NCT02032524

STATISTICAL ANALYSIS PLAN

An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of neoGAA in patients with Pompe disease

Compound: Avalglucosidase alfa (GZ402666)

Sanofi Protocol Number: LTS13769

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ATC:	anatomic category class
BMS:	biomedical system
ENT:	ear, nose, throat
GLI:	global lung initiative
ITT:	intent to treat
IV:	intravenous
LTS-switch:	patients switched to the 20 mg/kg dose after entering LTS13769
MRD:	minimal required dilution
neoGAA:	avalglucosidase alfa
PD:	pharmacodynamic
qow:	every other week
SD:	standard deviation

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

LTS13769 is an open-label, multicenter, and multinational extension study with repeated IV infusions of avalglucosidase alfa. Safety, pharmacokinetic, pharmacodynamic, pharmacogenetic, and exploratory efficacy data will be collected during this long-term study. The population will be patients with Pompe disease who have completed study avalglucosidase alfa TDR12857. Patients who received avalglucosidase alfa intravenous (IV) infusion 20 mg/kg of body weight every other week (qow) in the TDR12857 study will continue to receive the same dose in the extension study, while patients who previously received the 5 or 10 mg/kg qow dose will first continue on the same dose that they received in the TDR12857 study, and then provide consent to switch to the 20 mg/kg qow regimen for the remaining duration of the LTS13769 study (henceforth called the LTS-switch group in this document).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objectives of the LTS13769 study are to assess the long-term safety and pharmacokinetics (PK) of avalglucosidase alfa in patients with Pompe disease who have previously completed an avalglucosidase alfa study.

1.2.2 Secondary objectives

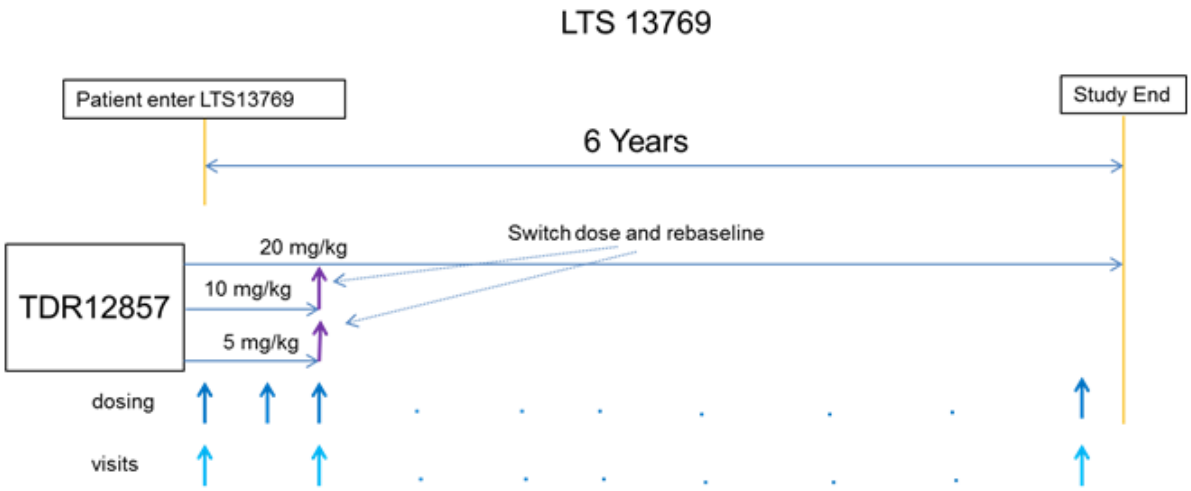
The secondary objectives of the LTS13769 study are to assess if the benefits of avalglucosidase alfa are maintained and the time course of response, by examining the long-term effect of avalglucosidase alfa on pharmacodynamic (PD) and exploratory efficacy variables.

1.3 DETERMINATION OF SAMPLE SIZE

Sample size for the TDR12857 study was based upon empirical considerations. LTS13769 is the extension study of TDR12857; therefore, the number of patients in LTS13769 was determined by the subgroup of TDR12857 patients who consented to continue in the extension study. Thus, no formal sample size calculations have been performed for the TDR12857 or the LTS13769 study.

1.4 STUDY PLAN

The following diagram is a flowchart of the study: more detailed graphical design and study flow charts are presented in Section 1 of study protocol.



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The following main modifications have been made in this version of SAP:

- Added Global Lung Initiative (GLI) 2012 reference equations to calculate FVC % predicted values
- Updated immunogenicity analysis. Some revisions of immunogenicity analysis are made to be consistent with integrated immunogenicity analysis plan.
- Added the second equations for calculating reference value for percentage of predicted total distance walked in 6MWT
- Added Algorithm-defined IARs to be consistent with integrated safety analysis plan
- Updated drug compliance definition to be consistent with COMET and mini-COMET studies
- Added K-M analysis for treatment-emergent adverse events
- The Appendix on Potentially Clinically Significant Abnormalities Criteria was updated

2 STATISTICAL AND ANALYTICAL PROCEDURES

The statistical analysis and reporting will be based on all data from study TDR12857 and its extension study, LTS13769. The baseline value is defined as the last non missing value prior to first TDR12857 treatment, unless otherwise specified. The rebaseline values will be the last non-missing assessment before patients switch to 20 mg/kg dose for LTS-switch patients.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

Demographic information, Pome disease history, gene mutations (GAA and ACE genotyping), and aspects of disability will be imported from the TDR12857 study database. Medical/surgical history information will be taken from LTS13769 study.

Demographic characteristics

Demographic variables are

- Gender (Male, Female)
- Race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)
- Ethnicity (Hispanic, nonHispanic)
- Age in years at TDR12857 study enrollment
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Medical / Surgical History

Collected data regarding any past and/or concomitant diseases or past surgeries include:

- Site/system, eg, Infectious Disease, Allergic, Metabolic/Endocrine/Nutritional, etc.
- Description of diagnosis, symptoms, conditions, or surgeries
- Date started/ended
- Ongoing or not

Pompe Disease Characteristics

Pompe disease history includes:

- Age at first symptoms of Pompe disease
- Age at diagnosis of Pompe disease

- Pompe medical history: cardiovascular, ENT (ear, nose, throat), gastrointestinal, respiratory, and musculoskeletal characteristics
- Family Pompe disease history: number of family members with confirmed Pompe disease in categories of relationship (siblings, parents, cousins, and children)

2.1.2 Prior and concomitant medication/therapy

All medications taken within 28 days before the TDR12857 screening/baseline evaluation visit, during the study periods of both TDR12857 and LTS13769, as well as during the period between the end of TDR12857 and the signing of the informed consent for the extension study, until the end of the LTS13769 study are to be reported in the case report form (CRF) pages.

- Prior medications are those the patient used prior (including 28 days before the screening/baseline visit of the TDR12857 study) to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during the treatment phase. Prior medications that continue to be administered during the treatment phase will be classified as both prior and concomitant medications.
- Concomitant medications are any treatments received by the patient concomitantly to IMP, from first study treatment in the TDR12857 study to the end of treatment + 28 days. As mentioned above, a given medication can be classified as both a prior medication and a concomitant medication if a patient receives the medication before and after the first administration of the study drug. Concomitant medications do not include medications started during the posttreatment period.

All medications will be coded using the version of WHO Drug Dictionary Enhanced extended with the Herbal Dictionary (WHO DDE+HD) in effect at Sanofi at the time of database lock.

2.1.3 Efficacy endpoints

As the primary objective of this study is to assess the long-term safety and pharmacokinetics (PK) of avalglucosidase alfa (neoGAA) in patients with Pompe disease who have previously completed TDR12857, a neoGAA study, there is no primary efficacy for this extension study. However, as part of the secondary objective, exploratory efficacy endpoints will be assessed to see if the benefits of neoGAA are maintained.

2.1.3.1 Primary efficacy endpoint(s)

Not applicable.

2.1.3.2 Secondary efficacy endpoint(s)

The exploratory efficacy endpoints include the six-minute walk test (6MWT) and the pulmonary function testing (PFT). These assessments were performed at baseline, Week 13, and Week 25 in the TDR12857 study, at the baseline for roll over to LTS 13769, and performed every 6 months, at the rebaseline visit (for patients previously in the 5 and 10 mg/kg dose groups only; see Section 1.4), and at the end of study visit in the LTS13769 study.

Six-minute walk test (6MWT)

The 6MWT assessments include: the distance walked in 6 minutes, measured in meters; the percentage of predicted distance; and the amount of time walked to quantify endurance (as all patients may not complete the full 6-minute walk). In addition, data will be collected for pretest versus posttest changes in heart rate and assistive device use. The distance (in meters) will be recorded and the corresponding percentage of predicted value will be calculated. The percentage of predicted distance walked will be calculated based on the normal reference equation in Table 1. For analysis purposes, the age at each assessment will be calculated based on (assessment date - birth date + 1)/365.25.

Table 1 - Equations for calculating reference value for percentage of predicted total distance walked in 6MWT (1)

Age at baseline	Gender	Equation
≥18 years	Male and Female	868.8 - 2.99 * age - 74.7 * sex

Age in years; sex = 0 if male and sex = 1 if female.

In order to compare the percent predicted values with studies using several percent predicted equations, the percentage of predicted distance walked will be calculated based on the normal reference equation in Table 2. For analysis purposes, the age at each assessment will be calculated based on (assessment date - birth date + 1)/365.25, weight is collected at the time of the assessment and height will be baseline height for the study.

Table 2 - Equations for calculating reference value for percentage of predicted total distance walked in 6MWT (2)

Gender	Equation
Male	7.57*height (cm)-5.02*age (year)-1.76*weight (kg)-309
Female	2.11*height (cm)-5.78*age (year)-2.29*weight (kg)+667

Additional supportive analysis of 6MWT based on subjects who completed the full 6 minute walk by excluding subjects that walked less than 6 minutes will be provided.

Pulmonary function test

Pulmonary Function Testing (PFT) will include the assessments of forced vital capacity (FVC), forced expiratory volume in the first second of the FVC maneuver (FEV1), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow (PEF) in the supine and standing positions.

Predicted values for MIP and MEP are derived using the formulas below (3):

Male:

MIP (predicted) = 120 – (0.41 x age)

MEP (predicted) = 174 – (0.83 x age)

Female:

MIP (predicted) = 108 – (0.61 x age)

MEP (predicted) = 131 – (0.86 x age)

Predicted values for FVC, FEV1, and PEF are derived using the formulas below (4):

ht patient height (cm) at baseline

age patient age (years) at the time of the assessment

Male (20 years or older):

$$FEV1\ (predicted) = 0.5536 – (0.01303 \times age) – (0.000172 \times age^2) + (0.00014098 \times ht^2)$$

$$PEF\ (predicted) = 1.0523 + (0.08272 \times age) – (0.001031 \times age^2) + (0.00024962 \times ht^2)$$

Female (20 years or older):

$$FEV1\ (predicted) = 0.4333 – (0.00361 \times age) – (0.000194 \times age^2) + (0.00011496 \times ht^2)$$

$$PEF\ (predicted) = 0.9267 + (0.06929 \times age) – (0.001031 \times age^2) + (0.00018623 \times ht^{2)}$$

FVC will be reported in absolute value in liters, as well as the percent of predicted normal values based on Global Lung Initiative (GLI) 2012 reference equations (5). The FVC percent of predicted values will be calculated based on FVC in liters, gender, race (classified as Caucasian, Asian and African-American, and Other/Mixed), age (at least one decimal place in years), and height (in cm) at baseline and will be reported centrally from Biomedical Systems (BMS), following pulmonary software specification and user requirement (6).

The FVC percent predicted value is calculated as:

(actual FVC measurement/predicted value of FVC) * 100.

The GLI-2012 regression equations and lookup tables are used to calculate predicted values of FVC (1). FVC is predicted according to the following equation:

$M = \exp(a0 + a1 \cdot \ln(Height) + a2 \cdot \ln(Age) + a3 \cdot black + a4 \cdot NEAsia + a5 \cdot SEAsia + a6 \cdot Other + Mspline)$

Where

black = 1 if a subject is African American, otherwise = 0

NEAsia = 1 if a subject is from North East Asia, otherwise = 0

SEAsia = 1 if a subject is from South East Asia, otherwise = 0

Other = 1 if subject is 'other ethnic group' or mixed ethnicity, otherwise = 0

Coefficients a(n) depend on sex and are given by lookup table

Mspline is age-varying coefficients, given by lookup table for each type of sex

For the analysis purpose, the age will be calculated based on (assessment date - birth date + 1)/365.25.

2.1.4 Safety endpoints

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

Observation period

The observation period will be divided into the following epochs:

- The screening epoch is defined as the study period preceding treatment, starting from the signed informed consent date (TDR12857) up to the first administration of IMP. (Note: medications known to have been taken by the patients within 28 days of the TDR12857 screening/baseline visit will be recorded in the CRF as well.)
- The treatment epoch is defined as the time from the start of the first administration of the IMP in the TDR12857 through the completion of the last administration of the IMP.
  - Before- and after-rebaseline periods within the treatment epoch will be used for select analyses
- The residual treatment epoch is defined as the time subsequent to the treatment epoch, from the completion of the last administration of the IMP through the last administration of the IMP + 28 days or the end of the protocol-defined follow-up period, whichever is earlier.

The treatment-emergent adverse event (TEAE) period will include both treatment and residual treatment epochs.

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up through the end of the study.

The on-study observation period is defined as the time from start of treatment in the TDR12857 until the end of the LTS13769 study (defined as the last follow-up visit as defined in LTS13769 protocol Section 10.1.2.9).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious during the screening epoch
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

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

Recording of the occurrence of adverse events (including SAEs and AESIs) will be from the time of signed informed consent of the TDR12857 study until the end of the patient's participation in the TDR12857 or LTS13769 study.

Adverse event of special interest (AESI)

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them.

AESIs will include the following:

Infusion-associated reactions (IAR):

Two definitions will be used in the analysis of IARs:

- Protocol-defined IARs: As defined in the protocol, IARs are defined as AEs that occur during either the infusion or the post-infusion observation period (ie, up to 2 hours or longer following the infusion as per the Investigator's discretion) which are deemed to be related or possibly related to the IMP. At the discretion of the Investigator, AEs occurring after the completion of the post-infusion observation period that are assessed as related may also be considered IARs by the Investigator.
- Algorithm-defined IARs: an alternative definition of IAR is defined as any treatment-emergent AEs meeting one of the following criteria:
  a) Event occurs from the start of infusion to the end of infusion plus 24 hours window, and considered related to study drug;
  b) If AE start date is non-missing but time component is missing, compare AE Start date with infusion start date (date component only) and infusion end date (date component only). If AE Start date is between infusion start date and infusion end date plus one day, consider such AE as algorithm-defined IAR if AE is related to study drug.

Pregnancy

- Pregnancy occurring in a female patient will be recorded as an AESI with immediate notification in all cases, and follow-up is mandatory until the outcome has been determined. It will be qualified as an SAE only if it fulfills the SAE criteria. IMP should be discontinued.
- Pregnancy occurring in a sexual partner of a male patient will be considered as an AESI and the patient will be instructed to notify the Investigator immediately. Follow-up of the pregnancy is mandatory until the outcome has been determined.

Overdose

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose within the intended therapeutic interval.

Clinical laboratory (change from baseline, ie, prior to the first dose in TDR12857)

- ALT or AST increase of ≥3 x the upper limit of normal (ULN) if baseline is <ULN, or ALT or AST increase ≥2 x the baseline value if baseline is ≥ULN
- A maximum ALT value of ≥400 IU/L or AST value of ≥500 IU/L or an increase in direct, indirect, or total bilirubin of ≥2 x ULN
- Serum creatinine increase of >1.5 x the baseline value (and final serum creatinine value is >ULN)

Severe cutaneous and immune-mediated reactions

A listing of potential immune mediated reactions will be provided using the search criteria. Search criteria will include but not be limited to the MedDRA PTs of glomerulonephritis, nephrotic syndrome, proteinuria, haematuria, vasculitis SMQ, serositis, myocarditis, severe cutaneous adverse reactions SMQ, skin lesion, skin necrosis, arthralgia, arthritis, myalgia, arthropathy, lymphadenopathy, serum sickness, type III immune complex mediated reaction and influenza like illness. A medical review of these cases will be performed.

Note that the preferred terms utilized for case identification at the time of analysis will be based on the MedDRA version in effect at Sanofi at the time of database lock. A medical review will be performed by Global Pharmacovigilance (GPV) to determine whether the selected AEs meet the definitions for severe cutaneous and immune-mediated reactions.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death posttreatment: deaths occurring during the posttreatment period
- Death poststudy: deaths occurring after the end of the study

2.1.4.3 Laboratory safety variables

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

Blood samples for clinical laboratories will be taken as specified in the study protocol. The laboratory parameters will be classified as follows:

- Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets,
- Biochemistry
  - Plasma/serum electrolytes: sodium, potassium, chloride, calcium
  - Liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase, total, direct and indirect bilirubin,
  - Renal function: creatinine, blood urea nitrogen, uric acid,
  - Metabolic panel: glucose, albumin, total proteins, total cholesterol, triglycerides,
  - Potential muscle toxicity: creatine kinase, creatine kinase with MB fraction, lactate dehydrogenase,

Urinalysis will include urine color, appearance, specific gravity, proteins, glucose, erythrocytes, leukocytes, ketone bodies, and pH to be assessed:

- Qualitatively: A dipstick is to be performed on a freshly voided specimen for qualitative detection using a reagent strip.
- Quantitatively: A quantitative measurement for protein, erythrocytes, and leukocytes count will be required in the event that the urine sample test is positive for any of the above parameters by urine dipstick (eg, to confirm any positive dipstick parameter by a quantitative measurement)

2.1.4.4 Vital signs variables

Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation. Vital signs are to be assessed prior to infusion, with each infusion rate change, at the end of the infusion, and at the end of postinfusion observation period. Collection windows are ±15 minutes.

2.1.4.5 Electrocardiogram variables

Standard 12-lead ECG parameters will be recorded after at least 15 minutes in the supine position, including heart rate, rhythm, interval between the peaks of successive QRS complexes (RR), intervals from the beginning of the P wave until the beginning of the QRS complex (PR), interval from the start of the Q wave to the end of the S wave (QRS), interval between the start of the Q wave and the end of the T wave (QT), QT interval corrected for heart rate (QT_C) automatic evaluation (by the ECG device), QRS axis, R voltage V6, voltage V1, left ventricular hypertrophy

criteria, right ventricular hypertrophy criteria, repolarization charges, and overall cardiac impression for each patient.

2.1.4.6 Anti-drug antibody and neutralizing antibody endpoints

Patients will be tested for anti-avalglucosidase alfa antibodies. Samples will be collected from patients for evaluation of ADA. ADA seropositive patient serum will be assessed for neutralizing antibodies to avalglucosidase alfa, including inhibition of enzyme activity and uptake.

The qualitative sample status of the ADA will be assessed and be categorized into the following classes:

- ADA-negative sample: a sample is considered negative if ADAs are not detected (ie, negative in screening assay or reactive in screening but negative in confirmatory assay).
- ADA-positive sample: sample in which ADA is detected, ie, sample generates an assay signal equal to or greater than the cut-point in the screening assay and is tested positive in the confirmatory assay.

The ADA titer of the positive samples will also be assessed. A titer represents a quasi-quantitative information on the level of ADA present in a sample. Confirmed positive samples are serially diluted until a negative result is achieved. The titer is subsequently defined as the reciprocal of the last dilution that tests positive. The minimal required dilution (MRD) will be incorporated in the final calculation.

The ADA attributes will be determined by the following conditions :

- Pre-existing ADAs: antibodies reactive with the study drug present in subjects before treatment.
- Treatment induced ADAs: ADAs developed de novo (seroconversion) following administration of the study drug. If the baseline ADA sample is missing or non-reportable and at least one reportable on-treatment ADA sample is available, the baseline sample will be considered as “negative”.
- Treatment boosted ADAs: Pre-existing ADAs that were boosted at least two titer steps from baseline (i.e., 4 fold increase in titers) following administration of the study drug (any time after the first drug administration).

The following kinetics of the ADAs will be analyzed:

- Onset of ADA is defined as the time period (in weeks) between the first study drug administration and the first instance of treatment induced ADAs.
- Duration of ADA will be calculated as the date of last treatment induced ADA sample minus date of first treatment induced ADA sample + 1.

The following ADA response classifications will be used:

1. Treatment-induced ADA- patients are ADA negative at baseline and have developed an ADA response
   a) Transient ADA response is defined as: 1) Treatment-inducted ADA detected only at one sampling timepoint post-baseline (excluding the last sampling time point); or 2)

Treatment-inducted ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of less than 16 weeks, and the subject's last sampling time point is ADA-negative

b) Persistent ADA response is defined as: 1) Treatment-inducted ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks; or 2) Treatment-inducted ADA detected in the last two sampling time points, irrespective of the time period in between.

The following subclassifications for persistent ADA response will be considered as well.

- Low response – if a patient peak titer ≤800 and positive at final assessment. This represents the first titer that is greater than a 4-fold increase from the assay minimum required dilution (MRD). Titers within this range would be considered as Low response.
- Intermediate response – if a patient was persistently seropositive but peak titer is 1600-6400 and is positive at final assessment.
- High response – if a patient was persistently seropositive and peak titer is ≥12800 and is positive at final assessment.

c) Tolerized – if a patient was persistently seropositive, but negative at the final assessment.

Time to tolerization is defined as (date of tolerization - date of initial seroconversion)/7

Tolerization date = date of the first negative values followed by all subsequent values negative.

d) Indeterminate ADA response – if the patient developed ADA at the last time point and all previous samples are ADA negative, therefore cannot determine whether the response will be transient or persistent in duration. Other timing that does not comply with transient or persistent definitions.

2. Treatment-boosted ADA – patients who have pre-existing ADA (positive at baseline) and have ADA titers boosted to a higher level by a greater than or equal to 4-fold increase (i.e., by greater than at least twice the 2-fold dilution level).
3. Treatment emergent ADA- combination of treatment induced and treatment boosted

2.1.5 Pharmacokinetic variables

The blood samples for evaluation of avalglucosidase alfa PK were/will be collected according to TDR12857 protocol section 9.3 and LTS13769 protocol section 9.2. PK parameters: including but not be limited to C_{max}, AUC_{last}, AUC, t_{last}, $t_{1/2z}$, CL, and Vd will be calculated by PKDM, using noncompartmental methods from plasma avalglucosidase alfa concentrations obtained after single and repeat dose administration.

2.1.6 Pharmacodynamic endpoints

Skeletal muscle MRI

Skeletal muscle magnetic resonance imaging (MRI), aiming to assess disease severity and detect treatment effects, will be performed prior to the muscle needle or open biopsy procedure, using both qualitative (T1) and quantitative (T2, Dixon) modalities. The images will be read and analyzed centrally.

T1 weighted axial data will be analyzed using the Mercuri scale, which determines degree of intact muscle and fatty replacement, providing a qualitative measure of overall disease severity. The Mercuri scale (grade 1-4) is as follows: (1) normal appearance, (2) mild involvement, (3) moderate involvement, and (4) severe involvement.

Volumetry: trophicity changes will be evaluated for 5 muscle groups, including the upper leg muscles (quadriceps, hamstring) and the lower leg muscles (triceps, extensors, fibularis). The measured area of each muscle group, cross-sectional area (CSA), will be provided (in mm^2).

T2: multi-slice multi-spin echo **(**MSME) and B1 mapping will provide a quantitative measure of disease activity (edema, inflammation) within muscles, measured in milliseconds (ms) (abnormal value defined as >39 ms).

Three-point Dixon imaging will provide quantification of fat content in muscles (fat fraction [FF], described in percentages). The fat fraction will also be combined with the CSA measurements trophicity) to provide an Index of Real Muscle Mass (IRMM) in mm^2 (IRMM = CSA * [1 – FF]).

Skeletal muscle needle or open biopsy

Skeletal muscle needle or open biopsy will be performed on the lower extremity (quadriceps) muscle to assess glycogen content. The MRI appearance of the muscle will be used to determine the level (axial slice position) that the biopsy procedure should target (avoiding fatty replaced tissue). Glycogen content will be measured by histomorphometric analysis or severity grading to determine how effectively avalglucosidase alfa is able to remove glycogen from muscle.

Urinary Hex4 level

Assessment of urinary Hex4 concentrations will be assessed from fasted urine samples.

Exploratory urine and plasma biomarkers

Fasted plasma and urine samples will be collected prior to IMP infusion for the assessment of exploratory biomarkers. The analysis of biomarkers will be planned and reported separately.

2.1.7 Pharmacogenetics

Serum skeletal muscle RNA expression analysis

Patients qualified for the muscle biopsy procedures will have additional serum samples taken to assess whether any of the mRNA targets identified in muscle are expressed in serum, which could subsequently be assessed as a serum-based marker of Pompe disease. The analysis of novel serum biomarkers will be planned and reported separately.

Plasma circulating microRNA analyses

Plasma samples will be collected and assessed for circulating microRNA concentrations on both the whole-genome and individual gene levels. The analysis of microRNA targets will be planned and reported separately.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent. Patients who enrolled in the extension study, LTS13769, must have signed informed consent for the extension study, and met the additional inclusion/exclusion criteria, with one of the criteria being the completion of the TDR12857 study.

For patient study status, information in the following categories for either TDR12857 or LTS13769 will be presented in the clinical study report:

- Screened patients
- Screen failure patients
- Treated patients
- Completed TDR12857 study
- Patients who entered the LTS13769 study
- Completed LTS13769 study
- Patients who did not complete the study treatment (either in TDR12857 or LTS13769) by main reason

Number and percentage of patients treated in TDR12857 that fall into each category will be presented in a summary table. Percentages will not be calculated for the screened patients and screen failures. Reasons for treatment discontinuation will be supplied in table(s) giving numbers and percentages by study, dose, and patient groups.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit and if the time from the last successful contact to the last protocol planned visit is greater than 30 days.

All critical or major deviations will be summarized in tables giving numbers and percentages of deviations by patient group.

Additionally, the analysis populations for safety, pharmacokinetics (PK), pharmacodynamics, and efficacy will be summarized by number of patients enrolled in the TDR12857 study:

- Full Analysis (FA) Set
- Safety Analysis Set
- PK/Pharmacodynamics/Efficacy Analysis Set

2.2.1 Randomization and drug dispensing irregularities

Neither the TDR12857 nor the LTS13769 study was randomized.

Drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All drug-dispensing irregularities will be documented in the clinical study report. Whether any of these constitute a major protocol deviation is deferred to the decision by the clinical team before the database lock.

Drug-dispensing irregularities to be prospectively identified include but are not limited to:

Table 3 - Drug allocation irregularities

Drug allocation irregularities
Erroneous kit dispensation
Kit not available
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Neither the TDR12857 nor the LTS13769 study was randomized. Patients will be analyzed according to the treatment they actually received instead of the intent to treat (ITT) approach.

2.3.1 Full analysis (FA) set

The FA set consists of all patients who received at least 1 complete infusion of IMP. It will be used for efficacy analysis.

2.3.2 Safety analysis set

The safety analysis set consists of all patients who received at least 1 complete infusion of IMP. It will be used as the basis for all safety analyses.

2.3.3 Pharmacokinetics/pharmacodynamics/efficacy analysis Set

Enrolled patients without any critical deviations related to IMP administration, and for whom any pharmacokinetics/pharmacodynamics/efficacy data are available, will be included for the analyses of PK, PD, and/or efficacy data, respectively.

2.3.4 ADA evaluable set

All enrolled patients who received at least 1 infusion (partial or completed) of avalglucosidase alfa and had at least one ADA sample taken post-baseline after avalglucosidase alfa infusion that is appropriate for ADA testing with a reportable result.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each dose and patient group. Categorical and ordinal data will be summarized using the number and percentage of patients in each dose and patient group.

Parameters described in Section 2.1.1 will be summarized by dose and patient group using descriptive statistics.

P-values on demographic and baseline characteristic data will not be calculated.

No specific description of the safety/efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/efficacy analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for all patients enrolled in TDR12857, whether or not they continued in the extension study LTS13769.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category class (ATC) 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 and 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 within each category, alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, number of infusions, and amount of dose received. The extent of IMP exposure will be summarized in safety population.

Duration of IMP exposure is defined as last dose date – first dose date + 14 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or

incomplete data). Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: <6 months, 6 months to <1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years, 5 to <6 years, and ≥6 years.

The cumulative dose information will be assessed by the total number of infusions received. These data will be summarized descriptively.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose (eg, missed dose, overdose, or underdose) of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Compliance is calculated as the total amount of drug actually taken by a patient divided by the total amount of drug expected to be taken multiplied by 100. The number and percentage of patients with noncompliance (missed 2 or more consecutive infusions, or missed ≥20% of total doses in the treatment or extension period) will be provided.

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized.

Additional dose related non-compliance will be summarized as protocol deviations.

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

Efficacy endpoints will be summarized with both the FA set and the efficacy analysis set. Observed measurements, changes from baseline, and changes from rebaseline (LTS-switch patients only) to each applicable study time point in 6MWT distance walked (actual and % predicted based on both Enright and Gibbons equations) and PFT parameters (actual and % predicted, supine and standing FVC, FEV1, MIP, MEP, and PEF) will be summarized using summary statistics. 95% CIs will be used to estimate the change from baseline at each study visit. Missing data will not be imputed. Spaghetti plots showing patient data over time will be presented. A listing of assistive device use during the 6MWT will be provided.

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

The summary of safety results will be presented by dose and patient group. Corresponding listings will also be presented.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last value prior to the first dose of GZ402666 in the TDR12857 study
- The re-baseline values is defined as the last non-missing assessment before patients switch to 20 mg/kg dose for LTS-switch patients.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by dose and patient group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks between groups and their 95% confidence intervals may be provided, if relevant.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present adverse events grouped by SOC and PT, including the number and percentage of patients experiencing AEs in each SOC/PT category and the associated event counts (see the paragraph below for sorting order). Multiple occurrences of the same event in the same patient will be counted only once in the tables within observation period presented

(pretreatment, treatment-emergent, and posttreatment). The denominator for computation of percentages is the safety population within each patient and dose group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting according to frequency of PTs will be based on the sum of patient counts for the patients in the 20mg/kg dose groups. In the case of the AE by maximal severity tables, the sum of patient counts for the severe AEs from patients in the 20 mg/kg dose groups will be used for the sorting of PTs.

For patients previously assigned to the 5 or 10 mg/kg dose groups in the TDR12857, entered the LTS13769 study, and switched to the 20 mg/kg dose group (LTS-switch group), additional AE summaries, as indicated in respective subsections below, will be generated for comparison of before- and after-rebaseline adverse events in these patients.

Analysis of all treatment-emergent adverse events

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

- Overview of treatment-emergent adverse events, summarizing number and percentage of patients and number of events with any
  - Treatment-emergent adverse event(s)
  - Severe treatment-emergent adverse event(s)
  - Serious treatment-emergent adverse event(s)
  - Treatment-emergent AESI(s)
  - IARs (protocol- and algorithm-defined)
  - Treatment-emergent adverse event(s) leading to permanent treatment discontinuation
  - Treatment-emergent adverse event leading to death
- All treatment-emergent adverse events by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event and number of events sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events, 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.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group
- All treatment-emergent adverse events by PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events, sorted by decreasing incidence of PTs.

- All treatment-emergent adverse events regardless of relationship and related by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events, sorted by the internationally agreed SOC order. The PT levels will be presented in alphabetical order.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group
- 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 and number of events by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group
- A by-patient listing of AEs, ADA, and IgE, sorted chronologically, will be presented.

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 and number of events, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event and number of events, sorted by the internationally agreed SOC order. The PT levels will be presented in alphabetical order.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group
- All treatment-emergent serious adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
  - Additional summaries of before- and after-rebaseline periods will be presented for the LTS-switch group

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 and number of events sorted by the internationally agreed SOC order. The PT level will be presented in alphabetical order

Analysis of standardized MedDRA query

A comprehensive programming search of AEs which meet the Standardized MedDRA Query (SMQ) criteria for hypersensitivity and anaphylactic reaction will be used to identify adverse events that potentially are associated with symptoms of anaphylactic and hypersensitivity reaction.

Results of this search will be provided in a by patient listing by group. The most recent version of MedDRA SMQ will be used at the time of analysis. A medical review of these cases will be performed.

A listing of potential immune mediated reactions will be provided. All treatment-emergent adverse events, by standardized MedDRA query (SMQ) and PT, showing the number (%) of patients and number of events with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ.

Analysis of adverse events with AESIs

- Treatment-emergent AESIs by Primary SOC and PT, showing the number (%) of patients and number of events, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent AESIs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Summary tables of infusion associated reactions (IARs) as defined by the 2 definitions will be presented by Primary SOC and PT for each patient group and dose level.
- All IARs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event and number of events by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- A detailed listing of patients who experience IARs including information on severity, seriousness, relationship to IMP, timing from first infusion to the onset of the IAR, IAR definition(s) met, action taken regarding study treatment, other action taken, and patient outcome, will be provided.

Severe cutaneous and immune-mediated reactions

- Treatment-emergent severe cutaneous and immune-mediated reactions by Primary SOC and PT, showing the number (%) of patients and number of events, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment adverse events will be presented in a patient listing.
- All posttreatment adverse events will be presented in a patient listing.

Kaplan-Meier estimates

- A summary table of Kaplan-Meier estimates of TEAEs by 6-month time intervals will be provided.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, posttreatment, and poststudy) and, if captured, reasons for death Treatment-emergent adverse events leading to

death (death as an outcome on the adverse event CRF page as reported by the Investigator) by primary SOC and PT showing number (%) of patients and number of events sorted by internationally agreed SOC order, with PT presented in alphabetical order within each SOC.

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, changes from baseline, and changes from rebaseline [LTS-switch group only]) will be calculated for each applicable visit or study assessment (baseline, each postbaseline time point) by patient and dose group. For select laboratory assessments (alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, creatine kinase (CK), and creatine kinase MB band (CK-MB)), mean changes from baseline with the corresponding standard error will be plotted over time in each patient group and dose level. This section will be organized by biological function as specified in Section 2.1.4.3.

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 treatment group according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity.

The following analyses will be performed:

- Time to onset of the initial ALT or AST elevation (>3 × ULN) and total bilirubin elevation (>2 × ULN), whichever comes first will be analyzed using Kaplan Meier estimates by study cohort and treatment arm, if necessary.
- A graph of distribution of peak values of ALT versus peak values of total bilirubin (in logarithmic scale or in the scale of x ULN if appropriate) will also be presented. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin if necessary. A similar graph will be provided for peak values of AST versus peak values of total bilirubin.
- Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT or AST >3 x ULN, and associated with an increase in bilirubin >2 x ULN) with ALT, AST, alkaline phosphatase and total bilirubin values if necessary.
- Summary of the incidence of liver-related adverse events by treatment group if necessary. The selection of preferred terms will be based on the hepatic disorder SMQ.

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 (observed values and changes from baseline) will be provided for pre-infusion measurements and the change from pre-infusion to the completion of the infusion by visit and by patient and dose group. The vital signs measurements at each infusion rate change will not be summarized, but will be included in the patient listing.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by patient and dose group according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criteria

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all ECG variables (laboratory values, changes from baseline, and changes from rebaseline [LTS-switch group only]) will be calculated for each applicable visit or study assessment (baseline, each postbaseline time point) by patient and dose group. A listing of abnormal findings will be provided.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by patient and dose group or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.6 Analyses of Immunogenicity

ADA incidence and characterization

ADA status: ADA seroconversion is classified as always negative and ever positive. Baseline ADA status will be reported as negative or pre-existing ADA at initiation of treatment.

The following incidence rates will be summarized descriptively for each treatment group:

- ADA prevalence rate, defined as

  100 x (number of patients with treatment-induced ADA + pre-existing ADA)/ (number of evaluable patients)

- Treatment emergent ADA incidence, defined as

  100 x (treatment boosted + treatment induced ADA positive patients)/(number of evaluable patients),

- Treatment induced ADA incidence, defined as,

  100 x (treatment induced ADA positive patients)/(number of evaluable patients with ADA negative at baseline),

- Treatment boosted ADA incidence, defined as

100 x (treatment boosted ADA positive patients)/(number of evaluable patients with ADA positive at baseline).

Duration of ADA

The kinetics and duration of the immune responses will be analyzed as follow:

- Onset time of ADA will be analyzed descriptively using summary statistics minimum, Q1, median, Q3 and maximum.
- Duration of ADA will be analyzed descriptively using summary statistics minimum, Q1, median, Q3 and maximum. It will only be calculated for the patients with at least two ADA positive samples. The median duration and the quartiles will be reported.

ADA titers

- ADA peak titer, last titer, and geometric mean titer will be summarized.
- Graphs of ADA titer over time and boxplots of the highest post-baseline ADA titer will be provided.

ADA Response Classification

Response type classification will be provided.

- The number and percent of transient ADA response will be summarized descriptively. This will be performed for the patients with at least two post baseline samples where the last sampling timepoint is negative.
- The number and percent of persistent ADA response and its subclassifications will be summarized descriptively. This will be performed for the patients with treatment-induced ADA detected at two or more sampling time points post-baseline.
- The number and percent of indeterminate ADA response will be summarized descriptively. This will be performed for the patients with at least one post baseline sample.

Neutralizing ADA

- Incidence of neutralizing antibodies (inhibition of enzyme activity and inhibition of enzyme uptake) will be reported for both treatment naïve and switch patients
- Onset time of neutralizing ADA will be analyzed descriptively using summary statistics minimum, Q1, median, Q3 and maximum.
- Duration of neutralizing ADA will be analyzed descriptively using summary statistics minimum, Q1, median, Q3 and maximum. It will only be calculated for the patients with at least two ADA positive samples.

The following listings will be provided:

- Anti-avalglucosidase alfa alfa antibody titer values, neutralizing antibody, circulating immune complex, anti-avalglucosidase alfa IgE antibody, serum tryptase activity, complement activation, and skin testing performed
- Listings of anti-avalglucosidae alfa ADA and inhibitory antibodies
- Listings of anti-alglucosidae alfa ADA and inhibitory antibodies

Association of ADA with PK

The following analysis will be considered for switched patients: 1. Within Subject level AUC change from baseline to the last injection will be plotted by peak titer category. Gender will be separated by different color. 2. Between subject comparison of ADA-positive vs. ADA negative. Plot of AUC at baseline compared to timepoints where full PK assessment is available. Patients will be evaluated by titer categories based on titer category at the time of PK assessment. Patients will be separated based on treatment groups. 3. Summary table to include AUC and % change from Day 1 at each scheduled visit by peak titer categories. 4. Data will be assessed for switch patients as appropriate.

Association of ADA and PD marker

Hex-4 is a clinically relevant PD marker that is related to the drug's mechanism of action. Summary table of number (%) of patients with elevated urinary hex-4 by titer value at the specified visit (eg, peak titer categories) over time will be provided.

Evaluation of ADA on Relevant Safety Parameters

To evaluate the effect of ADA and NAb on AEs, the number and percentage of patients experiencing any TEAEs, any treatment-emergent SAEs, or any IARs, hypersensitivity (narrow SMQ), and Anaphylactic reaction (narrow SMQ) will be presented by the following sub-categories: 1. ADA status (ever positive, always negative) 2. ADA peak titer category (always negative, peak titer 100-800, 1600-6400, ≥12,800) 3. ADA response type (always negative, transient response (if occur), and persistent responses subcategories: low response, intermediate response, high ADA response and tolerized at defined timepoints. 4. Correlation of frequency of IAR and ADA peak titer. 5. Neutralizing antibody status (always negative, ever positive).

Association of ADA with selected efficacy

Correlation analysis will be performed between immunogenicity (ADA titers, response categories and neutralizing ADA) and FVC, 6MWT, (raw and percent predicted), MIP, MEP.

2.4.5.7 Analyses of physical examination variables

Percentage of patients in each category of physical examination findings will be summarized by visit, site/system, and patient/dose group. Shift from baseline to worst and last postbaseline findings will also be summarized by site/system and patient/dose group.

2.4.6 Analyses of pharmacokinetic variables

All the pharmacokinetic parameters described in Section 2.1.5 will be analyzed using the pharmacokinetic population.

Individual assessments and descriptive statistics (mean, standard deviation [SD], median, minimum, maximum, geometric mean, and percent coefficient of variation [CV%]) will be presented for plasma concentration time data and PK parameters for each dose level and visit. Individual and mean (SD) plasma concentration time profile will be presented graphically for each visit.

To evaluate the effect of immunogenicity on the PK of avalglucosidase alfa, the following plots will be presented:

- Individual profiles of avalglucosidase alfa concentrations over time at 6-month visit and yearly thereafter, grouped by patient/dose group and ADA status (ever positive, always negative, baseline ADA positive [preexisting ADA], neutralizing antibody positive)
- Median (SD) trough avalglucosidase alfa concentrations over time at 6-month visit and yearly thereafter, grouped by patient/dose group and ADA status (ever positive, always negative, baseline ADA positive [preexisting ADA], neutralizing antibody positive)

If relationships are apparent, further quantitative/statistical analysis may be performed (eg, statistical significance, correlation coefficients).

2.4.7 Analyses of pharmacodynamic variables

Pharmacodynamic variables are described in Section 2.1.6.

Descriptive statistics (including mean, SD, median, minimum, maximum, and 95% confidence intervals (CI) of changes) for both observed and change from baseline (and/or rebaseline, if specified) by study visit will be provided for quantitative parameters, by group and by each patient group/dose level, unless otherwise specified. Qualitative results that are categorical will be presented with number and percentage of patients in each category. If a linear trend in the change of a pharmacodynamic endpoint is observed, a longitudinal model may be employed to model change from baseline over time.

Muscle MRI

MRI data collected from the TDR12857 and LTS13769 studies will be summarized separately, due to the updated methods used for LTS13769. The Week 27 results from TDR12857 will be used as the LTS13769 baseline for LTS13769 study (see Section 2.5.1). Descriptive statistics will be used for quantitative parameters to summarize changes over time from baseline/rebaseline for each study. The Mercuri grading will be presented both as a categorical variable (ie, number and percentage of patients in each grade over time will be presented) and as a continuous variable (ie, number, mean, SD, median, minimum, maximum, and 95% CI will be presented at each visit). Additional summaries will be presented for the patients previously allocated to the 5 or 10 mg/kg dose groups in the TDR13857 study and switched to 20 mg/kg in the LTS13769 study (see Section 2.5.1).The number of patients with abnormally high values for any specific muscle, as indicated by a T2 of >39 ms, will be presented using descriptive statistics.

Muscle biopsy

Changes from the TDR12857 baseline over time will be used to summarize continuous variables. For qualitative measures, number and patients in each category over time will be presented.

A correlative measure comparing the biopsied muscle and its MRI counterpart will also be performed.

Urine Hex4

Urine Hex4 levels will be summarized using descriptive statistics at each scheduled study visit. Observed measurements, as well as change from baseline, will be summarized. If a linear trend in the change of urine Hex4 levels is observed, a longitudinal model may be employed to model change from baseline over time. In addition, 95% CIs of changes will be presented. Due to the small number of patients, nonlinear relationship will not be formally characterized.

PK and urine Hex4

To explore the relationship between PK endpoints and urine Hex4 levels, correlational statistics (Spearman or Pearson) at select visits where PK and urine Hex4 are assessed will be used. In addition, scatter plots and linear regression analysis may be used to describe the relationship between PK endpoints and urine Hex4 levels as appropriate.

2.4.8 Pharmacogenetics

Analyses of serum skeletal muscle RNA expression analysis and plasma circulating microRNA levels will be reported in a separate report.

2.4.9 Analyses of quality of life/health economics variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Baseline is defined as the last observation prior to the first treatment in the TDR12857 study, unless otherwise specified. In addition, a rebaseline value may be used for the summaries of select assessments for patients who previously enrolled in the 5 and 10 mg/kg dose groups and switched to the 20 mg/kg dose in the LTS13769 study, in order to compare changes before and after the switch. (In some cases, assessments were not repeated at the rebaseline visit, depending on the last available assessment dates [see protocol Section 10.1.2.7]. In such circumstances, the last available assessments prior to dose switch will be used for the rebaseline values of the parameters of interest.)

Due to the centralized MRI reading procedures, there will be multiple Week 27 values, as the Week 27 image will be reread in accompany to each LTS13769 MRI read. The LTS13769 baseline will be the mean of the multiple Week 27 of the particular parameter. The previous Week 27 reads performed during the TDR12857 study will be presented in the presentation of data collected during the TDR12857 study period, but excluded in the calculation of the LTS13769 baseline, as the vendor [same vendor used for TDR12857] has upgraded their image processing capabilities.

2.5.2 Data handling conventions for secondary efficacy variables

None.

2.5.3 Missing data

No imputation (single or multiple) is planned for this study.

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

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

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment CRF page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the CRF and should not be approximated by the last returned package date.

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 first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the CRF and should not be approximated by the last returned package date.

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 of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

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.

Handling of Repeat Laboratory measurements on the same day

The average values will be used for the repeat laboratory measurements taken on the same day for each visit.

Handling of ADA titer with missing or non-numerical values

If the ADA titer is reported as "<value", then the actual value is imputed as this value. For example, "<100" will be imputed as 100. A negative ADA status will be assumed as a value of 0 (will be excluded when geometric mean of the group needs to be calculated).

2.5.4 Windows for time points

For the purpose of changes over time analyses, select assessments will be assigned analysis visits by comparing actual visit dates with target visit dates and pre-defined visit windows. Specific algorithms in the assignments of the analysis visits such as the target study days and the corresponding visit windows are listed in Appendix B.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries if scheduled visit measurements are not available. If unscheduled visit happened on the same day of the scheduled visit in lab, the average value of those measurements will be used. The unscheduled visit measurements will be used for computation of baseline and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Investigation of the effects of geographic regions may be performed on an exploratory basis.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

A clinical study report will be produced at study completion. An interim report will also be produced if a sub-study analysis of data is performed to support regional regulatory requirements.

4 DATABASE LOCK

The database is planned to be locked at 30 days after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Version 9.4 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria

Table 5 - Criteria for potentially clinically significant abnormality

Measures	Adult Criteria	Pediatric Criteria
Liver function tests		
ALT	>3 x ULN >5 x ULN >10 x ULN >20 x ULN	≥3 x ULN ≥5 x ULN ≥10 x ULN ≥20 x ULN
AST	>3 x ULN >5 x ULN >10 x ULN >20 x ULN	≥3 x ULN ≥5 x ULN ≥10 x ULN ≥20 x ULN
Alkaline Phosphatase	>1.5 x ULN	≥1.5 x ULN
Total Bilirubin	>1.5 x ULN >2 x ULN	≥1.3 x ULN
ALT and Total Bilirubin	ALT >3 x ULN and Total Bilirubin >2 x ULN	ALT ≥3 x ULN and Total Bilirubin ≥2 x ULN
Hematology		
White Blood Cell (WBC)	<3.0 GIGA/L (non-Black), <2.0 GIGA/L (Black), ≥16.0 GIGA/L	Birth/0 to 27 days old (Neonates) <4.0 GIGA/L >25.0 GIGA/L 28 days/1 month to 23 months old (Infants) <4.0 GIGA/L >20.0 GIGA/L 24 months/2 years to <6 years old (Children) >3.0 GIGA/L >16.0 GIA/L 6 to <12 years old (Children) <5.0 GIGA/L >17.0 GIGA/L 12 to 16/18 years old (Adolescents) <4.5 GIGA/L >13.5 GIGA/L

Measures	Adult Criteria	Pediatric Criteria
Lymphocytes	>4.0 GIGA/L	Birth/0 to 27 days old (Neonates) <1.2 GIGA/L >17.0 GIGA/L 28 days/1 month to 23 months old (Infants) <2.0 GIGA/L >13.5 GIGA/L 24 months/2 years to <6 years old (Children) <1.0 GIGA/L >9.5 GIGA/L 6 to <12 years old (Children) <1.0 GIGA/L >8.0 GIGA/L 12 to 16/18 years old (Adolescents) <0.6 GIGA/L >6.0 GIGA/L
Neutrophils	<1.5 GIGA/L (non-Black) <1.0 GIGA/L (Black)	Birth/0 to 27 days old (Neonates) <4.0 GIGA/L (1 day old) <1.5 GIGA/L (2 – 7 days old) <1.25 GIGA/L (>7 day – 1 month old) >1 ULN 28 days/1 month to 23 months old (Infants) <1.0 GIGA/L (1 – 3 months) <1.2 GIGA/L (3 – 24 months) >1 ULN 24 months/2 years to <6 years old (Children) <1.2 GIGA/L >1 ULN 6 to <12 years old (Children) <1.2 GIGA/L >1 ULN 12 to 16/18 years old (Adolescents) <1.2 GIGA/L >1 ULN
Monocytes	>0.7 GIGA/L	
Basophils	>0.1 GIGA/L	
Eosinophils	>0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA /L	>0.5 GIGA/L Or >ULN if ULN >0.5 GIGA/L

Measures	Adult Criteria	Pediatric Criteria
Hemoglobin	Males: ≤115 g/L (≤7.14 mmol/L), ≥185 g/L (≥11.48 mmol/L) Females: ≤95 g/L (5.9 mmol/L), ≥165 g/L (10.24 mmol/L) Decrease from Baseline: ≥20 g/L (1.24 mmol/L)	Birth/0 to 27 days old (Neonates) <86 mmol/L or 12.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL 28 days/1 month to 23 months old (Infants) <1.40 mmol/L or 9.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL 24 months/2 years to <16/18 years old (Children, Adolescents) <1.55 mmol/L or 10.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL
Hematocrit	Males : ≤0.37 v/v, ≥0.55 v/v Females : ≤0.32 v/v, ≥0.5 v/v	Birth/0 to 27 days old (Neonates) <0.39 l/l or 40% >0.61 l/l or 47% 28 days/1 month to 23 months old (Infants) <0.29 l/l or 29% >0.42 l/l or 42% 24 months/2 years to <16/18 years old (Children, Adolescents) <0.32 l/l or 32% >0.47 l/l or 47%
RBC	≥6 TERA/L	
Platelets	<100 GIGA/L ≥ 700 GIGA/L	<100 GIGA/L >700 GIGA/L

ECG – PCSA criteria

HR	<50 bpm	Birth/0 to 27 days old (Neonates)
	<50 bpm and decrease from baseline ≥20 bpm	≤90 bpm and decrease from baseline≥20 bpm
	<40 bpm	≥190 bpm and increase from baseline
	<40 bpm and decrease from baseline ≥20 bpm	≥20 bpm
	<30 bpm	28 days/1 month to 23 months old (Infants)
	<30 bpm and decrease from baseline ≥20 bpm	≤80 bpm and decrease form baseline
		≥20 bpm
	>90 bpm	≥175 bpm and increase from baseline
	>90 bpm and increase from baseline ≥20bpm	≥20 bpm
	>100 bpm	24 months/2 years to <6 years old (Children)
	>100 bpm and increase from baseline ≥20bpm	≤75 bpm and decrease from baseline
	>120 bpm	≥20 bpm
	>120 bpm and increase from baseline ≥20 bpm	≥140 bpm and increase from baseline
		≥20 bpm
		6 to <12 years old (Children)
		≤50 bpm and decrease from baseline
		≥20 bpm
		≥120 bpm and increase from baseline
		≥20 bpm
		12 to 16/18 years old (Adolescents)
		≤50 bpm and decrease from baseline
		≥20 bpm
		≥120 bpm and increase from baseline
		≥20 bpm
PR	>200 ms	Birth/0 to 27 days old (Neonates) ≥120 ms
	>200 ms and increase from baseline ≥25%	28 days/1 month to 23 months old (Infants) ≥140 ms
	> 220 ms	24 months/2 years to <6 years old (Children) ≥160 ms
	>220 ms and increase from baseline ≥25%	6 to <12 years old (Children) ≥170 ms
	> 240 ms	12 to 16/18 years old (Adolescents) ≥180 ms
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Birth/0 to 27 days old (Neonates) ≥85 ms
	>110 msec and increase from baseline ≥25%	28 days/1 month to 23 months old (Infants) ≥85 ms
	>120 ms	24 months/2 years to <6 years old (Children) ≥95 ms
	>120 ms and increase from baseline ≥25%	6 to <12 years old (Children) ≥100 ms
		12 to 16/18 years old (Adolescents) ≥110 ms

QTc (either QTcF or QTcB)	Absolute values (ms >450 ms >480 ms >500 ms Increase from baseline 30-60 ms >60 ms	Birth/0 to <12 years old (Neonates, Infants, Children) Absolute values (ms) Borderline: 431 – 450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30 – 60 ms Prolonged*: Increase from baseline >60 ms 12 to 16/18 years old (Adolescents) Absolute values (ms) Borderline: 431 – 450 ms (Boys);451 – 470 ms (Girls) Prolonged*: >450 ms (Boys);>470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Birth/0 to <12 years old (Neonates, Infants, Children) Absolute values (ms) Borderline: 431 – 450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30 – 60 ms Prolonged*: Increase from baseline >60 ms 12 to 16/18 years old (Adolescents) Absolute values (ms) 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 baseline30 – 60 ms Prolonged*: Increase from baseline >60 ms

*QTc prolonged and ΔQTc >60 ms are the PCSA to be identified in individual subjects/patients listings.

Clinical chemistry

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	Birth/0 to 27 days old (Neonates) ≥4.3 mmol/L or 12 mg/dl 28 days/1 month to 16/18 years old (Infants, Children, Adolescents) ≥6.4 mmol/L or 18 mg/dl
Chloride	<80 mmol/L >115 mmol/L	≤80 mmol/L ≥115 mmol/L
Sodium	≤129 mmol/L ≥160 mmol/L	≤129 mmol/L ≥150 mmol/L
Potassium	<3 mmol/L ≥5.5 mmol/L	Birth/0 to 27 days old (Neonates) ≤3.0 mmol/L ≥7.0 mmol/L 28 days/1 month to 23 months old (Infants) ≤3.5 mmol/L ≥6.0 mmol/L 24 months/2 years to 16/18 years old (Children, Adolescents) ≤3.5 mmol/L ≥5.5 mmol/L
Glucose		
Hypoglycemia	≤3.9 mmol/L and <LLN	<2.7 mmol/L
Hyperglycemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	≥7 mmol/L (fasted after >12 hours of fast); ≥10.0 mmol/L (unfasted)
Albumin	≤25 g/L	

Vital signs

Heart rate	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	Birth/0 to 27 days old (Neonates) ≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm 28 days/1 month to 23 months old (Infants) ≤80 bpm and decrease form baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm 24 months/2 years to <6 years old (Children) ≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm 6 to <12 years old (Children) ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm 12 to 16/18 years old (Adolescents) ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
Systolic BP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	Birth/0 to 27 days old (Neonates) ≤60 mmHg and decrease from baseline ≥20 mmHg ≥85 mmHg and increase from baseline ≥20 mmHg 28 days/1 month to 23 months old (Infants) ≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg 24 months/2 years to <6 years old (Children) ≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old (Children) ≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old (Adolescents) ≤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	Birth/0 to 27 days old (Neonates) ≤34 mmHg and decrease from baseline ≥10 mmHg ≥50 mmHg and increase from baseline ≥10 mmHg 28 days/1 month to 23 months old (Infants) ≤34 mmHg and decrease from baseline ≥10 mmHg ≥54 mmHg and increase from baseline ≥10 mmHg 24 months/2 years to <6 years old (Children) ≤34 mmHg and decrease from baseline ≥10 mmHg ≥59 mmHg and increase from baseline ≥10 mmHg 6 to <12 years old (Children) ≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mmHg and increase from baseline ≥10 mmHg 12 to 16/18 years old (Adolescents) ≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg

Appendix B Visit windows

The analysis visits are assigned by comparing the distance between the calculated study day of each assessment (defined as time elapsed from the start of study drug in the TDR12857 study till the time of the assessment) with the listed target study days and the corresponding analysis windows of the applicable group of assessments, utilizing the general rules below:

1. If more than one non-missing values are assigned to the same analysis visit, then the assessment performed closest to the target study day will be used in the by-visit analysis.
2. Multiple values assessed on the same date will be averaged prior to being assigned an analysis visit.
3. If two assessments are assessed on different dates but equidistant from the target date, the values assessed on a later date will be used.
4. Use a combination of 2 & 3 in cases where there are multiple records equidistant from the target study day. For example, for a post-baseline visit, if there are 2 records, 7 days before the infusion and 3 records 7 days after the infusion, then take the 3 records after the infusion and average them for analysis value.

All visits in the applicable datasets will be used, including scheduled and unscheduled visits. (For change from TDR12857 baseline analyses, rebaseline visit and assessments performed after rebaseline will be handled in the same manner.) Note that baseline is defined as the latest available observation before the first infusion in the TDR12857.

Table 1 — Analysis windows for 6MWT, PFTs, ECG, hematology, and urinalysis:

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline	Baseline	
Week 1[@] in TDR (1)	Week 1	1 to 42 days
Week 13 in TDR (85)	Week 13	43 to 127 days
Week 25 in TDR (169)	Week 25	128 to 273 days/(1st day of LTS – 1)**
Month 6 in LTS (365)	Week 52	(1st day of LTS) to 456 days
Month 12 in LTS (547)	Week 78	457 to 638 days
Month 18 in LTS (730)	Week 104	639 to 821 days
Month 24 in LTS (912)	Week 130	822 to 1003 days
Month 30 in LTS (1095)	Week 156	1004 to 1186 days
Month 36 in LTS (1277)	Week 182	1187 to 1368 days
Month 42 in LTS (1460)	Week 208	1369 to 1551 days
Month 48 in LTS (1642)	Week 234	1552 to 1733 days
Month 54 in LTS (1825)	Week 260	1734 to 1916 days
Month 60 in LTS (2007)	Week 286	1917 to 2098 days
Month 66 in LTS (2190)	Week 312	2099 to 2281 days
Month 72 in LTS (2372)	Week 338	2282 to 2402 days

[@] Week 1 visit only applies to ECG, hematology, and urinalysis.
*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 273 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 273 as cutoff.

Table 2 – Immunogenicity (anti-alglucosidase alfa IgG antibody) – Group 2 patients only

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline/Week 1	Baseline	
Week 25 in TDR (169)	Week 25	92 to 273 days/(1st day of LTS – 1)**
Month 6 in LTS (365)	Week 52	(1st day of LTS) to 456 days
Month 12 in LTS (547)	Week 78	457 to 638 days
Month 18 in LTS (730)	Week 104	639 to 821 days
Month 24 in LTS (912)	Week 130	822 to 1003 days
Month 30 in LTS (1095)	Week 156	1004 to 1186 days
Month 36 in LTS (1277)	Week 182	1187 to 1368 days
Month 42 in LTS (1460)	Week 208	1369 to 1551 days
Month 48 in LTS (1642)	Week 234	1552 to 1733 days
Month 54 in LTS (1825)	Week 260	1734 to 1916 days
Month 60 in LTS (2007)	Week 286	1917 to 2098 days
Month 66 in LTS (2190)	Week 312	2099 to 2281 days
Month 72 in LTS (2372)	Week 338	2282 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 273 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 273 as cutoff.

Table 3 – Immunogenicity (anti-avalglucosidase alfa [neoGAA] antibodies)

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline/Week 1	Baseline	
Week 5 in TDR (35)	Week 5	23 to 50 days
Week 9 in TDR (63)	Week 9	51 to 78 days
Week 13 in TDR (91)	Week 13	79 to 106 days
Week 17 in TDR (119)	Week 17	107 to 134 days
Week 21 in TDR (148)	Week 21	135 to 163 days
Week 25 in TDR (176)	Week 25	164 to 183 days
Week 27 in TDR (190)	Week 27	184 to 198 days/(1st day of LTS - 1)
Month 1 in LTS (213)	Week 32	(1st day of LTS) to 228 days
Month 2 in LTS (244)	Week 36	229 to 259 days
Month 3 in LTS (274)	Week 40	260 to 289 days
Month 4 in LTS (304)	Week 44	290 to 319 days
Month 5 in LTS (335)	Week 48	320 to 350 days
Month 6 in LTS (365)	Week 52	351 to 411 days
Month 9 in LTS (456)	Week 65	412 to 502 days
Month 12 in LTS (547)	Week 78	503 to 594 days
Month 15 in LTS (639)	Week 91	595 to 685 days
Month 18 in LTS (730)	Week 104	686 to 776 days
Month 21 in LTS (821)	Week 117	777 to 867 days
Month 24 in LTS (912)	Week 130	868 to 959 days
Month 27 in LTS (1004)	Week 143	960 to 1050 days
Month 30 in LTS (1095)	Week 156	1051 to 1141 days
Month 33 in LTS (1186)	Week 169	1142 to 1232 days

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Month 36 in LTS (1277)	Week 182	1233 to 1324 days
Month 39 in LTS (1369)	Week 195	1325 to 1415 days
Month 42 in LTS (1460)	Week 208	1416 to 1506 days
Month 45 in LTS (1551)	Week 221	1507 to 1597 days
Month 48 in LTS (1642)	Week 234	1598 to 1689 days
Month 51 in LTS (1734)	Week 247	1690 to 1780 days
Month 54 in LTS (1825)	Week 260	1781 to 1871 days
Month 57 in LTS (1916)	Week 273	1872 to 1962 days
Month 60 in LTS (2007)	Week 286	1963 to 2054 days
Month 63 in LTS (2099)	Week 299	2055 to 2145 days
Month 66 in LTS (2190)	Week 312	2146 to 2236 days
Month 69 in LTS (2281)	Week 325	2237 to 2327 days
Month 72 in LTS (2372)	Week 338	2328 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 273 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 273 as cutoff.

Table 4 – Biochemistry

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline	Baseline	
Week 1 in TDR (1)	Week 1	1 to 8 days
Week 3 in TDR (15)	Week 3	9 to 21 days
Week 5 in TDR (29)	Week 5	22 to 35 days
Week 7 in TDR (43)	Week 7	36 to 49 days
Week 9 in TDR (57)	Week 9	50 to 63 days
Week 11 in TDR (71)	Week 11	64 to 77 days
Week 13 in TDR (85)	Week 13	78 to 91 days
Week 15 in TDR (99)	Week 15	92 to 105 days
Week 17 in TDR (113)	Week 17	106 to 119 days
Week 19 in TDR (127)	Week 19	120 to 133 days
Week 21 in TDR (142)	Week 21	134 to 148 days
Week 23 in TDR (156)	Week 23	149 to 162 days
Week 25 in TDR (169)	Week 25	163 to 176 days/(1st day of LTS – 1)**
Day 1/Week 0 in LTS (183)	Week 28	(1st day of LTS) to 198 days
Month 1 in LTS (213)	Week 32	199 to 228 days
Month 2 in LTS (244)	Week 36	229 to 259 days
Month 3 in LTS (274)	Week 40	260 to 289 days
Month 4 in LTS (304)	Week 44	290 to 319 days
Month 5 in LTS (335)	Week 48	320 to 350 days
Month 6 in LTS (365)	Week 52	351 to 380 days
Month 7 in LTS (396)	Week 56	381 to 411 days
Month 8 in LTS (426)	Week 61	412 to 441 days

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Month 9 in LTS (456)	Week 65	442 to 471 days
Month 10 in LTS (487)	Week 69	472 to 502 days
Month 11 in LTS (517)	Week 74	503 to 532 days
Month 12 in LTS (547)	Week 78	533 to 562 days
Month 13 in LTS (578)	Week 82	563 to 593 days
Month 14 in LTS (609)	Week 87	594 to 624 days
Month 15 in LTS (639)	Week 91	625 to 654 days
Month 16 in LTS (670)	Week 96	655 to 685 days
Month 17 in LTS (700)	Week 100	686 to 715 days
Month 18 in LTS (730)	Week 104	716 to 745 days
Month 19 in LTS (761)	Week 108	746 to 776 days
Month 20 in LTS (791)	Week 112	777 to 806 days
Month 21 in LTS (821)	Week 117	807 to 836 days
Month 22 in LTS (852)	Week 121	837 to 867 days
Month 23 in LTS (883)	Week 126	868 to 898 days
Month 24 in LTS (912)	Week 130	899 to 927 days
Month 25 in LTS (944)	Week 134	928 to 959 days
Month 26 in LTS (974)	Week 139	960 to 989 days
Month 27 in LTS (1004)	Week 143	990 to 1019 days
Month 28 in LTS (1035)	Week 147	1020 to 1050 days
Month 29 in LTS (1065)	Week 152	1051 to 1080 days
Month 30 in LTS (1095)	Week 156	1081 to 1110 days
Month 31 in LTS (1126)	Week 160	1111 to 1141 days
Month 32 in LTS (1157)	Week 165	1142 to 1172 days

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Month 33 in LTS (1186)	Week 169	1173 to 1201 days
Month 34 in LTS (1218)	Week 173	1202 to 1233 days
Month 35 in LTS (1248)	Week 178	1234 to 1263 days
Month 36 in LTS (1277)	Week 182	1264 to 1324 days
Month 39 in LTS (1369)	Week 195	1325 to 1415 days
Month 42 in LTS (1460)	Week 208	1416 to 1506 days
Month 45 in LTS (1551)	Week 221	1507 to 1597 days
Month 48 in LTS (1642)	Week 234	1598 to 1689 days
Month 51 in LTS (1734)	Week 247	1690 to 1780 days
Month 54 in LTS (1825)	Week 260	1781 to 1871 days
Month 57 in LTS (1916)	Week 273	1872 to 1962 days
Month 60 in LTS (2007)	Week 286	1963 to 2054 days
Month 63 in LTS (2099)	Week 299	2055 to 2145 days
Month 66 in LTS (2190)	Week 312	2146 to 2236 days
Month 69 in LTS (2281)	Week 325	2237 to 2327 days
Month 72 in LTS (2372)	Week 338	2328 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 176 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 176 as cutoff.

Table 5 – Urine Hex4

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline	Baseline	
Week 1 in TDR (1)	Week 1	1 to 8 days
Week 3 in TDR (15)	Week 2	9 to 21 days
Week 5 in TDR (29)	Week 5	22 to 35 days
Week 7 in TDR (43)	Week 7	36 to 49 days
Week 9 in TDR (57)	Week 9	50 to 63 days
Week 11 in TDR (71)	Week 11	64 to 77 days
Week 13 in TDR (85)	Week 13	78 to 91 days
Week 15 in TDR (99)	Week 15	92 to 105 days
Week 17 in TDR (113)	Week 17	106 to 119 days
Week 19 in TDR (127)	Week 19	120 to 133 days
Week 21 in TDR (142)	Week 21	134 to 148 days
Week 23 in TDR (156)	Week 23	149 to 162 days
Week 25 in TDR (169)	Week 25	163 to 176 days/(1st day of LTS – 1)**
Month 6 in LTS (365)	Week 52	(1st day of LTS) to 548 days
Month 18 in LTS (730)	Week 104	549 to 913 days
Month 30 in LTS (1095)	Week 156	914 to 1278 days
Month 42 in LTS (1460)	Week 208	1279 to 1643 days
Month 54 in LTS (1825)	Week 260	1644 to 2008 days
Month 66 in LTS (2190)	Week 312	2009 to 2373 days
Month 72 in LTS (2372)	Week 338	2374 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 176 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 176 as cutoff.

Table 6 – Plasma concentration of avalglucosidase alfa

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline	Baseline	
Week 1 in TDR (1)	Week 1	1 to 42 days
Week 13 in TDR (85)	Week 13	43 to 127 days
Week 25 in TDR (169)	Week 25	128 to 273 days/(1st day of LTS – 1)**
Month 6 in LTS (365)	Week 52	(1st day of LTS) to 548 days
Month 18 in LTS (730)	Week 104	549 to 913 days
Month 30 in LTS (1095)	Week 156	914 to 1278 days
Month 42 in LTS (1460)	Week 208	1279 to 1643 days
Month 54 in LTS (1825)	Week 260	1644 to 2008 days
Month 66 in LTS (2190)	Week 312	2009 to 2373 days
Month 72 in LTS (2372)	Week 338	2374 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 273 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 273 as cutoff.

Table 7 –MRI, muscle biopsy

VISIT (target study day*)	Analysis Visit	Analysis Visit Window (in study days*)
Baseline	Baseline	
Week 27 in TDR (184)	Week 27	92 to 273 days/(1st day of LTS – 1)**
Month 24 in LTS (365)	Week 52	(1st day of LTS) to 1278 days
Month 48 in LTS (1095)	Week 156	1279 to 2008 days
Month 72 in LTS (2372)	Week 338	2009 to 2402 days

*Study days are days since the first infusion in the TDR12857 study.
**For patients who enrolled in LTS13769, the upper boundary of the window is 273 days or (1st day of LTS – 1), whichever is earlier; for patients who didn't enroll in LTS13769, use study day 273 as cutoff.

Other assessments not specified above, if presented in by-visit summary tables, will use the recorded visits, rather than defined analysis visits.

By visit analyses of changes over time from rebaseline will use the rebased visits recorded.

Signature Page for
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Approve & eSign	[Name] Clinical 26-Mar-2020 21:03:03 GMT+0000

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