evaluated in these studies, insufficient duration of the controlled study to permit robust demonstration of efficacy, and possibly selection of a patient population less susceptible to benefits on the parameters examined than a different portion of the disease patient population.

Appendix A: Tertiary Endpoints of Study ALID-003

Total Respiratory Events Index of the Sleep Study

The total respiratory event index is calculated from data generated in the baseline and week 26 sleep studies, as follows: number of apneas + number of hypopneas + respiratory effort-related arousals / hours of sleep. Mean changes from baseline to week 26 were compared in the treatment groups by ANOVA. Biomarin also assessed the total amount of sleep time spent with oxygen saturation below 90 % and below 80 % during the sleep studies. This index of hypoxemia was only descriptively summarized in the 2 treatment groups, and was not subject to hypothesis testing.

The laronidase-treated group showed a mean reduction of 3.1 events / hour, whereas the placebo-treated group had an increase of 0.3 events / hour at week 26. The difference from placebo did not reach statistical significance ($p=0.118$). These results were consistent across study centers. No clinical significance can be attributed to these data.

Pain Scales from the CHAQ / HAQ

The range of the pain scale is 0 to 3 with lower scores indicating less pain. The endpoint for the statistical comparison using ANOVA was the mean change in pain scores from baseline to week 26 between the treatment groups. The mean (\pm SD) baseline scores for the placebo-treated and laronidase-treated subjects were low and similar, at 1.0 (\pm 0.6) and 1.1 (\pm 0.89), respectively. Changes at week 26 for both groups were small, with scores of 0.8 ± 0.79 for placebo and 0.7 ± 0.87 , and the difference in the adjusted mean changes from placebo was not statistically significant, using ANOVA ($p=0.51$).

Joint Range of Motion (ROM) Variables

Table 36 shows mean changes in joint ROM (angles) from baseline to week 26.

Joint		Laronidase	Placebo	p value
R Shoulder extension	Baseline	22.9 ± 13.3	28.9 ± 14.1	
	Week 26	27.7 ± 10.7	27.0 ± 8.6	
	Change	5.1	- 1.9	0.05
L Shoulder extension	Baseline	25.6 ± 10.6	28.0 ± 12.2	
	Week 26	27.7 ± 9.6	27.1 ± 6.9	
	Change	2.3	- 0.8	0.46
R Knee extension	Baseline	- 12.1 ± 13.4	- 14.3 ± 16.3	
	Week 26	- 9.0 ± 11.5	- 15.6 ± 16.7	
	Change	- 1.9	- 1.3	0.88
L Knee extension	Baseline	- 12.3 ± 13.8	- 15.4 ± 17.1	
	Week 26	- 9.6 ± 11.9	- 14.9 ± 16.6	
	Change	- 4.0	0.5	0.48
R knee flexion	Baseline	106.7 ± 19.9	114.4 ± 11.3	
	Week 26	115.1 ± 18.0	118.6 ± 12.3	
	Change	8.0	4.2	0.40
L knee flexion	Baseline	107.4 ± 20.3	117.0 ± 11.4	
	Week 26	116.6 ± 17.0	118.5 ± 15.7	
	Change	8.9	1.5	0.09

Higher values (in angles of flexion or extension) reflect less severe disease. For knee extension, the measures represent degrees of hyperflexion, and a more negative value reflects more severe disease. In the laronidase-treated subjects, modest improvements were observed after 26 weeks of study in the range of motion of all 6 joints. These differences were slightly more pronounced in the comparisons among the more severely affected subjects (below the median aggregate value for each joint assessed). The findings were consistent across clinical sites, except for worsening of bilateral knee extension and flexion in the laronidase-treated subjects in the United Kingdom.

Reviewer comment: Biomarin did not present the range of motion for the joints studied in the subset of less affected individuals, so an impression on the absolute level of impairment at baseline cannot be formed. A conclusion on the clinical significance of the changes shown cannot be drawn. Furthermore, the high degree of multiplicity of tests on this tertiary endpoint impairs the ability to form and definitive conclusions.

Global Components of the Child Health Questionnaire (parent / caregiver and child subject components) or from the Short-Form 36 (SF-36)

There were multiple analyses performed on components of these tools. Most did not show statistically significant differences between groups. These analyses provide no support for efficacy of laronidase.

Height in pre-pubertal subjects

Only pre-pubertal subjects who had not reached Tanner Stage 2 by the end of week 26 were included in the analysis (7 subjects in each treatment group). Based on mean changes over the 26 week study period, the 7 laronidase-treated subjects grew 4.7 cm compared to 2.7 cm for the placebo-treated subset. The normal pre-pubertal height increase is approximately 5 cm per year. Many subjects had joint contractures at baseline, particularly at the knee. During the course of the study a slightly favorable trend in improved ROM of the knee in the laronidase-treated group was observed. The consequent release of these contractures may have accounted for some of the gains in height, more so in the laronidase group than in the placebo group. Therefore these data may not reflect linear growth, and no conclusions can be formed.

There were even fewer subjects with more than one historical standing height to be able to calculate pre-study slope values of growth velocity; therefore a clinically meaningful comparison of growth velocity was not possible between the treatment groups.

Shifts in Ophthalmology Measures, Visual Acuity and Tonometry

No conclusive data is derived from these assessments in the 2 treatment groups.

Cardiac Function based on EKG and echocardiography

Using standard EKG tracings, no clinically relevant changes in any parameters (heart rate, intervals, sinus rhythm, left or right ventricular hypertrophy, evidence of prior MI, non-specific ST wave abnormalities) were present in either treatment group.

No clinically relevant changes were seen in any of the echocardiographic parameters in either treatment group. Hypothesis testing failed to reveal any statistically significant changes in these parameters.

Investigator Global Assessment

This assessment is the investigator's global perception at week 26 as compared to baseline for each subject. Six of 22 laronidase subjects were considered as having marked or moderate improvement, whereas 2 of 23 placebo-treated subjects were considered by the investigators to have had the same improvement magnitude. 19 / 22 placebo-treated subjects and 13 / 22 laronidase-treated subjects were considered to have mild improvement or no change at week 26. Only one subject was designated as having marked worsening, laronidase-treated subject 30806, who had complications following heart valve surgery unrelated to the treatment group allocation. No benefits were apparent from these data.

Forced Expiratory Volume (FEV), Total Lung Capacity (TLC), and Diffusing Capacity (DL)

Baseline values for the 3 parameters were similar. Changes from baseline to week 26 were small and similar for both treatment groups.

Resource Utilization

Data on this endpoint was not included in the study report. The sponsor states: “Analyses of these data will be documented in a separate report.”

Heart Rate, Respiratory Rate and Oxygen Saturation

Heart and respiratory rates, as well as O₂ saturation were determined before, immediately after and 2 minutes after the 6 minute walk distance test. No statistically or clinically meaningful differences were presented in these measurements between the treatment groups at baseline or at any of the timepoints for assessment, including week 26.

Composite endpoint

BioMarin created a post-hoc composite endpoint for a post-hoc exploratory analysis. The composite endpoint is based on changes in % FVC, 6MWD, AHI, shoulder flexion and liver volume. A responder to this composite endpoint is a subject who shows net improvements across the 5 domains. Using these exploratory criteria, 77 % of laronidase-treated subjects were responders and 17 % of placebo-treated subjects were responders. Even when the domain of hepatomegaly (which is not interpretable in terms of clinical meaningfulness) is removed from the composition of the endpoint the resulting analysis still shows 13 of 22 laronidase-treated subjects as responders, and 5 / 23 placebo-treated subjects as responders.

Reviewer comment: This post hoc analysis has several flaws that undermine a suggestion of clinical significance for the laronidase based on the data analyzed. It is an analysis conducted only after the data was unblinded. Bias in selection of which endpoints are included cannot be ruled out. The nature of the composite may also make it difficult to interpret, combining potentially clinically meaningful evaluations with one that is not readily interpretable. By categorizing each domain into improved and not improved, it also implies that any degree of improvement in a specific domain is clinically significant (to be consider it a response), which is unsubstantiated.

Other composites of similar or other endpoints can also be formulated, and the multiplicity problem will confound drawing any conclusions based on such analyses.

Appendix B: Tertiary Endpoints of Study ALID-006

Total respiratory event index and total sleep time with hypoxemia

The placebo/laronidase group had a small improvement in this index (16.6 ± 14.0 at study 006 entry to 13.0 ± 7.8 at week 24) compared with the laronidase/laronidase group, with a small degree of worsening during Study 006 (from 19.7 ± 16.8 at study entry to 21.9 ± 21.4 at week 24). No significant changes were also noted for either treatment group for the time spent with oxygen saturation below 90 % during sleep.

Pain scale

The pain scale component of the CHAQ / HAQ reflects partially the functional status of the subjects, with a lower score indicating less pain. The scale range is 0 to 3. The mean change from entry to week 24 for the placebo/laronidase group was -0.3 and the mean change for the laronidase/laronidase group during the same period was 0.1 . Over the course of the 50 weeks of Study 003 and 006 combined small improvement in the degree of pain was noted for both groups.

Reviewer's comments: Assessment of pain in a scale, even with appropriate methodology, validated scales and measures to prevent bias, is difficult to accomplish without taking into account the concomitant use of drugs or physical measures to relieve pain. In addition, the pain here relates to a variety of causes, ranging from arthritic pains to headaches related to sinusitis or increased intra-cranial pressure. In this context, evaluation of changes in perception of pain of a multifactorial nature is difficult.

Joint Range of Motion

For shoulder extension and for knee flexion higher values of ROM reflect less severe disease. For knee extension, more negative values reflect more severe disease. Table 37 shows only modest improvements or no change for the joint range of motion in the 3 joint groups assessed for both treatment groups.

Table 37. Mean \pm SD during Studies 003 and 006 for Joint ROM for the 2 treatment groups

Joint		Laronidase/laronidas e	n	Placebo/laronidase	n
R Shoulder extension	Baseline	22.9 \pm 13.3	18	28.9 \pm 14.1	23
	Entry	27.7 \pm 10.7	20	27.0 \pm 8.6	23
	Week 24	29.8 \pm 14.0	20	32.2 \pm 11.2	23
L Shoulder extension	Baseline	25.6 \pm 10.6	18	28.0 \pm 12.2	23
	Entry	27.7 \pm 9.6	20	27.1 \pm 6.9	23
	Week 24	29.4 \pm 13.1	20	30.3 \pm 11.9	23
R Knee extension	Baseline	- 12.1 \pm 13.4	19	- 14.3 \pm 16.3	23
	Entry	- 9.0 \pm 11.5	22	- 15.6 \pm 16.7	23
	Week 24	- 6.2 \pm 9.8	22	- 12.4 \pm 16.3	23
L Knee extension	Baseline	- 12.3 \pm 13.8	19	- 15.3 \pm 17.1	23
	Entry	- 9.5 \pm 11.9	22	- 14.9 \pm 16.6	23
	Week 24	- 6.3 \pm 12.1	22	-12.6 \pm 15.4	23
R knee flexion	Baseline	106.7 \pm 19.9	20	114.4 \pm 11.3	23
	Entry	115.1 \pm 18.0	22	118.6 \pm 12.3	23
	Week 24	116.1 \pm 17.1	22	118.3 \pm 15.1	23
L knee flexion	Baseline	107.4 \pm 20.3	20	117.0 \pm 11.4	23
	Entry	116.6 \pm 17.0	22	118.5 \pm 15.7	23
	Week 24	117.7 \pm 16.6	22	119.9 \pm 15.6	23

Global Components of CHQ or SF-36

The CHQ was used to assess global components for each subject. A parent or caregiver completed one section of the questionnaire (CHQ-PF50), and the child completed another part (CHQ-CF-87). Higher scores reflect better responses. In addition, parents evaluated their own QoL by using SF-36. In the latter instrument, higher scores also reflect better responses. No conclusion can be drawn from the data and there were no differences between the 2 treatment groups.

Growth Velocity

Changes in height were assessed in pre-pubertal children through Studies 003 and 006. Subjects who have not reached Tanner Stage 2 by Week 24 of the open label study

were included. Normal pre-pubertal height increase is approximately 5 cm per year. As mentioned in the report for Study 003, too few pre-pubertal subjects had more than one historical standing height for calculation of pre-study growth slope values. After completion of Study 003, some of the pre-pubertal subjects entered puberty during the 24 weeks of the open label extension. Some of the growth in height can also be attributed to release of joint contractures, particularly in the knees, rather than a true effect on linear growth.

Laronidase/laronidase group: Seven subjects randomized to laronidase during Study 003 had a mean growth of 4.7 cm. Two of these subjects entered puberty during Study 006. The remainder 5 pre-pubertal children had grown a mean of 4.6 cm from baseline in Study 003 to week 24 of Study 006. The mean growth from entry into Study 006 until Week 24 for these 5 children was 0.4 cm.

Placebo/laronidase group: Seven subjects randomized to placebo during Study 003 had a mean growth of 2.7 cm. Three of these subjects entered puberty during Study 006. The remainder 4 pre-pubertal children had grown a mean of 4.9 cm from baseline in Study 003 to week 24 of Study 006. The mean growth from entry into Study 006 until week 24 for these 4 children was 1.7 cm.

Visual acuity, ophthalmologic and slit lamp exam, tonometry, fundoscopy

Fundoscopy examination: From the subjects that had baseline and/or study 006 entry abnormal fundoscopic findings, the proportion of shifts to a normal fundoscopy were identical in the 2 treatment groups: 1 left eye and 1 right eye shifted from abnormal to normal in each of the treatment groups.

Slit lamp measurements: No shifts were observed from abnormal to normal during study 006 in either treatment group. In each group, 1 subject (one eye) shifted from normal to abnormal slit lamp findings.

Visual acuity: No conclusion on the laronidase effect can be formed from the visual acuity data assessed with the Snellen chart.

Tonometry: Most subjects in both treatment groups had normal eye pressures at Study 003 baseline and at Study 006 entry. Shifts from abnormal to normal or vice versa were too few and no conclusive effect of treatment can be assessed from the data.

Cardiac Function

No clinically significant changes were observed in the electrocardiographic tracings in subjects of both treatment groups during the 24 weeks of Study 006.

There were only 2 clinically significant echocardiographic changes during Study 006: one subject in the placebo/laronidase group had mild pericardial thickening at week 24 which was not present at study entry, and one subject on the laronidase/laronidase group had moderately enlarged left atrium, a finding also not present at study entry.

Forced expiratory volume in one second

No mean changes were seen in either treatment group in the FEV1 from baseline to study 006 entry or from study entry to week 24.

Total Lung Capacity

No mean changes were seen in either treatment group in the TLC from baseline to study 006 entry or from study entry to week 24.

Diffusing Capacity

No mean changes of clinical significance were seen in either treatment group in the diffusing capacity from baseline to study 006 entry or from study entry to week 24.

Heart rate, respiratory rate and O₂ saturation

No mean changes of clinical significance were seen in either treatment group in the heart rate, respiratory rate or in O₂ saturation from baseline to study 006 entry or from study entry to week 24.