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AMENDED CLINICAL TRIAL PROTOCOL 2

COMPOUND: GZ419829 - Alglucosidase Alfa

A Prospective Safety Sub-Registry to Assess Anaphylaxis and Severe Allergic Reactions, and Severe Cutaneous and Systemic Immune-Mediated Reactions with Alglucosidase Alfa Treatment

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TITLE:

A Prospective Safety Sub-Registry to Assess Anaphylaxis and Severe Allergic Reactions, and Severe Cutaneous and Systemic Immune-Mediated Reactions with Alglucosidase Alfa Treatment

OBJECTIVES:

The objectives of this Safety Sub-Registry are to collect uniform and meaningful data on patients with Pompe disease who experience anaphylaxis, severe allergic reactions, and/or signals of severe cutaneous and/or systemic immune-mediated reactions following treatment with alglucosidase alfa. This Safety Sub-Registry also will assess:

- the symptoms, severity, outcome, and occurrence of those adverse events (AEs; anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune mediated reactions);
- the effect of antibody responses (both timing and pattern of responses) and cross-reacting immunologic material (CRIM) status (in patients with age at symptom onset less than or equal to 12 months only) on the occurrence of such AEs.

METHODOLOGY:

The Pompe Safety Sub-Registry is a multi-center, international, longitudinal, observational program for patients with Pompe disease that was designed to collect uniform and meaningful data on patients with Pompe disease who experience anaphylaxis, severe allergic reactions, and/or signals of severe cutaneous and/or systemic immune-mediated reactions following treatment with alglucosidase alfa. Data from the Safety Sub-Registry are also used to fulfill various global regulatory commitments, to support product development/reimbursement, and for other research and non-research-related purposes. The long-term program will proceed until data from 100 patients have been collected for 4 years as specified in the protocol.

The Safety Sub-Registry database will be integrated with the Pompe Registry database and has been designed to collect adverse event, laboratory assessments, and vital sign data. As per the Pompe Registry protocol, no experimental intervention is given, thus, a patient will undergo clinical assessments and receive standard-of-care treatment as determined by the patient's physician. While the Pompe Registry protocol provides a Recommended Schedule of Assessments, which has been developed based on the input of physicians from the international medical community with expertise in the care of patients with Pompe disease and from regulatory agencies; each physician is solely responsible for determining the appropriate clinical care for each patient.

It is the responsibility of Genzyme to collect, review, and report adverse drug reactions (ADRs) during and after administration of alglucosidase alfa. Genzyme requests physicians report all ADRs associated with the use of alglucosidase alfa within 24 hours of the physician's first knowledge. Genzyme will follow-up on all reported ADRs. All AEs listed in **TABLE 8-1** of the Safety Sub-Registry protocol, including ADRs, will also be recorded in the Registry database as part of this Safety Sub-Registry and reported to Genzyme within 24 hours of the physician's first knowledge.

INCLUSION CRITERIA/DIAGNOSIS:

At least 100 patients enrolled in the Pompe Registry at selected sites around the world who meet the inclusion criteria for this Safety Sub-Registry are eligible to participate in the Safety Sub-Registry. This includes patients with onset of clinical signs/symptoms at ≤12 months of age (infantile-onset Pompe disease), as well as those with symptom onset at >12 months of age (late-onset Pompe disease). No single participating site is allowed to enroll more than 20% of the total Safety Sub-Registry patient population. Patients currently treated with alglucosidase alfa and treatment-naïve patients who initiate treatment at time of enrollment in the Safety Sub-Registry are targeted for enrollment at each site.

INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for inclusion in this Safety Sub-Registry:

- be enrolled in the Pompe Registry;
- provide a signed Patient Information and Authorization form;
- have a confirmed diagnosis of Pompe disease (confirmation of diagnosis is defined as documented acid α-glucosidase (GAA) enzyme deficiency from any tissue source and/or documentation of 2 GAA gene mutations);
- be naïve to and plan to be treated with alglucosidase alfa at or prior to enrollment, or are being treated with alglucosidase alfa.

EXCLUSION CRITERIA

Patients will be excluded if they have received an investigational drug (excluding alglucosidase alfa) within 30 days prior to signing a Safety Sub-Registry Patient Information and Authorization form, or if they are taking or plan to take any investigational product while enrolled in the Safety Sub-Registry.

STATISTICAL METHODS:

Genzyme Registry staff will perform the statistical analysis of the data derived from the Registry, using the SAS® statistical software.

1 TABLE OF CONTENTS

2 LIST OF IN-TEXT TABLES

3 ABBREVIATIONS AND TERMS

ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CIC	circulating immune complex(es)
CK	creatine kinase
CK-MB	creatine kinase muscle-brain isoform
CRF(s)	case report form(s)
CRIM	cross-reacting immunologic material
DBS	dried blood spot
ERT	enzyme replacement therapy
GAA	acid α-glucosidase
GPE	Global Pharmacovigilance and Epidemiology
IAR	infusion-associated reaction
ID	identification [number]
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IRB	Institutional Review Board
L	liter
LDH	lactic dehydrogenase
mm Hg	millimeters of mercury

PT	prothrombin time
PTT	partial thromboplastin time
rhGAA	recombinant human acid α-glucosidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model

4 INTRODUCTION

Pompe disease, also known as acid maltase deficiency, glycogen storage disease type II, or glycogenosis type II, has an estimated global incidence of between 1:40,000 and 1:300,000 (Chien, 2008); incidence appears to vary by ethnic group (Hirschhorn, 2001). Pompe disease is a rare, progressive, debilitating, and often fatal metabolic myopathy caused by a deficiency of GAA, an enzyme that degrades lysosomal glycogen. Acid α-glucosidase (GAA) deficiency leads to glycogen accumulation, the eventual rupture of lysosomes, and cellular dysfunction in muscle fibers.

Clinical signs and symptoms of Pompe disease can present at any age, although the disease has been classified into different subtypes based on age at onset of clinical manifestations, extent of organ involvement, and rate of progression to death. Essentially, there is a broad spectrum of disease, ranging from a rapidly progressive form with onset of signs in the first year of life to more slowly progressive forms with onset of symptoms after one year of age, with considerable clinical variability (Chen, 2000; Hirschhorn, 2001; van den Hout, 2003; Kishnani, 2004).

Infants with the "classic" form of the disease experience the onset of clinical signs or symptoms within the first year of life (generally between 1.6 and 2.0 months of age), including hypertrophic cardiomyopathy, hypotonia, delay or failure of motor development, recurrent respiratory infections, and failure to thrive. The disease progresses rapidly and is almost invariably fatal if untreated. In older children and adults, symptom onset occurs anywhere from the first through the seventh decade of life; the disease progresses more slowly but can lead to significant muscle weakness, motor and respiratory function impairment, and death (van den Hout, 2003; Kishnani, 2006; van der Ploeg, 2008). Most juvenile and adult patients experience a progressive deterioration of skeletal muscles, initially of the lower limbs, trunk, diaphragm, and intercostal muscles, ultimately progressing to the upper limbs. Respiratory failure is the leading cause of death in such patients (Winkel, 2005; Hagemans, 2007; Mellies, 2009). Delays in diagnosis are common, as signs and symptoms can be shared with other disorders. The advent of newborn screening programs using dried blood spot (DBS; see Chien, 2008), may encourage earlier diagnosis in infants. The use of DBS as an early prognosticator of Pompe disease in patients of all ages was discussed by Goldstein (2009).

Genzyme, a Sanofi company, has developed alglucosidase alfa, a recombinant human acid α-glucosidase (rhGAA), as an enzyme replacement therapy (ERT) for the treatment of Pompe disease. Alglucosidase alfa (marketed under the names Myozyme® and Lumizyme®) is the first disease-specific treatment approved for Pompe disease. Alglucosidase alfa is approved in more than 65 countries for all patients with a confirmed diagnosis of Pompe disease. In countries where no approved treatment exists, patients with Pompe disease may be treated through Genzyme-sponsored charitable access programs or may continue to be managed with supportive and palliative methods.

Treatment with alglucosidase alfa has resulted in events of anaphylaxis and immune-mediated reactions in some patients. Anaphylactic and severe allergic reactions have been observed during and up to 3 hours after starting the alglucosidase infusion. Immune-mediated reactions have been observed several weeks to 3 years after initiation of alglucosidase infusion. Consequently, patients in this Safety Sub-Registry will be followed prospectively for 4 years.

All patients with Pompe disease who meet the eligibility criteria as defined in Section 6.1 and Section 6.2 are eligible to participate in the Pompe Safety Sub-Registry.

Genzyme reserves the right to discontinue the Safety Sub-Registry at any time.

5 OBJECTIVES OF THE POMPE REGISTRY SAFETY SUB-REGISTRY

The objectives of this Safety Sub-Registry are to collect uniform and meaningful data on patients with Pompe disease who experience anaphylaxis, severe allergic reactions, and/or signals of severe cutaneous and/or systemic immune-mediated reactions following treatment with alglucosidase alfa. This Safety Sub-Registry also will assess:

1. the symptoms, severity, outcome, and occurrence of those adverse events (AEs; anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune mediated reactions);
2. the effect of antibody responses (both timing and pattern of responses) and cross-reacting immunologic material (CRIM) status (in patients with age at symptom onset less than or equal to 12 months only) on the occurrence of such AEs.

6 PATIENT POPULATION AND SELECTION

At least 100 patients enrolled in the Pompe Registry at selected sites around the world who meet the inclusion criteria for this Safety Sub-Registry are eligible to participate in the Safety Sub-Registry. This includes patients with onset of clinical signs/symptoms at ≤12 months of age (infantile-onset Pompe disease), as well as those with symptom onset at >12 months of age (late-onset Pompe disease). No single participating site is allowed to enroll more than 20% of the total Safety Sub-Registry patient population. Patients currently treated with alglucosidase alfa and treatment-naïve patients who initiate treatment at time of enrollment in the Safety Sub-Registry are targeted for enrollment at each site.

6.1 INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for inclusion in this Safety Sub-Registry:

- be enrolled in the Pompe Registry;
- provide a signed Patient Information and Authorization form;
- have a confirmed diagnosis of Pompe disease (confirmation of diagnosis is defined as documented GAA enzyme deficiency from any tissue source and/or documentation of 2 GAA gene mutations);
- be naïve to and plan to be treated with alglucosidase alfa at or prior to enrollment, or are being treated with alglucosidase alfa.

6.2 EXCLUSION CRITERIA

Patients will be excluded if they have received an investigational drug (excluding alglucosidase alfa) within 30 days prior to signing a Safety Sub-Registry Patient Information and Authorization form, or if they are taking or plan to take any investigational product while enrolled in the Safety Sub-Registry.

6.3 PATIENT WITHDRAWAL

Any patient is free to withdraw authorization and discontinue his/her participation in the Safety Sub-Registry at any time, without prejudice to further treatment. The patient's participation in the Safety Sub-Registry may be discontinued at any time at the discretion of the treating physician. The following may be justifiable (but not exhaustive) reasons for the treating physician to remove a patient from the Safety Sub-Registry:

- the patient was erroneously included in the Safety Sub-Registry;
- the patient is taking an investigational product during participation in the Safety Sub-Registry;

- the Safety Sub-Registry is terminated by Genzyme.

Patients who withdraw, or are withdrawn from this Safety Sub-Registry are still permitted to participate in the global Pompe Registry.

6.4 PATIENTS WHO RECEIVE HOME INFUSIONS OR INFUSIONS AT SATELLITE CLINICS

Patients enrolled in the Pompe Registry who receive or will receive home infusions or infusions at clinics other than at the enrolling Pompe Registry clinic where the Principal Investigator is located (referred to as "satellite clinics"), may be eligible to participate in the Safety Sub-Registry. Per local regulations, some patients may only receive treatment by a primary, treating physician. If local regulations permit, it is the responsibility of the primary, treating physician to initiate home infusion or infusion at a satellite clinic and to maintain oversight to safeguard patient's safety when infusion administration is conducted at home or at a satellite clinic. Local, standard-of-care guidelines should be followed.

Because of the possibility of anaphylactic reactions, severe allergic reactions, and immune-mediated reactions with alglucosidase alfa administration and the importance of assessing, documenting, and reporting protocol specified adverse events, personnel competent in recognizing and treating adverse reactions (including anaphylactic reactions) should be readily available throughout the home/satellite clinic infusion. In order for a patient who receives or will receive treatment infusions either at home or at a satellite clinic to be enrolled or to continue participating in this Safety Sub-Registry, the following conditions must be met:

- The home infusion agency/satellite clinic staff must have access to and be trained on proper safety equipment, including but not limited to cardiopulmonary resuscitation equipment, as well as, the collection of blood samples necessitated by specified adverse events (immunoglobulin E [IgE], tryptase, complement activation, and circulating immune-complex [CIC]).
- The Principal Investigator should refer to available local guidance manuals that focus on home/satellite clinic infusions.
- The home infusion agency/satellite clinic staff must keep source documentation of the infusion, including documentation of any AEs. The home infusion agency/satellite clinic staff must be able to provide specific source documentation to the Principal Investigator and agree to be monitored. The Principal Investigator will continue to be responsible for all medical procedures and data collection performed by home infusion agency/satellite clinic staff, oversight of home infusion agency staff/satellite clinic, and patient's safety even when delegating infusion administration, documentation of required data (AE, vital signs), and applicable lab sample collection responsibilities to the home infusion agency/satellite clinic.
- The Principal Investigator is responsible for discussing each home/satellite clinic infusion administration with the respective home infusion agency/satellite clinic staff and ensuring s/he receives written documentation to ensure accurate/timely follow-up and data entry.

- If required, the Principal Investigator will notify the Independent Review Board/Independent Ethics Committee (IRB/IEC) when an enrolled patient transitions to home/satellite clinic infusions or receives home/satellite clinic infusions at time of enrollment.
- Compliance with any additional Institutional and/or IRB/IEC requirements.

The Principal Investigator is ultimately responsible for the safety of the patient and the integrity of the data collected during this clinical study. If the above criteria cannot be met, the patient will either be withdrawn from the Safety Sub-Registry or not enrolled.

7 SAFETY SUB-REGISTRY

7.1 DESIGN

This Safety Sub-Registry is a prospective, observational, exploratory registry of patients enrolled in the Pompe Registry (a multi-center, multi-national, observational program that tracks the natural history and outcomes of patients with Pompe disease), who receive or plan to receive ERT with alglucosidase alfa. Participation in the Pompe Registry is voluntary on the part of patients; however, the Pompe Registry is required to provide data on an ongoing basis to regulatory authorities.

No experimental intervention is involved. Participating patients will undergo clinical assessments and receive the standard-of-care treatment for Pompe disease, as determined by their treating physicians and using the Safety Sub-Registry Recommended Schedule of Assessments as a guideline (see Section 7.2), as well as those assessments recommended in the Pompe Registry protocol. The CRIM status for patients with onset of symptoms on or before 12 months of age and who are diagnosed with Pompe disease will be submitted to the Pompe Registry and recorded in the Registry database. Patients will undergo routine antibody and expedited antibody testing for reactions consistent with suspected anaphylaxis and/or a severe cutaneous or systemic immune-mediated reaction, when clinically warranted.

Patients will complete and sign a Patient Information and Authorization form/Informed consent form specific to this Safety Sub-Registry before participating. Patients will be followed for a period of 4 years from enrollment in the Safety Sub-Registry.

Select data from patient case report forms (CRFs) will be monitored periodically against source documents at the treating physician's site by a representative of Genzyme (or its designee) to ensure data completeness and accuracy. Refer to Section 11.1 for further details.

7.2 RECOMMENDED SCHEDULE OF ASSESSMENTS

Assessments will be performed in accordance with the participating site standard-of-care, and the Safety Sub-Registry Recommended Schedule of Assessments in **TABLE 7-1**. Additional assessments will be performed, as specified in the global Pompe Registry Recommended Schedule of Assessments.

TABLE 7-1: SAFETY SUB-REGISTRY RECOMMENDED SCHEDULE OF ASSESSMENTS

Assessment	**Frequency / Timing**	**Comments**
CRIM status	At enrollment[A]	Patients with age at symptom onset ≤12 months of age
Serum anti-rhGAA immunoglobulin G (IgG) antibody formation	Routine testing: every 3 months for the duration of the patient's participation in the Safety Sub-Registry. Expedited antibody testing for reactions consistent with suspected anaphylaxis and/or a severe cutaneous or systemic immune-mediated reaction, as needed when clinically warranted.	Samples must be drawn prior to infusion or at least 72 hours following the end of the infusion period.
Neutralizing antibodies	Testing for neutralizing antibodies: at the time of seroconversion for patients who test positive for IgG antibody formation and every 3 months thereafter in these patients and when clinically warranted for patients in whom a possible decrease in treatment response is observed and antibody formation is suspected as a potential cause for the decreased response.	Samples must be drawn prior to infusion or at least 72 hours following the end of the infusion period.
Complement activation	Within 1 to 3 hours of an infusion reaction [B]	Plasma sample
Serum tryptase	Within 1 to 3 hours of an infusion reaction [B]	Serum sample
Circulating immune complexes (CIC)	Within 3 hours of completion of infusion in patients with a reaction suspected of being due to CIC.	Serum sample
Serum anti-rhGAA immunoglobulin E (IgE) antibodies	No sooner than 3 days following an infusion reaction [B]	Serum samples must be drawn prior to infusion or at least 72 hours following the end of the infusion period.
Skin testing	Skin testing may be performed in patients who experience an infusion-associated reaction (IAR) that meets the following criteria: • IAR that is suggestive of IgE-mediated etiology, with persistent symptoms of bronchospasm, hypotension, and/or urticaria requiring intervention, OR any	Skin testing is optional at the discretion of Genzyme Global Pharmacovigilance and Epidemiology (GPE) and the treating physician.

	other signs or symptoms at the discretion of the treating physician; • Skin testing is a sensitive predictor of IgE-mediated reaction and may be suggested for confirmation of the IgE results.	
Immune-mediated reaction[C]	If a patient exhibits evidence of symptoms suggestive of immune complex disease (e.g., proteinuria), serum samples will be obtained for the evaluation of CIC, in addition to the testing of prior serum samples that have been archived.	Samples must be drawn prior to infusion or at least 72 hours following the end of the infusion period.
Vital Signs	Vital signs only need to be recorded on the Safety Sub-Registry Vital Signs CRFs for all AEs defined in **TABLE 8-1**. Vital signs that are collected for applicable AEs that occur during or within the post-infusion observation period while under medical supervision should be recorded on the Safety Sub-Registry Vital Signs CRF.	When indicated, vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be recorded on the Safety Sub-Registry Vital Signs CRFs for the following time-points: pre-infusion, at time the AE is detected and at the time the event resolves or when the patient is no longer under medical supervision whichever time occurs first.
Chemistry, hematology, and urinalysis[D]	In accordance with the Pompe Registry protocol Recommended Schedule of Assessments, and as deemed appropriate by the treating physician in the presence of an infusion reaction.	
Adverse Event Reporting	Continuous monitoring, and reporting as appropriate	For all patients receiving treatment with alglucosidase alfa. All adverse events collected as part of this Safety Sub-Registry should be recorded on the CRF and documented on an Adverse Event (AE) Report Form and faxed to GPE within 24 hours of physician's first knowledge of the event being reported. Refer to **TABLE 8-1**.

The Safety Sub-Registry Recommended Schedule of Assessments represents the core safety assessments that should be performed in the presence of an adverse event that is consistent with the signs of anaphylaxis, severe allergic reaction, and/or severe cutaneous and systemic immune-mediated reaction following treatment with alglucosidase alfa. Frequency of assessments will be determined by the frequency of adverse events, or as deemed appropriate by the treating physician, unless specified otherwise in the table above.

[A] CRIM status will be assessed as per standard-of-care at Safety Sub-Registry enrollment, unless previously assessed and results previously reported to the Pompe Registry.

[B] IgE, complement activation, and serum tryptase testing may also be performed at the request of Global Pharmacovigilance and Epidemiology (GPE), in consultation with the treating physician, for patients with recurrent IARs suggestive of hypersensitivity.

[C] Refer to Section 8.1.4.4 for a list of terms that will be reviewed.

[D] Chemistry and hematology will include the following: serum creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatine kinase (CK), creatine kinase muscle-brain isoform (CK-MB), lactic dehydrogenase (LDH), prothrombin time (PT), partial thromboplastin time (PTT), and factor VII (proconvertin stable factor). Urinalysis will include urine protein, creatinine, specific gravity, and blood. Microscopy will be performed if clinically indicated.

8 ADVERSE EVENTS

It is the responsibility of Genzyme to collect, review and communicate to appropriate regulatory authorities all relevant information regarding treatment-emergent AEs for patients receiving alglucosidase alfa in countries where the drug is under clinical investigation or approved for marketing. As this Safety Sub-Registry is designed to assess the symptoms, severity, outcome, and occurrence of anaphylaxis, severe allergic reactions, and/or signals of severe cutaneous and/or systemic immune-mediated reactions, Genzyme strongly encourages physicians to report any such events experienced by Registry patients. For details on reporting AEs as part of this Safety Sub-Registry, please refer to Section 8.2.

8.1 DEFINITIONS

8.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject, which does not necessarily have a causal relationship with the medicinal product (active or placebo drug, biologic, or device). An AE can, therefore, be any unfavorable or 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 physician or medical staff;
- Test abnormalities (laboratory tests, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during participation in the Registry.

All adverse events listed in **TABLE 8-1** should be reported on an Adverse Event Report Form and faxed to Genzyme within 24 hours of physician's first knowledge.

Treatment-emergent AEs are events that occurred on or after the date of first alglucosidase alfa infusion; hereafter in this protocol, AEs refer to treatment-emergent events.

8.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any AE that results in any of the following:

- Death: the patient died as a result of the event;
- Life-threatening event: any AE that places the patient, in the view of the physician, 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 physician;
- 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 medicinal 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 and may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether events are classified as serious. Examples include, but are not limited to: allergic bronchospasm, dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3 Severity grading of adverse events

Severity Grading

The treating physician will assess the severity of all AEs/SAEs as Mild, Moderate, or Severe, based on the following definitions (developed from Clinical Data Interchange Standards Consortium [CDISC] Study Data Tabulation Model [SDTM] standard terminology version 3.1.1.1).

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.

8.1.4 Safety Sub-Registry definitions

8.1.4.1 Adverse drug reaction (ADR)

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product at any dose, for which there is a reasonable possibility that the product caused the response. The phrase "response to a medicinal product" means that a causal relationship between a medicinal

product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out; ICH E2A 27 October 1994; Section II A 2).

All ADRs should be recorded on the CRF for this Safety Sub-Registry and should also be reported to GPE by submitting of an AE report form within 24 hours of physician's first knowledge.

8.1.4.2 Infusion-associated reaction (IAR)

An Infusion Associated Reaction (IAR) is defined as an adverse event that occurs on the day of the infusion (during the infusion or following completion of the infusion up and to 24 hours following the infusion onset) and considered related to Enzyme Replacement Therapy (ERT) by the reporter or company. 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 reporter or company.

All IARs should be recorded on the CRF for this Safety Sub-Registry and should also be reported to GPE by submitting of an AE report form within 24 hours of physician's first knowledge.

8.1.4.3 Anaphylaxis

As defined by the second symposium of the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN), anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (Sampson, 2006).

In accordance with the NIAID/FAAN guidelines, anaphylaxis after administration of a likely allergen (in this case, alglucosidase alfa) is suggested by, but not limited to, meeting one of the 2 following criteria:

1. Two or more of the following that occur rapidly (minutes to several hours) after exposure:

    a. Involvement of the skin-mucosal tissue

        (e.g, generalized hives, pruritus, flushing, swollen lips-tongue-uvula, laryngeal edema)

    b. Respiratory compromise

        (e.g, dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

    c. Reduced blood pressure (BP) or associated symptoms

        (e.g, lightheadedness, syncope, hypotonia/weakness)

    d. Persistent gastrointestinal symptoms

        (e.g, crampy abdominal pain, vomiting)

2. Reduced BP occurring rapidly (minutes to several hours) after exposure:

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP from that person's baseline*

b. Adults: systolic BP of less than 90 millimeters of mercury (mm Hg) or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

All anaphylactic and allergic reactions that do not meet the criteria for anaphylaxis should be recorded on the CRF for this Safety Sub-Registry and should also be reported to GPE by submitting of an AE report form within 24 hours of physician's first knowledge.

8.1.4.4 Immune-mediated reactions

Immune complex disease is a local or systemic disease caused by the formation of circulating immune complexes and their deposition in tissue or in vascular endothelium (Crespo, 2005; Hiltz, 1994). Small immune complexes formed in antigen excess are easily filtered from the circulation by macrophages without triggering further inflammation. In the next phase of slight antigen excess, intermediate-sized immune complexes form. These are large enough to activate complement and small enough to cross the endothelial barrier, leading to tissue inflammation (skin, myocardium, joints, and kidney). Immune-mediated syndromes may result in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, hematuria, proteinuria, papular rash, purpura-like eruptions, arthritis, serositis, and vasculitis. Reactions are self-limited and usually develop within 7 to 10 days of antigen injection starting with some constitutional flu-like symptoms of fever, myalgia, arthralgia, and rash, although reactions can occur much sooner if a patient has already been sensitized. Clinical recovery is usually apparent after 7 to 28 days, as intermediate-sized immune complexes are cleared by the reticuloendothelial system. Free antigen continues to clear from the blood, leading to antibody excess and the formation of large immune complexes, which are quickly removed by circulating macrophages. Finally, the antigen is no longer detectable, and the level of circulating antibodies continues to rise (Alissa, 2009).

The identification of potential immune-mediated reactions to alglucosidase alfa will be performed by a 2-step process. First, each onset of significant AEs of the following types will be recorded on the CRF for this Safety Sub-Registry:

- deterioration from baseline in renal function (blood urea nitrogen [BUN], estimated glomerular filtration rate [GFR], or serum creatinine) with documented proteinuria or hematuria, or with the presence of sediment;
- symptoms consistent with vasculitis or new onset of joint pain (e.g., arthralgia, myalgia, or arthritis)

- events consistent with serum sickness or constitutional flu-like symptoms of fever, myalgia, arthralgia, and rash; and
- skin lesions (e.g., new and significant generalized pruritus, prolonged or recurrent skin rashes that last for several days following infusion, or include ulcerations, or persistent purpuric skin rashes that last for several days following infusion).

Second, following review of the CRF data, a medical review of these cases, including relevant medical history, risk factors, and other confounding factors that may have contributed to the event onset (other than the immune-mediated mechanism), and available immunogenicity data such as immunoglobulin G (IgG), IgE, and CIC, will be performed by GPE to determine whether the events are consistent with an immune-mediated syndrome.

All immune-mediated reactions should be recorded on the CRF for this Safety Sub-Registry and should also be reported to GPE by submitting of an AE report form within 24 hours of physician's first knowledge.

8.2 REPORTING ADVERSE EVENTS

AEs that occur during and up to 48 hours post treatment administration, immune-mediated, and allergic and anaphylactic reactions consistent with the definitions in Section 8.1.1, Section 8.1.4.3 and Section 8.1.4.4 regardless of seriousness or relationship to treatment with alglucosidase alfa should be reported to the Genzyme GPE department within 24 hours of physician's first knowledge. ADRs and IARs consistent with the definitions in Section 8.1.4.1 and Section 8.1.4.2 should also be reported to the Genzyme GPE department within 24 hours of physician's first knowledge.

Allergic reactions that do not meet the criteria for anaphylaxis in Section 8.1.4.3 also should be reported. For allergic reactions, a description of the reaction (e.g. "post administration reaction characterized by acute hypotension, pulmonary edema, etc.) should be recorded on the AE CRF. Each related sign or symptom should be recorded on the AE CRF as a separate AE. For any AE reported to GPE as part of this Safety Sub-Registry, a detailed written description, including relevant medical history, duration of the event, time of event onset in relation to initiation of infusion, change from baseline in vital signs, intervention and action taken regarding infusion (including details on attempts to re-challenge with alglucosidase alfa), and copies of relevant patient records, autopsy reports, and other documents, as appropriate, should also be forwarded to the Genzyme GPE department with the completion of the AE report form.

The following adverse events will be assessed and recorded on the AE CRF and reported to GPE as part of the Safety Sub-Registry:

TABLE 8-1: ADVERSE EVENT (AE) REPORTING INSTRUCTIONS FOR INVESTIGATORS

Event Category	**Reporting timeframe to Sponsor by Investigator**	**Data Entry of Information**
1. AEs that occur during or within 0-48 hrs. post end of treatment infusion regardless of seriousness or relationship to treatment.	Expedited (within 24 hours of physician's first knowledge) Complete an AE form and submit to GPE within 24 hours.	Record in CRF
2. Immune-mediated reactions regardless of seriousness, relationship or timing to treatment infusion.	Expedited (within 24 hours of physician's first knowledge) Complete an AE form and submit to GPE within 24 hours.	Record in CRF
3. ADRs that do not fall within event category 1 or 2.	Expedited (within 24 hours of physician's first knowledge) Complete an AE form and submit to GPE within 24 hours.	Record in CRF

Abbreviation Key:

ADR = Adverse Drug Reaction - These include adverse reactions for which there is at least a possible causal relationship between the alglucosidase alfa and the AE.

AE = Adverse Event

CRF = Electronic Case Report form

GPE = Global Pharmacovigilance and Epidemiology

9 ANTIBODY TITER FORMATION AND TESTING FOR SEVERE ALLERGIC REACTION

9.1 ANTIBODY RESPONSES

This Safety Sub-Registry will assess the occurrence of antibody formation and the effect of antibody response in relation to anaphylaxis, severe allergic reactions, and signals of cutaneous and systemic immune-mediated reactions (timing and pattern of formation and response) experienced by all enrolled patients who have been treated with at least one infusion of ERT with alglucosidase alfa. The Safety Sub-Registry will also assess the role of CRIM status in relation to AEs experienced by patients with symptom onset ≤12 months of age.

Patients will be monitored for IgG antibody formation every 3 months for the duration of the patient's participation in the Safety Sub-Registry, and as deemed appropriate by the treating physician in the presence of an event. Testing for IgG titers also may be considered if a patient develops an allergic or other immune-mediated reaction, including anaphylaxis and/or signals of severe cutaneous and systemic immune-mediated reaction. IgG inhibitory (neutralizing) antibody testing should be performed at the time of seroconversion for patients who test positive for IgG antibody formation and every 3 months thereafter in these patients and when clinically warranted for patients in whom a possible decrease in treatment response is observed and antibody formation is suspected as a potential cause for the decreased response. Patients who experience anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis.

9.1.1 Cross-reacting immunologic material (CRIM) status

CRIM-negative patients have been shown to develop higher and sustained titers in the presence of alglucosidase alfa treatment and to seroconvert earlier than CRIM-positive patients (Kishnani, 2010). The cause of a poorer clinical response in these patients is not fully understood, and studies are currently underway to potentially improve clinical outcome in these patients by administering a prophylactic immunomodulatory regimen to attempt to induce immune tolerance. For patients in this Safety Sub-Registry who are determined to have symptom onset within the first year of life, CRIM status should be determined and recorded in the Registry database. In addition to the Western blot assay, a patient's GAA gene mutations can also be used to predict CRIM status for the majority of patients (Bali et al., 2012). New commercial blood based CRIM tests might also become available. All AEs reported in patients with onset of clinical signs/symptoms ≤12 months of age will be examined to identify events that may correlate to CRIM status. A medical review of these cases, including all relevant medical history and available immunogenicity data, will be performed by GPE to determine whether CRIM status plays a role in event occurrence, severity, and/or duration.

9.2 TESTING FOR MODERATE, SEVERE, OR RECURRENT INFUSION-ASSOCIATED REACTIONS

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of allergic reaction, additional blood samples should be collected for complement activation, serum tryptase, and serum anti-rhGAA IgE antibody testing. At the request of Genzyme GPE, after consultation with the treating physician, additional blood samples may be collected for recurrent IARs suggestive of a hypersensitivity reaction. Skin testing also may be performed, if clinically indicated.

9.2.1 Complement activation testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of allergic reaction, a plasma sample may be drawn within 1 to 3 hours of the event for complement activation testing, when clinically indicated. At the request of Genzyme GPE, after consultation with the treating physician, a plasma sample for complement activation testing also may be collected for patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.2.2 Serum tryptase testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of allergic reaction, a serum sample may be drawn within 1 to 3 hours of the event for serum tryptase testing, when clinically indicated. At the request of Genzyme GPE, after consultation with the treating physician, a serum sample for tryptase testing also may be collected prior to the patient's next scheduled infusion of alglucosidase alfa for those patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.2.3 Serum anti-rhGAA IgE antibody testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of allergic reaction, the patient should return to the treating physician's office no sooner than 3 days following the day of the event to have a serum sample collected for anti-rhGAA IgE antibody testing, when clinically indicated. At the request of Genzyme GPE, after consultation with the treating physician, a serum sample for IgE testing also may be collected prior to the patient's next scheduled infusion of alglucosidase alfa for those patients with recurrent IARs suggestive of a hypersensitivity reaction.

9.2.4 Skin testing

Skin testing may be performed following consultation with the treating physician and Genzyme GPE on those patients who experience an IAR that meets the following criteria:

- IAR that is suggestive of IgE-mediated etiology, with persistent symptoms of bronchospasm, hypotension, and/or urticaria requiring intervention, OR any other signs or symptoms at the discretion of the treating physician;

- Skin testing is a sensitive predictor of IgE-mediated reaction and may be suggested for confirmation of the IgE results.

Skin testing will be performed in accordance with the treating physician's site standards. Genzyme's standard skin-testing protocol is available upon request.

9.2.5 Circulating immune complex detection

In the event that a patient exhibits evidence of symptoms suggestive of Immune Complex Disease, serum samples will be obtained for the evaluation of circulating immune complexes in addition to the testing of serum samples that have been archived. 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 will be at the discretion of the Investigator.

10 STANDARD LABORATORY ASSESSMENTS

The following chemistry, hematology, and urinalysis parameters are deemed to be important when evaluating anaphylaxis, severe allergic reaction, and/or signals of severe cutaneous and/or systemic immune-mediated reactions following treatment with alglucosidase alfa, and will be measured in accordance with the schedule established in the Recommended Schedule of Assessments for the Pompe Registry:

- serum creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, BUN, creatine kinase (CK), creatine kinase muscle-brain isoform (CK-MB), lactic dehydrogenase (LDH), prothrombin time (PT), partial thromboplastin time (PTT), and factor VII (proconvertin stable factor);
- urine protein, creatinine, specific gravity, and blood. Microscopy will be performed if clinically indicated;

The treating physician has the discretion to order additional laboratory testing at additional intervals as necessary. Analysis of blood and urine samples will be performed locally per institutional procedures. Laboratory reports should be reviewed promptly and prior to the patient's next scheduled infusion of alglucosidase alfa to ensure that the patient is stable enough to continue ERT; the data should be reported to the Pompe Registry in a timely manner.

10.1 CROSS-REACTING IMMUNOLOGIC MATERIAL (CRIM) TEST INFORMATION

Physicians collecting samples from patients with onset of signs or symptoms ≤12 months of age for analysis of their CRIM status should contact GPE for CRIM testing inquiries.

11 DATA COLLECTION AND SUBMISSION

The purpose of this Pompe Safety Sub-Registry is to collect uniform and meaningful clinical data on patients with Pompe disease who experience one or more AEs in the form of serious risk of anaphylaxis, severe allergic reaction, and/or signs of severe cutaneous and/or systemic immune-mediated reactions following ERT with alglucosidase alfa.

A set of CRFs designed for this Safety Sub-Registry will be used by participating sites. In addition, specified Pompe Registry CRFs will also be completed as part of this Safety Sub-Registry. Data collected by Pompe Registry physicians or their designees will be submitted to the Pompe Registry for central processing and evaluation. A primary Pompe Registry contact person located at the participating site should be designated as the individual responsible for completing and entering data in the CRFs in the Registry database.

In some cases, other third parties may submit clinical information to the Pompe Registry for processing, as described in the informed consent form. For example, a laboratory that processes tests on rare disease patients as part of standard clinical care may be set up to send test results both to the treating physician (for clinical care) and to the Pompe Registry (where a patient participates in the Pompe Registry). These third party laboratories will not have access to the Pompe Registry database itself, but will send test results to the Pompe Registry team to include in the Pompe Registry, using a unique identifier to link the test results to the remainder of the patient's data in the Pompe Registry.

Information on AEs should be submitted to Genzyme GPE, as directed in Section 8.2. Laboratory information should be submitted as directed in Section 10.

11.1 DATA QUALITY ASSURANCE

A clinical monitor from Genzyme (or its designee) will manually review select data in the CRFs for this Safety Sub-Registry against source documents at the treating physician's site during periodic monitoring visits 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 site will be contacted for corrections and/or clarification of the data. In addition, a clinical monitor from Genzyme (or its designee) will also review documentation related to IRB/IEC submissions/approvals, informed consent, and any patient authorization documents required by local law.

All data will be entered in a validated computing environment for analysis and reporting.

12 STATISTICAL METHODS AND DATA REPORTING

Data from this Safety Sub-Registry will be analyzed on an interim basis, according to pre-specified intervals for annual reports such as those to regulatory authorities. 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 (SAP).

Analyses will be performed by Genzyme Biostatistics using SAS® statistical software. All data collected will be presented using by-patient listings, summary tables and/or figures.

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 data, medical, laboratory, immunology, and AE data will be summarized. The relationships between AEs and CRIM status and between AEs and antibody levels will be explored.

Data that are collected by Genzyme's GPE department or Clinical Specialty Laboratory will be submitted to the Registry via external datasets. Reconciliation will be performed, as needed.

Analyses will be performed based on each patient's age of onset category, as defined in the SAP.

13 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

This Safety Sub-Registry protocol, informed consent form, the Patient Information and Authorization form, as well as any locally required authorization documents, relevant supporting information should be submitted to a fully constituted IRB/IEC for review and approval at the discretion of the participating physician, and in accordance with site-specific requirements. The submission of the above documents may not be necessary if the site provides documentation to the Safety Sub-Registry team (either with respect to the Safety Sub-Registry as a whole or with respect to a particular document) that such review is not required under local country laws or has been waived by a particular IRB/IEC. Since no experimental procedures are included in the protocol, the committee chairperson may decide that a full IRB/IEC review is not warranted, and that it may only be necessary to approve the Patient Information and Authorization form or Informed Consent form.

During the conduct of the Safety Sub-Registry, any amendment or modification to the Safety Sub-Registry protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC and the Genzyme Safety Sub-Registry team should be informed as soon as possible.

14 CONFIDENTIALITY

14.1 PATIENT CONFIDENTIALITY

To maintain patient confidentiality, all patients will be referenced by the Pompe Registry identification (ID) number, patient initials, and date of birth, where allowed by local law, not by name.

14.2 PHYSICIAN CONFIDENTIALITY

Furthermore, physician-specific patient data (i.e., individual patient data that could be linked to a particular site) will remain confidential and will not be released to other physicians without prior written approval from the physician in accordance with applicable laws related to the confidentiality of patient information. No physician-to-physician data comparisons will be made.

15 REGISTRY AND SAFETY SUB-REGISTRY SPONSOR AND CONTACT INFORMATION

The Pompe Registry and all related sub-registries are sponsored by Genzyme, a Sanofi company.

North America	**Europe / Middle East**
Genzyme, a Sanofi company 500 Kendall Street Cambridge, MA 02142 United States Tel. 1.800.745.4447, ext. 1-5500 +1.617.591.5500 (outside the United States) FAX +1.617.374.7339	Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands Tel. +31.35.699.1200 FAX +31.35.699.8688
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LTS13930 Aglu06909 Amended Protocol2

ELECTRONIC SIGNATURES

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