PHASE 3/4 CLINICAL STUDY PROTOCOL

A PHASE 3/4 PROSPECTIVE STUDY TO CHARACTERIZE THE PHARMACOKINETICS OF ALGLUCOSIDASE ALFA IN PATIENTS WITH POMPE DISEASE

Pharmacokinetics of Alglucosidase Alfa in Patients with Pompe Disease (PAPAYA)

Protocol Number: AGLU07710/MSC12790
EudraCT: 2010-022231-11

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Protocol Amendment 3: 18 July 2016

Sponsor: Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA

Clinical Project Manager: [redacted]

Medical Monitor:

Global Safety Officer:

Statistician:

This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of GCP as stated in the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws. I have read and agree to abide by the requirements of this protocol.
Investigator Signature Date
Investigator Name (please print or type)

Signature Page for Sponsor's Representative

I have reviewed and approved the protocol entitled, "A Phase 3/4 Prospective Study to Characterize the Pharmacokinetics of Alglucosidase Alfa in Patients with Pompe Disease"

[redacted]

1 SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA **NAME OF FINISHED PRODUCT** **NAME OF ACTIVE INGREDIENT** alglucosidase alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE:

A Phase 3/4 Prospective Study to Characterize the Pharmacokinetics of Alglucosidase Alfa in Patients with Pompe Disease

PROTOCOL NO.:

AGLU07710/MSC12790

INVESTIGATOR STUDY SITES:

It is anticipated that this study will be conducted at multiple sites in one or more regions as needed to allow enrollment of sufficient numbers of patients in a reasonable timeframe.

OBJECTIVES:

The primary objective of this study is to characterize the pharmacokinetics (PK) of alglucosidase alfa manufactured at the 4000 L scale in patients who have a confirmed diagnosis of Pompe disease.

A secondary objective of this study is to evaluate and explore the relationship between anti-recombinant human acid α-glucosidase (rhGAA) antibody titers and the PK of alglucosidase alfa.

METHODOLOGY:

This is a prospective, open-label, multicenter study of patients with Pompe disease who are naïve to treatment with alglucosidase alfa or who have been previously treated with alglucosidase alfa for at least 6 months. The patient or the patient's legal guardian(s) must provide informed consent prior to performing any protocol-related procedure. Eligible patients will receive one intravenous (IV) infusion of alglucosidase alfa of 20 mg/kg of body weight.

Pharmacokinetic and safety assessments will be performed at the scheduled treatment visit. Adverse events (AE) and concomitant medications/therapies will be monitored continuously throughout the study. Patients who are withdrawn from the study will not be replaced (ie, a patient's study number will not be reused); however, additional patients may be enrolled to offset patient dropouts.

An independent Data and Safety Monitoring Board (DSMB) will perform ad hoc reviews of safety data as outlined in the DSMB Charter, which is maintained separately from the study protocol. An immunologist will be consulted, when necessary, to review information and provide treatment recommendations for infusion-associated reactions (IARs).

NUMBER OF PATIENTS:

Approximately 20 patients will be enrolled (10 patients <18 years old and 10 patients ≥18 years old). Additional patients may be enrolled to offset patient dropouts.

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 USA **NAME OF FINISHED PRODUCT** **NAME OF ACTIVE INGREDIENT** alglucosidase alfa	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A patient must meet all of the following criteria to be eligible for this study.

1. The patient and/or the patient's parent/legal guardian is willing and able to provide signed informed consent.
2. The patient has a confirmed GAA enzyme deficiency from skin, blood, or muscle tissue and/or 2 confirmed GAA gene mutations.
   2.1 Infant and toddler Pompe disease patients can be included in the study only under condition (minimal body weight) that the trial-related blood loss (including any losses in the maneuver) will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time.
3. The patient, if female and of childbearing potential, must have a negative pregnancy test (urine beta-human chorionic gonadotropin) at screening. Note: All female patients of childbearing potential and sexually mature males must agree to use a medically accepted method of contraception throughout the study.
4. For patients previously treated with alglucosidase alfa the patient has received alglucosidase alfa for at least 6 months.

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from this study.

1. The patient is participating in another clinical study using an investigational product.
2. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Patients will receive one IV infusion of alglucosidase alfa 20 mg/kg body weight. Prior to the infusion, the patient should be assessed by the Investigator or appropriate designee to determine if the patient is free of acute illness and is clinically stable to receive the infusion. Infusion will be administered in a step-wise manner. It is recommended that the infusion be administered at an initial rate of approximately 1 mg/kg/hr and may be augmented by 2 mg/kg/hr every 30 minutes, if there are no signs of IARs, until a maximum rate of approximately 7 mg/kg/hr is reached.

REFERENCE TREATMENT:

There is no reference treatment.

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CRITERIA FOR EVALUATION:

Efficacy:

No efficacy data will be collected.

Safety:

Safety will be evaluated in terms of continuous monitoring of AEs (all treatment-emergent AEs and events by relationship, seriousness, and severity), IARs, and discontinuations due to AEs. Scheduled clinical and laboratory safety assessments include: clinical hematology, chemistry, and urinalysis; anti-rhGAA IgG antibody and inhibitory/neutralizing antibody formation in patients testing positive for immunoglobulin G (IgG); vital signs (blood pressure, heart rate, respiratory rate, and temperature); physical examinations; electrocardiograms (ECG); and for women of childbearing potential, urine pregnancy tests.

Additional exploratory laboratory safety assessments will be conducted when clinically indicated, including (1) circulating immune complex detection; and (2) immunoglobulin E (IgE), serum tryptase, and complement activation, following moderate, severe, or recurrent IARs suggestive of hypersensitivity reactions. Additionally, skin testing may be performed for IARs suggestive of IgE-mediated hypersensitivity reaction. These tests will be performed to gain additional research information as to individuals' responses to alglucosidase alfa and for the active clinical management of patients, as needed.

Pharmacokinetics:

Blood samples (1 mL each) for evaluation of PK will be collected before, during, and over a 24 hour period after infusion on Day 1. A maximum of 11 mL of blood will be drawn for PK sampling. Per patient, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of 4 weeks or 1% at a single time.

Pharmacokinetic sampling schedule: pre-dose (prior to infusion); immediately (within a few minutes) before the infusion rate changes from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr; immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after end of infusion. In case of IAR, IAR(s) should be appropriately managed and PK sample has to be collected before any first time increase in infusion rate from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr achieved during administration of the remaining dose, immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after end of infusion.

STATISTICAL METHODS:

All patients who received an infusion of alglucosidase alfa will be included in the analysis. Data collected in this study will be documented using summary tables, figures, and patient data listings. For continuous variables, number of patients with observed results and mean, median, standard deviation (SD), minimum, and maximum of observed values will be presented. For categorical variables, shift tables and/or frequencies and percentages will be presented. Graphical displays will be presented as appropriate.

Power and Sample Size:

Approximately 20 patients will be enrolled in this study (10 patients <18 years old and 10 patients ≥18 years old). This study is not powered to make any statistical inferences.

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Analysis Sets:

Primary analysis population will consist of all patients who received any amount of alglucosidase alfa.

Demographics and Baseline Characteristics:

Demographic and baseline data on medical/surgical history and Pompe disease history including GAA gene mutations will be summarized using descriptive statistics.

Efficacy:

No efficacy data will be collected.

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities, and categorized by system organ class and preferred term. All AEs will be displayed in patient listings. Adverse events will be categorized and tabulated for the treatment group overall by severity, seriousness, and relationship to study treatment. Additionally, IARs and discontinuations due to AEs will be summarized. Information collected prior to the alglucosidase alfa infusion will be presented separately from treatment-emergent signs and symptoms. Potential clinically significant changes in vital signs from pre- to post-infusion will also be summarized as appropriate.

Pharmacokinetics:

Plasma samples data will be analyzed using validated methods to quantify the plasma concentrations of rhGAA. The concentration-time data will be analyzed using non-compartmental methods. The following PK parameters will be reported: maximum observed concentration (C_{max}), actual sampling time to reach maximum observed concentration (T_{max}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}), area under the concentration-time curve from time 0 and extrapolated to infinite time (AUC_{inf}), terminal elimination half-life ($T_{1/2}$), total systemic clearance (CL), and volume of distribution (V_d). If data do not lend to non-compartmental analysis, data analysis may be undertaken using model-based approaches such as nonlinear mixed effects modeling. The analysis will be conducted using actual sampling and dosing timepoints. Individual assessments and descriptive statistics (mean, SD, median, minimum, maximum, geometric mean and percent coefficient of variation) will be presented for each patient and patient group (treatment naïve versus treatment experienced, if appropriate). Pharmacokinetic parameters will be assessed in relation to rhGAA antibody titers.

2 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

Not Applicable.

LIST OF IN-TEXT FIGURES

Not Applicable.

3 ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AoR	Acknowledgement of Receipt
AUC_{inf}	area under the concentration-time curve from time 0 and extrapolated to infinite time
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
CL	total systemic clearance
C_{max}	maximum observed concentration
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
GAA	acid α-glucosidase
GCP	Good Clinical Practice
GPE	Global Pharmacovigilance and Epidemiology
IAR	infusion-associated reaction
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgE	immunoglobulin E
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
6MWT	6-minute walk test
PK	pharmacokinetic(s)
qow	every other week
rhGAA	recombinant human acid α-glucosidase
SAE	serious adverse event
SD	standard deviation
SOM	Study Operations Manual
$T_{1/2}$	terminal elimination half-life
T_{max}	actual sampling time to reach maximum observed concentration
V_d	volume of distribution

4 INTRODUCTION

Pompe disease is a rare, autosomal recessive disease caused by the deficiency of lysosomal acid α-glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac, respiratory-specific, and major skeletal muscle groups, disrupts the architecture and function of affected cells leading to multisystemic pathology and ultimately death. In addition to being a lysosomal storage disorder, Pompe disease is also considered a neuromuscular disease, a metabolic myopathy, and a glycogen storage disorder.

Pompe disease is an ultra-orphan disease, affecting some 5,000 to 10,000 individuals globally. Pompe 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, the disease manifests as a broad clinical spectrum with a continuum of clinical manifestations, ranging from a rapidly progressive infantile-onset form to a more slowly progressive late-onset form with considerable variability and overlap between these 2 extremes (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; van den Hout, 2003, *Pediatrics*). The majority of patients with Pompe disease are classified with the late-onset subtype.

Late-onset Pompe patients manifest signs and symptoms of the disease anywhere from early childhood through the 6th decade of life and usually present with slowly progressive myopathy, predominantly of the proximal muscles in the trunk and pelvic and shoulder girdles, and a variable degree of respiratory involvement. While the heart is typically spared, cardiomegaly has been reported to occur in up to 4% of patients with late-onset Pompe disease (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*) and other cardiac manifestations secondary to chronic respiratory failure have been observed (Felice, 1995, *Medicine*; Kurz, 1998, *Respiration*). Initial myopathic signs can be very subtle and may include difficulty combing the hair, rising from a chair, climbing stairs, or rising from a squat. However, over time there is increasing involvement of proximal lower limb, truncal, and upper body muscles, and most patients ultimately become wheelchair bound. Initial respiratory symptoms may be related to sleep apnea and include somnolence and morning headache. As the disease progresses, orthopnea and/or exertional dyspnea develop and many patients eventually require noninvasive or invasive ventilation and ultimately progress to respiratory failure, the leading cause of death in these patients (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Mellies, 2001, *Neurology*; Raben, 2002, *Curr. Mol. Med.*; Reuser, 1995, *Muscle Nerve*).

Overall, the presentation and course of late-onset Pompe disease is much less predictable than the classic infantile form. Some patients experience a rapid deterioration in skeletal (appendicular and respiratory) muscle function leading to loss of ambulation and respiratory failure, while others progress less rapidly. In others, the rate of progression of skeletal (appendicular and respiratory) muscle involvement diverges (Laforêt, 2000, *Neurology*).

Alglucosidase alfa has been developed as an enzyme replacement therapy for the treatment of Pompe disease. Clinical trials have been completed in patients with infantile- and late-onset Pompe disease, thus covering the extremes of severity of the disease spectrum (Kishnani, 2007, *Neurology*; Nicolino, 2009, *Genet. Med.*; van der Ploeg, 2010, *N. Engl. J. Med.*).

In a randomized, double-blind, placebo-controlled study in patients with late-onset Pompe disease (study AGLU02704), the pharmacokinetics (PK) of alglucosidase alfa were studied in a subset of 34 patients 20 to 70 years of age at the time of first infusion. A small study of 5 juvenile patients 5 to 15 years of age was previously conducted (AGLU02804). The present study aims to further characterize the PK of alglucosidase alfa manufactured at the 4000 L scale.

4.1 Summary of Potential Risks

Study specific procedures and associated risks are bulleted below.

- Repeat blood draws: momentary discomfort, bruising, excessive bleeding, infection, fainting, and possible anemia.

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

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. Alglucosidase alfa has also demonstrated clinical benefit in patients with late-onset Pompe disease; these benefits included stabilization of respiratory function, slowing the progressive decline that was seen in untreated patients with late-onset Pompe disease, and improvement in distance walked as measured by the 6-minute walk test (6MWT) observed in Study AGLU02704. Results from the extension Study AGLU03206 further support the beneficial effects of alglucosidase alfa treatment on stabilizing 6MWT, upright forced vital capacity, quantitative motor test parameters, and pulmonary function. Patients will receive one infusion of the commercially approved dose of alglucosidase alfa.

The tests performed during this study are not expected to provide a direct benefit to the individual patient beyond the standard of care. Benefit is expected for the total population of Pompe disease patients by characterizing the PK and the relationship between anti-recombinant human acid α-glucosidase (rhGAA) antibody titers and the PK of alglucosidase alfa.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to characterize the PK of alglucosidase alfa manufactured at the 4000 L scale in patients who have a confirmed diagnosis of Pompe disease.

5.2 Secondary Objectives

A secondary objective of this study is to evaluate and explore the relationship between anti-rhGAA antibody titers and the PK of alglucosidase alfa.

6 INVESTIGATIONAL PLAN

6.1 Endpoints

6.1.1 Efficacy Endpoints (Not Applicable)

6.1.2 Safety Endpoints

Routine safety assessments are not considered endpoints of this study and are described in Section 9.4 and Section 10.

6.1.3 Pharmacokinetic Endpoints

The PK endpoint is to characterize the PK after single dose administration of alglucosidase alfa, dosed as an intravenous (IV) infusion at 20 mg/kg.

Additional endpoints include, characterizing the effect of antibodies (immunoglobulin G [IgG] and inhibitory/neutralizing antibodies) on the PK of alglucosidase alfa.

6.2 Study Design

This is a prospective, open-label, multicenter study of patients with Pompe disease who are naïve to treatment with alglucosidase alfa or who have been previously treated with alglucosidase alfa for at least 6 months. The patient or the patient's legal guardian(s) must provide informed consent prior to performing any protocol-related procedure. Eligible patients will receive one IV infusion of alglucosidase alfa 20 mg/kg body weight at visit 2 (Day 1).

Approximately 20 patients (10 patients <18 years old and 10 patients ≥18 years old) with Pompe disease who have confirmed GAA enzyme deficiency from skin, blood, or muscle tissue and/or 2 confirmed GAA gene mutations who meet all other eligibility criteria as outlined in Section 7 will be enrolled in the study. Patients will be monitored for adverse events (AEs) for a minimum of 2 hours after infusion.

Alglucosidase alfa will be administered by IV infusion at a dose of 20 mg/kg body weight as outlined in Section 8. Prior to the infusion, the patient should be assessed by the Investigator or appropriate designee to determine if the patient is free of acute illness and is clinically stable to receive the infusion.

Pharmacokinetic (PK) and safety assessments will be performed at the scheduled visit. Adverse events and concomitant medications/therapies will be monitored continuously throughout the study. Patients who are withdrawn from the study will not be replaced (ie, a patient's study number will not be reused); however, additional patients may be enrolled to offset patient dropouts.

Patients who complete or withdraw from the study will have a follow-up assessment performed 30 days following their administration of investigational product for all ongoing AEs at the time of administration of investigational product. All serious adverse events (SAEs) ongoing at time of administration of investigational product should be followed up until resolution.

An independent Data and Safety Monitoring Board (DSMB) will perform ad hoc reviews of safety data as outlined in the DSMB Charter, which is maintained separately from the study protocol. An immunologist will be consulted, when necessary, to review information and provide treatment recommendations for infusion-associated reactions (IARs).

6.2.1 Completion of a Patient's Participation in the Study and Overall Study Completion

6.2.1.1 Completion of a Patient's Participation in the Study

The length of a patient's participation will be from the time the informed consent form is signed until the patient completes the last planned assessment/visit and will be approximately 4 to 9 weeks depending on duration of screening period.

A patient will be considered "completed" when the Week 4/Follow-up call has occurred per protocol.

6.2.1.1.1 Premature Patient Discontinuation from the Study

Patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

The reasons indicated in Section 8.3.3 for withdrawing a patient from treatment may also be justifiable reasons for the Investigator or Sponsor to remove a patient from the study. Patients may be discontinued from the study if the study is terminated by the Sponsor (see Section 13.5.5).

Patients who are prematurely withdrawn from the study will be asked to complete all assessments prior to withdrawal, if possible. Post-study SAEs will be reported according to Section 10.3.4. A patient will be considered early terminated if the patient does not complete all of the required study visits outlined in the protocol after being enrolled. A patient will be considered discontinued due to an AE if the patient received infusion or partial infusion of the investigational product, but did not complete the study because of an AE, whether or not considered drug related.

At the end of the patient's participation in the study the Investigator will complete the discontinuation electronic case report form (eCRF), documenting the reason(s) for study discontinuation.

In the event that a patient dies, permission will be sought (through a separate informed consent form) from the next of kin for a research autopsy or post-mortem research biopsy. Samples collected from these procedures will be used for research purposes only and data will not be included in any study analyses.

Patients who are withdrawn from the study will not be replaced (ie, a patient's study number will not be reused); however, additional patients may be enrolled to offset patient dropouts.

6.2.1.2 Overall Study Completion

The study will be considered to be complete when the last patient's participation ends (either through premature discontinuation from the study or completion of all study requirements). The end of the study is defined as the date the last active patient completes the last required study visit.

6.3 Discussion of Study Design, Including Choice of Control Group

This is a single arm study designed to characterize the PK of alglucosidase alfa in Pompe patients naïve to enzyme replacement therapy before the study or who have been previously treated with alglucosidase alfa for at least 6 months. No control group will be used.

One of the objectives of this study is to evaluate and explore the relationship between anti-rhGAA antibody titers and the PK of alglucosidase alfa; therefore, both patients who are treatment-naïve before the study and patients who have been previously treated with alglucosidase alfa will be evaluated.

7 PATIENT POPULATION AND SELECTION

7.1 Inclusion Criteria

A patient must meet all of the following criteria to be eligible for this study.

1. The patient and/or the patient's parent/legal guardian is willing and able to provide signed informed consent.
2. The patient has a confirmed GAA enzyme deficiency from skin, blood, or muscle tissue and/or 2 confirmed GAA gene mutations.
   2.1 Infant and toddler Pompe disease patients can be included in the study only under condition (minimal body weight) that the trial-related blood loss (including any losses in the maneuver) will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time.
3. The patient, if female and of childbearing potential, must have a negative pregnancy test (urine beta-human chorionic gonadotropin) at screening. Note: All female patients of childbearing potential and sexually mature males must agree to use a medically accepted method of contraception throughout the study.
4. For patients previously treated with alglucosidase alfa the patient has received alglucosidase alfa for at least 6 months.

7.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. The patient is participating in another clinical study using an investigational product.
2. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

8 TREATMENTS

8.1 Treatments Administered

Alglucosidase alfa will be administered by IV infusion at a dose of 20 mg/kg body weight. Infusion will be administered in a step-wise manner. It is recommended that the infusion be administered at an initial rate of approximately 1 mg/kg/hr and may be augmented by 2 mg/kg/hr every 30 minutes, if there are no signs of IARs, until a maximum rate of approximately 7 mg/kg/hr is reached. The infusion length will be dependent on the dose. The length of infusion is approximately 4 hours. Specific details pertaining to the infusion volumes and rates can be found in the Pharmacy Manual.

Guidelines for management of IARs can be found in the Study Operations Manual (SOM).

Patients will be monitored for AEs for 2 hours after infusion. Patients may be required to stay for a longer observation period at the Investigator's discretion.

A central venous catheter is recommended for delivery of the investigational drug but placement will be at the discretion of the Investigator. Medical personnel authorized by the Investigator will be responsible for the administration of medication throughout the study.

Safety will be evaluated in consultation with the DSMB on an ad hoc basis. An immunologist will be consulted, when necessary, to review information and provide treatment recommendations for IARs.

8.2 Investigational Product(s)

Alglucosidase alfa will be supplied as a preservative free, lyophilized product in single-use 20-mL vials containing 50 mg of alglucosidase alfa per vial (extractable), 25 mM sodium phosphate, 2% mannitol, and 0.005% polysorbate 80 at a pH of 6.2. Alglucosidase alfa is reconstituted with 10.3 mL of sterile water for injection to yield a concentration of 5 mg/mL.

8.2.1 Packaging and Labeling

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.2.2 Storage

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the compound should be managed according to the rules provided by the Sponsor.

Temperature excursions will be handled as described in the Pharmacy Manual.

8.2.3 Preparation and Administration of the Investigational Product

The infusion must be prepared by a qualified, authorized pharmacist (or designee) using aseptic technique. The pharmacist or designee will determine the quantity of vials required based on the patient's weight and dose.

Each vial is reconstituted with 10.3 mL of sterile water for injection. After reconstitution, each alglucosidase alfa vial will yield a concentration of 5 mg/mL. The reconstituted solution is further diluted into 0.9% sodium chloride for injection.

The infusion will be prepared based on patient weight (kg) and dose (20 mg/kg). The infusion is prepared to a final study drug concentration between 0.5 mg/mL and 4 mg/mL. The total volume of the infusion will be dependent on the patient's weight and total dose, as recommended in the Pharmacy Manual.

The diluted solution should be filtered through a 0.2 – 0.22 micron, low protein-binding, in-line filter during administration to remove any visible particles.

Alglucosidase alfa should not be infused in the same IV line with other products.

Further information on preparation and administration of alglucosidase alfa is provided in the Pharmacy Manual.

8.3 Dosing Considerations

8.3.1 Dose Selection Rationale

In preclinical studies, alglucosidase alfa effectively depleted tissue glycogen in GAA knockout mice in a dose-dependent fashion. The every other week (qow) dosing regimen is supported by separate nonclinical studies of glycogen clearance in GAA knockout mice, which demonstrated that qow dosing of 10, 20, 40 or 100 mg/kg of alglucosidase alfa was at least as effective as weekly dosing of the same total dose in terms of glycogen removal from the heart and skeletal muscle.

A range of dosing regimens from 10 mg/kg every week (qw) to 40 mg/kg qow has been used in clinical studies with alglucosidase alfa in patients with infantile- and late-onset Pompe disease.

Current human experience with alglucosidase alfa indicates that doses from 10 mg/kg qw to 40 mg/kg qow have been well tolerated. Clinically relevant responses in efficacy measurements have been observed in patients with infantile- as well as late-onset Pompe disease at all dose levels of alglucosidase used to date. In late-onset patients, alglucosidase alfa administered at a dose of 20 mg/kg qow for 78 weeks in Study AGLU02704 demonstrated stabilization of respiratory function, slowing the progressive decline that was seen in untreated patients, and improvement in distance walked as measured by the 6MWT. Furthermore, data analyses from Study AGLU01602 indicate no marked difference in several efficacy outcomes between the 2 dose arms of 20 and 40 mg/kg qow after 52 weeks of alglucosidase alfa treatment.

Based upon the nonclinical data outlined above, as well as relevant human experience with alglucosidase alfa in patients with Pompe disease to date, a single administration of the commercially approved dose of 20 mg/kg qow is expected to have a tolerable risk-benefit profile in this patient population.

8.3.2 Dose Modification, Reduction, or Delay

Prior to infusion, the patient should be assessed by the Investigator or appropriate designee to determine if the patient is free of acute illness and is clinically stable to receive the infusion. Infusion will be postponed if the patient is acutely ill on the scheduled day of infusion.

Dose increase and dose reduction is not permitted unless it is due to an AE, in which case it is not a protocol violation, but the Investigator must consult with the Sponsor in the event of a dose change.

8.3.3 Treatment Discontinuation

A patient's study treatment may be discontinued at any time at the patient's request or at the discretion of the Investigator or Sponsor. The following may be justifiable reasons for the Investigator or Sponsor to discontinue a patient from treatment:

- The patient was erroneously included in the study (ie, was found to not have met the inclusion/exclusion criterion).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol.
- The patient participates in another investigational study without the prior written authorization of the Sponsor.
- The patient becomes pregnant.
- The patient becomes lost to follow up.

Discontinuation of treatment does not imply withdrawal from the study; refer also to Section 6.2.1.1.1.

Patients who received a partial dose of investigational product and who are withdrawn from treatment, but not withdrawn from the study, will be asked to:

- Continue to perform all safety assessments to the extent possible according to protocol including Week 4 follow up call.

The Investigator will document the reason(s) for treatment discontinuation on the eCRF.

Additional patients may be enrolled to offset effects of premature discontinuations.

8.4 Prior and Concomitant Medications and Therapeutic Procedures

Medications and therapies taken by the patient during the 30-day period prior to the baseline evaluation visit and during the course of the study will be recorded in the Concomitant Medication eCRF/Concomitant Therapies eCRF. Similarly, pre-infusion medications will be recorded in the Concomitant Medication eCRF and assistive devices will be recorded in the Concomitant Therapies eCRF.

In clinical trials, some patients were pre-treated with antihistamines, antipyretics and/or corticosteroids. Infusion reactions occurred in some patients after receiving antipyretics, antihistamines or corticosteroids. In general, the use of pre-treatment is at the discretion of the Investigator. The routine use of pre-treatment is not recommended, especially in patients with previous immunoglobulin E (IgE) mediated hypersensitivity reaction. Antihistamines can mask

early symptoms of a hypersensitivity reaction (skin reaction) making it difficult for the infusion staff to recognize the initial signs of distress and the need to decrease the infusion rate and/or otherwise intervene. Additionally, in cases where significant histamine is released, antihistamines administration will not be effective (Vervloet, 1998, *BMJ*).

Careful consideration should be given to the potential long term side-effects of pretreatment with corticosteroids (Buchman, 2001, *J Clin Gastroenterol*), antipyretics, and antihistamines.

Patients are restricted from participating in other concurrent investigational protocols that are not restricted to data and/or sample collection for patient demographic and/or disease purposes.

8.5 Method of Assigning Patients to Treatment

This is a single-treatment arm study. All eligible patients will receive alglucosidase alfa at the same dose of 20 mg/kg body weight.

8.6 Blinding and Randomization

This is an open-label study.

8.7 Treatment Compliance

The patient's compliance with the treatment regimen will be monitored in terms of the patient receiving the study drug infusion. Incomplete infusion will be clearly documented and considered in the analysis.

9 EFFICACY AND SAFETY ASSESSMENTS

9.1 Study Schedule of Events

The study will be conducted as outlined in the following sections. Appendix A summarizes the study events at each visit. Study visits will be based on calendar days relative to the date of infusion (Day 1). Additional information about these study procedures, including the order in which study procedures should be performed, is contained in the SOM.

9.2 Demographic and Screening Assessments

The patient's medical/surgical history and Pompe disease history including GAA gene mutations will be obtained to determine the patient's eligibility for the study, per the inclusion and exclusion criteria in Section 7, prior to enrollment. Demographic data, height, and weight will also be recorded at the Screening visit.

9.3 Efficacy Assessments (Not Applicable)

9.4 Safety Assessments

Safety will be assessed for all patients from the time of signing of the informed consent up to 30 days after the patient's administration of investigational product. Safety parameters include physical examination, vital signs, clinical laboratory tests, urine pregnancy tests and use of contraception, electrocardiogram, and development of antibodies to alglucosidase alfa as described in Sections 9.4.1 through 9.4.6, and AEs, as described in Section 10.

9.4.1 Physical Examination

A complete physical examination will be conducted at the timepoint specified in Appendix A. The examination will include an assessment of the patient's general appearance; skin; head, eyes, ears, nose, and throat; examinations of lymph nodes, heart, lungs, abdomen, extremities/joints, neurological, mental status, and reflexes. Whenever possible, the same physician should perform the examination at each study visit.

Any abnormal findings that meet the definition of an AE per Section 10.1.1 will be recorded on the AE page of the eCRF. 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.

9.4.2 Vital signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be measured at the timepoint specified in Appendix A. Vital signs will be taken immediately prior to infusion and immediately prior to any infusion rate change, as well as after completion of the post-infusion observation period (with a window of ±30 minutes for timepoints after the start of infusion).

Any abnormal findings that meet the definition of an AE per Section 10.1.1 (eg, that result in an alteration in medical care, diagnostic or therapeutic) will be recorded on the AE page of the eCRF. 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.

9.4.3 Clinical Laboratory Tests

The following clinical laboratory tests will be assessed by a central laboratory at the timepoint specified in Appendix A.

- Blood Chemistry: sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatine kinase, creatine kinase with MB fraction, lactate dehydrogenase, alkaline phosphatase, total protein, albumin, glucose, phosphorus, gamma-glutamyl transpeptidase.
- Hematology: complete blood count with differential and platelets, including hematocrit, hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils.
- Urinalysis: urine color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, hemoglobin, urine creatinine, and microscopy if indicated.

A central laboratory will provide collection supplies, arrange collection, and perform analysis of clinical laboratory evaluations. Procedures for the handling and shipment of all central laboratory samples will be included in the Laboratory Manual. Specimens will be appropriately processed by the central laboratory facility and laboratory reports will be made available to the Investigator in a timely manner to ensure appropriate clinical review.

The Investigator is responsible for reviewing and signing all laboratory reports. Any abnormal findings that meet the definition of an AE per Section 10.1.1 (eg, that result in an alteration in medical care, diagnostic or therapeutic) will be recorded on the AE page of the eCRF. 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 study drug or other protocol-specific procedures, or (3) in the judgment of the Investigator, follow up is deemed no longer medically necessary.

9.4.4 Urine Pregnancy Tests and Use of Contraception

No studies of alglucosidase alfa have been conducted in pregnant women. To ensure patient safety, female patients of childbearing potential must have a negative pregnancy test prior to completing the study procedures at the time specified in Appendix A. In addition, all female patients of childbearing potential and sexually mature males will be required to use a medically accepted method of contraception throughout the study.

See Section 10.7 for information on pregnancy reporting.

9.4.5 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be conducted at the time specified in Appendix A. The following will be assessed: heart rate, rhythm, RR, PR, QRS, QT, QTc, QRS axis, R voltage V6, S voltage V1, left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, repolarization changes, and overall cardiac impression for each patient. The study site cardiologist should review the ECG in a timely manner for clinical management of the patient. Any abnormal findings that meet the definition of an AE per Section 10.1.1 (eg, that result in an alteration in medical care, diagnostic or therapeutic) will be recorded on the AE page of the eCRF. 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.

9.4.6 Development of Antibodies to Alglucosidase Alfa

9.4.6.1 Routine Anti-rhGAA IgG Antibody Testing

Serum samples for anti-rhGAA IgG antibody testing will be obtained pre-infusion at the time specified in Appendix A. Refer to the SOM for guidelines on the collection and shipment of serum samples.

9.4.6.2 IgG Inhibitory/Neutralizing Antibody Testing

Serum samples of all IgG seropositive patients will also be tested, as appropriate, for the presence of IgG inhibitory/neutralizing antibodies to alglucosidase alfa. Testing will be conducted for research purposes only to evaluate responses to alglucosidase alfa, and not for the active clinical management of patients. Refer to the SOM for guidelines on the collection and shipment of serum samples.

9.4.6.3 Additional Testing for Moderate, Severe, or Recurrent Infusion-Associated Reactions

Additional exploratory laboratory safety assessments will be conducted when clinically indicated. In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, additional blood samples will be collected as described below in Sections 9.4.6.3.1 through 9.4.6.3.3. Skin testing may also be performed, if clinically indicated, as described in Section 9.4.6.3.4. Suggested guidelines for the management of IARs during the event and pre-infusion medication guidelines are summarized in the SOM (also refer to Section 8.4).

Refer to the SOM for guidelines on the collection and shipment of samples. The Sponsor's Global Pharmacovigilance and Epidemiology (GPE) department should be apprised of sample shipments. Testing is conducted for research purposes to gain additional information as to individuals' responses to study drug, and for the active clinical management of patients, as needed.

9.4.6.3.1 Complement Activation Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, a plasma sample will be drawn within 1 to 3 hours of the event for complement activation testing. Testing also can be initiated at the request of the Sponsor after consultation with the Investigator.

9.4.6.3.2 Serum Tryptase Activity Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, a serum sample will be drawn within 1 to 3 hours of the event for serum tryptase activity testing. Testing also can be initiated at the request of the Sponsor after consultation with the Investigator.

9.4.6.3.3 Serum Anti-rhGAA IgE Antibody Testing

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, the patient should return to the study center no sooner than 3 days following the day of the event to draw a serum sample that will be tested for anti-rhGAA IgE antibodies. Testing also can be initiated at the request of the Sponsor after consultation with the Investigator.

9.4.6.3.4 Skin Testing

Skin testing may be performed following consultation with the Investigator, the Sponsor, and, as appropriate, the immunologist appointed to review IAR cases in patients who experience an IAR that meets the following criteria:

- IAR is suggestive of IgE-mediated 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 the Sponsor.
- Skin testing may be another predictor of IgE-mediated reaction and may be suggested for confirmation of the IgE results.

Refer to the SOM for skin testing procedures.

9.4.6.4 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. Refer to the SOM for guidelines on the collection and shipment of serum samples.

9.5 Pharmacokinetic Assessments

Blood samples will be collected at pre-dose (prior to infusion); immediately (within a few minutes) before the infusion rate changes from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr; immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after infusion (times from end of infusion) on Day 1. In case of IAR, IAR(s) should be appropriately managed and PK sample has to be collected before any first time increase in infusion rate from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr achieved during administration of the remaining dose, immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after end of infusion. A maximum of 11 blood samples (1 mL each) will be drawn for PK sampling. Per patient, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of 4 weeks or 1% at a single time.

Plasma will be isolated from these samples and analyzed using validated, sensitive, and specific bioanalytical methods, namely, a fluorometric assay using a 4-methylumbelliferyl-α-D-glucoside (4-MUG) substrate to detect GAA activity in plasma quantified relative to the activity of an 8-point rhGAA standard curve prepared from a dilution series of reference alglucosidase alfa. Actual dosing and sampling timepoints must be recorded for all days when blood sampling for pharmacokinetics occurs. Refer to the SOM for complete collection and processing instructions.

From the plasma concentration time data, the following pharmacokinetic parameters will be assessed:

C_{max}	The maximum observed concentration
T_{max}	The actual sampling time to reach maximum observed concentration
AUC_{last}	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration

If data permit,

AUC_{inf}	Area under the concentration-time curve from time 0 and extrapolated to infinite time
$T_{1/2}$	Terminal elimination half-life
CL	Total systemic clearance
V_d	Volume of distribution

Additional parameters may be analyzed and reported, as appropriate. Industry standard, validated software such as WinNonlin® or Phoenix NLME® will be used for PK data analysis.

10 ADVERSE EVENT REPORTING

At each study visit, patients will be evaluated for new AEs and the status of existing AEs. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications. Adverse events will be collected from the time of signing of the informed consent through Visit 2. Additional AEs/SAEs assessed as related to the study drug or study procedures that occur during the 30-day follow-up period will be collected in the clinical database.

10.1 Definitions

10.1.1 Definition of an Adverse Event

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

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, ECG, 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 the study.

10.1.2 Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following:

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

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

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

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

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

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

For this particular protocol, due to the medical significance of any new ventilator use in this patient population, any new use of invasive ventilatory support (not including planned surgical procedures, if total duration of ventilatory support is less than 3 days) will be considered an important medical event and will be reported as an SAE. If a patient requiring ventilatory support becomes ventilator independent, the next instance of invasive ventilatory support (if applicable) will be considered a new SAE.

10.1.3 Additional Definitions with Relevance to Safety Reporting

10.1.3.1 Product Administration-Associated Reactions or Events

IARs are defined as adverse events that occur during either the infusion or the observation period following the infusion which are deemed to be related or possibly related to study drug. At the discretion of the Investigator, adverse events occurring after completion of the post-infusion observation period that are assessed as related may also be considered IARs.

These events should be reported to the Sponsor's GPE department within 24 hours of the Investigator's first knowledge of the event. Refer to Section 9.4.6.3 for additional testing in the event a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions. Suggested guidelines for the management and reporting of IARs are summarized in the SOM.

10.2 Evaluation of Adverse Events/Serious Adverse Events

10.2.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. This assessment is to be made in blinded studies and also for known comparators. For each AE/SAE the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time.

The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

10.2.2 Relationship to Study Procedures

Relationship to study procedures will be recorded on the eCRF.

SAEs that are attributed to a study procedure should have that information explicitly included in the narrative.

10.2.3 Severity Grading of Adverse Event Scoring

Note that this is not the same as "seriousness," which is defined in Section 10.1.2. Seriousness serves as a guide for defining regulatory reporting obligations.

Severity Grading

The Investigator 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 Study Data Tabulation Model standard terminology v3.1.1).

Definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.4 Outcome

Outcome describes the status of the AE.

The Investigator will provide information regarding the patient outcome of each AE.

Definitions for possible results of an AE outcome:

- Fatal: The termination of life as a result of an AE.
- Not recovered/not resolved: The patient has not recuperated or the AE has not improved.
- Recovering/resolving: The patient is recuperating or the AE is improving.
- Recovered/resolved: The patient has recuperated or the AE has resolved.
- Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.
- Unknown: Not known, not observed, not recorded, or refused.

10.2.5 Action Taken Regarding the Investigational Product

The Investigator will be required to provide the action taken regarding investigational product (eg, active, comparator) in response to the AE.
Options include:

- Dose increased: Increase in the frequency, strength or amount of investigational product administered.
- Dose not changed: No change in administration of the investigational product.
- Dose reduced: Reduction in the frequency, strength or amount of investigational product administered.
- Drug (investigational product) interrupted: Temporary interruption (termination) in administration of the investigational product.
- Drug (investigational product) withdrawn: Administration of the investigational product terminated (no further dosing).
- Not applicable: Determination of a value is not relevant in the current context.
- Unknown: Not known, not observed, not recorded, or refused.

10.3 Timeframe for Collection of Adverse Events/Serious Adverse Events

10.3.1 Adverse Events Occurring Prior to Study Treatment

Adverse events will be collected from the time of signing of the written informed consent until the patient's first receipt of investigational product.

Serious AEs will be collected from the time of signing of the written informed consent until the patient's first receipt of investigational product.

10.3.2 Adverse Events Occurring After Study Treatment

Adverse events will be collected from the time of the patient's first receipt of investigational product until the patient completes the study or terminates from the study.

Serious AEs will be collected from the time of the patient's first receipt of investigational product until the patient completes the study or terminates from the study.

10.3.3 Adverse Events Occurring Following Patient Discontinuation of Treatment

For patients who prematurely discontinue study treatment (see Section 8.3.3), but who are not withdrawn from the study, AEs will continue to be recorded until the patient completes the study (see Section 6.2.1.1 for definition of patient completion). See Section 10.3.4 for reporting requirements after the patient completes the study.

10.3.4 Serious Adverse Events Occurring Following Patient Completion of the Study

If, at any time after the patient has completed participation in the study (as defined in Section 6.2.1.1), the Investigator or study staff becomes aware of an SAE that they believe is possibly related or related to the investigational product (see Section 10.2.1), then the event and any known details should be reported promptly to the Sponsor. Follow the reporting instructions in Section 10.5.

10.4 Recording of Adverse Events/Serious Adverse Events

All AEs/SAEs experienced by the patient will be recorded on the eCRF. Information including a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, relationship to investigational product; and action taken regarding the investigational product will be recorded. Vital signs, laboratory results, and other safety assessments noted in Section 9.4 will be recorded, if they meet the definition of an AE (see Section 10.1.1). When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the patient will be recorded on an SAE Report Form and reported to the Sponsor according to Section 10.5.

10.5 Reporting of Serious Adverse Events

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

- All SAEs must be reported to the Sponsor's GPE Department within 1 calendar day of the Investigator's first knowledge of the event by fax or e-mail regardless of relationship to study procedures or treatment. The Investigator is requested to supply detailed information regarding the event at the time of the initial report.
- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with additional supporting documents (eg, discharge letters, autopsy reports, and other documents) will be faxed to the Sponsor's GPE Department within 2 calendar days of the Investigator's first knowledge of the event. (If faxed within 1 calendar day of the Investigator's first knowledge, this form may serve as the initial notification).
- Follow-up information, which may include copies of relevant patient records and other documents not available at the time the initial SAE Report Form was completed, must be sent to the Sponsor's GPE Department as soon as available. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to treatment. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant patient/hospital records, and pathology or autopsy reports.
- The Sponsor's GPE Fax is available for SAE reporting on a 24-hour basis and is reviewed during normal business hours.

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- Fax: +33 1 60 49 70 70 - Email: CL-CPV-receipt@sanofi.com

- Investigators will receive copies of expedited safety reports that the Sponsor sends to regulatory agencies. The Investigator is responsible for fulfilling local reporting requirements to their Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). Investigators in the US will report events to their IRB in accordance with applicable standard operating procedures and/or local reporting requirements. In the European Union, the Sponsor will be responsible for notifying the IEC and Competent Authorities of any serious unexpected related adverse events (ie, Suspected Unexpected Serious Adverse Reaction). Investigators must forward copies of the IRB/IEC notification to the Sponsor or its designee.

10.6 Follow Up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed by the Investigator at subsequent visits/contacts.

The Investigator will provide follow-up information for any SAE to the Sponsor's GPE department, as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an SAE.

All AEs will be followed until resolution or study termination. Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary. Rules for AE/SAE follow up apply to all patients, including those withdrawn prematurely to the extent allowed by the patient's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate medical management and patient consent to elucidate the nature and/or causality of the AE/SAE.

For the purposes of the study, status of ongoing and new AEs/SAEs will be assessed 30 days after the patient's administration of investigational product. Any new AE or SAE that occurs during the 30-day follow-up period and prior to initiation of commercial therapy and is assessed as related to the drug or study procedures will be reported/collected in the clinical database. All AEs will continue to be followed until the 30-day assessment. Ongoing SAEs at the 30-day follow-up assessment will need to be further followed until resolution, until the Investigator deems follow up is no longer medically necessary or until the patient is lost to follow up. Adverse events and SAEs reported after the initiation of commercial product will be considered spontaneous reports for the purposes of regulatory reporting. Refer to the SOM for details of this assessment.

10.7 Pregnancy Reporting

Female patients will be instructed to notify the Investigator immediately if they discover they are pregnant. Pregnant female patients will be discontinued from the study. Investigators are encouraged to enroll pregnant patients in the Pompe Registry.

Male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant.

If the Investigator learns of a report of pregnancy at any time after signing the informed consent, the Investigator should follow the instructions in Section 10.5 to contact GPE within 24 hours; however, the Investigator will be asked to complete the Pregnancy forms rather than SAE forms, because healthy pregnancy is not an AE. The patient will be followed until the outcome of the pregnancy is known (eg, live birth or stillbirth). The Investigator will be responsible for this follow up.

If not otherwise established, the Investigator will inform the patient that the Sponsor is required to gather information regarding the course and outcome of the pregnancy after exposure to a study product. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional timepoints. All study related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the CRF as an AE unless the Investigator suspects an interaction between the study treatment and the contraceptive method. Additionally all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the patient is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths are reported as SAEs.

11 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

11.1 Recording of Data

The Investigator must provide the Sponsor or its designee direct access to each patient's source documents. Source documents may include, but are not limited to, the following original documents, data, and records where information was first recorded:

- Hospital records.
- Medical histories and narrative statements relating to the patient's progress.
- Clinical and office charts.
- Operative reports.
- Laboratory notes/reports.
- Memoranda and telephone notes/records.
- Patients' evaluation checklists.
- Pharmacy dispensing records.
- Recorded data from automated instruments.
- Copies of transcriptions certified after verification as being accurate copies.
- Project-specific worksheets (eg, for study visits), including all worksheets developed specifically for this study.
- X-ray images and corresponding reports.
- MRI image sets and corresponding reports.
- Video recordings of surgery.

Required data for this study will be captured on eCRFs via electronic data capture (EDC) unless otherwise specified in this document. Except for data points for which the protocol or SOM indicates that the eCRF may serve as source documentation, data are to be obtained from the patient's source documents and then entered into the eCRF by authorized site personnel. Clinical data that are not recorded on the eCRF will be captured and transferred to the Sponsor or its designee.

11.2 Data Quality Assurance

The eCRFs will be reviewed by a clinical monitor from the Sponsor or its designee for completeness and accuracy. Source document verification will be performed. The data will also be reviewed internally by the Sponsor's Data Management department or its designee and, if necessary, the investigational sites will be queried for corrections and/or clarifications. Upon completion of data entry and reconciliation, all EDC user access privileges will be changed to read only.

Copies of pertinent records in connection with the study, including eCRFs and queries, as well as source documents will be maintained at the site (see Record Retention, Section 13.5.3).

11.3 Data Management

The format and content of the eCRFs will be approved by the Sponsor or its designee prior to the start of the study. The Sponsor or its designee will be responsible for database creation, data entry if applicable, and management of data from sources other than the clinical database (e.g., lab data).

Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data for each patient will be made by the appropriate clinical and statistical personnel. Any exclusion of patient data will be documented, as appropriate. Protocol deviations discovered during the data reconciliation process will be tracked by the Sponsor or its designee.

12 STATISTICAL METHODS AND PLANNED ANALYSES

The Sponsor will be responsible for data collection and editing, reviewing and validating all the information in the eCRFs, statistical analysis, and generation of the clinical report.

Prior to locking the database, all data editing will be complete and decisions regarding the evaluability of all patient data for inclusion in the statistical analysis will be made. The rationale for excluding any data from the statistical analyses will be prospectively defined, and classification of all or part of a patient's data as non-evaluable will be completed and documented before the entire database is locked. The analysis will be performed using the SAS® statistical software system.

12.1 General Considerations

Data collected in this study will be reported using summary tables, figures and patient data listings. Descriptive statistics will be calculated: n (number of patients with observed results), mean, median, standard deviation (SD), minimum and maximum for the continuous variables and shift tables and/or frequencies and percentages for the categorical variables. No formal inferential statistical tests will be performed.

12.2 Determination of Sample Size

Approximately 20 patients will be enrolled in this study (10 patients <18 years old and 10 patients ≥ 18 years old). No formal sample size calculations have been performed. This study is not powered to make any statistical inferences.

12.3 Analysis Sets

Primary analysis population will consists of all patients who received any amount of alglucosidase alfa.

12.4 Demographics and Baseline Characteristics

Demographic and baseline data on medical/surgical history and Pompe disease history including GAA gene mutations will be summarized using descriptive statistics

Concomitant medication/therapy data will be coded using the WHO-DRUG dictionary. Number and percentages of patients receiving each concomitant medication/therapy will be tabulated.

All data will be presented in by-patient listings.

12.5 Patient Accountability

Data from all patients who are enrolled in the study will be included in the summary of patient accountability. The frequency and percentage of patients who are enrolled in the study, discontinued from the study, and completed the study, along with reasons for discontinuation, will be summarized.

12.6 Study Treatment Usage and Compliance

Number of study drug infusions received by patients will be summarized using summary statistics.

12.7 Efficacy Analyses (Not Applicable)

12.8 Safety Analyses

12.8.1 Physical Examination and Vital Signs

Observed measurements and changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) from pre- to post-infusion will be summarized as appropriate. Listings of potentially clinically significant abnormal findings/values will be presented.

12.8.2 Clinical Laboratory Tests

Observed measurements in clinical chemistry, hematology, and urinalysis will be descriptively summarized. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Frequencies of abnormal values and clinically significant abnormal values will be summarized. All data will be presented in listings along with individual listings of patients with clinically significant abnormal laboratory values.

12.8.3 Adverse Events

Adverse events, SAEs, and IARs will be coded using the Medical Dictionary for Regulatory Activities and summarized by primary system organ class and preferred term. Detailed listings of patients who experience AEs, SAEs, and IARs will be presented. The incidence of treatment-emergent AEs, IARs, and SAEs will be tabulated (frequencies and percentages) by severity, and by relationship to treatment. Adverse event severity will be categorized as mild, moderate, or severe. In tabulating severity of AEs on a per patient basis, the greatest severity will be assigned to a patient should there be more than one occurrence of the same AE with different reported severities. Relationships of the AE to treatment will be categorized as not related, unlikely related, possibly related, or related. The highest level of association will be reported in patients with differing relationships for the same AE. Listings of AEs, SAEs, and IARs for all patients will be provided, which will include severity and relationship to treatment, as well as actions taken regarding treatment, and patient outcome. A separate listing for patients who withdraw from the study due to AEs will be provided. The incidence of AEs leading to study discontinuations will also be summarized.

12.8.4 Other Safety Assessments

12.8.4.1 Electrocardiogram

Listings of patients with abnormal findings/values will be presented.

12.8.4.2 Anti-rhGAA IgG Antibodies, Inhibitory/Neutralizing Antibodies, and Other Immunogenicity Testing

Anti-rhGAA IgG antibody titer values will be summarized using summary statistics. All data will be presented in listings for each patient.

By patient listings will also display results of inhibitory/neutralizing antibody, circulating immune complex, anti-rhGAA IgE antibody, serum tryptase activity, complement activation, and skin testing performed. Descriptive summaries may also be provided as appropriate.

12.9 Other Analyses

12.9.1 Pharmacokinetic Endpoints

Pharmacokinetic assessments will be conducted using a validated assay. Plasma concentration-time data will be analyzed using non-compartmental methods in accordance with Genzyme Guideline for Non-compartmental Analysis of Pharmacokinetic Data. Actual dosing and sampling timepoints will be used for data analysis. The following PK parameters will be assessed if data permit: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL and V_d. Based on previous data, no accumulation of drug is expected upon repeat dosing; hence, the PK analyses will treat all data as coming from single dose administrations.

If data do not lend to non-compartmental analysis, model-based approaches such as nonlinear mixed effects modeling may be utilized for data analysis.

Individual assessments and descriptive statistics (mean, SD, median, minimum, maximum, geometric mean and percent coefficient of variation) will be presented for plasma concentration time data and PK parameters. Individual and mean (SD) plasma concentration time profile will be presented graphically.

To evaluate the effect of immunogenicity on the PK of alglucosidase alfa, pre-dose IgG and inhibitory/neutralizing antibody titers for each patient will be analyzed graphically with respect to clearance for Day 1. If relationships are apparent, further quantitative/statistical analysis may be performed (e.g., statistical significance, correlation coefficients).

12.10 Other Statistical Issues

12.10.1 Significance Levels

Not applicable.

12.10.2 Missing or Invalid Data

All data will be analyzed as they were collected in the database. Missing data will not be imputed using statistical methods.

12.11 Interim Analysis

No interim analyses are planned.

13 SPECIAL REQUIREMENTS AND PROCEDURES

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

13.1 Institutional and Ethics Review

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

13.2 Data Monitoring Committee

The specific responsibilities of the DSMB are described in the DSMB Charter, which is maintained as a separate document.

An independent DSMB appointed by the Sponsor will review the protocol and will thereafter provide medical and ethical guidance related to the conduct of this study. The DSMB will also review data on an ad hoc basis to assist in determining if AEs should preclude continued treatment with alglucosidase alfa. The DSMB will review study information as outlined in the DSMB Charter. 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 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 Sponsor's Chief Medical Officer and GPE Global Safety Officer, taking into consideration the DSMB opinion (as applicable).

13.3 Allergic Reaction Review

IARs and other events which could require consultation of allergist/ immunologist will be reviewed by an immunologist.

Should any major safety issues arise, final decisions regarding the study will be made by the Sponsor's Chief Medical Officer and Global Safety Officer, taking into consideration the immunologist opinion (as applicable).

13.4 Changes to the Conduct of the Study or Protocol

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

13.5 Investigator's Responsibilities

Refer to the SOM for further details regarding the Investigator's responsibilities as outlined in the sections below.

13.5.1 Patient Informed Consent

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

Inclusion of children in this study is justifiable on the grounds that the consent process is expected to enable the patient's legal guardian(s) to adequately assess the potential risks of study participation to this population.

13.5.2 Case Report Forms

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

Data will be entered by the site onto the eCRFs in the EDC system. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

Applicable laboratory data will be uploaded separately into the database.

13.5.3 Record Retention

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

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

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

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

13.5.4 Monitoring

A representative of the Sponsor or its designee will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Non-compliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, as necessary. It is the responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

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

13.5.5 Study or Site Termination

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

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

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

13.5.6 Investigational Product Control

13.5.6.1 Receipt of Investigational Product

Upon receipt, the study site person responsible for products management (eg, Investigator/Pharmacist, or a designee) should unpack the shipping box as soon as possible, check the temperature during shipment by examination of the temperature monitoring device, and store products according to the storage requirements.

At the time of the shipment receipt, the Acknowledgement of Receipt (AoR) on the shipping form (ie, Investigational Shipping Order 2 or equivalent) must be completed and signed. The AoR must be sent back to Sponsor in the case of a manual process without interactive response technology (IRT), or filed at the site level when IRT is used. In all cases, the product inventory log and center inventory form must be completed.

13.5.6.2 Disposition of Unused Investigational Product

Products can be destroyed for many reasons, including, but not limited to, expired batch, study completion, project stopped, obsolete labelling, used products, or if rejected due to quality considerations. No destruction will take place without the Sponsor's written authorization. Storage conditions must be maintained until approval of the Sponsor to remove the products.

Whenever possible, it is preferred to destroy the products at the Investigator's site per institutional procedures. A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy IMP unless the Sponsor provides written authorization.

When products cannot be destroyed at site, they will be sent back to the Sponsor. Storage conditions must be maintained until approval of the Sponsor to remove the product from its storage location (eg, refrigerator).

13.5.6.3 Product Handling and Complaints Reporting

Any issues related to the products must be reported to the Sponsor within 24 hours. For any complaints, a complaint form must be completed by the CRA or site staff. Once completed, the complaint form will be sent to Sanofi R&D Complaint Officer (preferably by e-mail). The form should not be handwritten.

Additional details can be found in the Pharmacy Manual.

13.5.7 Disclosure of Data

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

13.5.8 Clinical Study Report

A final clinical study report will be produced after study completion.

A Coordinating Investigator will be designated to review and sign the completed clinical study report. The Coordinating Investigator will be the individual first to enroll the largest number of patients.

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15 APPENDICES

15.1 Appendix A: Schedule(s) of Study Events

Written informed consent must be obtained prior to any protocol-required procedure.

	Screening	Treatment	Follow Up[a]
	Visit 1	**Visit 2**	**Call**
	(2 days to 4 weeks)	Day 1	Week 4 (≥30 days)
Obtain Informed Consent	X		
Confirm Study Eligibility	X	X	
Demographics, Baseline Characteristics, Medical/Surgical History and Pompe Disease History	X		
Urine Pregnancy Test[b]	X		
Physical Examination	X		
Weight	X		
Electrocardiogram (ECG)		X	
Serum Chemistry, Hematology, and Urinalysis	X		
IgG and Inhibitory/Neutralizing Antibodies in IgG Positive Patients		X	
Pharmacokinetic Sampling		X[c]	
Vital Signs		X[d]	
Infusion		X	
AE Assessment	Continuous Monitoring		
Concomitant Medications/Therapies	Continuous Monitoring		

[a] The follow-up call represents the last contact for the patient to conduct safety follow up and should occur at least 30 days after the patient's administration of investigational product.

[b] For female patients of child bearing potential only.

[c] Pharmacokinetic sampling schedule: pre-dose (prior to infusion); immediately (within a few minutes) before the infusion rate changes from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr; immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after end of infusion. In case of IAR, IAR(s) should be appropriately managed and PK sample has to be collected before any first time increase in infusion rate from 1 to 3 mg/kg/hr, from 3 to 5 mg/kg/hr, and from 5 to 7 mg/kg/hr achieved during administration of the remaining dose, immediately before the end of infusion; and at 1, 2, 4, 8, 12, and 24 hours after end of infusion.

[d] Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be taken immediately prior to infusion and immediately prior to any infusion rate change, as well as after completion of the post-infusion observation period.

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ELECTRONIC SIGNATURES

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