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CLINICAL STUDY PROTOCOL

Protocol: AGLU03606/LTS12869

A Long-term Study to Evaluate Growth and Development Outcomes in Patients with Infantile-Onset Pompe Disease Who Are Receiving Alglucosidase Alfa

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Study Manager: [redacted]

Medical Monitor:

Statistician:

[redacted]

Medical Monitor Signature Date

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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

Investigator Signature Date

1. SYNOPSIS

NAME OF COMPANY Genzyme Corporation, a Sanofi Company 500 Kendall Street Cambridge, MA 02142 **NAME OF FINISHED PRODUCT** Myozyme® / Lumizyme® (alglucosidase alfa) **NAME OF ACTIVE INGREDIENT** alglucosidase alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE:

A Long-term Study to Evaluate Growth and Development Outcomes in Patients with Infantile-Onset Pompe Disease Who Are Receiving Alglucosidase Alfa

INVESTIGATOR STUDY CENTERS:

The number of study centers will not be limited prospectively.

OBJECTIVES:

The overall objective is to evaluate long-term growth and development of patients with infantile-onset Pompe disease who begin treatment with alglucosidase alfa before 1 year of age. Patients will be followed for a 10-year period. An additional objective is to collect long-term safety data on patients with infantile-onset Pompe disease. As an exploratory objective, the effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) will be evaluated. For research purposes only, cross-reacting immunologic material (CRIM) status and GAA mutation analysis will be evaluated.

METHODOLOGY:

This is a multicenter study of patients with infantile-onset Pompe disease who begin alglucosidase alfa treatment prior to 1 year of age. Patients with a confirmed diagnosis of Pompe disease who begin alglucosidase alfa treatment prior to their first birthday will be followed in this study for 10 years.

The patient's legal guardian(s) must sign the informed consent form prior to performance of any of the study assessments outlined in Table 9-1.

An independent Data Safety Monitoring Board (DSMB) will review safety information on an ad hoc basis as outlined in the DSMB charter, which is maintained separately from the study protocol.

An independent Allergic Reaction Review Board (ARRB) will be consulted on an ad hoc basis as outlined in the ARRB charter, which is also maintained separately from this protocol.

NUMBER OF SUBJECTS:

The number of patients followed in this study will not be limited prospectively.

DIAGNOSIS/INCLUSION CRITERIA:

Inclusion Criteria:
(1) the patient's legal guardian(s) must provide written informed consent prior to study assessments being performed; (2) the patient must have a confirmed diagnosis of Pompe disease as determined by deficient endogenous GAA activity or GAA mutation analysis; and (3) the patient must be <1 year of age at time of study enrollment (and receive alglucosidase alfa treatment before 1 year of age), or the patient must be between 1 year and 24 months of age and must have initiated alglucosidase alfa treatment prior to turning 1 year of age.

Exclusion Criteria:
(1) the patient is participating in another clinical study using alglucosidase alfa or any investigational therapy.

DOSE/ROUTE/REGIMEN:

NAME OF COMPANY Genzyme Corporation, a Sanofi Company 500 Kendall Street Cambridge, MA 02142 NAME OF FINISHED PRODUCT Myozyme® / Lumizyme® (alglucosidase alfa) NAME OF ACTIVE INGREDIENT alglucosidase alfa	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Alglucosidase alfa will be administered at 20 mg/kg body weight as prescribed by the treating physician every 2 weeks as an intravenous infusion. If clinically feasible, all patients will continue at the same dose throughout the study. Any modification to the dose and/or frequency of dosing is not permitted unless it is due to disease progression or to an adverse event (AE), in which case it is not a protocol deviation, but the Investigator must consult with the Sponsor's Medical Monitor and Global Safety Officer in the event of a dose change. The dosing change and the reasons for it will be documented on the appropriate case report forms.

It is recommended that the reconstitution and administration instructions in the current prescribing information be followed.

Patients who meet specific criteria may have the option for home infusions. Because of the possibility of anaphylactic reactions, personnel competent in recognizing and treating adverse reactions (including anaphylactic reactions) should be readily available throughout the home infusion. The following criteria must be documented in the patient's medical record:

- The patient must be clinically stable with no history of moderate or severe IARs within 6 months prior to planned transition to home infusion.
- The patient must have no ongoing serious adverse events (SAEs) that, in the opinion of the Investigator, may impact the patient's ability to tolerate infusion.
- The home infusion agency staff must be trained by the Investigator prior to beginning home infusions. Any new staff member must be trained by the Investigator prior to beginning home infusions.
- The home infusion agency staff must have access to and be trained on proper safety equipment, including but not limited to cardiopulmonary resuscitation equipment.
- If recurrent IARs or hypersensitivity/anaphylactic reactions occur, the Investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion. Genzyme should be notified about all IARs and consulted (as needed) if the patient experiences IARs suggestive of hypersensitivity reactions (refer to Section 9.5.2).
- Home Infusion Agency must keep source documentation of the infusion, including documentation of any AEs. Home Infusion Agency must be amenable to providing specific source documentation to Genzyme and agree to be monitored. The Principal Investigator is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company.

The Principal Investigator is responsible for approving a patient's initiation with home infusions and is ultimately responsible for the safety of the patient during this clinical study. Refer to the Study Manual and Home Infusion Manual for further details regarding home infusions.

REFERENCE TREATMENT:
There will be no comparator treatment or placebo in this study.

CRITERIA FOR EVALUATION:
Efficacy: The following efficacy assessments will be performed at scheduled visits during the study:

- Growth as measured by recumbent length/height, weight and head circumference

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- Motor development and function, as measured by changes in the motor subscale of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), Gross Motor Function Measure (GMFM-88) and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI)
- Cognitive Development, as measured by the cognitive and language subscales of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), change in the Brief IQ score of the Leiter International Performance Scale – Revised (Leiter-R) and/or the change in the Nonverbal IQ score of the Leiter International Performance Scale - 3rd Edition (Leiter-3) (starting at the final assessment of the Bayley-III before 42 months of age).

For patients treated with alglucosidase alfa prior to age 1 (prior to study entry), available retrospective growth and development data will be collected. Parameters for retrospective data collection will include available standard-of-care growth (height, weight, head circumference) and motor milestone information (e.g. head support, sitting, standing, and walking ability) from the time of treatment initiation.

Safety: The following safety assessments will be performed during the study: AE monitoring, laboratory tests (clinical chemistry, hematology and urinalysis), anti-rhGAA antibody (immunoglobulin G [IgG]) collection, neuroimaging (at the discretion of the Investigator), vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations, electrocardiograms (ECGs), hearing testing and visual screening.

Additional safety evaluations will include the assessment of: (1) immunoglobulin E (IgE), serum tryptase, complement activation and skin testing, when clinically indicated following moderate, severe, or recurrent IARs suggestive of hypersensitivity; and (2) circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease.

Inhibitory antibody (activity and uptake) will be assessed when clinically indicated (e.g., requirement for new invasive ventilator use, plateau or decline in response in the presence of adequate dosing).

EXPLORATORY:

The effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) will be evaluated.

RESEARCH PURPOSES ONLY:

The potential effect of CRIM status and GAA mutation on efficacy outcomes will be analyzed.

STATISTICAL METHODS:

The statistical analysis of all growth and development parameters and other efficacy outcomes and safety measurements will be conducted on all patients who receive alglucosidase alfa. All data collected in this study will be documented using summary tables, figures and patient data listings. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented.

Analyses will be performed using the SAS® statistical software system. Detailed descriptions of the analyses will be provided in a Statistical Analysis Plan.

STATISTICAL METHODS:

The statistical analysis of all growth and development parameters and other efficacy outcomes and safety measurements will be conducted on all patients who receive alglucosidase alfa. All data collected in this study will be documented using summary tables, figures and patient data listings. For categorical

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variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented.

Analyses will be performed using the SAS® statistical software system. Detailed descriptions of the analyses will be provided in a Statistical Analysis Plan.

Baseline demographic and background variables will be summarized for the patients enrolled in the study using descriptive statistics.

In addition to descriptive statistics by visit, longitudinal repeated measures modeling will be used to analyze the trends in key growth and development parameters over time.

Analyses of key variables may be stratified by relevant baseline factors.

Besides standard safety analyses of the incidence of AEs and SAEs, additional analyses will be carried out to examine the trends in incidence and prevalence of AEs, SAEs and other relevant safety parameters over time. Key safety analyses will be also carried out by gender.

EXPLORATORY:

The effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) will be evaluated.

RESEARCH PURPOSES ONLY:

The potential effect of CRIM status and GAA mutation on efficacy outcomes will be analyzed.

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3. ABBREVIATIONS AND TERMS

AE	Adverse event
AM Battery	Attention and Memory Battery
ARRB	Allergic Reaction Review Board
BAB	Butyl-p-aminobenzoate
BAER	Brainstem-auditory evoked response
Bayley-III	Bayley Scales of Infant and Toddler Development
BUN	Blood urea nitrogen
°C	Degrees centigrade
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations (USA)
CK	Creatine kinase
CK-MB	Creatine kinase muscle, brain isoform
CRF	Case report form
CRIM	Cross-reacting immunologic material
CS	Clinically significant
CSSF	Clinical Supply Shipment Form
DSMB	Data Safety Monitoring Board
DUMC	Duke University Medical Center
EC	European Community
ECG	Electrocardiogram
EMEA	European Medicines Agency
ERT	Enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GAA	Acid α-glucosidase
GCP	Good Clinical Practice
Glc4 (Hex4)	Glcα1-6Glcα1-4Glcα1-4Glc (a tetraglucose oligomer)
GMFM-88	Gross Motor Function Measure-88
H	Out of range high (on laboratory reports)
HPLC	High pressure liquid chromatography
IAR	Infusion-associated reaction
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IQ	Intelligence quotient
IRB	Institutional Review Board
kg	Kilogram
L	Out of range low (on laboratory reports)

Leiter-3	Leiter International Performance Scale- 3rd Edition
Leiter-R	Leiter International Performance Scale–Revised
LVH	Left ventricular hypertrophy
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MRI	Magnetic resonance imaging
MS	Mass spectrometry
NCS	Not clinically significant
OAE	Oto-acoustic emission
PEDI	Pediatric evaluation of disability inventory
PI	Principal Investigator
rhGAA	Recombinant human acid α-glucosidase
RVH	Right ventricular hypertrophy
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SM	Study Manual
US/USA	United States of America
UV	Ultraviolet
VR Battery	Visualization and Reasoning Battery
WHO	World Health Organization

4. INTRODUCTION

Pompe disease is a rare autosomal recessive metabolic muscle disease caused by the deficiency of acid α glucosidase (GAA), an enzyme that degrades lysosomal glycogen. As opposed to the exclusively cytoplasmic accumulation of glycogen that occurs in other glycogen storage disorders, Pompe disease is characterized by organelle bound (lysosomal) and extra-lysosomal accumulation of glycogen in many body tissues, ultimately leading to multisystemic pathology.

Historically, Pompe disease has been arbitrarily classified into different subtypes based on the age at onset of symptoms, extent of organ involvement, and rate of progression to death. Essentially, there is a broad spectrum of disease ranging from a rapidly progressive form (infantile-onset) to a more slowly progressive form (late-onset) with considerable variability and overlap existing between these extremes (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; van den Hout, 2003, *Pediatrics*). It is important to note that all presentations of Pompe disease share a common underlying pathology; i.e., deficiency of GAA with subsequent accumulation of glycogen.

At the most rapidly progressive end of the disease spectrum are patients with the infantile-onset form of Pompe disease. These patients typically present with symptoms within the first 12 months of life. A massive deposition of glycogen in the heart and skeletal muscle results in rapidly progressive cardiomyopathy and generalized muscle weakness and hypotonia. Moreover, motor development is often completely arrested, or if motor milestones are achieved, they are subsequently lost. Death from cardiac and/or respiratory failure generally occurs before most patients reach 1 year of age (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Patients presenting with this typical disease course have been described in the literature as having 'classical' infantile-onset Pompe disease. A subset of patients with infantile-onset Pompe disease that survive beyond 1 year has been described by Slonim and colleagues (Slonim, 2000, *J Pediatr*). The clinical course of disease in these patients is characterized by a slower progression of cardiomyopathy and longer survival, with patients generally developing respiratory failure between 1 and 2 years of age. Although some patients die before 1 year of age, others may survive beyond 2 years.

The late-onset form of Pompe disease progresses less rapidly than the infantile-onset form. Symptoms appear during childhood or as late as the sixth decade of life. Patients present with progressive myopathy, predominantly of the proximal muscles in the pelvic and shoulder girdles, and a variable progression of respiratory involvement. Typically these patients develop minimal or no cardiomyopathy (Chen, 2000, *Mol Med Today*; Laforêt, 2000, *Neurology*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). The course of late-onset Pompe disease is less predictable than the infantile form, with some patients experiencing a rapid deterioration in skeletal and respiratory muscle function leading to loss of ambulation and

respiratory failure, others progressing less rapidly, and yet others with dissociation in the progression of skeletal and respiratory muscle involvement (Laforêt, 2000, *Neurology*). Eventually, most patients become wheelchair-bound, require ventilator support and ultimately succumb to respiratory failure (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

Genzyme Corporation has been involved in development of enzyme replacement therapy (ERT) for the treatment of Pompe disease since 1998. Initially, the clinical development program focused primarily on demonstration of safety and efficacy in patients with the infantile-onset form of Pompe disease. Based on the findings of the clinical trials, Myozyme received marketing approval in the United States (US), European Union (EU) and Canada in 2006 for long-term ERT in patients with a confirmed diagnosis of Pompe disease while research to establish the benefit of alglucosidase alfa in late-onset Pompe disease continued. Lumizyme received marketing approval in the United States (US) in 2010 for use in late-onset Pompe disease patients 8 years of age and older. In 2014, the indication was expanded for Lumizyme to include all patients with a confirmed diagnosis of Pompe disease, irrespective of age or phenotype. The recommended dosage regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks as an intravenous solution. A brief overview of results of ERT in Pompe disease is provided below.

In the infantile-onset patients, alglucosidase alfa markedly extended survival as compared to an untreated historical cohort (Kishnani, 2007, *Neurology*). ERT with alglucosidase alfa also reversed indices of cardiomyopathy and improved cardiac function in the vast majority of patients. Moreover, consistent gains in motor function were observed, with a subset of patients achieving independent ambulation. These findings contrast sharply to the severe and unremitting clinical deterioration observed in virtually all untreated patients with infantile-onset Pompe disease (van den Hout, 2003, *Pediatrics*).

In patients with late-onset Pompe disease, alglucosidase alfa was associated with maintenance or improvements in pulmonary function, muscle strength, gross motor function, and functional status/disability. In a study of 5 pediatric patients with late-onset Pompe disease, improvement in Forced Vital Capacity (FVC) and Six Minute Walk Test (6MWT) results were observed after 26 weeks of treatment with alglucosidase alfa in 3 patients. While all 5 patients were symptomatic at Baseline, they were still ambulatory and ventilator-free during daytime hours, suggesting significant residual muscle function prior to initiation of alglucosidase alfa. It is likely that such preservation of muscle function contributed to their response to treatment. In contrast, published data on the use of ERT in patients with advanced late-onset Pompe disease have reported major clinical improvements in a patient after years rather than weeks of treatment (Winkel, 2004, *Ann Neurol*). Given the severity of illness in these patients and the progressive

nature of late-onset Pompe disease (Laforêt, 2000, *Neurology*), lack of deterioration in treated patients could represent clinical stabilization of the disease by ERT with alglucosidase alfa.

4.1 Summary of Potential Risks

Identified safety risks of alglucosidase alfa treatment include development of infusion-associated reactions (IARs) including hypersensitivity and life-threatening anaphylactic shock and/or cardiac arrest; immune-mediated reactions, immunologic response and acute cardiorespiratory failure associated with fluid overload. Patients in this study will be closely monitored for IARs and other adverse reactions. As with all ongoing clinical studies of alglucosidase alfa, an independent Data Safety Monitoring Board (DSMB) appointed by Genzyme will review safety data on an ad hoc basis and an independent Allergic Reaction Review Board (ARRB) appointed by Genzyme Corporation will also be consulted, when necessary, to review information and provide treatment recommendations for IARs.

For further details concerning warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the Investigator's Brochure (IB).

4.2 Summary of Potential Benefits

Alglucosidase alfa is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency) and is an element of the standard of care. Enzyme replacement therapy with alglucosidase alfa has shown positive effects on survival, invasive ventilator-free survival, and motor development in patients with infantile-onset Pompe disease.

The treatment administered and assessments performed during this study are not expected to provide a direct benefit to the individual patient beyond the standard of care, other than to evaluate the long-term growth and development outcomes in patients with infantile-onset Pompe disease who are receiving ERT with alglucosidase alfa. The data obtained in this study are expected to benefit the population of patients with Pompe disease as a whole through collection of long-term safety data.

5. STUDY OBJECTIVES

The overall objective is to evaluate long-term growth and development of patients with infantile-onset Pompe disease who begin treatment with alglucosidase alfa before 1 year of age. Patients will be followed for a 10-year period. An additional objective is to collect long-term safety data on patients with infantile-onset Pompe disease. As an exploratory objective, the effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) will be evaluated. For research purposes only, cross-reacting immunologic material (CRIM) status and GAA mutation analysis will be evaluated.

6. INVESTIGATIONAL PLAN

6.1 Study Design

This is a multicenter study of patients with infantile-onset Pompe disease who begin alglucosidase alfa treatment prior to 1 year of age. Patients with a confirmed diagnosis of Pompe disease who begin alglucosidase alfa treatment prior to their first birthday will be followed in this study for 10 years. The number of patients followed in this study will not be limited prospectively.

The patient's legal guardian(s) must sign the informed consent form prior to performance of any of the study assessments outlined in Table 9-1.

An independent Data Safety Monitoring Board (DSMB) will review safety information on an ad hoc basis as outlined in the DSMB Charter, which is maintained separately from the study protocol.

An independent Allergic Reaction Review Board (ARRB) will be consulted on an ad hoc basis as outlined in the ARRB Charter, which is also maintained separately from this protocol.

Efficacy will be evaluated in terms of physical growth, as measured by changes in recumbent length/height, weight and head circumference; motor development and function, as measured by changes in the motor subscale of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), Gross Motor Function Measure (GMFM-88) and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI); and cognitive development, as measured by changes in the cognitive and language subscales of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), change in the Brief IQ score of the Leiter International Performance Scale – Revised (Leiter-R) and/or the change in the Nonverbal IQ score of the Leiter International Performance Scale – 3rd Edition (Leiter-3) (starting at the final assessment of the Bayley-III before 42 months of age). As an exploratory objective, the effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4) will be evaluated. For research purposes only, cross-reacting immunologic material (CRIM) status and GAA mutation will be evaluated.

For patients treated with alglucosidase alfa prior to age 1 (prior to study entry), available retrospective growth and development data will be collected. Parameters for retrospective data collection will include available standard-of-care growth (height, weight, head circumference) and motor milestone information (e.g. head support, sitting, standing, and walking ability) from the time of treatment initiation.

Safety will be evaluated in terms of AE monitoring, laboratory tests (clinical chemistry, hematology, and urinalysis), anti-rhGAA antibody (IgG) formation, neuroimaging (at the discretion of the Investigator), vital signs (blood pressure, heart rate, respiratory rate, and

temperature), physical examinations, electrocardiograms (ECGs), hearing testing and visual screening.

Additional safety evaluations will include the assessment of: (1) IgE, serum tryptase, complement activation and skin testing, when clinically indicated following moderate, severe, or recurrent IARs suggestive of hypersensitivity; and (2) circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease. Inhibitory antibody activity and uptake will be assessed when clinically indicated (e.g., requirement for new invasive ventilator use, plateau or decline in response in the presence of adequate dosing).

7. PATIENT POPULATION AND SELECTION

Male and female patients with Pompe disease may participate.

7.1 Inclusion Criteria

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

1. The patient's legal guardian(s) must provide written informed consent prior to study assessments being performed;
2. The patient must have a confirmed diagnosis of Pompe disease as determined by deficient endogenous GAA activity or GAA mutation analysis; and
3. The patient must be <1 year of age at time of study enrollment (and receive alglucosidase alfa treatment before 1 year of age), or the patient must be between 1 year and 24 months of age and must have initiated alglucosidase alfa treatment prior to turning 1 year of age.

7.2 Exclusion Criteria

A patient will be excluded from this study if the following criterion is met:

1. The patient is participating in another clinical study using alglucosidase alfa or any investigational therapy.

7.3 Patient Withdrawal

A patient's legal guardian(s) is free to withdraw authorization and discontinue participation in the study at any time, and without prejudice to further alternate treatment. If a patient's legal guardian(s) decides to discontinue participation in the study, the Investigator should immediately contact the patient's legal guardian in order to obtain information about the reason(s) for discontinuation. The Investigator should collect information pertaining to current AEs and follow-up ongoing AEs. All patients should have final clinical assessments conducted.

All AEs ongoing at the time of withdrawal or study termination require a 30-day follow up. The Investigator will be asked to follow all SAEs that were ongoing at the time of withdrawal or study completion until resolution, until follow-up is deemed no longer medically necessary or

until the patient is lost to follow-up. The Investigator will provide an explanation on the case report form (CRF) describing the reason for discontinuation.

In the event that a patient dies, permission will be sought (through a separate informed consent form) from the patient's legal guardian(s) for a research autopsy or post-mortem research biopsy. Samples collected from this procedure will be used for research purposes only and data will not be provided to the Investigator or be included in any study analyses. Refer to the Study Manual (SM) for research autopsy and post-mortem research biopsy procedural guidelines.

A patient's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- The patient and/or patient's legal guardian(s) is uncooperative, including failure to appear at study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion or suffers an unmanageable AE.
- The study is terminated by the Sponsor.
- The patient and/or patient's legal guardian(s) refuses alglucosidase alfa administration.
- Participation in an investigational study without the prior authorization of Genzyme.

To facilitate long-term data collection, patients will be encouraged to enroll in the Pompe Disease Registry via their treating physician after study completion or discontinuation.

7.4 Study or Site Termination

If the Sponsor, an Investigator, a clinical monitor, or national regulatory authority official discover conditions during the study that indicate the study or a study site should be terminated, this action may be taken after appropriate consultation between the Sponsor, the Investigator, the clinical monitor, and the DSMB, as appropriate. Conditions that may warrant termination of the study or a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study.
- The decision on the part of Genzyme Corporation to end the study.
- Failure of the Investigator to comply with pertinent regulatory authorities.
- Submission of knowingly false information from the research facility to the Sponsor, the clinical monitor, or regulatory authorities.
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR 312.

8. TREATMENTS

8.1 Treatments Administered

Alglucosidase alfa will be administered at 20 mg/kg body weight as prescribed by the treating physician every 2 weeks as an intravenous infusion. If clinically feasible, all patients will continue at the same dose throughout the study. Any modification to the dose and/or frequency of dosing is not permitted unless it is due to disease progression or to an AE, in which case it is not a protocol deviation, but the Investigator must consult with the Sponsor's Medical Monitor and Global Safety Officer in the event of a dose change. The dosing change and the reasons for it will be documented on the appropriate CRFs.

It is recommended that the reconstitution and administration instructions in the current prescribing information be followed.

Patients who meet specific criteria may have the option for home infusions. Because of the possibility of anaphylactic reactions, personnel competent in recognizing and treating adverse reactions (including anaphylactic reactions) should be readily available throughout the home infusion. The following criteria must be documented in the patient's medical record:

- The patient must be clinically stable with no history of moderate or severe IARs within 6 months prior to planned transition to home infusion.
- The patient must have no ongoing SAEs that, in the opinion of the Investigator, may impact the patient's ability to tolerate infusion.
- The home infusion agency staff must be trained by the Investigator prior to beginning home infusions. Any new staff member must be trained by the Investigator prior to beginning home infusions.
- The home infusion agency staff must have access to and be trained on proper safety equipment, including but not limited to cardiopulmonary resuscitation equipment.
- If recurrent IARs or hypersensitivity/anaphylactic reactions occur, the Investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion. Genzyme should be notified about all IARs and consulted (as needed) if the patient experiences IARs suggestive of hypersensitivity reactions (refer to Section 9.5.2).
- Home Infusion Agency must keep source documentation of the infusion, including documentation of any AEs. Home Infusion Agency must be amenable to providing specific source documentation to Genzyme and agree to be monitored. The Principal Investigator is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company.

The Principal Investigator (PI) is responsible for approving a patient's initiation with home infusions and is ultimately responsible for the safety of the patient during this clinical study. Refer to SM and Home Infusion Manual for further details regarding home infusions.

8.2 Prior and Concomitant Medications/Therapies

From the time informed consent is obtained through study completion, all medications taken by the patient for AEs, pre-infusion medications and medications for long-term disease management will be recorded in the Concomitant Medication CRF. Concomitant therapies and assistive devices will be recorded in the Concomitant Therapies CRF.

8.3 Treatment Compliance

The patient's compliance with the treatment regimen will be monitored in terms of the patient receiving the alglucosidase alfa infusion on a regular basis. Missed or incomplete infusions will be clearly documented and considered in the statistical analyses.

9. EFFICACY, SAFETY, AND EXPLORATORY VARIABLES

9.1 Schedule of Assessments

The study will be conducted in conjunction with the patient's standard of care as outlined in the following sections. Table 9-1 summarizes the Schedule of Assessments at each visit period for patients enrolled into this study. With the exception of the Baseline, Day 0 and biweekly study assessments, all other assessments have a window of +/- 60 days. Any assessments conducted as standard of care 30 days before start of first study infusion may be utilized for baseline assessment provided all required information is captured. Infusions received after signing of the informed consent form and before completion of baseline assessments will be captured as a Concomitant Medication on CRF. Details of the assessments are provided in the SM.

Table 9-1 Schedule of Assessments

	Baseline (Prior to Initiation of Study Infusion)	First Infusion (Day 0) and Every Other Week	Every 3 Months	Every 6 Months	Every 12 Months (or on withdrawal)
Informed Consent[1]	X				
Inclusion/Exclusion Criteria	X				
Demography	X				
Medical/Surgical History[2]	X				
Recumbent length/height, weight and head circumference[3]	X		AGE < 3 YEARS	AGES 3 TO 5 YEARS	AGE ≥ 5 YEARS
Bayley-III[4,5,6]	X			AGES 1 MONTH to 42 MONTHS	
Leiter-R or updated Leiter-3 Scale[6]					FROM FINAL Bayley-III assessment <42 MONTHS OF AGE
GMFM-88[5]	X			AGE < 5 YEARS	AGE ≥ 5 YEARS
Pompe PEDI[5]	X			AGE < 5 YEARS	AGE ≥ 5 YEARS
Oligosaccharide (Hex4) levels in urine[7]	X			TO STUDY MONTH 24	FROM STUDY MONTH 24
Skin Biopsy for CRIM status assay[8]	X				
GAA mutation analysis[9]	X				
Chemistry, hematology and urinalysis	X				X
Serum IgG collection[10]	X (collected just prior to first study infusion)		TO STUDY MONTH 24		FROM STUDY MONTH 24
Neuroimaging (at the discretion of the Investigator)[11]	X				X
Vital Signs[12]	X	X			
Physical examination	X				X
ECG	X				X
Audiometry Exam	X				X
Visual Assessment	X				X
Alglucosidase alfa Infusion[13]		ONGOING ADMINISTRATION			
Adverse Event/Concomitant Medications/Therapies	← CONTINUOUS MONITORING →				

The Schedule of Study Assessments will be repeated in 12 month modules (e.g. Year 1, Year 2, etc.). With the exception of the Baseline, Day 0 and biweekly study assessments, all other assessments have a window of +/- 60 days.

[1] Informed consent must be obtained prior to enrollment into the study.

[2] Available retrospective growth and development data including motor milestone information (e.g., head support, sitting, standing and walking ability) for those patients treated with alglucosidase alfa prior to study entry will be collected to summarize clinical status information for each patient at the time of initiation of treatment with alglucosidase alfa to allow for assessment of changes in growth and development over time with treatment with alglucosidase alfa for all patients enrolled.

[3] At each time point, growth measurements (recumbent length or height, weight and head circumference) will be measured 3 times in a row and averaged. All measurements should be recorded to the nearest tenth of a centimeter. The measurement of recumbent length or height, weight and head circumference should be performed by an individual, who does not have access to the records of the patient's earlier measurements in the study and, as far as possible, by the same individual at each patient visit.

[4] Bayley-III is to be discontinued when the patient reaches 42 months of age. The Bayley-III will be administered to patients from 1 month of age until the maximum score on each of the 3 administered scales has been obtained. Once the maximum score for a scale has been achieved, only the remaining scales will be administered.

[5] Additional anti-alglucosidase alfa IgG antibody testing should be performed upon determination of any notable deterioration in a patient's motor function.

[6] Modified Leiter-R Scale or updated Leiter-3 Scale assessment is to be performed at the last assessment of the Bayley-III Cognitive and Language Scales prior to the patient reaching 42 months of age and annually thereafter until the patient reaches the end of the follow up period. If previous assessments have been performed using Leiter-R and switch to Leiter-3 Scale is planned, then both assessments need to be performed at the same time of the initial administration of the Leiter-3, in order to create a baseline. The dates of the two tests should be recorded appropriately in the CRFs and the scores recorded on the appropriate test score sheets.

[7] Oligosaccharide (Hex4) testing will be performed every 6 months until the 24th month and then yearly.

[8] Genzyme Corporation or their designee will perform the CRIM analysis in skin biopsies. CRIM will be conducted only if written results are not available.

[9] GAA mutation analysis is to be conducted only if written results are not available.

[10] To be collected every 3 months up to Study Month 24 (3, 6, 9, 12, 15, 18, 21 and 24) and annually thereafter. Additional testing should be performed upon determination of any notable deterioration in a patient's motor function. Serum IgG samples should always be collected pre-infusion at each time point.

[11] Serial brain magnetic resonance imaging (MRI) will be performed at the discretion of the Investigator.

[12] In addition to a Baseline vital sign measurement, vital signs will be monitored prior to the start of each infusion, at the end of each infusion, and upon the occurrence of any IARs.

[13] Prior to each infusion, the patient should be assessed by the PI or appropriate designee to determine if the patient is free of acute illness and clinically stable to receive the infusion.

9.1.1 Baseline

The following procedures will be performed.

- Informed consent
- Inclusion/exclusion criteria
- Demography
- Medical/Surgical history (including available major motor milestone information (e.g., head support, sitting, standing and walking ability)
- Recumbent length/height, weight and head circumference
- Bayley-III
- GMFM-88
- Pompe PEDI
- Oligosaccharide (Hex4) levels in urine
- Skin biopsy for CRIM assay
- GAA mutation analysis
- Chemistry, hematology and urinalysis
- Serum IgG collection (collected just prior to first study infusion)
- Neuroimaging (at the discretion of the Investigator)
- Vital signs
- Physical examination
- ECG
- Audiometry exam
- Visual assessment
- Adverse event/concomitant medications/therapies

Upon confirmation that the patient meets all eligibility criteria and signing of the informed consent form, eligible patients will then be assigned a Patient Identification number.

9.1.2 First Infusion (Day 0) and Every Other Week

Following the Baseline procedures,

- Alglucosidase alfa infusions are to be administered per the Investigator. Prior to each infusion, the patient should be assessed by the PI or appropriate designee to determine if the patient is free of acute illness and clinically stable to receive the infusion.
- Vital signs monitored prior to the start of each infusion, at the end of each infusion and upon the occurrence of any IARs
- Continuous adverse event/concomitant medications/therapies monitoring

9.1.3 Every 3 Months (Months 3, 6, 9, 12, 15, 18, 21, 24, etc.)

The following procedures will be performed:

- Recumbent length/height, weight and head circumference (up to 3 years of age)
- Serum IgG collection (up to Study Month 24)

9.1.4 Every 6 Months (Months 6, 12, 18, 24, etc.)

The following procedures will be performed:

- Recumbent length/height, weight and head circumference (ages 3 to 5 years)
- Bayley-III (to be discontinued when the patient reaches 42 months of age)
- GMFM-88 (performed every 6 months until 5 years of age, at which point assessment will be performed yearly)
- Pompe PEDI (performed every 6 months until 5 years of age, at which point assessment will be performed yearly)
- Oligosaccharide (Hex4) levels in urine (performed every 6 months up to Study Month 24, after which point assessment will be performed yearly)

9.1.5 Every 12 Months (Or on Withdrawal from the Study)

The following procedures will be performed:

- Recumbent length/height, weight and head circumference (yearly once patient reaches age ≥ 5 years)
- Leiter-R Brief IQ scale and/or updated Leiter-3 Nonverbal IQ scale (to begin concurrent with the last assessment of the Bayley-III Cognitive and Language Scales prior to the patient reaching 42 months of age)
- GMFM-88 (yearly once patient reaches age ≥ 5 years)
- Pompe PEDI (yearly once patient reaches age ≥ 5 years)
- Oligosaccharide (Hex4) levels in urine (yearly after Study Month 24)
- Chemistry, hematology and urinalysis
- Serum IgG collection (after Month 24)
- Neuroimaging (at the discretion of the Investigator)
- Physical examination
- ECG
- Audiometry exam
- Visual assessment
- Adverse event/concomitant medications/therapies

9.2 Efficacy and Additional Exploratory Efficacy Assessments

9.2.1 Physical Growth

Physical growth will be assessed at the times specified in Table 9-1.

Recumbent length will be measured in young children (generally those less than 3 years of age) using a firm box with an inflexible board that accommodates the head on one side and has a movable slab on the other side that can be pressed against the soles of the feet with the legs fully extended. Standing height will be measured in older children using a stadiometer that has been calibrated immediately prior to measurement of height if it has not been calibrated in the previous 4 hours. Weight will be measured with the patient unclothed. Head circumference will be measured using a measuring tape that is placed over the mid forehead and that is extended circumferentially to include the most prominent portion of the occiput so that the greatest volume of the cranium is measured. Head circumference will be measured beyond 2 years of age to rule out the potential concern of glycogen deposition in the central nervous system with resultant macroencephaly.

Length/height, weight, and head circumference will each be performed 3 times in a row and the average of these 3 measurements (refer to the SM for additional instructions) will be entered in the CRF for the appropriate measurement. All measurements should be recorded to the nearest tenth of a centimeter. To the extent possible, the individual performing the measurements of recumbent length, height, weight and head circumference should not have access to records of the patient's earlier measurements. As far as possible, these measurements will be performed by the same individual at each patient visit.

9.2.2 Cognitive Function and Motor Development Assessments

9.2.2.1 Bayley Scales of Infant and Toddler Development (Bayley-III)

The Bayley-III (Bayley, 2005, *Bayley Scales of Infant and Toddler Development, Third Edition*) will be administered by a trained clinician to assess cognitive language and motor development. The Bayley-III consists of three administered scales (cognitive, language and motor) with 5 subtests (cognitive, receptive language, expressive language, fine motor and gross motor). The Cognitive Scale assesses how a child thinks, responds and learns about the world. The Language Scale assesses how well a child can communicate using gestures, sounds and words in the Expressive Communication subscale, and how well a child recognizes sounds and understands instructions and spoken language in the Receptive Communication subscale. The Motor Scale assesses how well a child can use his or her hands and fingers to perform activities in the Fine Motor subscale, and how well a child can move his or her body in the Gross Motor subscale. Normative data is available for the Bayley-III from 1 month to 42 months of age and was derived from a sample of US infants and children in 2004. Data was also collected from 668 children with specific clinical diagnoses, including Down syndrome, prematurity, cerebral palsy, language impairment, pervasive developmental disorder and fetal alcohol exposure. Raw scores, scaled scores, and composite scores with percentile rank and confidence intervals will be reported for each of the three administered scales for patients from 1 month to 42 months of age.

All clinicians administering the Bayley-III will be provided with a training video and instruction manual. The Bayley-III will be administered to patients from 1 month of age up to 42 months of age or until the maximum score on each of the 3 administered scales has been obtained according to the times specified in Table 9-1. Once the maximum score for a scale has been achieved, only the remaining scales will be administered. Test administration takes approximately 90 minutes. Test results will be centrally scored by a trained clinician.

9.2.2.2 Leiter International Performance Scale-Revised (Leiter-R) & Leiter International Performance Scale-Updated (Leiter-3)

The Leiter-R Scale (Roid, 1997, *Leiter International Performance Scale-Revised*) and/or the updated Leiter-3 Scale (Roid, 2013, *Leiter International Performance Scale- 3rd Edition (Leiter 3))* will be administered by a trained clinician to assess intellectual ability. The Leiter Scale was designed as a nonverbal measure of intellectual function, memory and attention for individuals who could not be validly assessed with standard intelligence tests. Special populations for whom the Leiter Scale was intended include those with communication disorders, hearing impairments, motor impairments, and certain types of learning disabilities.

The Leiter-R Scale consists of two groups of subtests, the Visualization and Reasoning Battery (VR Battery) and the Attention and Memory Battery (AM Battery). Four subtests of the VR Battery have been assembled into a Brief Scale IQ test for the estimation of intellectual ability. The subtests in the Leiter-R are Figure Ground, Form Completion, Sequential Order and Repeated Patterns. The Brief Scale IQ test will be administered in this study to estimate global intellectual ability. Raw and scaled scores will be reported for each of the administered subtests in addition to the Brief Scale IQ Composite score.

The Leiter-3, published in 2013, is an updated version of the Leiter-R. The Leiter-3 consists of two groups of subtests, the Cognitive Battery and the Attention/Memory Battery. Nonverbal Intelligence will be used in this study to estimate global intellectual ability. The first four subtests of the Cognitive Battery are compiled to assess Nonverbal Intelligence. These subtests are: Figure Ground, Form Completion, Sequential Order, and Classification-Analogies. The fifth subtest (Visual Patterns) is an optional subtest, which may be administered if one of the four subtests is compromised. Raw and scaled scores will be reported for each administered subtest in addition to the Nonverbal IQ Composite score.

All clinicians administering the Leiter-R and /or the Leiter-3 will be provided with a training video and instruction manual. The Leiter-R and/or the Leiter-3 will be administered to patients starting at the last assessment of the Bayley-III Cognitive and Language Scales prior to the patient reaching 42 months of age and annually thereafter until the patient reaches the end of the follow up period, as specified in Table 9-1. If previous assessments have been performed using Leiter-R and switch to Leiter-3 Scale is planned, then both assessments need to be performed at

the same time of the initial administration of the Leiter-3 in order to create a baseline. The dates of the two tests should be recorded appropriately in the CRFs and the scores recorded on the appropriate test score sheets. Test administration takes approximately 60 minutes. Test results will be centrally scored by a trained clinician.

9.2.2.3 Gross Motor Function Measure (GMFM-88)

The GMFM-88 was designed to measure gross motor function in children with cerebral palsy. The GMFM-88 was developed specifically to detect quantitative changes in gross motor function. There is no age cut-off for the GMFM-88.

The GMFM-88 consists of 88 items organized into 5 dimensions:

- lying and rolling
- sitting
- crawling and kneeling
- standing
- walking, running and jumping

Items were selected to represent motor functions typically performed by children without motor impairments by age of 5 years.

Each item is scored on a 4-point Likert scale (i.e., 0 = cannot do; 1 = initiates [< 10% of the task]; 2 = partially completes [10 to < 100 % of the task]; 3 = task completion). The score for each dimension is expressed as a percentage of the maximum score for that dimension. The total score is obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions. Therefore, each dimension contributes equally to the total score. Test results will be centrally scored by a trained clinician.

Validity and reliability has been shown in patients with cerebral palsy. The GMFM-88 was validated on 136 children with cerebral palsy, 25 children with acute head injuries and 34 children without motor delays who ranged in age from 1 month to 4.3 years. The subjects were measured twice over a period of 6 months. Change scores were correlated with the ratings of change by independent physical therapists from videotapes on the initial and 6-month test in random order. The correlation made between the GMFM-88 change scores and the ratings made from the videotapes was 0.82.

In addition, the GMFM-88 has been validated in children with Down syndrome. One hundred twenty-three children were assessed twice over a period of 6 months using the GMFM-88 and the Modified Bayley Scales of Infant Development II. Test-retest and inter-rater variability were all > 0.90 (Russell, 1989, *Dev Med Child Neurol*). While not originally validated for children with diagnoses other than cerebral palsy, the GMFM-88 has been used for other children with

motor difficulties including children with osteogenesis imperfecta (Ruck-Gibis, 2001, *Pediatr Phys Ther*), and acute lymphoblastic leukemia (Wright, 1998, *Med Pediatr Oncol*).

9.2.2.4 Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI)

A disease-specific version of the PEDI was developed to assess functional capabilities and performance in children with Pompe disease from 2 months through adolescence (Haley, 2005, *Dev Med Child Neurol*; Haley, 2004, *Pediatr Neurol*; Haley, 2003, *Pediatr Rehabil*; Haley, 2003, *Dev Med Child Neurol*). All patients will be administered the Pompe PEDI, regardless of age. The Pompe PEDI includes all items from the original PEDI, as well as additional items in the Functional Skills Mobility and Self-Care domains to reflect clinically relevant functional skills for children with Pompe disease. Norm-based scoring was developed for these new items and scoring algorithms for the PEDI have been adjusted to reflect the additional normative data collected for the Pompe PEDI. A trained clinician will administer the Pompe PEDI with input from the patient or patients' legal guardian. Test administration requires approximately 60 minutes. The Pompe PEDI will be centrally scored. Results are reported as raw score, normative standard score (with standard error) and scaled score (with standard error).

9.2.3 Urinary Oligosaccharide (Hex4) Levels

As an exploratory measure, collection of urine for oligosaccharide levels will be performed at the times specified in Table 9-1. A tetraglucose oligomer, Glcα1-6Glcα1-4Glcα1-4Glc, designated Glc4 (Hex4), has been shown to be elevated in the urine (Hallgren, 1974, *Eur J Clin Invest*; Chester, 1983, *Lancet*; Peelen, 1994, *Clin Chem*; An, 2000, *Anal Biochem*; An, 2005, *Mol Genet Metab*) in patients with Pompe disease. Hence determination of Hex4 may be a means by which the efficacy of treatments may be monitored. HPLC-UV (An, 2000, *Anal Biochem*) and stable isotope dilution ESI-MS/MS (Young, 2003, *Anal Biochem*) are two different methods available for the analysis of Hex4 in biological fluids as the butyl-p-aminobenzoate (BAB) derivative. Oligosaccharide levels in urine will be measured by a central laboratory, and additional information for the collection and handling of these samples can be found in the SM.

9.2.4 CRIM Status

The potential effect of CRIM status will be investigated for research purposes only.

The GAA Western blot will be used to assess CRIM status in baseline skin biopsy samples from patients with Pompe disease. The CRIM Western blot assay was developed to detect the major protein forms of GAA known to exist in the cell, including 110, 95, 76, or 70 kDa forms. A patient is considered CRIM positive if the presence of any bands corresponding to the apparent molecular weight of these forms of GAA is detected in samples prepared from patient fibroblasts in the Western blot assay.

CRIM status testing will be performed by Genzyme Corporation or their designee using an assay that recognizes both recombinant and native GAA. Information for the collection and handling of these samples can be found in the SM.

9.2.5 GAA Mutation Analysis

Deoxyribonucleic acid (DNA) will be isolated from peripheral blood samples obtained from enrolled patients using established methods. DNA sequencing will be performed on these samples to fully characterize both deleterious mutations and background variation within the GAA gene. GAA mutation analysis is to be conducted only if written results are not available.

9.3 Safety Assessments

9.3.1 Neuroimaging Assessment

In previous clinical trials, a small number of patients with infantile-onset Pompe disease have been found to have a pattern of delayed myelination and/or white matter signal abnormalities in the brain, as evaluated by neuroimaging assessments conducted prior to and following the onset of treatment with alglucosidase alfa. Consequently, serial brain MRIs will be conducted at the discretion of the Investigator as sedation for this procedure may be required for young patients and may pose an unacceptable risk in patients who have cardiopulmonary involvement. MRIs will be conducted according to standard procedures (specified in the SM) at the times specified in Table 9-1 in order to evaluate possible changes in brain structures over time.

If clinically significant changes in neuroimaging findings as compared to Baseline results are noted, the changes will be documented as AEs on the AE CRF. Clinical significance is defined as any variation in neuroimaging findings that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.3.2 Hearing Testing

Hearing loss has been reported in patients with glycogen storage disorders (Galton, 1976, *Acta Paediatr Scand*; Jurecka, 1985, *Arch Dermatol).* Furthermore, cochlear involvement has been demonstrated in a mouse model of Pompe disease, and hearing loss found in patients with infantile-onset Pompe disease (Kamphoven, 2004, *Neurobiol Dis*).

Hearing will be assessed at the times specified in Table 9-1 using an age-appropriate method of hearing assessment, as determined by the Investigator. Refer to Table 9-2 for a list of commonly available hearing tests appropriate for infants and children of various ages. Abnormal hearing tests should be confirmed by more than 1 method, and should be correlated with the presence or

absence of middle ear effusion. Results of the hearing testing will be recorded on the CRF. Refer to the SM for specific details on hearing testing procedures.

Table 9-2 Hearing Assessments Appropriate for Age

Auditory test	Developmental age of child
Conditioned-oriented responses	9 months to 2.5 years
Visual reinforcement audiometry	9 months to 2.5 years
Play audiometry	2.5 years to 4 years
Conventional audiometry	4 years and older
Otoacoustic emission testing	All ages
Brainstem auditory evoked response *	Birth to 9 months of age

Source: (Cunningham, 2003, *Pediatrics*)

*BAER should only be performed if the results of other hearing testing are inconclusive as BAER may require sedation in young children which could pose unacceptable risks to patients who have significant cardiopulmonary compromise. BAER should only be performed at the discretion of the investigator.

If clinically significant changes in hearing as compared to Baseline results are noted, the changes will be documented as AEs on the AE CRF. Clinical significance is defined as any variation in hearing tests that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.3.3 Visual Screening

As visual impairment may impact the patient's ability to perform developmental tests, vision testing is being performed in this study to help in the interpretation of developmental testing. Ophthalmologic evaluation is to be performed by the Investigator in accordance with the guidelines described by the American Association of Pediatrics (AAP, 1996, *Pediatrics*). The type of visual screening will be determined by the patient's age at the time of the assessment. All patients will have an exam of the eye, test ocular motility and the red reflex exam. Patients 3 years of age and over will have the same assessments described previously plus a visual acuity test. Patients 4 years of age and over will have each of the previously described assessments plus fundoscopy. In accordance with AAP guidelines for vision screening, abnormal vision screening results should be followed with evaluation by an ophthalmology specialist and follow up should include slit lamp examination, if deemed necessary. Testing will occur at the times specified in Table 9-1.

If clinically significant changes in vision as compared to Baseline results are noted, the changes will be documented as AEs on the AE CRF. Clinical significance is defined as any variation that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.3.4 Electrocardiogram

A standard 12-lead ECG will be conducted at the times specified in Table 9-1. The following will be assessed: heart rate, rhythm, RR, PR, QRS, QT, QTc, QRS axis, R voltage V6, S voltage V1, LVH criteria, RVH criteria, and repolarization changes.

The ECG should be reviewed by a site cardiologist, preferably a pediatric cardiologist, in a timely manner for derivation of study data and clinical management of the patient. Interpretation will include an assessment of heart rate, cardiac rhythm, intervals, axis, conduction defects, and overall cardiac impression for each patient. QTc should be analyzed using both the Fridericia and Bazett's correction formulae in accordance with the FDA's *Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* and *Questions and Answers (R1);* references to these documents can be found in the SM.

If clinically significant ECG changes from Baseline are noted, the changes will be documented as AEs on the AE CRF. Clinical significance is defined as any variation in ECG parameters that has medical relevance resulting in an alteration in medical care. The Investigator will continue to monitor the patient with additional ECGs until the ECG returns to Baseline or the Investigator determines that follow-up is no longer necessary.

9.3.5 Safety Laboratory Assessments

Safety laboratory assessments will be performed pre-infusion at the times specified in Table 9-1. The following chemistry and urinalysis variables will be measured:

- Blood urea nitrogen (BUN), creatinine, glucose, uric acid, calcium, phosphorus, albumin, total protein, sodium, potassium, chloride, bicarbonate, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, total bilirubin, creatine kinase (CK), and creatine kinase muscle, brain isoform (CK-MB).
- Complete blood count with differential.
- Urine appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, and blood. Microscopy will be performed if clinically indicated.

Analysis of blood and urine samples will be conducted and reported by each participating site's laboratory. The Investigator should review lab reports in a timely manner.

The Investigator must indicate if out of range laboratory values are either clinically significant (CS), or not clinically significant (NCS). It is anticipated that some laboratory values may be

outside of the normal value range due to the underlying disease. As in routine practice the Investigators should use their clinical judgment when considering clinical significance. Clinical significance is defined as any variation in laboratory parameters, which has medical relevance and may result in an alteration in medical care. If CS laboratory changes from Baseline are noted, the changes will be documented on the AE CRF. The Investigator will also assess the relationship of all clinically significant out of range values to alglucosidase alfa as being not related, remote/unlikely, possible, probable, or definite. The Investigator will continue to monitor the patient with additional laboratory assessments until (1) values have reached normal range and/or Baseline, or, (2) in the judgment of the Investigator, out of range values are not related to the administration of alglucosidase alfa or other protocol-specific procedures.

9.3.6 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be recorded at baseline, prior to the start of each infusion, at the end of each infusion, and if the patient experiences an IAR, as specified in Table 9-1. All IARs should be captured on the SAE/IAR page and submitted to Global Pharmacovigilance and Epidemiology per Section 9.5.2.

9.3.7 Immunologic Testing

9.3.7.1 Routine Anti-rhGAA IgG Antibody Testing

Serum samples for anti-rhGAA IgG antibody testing will be obtained pre-infusion at the times specified in Table 9-1. Additional anti-glucosidase IgG antibody testing should be performed upon determination of any notable deterioration in a patient's motor function. Refer to the SM for guidelines on the collection and shipment of serum samples.

9.3.7.2 Inhibitory Antibody Testing

Inhibitory antibody (activity and uptake) will be assessed when clinically indicated (e.g., plateau or decline in response in the presence of adequate dosing). Refer to the SM for guidelines on the collection and shipment of serum samples.

9.3.7.3 Additional Testing for Moderate or Severe or Recurrent IARs

In the event that a patient experiences a moderate, severe, or recurrent IAR, additional blood samples should be collected as described in Sections 9.3.7.3.1 to 9.3.7.3.3. At the request of Genzyme, after consultation with the Investigator, additional blood samples may be collected for recurrent IARs suggestive of a hypersensitivity reaction. Refer to the SM for guidelines on the collection and shipment of samples. Global Pharmacovigilance and Epidemiology should be apprised of sample shipments. Testing is conducted for research purposes to gain additional information as to individuals' responses to alglucosidase alfa, and is not intended as the sole means of clinical management of patients. Skin testing may also be performed, if clinically indicated, as described in Section 9.3.7.3.4. Suggested guidelines for the management of IARs

during the event and pretreatment guidelines are summarized in the current version of the Investigator's Brochure.

9.3.7.3.1 Complement Activation Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR, a plasma sample should be drawn within 1 to 3 hours of the event for complement activation testing, when clinically indicated.

At the request of Genzyme, after consultation with the Investigator, a plasma sample for complement activation testing may also be collected for patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.3.7.3.2 Serum Tryptase Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR, a serum sample should be drawn within 1 to 3 hours of the event for serum tryptase testing, when clinically indicated.

At the request of Genzyme, after consultation with the Investigator, a serum sample for tryptase testing may also be collected for patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.3.7.3.3 Serum IgE Antibody Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR, the patient should return to the study center at least 72 hours after the infusion ends to draw a serum sample that will be tested for IgE antibodies, when clinically indicated. For patients on home infusion, whole blood for testing of IgE antibodies may be drawn at home at least 72 hours after the infusion ends.

At the request of Genzyme, after consultation with the Investigator, a serum sample for IgE testing may also be collected for patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.3.7.3.4 Skin Testing

Skin testing may be performed following consultation with the Investigator, Sponsor, and ARRB in patients who experience an IAR that meets the following criteria:

- IAR is assessed as moderate or severe in intensity by the Investigator or recurrent IAR AND
- IAR is suggestive of an IgE-mediated acute-type hypersensitivity reaction, with persistent symptoms of bronchospasm, hypotension and/or urticaria requiring intervention OR any other signs or symptoms at the discretion of the Investigator or Genzyme.

9.3.7.4 Circulating Immune Complexes

In the event that patients exhibit evidence of symptoms suggestive of Immune Complex Disease (e.g., proteinuria), serum samples will be obtained for the evaluation of circulating immune complexes. Immune complex results will be used as a tool to assist in the clinical evaluation of the patient and clinical management will not be dependent solely on these results. The patient will continue to be monitored for immune complex symptomatology, and serum samples will continue to be obtained for the evaluation of circulating immune complexes, as appropriate. Consideration for further evaluation of possible immune complex disease (i.e., renal biopsy) will be at the discretion of the Investigator. Refer to the SM for guidelines on the collection and shipment of serum samples.

9.4 Other Assessments

9.4.1 Concomitant Medications/Therapies

From the time of informed consent through study completion, all medications and therapies (e.g., tube feeds) taken by the patient to treat AEs and any long-term disease management will be recorded on the CRFs.

9.5 Adverse Events

AEs will be assessed at screening/baseline. At every infusion visit the patient's legal guardian(s) will be asked "Since your last questioning or visit, has the patient experienced any health problems?"

An AE is defined as any undesirable physical, psychological or behavioral effect experienced by a patient or subject during their participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. This includes any untoward signs or symptoms experienced by the patient from the time of signing of the informed consent until completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the Investigator or medical staff
- Findings at physical examinations
- Laboratory abnormalities of clinical significance

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product (i.e., prior to participation in the AGLU03606 study) are <u>not</u> considered AEs after treatment <u>unless</u> they recur after the patient has recovered from the preexisting condition or in the opinion of the Investigator they represent a clinically significant exacerbation in intensity or frequency.

Any signs and symptoms experienced by the patient from the time of signing of the informed consent through the final study visit will be recorded on the CRF.

If clinically significant worsening from Baseline is noted, the changes will be documented as AEs on the AE CRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.5.1 Serious Adverse Events

An SAE is 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
- Important medical events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

  Life-threatening experience: Any AE that places the patient, in the view of the reporter, 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.

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

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

The Investigator will be asked to assess the severity of the adverse drug/biologic experience using the following categories: Mild, Moderate, and Severe. This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar type events observed in clinical practice. Below are listed guidelines for severity assessment:

- Mild: Symptom(s) barely noticeable to the subject/patient or does not make the subject/patient uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

- Moderate: Symptom(s) of a sufficient severity to make the subject/patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
- Severe: Symptom(s) of a sufficient severity to cause the subject/patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) may be given.

Severity is not equivalent to seriousness.

9.5.1.1 Autopsy and Post-Mortem Biopsy

In the event that a patient dies, permission will be sought (through a separate informed consent form) from the patient's legal guardian(s) for a research autopsy or post-mortem research biopsy. If consented, samples collected from this procedure will be sent to Genzyme Corporation and used for research purposes only; data will not be provided to the Investigator or be included in any analyses. Refer to the SM for research autopsy and post-mortem research biopsy procedural guidelines.

9.5.2 Infusion-Associated Reactions

Infusion-associated reactions are defined as AEs that occur during the infusion or within up to 24 hours after the start of infusion and are considered as related or possibly related to the ERT by the Investigator or the Sponsor. An event occurring ≥24 hours after the start of an infusion may be judged an IAR if a delayed reaction is considered possible by the Investigator or the Sponsor. These events should be reported to Global Pharmacovigilance and Epidemiology within 24 hours of the Investigator's first knowledge of the event. Refer to Section 9.3.7.3 for additional testing in the event a patient experiences a moderate, severe, or recurrent IAR. Suggested guidelines for the management of IARs are summarized in the current version of the Investigator's Brochure.

9.5.3 Adverse Experience and Serious Adverse Experience Reporting

The necessity and time requirements for reporting of AEs to Genzyme or designee and/or regulatory agencies are as follows:

- All SAEs and IARs (non-serious and serious) should be reported within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to alglucosidase alfa. Such communications are to be directed to:

Global Pharmacovigilance and Epidemiology
Fax: +33 160-49-70-70 E-mail: CL-CPV-receipt@sanofi.com

- All SAEs will include a detailed description of the event(s). Copies of relevant patient records, autopsy reports, and other documents may be requested by and will be sent to Global Pharmacovigilance and Epidemiology Department.

Additionally, the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be notified in writing of any expedited SAEs. It is the responsibility of the Investigator to notify the IRB/IEC. All unexpected SAEs associated with the use of alglucosidase alfa should be immediately reported to appropriate regulatory agencies by Genzyme Corporation if there is a reasonable possibility that the drug caused the adverse experience.

Any AEs or SAEs experienced by the patient from the time of signing of the informed consent through completion of the final study assessments must be reported as described and recorded on the CRF.

After completion of the final study assessments, all patients must be followed an additional 30 days. At the follow-up assessment, outcome for ongoing AEs and SAEs should be documented in the CRF as not yet recovered. Ongoing SAEs should, however, continue to be followed (and information reported to Global Pharmacovigilance and Epidemiology) until resolution, until the Investigator deems follow-up is no longer medically necessary or until the patient is lost to follow-up.

10. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

10.1 Recording of Data

All required data will be recorded on the CRF provided by Genzyme Corporation. Copies of score sheets for cognitive function and motor development assessments will be sent to a central Genzyme representative for centralized scoring. All missing data will be explained. Clinical data that are not recorded on the CRF will be captured and transferred to Genzyme's Department of Biostatistics.

10.2 Data Quality Assurance

Data entered on the CRF must be verifiable against source documents at the investigational site. A clinical monitor from Genzyme Corporation or a representative of Genzyme Corporation will manually review the CRFs against the source documents at the investigational site for validity and completeness. All data captured in the CRFs will be made available to Genzyme or its designee for data management and analysis. If necessary, the study site will be contacted for corrections and/or clarifications of the data.

10.3 Data Management

Genzyme will be responsible for:

- Database creation and validation
- Data entry and editing
- CRF review and data validation
- Locking the final database

Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data for each subject will be determined by appropriate medical and statistical personnel. Any and all exclusions related to either safety or efficacy will be documented in patient listings.

11. STATISTICAL METHODS AND PLANNED ANALYSES

Prior to data analysis, 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 prior to commencing with statistical analysis, as part of the Statistical Analysis Plan.

The Genzyme Department of Biostatistics will perform the statistical analysis of the data derived from this study. Details of the statistical analysis will be specified in the Statistical Analysis Plan. Analyses will be performed using the SAS® statistical software system.

All enrolled patients who receive at least one infusion (complete or partial) of alglucosidase alfa in this study will comprise the analysis population for the efficacy and safety analyses.

All data collected will be presented in the form of individual patient listings. Provided the data are not too sparse, summary tables will be created for the efficacy and safety variables.

Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum and maximum). Categorical variables will be summarized using frequencies and percentages.

Baseline demographic and background variables will be summarized and also presented in patient listings. Efficacy endpoints include physical growth, development, and cognitive function.

Physical growth is assessed by body height/length, weight and head circumference. Changes from baseline to study time points will be summarized descriptively for body height/length, weight and head circumference. Changes in Z-scores (standardized age and gender adjusted values) for height/length, weight and head circumference with reference to Center for Disease Control (CDC) Growth Charts will also be summarized descriptively.

The Bayley-III consists of 3 administered scales – cognitive, language and motor and will be administered to patients from 1 month to 42 months of age. Changes from baseline to study time points in the raw scores, scaled scores and composite scores reported for each of the 3 administered scales will be summarized descriptively.

Cognitive function is assessed by the Leiter-R and/or the updated Leiter-3 instrument for patients 42 months of age and older. The Brief Scale IQ (Leiter-R) and/or Nonverbal IQ Scale (Leiter-3) that will be administered each consist of 4 subtests. All data collected will be presented in the patient listings. The changes from baseline to study time points in the raw and scaled scores for the 4 subtests may be summarized descriptively.

The GMFM-88 will be used to measure the change over time in the gross motor abilities of the patients. Change from baseline to study time points in the total score and dimension scores will be summarized descriptively.

The Pompe PEDI was developed to assess functional capabilities and performance in children with Pompe disease. Changes from baseline to study time points in the raw scores, normative standard scores and scaled scores for the Functional Skills Mobility and Self-Care domains will be summarized descriptively.

The potential effect of urinary oligosaccharide levels, CRIM status, and GAA mutation on efficacy outcomes may be analyzed.

Safety assessments include neuroimaging, hearing testing, visual screening, ECG, laboratory assessments, immunologic testing. All data from safety assessments will be presented in patient

listings. For laboratory assessments, summary statistics will be presented for change in laboratory parameters from baseline to analysis time points.

Concomitant medication will be coded using the WHO drug dictionary. Concomitant medications and concomitant therapies will be listed by patient. Summary tables giving the frequencies and percentages of the concomitant medications used will be provided.

AEs, SAEs and IARs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs, SAEs and IARs will be presented in patient listings. Summary tables showing the frequencies and percentages of patients with AEs, SAEs and IARs will be presented. The frequencies and percentages of AEs, SAEs and IARs will also be presented.

In addition, longitudinal repeated measures modeling will be used to analyze trends in key growth and development parameters over time. The impact of patient discontinuation prior to study completion will be assessed. Analyses of key variables may be stratified by relevant baseline/demographic factors.

No formal statistical sample size calculations were performed.

12. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations. These requirements are stated in federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

12.1 Data Safety Monitoring Board (DSMB)

An independent DSMB appointed by Genzyme Corporation will review the protocol and will thereafter provide medical and ethical guidance related to the conduct of this study on an ad hoc basis to assist in determining if AEs should preclude continued treatment with alglucosidase alfa. The ad hoc reviews will be performed in accordance with procedures outlined in the DSMB charter, which is maintained separately from the study protocol. This committee will be comprised of 4 physicians who are knowledgeable in aspects of Pompe disease, and who have no direct relationship with the study. One physician will also have expertise in the field of allergy/immunology. Each DSMB member will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interests as a condition for membership on the board. These documents, along with all members' curricula vitae, will be filed centrally at the end of the study within the protocol study files at Genzyme Corporation, Cambridge, MA (USA).

Should any major safety issues arise, final decisions regarding the study will be made by the Genzyme Corporation Chief Medical Officer, Global Safety Officer, and the DSMB.

12.2 Allergic Reaction Review Board

An independent ARRB, appointed by Genzyme Corporation, may review information pertaining to IARs. The ARRB responsibilities will serve in a consultancy manner and will provide guidance on IAR management as outlined in the ARRB Charter, maintained separately from the study protocol. Communication with the board should be directed to members of the Global Pharmacovigilance and Epidemiology group.

The ARRB will consist of at least 1 Allergist/Immunologist. Each member of the ARRB will be a physician and will not be directly involved in the study. Each ARRB member will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interests as a condition for membership on the board. These documents, along with all members' curricula vitae, will be filed centrally at the end of the study within the protocol study files at Genzyme Corporation, Cambridge, MA.

Should any major safety issues arise, final decisions regarding the study will be made by the Genzyme Corporation Chief Medical Officer, Global Safety Officer, and the ARRB.

12.3 Institutional and Ethical Review

This protocol and patient authorization form must be reviewed and approved by an IRB or IEC complying with the requirements of 21 CFR 56 and the ICH before enrollment of patients. The letter or certificate of approval from the IRB or IEC must be received by Genzyme prior to delivery of clinical supplies.

12.4 Changes to the Conduct of the Study or Protocol

No change in the study procedures shall be effected without the mutual agreement of the Investigator and Genzyme. All protocol amendments will be issued by Genzyme and must be signed by the Investigator. If changes are made that affect the design of the study, the amendment must be submitted to, and approved by the IRB/IEC. In addition, Genzyme will submit protocol amendments to the regulatory authorities as appropriate.

12.5 Investigator's Responsibilities

12.5.1 Patient Informed Consent

Written informed consent is required prior to enrollment in the study. It is the responsibility of the Investigator to obtain such consent. Investigators must comply with the Declaration of Helsinki and local guidelines and regulations when developing the patient informed consent.

The Investigator must furnish Genzyme with a photocopy of the proposed consent form prior to submitting to the IRB/IEC so that Genzyme may ensure that all appropriate elements are incorporated into the document. Upon approval by the IRB/IEC, the Investigator must furnish: (1) a photocopy of the approved informed consent, and (2) the letter stating that formal approval has been granted by the institution, prior to collecting any data on the patient.

12.5.2 Case Report Forms

Data will be entered onto CRFs at each site.

Copies of pertinent records in connection with the study, including patient charts, laboratory data, etc. will be made available to Genzyme on request in a timely manner throughout the course of the study, with due precaution towards protecting the privacy of the patient.

12.5.3 Record Retention

The Investigator must retain paper copies of study records as required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these documents. The study records should be retained until at least 2 years after the last approval of a marketing application in the US or an ICH region and until there are no pending or contemplated marketing applications in the US or an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must retain patient identification codes for at least 15 years after the completion or discontinuation of the study. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. Should Investigators be unable to continue maintenance of patient files for the full 15 years, Genzyme will assist in this regard.

12.5.4 Monitoring

A representative of Genzyme will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. It is the responsibility of the Investigator to be present or available for consultation during such scheduled 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.

An audit may be performed at any time during or after completion of the clinical study by Genzyme Corporation personnel or their designee. All study-related documentation must be made available to the designated auditor.

In addition, a representative of the FDA or other regulatory agency may choose to inspect a study center at any time prior to, during, or after completion of the clinical study. A Genzyme Corporation representative will be available to assist in the preparation for such an inspection. All pertinent study data should be made available to the regulatory authority for verification, audit, or inspection purposes.

12.5.5 Warnings, Precautions, Contraindications

For more specific information concerning warnings, precautions, and contraindications, the Investigator is asked to refer to the appropriate section of the Investigator's Brochure as well as the full prescribing information for alglucosidase alfa. Because of the possibility of AEs, proper

safety equipment, including but not limited to cardiopulmonary resuscitation equipment, and personnel competent in recognizing and treating adverse reactions of all types should be readily available.

12.5.6 Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential and written permission from Genzyme is required prior to disclosing any information relative to this study. Manuscripts prepared for publication will be in accordance with the policy established and presented to the Investigator previously by Genzyme. Submission to Genzyme Corporation for review and comment prior to submission to the publisher will be required. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

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LTS12869 Amended Protocol7

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
	Clinical Approval	
	GPE Approval	
	Regulatory Approval	