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STATISTICAL ANALYSIS PLAN

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)

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TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN **1**

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **5**

1 OVERVIEW AND INVESTIGATIONAL PLAN **6**

1.1 STUDY DESIGN AND RANDOMIZATION 6

1.2 OBJECTIVES 6

1.2.1 Primary objectives 6

1.2.2 Secondary objectives 6

1.3 DETERMINATION OF SAMPLE SIZE 6

1.4 STUDY PLAN 6

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL 8

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN 8

2 STATISTICAL AND ANALYTICAL PROCEDURES **9**

2.1 ANALYSIS ENDPOINTS 9

2.1.1 Demographic and baseline characteristics 9

2.1.2 Prior or concomitant medications 10

2.1.3 Efficacy endpoints 10

2.1.3.1 Primary efficacy endpoint(s) 10

2.1.3.2 Secondary efficacy endpoint(s) 10

2.1.4 Safety endpoints 10

2.1.4.1 Adverse events variables 11

2.1.4.2 Deaths 11

2.1.4.3 Laboratory safety variables 12

2.1.4.4 Vital signs variables 12

2.1.4.5 Electrocardiogram variables 12

2.1.4.6 Other safety endpoints 12

2.1.5 Pharmacokinetic variables 14

2.1.6 Pharmacodynamic/genomics endpoints 15

2.1.7 Quality-of-life endpoints 15

2.1.8 Health economic endpoints 15

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study 15

2.2 DISPOSITION OF PATIENTS 15

2.2.1 Randomization and drug dispensing irregularities 15

2.3 ANALYSIS POPULATIONS 15

2.3.1 Efficacy populations 15

2.3.2 Safety population 16

2.3.3 Pharmacokinetic population 16

2.4 STATISTICAL METHODS 16

2.4.1 Demographics and baseline characteristics 16

2.4.2 Prior or concomitant medications/therapies 16

2.4.3 Extent of investigational medicinal product exposure and compliance 16

2.4.4 Analyses of efficacy endpoints 17
2.4.4.1 Analysis of primary efficacy endpoint(s) 17
2.4.4.2 Analyses of secondary efficacy endpoints 17
2.4.4.3 Multiplicity issues 17
2.4.4.4 Additional efficacy analysis(es) 17

2.4.5 Analyses of safety data 17
2.4.5.1 Analyses of adverse events 17
2.4.5.2 Deaths 18
2.4.5.3 Analyses of laboratory variables 18
2.4.5.4 Analyses of vital sign variables 18
2.4.5.5 Analyses of electrocardiogram variables 18
2.4.5.6 Analyses of other safety endpoints 19

2.4.6 Analyses of pharmacokinetic variables 19

2.4.7 Analysis of pharmacokinetics and immunogenicity 19

2.4.8 Analyses of quality of life/health economics variables 19

2.5 DATA HANDLING CONVENTIONS 20

2.5.1 General conventions 20

2.5.2 Data handling conventions for secondary efficacy variables 20

2.5.3 Missing data 20

2.5.4 Windows for time points 21

2.5.5 Unscheduled visits 21

2.5.6 Pooling of centers for statistical analyses 21

2.5.7 Statistical technical issues 21

3 INTERIM ANALYSIS 22

4 DATABASE LOCK 23

5 SOFTWARE DOCUMENTATION 24

6 REFERENCES 25

7 LIST OF APPENDICES 26

APPENDIX A POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA 27

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse events
AUCinf:	area under the concentration-time curve from time 0 and extrapolated to infinite time
AUClast:	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
CL:	total systemic clearance
Cmax:	the maximum observed concentration
DSMB:	data and safety monitoring board
ECG:	electrocardiogram
eCRF:	electronic case report form
GAA:	acid α-glucosidase
HLT:	high-level term
IARs:	infusion-associated reactions, infusion-associated reactions
IgE:	immunoglobulin E
IgG:	immunoglobulin G
IMP:	investigational medicinal product
IV:	intravenous
MedDRA:	Medical Dictionary for Regulatory Activities
PCSA:	potentially clinically significant abnormalities
PK:	pharmacokinetic
PT:	preferred term, preferred term
rhGAA:	recombinant human acid á-glucosidase, recombinant human acid α-glucosidase
SOC:	System Organ Class
SOM:	Study Operations Manual
T1/2:	terminal elimination half-life
TEAE:	treatment-emergent adverse events
Tmax:	the actual sampling time to reach maximum observed concentration
Vd:	volume of distribution

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

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. Eligible patients will receive one intravenous (IV) infusion of alglucosidase alfa of 20 mg/kg of body weight.

This is a single arm study, no randomization will be performed.

1.2 OBJECTIVES

1.2.1 Primary 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.

1.2.2 Secondary objectives

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.

1.3 DETERMINATION OF 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.

1.4 STUDY PLAN

Eligible 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 infusion-associated reactions (IARs), until a maximum rate of approximately 7 mg/kg/hr is reached.

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 IARs.

Table 1 - 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.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the patient's administration of investigational product.

All baseline safety parameters are presented along with the on-treatment summary statistics in the safety section (Section 2.4.5).

Demographic characteristics

Demographic variables are gender (Male, Female), race (American Indi-an or Alaska Native; Asian; Black; Native Hawaiian or Other Pacific Islander; White; Not Reported; Unknown), age in years and ethnicity (Hispanic or Latino; Non-Hispanic or Non-Latino).

Medical or surgical history, physical examination

Medical (or surgical) history includes medical history at Screening of past and/or concomitant diseases or past surgeries.

Abnormal physical examination findings reported by the investigators will be tabulated in data listings in detail.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease history includes

- Date of First Symptoms of Pompe Disease.
- Date of Diagnosis of Pompe Disease.
- Duration of treatment on Myozyme (months).
- Pompe Disease cardiovascular, ENT, gastrointestinal, respiratory, and muscular characteristics.
- GAA Gene Mutation.

Any technical details related to computation, dates, and imputation for missing dates is described in Section 2.5.

2.1.2 Prior or concomitant medications

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 electronic case report form (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.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior (30 days before baseline evaluation) to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the time when IMP is administrated to study completion or termination. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment period (as defined in the observation period in Section 2.1.4).

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Not applicable.

2.1.3.1 Primary efficacy endpoint(s)

Not applicable.

2.1.3.2 Secondary efficacy endpoint(s)

Not applicable.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG, etc.

Observation period

The observation period will be divided into 2 epochs:

- The **prior treatment** epoch is defined as the time from the signed informed consent date up to IMP administration.
- The **after treatment** epoch is defined as the time from the IMP administration to study completion or termination.

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with prespecified monitoring).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious after treatment.

All adverse events (including serious adverse events and adverse events with prespecified monitoring) will be coded to a preferred term (PT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The occurrence of adverse events (including serious adverse events and adverse events with prespecified monitoring) is recorded from the time of signed informed consent until the end of the study. Information including a concise description of the event: date and time of event onset and date and time of resolution, determination of seriousness (Yes, No), determination of IAR (Yes, No), severity (Mild, Moderate, Severe), outcome (Fatal, Not Recovered/Not Resolved, Recovering/Resolving, Recovered/Resolved, Recovered with Sequelae/Resolved with Sequelae, Unknown), relationship to treatment (Not Related, Unlikely Related, Possibly Related, Related), action taken regarding treatment (Dose Increased, Dose Not Changed, Dose Reduced, Drug Interrupted, Drug Withdrawn, Not Applicable, Unknown), and other action taken (None, Medication, Non-drug therapy, Hospitalized) is recorded.

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.

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.

2.1.4.2 Deaths

Death is recorded on the eCRF as an outcome of the AE(s) that resulted in death. In addition, the date of death, cause of death, whether an autopsy was performed, and if yes, autopsy results are also recorded on the eCRF.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at screening visit unless otherwise specified. The laboratory parameters will be classified as follows:

- 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

2.1.4.4 Vital signs variables

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be measured at Visit 2 specified in Table 1. 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 time points after the start of infusion).

2.1.4.5 Electrocardiogram variables

A standard 12-lead electrocardiogram (ECG) will be conducted at Visit 2 as specified in Table 1. 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 protocol (1) 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.

2.1.4.6 Other safety endpoints

2.1.4.6.1 Routine Anti-rhGAA IgG Antibody Testing

Serum samples for anti-rhGAA IgG antibody testing will be obtained pre-infusion at the time specified in Table 1.

2.1.4.6.2 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.

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

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 in Sections 2.1.4.6.3.1 through 2.1.4.6.3.3.

2.1.4.6.3.1 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.

2.1.4.6.3.2 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.

2.1.4.6.3.3 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.

2.1.4.6.3.4 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.

2.1.4.6.4 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. 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.

2.1.5 Pharmacokinetic variables

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.

Actual dosing and sampling timepoints must be recorded for all days when blood sampling for pharmacokinetics occurs.

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
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration

If data permit,

AUC	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
Vd	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.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

Not applicable.

2.1.8 Health economic endpoints

Not applicable.

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Healthcare provider will decide what treatment patient will continue to receive after the end of the study (standard of care therapy).

2.2 DISPOSITION OF PATIENTS

Enrolled patients are defined as patients who met the inclusion/exclusion criteria and signed the informed consent.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a summary table:

- Screened patients.
- Treated patients.
- Patients who did not complete the study treatment as per protocol by main reasons.

For all categories of patients (except for the screened patients) percentages will be calculated using the number of enrolled patients as the denominator.

2.2.1 Randomization and drug dispensing irregularities

Not applicable.

2.3 ANALYSIS POPULATIONS

Full Analysis Set: will consist of all patients who received any amount of alglucosidase alfa.

2.3.1 Efficacy populations

Not applicable.

2.3.2 Safety population

Same as full analysis set.

2.3.3 Pharmacokinetic population

Same as full analysis set.

2.4 STATISTICAL METHODS

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 frequencies and percentages and/or shift tables for the categorical variables. No formal inferential statistical tests will be performed.

2.4.1 Demographics and baseline characteristics

Demographic and baseline variables will be presented in patient listings. Summary statistics will be presented for the following variables: age (years), years (since first symptoms of pompe), years (since diagnosis of pompe), Acid α-glucosidase (GAA) gene mutations, gender, ethnicity/race, weight (kg), height (cm) at baseline.

2.4.2 Prior or concomitant medications/therapies

All medications and therapies reported by the patients during the 30-day period prior to the baseline evaluation visit and during the course of the study will be included in the analysis. Concomitant medications/therapies will be listed by patient. Summary tables giving the frequencies and percentages of the concomitant medications used will be provided.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior/concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The actual dose sequence and cumulative dose received over study period will be presented in the patient listing. The cumulative doses will also be summarized within the full analysis set. Compliance to the treatment regimen will be described and summarized in terms of the percentage of scheduled infusions the patient receives.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Not applicable.

2.4.4.2 Analyses of secondary efficacy endpoints

Not applicable.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.4.4 Additional efficacy analysis(es)

Not applicable.

2.4.5 Analyses of safety data

All safety analyses will be conducted on the Full Analysis Set.

2.4.5.1 Analyses of adverse events

The table of all treatment-emergent adverse events will be presented by System Organ Class (SOC) and Preferred Term (PT) sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase.

Analysis of all treatment-emergent adverse events (TEAE)

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any:
  - Treatment-emergent adverse event,
  - Serious treatment-emergent adverse event,
  - Treatment-emergent adverse event leading to death,
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.

- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

2.4.5.2 Deaths

All deaths reported in the study will be presented as a listing, indicating the date of death, cause of death, whether an autopsy was performed and if yes, autopsy results. Also, any AEs leading to death will be listed.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment by age group.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and age group.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by age group.

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment by age group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by age group.

2.4.5.6 Analyses of other safety endpoints

Anti-rhGAA IgG Antibody, 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.

Infusion associated reactions

Summary table of IARs by SOC and PT will be presented. A detailed listing of patients who experience IARs including information on severity, relationship to treatment, timing from first infusion to the onset of the IAR, action taken regarding study treatment, other action taken, and patient outcome, will be provided.

2.4.6 Analyses of pharmacokinetic variables

Alglucosidase alfa concentration values below the plasma assay limit will be treated as zero in calculating mean values. Mean values below LLOQ will be reported as LLOQ in the tables and not plotted in the figures if after $C_{max.}$

Plasma concentrations and pharmacokinetic parameters will be summarized by arithmetic mean, geometric mean, standard deviation, coefficient of variation (CV (%)), minimum, median, maximum, and number of observations by age groups and study visits (if applicable).

2.4.7 Analysis of pharmacokinetics and immunogenicity

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 PK parameters for Day 1.

The relationship between anti-rhGAA antibody titers and the PK of alglucosidase alfa will be presented by summary of the assessed PK parameters grouped by anti-rhGAA antibody negative subjects, anti-rhGAA antibody positive subjects and anti-rhGAA antibody positive subjects with IgG inhibitory/neutralizing antibodies to alglucosidase alfa.

If data allows, anti-rhGAA antibody titers will be plotted against the assessed PK parameters.'

2.4.8 Analyses of quality of life/health economics variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age in years at signing of informed consent = integer part of ((date of informed consent – date of birth)/365.25).

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

Not applicable.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the IMP administration is missing, all adverse events should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

"Unknown" will be combined with "Severe" in the summary table.

Handling of potentially clinically significant abnormalities (PCSA)

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

Not applicable.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries, but will be used for computation of baseline. Worst values will be chosen as baseline.

2.5.6 Pooling of centers for statistical analyses

No pooling is planned.

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analyses are planned.

4 DATABASE LOCK

The database is planned to be locked at 6 weeks after last patient's follow up call.

5 SOFTWARE DOCUMENTATION

All analyses will be generated using Statistical Analysis Software (SAS, most current version at the time of analysis).

6 REFERENCES

1. Clinical Study Protocol: AGLU07710/MSC12790-amended-protocol3, June 2016

2. Sanofi Research and Development Quality Document. Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report.Version 3.2014.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix A Potentially clinically significant abnormalities criteria

Table 2 - PCSA abnormalities (2)

Parameter	PCSA Category (Adults)	PCSA Category (Pediatric)
Clinical Chemistry		
ALT	>3 ULN >5 ULN >10 ULN >20 ULN	≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN
AST	>3 ULN >5 ULN >10 ULN >20 ULN	≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN
Alkaline Phosphatase	>1.5 ULN	≥1.5 ULN
Total Bilirubin	>1.5 ULN >2 ULN	≥1.3 ULN
Conjugated Bilirubin	>35% Total Bilirubin and Total Bilirubin >1.5 ULN	>35% Total Bilirubin and Total Bilirubin >1.3 ULN
ALT and Total Bilirubin	ALT >3 ULN and Total Bilirubin >2 ULN	ALT ≥3 ULN and Total Bilirubin ≥2 ULN
CPK	>3 ULN >10 ULN	≥3 ULN
Creatinine	≥150 µmol/L (Adults) ≥30% increase from baseline ≥100% increase from baseline	Birth/0 to 6 years old (Neonates, infants, children): >53 µmol/L or 0.6 mg/dL 6 years to <12 years old (children): ≥90 µmol/L or 1.1 mg/dL 12 years to 16/18 years old (adolescents) ≥132 µmol/L or 1.5 mg/dL
Blood urea nitrogen	≥17 mmol/L	28 days/1 month to 16 18 years old (infants, children, adolescents): ≥6.4mmol/L or 18 mg/dL
Chloride	<80 mmol/L >115 mmol/L	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L

Parameter	PCSA Category (Adults)	PCSA Category (Pediatric)
Sodium	≤129 mmol/L ≥160 mmol/L	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L
Potassium	<3 mmol/L ≥5.5 mmol/L	24 months/2 years to 16/18 years old (children, adolescents): ≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L
Glucose	Hypoglycemia: ≤3.9 mmol/L and < LLN Hyperglycemia: ≥11.1 mmol/L (unfasted), ≥7 mmol/L (fasted)	Hypoglycaemia: <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast; ≥10.0 mmol/L or 180 mg/dL (unfasted)
Hematology		
WBC	<3.0 GIGA/L (non-Black), <2.0 GIGA/L (Black) ≥16.0 GIGA/L	24 months/2 years to <6 years old: <3.0 GIGA/L or 3000/mm^3 >16.0 GIGA/L or 16000/mm^3 6 to <12 years old: <5.0 GIGA/L or 5000 /mm^3 >17.0 GIGA/L or 17000 /mm^3 12 to 16/18 years old: <4.5 GIGA/L or 5000 /mm^3 >13.5 GIGA/L or 17000 /mm^3
Lymphocytes	> 4.0 GIGA/L	24 months/2 years to <6 years old: <1.0 GIGA/L or 1000/mm^3 >9.5 GIGA/L or 9500/mm^3 6 to <12 years old: <1.0 GIGA/L or 1000/mm^3 >8.0 GIGA/L or 8000/mm^3 12 to 16/18 years old: <0.6 GIGA/L or 600/mm^3 >6.0 GIGA/L or 6000/mm^3
Neutrophils	<1.5 GIGA/L (non-Black), <1.0 GIGA/L (Black)	24 months/2 years to <6 years old: <1.2 GIGA/L or 1200/mm^3 >1 ULN 6 to <12 years old: <1.2 GIGA/L or 1200/mm^3 >1 ULN 12 to 16/18 years old: <1.2 GIGA/L or 1200/mm^3 >1 ULN
Eosinophils	>0.5 GIGA/L or > ULN if ULN ≥0.5 GIGA/L	>0.5 GIGA/L or 500/mm^3, or > ULN if ULN >0.5 GIGA/L or 500/mm^3

Parameter	PCSA Category (Adults)	PCSA Category (Pediatric)
Hemoglobin	Males: ≤115 g/L, ≥185 g/L Female: ≤95 g/L, ≥165 g/L Decrease from baseline: 20 g/L	24 months/2 years to 16/18 years old: <1.55 mmol/L or 10.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL
Hematocrit	Male: ≤0.37 v/v, ≥0.55 v/v Female: ≤0.32 v/v, ≥0.5 v/v	24 months/2 years to 16/18 years old: <0.32 l/l or 32% >0.47 l/l or 47%
Platelets	<100 GIGA/L ≥700 GIGA/L	<100 GIGA/L or 100000/mm^3 >700 GIGA/L or 700000/mm^3
ECG		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	24 months/2 years to <6 years old: ≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm 6 to <12 years old: ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm 12 to 16/18 years old: ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
PR	≥200 ms and increase from baseline ≥25%	24 months/2 years to <6 years old: ≥160 ms 6 to <12 years old: ≥170 ms 12 to 16/18 years old: ≥180 ms
QRS	≥120 ms	2 to <6 years old: ≥95 ms 6 to <12 years old: ≥100 ms 12 to 16/18 years old: ≥110 ms

Parameter	PCSA Category (Adults)	PCSA Category (Pediatric)
QTc	Absolute values (ms) >450 ms, >480 ms, >500 ms Increase from baseline 30-60 ms, >60 ms	Birth/0 to <12 years old: Absolute values: Borderline: 431-450 ms, Prolonged: >450 ms, Additional: ≥500 ms Increase from baseline: Borderline: increase from baseline 30-60 ms Prolonged: increase from baseline >60 ms 12 to 16/18 years old: Absolute values: Borderline: 431-450 ms (Boys), 451-470 ms (Girls); Prolonged: >450 ms (Boys), >470 ms (Girls); Additional: ≥500 ms AND Increase from baseline: Borderline: increase from baseline 30-60 ms Prolonged: increase from baseline >60 ms
Vital signs		
Systolic BP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	24 months/2 years to <6 years old: ≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old: ≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old: ≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg
Diastolic BP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	24 months/2 years to <6 years old: ≤34 mmHg and decrease from baseline ≥20 mmHg ≥59 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old: ≤48 mmHg and decrease from baseline ≥20 mmHg ≥72 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old: ≤54 mmHg and decrease from baseline ≥20 mmHg ≥78 mmHg and increase from baseline ≥20 mmHg

MSC12790 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

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