STATISTICAL ANALYSIS PLAN

Protocol title:	**A Long-term Study to Evaluate Growth and Development Outcomes in Patients with Infantile-Onset Pompe Disease Who Are Receiving Alglucosidase Alfa**
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Compound number (INN/Trademark):	**GZ419829/LTS12869 ([alglucosidase alfa] Myozyme® / Lumizyme®)**
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VERSION HISTORY

This amended statistical analysis plan (SAP) for study AGLU03606 is based on the amended protocol dated 02 December 2014. This section summarizes the major changes to the statistical analysis features in the SAP. The first patient was treated on 26-Aug-2008.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	01-Mar-2017	Not Applicable	Original version
2.0	27-Sep-2021	• Added potential IAR by algorithm definitions • Clarified specific SMQs used for analysis • Added Hex4 and IgG analysis windows • Removed summary tables and by-visit plots for efficacy endpoints • Clarified that repeated measures longitudinal analysis will not be performed • Added percentiles and the possibility of using WHO growth charts for patients <24 months old in the analyses for physical growth • Updated immunogenicity analyses to be better aligned with current classifications	To clarify and update analysis methods, provide analysis windows, and be better aligned with other Pompe studies

1 INTRODUCTION

1.1 STUDY DESIGN

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

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.

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

Eligible patients will receive an intravenous infusion of alglucosidase alfa at a dose of 20 mg/kg body weight every 2 weeks. If clinically feasible, all patients will continue at the same dose throughout the study. Any modification to the dose and/or frequency of dosing is not permitted unless it is due to disease progression or to an adverse event (AE), in which case it is not a protocol deviation, but the Investigator must consult with the Sponsor's Medical Monitor and Global Safety Officer in the event of a dose change. Patients must have a confirmed diagnosis of Pompe disease as determined by deficient endogenous GAA activity or GAA mutation analysis.

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

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

Safety will be evaluated in terms of AE monitoring, laboratory tests (clinical chemistry, hematology, and urinalysis), anti-rhGAA antibody (IgG) formation, neuroimaging (at the discretion of the Investigator), vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations (PE), electrocardiograms (ECGs), hearing testing, and visual screening.

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

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• to evaluate long-term growth and development of patients with infantile-onset Pompe disease who begin treatment with alglucosidase alfa before 1 year of age.	• Physical growth as assessed by recumbent height/length, weight, and head circumference • Motor development and function as measured by changes in the motor subscale of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), Gross Motor Function Measure (GMFM-88), and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI). • Cognitive development as measured by the cognitive and language subscales of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), change in the Brief IQ score of the Leiter International Performance Scale - Revised (Leiter-R), and/or the change in the Nonverbal IQ score of the Leiter International Performance Scale - 3rd Edition (Leiter-3) (starting at the final assessment of the Bayley-III before 42 months of age).

Objectives	Endpoints
Secondary	
• to collect long-term safety data on patients with infantile-onset Pompe disease.	• reported adverse events, laboratory tests (clinical chemistry, hematology, and urinalysis), anti-rhGAA antibody (IgG) formation, neuroimaging (at the discretion of the Investigator), vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations (PE), electrocardiograms (ECGs), hearing testing, and visual screening.
Tertiary/exploratory	
• To evaluate effect of alglucosidase alfa treatment on urinary oligosaccharides (Hex4)	• Oligosaccharide levels in urine as measured by a central laboratory.

2 SAMPLE SIZE DETERMINATION

No formal statistical sample size calculation was performed. The number of patients followed in this study will not be limited prospectively.

3 ANALYSIS POPULATIONS

The following population for analyses is defined:

Table 3 - Populations for analyses

Population	Description
Full Analysis Set (FAS)	All enrolled patients who receive at least one infusion (complete or partial) of alglucosidase alfa. This study population will be used for all analyses (efficacy and safety), unless otherwise specified.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the counts and percentages of patients.

The baseline value is defined as the value measured at the Screening/Baseline visit prior to the first infusion during this study. In cases where a patient has more than one value measured during Screening/Baseline, the latest value will be the one used as baseline.

Unless otherwise specified, analyses will be performed for Full Analysis Set (FAS).

Observation period

The observation period will be divided into 2 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration (ie, when the patients started receiving the alglucosidase alfa in the study, even if the patient had received alglucosidase alfa prior to entering the study).
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration in the study to the last study assessment.

The on-study period is defined as the time from the signing of the informed consent until the end of the study (defined as the completion date or the discontinuation date collected on the case report form (CRF) page “Completion/Discontinuation”.

4.2 PATIENT DISPOSITIONS

The number (%) of patients included in the analysis population listed in Table 3 will be summarized.

The number (%) of patients in the following categories will be provided:

- Screened patients
- Enrolled patients
- Enrolled and treated patients
- Patients who completed the study period as per protocol
- Patients who did not complete the study period as per protocol and main reason for study discontinuation
- Patient status at last study contact (alive, deceased)

A listing will be provided with completion/discontinuation dates, study duration (days), and all discontinuation reasons.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled population.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

Physical growth

The endpoints for physical growth are defined as changes from baseline to study time points in recumbent height/length, weight, and head circumference. Changes in Z-scores (standardized age and gender adjusted values) for height/length, weight, and head circumference based on Center for Disease Control (CDC) Growth Charts will also be calculated. Refer to protocol Section 9.2.1 for the details of measurement. Also refer to Section 5.2 for the rationale to incorporate World Health Organization (WHO) growth charts for children <24 months of age.

Motor development

Motor development and function is measured by changes in the motor subscale of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), Gross Motor Function Measure (GMFM-88), and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI). Change from baseline to study time points will be calculated for the following parameters:

- Bayley-III: raw scores, scaled scores, and composite scores reported for each of the 3 administered scales (cognitive, language, and motor) for patients from 1 month to 42 months of age.
  - The Language scale includes the Receptive and Expressive subtests
  - The Motor scale includes the Fine Motor and Gross Motor subtests
- GMFM-88: total raw score, total score (average of dimension percentage scores) and dimension scores of 5 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping). GMFM-88 summary score will be calculated as described in protocol Section 9.2.2.3.
- Pompe PEDI: scores (raw, scaled, normative standard) by scale (functional skills, caregiver assistance) and domain (self-care, mobility, social function)

Refer to protocol Section 9.2.2 for the definitions and measurement details of Bayley-III, GMFM-88 and Pompe PEDI.

Cognitive function

Cognitive function is measured by the cognitive and language subscales of the Bayley Scales of Infant and Toddler Development (Bayley-III) (up to 42 months of age), change in the Brief IQ score of the Leiter International Performance Scale - Revised (Leiter-R) and/or the change in the Nonverbal IQ score of the Leiter International Performance Scale - 3rd Edition (Leiter-3) (starting at the final assessment of the Bayley-III before 42 months of age). Change from baseline to study timepoints in the raw and scaled scores for the 4 subtests will be calculated. Refer to protocol Section 9.2.2 for the definitions and measurement details of Bayley-III, Leiter-R, and Leiter-3.

During the study, the Leiter-R was replaced with the updated Leiter-3. Patients that had previously been evaluated with the Leiter-R had a concurrent assessment with the Leiter-3 before transitioning to the Leiter-3 throughout the study in order to monitor impact of tool differences on change in scores. For these patients, multiple Leiter assessments at the transition study visit will be reported.

Pompe PEDI, Bayley-III, Leiter-R, and Leiter-3 will be centrally scored by an external consultant.

All efficacy assessments collected during the study will be used, including any obtained after IMP discontinuation.

4.3.2 Main analytical approach

All data collected will be presented in the form of individual patient listings. Relevant plots of efficacy endpoints by patient age over time will be provided.

4.3.3 Sensitivity analysis

Not applicable.

4.3.4 Supplementary analyses

Not applicable.

4.3.5 Subgroup analyses

Due to the small number of patient population, subgroup analyses will not be performed.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

See Section 4.7 Safety Analysis.

4.4.1 Key/Confirmatory secondary endpoint(s)

Not appliable.

4.4.1.1 Definition of endpoint(s)

Not applicable.

4.4.1.2 Main analytical approach

Not applicable.

4.4.2 Supportive secondary endpoint(s)

Not applicable.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Urinary oligosaccharide (Hex4) levels will be measured by a central laboratory every 6 months to study month 24 and then every 12 months after that.

4.5.2 Main analytical approach

Nominal and change from baseline will be summarized by visit.

4.6 MULTIPLICITY ISSUES

There is no issue with multiplicity.

4.7 SAFETY ANALYSES

All safety analyses will be performed on the FAS population as defined in Section 3; unless otherwise specified, safety analyses will be descriptive, and no testing is planned.

4.7.1 Extent of exposure

Duration on study drug and number of study drug infusions will be presented using summary statistics. Frequency and percentages of patients who receive therapy up to certain time intervals and until the end of study will also be presented.

The extent of IMP exposure and compliance will be assessed by the duration of IMP exposure, total dose received at each study visit, cumulative dose received during the study period, and percentages of planned infusions received.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date - first IMP administration date +14, regardless of intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: missing duration, <26 weeks, 26 to <52 weeks, 52 to <78 weeks, 78 to <104 weeks, 104 to <130 weeks, 130 to <156 weeks, 156 to <208 weeks, 208 to <260 weeks, 260 to <312 weeks, 312 to <364 weeks, 364 to <416 weeks, 416 to <468 weeks, ≥468 weeks.

Additionally, the total dose received at each study visit and cumulative duration of treatment exposure over the study period for each patient will be provided in a listing.

Treatment compliance

Compliance to the treatment regimen will be described in terms of the percentage of scheduled infusions the patient receives through the treatment period.

Percentage of treatment compliance for a patient will be defined as 100 x (Total number of infusions received by a patient from Day 0 to the end of the treatment period or withdrawal) / (Target total number of expected infusions).

Treatment compliance will be summarized quantitatively and categorically: 100%, 85% to <100%, 70% to <85%, 50% to <70%, >0% and <50%.

4.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 2 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened, or became serious during the treatment-emergent period

Deaths during the study period will be provided in a listing.

The primary focus of AE reporting will be on TEAEs. Pre-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to categorize it as a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]

a Sorting will be based on the overall number of patients.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with event count and number (%) of patients will be generated:

- Any AE
- Any TEAE
  - TEAE related to the study drug
  - TEAE unrelated to the study drug
- TEAEs by severity (mild, moderate, severe)
- TEAEs by gender
- Any treatment emergent SAE
- Any treatment emergent SAE considered related to study drug
- Any protocol-defined infusion-associated reactions
- Any TEAE leading to treatment adjusted
- Any TEAE leading to treatment interrupted
- Any TEAE leading to permanent intervention discontinuation
- TEAE leading to death

The AE summaries of Table 5 will be generated with event count and number (%) of patients experiencing at least one event.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAEs	Primary SOC and PT
TEAEs related to IMP	Primary SOC and PT
TEAEs by maximal severity	Primary SOC and PT
Related TEAEs by maximal severity	Primary SOC and PT
Treatment emergent SAEs	Primary SOC and PT
Treatment emergent SAEs related to IMP	Primary SOC and PT
TEAEs leading to permanent intervention discontinuation	Primary SOC and PT
TEAEs leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pretreatment AE	Primary SOC and PT

Subgroup analysis

TEAEs stratified by the following categories will also be presented by primary SOC and PT:

- Status of high ADA response (with, without)
- Seroconversion status (negative, positive) and peak ADA categories for those who seroconverted

Analysis of deaths

A listing of patients who died during the study will be provided.

Analysis of infusion-associated reactions (IARs) and other AEs of interest

Protocol--defined IARs

Infusion-associated reactions (IARs) are defined as AEs that occur during the infusion or within up to 24 hours after the start of infusion and are considered as related or possibly related to the ERT by the Investigator or the Sponsor. At the discretion of the Investigator, AEs occurring ≥24 hours after the start of the infusion that are assessed as related may also be considered IARs.

Algorithm-defined IARs

An alternative definition of IAR which does not rely on the investigators' assessments of an AE's relationship to the treatment will also be employed. It includes potential IARs (all AEs occurring during an infusion or within 2 hours after the completion of an infusion; and all AEs occurring from >2 to 24 hours after the completion of an infusion).

Protocol-defined infusion-associated reactions and algorithm-defined potential IARs will be selected for analyses as indicated in Table 6. Number of events and number (%) of patients experiencing at least one event will be provided for each event of interest for the IARs. Tables will be sorted as indicated in Table 4.

Anaphylactic/hypersensitivity reactions and immune-mediated reactions

AEs for potential anaphylactic reactions, immune mediated reactions, and hypersensitivity reactions will be identified by respective standardized MedDRA queries (SMQ) (see Table 6). The results of the searches will be presented in listings. The most recent version of each MedDRA SMQ at the time of analysis will be used.

Table 6 - Selections for IARs and other TEAEs of interest

IARs and other TEAEs of interest	Selection
Protocol-defined IARs	e-CRF specific tick box on the AE page
Algorithm-defined potential IARs	all AEs occurring during an infusion or within 2 hours after the completion of an infusion; and all AEs occurring from >2 to 24 hours after the completion of an infusion
Potential anaphylactic reactions	MedDRA SMQ[b] of anaphylactic reactions
Potential immune mediated reactions	MedDRA SMQs[b] of Vasculitis and Severe cutaneous adverse reactions plus the Preferred Terms of glomerulonephritis, nephrotic syndrome, proteinuria, hematuria, vasculitis, serositis, myocarditis, skin lesion, skin necrosis, arthralgia, arthritis, myalgia, arthropathy, lymphadenopathy, serum sickness, type III immune complex mediated reaction, and influenza like illness[a]
Potential hypersensitivity reactions	MedDRA SMQ[b] of hypersensitivity

a The list of terms may be adjusted according to MedDRA version changes.
b The most recent version of each MedDRA SMQ at the time of analysis will be used.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs, physical examinations (PE), and electrocardiograms (ECGs)

The following laboratory variables, vital signs, physical examinations (PE), and electrocardiogram (ECG) variables will be analyzed.

- Hematology:
  - Complete blood count with differential
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine kinase (CK), creatine kinase MB (creatine kinase muscle, brain isoform [CK-MB]), creatine kinase MB/total creatine kinase
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate
  - Renal function: creatinine, blood urea nitrogen (BUN), uric acid (urate)
  - Liver function: alanine aminotransferase (ALT) [serum glutamic pyruvic transaminase (SGPT)], aspartate aminotransferase (AST) [serum glutamic oxaloacetic transaminase (SGOT)], alkaline phosphatase, total bilirubin

- Urinalysis:
  - Urinalysis for quantitative analysis: urine appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, and blood.
  - Microscopy will be performed if clinically indicated.
- Vital signs: heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature
- PE body systems: General Appearance, Skin, HEENT, Lymph Nodes, Heart, Lungs, Breasts, Abdomen, External Genitalia, Pelvic, Rectal, Extremities/Joints, Neurological, Mental Status examinations
- 12-lead ECG variables:
  - Intervals and measurements: heart rate, RR, PR, QRS duration, QRS axis, QT, QTc (Bazett and Fridericia correction)
  - Findings: sinus rhythm, LVH, RVH, conduction abnormalities

For summary tables, data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, while data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

Analyses of quantitative variables

For all laboratory variables and quantitative ECG variables (intervals and measurements) above, descriptive statistics for results and changes from baseline will be provided for each planned visit during the on-treatment period. Vital signs data will be provided in a listing.

PE findings

PE findings (normal, abnormal, not examined) for each body system will be presented in a listing.

Analyses of ECG findings

For ECG, the incidence of patients with at least one abnormal ECG during the treatment-emergent period will be summarized according to the following baseline status categories:

- Normal/missing
- Abnormal

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA criteria defined in Sanofi business and technical document BTD-009536, in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (whether local or central, scheduled, nonscheduled or repeated).

For laboratory variables, vital signs, and ECG variables (intervals and measurements) above, the incidence of patients with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level.

4.7.3.2 Neuroimaging Assessment

As described in protocol Section 9.3.1, serial brain MRIs will be conducted at the discretion of the Investigator as sedation for this procedure may be required for young patients and may pose an unacceptable risk in patients who have cardiopulmonary involvement. MRIs will be conducted according to standard procedures (specified in the study manual [SM]) at the times specified in protocol Table 9-1 in order to evaluate possible changes in brain structures over time.

Neuroimaging assessments will be presented in a listing.

4.7.3.3 Hearing Testing

As described in protocol Section 9.3.2, hearing will be assessed at the times specified in protocol Table 9-1 using an age-appropriate method of hearing assessment, as determined by the Investigator.

Hearing testing results will be presented in a listing.

4.7.3.4 Visual Screening

Ophthalmologic evaluation is to be performed by the Investigator in accordance with the guidelines described by the American Association of Pediatrics (AAP, 1996, Pediatrics). The type of visual screening will be determined by the patient's age at the time of the assessment. All patients will have an exam of the eye, test ocular motility and the red reflex exam. Patients 3 years of age and over will have the same assessments described previously plus a visual acuity test. Patients 4 years of age and over will have each of the previously described assessments plus fundoscopy.

Visual screening results will be presented in a listing.

4.8 OTHER ANALYSES

4.8.1 Immunogenicity analyses

Anti-rhGAA IgG Binding Antibody

Participant's ADA status, response variable, and kinetics of ADA responses (see definitions below) will be summarized for all patients with available ADA data.

Kinetics of ADA response

Kinetics of ADA response will be derived for patients ever ADA positive, whether with ADA already present at baseline or seroconverted during the study. Time to ADA onset (seroconversion) and time from seroconversion to first peak titer will be described with mean, SD, median, Q1, Q3, minimum, and maximum statistics.

- **Persistent ADA response** is defined as ADA positive at the last sample timepoint and meets one of the following two criteria:
  - ADA positive at two or more sampling time points post baseline, where the first and the last ADA-positive post-baseline samples (irrespective of any negative sample in between) are separated by at least 16 weeks; or
  - ADA positive at last two sampling time points, irrespective of the time in between.
- **High ADA response** is a subcategory of persistent ADA response and identifies a patient who was persistently seropositive positive, had a peak titer ≥12800, and was seropositive at final assessment.
- **Tolerized ADA response** is a subcategory of persistent ADA response and identifies a patient who was persistently seropositive, but seronegative at the final assessment.

The following definitions will also be used:

- **ADA peak titer** (highest ADA titer from first study infusion of alglucosidase alfa) for ever positive patients.
- **Time to ADA seroconversion from first alglucosidase alfa infusion in study**

  Time to seroconversion (days) from 1st alglucosidase alfa infusion in study will be calculated by (date of seroconversion - date of 1st alglucosidase alfa infusion in study + 1)
- **Time to first alglucosidase alfa ADA peak titer from seroconversion**

  Time to first peak titer (weeks) from seroconversion will be calculated by (date of first peak titer - date of seroconversion + 1) / 7
- **ADA peak titer category** (always negative, 100-800, 1600-6400, ≥12 800).
- **Last ADA titer** (final assessment after first study infusion of alglucosidase alfa) for ever positive patients.
- **ADA last titer category** (≤800, 1600-6400, ≥12 800).

Titer values will be presented using descriptive statistics (number, geometric mean [GM], geometric SD, median, Q1, Q3, minimum, and maximum, as well as by number and percentage in titer categories). ADA titer values over time for individual patients will also be presented graphically.

Please refer to Section 5.4.1 for the handling of ADA data.

Neutralizing ADA (inhibitory antibody) Status

Neutralizing ADA antibodies (NAbs that inhibit enzyme activity and NAbs that inhibit cellular uptake) measured during the study will be presented in a listing.

Additional Testing For Moderate or Severe IARs

Results of circulating immune complex, IgE antibody, serum tryptase, complement activation testing, and skin testing results will be presented in data listings.

4.8.2 Cross-reacting immunologic material (CRIM) status and GAA mutation analysis

CRIM status and GAA mutation are endpoints for research purposes only. (Refer to protocol Sections 9.2.4 and 9.2.5 for their definitions and measurement details.) The collected data will be displayed in a patient listing.

4.9 INTERIM ANALYSES

Not applicable. No interim analysis is planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
Bayley-III:	Bayley Scales of Infant and Toddler Development
BUN:	blood urea nitrogen
CDC:	Center for Disease Control
CK:	creatine kinase
CK-MB:	creatine kinase MB
ECG:	electrocardiogram
e-CRF:	electronic case report form
GM:	geometric mean
GMFM-88:	Gross Motor Function Measure
HEENT:	head, eyes, ears, nose, and throat
HLT:	high level term
IAR:	infusion-associated reaction
Leiter-3:	Leiter International Performance Scale - 3rd Edition
Leiter-R:	Leiter International Performance Scale - Revised
LLOQ:	lower limit of quantitation/detection limit
LLT:	lower-level term
LVH:	left ventricular hypertrophy
MedDRA:	medical dictionary for regulatory activities
NAb:	neutralizing antibody
PCSA:	potentially clinically significant abnormality
PE:	physical examinations
PEDI:	Pediatric Evaluation of Disability Inventory
PT:	preferred term
RVH:	right ventricular hypertrophy
SAP:	statistical analysis plan
SD:	standard deviation
SGOT:	serum glutamic oxaloacetic transaminase
SGPT:	serum glutamic pyruvic transaminase
SM:	study manual
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULOQ:	upper limit of quantification
WHO:	World Health Organization
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Regarding the calculation of z-scores for physical growth (recumbent length/height, weight, head circumference) the protocol referred to Center for Disease Control (CDC) Growth Charts. However, the CDC website recommended the World Health Organization (WHO) growth charts for children <24 months of age. If possible, we will incorporate this recommendation. In addition, percentiles of these measurements will be calculated as well.

It was planned to use longitudinal repeated measures modeling to analyze trends in key growth and development parameters over time; however, as out of the 12 patients enrolled 7 patients had withdrawn or died in less than 4 years, this analysis is not likely to be informative and will be omitted.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical/surgical history, alglucosidase alfa and Pompe disease history, and retrospective motor milestones

The following demographics and baseline characteristics, medical and surgical history, and disease characteristics at baseline will be summarized using descriptive statistics in the enrolled population.

Demographic and baseline characteristics:

- age (months) at signing of informed consent
- age group (Newborns [0-27 days], Infants and toddlers [28 days - 23 months], Children [2-11 years])
- age (months) at first alglucosidase alfa infusion*
- age (months) at Pompe diagnosis
- age (months) at first Pompe symptom
- time (months) from first Pompe symptom to first alglucosidase alfa infusion*
- time (months) from Pompe diagnosis to first alglucosidase alfa infusion*
- gender (Male, Female)
- race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- weight (kg, percentile) at treatment baseline
- recumbent length/height (cm, percentile) at treatment baseline
- BMI (kg/m^2)

- head circumference (cm, percentile) at treatment baseline
- CRIM status

*Note that patients may have received alglucosidase alfa prior to entering the study.

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical/surgical history (excluding those reported as part of the Pompe medical history) includes medical history according to body systems (infectious disease, allergic, metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, HEENT, breasts, respiratory, cardiovascular, gastrointestinal/hepatic, genitourinary/renal, neurologic, psychiatric/psychosocial). No coding will be done for medical/surgical history.

Alglucosidase alfa and Pompe disease history include the following:

- date of first symptoms of Pompe disease
- date of diagnosis of Pompe disease
- date of first alglucosidase alfa infusion
- eyes, ears, nose, and throat (enlarged tongue, chronic otitis media, tympanic membrane tube(s) placed, hearing loss, visual screening ever performed)
- respiratory (currently receiving ventilatory support, tracheostomy ever performed, pneumonia, sleep disturbances/apnea)
- cardiovascular (congestive heart failure, evidence of left ventricular hypertrophy, evidence of cardiac involvement [cardiomegaly], evidence of cardiac arrhythmia prior to receiving alglucosidase alfa)
- gastrointestinal and renal (hepatomegaly, failure to thrive, feeding difficulties, gastroesophageal reflux, currently fed by mouth, currently on nutritional support, renal insufficiency)
- musculoskeletal hypotonia, muscle weakness in upper extremities, muscle weakness in lower extremities, delayed motor milestones, regression of motor milestones, joint contractures)

Retrospective motor milestones assessed include the following (yes/no/unknown; if yes, date first noted):

- Holds head up
- Bear weight on legs
- Rolls
- Sits with support
- Sits without support
- Pulls to stand

- Walks with support
- Walks without support
- Runs
- Walks up steps
- Walks down steps

Prior or concomitant medications and therapies

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

- Prior medications and therapies (eg, tube feeds) are those the patient used prior to first IMP administration in the study (ie, alglucosidase alfa received prior to study entry will be counted as prior medication). Prior medications can be discontinued before first study administration or can be ongoing during the treatment period.
- Concomitant medications and therapies are any interventions received by the patient concomitantly to the IMP during the on-treatment period.
- A given medication can be classified as a prior medication and/or as a concomitant medication. If it cannot be determined whether a given medication was taken prior or concomitantly, it will be considered as both prior and concomitant medication.

The prior and concomitant medications will be summarized for the enrolled and exposed population by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence. In case of equal frequency, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 Derivations

The following formulas will be used for computation of parameters:

Age (months) at signing of informed consent = (date of informed consent - date of birth + 1)/30.4375

Age (months) at first alglucosidase alfa infusion = (date of first infusion - date of birth + 1)/30.4375

Age (months) at Pompe diagnosis = (date of Pompe diagnosis - date of birth + 1)/30.4375

Age (months) at first Pompe symptom = (date at first Pompe symptom - date of birth + 1)/30.4375

Time (months) from first Pompe symptom to first alglucosidase alfa infusion = (date at first infusion - date at first Pompe symptom + 1)/30.4375

Time (months) from Pompe diagnosis to first alglucosidase alfa infusion = (date at first infusion - date at Pompe diagnosis + 1)/30.4375

BMI = weight [kilograms] /(height [meters])^2

Computation of Z-scores (standardized age and gender adjusted values) and percentiles for height/length, weight, and head circumference will be according to Center for Disease Control (CDC) growth Charts(1) and World Health Organization (WHO) growth charts(2). The WHO growth charts are recommended for children <24 months of age.

5.4.2 Handling of lab data

Handling of potentially clinically significant abnormalities

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.

Handling of ADA titer with missing or non-numerical values

If the ADA titer is reported as "<value", then the limit value will be used for summary tables. For example, if a value is reported as "<100", 100 will be used for the data point in the calculation of the summary statistics. The respective listings will however still report the original data, eg, <100. No imputation will be performed for missing values.

5.4.3 Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, and exploratory variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. Except where specified otherwise, if the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then all the valid values of the day will first be averaged before applying the

aforementioned rules. (Note that the rule of using the later date of the window does not conflict with any protocol-specified procedure that has to be done pre-infusion (eg, IgG assessments), as all IgG assessments will be performed prior to infusion unless there was a protocol deviation.)

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Efficacy assessments

The schedule for the efficacy assessments is shown in the following table.

Efficacy assessments	Schedule
Recumbent length/height, weight, and head circumference	Every 3 months age < 3 years; every 6 months 3 to <5 years, every 12 months >=5 years
Bayley-III	every 6 months ages 1 month to 42 months
Leiter-R/Leiter-3	from final Bayley-III assessment < 42 months of age, every 12 months
GMFM-88	every 6 months age < 5 years; every 12 months >= 5 years
Pompe PEDI	every 6 months age < 5 years; every 12 months >= 5 years

Given that patients enter study at different ages, if we define analysis windows for the efficacy endpoints based on the assessment schedule, the definitions will vary depending on each patient's age at study entry. In addition, due to the small patient population, we will focus on individual patient growth by age. The following analysis windows for efficacy assessments will not be used in by-visit summary tables or figures, but may be used in the patient listing to associate observations to the nearest study visits.

Maximum age at signing of the informed consent was 1.9 years.

Table 7 - Analysis window definition for recumbent length/height, weight, and head circumference

Scheduled visit post baseline	Targeted study day	Analysis window in study day
Screening/Baseline	-30 to -1	
Week 13	91	[46, 136]
Week 26	182	[137, 227]
Week 39	273	[228, 319]
Week 52	365	[320, 456]
Week 78	547	[457, 638]
Week 104	730	[639,821]
Week 130	912	[822, 1003]
Week 156	1095	[1004, 1277]

Scheduled visit post baseline	Targeted study day	Analysis window in study day
Week 208	1460	[1278, 1642]
Week 260	1825	[1643, 2007]
Week 312	2190	[2008, 2372]
Week 364	2555	[2373, 2737]
Week 416	2920	[2738, 3102]
Week 468	3285	[3103, 3467]
Week 520	3650	[3468, 3650]

Study days are calculated considering Day 0 as the day of first administration of intervention.

Table 8 - Analysis window definition for Bayley-III and Leiter-R/Leiter-3

Scheduled Visit	Targeted study day	Analysis window in study day
Screening/Baseline	-30 to -1	
Week 26	182	[91, 273]
Week 52	365	[274, 547]
Week 104	730	[548, 912]
Week 156	1095	[913, 1277]
Week 208	1460	[1278, 1642]
Week 260	1825	[1643, 2007]
Week 312	2190	[2008, 2372]
Week 364	2555	[2373, 2737]
Week 416	2920	[2738, 3102]
Week 468	3285	[3103, 3467]
Week 520	3650	[3468, 3650]

Study days are calculated considering Day 0 as the day of first administration of intervention.

Table 9 - Analysis window definition for GMFM-88 and Pompe PEDI

Scheduled Visit	Targeted study day	Analysis window in study day
Screening/Baseline	-30 to -1	
Week 26	182	[91, 273]
Week 52	365	[274, 456]

Scheduled Visit	Targeted study day	Analysis window in study day
Week 78	547	[457, 638]
Week 104	730	[639, 821]
Week 130	912	[822, 1003]
Week 156	1095	[1004, 1277]
Week 208	1460	[1278, 1642]
Week 260	1825	[1643, 2007]
Week 312	2190	[2008, 2372]
Week 364	2555	[2373, 2737]
Week 416	2920	[2738, 3102]
Week 468	3285	[3103, 3467]
Week 520	3650	[3468, 3650]

Study days are calculated considering Day 0 as the day of first administration of intervention.

Safety and other exploratory assessments

Safety and other exploratory assessments are supposed to be conducted every 12 months with a window of ± 60 days, except for Serum IgG collection and urine Hex4.

- Neuroimaging assessment
- Hearing testing
- Visual screening
- ECG
- Safety laboratory assessments
- Serum IgG collection (every 3 months to study month 24 and then every 12 months after that)
- Urine Hex4 (every 6 months to study month 24 and then every 12 months after that)

Table 10 - Analysis window definition for serum IgG visits

Scheduled Visit	Visit window defined in protocol (±60 days)	Target study day	Analysis window in study day
Screening/Baseline	Day -30 to -1		-30 to -1
Week 13	Month 3	91	1 to 137
Week 26	Month 6	183	138 to 229
Week 39	Month 9	274	230 to 320
Week 52	Month 12	365	321 to 411
Week 65	Month 15	456	412 to 502
Week 78	Month 18	548	503 to 594

Scheduled Visit	Visit window defined in protocol (±60 days)	Target study day	Analysis window in study day
Week 91	Month 21	639	595 to 685
Week 104	Month 24	731	686 to 914
Week 156	Month 36	1096	915 to 1279
Week 208	Month 48	1461	1280 to 1644
Week 260	Month 60	1826	1645 to 2009
Week 312	Month 72	2192	2010 to 2375
Week 364	Month 84	2557	2376 to 2740
Week 416	Month 96	2922	2741 to 3105
Week 468	Month 108	3287	3106 to 3470
Week 520	Month 120	3653	3471 to 3836

Study days are calculated considering Day 0 as the day of first administration of intervention.

Table 11 - Analysis window definition for urine Hex4

Scheduled Visit	Visit window defined in protocol (±60 days)	Target study day for analysis windows	Range of study days for analysis window
Screening/Baseline	Day -30 to -1		-30 to -1
Week 26	Month 6	183	1 to 274
Week 52	Month 12	365	275 to 457
Week 78	Month 18	548	458 to 640
Week 104	Month 24	731	641 to 1096
Week 156	Month 36	1096	1097 to 1461
Week 208	Month 48	1461	1462 to 1826
Week 260	Month 60	1826	1827 to 2192
Week 312	Month 72	2192	2193 to 2557
Week 364	Month 84	2557	2558 to 2922
Week 416	Month 96	2922	2923 to 3287
Week 468	Month 108	3287	3288 to 3653
Week 520	Month 120	3653	3654 to 4018

Study days are calculated considering Day 0 as the day of first administration of intervention.

5.4.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG, and ADA will be used for computation of baseline, the last or worst on-treatment value, and analysis according to PCSAs.

The measured values of unscheduled visits will only be included in the by-visit summaries if they are re-allocated to scheduled visits based on the visit windows defined above.

5.4.5 Missing data

For categorical variables, patients with missing data will not be included in calculations of percentages unless otherwise specified. The analyses and summaries for variables with continuous scales will be based on observed data only.

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 and concomitant medication.

Missing first symptom of Pompe disease

For the calculation of age (months) at first symptom of Pompe disease and time (months) from first symptom of Pompe disease to first alglucosidase alfa infusion, if the month and year are available, the day of the month will be imputed to 15; if, however, only the year is available, the date will not be imputed but left missing.

Missing Assessment of Relationship of Adverse Events to Investigational Medicinal Product

If the assessment of the relationship of the AE to study drug is missing, the event will be considered related to the study drug. However, no imputation will be done at the data level.

Missing Severity of Adverse Events

If the adverse event severity is missing for 1 of the treatment emergent occurrences of an AE, and the maximal severity on the remaining occurrences is mild or moderate, then the worst severity of the event cannot be determined. Therefore, whenever a summary of TEAE by severity is to be presented, these events will be summarized in a separate ‘unknown’ category.

6 REFERENCES

1. Center for Disease Control (CDC). A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). [Online]. [Assessed 2021 Sep 3] [cited 2021 Sep 27]. Available from: URL:https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

2. Center for Disease Control (CDC). A SAS Program for the WHO Growth Charts (ages 0 to <2 years). [Online]. [Assessed 2021 Sep 3] [cited 2021 Sep 27]. Available from: URL: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm

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