# CLINICAL STUDY PROTOCOL

## Study Number ALID01803

## A Multicenter, Multinational, Open-Label Study of the Effects of Aldurazyme® (laronidase) Treatment on Lactation in Women with Mucopolysaccharidosis I (MPS I) and Their Breastfed Infants

**Final: 26 June 2003**
**Amendment 1: 14 January 2008**
**Amendment 2: 05 January 2011**

Sponsor: BioMarin/Genzyme LLC
500 Kendall Street
Cambridge, MA 02142, US

Study Manager: [redacted]

Biostatistician: [redacted]

This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of Good Clinical Practice as stated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws.

I have read and agree to abide by the requirements of this protocol.

_____ ____
Investigator Signature Date

_____
Medical Monitor Signature Date

## Signature Page for Sponsor's Representative

I have reviewed and approved the protocol entitled "A Multicenter, Multinational, Open-Label Study of the Effects of Aldurazyme® (laronidase) Treatment on Lactation in Women with Mucopolysaccharidosis I (MPS I) and Their Breastfed Infants," Amendment 2

[redacted]

## 1. SYNOPSIS

| NAME OF COMPANY<br>BioMarin/Genzyme LLC<br>500 Kendall Street<br>Cambridge, MA 02142<br>**NAME OF FINISHED PRODUCT**<br>Aldurazyme®<br>**NAME OF ACTIVE INGREDIENT**<br>laronidase | **SUMMARY TABLE**<br>Referring to Part<br>……<br>of the Dossier:<br>Volume:<br>Page:<br>Reference: | **FOR NATIONAL AUTHORITY USE ONLY:** |
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**TITLE:** A Multicenter, Multinational, Open-Label Study of the Effects of Aldurazyme (laronidase) Treatment on Lactation in Women with Mucopolysaccharidosis I (MPS I) and Their Breastfed Infants

**PROTOCOL NO.:** ALID01803

**INVESTIGATOR/STUDY CENTERS:** Investigators at up to 10 study centers will participate.

**OBJECTIVE:**

The objective of this study is to determine whether Aldurazyme affects lactation in women with MPS I disease by:

a. Determining whether laronidase activity is present in the breast milk of mothers with MPS I disease who are being treated with Aldurazyme during lactation.
b. Determining whether Aldurazyme affects the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with Aldurazyme during lactation.

**METHODOLOGY:** This is a multicenter, multinational, open-label study of lactation in postpartum women receiving Aldurazyme and the effects of Aldurazyme on the growth, development, and immunologic response of their breastfed infants. This study provides 2 options for participation: (1) full participation by both the mother and the infant (Full/Full) and (2) full participation by the mother and only umbilical chord blood, urine, and developmental assessments of the infant (Full/Partial).

**Mother (Both Participation Options):** Eligible women will be enrolled and tested at baseline, every 12 weeks (±5 days) thereafter, and at the end of the study to test for the formation or continued presence of immunoglobulin G (IgG) antibodies in blood and/or urine glycosaminoglycans (uGAG) in urine. Within 1 month after birth, every 12 weeks thereafter, and at the end of the study, samples of breast milk will be collected within 24 hours preceding an Aldurazyme infusion and within 60 minutes of completing an infusion of Aldurazyme to determine the presence of laronidase. The effects of Aldurazyme on lactation will be assessed through medical history, complete physical examinations, and breastfeeding status to determine if the mother is successfully breastfeeding.

**Infant:**

**Full/Full Participation Option:** Infants will be enrolled and, at birth, a sample of umbilical cord blood will be collected to determine baseline immunoglobulin M (IgM)

| NAME OF COMPANY<br>BioMarin/Genzyme LLC<br>500 Kendall Street<br>Cambridge, MA 02142<br>**NAME OF FINISHED PRODUCT**<br>Aldurazyme®<br>**NAME OF ACTIVE INGREDIENT**<br>laronidase | **SUMMARY TABLE**<br>Referring to Part<br>……<br>of the Dossier:<br>Volume:<br>Page:<br>Reference: | **FOR NATIONAL AUTHORITY USE ONLY:** |
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and IgG titers for the infant. The infant will then be tested every 12 weeks (±5 days) and at the end of the study to test for the formation or continued presence of IgG and IgM antibodies in blood and for the levels of GAG in urine. If 2 consecutive blood samples 12 weeks apart (not including the baseline blood draw), are negative for IgG and IgM antibodies, study participation for mothers and infants will last 12 months; otherwise, testing will continue for 18 months.

**Full/Partial Participation Option:** Infants will be enrolled and, at birth, a sample of umbilical cord blood will be collected to determine baseline IgM and IgG titers. Urine samples will be collected every 12 weeks (±5 days) and at the end of the study to test for the levels of uGAG. The effects of Aldurazyme on lactation will be assessed through medical history, complete physical examinations, and development assessment using the Denver II Developmental Screening Test, to determine if the infant is growing and developing normally. The duration of the study for this option will be 18 months.

**NUMBER OF SUBJECTS:** Up to 10 mothers and their infants (who must be receiving breast milk while the mother is receiving Aldurazyme therapy) will be enrolled in this study.

**DIAGNOSIS/INCLUSION CRITERIA:**

Mothers must meet the following criteria:

1. The patient must have a documented α-L-iduronidase deficiency with a fibroblast, plasma, serum, leukocyte, or dried blood spot α-L-iduronidase enzyme activity assay.
2. Be pregnant, planning to breastfeed postpartum, and receiving Aldurazyme while breastfeeding.
3. Provide signed, written informed consent prior to any protocol-related procedures. Consent of a legally authorized guardian is required for mothers younger than 18 years of age. If a mother is younger than 18 years of age and can understand the consent, written informed consent is required from both the mother and the authorized guardian.
4. Provide signed, written informed consent for their infants to participate as study subjects. If a mother is younger than 18 years of age, consent for mother and infant will be obtained from the legal guardian.

Mothers (and their infants) will be excluded from this study if any of the following exclusion criteria are met:

1. Have a medical condition, serious intercurrent illness, or other extenuating circumstance that may interfere with study compliance, including all prescribed evaluations and follow-up activities.
2. Have received an investigational drug within 30 days prior to study enrollment.

**DOSE/ROUTE/REGIMEN:** Mothers who are receiving Aldurazyme therapy will receive Aldurazyme at their prescribed dose and regimen. Each Aldurazyme infusion will be prepared as described in the appropriate country labeling for Aldurazyme.

**REFERENCE TREATMENT:** No reference treatment will be used in this open-label study.

**CRITERIA FOR EVALUATION:**

**Mother**

- Laronidase: Breast milk will be collected within 1 month of giving birth, every 12 weeks (±5 days) thereafter, and at the end of the study to check for the presence of laronidase.
- Breastfeeding Status: Breastfeeding status will be recorded within 1 month postpartum, every 12 weeks (±5 days) thereafter, and at the end of the study.
- Immunoglobulins: Mothers will be tested at baseline, within 1 month postpartum, every 12 weeks (±5 days) thereafter, and at the end of the study to test for the formation or continued presence of IgG antibodies.
- uGAG Level: Mothers will be tested at baseline, every 12 weeks (±5 days) thereafter, and at the end of the study to determine the level of uGAG.
- Safety: Adverse events (AEs) and concomitant medications will be summarized at each visit.

**Infant**

- Immunoglobulins: At birth, a sample of umbilical cord blood will be collected to determine baseline IgM and IgG titers.
- Breastfeeding Status: Breastfeeding status will be recorded within 1 month postpartum, every 12 weeks (±5 days) thereafter, and at the end of the study.
- uGAG Level: Urine samples will be collected at baseline, every 12 weeks (±5 days) thereafter, and at the end of the study to determine the level of uGAG.
- Development: The infant's growth and development will be monitored from birth to the end of the study through complete physical examinations and the Denver II Developmental Screening Test.
- Safety: AEs and concomitant medications will be summarized at each visit.

For the Full/Full Participation option only:

- Immunoglobulins: Blood samples to test for IgM and IgG antibodies to laronidase will be taken from the infant every 12 weeks. If 2 consecutive samples 12 weeks apart (not including the baseline blood draw) are negative for IgG and IgM antibodies, study participation will last 12 months; otherwise, testing will continue for 18 months.

**STATISTICAL AND ANALYTICAL PLANS:**

Genzyme Corporation will be responsible for data entry and editing, reviewing all the information in the Case Report Forms (CRFs), statistical analysis, and generation of

the clinical report.
Clinical data will be double-entered and validated in an Oracle database using Clintrial Version 4.5 on a VAX/VMS computer.

Prior to locking the database, all data editing will be complete and decisions regarding the evaluability of all patient data for inclusion in the statistical analysis will be made. The rationale for excluding any data from the statistical analyses will be prospectively defined, and classification of all or part of a patient's data as nonevaluable will be completed and documented before the entire database is locked and before the statistical analysis is begun. The statistical analysis will not begin until the entire database is locked and signed off, in accordance with the Standard Operating Procedures (SOPs) of the Biostatistics Department.

The Genzyme Biostatistics Department will perform the statistical analysis of the data derived from this study. The analysis will be performed using the SAS® statistical software system (SAS Institute Inc., 2008; *SAS® Language, Version 9.2*).

**Study Variables**
The analyses of the data from this study are designed to address the following questions:

- Is laronidase activity present in the breast milk of mothers with MPS I disease who are being treated with Aldurazyme during lactation?
- Does Aldurazyme affect the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with Aldurazyme during lactation?

Effects of Aldurazyme on lactation in mothers will be assessed in terms of the proportion of lactating women with serum IgG antibodies to laronidase, the levels of IgG antibody titers to laronidase, the proportion of women who breastfed, the proportion of women who were successful at breastfeeding, the proportion of women whose breast milk contained laronidase, the levels of laronidase in the breast milk of lactating mothers with MPS I disease, the proportion of women with abnormal uGAG levels, the levels of uGAG, and medical history and physical examination findings.

Effects of Aldurazyme on infants will be assessed in terms of the proportion of infants with abnormal uGAG levels, the levels of uGAG, medical history and complete physical examination findings (including growth), and the developmental assessment findings. For the infants participating in the Full/Full option, the effects of Aldurazyme will be assessed in terms of the proportion of infants with IgM and IgG antibodies present at any time point, the levels of IgG and IgM antibody titers to laronidase, and the time to development of IgM and IgG antibodies to laronidase**.**

**Patient Population**
The intent-to-treat (ITT) approach will be the main analysis for this study. This approach will include both mothers and infants of mothers who receive Aldurazyme during lactation. The ITT analysis will be the basis for determination of the effects of

Aldurazyme on lactation.

**Handling of Dropouts**
For the analyses, summary data for patients who terminate the study early or miss study visits (and consequently have missing data) will not be carried forward to the next time point. Hence, the analyses will be performed on an observed-cases basis.

**Statistical Methods**
All data collected in this study will be documented using summary tables, graphs, figures, and patient data listings.

No hypothesis testing will be performed.

**Statistical Methods: Demographics and Baseline Characteristics**
Demographic and baseline characteristics data for the mother and for the infant will be summarized descriptively. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n's, means, medians, standard deviations, minimums, and maximums) will be presented.

Prior medications will also be summarized descriptively (using frequencies and percentages).

**Statistical Methods: Patient Accountability**
Data from all patients (mothers and infants) who are enrolled in the study will be included in the summary of patient accountability. The frequency and percentage of patients enrolled in the study, attended each visit, are discontinued from the study, or complete the study will be summarized.

**Statistical Methods: Study Variables**
The following variables will be summarized descriptively:

**Mothers**

- The proportion of lactating women with serum IgG antibodies to laronidase
- Amount of IgG antibody titers to laronidase in lactating women
- The proportion of women who breastfed
- The proportion of women who were successful at breastfeeding
- The proportion of women whose breast milk contains laronidase
- Amount of laronidase in the breast milk of lactating mothers with MPS I disease
- The proportion of women with abnormal uGAG levels
- Amount of uGAG in the urine of women
- Medical history and physical examination findings

**Infants**

- The proportion of infants with abnormal uGAG levels
- Amount of uGAG in the urine of infants
- Medical history and physical examination findings (including growth)
- Developmental assessment findings
- For the Full/Full Participation option only:
  - The proportion of infants with IgM and IgG antibodies to laronidase present at any time point
  - The time to development of IgM and IgG antibodies to laronidase
  - Amount of IgG and IgM antibody titers to laronidase

In addition, the incidence of AEs will be summarized descriptively using the Medical Dictionary for Regulatory Activities (MedDRA) coding. Shifts in physical examination results from baseline (last baseline measurement) to the study time points will be summarized descriptively.

**Sample Size**

This study will enroll up to 10 mothers and their infants. No formal sample size calculations were performed.

**Interim Analysis**

After 3 infants have completed the study, an interim summary of the data will be provided as described above for the main analyses, in order to facilitate discussions with the FDA. As this is an open-label post-marketing study with no formal hypothesis testing, the usual adjustments to significance levels will not be required.

## 2. TABLE OF CONTENTS



## TABLE OF TABLES

## 3. ABBREVIATIONS AND TERMS

| | |
|---|---|
| AE | adverse event |
| CRF | case report form |
| FDA | Food and Drug Administration |
| GAG | glycosaminoglycan |
| GCP | Good Clinical Practice |
| GPS&RM | Global Patient Safety & Risk Management |
| IAR | infusion-associated reaction |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IRB | Institutional Review Board |
| ITT | intent-to-treat population |
| LLC | Limited Liability Company |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPS I | mucopolysaccharidosis I |
| SAE | serious adverse event |
| SOP | Standard Operating Procedures |
| uGAG | urinary glycosaminoglycans |

## 4. INTRODUCTION

Mucopolysaccharidosis I (MPS I) is a progressive and life-threatening lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-L-iduronidase (Neufeld, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Patients with MPS I disease accumulate excessive amounts of the glycosaminoglycans (GAG) heparan sulfate and dermatan sulfate in all organs and tissues of the body. Historically, patients with MPS I disease have been broadly categorized as Hurler, Hurler/Scheie, and Scheie, representing the most severe, intermediate, and less severe clinical phenotypes, respectively. These classifications are arbitrary categorizations of points on a spectrum of patient phenotypes and MPS I disease. Although the degree of severity may vary between patients, MPS I is always a serious disease. While the pathophysiologic basis for MPS I disease is clear, the diverse combination of medical problems and the rate of progression of specific clinical symptoms varies greatly between patients, and there is significant patient-to-patient heterogeneity. Clinical symptoms begin in infancy to late childhood, progress over a period of years, and ultimately lead to death during the first or second decade of life in most patients. Despite this heterogeneity, MPS I disease is characterized by enlargement of the liver and spleen and excessive levels of urinary GAG (uGAG) excretion. Additionally, cardiopulmonary and functional effects are consistently among the most important clinical manifestations of the disease (Neufeld, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

Lysosomal storage in MPS I disease is most clearly manifested clinically by enlargement of the liver and spleen due to engorgement of macrophages, as well as parenchymal cells, with GAG (Neufeld, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Enlargement of the liver and spleen may have a number of clinical consequences, including limitation of diaphragmatic excursion causing shortness of breath, early satiety, abdominal discomfort, poor self-image, and difficulty bending over. In addition, the excessive storage within the kidney, and particularly the collecting tubules, leads to the excretion of excessive amounts of uGAG. For this reason, uGAG levels are commonly used in the diagnosis of suspected MPS I disease. The storage of GAG is present in every tissue and nearly every cell type, as might be expected for a widespread macromolecule such as GAG. Stored GAG substrate also leads to coarsened facial features, abnormal bones, large tongue, and stiffened joints, in part due to synovial engorgement with GAG.

The functional capacity of patients with MPS I disease is also profoundly affected by GAG storage in a variety of tissues. Decreased cardiopulmonary function contributes to reduced physical ability (Semenza, 1988, *Medicine*), and direct accumulation of GAG within connective tissues affects mobility in patients with MPS I disease (Neufeld, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Joint stiffness, decreased range of motion, and pain often limit the usual activities of daily living, including walking. Skeletal storage causes short stature and skeletal deformities, which can also affect mobility. Ocular abnormalities include decreased visual acuity, corneal clouding, and glaucoma, which also affect daily activities (Kakkis, 1996, *Principles of Child*

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

While the storage of GAG is the fundamental pathophysiology of MPS I disease, an effective and safe therapeutic for MPS I disease must treat the underlying lysosomal storage disorder in addition to the impairments in respiratory and physical function experienced by MPS I patients.

On 30 April 2003, the U.S. Food and Drug Administration (FDA) granted a marketing approval for Aldurazyme (laronidase) for the treatment of MPS I in patients with Hurler and Hurler-Scheie syndromes as well as patients with moderate to severe symptoms of Scheie syndrome (Aldurazyme® United States Product Information, 2010, BioMarin/Genzyme LLC).

On 10 June 2003, the European Commission granted a Marketing Authorization for Aldurazyme in the European Union. Aldurazyme (laronidase) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease (Aldurazyme® Summary of Product Characteristics, 2010, Genzyme Europe B.V., 2010).

## 4.1 Summary of Risks and Benefits

For further details concerning efficacy, warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the approved country product label.

# 5. STUDY OBJECTIVE

## 5.1 Objective

The objective of this study is to determine whether Aldurazyme affects lactation in women with MPS I disease by:

a. Determining whether laronidase activity is present in the breast milk of mothers with MPS I disease who are being treated with Aldurazyme during lactation.

b. Determining whether Aldurazyme affects the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with Aldurazyme during lactation.

# 6. INVESTIGATIONAL PLAN

## 6.1 Study Design

This is a multicenter, multinational, open-label study in breastfeeding women receiving Aldurazyme during lactation and its effects on lactation and the growth, development, and immunologic response of their breastfed infants. This study provides 2 options for participation: (1) full participation by the mother and the infant (Full/Full) and (2) full participation by the mother and only umbilical chord blood, urine, and developmental assessments of the infant (Full/Partial).

Pregnant women may enroll in this study at any time after a confirmed diagnosis of pregnancy and prior to the birth of their infants. The effects of Aldurazyme on lactation will be assessed at each visit through medical history and complete physical examinations to determine if the mother is successfully breastfeeding and if the infant is growing and developing normally. An eligible mother and her infant will be considered separate study subjects and each will be assigned a 6-digit identification number once signed written consent is secured. Subsequently, mothers and infants will undergo a baseline visit to confirm study eligibility and to determine baseline measurements of several clinical parameters.

For mothers, samples of breast milk will be collected within 24 hours preceding an Aldurazyme infusion and within 60 minutes of completing an infusion of Aldurazyme within 1 month after birth and every 12 weeks (±5 days) thereafter to determine presence of laronidase. Mothers will be tested at baseline, every 12 weeks (±5 days) thereafter, and at the end of the study for immunoglobulin G (IgG) antibodies to laronidase in blood and/or GAG in urine.

For infants in both participation groups, a sample of umbilical cord blood will be collected at birth to determine baseline immunoglobulin M (IgM) and IgG titers. Urine samples will be collected at baseline, every 12 weeks (±5 days) thereafter, and at the end of the study to test uGAG levels. In addition, growth and development will be measured during complete physical examinations and by utilizing the Denver II Developmental Screening Test.

For infants in the Full/Full participation option, infants will be tested every 12 weeks (±5 days) for IgG and IgM antibodies to laronidase in blood.

Concomitant medications and adverse events (AEs) will be collected and summarized for both mothers and infants.

Mothers and infants will be evaluated for 18 months unless 1 of the following conditions occurs: (a) if 2 consecutive infant samples 12 weeks apart (not including the baseline blood draw, if performed) are negative for IgG and IgM antibodies, study participation for mothers and infants will last 12 months, (b) the mother withdraws

consent and discontinues study participation, (c) the mother or infant is discontinued from the study by the Investigator (refer to Section 7.3.1 for details), or (d) the study is terminated (Section 12.3.5). If the mother is no longer lactating, the mother will discontinue this study. The infant will be followed for urine and development only for the remainder of the study.

## 6.2 Study Rationale

In the past, pregnancies in females with MPS I disease have been rare. However, it is anticipated that with enzyme replacement therapy becoming widely available, more affected females will be able to become pregnant and to deliver viable infants. It is not known whether Aldurazyme is excreted in human milk, and there are limited data involving infants of mothers receiving Aldurazyme during lactation. This clinical study is being conducted to evaluate the effects of treatment with Aldurazyme on lactation in female patients with MPS I disease. This study will also examine the growth, development, and immunologic response of breastfed infants whose mothers are receiving Aldurazyme infusions during lactation. Antibody formation to laronidase in mothers and their infants will be monitored postpartum throughout the study; if 2 consecutive infant samples 12 weeks apart (not including the baseline blood draw, if performed) are negative for IgG and IgM antibodies, study participation for mothers and infants will last 12 months; otherwise, testing will continue for mothers and infants for 18 months. This study will also present the uGAG levels for the mothers and their infants.

Concomitant medications and AEs for both mother and infant will be collected at each visit and summarized using the Medical Dictionary of Regulatory Activities (MedDRA) coding.

### 6.2.1 Dosing Regimen

Mothers will receive Aldurazyme at their prescribed dose and regimen. The Aldurazyme infusion will be prepared as described in the appropriate country labeling for Aldurazyme at each study site.

### 6.2.2 Study Duration

For the Full/Full participation option: Mothers and infants will participate in this study for 12 months if 2 consecutive infant samples 12 weeks apart (not including the baseline blood draw, if performed) are negative for IgG and IgM antibodies; otherwise, testing will continue for mothers and infants for 18 months.

For the Full/Partial participation option: The study duration will be 18 months.

### 6.2.3 Study Population

Mothers treated with Aldurazyme who intend to breastfeed their infants while receiving Aldurazyme will be eligible for enrollment into this study. Mothers being treated with Aldurazyme infusion during lactation will have to provide signed

written informed consent for themselves and their infants prior to any protocol-related procedures being performed. Consent for all infants enrolled in the study will be obtained from the infant's legally authorized guardian. If a mother is younger than 18 years of age, consent for mother and infant will be obtained from the legal guardian.

# 7. PATIENT POPULATION AND SELECTION

Up to 10 mothers and their infants will be enrolled in this study, at up to 10 study centers.

## 7.1 Inclusion Criteria

Mothers must meet the following criteria to be enrolled in this study:

1. The patient must have a documented α-L-iduronidase deficiency with a fibroblast, plasma, serum, leukocyte, or dried blood spot α-L-iduronidase enzyme activity assay.

2. Be pregnant, planning to breastfeed postpartum, and receiving Aldurazyme while breastfeeding.

3. Provide signed, written informed consent prior to any protocol-related procedure. Consent of a legally authorized guardian is required for mothers younger than 18 years of age. If a mother is younger than 18 years of age and can understand the consent, written informed consent is required from both the mother and the legally authorized guardian.

4. Provide signed, written informed consent for their infants to participate as study subjects. If a mother is younger than 18 years of age, consent for mother and infant will be obtained from the legally authorized guardian.

## 7.2 Exclusion Criteria

Mothers (and their infants) will be excluded from this study if any of the following exclusion criteria are met:

1. Have a medical condition, serious intercurrent illness, or other extenuating circumstance that may interfere with study compliance including all prescribed evaluations and follow-up activities.

2. Have received an investigational drug within 30 days prior to study enrollment.

## 7.3 Withdrawal Criteria

### 7.3.1 Patient Withdrawal

A mother (or the legal guardian of a mother younger than 18 years of age) is free to withdraw consent and discontinue her participation, as well as her infant's participation, in the study at any time, without prejudice to further treatment. Study participation of an infant and mother may be discontinued at any time at the Investigator's discretion. If the mother is no longer

lactating, the mother will discontinue this study; the infant will be followed for only urine and developmental assessments for the remainder of the study.

If the mother and/or the infant discontinue(s) participation in the study, or their participation is discontinued by the Investigator, the Patient Completion/Discontinuation Case Report Form (CRF) describing the reason for discontinuation must be completed. Any AEs experienced by the mother or infant up to the point of discontinuation must be documented on the AE CRF.
Whenever possible the mother and/or infant should return to the study site for the final clinical assessments as specified in Section 9 Efficacy and Safety Variables (Table 9-1 and Table 9-2), as appropriate. The Study Investigator will describe the reason for discontinuation on the appropriate CRF.

If AEs are present at the time of study discontinuation and these events are deemed related to Aldurazyme, the relevant patient (mother or infant) will be re-evaluated if, in the opinion of the Investigator upon consultation with the Sponsor, follow-up is clinically warranted or relevant to the evaluation of safety of the trial treatment; results of re-evaluation will be recorded on the CRF. Serious adverse events (SAEs) will be followed until resolution. If the patient withdraws consent, the Investigator may not be able to obtain this data.

A follow-up safety call will be made 1 month (28 days) after any AE or SAE following discontinuation or withdrawal from the study. If any new AE or SAE is identified during the course of this follow-up of ongoing AEs, additional follow-up of these new AEs/SAEs may be performed if, in the opinion of the Investigator (upon consultation with the Sponsor), the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment.

## 8. TREATMENTS

8.1 Treatmnts Administered

Mothers will receive Aldurazyme treatment at their currently defined dosing regimen as determined by their treating physician. The Aldurazyme infusion will be prepared as described in the appropriate country labeling for Aldurazyme at each study site.

8.2 Investigational Product

Mothers enrolled in this study will receive commercially available Aldurazyme. Refer to appropriate country labeling information.

8.3 Patient Numbering

After signing the written informed consent, each mother will be assigned a 6-digit identification number. Each infant will be assigned a separate 6-digit identification number.

8.4 Packaging and Labeling

Refer to appropriate country labeling information for packaging and labeling information for Aldurazyme.

8.5 Prior and Concomitant Medications

All medications taken by mothers and infants from the time the Informed Consent Form is signed until the end of study participation will be recorded in the Concomitant Medication CRF.

# 9. EFFICACY AND SAFETY VARIABLES

Efficacy will not be measured in this study.

## 9.1 Schedule of Study Evaluations

After obtaining signed, written informed consent for both mother and infant, the study will be conducted as outlined in the following sections. Table 9-1 summarizes the schedule of study events at each visit for mothers and infants enrolled in the Full/Full participation option of the study. Table 9-2 summarizes the schedule of study events at each visit for mothers and infants enrolled in the Full/Partial participation option of the study. Refer to the *Study Operations Manual* for guidelines regarding test assessments and procedures for handling/shipment of all central laboratory samples.

The timing of study procedures will be based on calendar weeks starting with Week 1 (week of baseline assessments). The study procedures and assessments are scheduled so that the maximum time a mother or infant participates in the study is approximately 18 months.

## Table 9-1 Schedule of Study Evaluations - Mother (Full Participation) and Infant (Full Participation)

| Evaluation | Baseline[1] | Within 1 Month Postpartum | Every 12 Weeks (±5 days) | End of Study[2] |
|---|---|---|---|---|
| **Mother** | | | | |
| Entry criteria | X | | | |
| Written informed consent[3] | X | | | |
| Medical history and complete physical examination | X | X | X | X |
| IgG antibody[4] | X | | X | X |
| uGAG | X | | X | X |
| Laronidase in breast milk[5] | | X | X | X |
| Breastfeeding status | | X | X | X |
| Concomitant medications | Continuous Monitoring | | | |
| Adverse events | Continuous Monitoring | | | |
| **Infant** | | | | |
| Written informed consent (provided by parent[s]/legal guardian[s])[3] | X | | | |
| Medical history and complete physical examination | X[6] | X | X | X |
| IgG and IgM antibodies | X[7] | | X | X |
| Breastfeeding status | | X | X | X |
| uGAG | X[8] | | X | X |
| Development assessment[9] | | | X | X |
| Concomitant medications | Continuous Monitoring | | | |
| Adverse events | Continuous Monitoring | | | |

IgG, immunoglobulin G; IgM, immunoglobulin M; uGAG, urinary glycosaminoglycans

[1] Baseline is defined as birth (infant) and within 1 month prior to birth (mother).
[2] Mother and infant will participate in this study for 12 months if 2 consecutive infant samples 12 weeks apart, not including the baseline blood draw, are negative for IgG and IgM antibodies; otherwise, testing will continue for mother and infant for 18 months.
[3] Written informed consent may be given by mother (or legal guardian if mother is younger than 18 years of age) during pregnancy or after delivery.
[4] Blood samples must be drawn before breast milk samples are collected.
[5] Breast milk samples will be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.
[6] The baseline medical history and physical examination for the infant must be performed within the first week after birth.
[7] Baseline IgG and IgM are obtained from umbilical cord blood immediately after birth.
[8] Baseline urine sample in infants must be obtained within 72 hours of birth and prior to the next infusion of the mother.
[9] Infant development (personal-social, fine motor, language, and gross motor) is assessed with the Denver II Developmental Screening Test.

## Table 9-2 Schedule of Study Evaluations - Mother (Full Participation) and Infant (Partial Participation)

| Evaluation | Baseline[1] | Within 1 Month Postpartum | Every 12 Weeks (±5 days) | End of Study[2] |
|---|---|---|---|---|
| **Mother** | | | | |
| Entry criteria | X | | | |
| Written informed consent[3] | X | | | |
| Medical history and complete physical examination | X | X | X | X |
| IgG antibody[4] | X | | X | X |
| uGAG | X | | X | X |
| Laronidase in breast milk[5] | | X | X | X |
| Breastfeeding status | | X | X | X |
| Concomitant medications | Continuous Monitoring | | | |
| Adverse events | Continuous Monitoring | | | |
| **Infant** | | | | |
| Written informed consent (provided by parent[s]/legal guardian[s])[3] | X | | | |
| Medical history and complete physical examination | X[6] | X | X | X |
| Umbilical cord blood sample for IgG and IgM antibodies | X[7] | | | |
| Breastfeeding status | | X | X | X |
| uGAG | X[8] | | X | X |
| Development assessment[9] | | | X | X |
| Concomitant medications | Continuous Monitoring | | | |
| Adverse events | Continuous Monitoring | | | |

IgG, immunoglobulin G; IgM, immunoglobulin M; uGAG, urinary glycosaminoglycans

[1] Baseline is defined as birth (infant) and within 1 month prior to birth (mother).
[2] Mother and infant will participate in this study for 18 months.
[3] Written informed consent may be given by mother (or legal guardian if mother is younger than 18 years of age) during pregnancy or after delivery.
[4] Blood samples must be drawn before breast milk samples are collected.
[5] Breast milk samples are collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.
[6] The baseline medical history and physical examination for the infant must be performed within the first week after birth.
[7] Baseline IgG and IgM are obtained from umbilical cord blood immediately after birth.
[8] Baseline urine samples in infants must be obtained within 72 hours of birth and prior to the next infusion of the mother.
[9] Infant development (personal-social, fine motor, language, and gross motor) is assessed with the Denver II Developmental Screening Test.

## 9.2 Tests and Procedures

Mothers may enroll in this study any time after pregnancy is documented and prior to the birth of their infants. After entry criteria have been met and the mother or the mother's legal guardian has provided written informed consent for both mother and infant for study participation, mothers and infants will undergo the following assessments:

### 9.2.1 Tests and Procedures for Mother and Infant (Full/Full Participation)

#### 9.2.1.1 Baseline

**Mother** (within 1 month prior to infant's birth):

- Written informed consent for mother and infant
- Medical history and complete physical examination
- Blood samples for IgG antibody testing to laronidase
- Urine samples for uGAG testing
- Concomitant medications and AEs

**Infant** (at birth):

- Parent(s)/legal guardian(s) provide signed written informed consent for the infant. (May be collected/provided prior to birth.)
- Medical history and complete physical examination (within the first week)
- Umbilical cord blood sample from infant for IgG and IgM antibody testing to laronidase (immediately after birth)
- Urine samples for uGAG testing (within 72 hours of birth and prior to next infusion)
- Concomitant medications and AEs (prior to discharge)

#### 9.2.1.2 Within 1 Month Postpartum:

**Mother**:

- Medical history and complete physical examination
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion*.)
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Breastfeeding status
- Concomitant medications and AEs

9.2.1.3 Every 12 Weeks (±5 days):

**Mother**:

- Medical history and complete physical examination
- Blood samples for IgG antibody testing to laronidase
- Urine samples for uGAG testing
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.)*
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Blood sample for IgG and IgM antibody testing to laronidase
- Breastfeeding status
- Urine samples for uGAG testing
- Development assessment using the Denver II Developmental Screening Test
- Concomitant medications and AEs

9.2.1.4 End of Study:

**Mother**:

- Medical history and complete physical examination
- Blood samples for IgG antibody testing to laronidase
- Urine samples for uGAG testing
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.)*
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Blood samples for IgG and IgM antibody testing to laronidase
- Breastfeeding status
- Urine samples for uGAG testing
- Development assessment using the Denver II Developmental Screening Test
- Concomitant medications and AEs

9.2.2 Tests and Procedures for Mother and Infant (Full/Partial Participation)

9.2.2.1 Baseline

**Mother** (within 1 month prior to infant's birth):

- Written informed consent for mother and infant
- Medical history and complete physical examination
- Blood sample for IgG antibody testing to laronidase

- Urine samples for uGAG testing
- Concomitant medications and AEs

**Infant** (at birth):

- Parent(s)/legal guardian(s) provide signed written informed consent for the infant. (May be collected/provided prior to birth.)
- Medical history and complete physical examination (within the first week)
- Umbilical cord blood sample from infant for IgG and IgM antibody testing to laronidase (immediately after birth)
- Urine samples for uGAG testing (within 72 hours of birth and prior to next infusion)
- Concomitant medications and AEs (prior to discharge)

9.2.1.2 Within 1 Month Postpartum:

**Mother**:

- Medical history and complete physical examination
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion*.)
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Breastfeeding status
- Concomitant medications and AEs

9.2.2.3 Every 12 Weeks (±5 days):

**Mother**:

- Medical history and complete physical examination
- Blood samples for IgG antibody testing to laronidase
- Urine samples for uGAG testing
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.)*
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Breastfeeding status
- Urine samples for uGAG testing
- Development assessment using the Denver II Developmental Screening Test
- Concomitant medications and AEs

9.2.2.4 End of Study:

**Mother**:

- Medical history and complete physical examination
- Blood samples for IgG antibody testing to laronidase
- Urine samples for uGAG testing
- Breast milk samples to test for the presence of laronidase (*To be collected within 24 hours prior to Aldurazyme infusion and within 60 minutes after completion of Aldurazyme infusion.)*
- Breastfeeding status
- Concomitant medications and AEs

**Infant:**

- Medical history and complete physical examination
- Breastfeeding status
- Urine samples for uGAG testing
- Development assessment using the Denver II Developmental Screening Test
- Concomitant medications and AEs

## 9.3 Measurements

The effects of Aldurazyme treatment on lactation in women with MPS I disease and their breastfed infants will be monitored continuously throughout study participation and will be assessed in terms of incidence of AEs, physical examination results, vital signs, and immunogenicity testing. Refer to Tables 9-1 and 9-2 for the schedule of these assessments and to the *Study Operations Manual* for details.

### 9.3.1 Physical Examination

Each physical examination will include the following physical observations: General Appearance, Skin, Head, Ears, Eyes, Nose, and Throat, Lymph Nodes, Heart, Lungs, Abdomen, Extremities/Joints, Neurological, Mental Status, and the following, if appropriate, Breasts, External Genitalia, Pelvic, Rectal, Vital Signs, and Height/Weight.

If clinically significant worsening from baseline of the physical examination assessments is noted, the change will be documented as an AE on the AE CRF and will be followed as an AE consistent with the procedure outlined in Section 9.6. Clinical significance is defined as any variation in physical findings that has medical relevance resulting in an alteration in medical care.

### 9.3.2 Immunogenicity Testing

Blood samples for anti-laronidase IgG (mother and infant) and IgM (infant) antibody testing will be obtained at baseline and every 12 weeks thereafter throughout the study for the Full/Full participation option only. If 2

consecutive infant samples 12 weeks apart (not including the baseline blood draw) are negative for IgG and IgM antibodies, study participation for the mother and infant will last 12 months; otherwise, testing will continue for the mother and infant for 18 months.

## 9.4 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation patient, which does not necessarily have a causal relationship with the product (active or placebo drug, biologic, or device). An AE can, therefore, be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the product.

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, electrocardiogram, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the study medication are not considered AEs after treatment unless they re-occur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

Any AEs experienced by the mother or infant from the time of signing the Informed Consent Form through the completion of study participation, will be reported as described in Section 9.6 and recorded on the CRF. If AEs are present when the patient completes study participation or discontinues the study prematurely and these events are deemed related to Aldurazyme, the relevant patient (mother or infant) will be re-evaluated if, in the opinion of the Investigator (upon consultation with the Sponsor), the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment; results of re-evaluation will be recorded on the CRF. SAEs will be followed until resolution.

If any new AE or SAE is identified during the course of this follow-up of ongoing AEs, additional follow-up of these new AEs/SAEs may be performed if, in the opinion of the Investigator (upon consultation with the Sponsor), the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment.

### 9.4.1 Infusion-Associated Reactions

An infusion-associated reaction (IAR) is defined as an AE that occurs during the infusion or observation period following the infusion and assessed as causally related to laronidase. Related events occurring after the post-infusion period may be considered infusion reactions at the discretion of the reporter.

## 9.5 Serious Adverse Events

A SAE is defined as any AE that results in any of the following outcomes:

- Death
- Life-threatening experience
- Required or prolonged inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events, based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above

Death: The patient died as the result of the event.

Life-threatening event: Any AE that places the patient, in the view of the Investigator, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.

Required or prolonged inpatient hospitalization: The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product.

Important medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- Patient hospitalization for a pre-planned Cesarean Section will not be deemed an SAE unless complications occur that result in prolonged hospitalization.

**Severity Grading**

The Investigator will assess the severity of all AEs/SAEs as Mild, Moderate, or Severe, based on the following definitions (developed from CDISC SDTM standard terminology v3.1.1).

**Definitions**

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

## 9.6 Adverse Event and Serious Adverse Event Reporting

The necessity and time requirements for reporting SAEs to the Sponsor or designee and/or regulatory agencies are as follows:

- All SAEs will be reported within 24 hours of the Investigator's first knowledge of the event, even if the event does not appear to be related to the study drug. Such communications are to be directed to:

| **Genzyme Global Patient Safety and Risk Management** |
|---|
| Fax: 1-617-761-8506 (Global Triage)<br>E-mail: pharmacovigilancesafety@genzyme.com |

(See *Study Operations Manual* for pharmacovigilance study contacts during business hours.)

- All IARs (non-serious and serious) will be reported within 24 hours of the Investigator's first knowledge of the event. Such communications are to be directed to the office listed above.

- All SAEs will include a detailed written description of the event(s). Copies of relevant patient records, autopsy reports, and other documents may be requested by and will be sent to the Global Patient Safety & Risk Management (GPS&RM) Department.

Additionally, Institutional Review Boards (IRB) or Institutional Ethics Committees (IEC) must be notified in writing of any expedited SAEs (those AEs that are serious, unexpected, and related to study drug). It is the responsibility of the

Investigator to notify the IRB or IEC. All expedited SAEs associated with the use of the study drug will be reported by the Sponsor to appropriate regulatory agencies as per the required timelines.

All AEs and SAEs will be documented on the study CRF, with a full description including the nature, date and time of onset and resolution, determination of seriousness, severity, corrective treatment, outcome, and relationship to study drug.

If AEs or SAEs are ongoing when the patient completes or prematurely discontinues the study, and these events are deemed related to Aldurazyme, additional follow-up will be performed if, in the opinion of the Investigator (upon consultation with the Sponsor), the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment. SAEs will be followed until resolution.

If any new AE or SAE is identified during the course of this follow-up of ongoing AEs, additional follow-up of these new AEs/SAEs may be performed if, in the opinion of the Investigator (upon consultation with the Sponsor), the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment.

## 10. DATA QUALITY ASSURANCE

All required data will be recorded in the CRF provided by Genzyme Corporation in accordance with Section 12.3.2.

The CRFs will be reviewed manually at the study site for completeness by a clinical monitor from Genzyme Corporation or a designee, and returned to Genzyme Corporation or its designee, for data management and analysis. If necessary, the study site will be contacted for corrections and/or clarifications. All data will be entered into a study database for analysis and reporting. Any data captured electronically (e.g., laboratory data) will be electronically transferred to the database. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

## 11. STATISTICAL METHODS AND PLANNED ANALYSES

Genzyme Corporation will be responsible for data entry and editing, reviewing all the information in the CRFs, statistical analysis, and generation of the clinical report.

Clinical data will be double-entered and validated in an Oracle database using Clintrial Version 4.5.

Prior to locking the database, all data editing will be complete and decisions regarding the evaluability of all patient data for inclusion in the statistical analysis will be made. The rationale for excluding any data from the statistical analyses will be prospectively defined, and classification of all or part of a patient's data as nonevaluable will be completed and documented before the entire database is locked and before the statistical analysis is begun. The statistical analysis will not begin until the entire database is locked and signed off, in accordance with the Standard Operating Procedures of the Biostatistics Department.

The Genzyme Biostatistics Department will perform the statistical analysis of the data derived from this study. The analysis will be performed using the SAS® statistical software system (SAS Institute Inc., 2008; SAS® Language, Version 9.2).

### 11.1 Study Variables

The analyses of the data from this study are designed to address the following questions:

- Is laronidase activity present in the breast milk of mothers with MPS I disease who are being treated with Aldurazyme during lactation?
- Does Aldurazyme affect the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with Aldurazyme during lactation?

Effects of Aldurazyme on lactation in mothers will be assessed in terms of the proportion of lactating women with serum IgG antibodies to laronidase, the levels of IgG antibody titers to laronidase, the proportion of women who breastfed, the proportion of women who were successful at breastfeeding, the proportion of women whose breast milk contained laronidase, the levels of laronidase in the breast milk of lactating mothers with MPS I disease, the proportion of women with abnormal uGAG levels, the levels of uGAG, and medical history and physical examination findings.

Effects of Aldurazyme on infants will be assessed in terms of the proportion of infants with abnormal uGAG levels, the levels of uGAG, medical history and complete physical examination findings (including growth), and the developmental assessment findings. For the infants participating in the Full/Full option, the effects of Aldurazyme will be assessed in terms of the proportion of infants with IgM and IgG antibodies present at any time point, the levels of IgG and IgM antibody titers to laronidase, and the time to development of IgM and IgG antibodies to laronidase.

#### 11.1.1 Patient Populations

The intent-to-treat (ITT) approach will be the main analysis for this study. This approach will include both mothers and infants of mothers who will receive Aldurazyme during lactation. The ITT analysis will be the basis for determination of the effects of Aldurazyme on lactation.

#### 11.1.2 Handling of Dropouts

For the analyses, summary data for patients who terminate the study early or miss study visits (and consequently have missing data) will not be carried forward to the next time point. Hence, the analyses will be performed on an observed-cases basis.

#### 11.1.3 Statistical Methods

All data collected in this study will be documented using summary tables, graphs, figures, and patient data listings.

No hypothesis testing will be performed.

### 11.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics data for the mother and for the infant will be summarized descriptively. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n's, means, medians, standard deviations, minimums, and maximums) will be presented.

Prior medications will also be summarized descriptively (using frequencies and percentages).

### 11.3 Patient Accountability

Data from all patients (mothers and infants) who are enrolled in the study will be included in the summary of patient accountability. The frequency and percentage of patients who are enrolled in the study, attended each visit, are discontinued from the study, or complete the study will be summarized.

## 11.4 Study Variables

The following variables will be summarized descriptively:

**Mothers**

- The proportion of lactating women with serum IgG antibodies to laronidase
- Amount of IgG antibody titers to laronidase in lactating women
- The proportion of women who breastfed
- The proportion of women who were successful at breastfeeding
- The proportion of women whose breast milk contains laronidase
- Amount of laronidase in the breast milk of lactating mothers with MPS I disease
- The proportion of women with abnormal uGAG levels
- Amount of uGAG in the urine of women
- Medical history and physical examination findings

**Infants**

- The proportion of infants with abnormal uGAG levels
- Amount of uGAG in the urine of infants
- Medical history and complete physical examination (including growth)
- Developmental assessment findings
- For the Full/Full Participation option only:
  - The proportion of infants with IgM and IgG antibodies to laronidase present at any time point
  - The time to development of IgM and IgG antibodies to laronidase
  - Amount of IgG and IgM antibody titers to laronidase

In addition, the incidence of AEs will be summarized descriptively by using MedDRA coding. Shifts in physical examination results from baseline (last baseline measurement) to the study time points will be summarized descriptively.

## 11.5 Sample Size

This study will enroll up to 10 mothers and their infants. No formal sample size calculations were performed.

## 11.6 Interim Analysis

After 3 infants have completed the study, an interim summary of the data will be provided as described above for the main analyses, in order to facilitate discussions with the FDA. As this is an open-label post-marketing study with no formal hypothesis testing, the usual adjustments to significance levels will not be required.

## 12. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the International Conference on Harmonisation (ICH)/ Good Clinical Practice (GCP) guideline. These requirements are stated in the ICH Guideline Topic E6 entitled "Guideline for Good Clinical Practice."

### 12.1 Institutional and Ethics Review

This protocol and patient informed consent form must be reviewed and approved by an IRB/IEC before enrollment of patients and release of investigational product. Documentation of IRB/IEC and the approved consent form must be received by Genzyme Corporation or its designee prior to obtaining the patient's informed consent.

### 12.2 Changes to the Conduct of the Study or Protocol

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and BioMarin/Genzyme LLC. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval must be returned to Genzyme Corporation or its designee.

### 12.3 Investigator's Responsibilities

#### 12.3.1 Patient Informed Consent

Investigators must adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient informed consent form and when obtaining consent from the patient. Written informed consent is required prior to enrollment in the study. It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB/IEC approved consent form.

12.3.2 Case Report Forms

Copies of pertinent records in connection with the study, including all source documents, will be made available to Genzyme Corporation or its designee on request with due precaution towards protecting the privacy of the mother and infant.

Case report forms will be filled out legibly and completely. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the CRFs will be crossed out with a single line, initialed and dated, and the correct entry, if appropriate, will be recorded. Writing in the margins of the CRFs is not permitted. The original CRFs will be provided to Genzyme Corporation or its designee. A copy of the CRFs will be maintained in the Investigator's site file. Illegible or incomplete entries or entries needing additional explanation will be returned or queried to the Investigator for clarification.

12.3.3 Record Retention

The Investigator is responsible for oversight and maintenance of the study records and patient source documents. These records must be readily available for audit or inspection.

The Investigator must retain study records for at least 2 years after the last marketing approval has been granted, or at least 2 years have elapsed since the formal discontinuation of clinical program. However, these documents should be retained for a longer period, if required by other applicable requirements (e.g., applicable local regulatory requirement) or by an agreement with the BioMarin/Genzyme LLC or its designee. The Investigator should contact the BioMarin/Genzyme LLC or its designee prior to any record destruction.

Patient records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

12.3.4 Monitoring

A representative of BioMarin/Genzyme LLC or its designee will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Noncompliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, as necessary. It is the

responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

At any time prior to, during, or after completion of the clinical study, an audit may be performed by BioMarin/Genzyme LLC or its designee or a representative of a national regulatory agency may choose to inspect a study site. Investigators should notify BioMarin/Genzyme LLC or its designee upon notification of inspection by a representative of a national regulatory agency. A BioMarin/Genzyme LLC or designee representative will be available to assist in the preparation for study site inspections. All pertinent study data should be made available for verification, audit, or inspection purposes.

12.3.5 Study or Site Termination

If BioMarin/Genzyme LLC, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between BioMarin/Genzyme LLC and the Investigator. BioMarin/Genzyme LLC has the right to terminate the participation of either an individual site or the study at any time, for any reason which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study.
- Submission of knowingly false information from the study site to BioMarin/Genzyme LLC or regulatory authorities.
- Results of a planned interim analysis support terminating the study.

In the event that the study is terminated early, BioMarin/Genzyme LLC will provide specific guidance to investigational sites regarding the end-of-study procedures.

12.3.6 Investigational Product Control

There will be no clinical trial supplies provided for this study.

12.3.7 Disclosure of Data

All details related to the disclosure and publication of study data will be addressed in the Investigator's study contract.

12.3.8 Clinical Study Report

The Investigator will review and sign the completed clinical study report.

## 13. REFERENCES

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