Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease

Supplementary Materials: Table of Contents

Redacted Documents Approval Form

Product Code: GZ402666
Study Code / Name: LTS13769
Study Title: An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease

Documents reviewed:	☐ Clinical Study Report – Body ☒ Protocol and amendments (if any) ☐ Sample CRF ☐ Statistical Analysis Plan_____

Trial Disclosure Manager/ Medical Writer:	Cara Campora

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Clinical Development Physician or Medical Product Leader Comments

The redacted clinical documents as listed above were reviewed and approved

By: 

Name: Olivier Huynh-Ba

Date: 21Jul2021

AMENDED CLINICAL TRIAL PROTOCOL 09

COMPOUND: GZ402666 - avalglucosidase alfa (neoGAA, GZ402666)

An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease

STUDY NUMBER: LTS13769

STUDY NAME: NEO-EXT

VERSION DATE / STATUS: 21-Dec-2020 / Approved

Version Number:	1	EudraCT IND Number(s) WHO universal trial number	2013-003321-28 109569 U1111-1147-3439
Date:	21-Dec-2020	Total number of pages:	91

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 09	*All*	*21 December 2020, version 1 (electronic 9.0)*
Amended Clinical Trial Protocol 08	*Denmark only*	*30 September 2020, version 1 (electronic 8.0)*
Amended Clinical Trial Protocol 07	*All*	*21 January 2020, version 1 (electronic 7.0)*
Amended Clinical Trial Protocol 06	*All*	*06 September 2019, version 1 (electronic 6.0)*
Amended Clinical Trial Protocol 05	*France only*	*18 July 2018, version 1 (electronic 5.0)*
Amended Clinical Trial Protocol 04	*All*	*27 November 2017, version 1 (electronic 4.0)*
Amended Clinical Trial Protocol 03	*All*	*29 January 2016, version 1 (electronic 3.0)*
Amended Clinical Trial Protocol 02	*All*	*25 July 2014, version 1 (electronic 1.0)*
Amended Clinical Trial protocol 01	*All*	*09 December 2013, version 1 (electronic 1.0)*
Original Protocol		*30 September 2013, version 1 (electronic 1.0)*

Amended protocol 09 (21 December 2020)

This amended protocol (Amendment 09) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/Ethics Committee (EC) of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for this amendment is as follows:

- To include the recommendations that were developed for the COVID-19 pandemic period and were shared with the sites/Investigators. These recommendations will remain applicable after the end of the pandemic, especially the information regarding the post-infusion surveillance period.
- To revise the text in Sections 12, 13, and 14 as per the current Sanofi protocol template to use the updated wordings that are compliant with general guidance, including monitoring techniques.
- To update Section 8.1 for details regarding home infusions to harmonize this text across the different studies included in the avalglucosidase alfa development program.

Protocol amendment summary of changes table

Section Number and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes Table	Document formatting revision.	To update document history and provide overall rationale for the amendment.
Section 8.1 Investigational medicinal product	Requirement for patients to remain in the hospital or in the infusion center for the observation period related to onset of AEs was revised from 2 hours to 1 hour and the following text was added: "In case the patient does not stay for this observation period (eg, as part of contingency measures for a regional or national emergency that is declared by a governmental agency), the Investigator (or appropriate designee) will contact the patient to ensure that no AEs occurred during the observation period."	Due to COVID-19 pandemic restrictions, the observation period after the infusions were performed at the study site or infusion center was shortened or skipped for patient's safety reasons. Also to lighten this period after the end of the pandemic and in order to obtain information in case this observation period is not performed, the observation time after the end of infusion is reduced to 1 hour.
Section 8.1 Investigational medicinal product	Under "Home infusion" subsection, the text was updated to harmonize with other studies included in the avalglucosidase alfa development program.	The home infusion text is amended to allow patients to benefit from home infusion sooner in case of an unexpected event (ie, after 6 months free of IARs instead of 12 months) or to resume home infusion sooner after interruption for IAR during home infusion. Some text is also updated to harmonize across the other studies included in the avalglucosidase alfa development program.
Section 10.4.3 Instructions for reporting serious adverse events	Text was deleted regarding proactively sending the SAE-related reporting documents via fax or as photocopy.	As per recent Sanofi procedures, the direct sending of source documents to the Sponsor (except to Pharmacovigilance department) is no more recommended.
Section 12 Regulatory, ethical, and study oversight considerations; Section 13 Study monitoring; Section 14 Additional requirements	Headings, subsections, and corresponding text were fully updated in Sections 12, 13, and 14 to reflect current practices as outlined in the current protocol template, including monitoring techniques.	To align with current protocol template.
Section 17.2 Appendix 2: Protocol amendment history	Added new Section 17.2.8.	To incorporate the changes from amended protocol 07 to amended protocol 08.
Throughout	Typos have been corrected where necessary. Minor editorial and document formatting revisions are made.	To provide clarifications.

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Genzyme Corporation 50 Binney Street Cambridge, MA, 02142 USA
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: GZ402666 - avalglucosidase alfa (neoGAA, GZ402666)	**STUDY No.: LTS13769**
TITLE	An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease.
INVESTIGATOR/TRIAL LOCATION	Sites that have previously participated, or that are currently participating, in an avalglucosidase alfa study.
STUDY OBJECTIVES	**Primary objective:** 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. **Secondary objective:** To assess the long-term effect of avalglucosidase alfa on pharmacodynamic and exploratory efficacy variables to assess if the benefits of avalglucosidase alfa are maintained and to assess the time course of response.
STUDY DESIGN	Open-label, multicenter, multinational extension study of the long-term safety and PK of repeated biweekly infusions of avalglucosidase alfa in patients with Pompe disease.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Patients with Pompe disease who previously completed an avalglucosidase alfa study. I 02. The patient and/or their parent/legal guardian is willing and able to provide signed informed consent, and the patient, if <18 years of age, is willing to provide assent if deemed able to do so. I 03. The patient (and patient's legal guardian if patient is <18 years of age) must have the ability to comply with the clinical protocol. I 04. The patient, if female and of childbearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (B-hCG)] at baseline. Note: Sexually active female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or to use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device, or intrauterine system for the entire duration of the treatment period.

	Exclusion criteria: E 01. The patient is concurrently participating in another clinical study using investigational treatment. E 02. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study. E 03. The patient has clinically significant organic disease (with the exception of symptoms relating to Pompe disease), including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, precludes participation in the study or potentially decreases survival.
Total expected number of patients	This is an ongoing extension study, and therefore, the number of patients will be determined by enrollment from other avalglucosidase alfa studies.
Expected number of sites	The number of sites will be determined by enrollment of patients from other avalglucosidase alfa studies.
STUDY TREATMENT	
Investigational product	Avalglucosidase alfa (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan).
Formulation and route of administration	Sterile lyophilized powder administered by intravenous (IV) infusion following reconstitution and dilution.
Dose regimen	20 mg/kg of body weight every other week (qow).
PRIMARY ENDPOINT	**Primary endpoint:** **Safety:** Assessment of adverse events (AEs)/treatment-emergent AEs (TEAEs), including infusion-associated reactions (IARs) and deaths. Physical examination. Clinical laboratory evaluations including hematology, biochemistry, and urinalysis. Vital signs. Body weight. 12-lead electrocardiogram (ECG). Immunogenicity assessments.
SECONDARY AND EXPLORATORY ENDPOINTS	**Secondary endpoints:** **Pharmacokinetics** Estimates for C_{max}, AUC_{last}, AUC, $t_{1/2z}$, CL, and Vd. **Pharmacodynamics** Skeletal muscle magnetic resonance imaging (MRI). Skeletal muscle needle or open biopsy. Urinary Hex4. [redacted]. **Pharmacogenetics** Serum skeletal muscle ribonucleic acid (RNA) expression analysis. [redacted].

	Exploratory Endpoints: **Efficacy** 6-minute walk test (6MWT). Pulmonary function testing (PFT) endpoints.
ASSESSMENT SCHEDULE	Refer to study and period flow charts. Medical/surgical history, and Pompe disease history, including GAA gene mutations, will be imported from the patient's prior avalglucosidase alfa study file in the database when possible.
STATISTICAL CONSIDERATIONS	Out of range laboratory values, vital signs, and ECGs will be flagged by the Investigator as clinically significant or non-clinically significant abnormalities. The clinically significant abnormalities will be recorded as AEs and included in the TEAE counts. Treatment-emergent adverse events will be tabulated (counts and percentages). Infusion-associated reactions and discontinuations due to AEs will be summarized. Descriptive statistics will be generated by dose level and time points for selected parameters of interest. In addition, raw data and changes from baseline for selected parameters will be summarized by descriptive statistics and/or plots. Descriptive statistics for actual values and changes from baseline will be generated by time point for selected safety parameters of interest. Data may also be plotted. For the purpose of analysis, baseline will be prior to the first dose of GZ402666 in any prior avalglucosidase alfa study. **Pharmacokinetics** Pharmacokinetic parameters will be summarized for each dose level and study visit by means of descriptive statistics. **Pharmacodynamics** Changes over time in tissue glycogen content in the lower extremity muscle will be summarized using descriptive statistics. Evaluation of intact muscle and fatty replacement from MRI will be descriptive using a grading scale and, if feasible, quantitative using a numeric method of determining the degree (%) of overall fatty replacement of muscle from the skeletal muscle MRI and an individual (%) measure for the quadriceps. A correlative measure comparing the biopsied muscle and its MRI counterpart will also be performed. Relationship between pharmacodynamic and efficacy endpoints will be explored using graphic display or correlational analysis as appropriate. **Exploratory efficacy** Observed measurements and changes from baseline will be provided for each endpoint: 6MWT and PFT parameters.
DURATION OF STUDY (per patient)	The duration of the study for each patient is initially 6 years. Each patient will continue with the study until the patient withdraws, the Investigator withdraws the patient, or the Sponsor terminates the study. An additional follow-up phase will begin after the patient has completed the 6-year study period, and will last until avalglucosidase alfa is approved in the patient's country, except in the UK, Germany and

	Denmark, where the duration of the additional follow-up phase will be up to the approval in the country or limited to a maximum of 2 years, whichever occurs first (ie, for patients in the UK, Germany and Denmark, the total study duration per patient is 8 years at the maximum including the initial 6-year period and the additional 2-year follow-up).
STUDY COMMITTEES	**Steering Committee: No** **Data Monitoring Committee: Yes** **Adjudication Committee: No**

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

Baseline[a]	**Biweekly**[b]	**Monthly**	**Quarterly**	**Every 6 Months**	**At 6 Months, Yearly Thereafter**	**Every 2 Years**
• Informed consent • Inclusion/exclusion criteria • Urine pregnancy test (females only) • ECG • Demographics • Medical/surgical history • Pompe disease history, including GAA mutation • ECG, hematology, biochemistry and urinalysis data prior to first avalglucosidase alfa infusion • Results of MRI baseline from previous avalglucosidase alfa study to be obtained	• Infusion of avalglucosidase alfa • Vital signs	• Urine pregnancy test (females only) • For first 3 years since enrollment: Biochemistry • For first 6 months: Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients	• Body weight • After first 6 months: Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients • After first 3 years since enrollment: Biochemistry	• Physical examination • ECG • Hematology and urinalysis • Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa) • 6MWT • PFT	• avalglucosidase alfa plasma samples for PK analysis • Urine Hex4 sample collection [redacted]	• MRI • Skeletal muscle needle or open biopsy[c] • Serum samples for skeletal muscle RNA expression analysis[c]

Every Visit: Adverse event and concomitant medication collection

Re-baseline Visit	• Physical examination (within 1 month) • Urine pregnancy test (females only) • Body weight • Vital signs • ECG (within 1 month) • Hematology and urinalysis (within 1 month) • Biochemistry	• Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients • Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa) • avalglucosidase alfa plasma PK samples (within 6 months)	• MRI (within 6 months) • Skeletal muscle needle or open biopsy (within 6 months)[c] • Urine Hex4 sample collection (within 1 month) [redacted]	• 6MWT (within 1 month) • PFT (within 1 month) [redacted] • Serum samples for skeletal muscle RNA expression analysis (within 6 months)[c]

End of Study Visit	• Physical examination • Urine pregnancy test (females only) • Body weight • Vital signs • ECG • Hematology and urinalysis • Biochemistry	• Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients • Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa) • avalglucosidase alfa plasma PK samples	• MRI • Skeletal muscle needle or open biopsy (within 6 months)[c] • Urine Hex4 sample collection [redacted]	• 6MWT • PFT [redacted] • Serum samples for skeletal muscle RNA expression analysis (within 6 months)[c] • Infusion of avalglucosidase alfa

Follow-up Visit: Adverse event and concomitant medication collection

Additional Follow-up Phase: An additional follow-up phase will begin after the patient has completed the 6-year study period, and will last until avalglucosidase alfa is approved in the patient's country, except in the UK, Germany and Denmark, where the duration of the additional follow-up phase will be up to the approval in the country or limited to a maximum of 2 years, whichever occurs first (ie, for patients in the UK, Germany and Denmark, the total study duration per patient is 8 years at the maximum including the initial 6-year period and the additional 2-year follow-up).

a Note that medical/surgical history, and Pompe disease history, including GAA gene mutations will be imported from the patient's prior avalglucosidase alfa study file in the database when possible. ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study) will be entered by the study site into the database.

b In case of temporary treatment discontinuation visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa (GZ402666) as outlined in Section 10.1.3.8.

c Muscle biopsy is not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline.

6MWT = 6-minute walk test; ADA = anti-drug antibody, ECG = electrocardiogram; Hex4 = glucose tetrasaccharide; IgG = immunoglobulin G; MRI = magnetic resonance imaging; PFT = pulmonary function testing; PK = pharmacokinetic(s)

1.2 STUDY FLOW CHART

1.2.1 Patients receiving same dose as received in a prior avalglucosidase alfa study (inclusive of 20 mg/kg qow)

Phase	**Baseline**[a]	**Avalglucosidase alfa Treatment Phase**					
Timing[c]		**Biweekly**	**Monthly**[d]	**Quarterly**	**Every 6 months**	**At 6 months, yearly thereafter**	**Every 2 years**[b]
Informed consent for extension	X						
Visit at clinical site	<	-	-	-	-	-	>
Inclusion/exclusion criteria	X						
Demographic	X						
Concomitant medications	<	-	-	-	-	-	>
Study treatment administration	within a ±7-day window[e]						
avalglucosidase alfa infusion		X					
Vital signs		X					
Safety[f]	within a ±14-day window[e]						
Physical examination					X		
Urine pregnancy test[g]	X		X				
Body weight				X			
ECG	X				X		
Hematology, urinalysis[h]					X		
Biochemistry[h]			X For first 3 years since enrollment	X After first 3 years since enrollment			
Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients[i]			X For first 6 months	X After first 6 months			
Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa)					X		
Adverse event collection	<	-	-	-	-	-	>

Phase	Baseline[a]	Avalglucosidase alfa Treatment Phase					
Timing[c]		**Biweekly**	**Monthly[d]**	**Quarterly**	**Every 6 months**	**At 6 months, yearly thereafter**	**Every 2 years[b]**
Pharmacokinetics	within a ±14-day window[e]						
avalglucosidase alfa plasma samples						X	
Pharmacodynamics[f]	within a ±14-day window[e]						
MRI[j]							X
Skeletal muscle biopsy[k]							X
Urine Hex4 samples[h]						X	
[redacted]							
Efficacy[f]	within a ±14-day window[e]						
6MWT					X		
PFT					X		
Pharmacogenetics[f]	within a ±14-day window[e]						
[redacted]							
Serum samples for skeletal muscle RNA expression analyses[k]							X

a Medical/surgical history, and Pompe disease history, including GAA gene mutations, will be imported from the patient's prior avalglucosidase alfa study file in the database when possible. ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study) will be entered by the study site into the database.
b If the patient discontinues from the study early, then they should undergo the EOS and 30-Day follow-up visits; please refer to Section 1.2.3 for details of procedures to be performed during these visits.
c In case of temporary treatment discontinuation visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa (GZ402666) as outlined in protocol Section 10.1.3.8.
d Monthly assessments start at study Week 4.
e Patients should adhere to original target infusion and visit schedule based on first infusion in LTS13769.
f See Section 10.1 for specific details on the timing of each assessment relative to avalglucosidase alfa infusion during the treatment period.
g Females only.
h Fasted [redacted] urine, [redacted] sample.
i Additional samples may be taken for circulating immune complex detection, IgE, serum tryptase, and complement activation, following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions (see Section 8.8.2 for details).
j MRI obtained from the previous study will be used as baseline.
k Muscle biopsy is not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline.

<-> = collection at every visit; 6MWT = 6-minute walk test; ADA = anti-drug antibody, ECG = electrocardiogram; EOS = end of study; ERT = enzyme replacement therapy; Hex4 = glucose tetrasaccharide; IgG = immunoglobulin G; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PFT = pulmonary function testing.

1.2.2 Patients being switched to avalglucosidase alfa 20 mg/kg qow from previous different dose

Phase	**Re-baseline[a]**	**Avalglucosidase alfa Treatment Phase**					
Timing[c]		**Biweekly**	**Monthly[d]**	**Quarterly**	**Every 6 months**	**At 6 months, yearly thereafter**	**Every 2 years[b]**
Informed consent for patients switching to 20 mg/kg qow	X						
Visit at clinical site	<	-	-	-	-	-	>
Concomitant medications	<	-	-	-	-	-	>
Study treatment administration	within a ±7-day window[e]						
Avalglucosidase alfa infusion	X	X					
Vital signs	X	X					
Safety[f]	within a ±14-day window[e]						
Physical examination	X				X		
Urine pregnancy test[g]	X		X				
Body weight	X			X			
ECG	X				X		
Hematology, urinalysis[h]	X				X		
Biochemistry[h]	X		X For first 3 years since enrollment	X After first 3 years since enrollment			
Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients[i]	X		X For first 6 months	X After first 6 months			
Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa)	X				X		
Adverse event collection	<	-	-	-	-	-	>
Pharmacokinetics	within a ±14-day window[e]						
Avalglucosidase alfa plasma samples	X					X	

Phase	Re-baseline[a]	Avalglucosidase alfa Treatment Phase					
Timing[c]		**Biweekly**	**Monthly[d]**	**Quarterly**	**Every 6 months**	**At 6 months, yearly thereafter**	**Every 2 years[b]**
Pharmacodynamics[f]	within a ±14-day window[e]						
MRI	X						X
Skeletal muscle biopsy[j]	X						X
Urine Hex4 samples[h]	X					X	
[redacted]							
Efficacy[f]	within a ±14-day window[e]						
6MWT	X				X		
PFT	X				X		
Pharmacogenetics[f]	within a ±14-day window[e]						
[redacted]							
Serum samples for skeletal muscle RNA expression analyses[j]	X						X

a The "Re-baseline" will only apply to patients who have switched from 5 or 10 to 20 mg/kg. Medical/surgical history, and Pompe disease history, including GAA gene mutations, will be imported from the patient's prior avalglucosidase alfa study file in the database when possible. ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study) will be entered by the study site into the database.

b If the patient discontinues from the study early then they should undergo the EOS and 30-Day follow-up visits, please refer to Section 1.2.3 for details of procedures to be performed during these visits.

c In case of temporary treatment discontinuation visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in protocol Section 10.1.3.8.

d Monthly assessments start at study Week 4.

e Patients should adhere to original target infusion and visit schedule based on first infusion of 20 mg/kg in the LTS13769 study.

f See Section 10.1 for specific details on the timing of each assessment relative to avalglucosidase alfa infusion during the treatment period.

g Females only.

h Fasted [redacted] urine, [redacted] sample.

i Additional samples may be taken for circulating immune complex detection, IgE, serum tryptase, and complement activation, following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions (see Section 8.8.2 for details).

j Muscle biopsy is not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline.

<-> =collection at every visit; 6MWT =6-minute walk test; ADA =anti-drug antibody, ECG =electrocardiogram; EOS = end of study; ERT =enzyme replacement therapy; Hex4 =glucose tetrasaccharide; IgG =immunoglobulin G; IMP =investigational medicinal product; MRI =magnetic resonance imaging; PFT =pulmonary function testing; qow =every other week.

1.2.3 Additional follow-up phase

Phase	**Avalglucosidase alfa Follow-up Period**							**30-Day Follow-up Visit**[a]
Timing[b]	**Biweekly**	**Monthly**	**Quarterly**	**Every 6 Months**	**Yearly**	**Every 2 years**[c]	**End of Study Visit**	
Visit at clinical site	<	-	-	-	-	-	>	
Concomitant medications	<	-	-	-	-	-	-	>
Study treatment administration	within a ±7-day window[d]							
Avalglucosidase alfa infusion	X						X	
Vital signs	X						X	
Safety[e]	within a ±14-day window[d]							
Physical examination				X			X	
Urine pregnancy test[f]		X					X	
Body weight			X				X	
ECG				X			X	
Hematology, urinalysis[g]				X			X	
Biochemistry[g]				X			X	
Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients[h]				X			X	
Adverse event collection	<	-	-	-	-	-	-	>

Phase	Avalglucosidase alfa Follow-up Period							30-Day Follow-up Visit[a]
Timing[b]	**Biweekly**	**Monthly**	**Quarterly**	**Every 6 Months**	**Yearly**	**Every 2 years**[c]	**End of Study Visit**	
Pharmacodynamics[e]	within a ±14-day window[d]							
MRI						X	X	
Skeletal muscle biopsy[i]							X	
Urine Hex4 samples[g]							X	
[redacted]								
Efficacy[e]	within a ±14-day window[d]							
6MWT				X			X	
PFT				X			X	
Pharmacogenetics[e]	within a ±14-day window[d]							
[redacted]								

a The on-treatment period may end earlier (ie, 2 weeks after the last administration of IMP) if the patient enrolls in another study or receives commercially available ERT. In this case the follow-up period may be reduced from 4 to 2 weeks.
b In case of temporary treatment discontinuation visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in protocol Section 10.1.3.8.
c If the patient discontinues from the study early then they should undergo the EOS and 30-Day follow-up visits.
d Patients should adhere to original target infusion and visit schedule based on first infusion in LTS13769.
e See Section 10.1 for specific details on the timing of each assessment relative to avalglucosidase alfa infusion during the treatment period.
f Females only.
g Fasted [redacted] urine, [redacted] sample.
h Additional samples may be taken for circulating immune complex detection, IgE, serum tryptase, and complement activation, following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions (see Section 8.8.2 or details).
i Muscle biopsy is not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline.

<-> = collection at every visit; 6MWT = 6-minute walk test; ADA = anti-drug antibody, ECG = electrocardiogram; EOS = end of study; ERT = enzyme replacement therapy; Hex4 = glucose tetrasaccharide; IAR = infusion-associated reaction; IgE = immunoglobulin E; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PFT = pulmonary function testing.

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2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

6MWT:	6-minute walk test
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC:	area under the concentration curve
bis-M6P:	bis-mannose-6-phosphate
CI:	confidence interval
CL:	clearance
CPR:	cardiopulmonary resuscitation
CRF:	case report form
CTCAE:	common terminology criteria for adverse events
DMC:	Data Monitoring Committee
DPO:	Data Protection Officer
EC:	Ethics Committee
ECG:	electrocardiogram
eCRF:	electronic case report form
ERT:	enzyme replacement therapy
EU:	European Union
FDA:	Food and Drug Administration
FEV1:	forced expiratory volume in the 1st second of the FVC maneuver
FVC:	forced vital capacity
GAA:	acid alpha-glucosidase
GAAKO:	GAA knockout
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GSD:	glycogen storage disease
Hex4:	glucose tetrasaccharide
IAR:	infusion-associated reaction
IB:	Investigator’s Brochure
ICF:	Informed Consent Form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IgE:	immunoglobulin E
IgG:	immunoglobulin G
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IV:	intravenous
M6P:	mannose-6-phosphate
MedDRA:	Medical Dictionary for Regulatory Activities

MEP:	maximal expiratory pressure
MIP:	maximal inspiratory pressure
MRI:	magnetic resonance imaging
MUG:	methylumbelliferyl-α-D-glucoside
NCI:	National Cancer Institute
NOAEL:	no observed adverse effect level
PEF:	peak expiratory flow
PFT:	pulmonary function testing
PI:	Principal Investigator
PK:	pharmacokinetic(s)
PR:	interval from the beginning of the P wave until the beginning of the QRS complex
PT:	preferred term
qow:	every other week
QRS:	interval from start of the Q wave to the end of the S wave
QT:	interval between the start of the Q wave to the end of the T wave
QTc:	QT interval corrected for heart rate
rhGAA:	recombinant human acid alpha-glucosidase
RNA:	ribonucleic acid
RR:	interval between the peaks of successive QRS complexes
SAE:	serious adverse event
SD:	standard deviation
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
$t_{1/2}$:	terminal elimination half-life
TEAE:	treatment-emergent adverse event
TK:	toxicokinetic(s)
ULN:	upper limit of normal
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Pompe disease (also known as acid maltase deficiency or glycogen storage disease [GSD] Type II) is a rare, autosomal recessive genetic disorder caused by the deficiency of lysosomal acid α-glucosidase (GAA), an enzyme that degrades glycogen. Genzyme, a Sanofi company, has developed alglucosidase alfa, which contains the active ingredient recombinant human acid α-glucosidase (rhGAA), as long-term enzyme replacement therapy (ERT) for patients with a confirmed diagnosis of Pompe disease. Alglucosidase alfa treatment is globally approved (tradenames: Myozyme® and Lumizyme®) for the treatment of Pompe disease based on its efficacy to prolong invasive ventilator-free survival in infants (1) and its ability to improve walking distance and to stabilize respiratory function in children 8 years and older and adults (2). To achieve these benefits, alglucosidase alfa is administered at high doses (20 mg/kg every other week[qow]), relative to other ERTs. Echocardiogram measurements demonstrate that alglucosidase alfa works well in cardiac muscle. There is a more variable response to treatment in skeletal muscle. This is thought to be, at least in part, due to the relative low level of bis-mannose-6-phosphate (bis-M6P) on alglucosidase alfa. Therefore, increasing the level of bis-M6P on alglucosidase alfa may provide a mechanism to drive uptake into the skeletal muscle.

Genzyme is investigating a second generation therapy for Pompe disease called avalglucosidase alfa (neoGAA, GZ402666) (rhGAA conjugated with synthetic bis-M6P-Man6 glycan). Avalglucosidase alfa is a modification of alglucosidase alfa that results in the conjugation of a number of hexamannose structures containing 2 terminal M6P moieties to oxidized sialic acid residues on alglucosidase alfa, thereby increasing bis-M6P levels on the compound.

4.1.1 Safety pharmacology and toxicology

Four in vivo toxicology studies have been conducted to support the development of avalglucosidase alfa. These include 2 repeat dose studies (2 and 4 weeks) conducted in CD-1 mice, and 2 repeat dose studies (4 weeks and 6 months) conducted in cynomolgus monkeys. A safety pharmacology evaluation was also conducted as part of the 6-month toxicity study in cynomolgus monkeys. Additionally, a mouse micronuclei assessment was conducted in GAA knockout (GAAKO) mice to evaluate the potential genotoxicity of avalglucosidase alfa.

The toxicity of avalglucosidase alfa was first evaluated in CD-1 mice in a 14-day repeat dose study. Doses were administered as an intravenous (IV) bolus at 50 mg/kg every other day for 14 days. Administration of avalglucosidase alfa at 50 mg/kg was associated with macroscopic findings in the male reproductive tract (none of the male reproductive tract tissues were examined microscopically).

In the liver, minimal to mild multifocal necrosis and inflammatory infiltrates were present after administration of avalglucosidase alfa at 50 mg/kg, although no correlating serum chemistry alterations were observed. Terminal elevations in serum calcium, phosphorus, and potassium were

observed in males dosed with 50 mg/kg of avalglucosidase alfa. A definitive relationship of these alterations to the test article could not be established because of the possible confounding factor of carbon dioxide asphyxiation prior to blood collection in these animals. The above findings were further evaluated in the 28-day studies in CD-1 mice and cynomolgus monkeys, and in the 26-week study in cynomolgus monkeys.

The toxicity of avalglucosidase alfa was evaluated in 28-day repeat dose toxicity studies in the CD-1 mouse and the cynomolgus monkey. In both studies, avalglucosidase alfa was administered every week for 28 days (4 doses total) at 0, 4, 40, or 120 mg/kg via IV bolus to mice or via a 6-hour IV infusion to monkeys. Toxicokinetic data are summarized in Section 4.1.2.

Results from the study in CD-1 mice demonstrated that repeated administrations of avalglucosidase alfa were overall well tolerated. One death was noted and 1 early sacrifice was necessary within 1 hour of the fourth avalglucosidase alfa administration in the 4 mg/kg dose group. This was likely due to a hypersensitivity reaction following repeated administration of a human protein into a mouse. There were no significant changes noted in body weights, clinical observations, clinical chemistry and hematology parameters, or in organ weights and organ to body weight ratios. Histopathology of all animals at the terminal sacrifice showed no evidence of toxicity related to avalglucosidase alfa administration.

The no observed adverse effect level (NOAEL) was established at ≥120 mg/kg in CD-1 mice.

Results from the study in cynomolgus monkeys demonstrated that once weekly repeated administrations via a 6-hour IV infusion for 4 consecutive weeks was well tolerated by cynomolgus monkeys. There were no test article-related clinical signs or changes in body weight, body weight change (gain), physical examination findings, clinical pathology parameters, or macroscopic/microscopic findings that could be attributed to the administration of avalglucosidase alfa.

The NOAEL was established at ≥120 mg/kg in cynomolgus monkeys.

As hypersensitivity reactions are likely to occur in mice in long-term repeat dose toxicity assessments, and no differences in toxicological findings between species were noted in the 28-day studies, a 26-week repeat dose toxicity study was conducted in one species, the cynomolgus monkey. Avalglucosidase alfa was administered every other week for 26 weeks at doses of 0, 50, or 200 mg/kg via a 6-hour IV infusion, followed by a 4-week recovery period. Toxicokinetic data are summarized in Section 4.1.2.

Administration of avalglucosidase alfa was well tolerated and caused no changes in any parameter that was measured in this study. There were no test article-related changes in clinical observations, body weights, body weight changes, food consumption, ophthalmic evaluations, organ weights, or in macroscopic/microscopic evaluations. Furthermore, there were no macroscopic or microscopic findings in the male reproductive tract or in the liver.

There were 2 early sacrifices during the study. One female monkey on study was sacrificed in a moribund condition prior to receiving any test article. On Day 168, a second female monkey at 50 mg/kg was sacrificed in a moribund condition. The most likely cause of the moribund

condition was the result of systemic inflammation resulting from contamination of the venous access port and unrelated to the test article based on the macroscopic and microscopic findings.

The following evaluations were conducted as part of this study for evaluation of safety pharmacology and the results are as follows:

- Central nervous system: There were no changes in activity levels considered related to avalglucosidase alfa administration when compared to controls. All monkeys were observed to be in a normal quiet state (score of 2) to a high arousal state (score of 4) during the study. Observations for the presence of muscle fasciculations, facial muscle movements, and visual field were all normal.
- Respiratory rate, heart rate, and core body temperature: There were no changes considered related to avalglucosidase alfa administration when compared to controls.
- Electrocardiograms (ECGs): All monkeys maintained sinus rhythms throughout the study. One atrial and 1 ventricular premature depolarization were noted on Day 155. The ventricular premature depolarization occurred in a male animal administered vehicle, and the atrial premature depolarization was observed in a male monkey treated with 50 mg/kg of avalglucosidase alfa. These rhythm disturbances can occur in normal monkeys and were not test article related. Intravenous dosing once every 2 weeks with avalglucosidase alfa at up to 200 mg/kg/dose did not have any toxicologic effects on recorded ECGs in this study.

The NOAEL was established at 200 mg/kg in cynomolgus monkeys.

4.1.2 Absorption, distribution, metabolism, and excretion data

The pharmacokinetics (PK) of avalglucosidase alfa have been evaluated in a number of preclinical studies in the GAAKO mouse model of Pompe disease following administration of 20 mg/kg. Additionally, toxicokinetic (TK) evaluations were conducted as part of the 28-day toxicology study in CD-1 mice, the 28-day toxicology study in non-human primates, and the 26-week toxicology study in non-human primates.

Average PK parameters in GAAKO mice following a single IV administration at 20 mg/kg of avalglucosidase alfa are as follows: the terminal elimination half-life ($t_{1/2}$), 26.9 minutes; volume of distribution, 29.0 mL/kg; area under the concentration curve (AUC), 36.7 minutes*mg/mL; and clearance (CL), 0.55 mL/minutes/kg.

Avalglucosidase alfa TK was evaluated following single and repeat IV administration at dose levels of 4, 40, and 120 mg/kg in CD-1 mice (Table 1). Saturation kinetics were observed at the dose levels evaluated. This was characterized by increased $t_{1/2}$, decreased CL, and increased AUC/dose as the dose levels increased to 120 mg/kg. No consistent differences in TK parameters were noted when comparing the first and fourth dose, suggesting that there were no meaningful changes in TK parameters following repeated IV administration in CD-1 mice.

Table 1 - Toxicokinetic parameters for avalglucosidase alfa following the fourth intravenous dose to CD-1 mice at a dose of 4, 40, or 120 mg/kg

Parameter	4 mg/kg (n=1)	40 mg/kg (n=6)	120 mg/kg (n=5)
t1/2 (hr)	0.315	0.752 ±0.242	0.939 ±0.127
CL (mL/hr)	80.0	28.4 ±8.80	27.0 ±3.83
Vz (mL)	36.3	29.7 ±8.46	36.2 ±4.10
Cmax (µg/mL)	68.8	949 ±161	2866 ±656
AUC0-inf (µg x hr/mL)	50.0	1498 ±368	4513 ±589
AUC0-inf/Dose (µg x hr/mL/Dose)	12.5	37.4 ±9.19	37.6 ±4.91

Values represent mean ±SD.

Toxicokinetic parameters were also determined for avalglucosidase alfa in non-human primates following the first and fourth infusion at 40 and 120 mg/kg dose levels in a 28-day toxicology study (Table 2). There were limited serum concentration data available for the 4 mg/kg dose level at both the first and fourth doses, which did not allow for the estimation of TK parameters. Across both infusions analyzed, avalglucosidase alfa elimination was either monophasic or biphasic. Toxicokinetic parameters were calculated only from the first phase of elimination, as the second phase had limited data points for analysis (many animals had avalglucosidase alfa levels below the level of detection at later time points).

At both the first and fourth infusions of avalglucosidase alfa, saturation kinetics appear to be present. While this is only a trend at the first infusion, statistically significant differences occur in $t_{1/2}$ and CL at the fourth infusion. This suggests that saturation kinetics may become more prominent between 40 and 120 mg/kg after repeated infusions of avalglucosidase alfa.

No significant differences were noted for TK parameters between the first and fourth infusions at the 40 mg/kg dose level, but significant differences in TK parameters (decreased CL and increased $AUC_{0\text{-}inf}$/dose) were noted with repeated administration at the 120 mg/kg dose level. This suggests that repeated dosing in the monkey at this dose level affects the TK profile of avalglucosidase alfa. For both dose levels and infusions, avalglucosidase alfa TKs did not appear to differ between male and female monkeys.

Table 2 - Toxicokinetic parameters for avalglucosidase alfa following the first and fourth intravenous infusion to cynomolgus monkeys at doses of 4, 40, and 120 mg/kg

Parameter	First Dose			Fourth Dose		
	4 mg/kg (n=4)	40 mg/kg (n=4)	120 mg/kg (n=4)	4 mg/kg (n=4)	40 mg/kg (n=4)	120 mg/kg (n=4)
$t_{1/2}$ (hr)	N/A	0.533 ±0.189	0.729 ±0.179	N/A	0.508 ±0.184	0.919 ±0.199[a]
CL (mL/hr/kg)	N/A	53.5 ±21.5	40.3 ±10.6	N/A	43.3 ±8.84	20.5 ±2.22[b, d]
Vz (mL/kg)	N/A	38.4 ±10.5	44.0 ±20.2	N/A	33.0 ±18.5	27.0 ±6.01
C_{max} (µg/mL)	N/A	192 ±63.3	862 ±302	N/A	258 ±39.7	1273 ±214
$AUC_{0\text{-}inf}$ (µg x hr/mL)	N/A	824 ±260	3155 ±911	N/A	954 ±202	5900 ±660[e]
$AUC_{0\text{-}inf}$/Dose (µg x hr/mL/Dose)	N/A	20.6 ±6.49	26.3 ±7.59	N/A	23.9 ±5.05	49.2 ±5.50[c, e]

Values represent mean ±SD. Statistics performed below were unpaired t-tests.
a p value <0.05, TK parameter significantly different (40 vs 120 mg/kg fourth infusion).
b p value <0.01, TK parameter significantly different (40 vs 120 mg/kg fourth infusion).
c p value <0.001, TK parameter significantly different (40 vs 120 mg/kg fourth infusion).
d p value <0.05, TK parameter significantly different (120 mg/kg first vs fourth infusion).
e p value <0.01, TK parameter significantly different (120 mg/kg first vs fourth infusion).

Toxicokinetics were evaluated as part of the 6-month toxicology study in non-human primates. Avalglucosidase alfa TK parameters were evaluated following the 1st, 7th, and 13th infusion at the 50 and 200 mg/kg dose levels.

Across all infusions and both doses analyzed, avalglucosidase alfa elimination was biphasic. Toxicokinetics parameters were calculated only from the first phase of elimination, as the second phase had limited data points for analysis and represented GAA activity at, or very close to, background levels observed in vehicle-treated animals.

At infusion 1, 7, and 13 of avalglucosidase alfa, saturation kinetics were present (Table 3). These dose-related TK differences reached statistical significance with all 3 infusions analyzed. This strongly suggests that saturation kinetics is occurring between 50 and 200 mg/kg with avalglucosidase alfa in monkeys.

Intradose TK parameters appeared to change with successive infusions (ie, infusion 1, 7, and 13). These changes were characterized by increases in C_{max}, $t_{1/2}$, and AUC, and decreases in CL. Compared to the first infusion of 50 mg/kg, most TK parameters were significantly different for both the 7th and 13th infusions. At 200 mg/kg, compared to the first infusion, most TK parameters exhibited a trend for differences at infusion 7 and significant differences at infusion 13. Toxicokinetic parameter changes observed between infusion 1, 7, and 13 suggest that repeated dosing in the monkey at the dose levels tested affects the TK profile of avalglucosidase alfa.

For both dose levels and infusions, avalglucosidase alfa TK did not appear to differ between male and female monkeys.

Table 3 - Toxicokinetic parameters for avalglucosidase alfa following the 1st, 7th, and 13th intravenous infusion to cynomolgus monkeys at a dose of 50 and 200 mg/kg

	50 mg/kg			200 mg/kg		
Parameter	**1st Infusion (n=12)**	**7th Infusion (n=11)**	**13th Infusion (n=10)**	**1st Infusion (n=12)**	**7th Infusion (n=11)**	**13th Infusion (n=8)**
$t_{1/2}$ (hr)	0.525 ±0.092	0.577 ±0.114	0.737 ±0.228[b]	1.40 ±0.209[a]	1.72 ±0.100[a, b]	1.99 ±0.240[a, b, c]
Cl (mL/hr/kg)	22.3 ±6.83	15.7 ±3.82[b]	14.4 ±4.29[b]	10.9 ±1.59[a]	9.33 ±1.75[a]	7.88 ±2.44[a, b]
Vz (mL/kg)	16.3 ±3.12	12.7 ±2.33[b]	14.6 ±3.16	21.8 ±3.38[a]	23.0 ±4.01[a]	22.2 ±5.84[a]
C_{max} (µg/mL)	566 ±157	818 ±177[b]	861 ±189[b]	3892 ±506	4347 ±894	5284 ±1440[b]
$AUC_{0\text{-}inf}$ (µg X hr/mL)	2423 ±682	3341 ±748[b]	3712 ±977[b]	18728 ±2866	22463 ±6268	28162 ±10694[b]
$AUC_{0\text{-}inf}$/Dose (µg X hr/mL/Dose)	48.5 ±13.6	66.8 ±15.0[b]	74.2 ±19.5[b]	93.6 ±14.3[a]	112 ±31.3[a]	141 ±53.5[a, b]

a p<0.05 TK parameter significantly different (50 vs 200 mg/kg).
b p <0.05, TK parameter significantly different (compared to first infusion at the same dose).
c p <0.05, TK parameter significantly different (compared to seventh infusion at the same dose).

Biodistribution studies were also conducted with avalglucosidase alfa to evaluate the tissue distribution in GAAKO mice following a single 20 mg/kg dose. Results indicate that the majority of avalglucosidase alfa (~60% of injected dose) was detected in the liver, while less than 2% and 1% of injected dose was present in the heart and skeletal muscle, respectively.

More detailed information on the compound is provided in the Investigator's Brochure (IB).

4.2 STUDY DESIGN AND RATIONALE OF SPECIFIC PARAMETERS

4.2.1 Study design

LTS13769 is an open-label, multicenter, 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 an avalglucosidase alfa study.

4.2.2 Specific parameters rationale

4.2.2.1 Safety

Safety parameters include adverse event (AE) collection, physical examination, urine pregnancy test for women of childbearing potential, body weight, vital signs, hematology, biochemistry, urinalysis, and ECG.

Patients will receive an IV infusion of avalglucosidase alfa every other week (qow). Prior to each infusion, the patient should be assessed by the Investigator or appropriate designee to determine if the patient is free of acute illness and is clinically stable to receive the infusion. Detailed infusion administration procedures can be found in the pharmacy manual.

The follow-up observation period for the end-of-study visit and for treatment-emergent adverse events (TEAE) is anticipated to be approximately 4 weeks after the last administration of avalglucosidase alfa considering the long tissue half-life of ERTs used to treat lysosomal storage diseases.

An immune reaction against an exogenously administered recombinant protein plays a critical role in the safety of the compound. Therefore, safety assessments will include blood samples for anti-avalglucosidase alfa antibodies, neutralizing antibody formation in anti-drug antibody (ADA) seropositive patients, and anti-alglucosidase alfa immunoglobulin G (IgG) antibodies (only patients who were previously treated with alglucosidase alfa).

Additional exploratory safety assessments will be conducted when clinically indicated. In the event that a patient experiences a moderate, severe, or recurrent mild infusion-associated reactions (IARs) suggestive of hypersensitivity reactions, additional blood samples will be collected for the evaluation of:

- Circulating immune complex detection; and
- Immunoglobulin E (IgE), serum tryptase, and complement activation.

Additionally, skin testing may be performed, as appropriate, in patients who experience an IAR that meets the following criteria:

- Infusion-associated reaction is suggestive of IgE-mediated hypersensitivity reaction, with persistent symptoms of bronchospasm, hypotension, and/or urticaria requiring intervention OR any other signs or symptoms at the discretion of the Investigator or the Sponsor.

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

4.2.2.2 Pharmacodynamic [redacted] assessments

Glucose tetrasaccharide (Hex4), a tetraglucose oligomer, has been shown to be elevated in the urine of patients with Pompe disease. Hence, determination of fasted Hex4 levels may be a means by which the efficacy of treatments may be monitored.

[redacted]

Skeletal muscle magnetic resonance imaging (MRI) will be taken to guide site selection for muscle needle or open biopsies and to explore the effects of therapy on muscle pathology. When a muscle biopsy is available pharmacodynamic activity of avalglucosidase alfa will be assessed through tissue glycogen measurements from biopsies of the lower extremity (quadriceps).

Glycogen content will be measured by histomorphometric analysis or severity grading to determine how effectively avalglucosidase alfa is able to remove glycogen from muscle.

4.2.2.3 Exploratory efficacy

Exploratory avalglucosidase alfa efficacy will be evaluated in terms of functional capacity using the 6-minute walk test (6MWT) distance walked and pulmonary function testing (PFT; including the assessment of forced vital capacity [FVC], forced expiratory volume in the 1st second of the FVC maneuver [FEV1], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and peak expiratory flow [PEF] in the upright and supine positions).

4.2.2.4 Pharmacogenomics

Previous studies in Pompe muscle biopsies have shown a number of RNA species whose expression is correlated with disease progression. Measurements of circulating muscle creatine kinase indicate that muscle cell contents can be observed in the blood of patients with Pompe disease, suggesting the possibility of measuring muscle derived RNAs among the cell-free RNA in the blood, as has been done in cancer and for prenatal diagnosis. [redacted]

When a muscle biopsy is available, skeletal muscle tissue samples, taken by needle or open biopsy, will be evaluated for [redacted]. Such data will be used to evaluate if transcriptional changes are predictive of disease course and if the pattern indicates response to treatment. An additional serum sample will be collected in connection with this analysis. This serum sample will be used to assess whether any of the targets that are identified in muscle are expressed in serum and therefore could be assessed as a serum-based marker of Pompe disease.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective is to assess the long-term safety and PK of avalglucosidase alfa in patients with Pompe disease who have previously completed an avalglucosidase alfa study.

5.2 SECONDARY

The secondary objective is to assess the long-term effect of avalglucosidase alfa on pharmacodynamic and exploratory efficacy variables to assess if the benefits of avalglucosidase alfa are maintained and to assess the time course of response.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

LTS13769 is an open-label, multicenter, multinational extension study with repeated IV infusions of avalglucosidase alfa (neoGAA, GZ402666). 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 an avalglucosidase alfa study. The graphical design and study flow charts are presented in Section 1.

Patients who have provided signed written informed consent and have met all of the inclusion criteria and have not met the exclusion criterion will be enrolled in the study.

Safety, pharmacokinetic, pharmacodynamic, pharmacogenetic, and efficacy assessments will be performed at scheduled visits throughout the extension study. Adverse events and concomitant medications will be collected continuously throughout the study.

An independent Data Monitoring Committee (DMC) will review safety information during periodic bi-annual safety reviews, as well as on an ad hoc basis as outlined in the DMC charter, which is maintained separately from the study protocol. An immunologist will be consulted, when necessary, to review information and provide treatment recommendations for IARs.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The duration of the study for each patient is initially 6 years. Each patient will continue with the study until the patient withdraws, the Investigator withdraws the patient, or the Sponsor terminates the study. An additional follow-up phase will begin after the patient has completed the 6-year study period, and will last until avalglucosidase alfa is approved in the patient's country, except in the UK, Germany and Denmark, where the duration of the additional follow-up phase will be up to the approval in the country or limited to a maximum of 2 years, whichever occurs first (ie, for patients in the UK, Germany and Denmark, the total study duration per patient is 8 years at the maximum including the initial 6-year period and the additional 2-year follow-up) (refer to Appendix 1 [Section 17.1] for definition applicable for patients in the UK, Germany and Denmark).

6.2.2 Determination of end of clinical trial (all patients)

The clinical trial will end when the last patient completes the last follow-up visit.

6.3 STUDY CONDUCT

6.3.1 Data Monitoring Committee

An independent DMC, appointed by the Sponsor, will review the protocol and will thereafter provide medical and ethical guidance related to the conduct of this study. The DMC will review safety information as outlined in the DMC charter, which is maintained separately from the study protocol.

During the course of the study bi-annual periodic reviews of safety data will be performed by the DMC. In addition, the DMC will review safety data on an ad hoc basis if any AE meets the individual patient or study stopping criteria as discussed in Section 6.3.3.1 and Section 6.3.3.2, or if any AE that, in the opinion of the Investigator or Sponsor, raises significant concerns regarding the safety of the avalglucosidase alfa administered dose. Should any major safety issues arise, final decisions regarding the study will be made by the Sponsor's Chief Medical Officer and Global Safety Officer, taking into consideration the DMC opinion (as applicable).

6.3.2 Allergic Reaction Review

Infusion-associated reactions and other events which could require consultation of an allergist/immunologist will be reviewed by an immunologist.

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

6.3.3 Guidance for stopping rules

For the purpose of this study, the following criteria should be considered as guidance for the decision to stop avalglucosidase alfa administration to a patient or to stop the trial.

6.3.3.1 Individual patient stopping criteria

If any of the following AEs occur, dosing will be temporarily stopped for the specific patient who experienced the AE, pending ad hoc DMC review and recommendations:

- Any life-threatening Grade 4 AE as graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.03) not related to the patient's underlying condition.
- More than 1 AE of CTCAE Grade 3 or greater, not related to the patient's underlying condition, for which the relationship to treatment cannot be reasonably excluded.
- Any increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, or alkaline phosphatase >3x the baseline value, ie, prior to the first dose of GZ402666 in any prior avalglucosidase alfa study.

- Any increase in ALT or AST >3x the upper limit of normal, in the presence of total bilirubin >2x the upper limit of normal.
- Any AE that, in the opinion of the Investigator or Sponsor, raises significant concerns regarding the safety of avalglucosidase alfa administered dose.

6.3.3.2 Study stopping criteria

If either of the following events occurs, an ad hoc DMC review will be requested immediately:

- Two patients develop the same life-threatening AE (eg, anaphylactic reaction), not related to their underlying condition.
- Any avalglucosidase alfa-related death.

After consideration of DMC recommendations, final decisions for discontinuation of study drug for all or selected clinical trial patients will be made by the Sponsor.

In the event a significant safety concern arises, the Sponsor may immediately decide to discontinue study drug dosing in all clinical trial patients, prior to receipt of DMC recommendation. Investigational sites will be notified within 24 hours of the Sponsor's notification of the event(s).

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with Pompe disease who previously completed an avalglucosidase alfa study.

I 02. The patient and/or their parent/legal guardian is willing and able to provide signed informed consent, and the patient, if <18 years of age, is willing to provide assent if deemed able to do so.

I 03. The patient (and patient's legal guardian if patient is <18 years of age) must have the ability to comply with the clinical protocol.

I 04. The patient, if female and of childbearing potential, must have a negative pregnancy test (urine beta-human chorionic gonadotropin [β-HCG]) at baseline. Note: Sexually active female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or to use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device, or intrauterine system for the entire duration of the treatment period.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria:

E 01. The patient is concurrently participating in another clinical study using investigational treatment.

E 02. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

E 03. The patient has clinically significant organic disease (with the exception of symptoms relating to Pompe disease), including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, precludes participation in the study or potentially decreases survival.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

Avalglucosidase alfa, the investigational medicinal product (IMP), will be supplied as a sterile, nonpyrogenic, lyophilized product in single-use 20 mL vials containing approximately 100 mg of avalglucosidase alfa in 10 mM histidine, 2% glycine, 2% mannitol, and 0.01% polysorbate 80, with a pH of 6.2.

Avalglucosidase alfa will be administered by IV infusion following reconstitution and dilution at a dose of 20 mg/kg body weight qow.

The total amount of investigational product administered may be adjusted as needed to account for changes in body weight. Most recent body weight should be used for dose calculation. Each avalglucosidase alfa IV infusion will be administered in a step-wise manner. The rate will begin at a slow initial rate and will be gradually increased if there are no signs of IARs, until a maximum rate is reached. The infusion length will be dependent on the dose. Specific details pertaining to the infusion volumes and rates as well as dose calculation can be found in the pharmacy manual.

Prior to each infusion, the patient should be assessed by the Investigator or appropriate designee (ie, qualified physician with the exception of patients who receive home infusion of avalglucosidase alfa as outlined below under the subsection “Home infusion”) to determine if the patient is free of acute illness and is clinically stable to receive the infusion. Infusions will be postponed (see Section 8.7.1) if the patient is acutely ill on the scheduled day of infusion. Any modification to the dose and/or frequency of dosing is not permitted unless it is due to an AE, in which case it is not a protocol violation, but the Investigator must consult with the Sponsor in the event of a dose change. No dose increase above the maximum recommended dose of 20 mg/kg qow will be allowed for any patients.

Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each infusion; see below for the patients receiving home infusion. Patients may be required to stay for a longer observation period at the Investigator’s discretion. In case the patient does not stay for this observation period (eg, as part of contingency measures for a regional or national emergency that is declared by a governmental agency), the Investigator (or appropriate designee) will contact the patient to ensure that no adverse event occurred during the observational period.

Home infusion

Home infusion may be possible, where permitted by national and local regulations. Patients must meet the eligibility requirements outlined below. In addition, the Investigator and the Sponsor must agree that home infusion is appropriate. Patient’s underlying co-morbidities and ability to adhere to the requirements of the study need to be taken into account when evaluating patients for eligibility to receive home infusion. Any identified risk of noncompliance to monitoring of study

requirements or potential for loss to follow-up should lead to this patient not being eligible for home infusion.

The following criteria must be documented in the patient's medical record:

- The Investigator must agree in writing that home infusion is appropriate for the patient.
- The patient must be willing and able to comply with home infusion procedures.
- The patient has been trained on home infusion process.
- The patient must, in the Investigator's (or designee's) opinion, have been clinically stable with no history of moderate or severe IARs for at least 12 months, and must be on a stable avalglucosidase alfa dose. In case of unexpected event that prevent infusions to be performed at site for a prolonged period, (eg, as part of contingency measures for a regional or national emergency that is declared by a governmental agency), with DMC agreement, the required period of 12 months with no history of moderate or severe IAR may be reduced to 6 months, to allow home infusion to be resumed sooner.
- If this reduced period from 12 months to at least 6 months, is considered safe and after confirmation with the DMC (which will be documented in Trial Master File), it will be considered as a permanent criterion after the unexpected event is resolved (eg, contingency measures for a regional or national emergency that is declared by a governmental agency are terminated).
- No infusion rate increases will be allowed while a patient is receiving home infusions.
- The patient must have no ongoing (not yet recovered) SAEs that, in the opinion of the Investigator, may affect the patient's ability to tolerate the infusion.
- Home infusion infrastructure, resources, and procedures must be established and available according to applicable regional regulations (see Section 17.1 for regulations applicable specifically in France disallowing the option for home infusion). In exceptional circumstances, the Investigator may require a local vendor for home infusion services. In such circumstances, the Investigator will attest that this vendor meets the requirements to properly manage the home infusion of avalglucosidase alfa, including available resources and procedures.
- Patients experiencing a moderate or severe IAR while being infused at home will return to the study site for their following infusion and will continue to receive infusions at the site until the Investigator feels it is safe for the patient to resume home infusion.
- If recurrent IARs or hypersensitivity/anaphylactic reactions have occurred prior to start of home infusions or occur during home infusions, the Investigator should assess whether or not it is safe for the patient to start or to continue to be treated via home infusion.
- The Sponsor should be notified about all IARs and consulted (as needed) if the patient experiences IARs suggestive of hypersensitivity reactions (refer to Section 8.8.2).
- In the event of manufacturing scale change, the patient will be required to receive the first infusion at the site. All criteria for return to home infusion will apply.

- Prior to beginning home infusions, the home infusion agency staff, including new staff members, must have been trained by the site on proper procedures to administer infusions, monitor patients, document procedures, and report to site on a timely basis. Any new staff member must be trained by the site prior to resuming home infusions. The site must confirm that the home infusion agency staff has received training at least equivalent to that provided to new staff members.
- Because of the possibility of anaphylactic reactions, medical personnel competent in recognizing and treating adverse reactions (including anaphylactic reactions) should be readily available throughout the home infusion.
- The home infusion agency staff should remain at the patient's home for the duration of the infusion and through the post-infusion observation period, which is required to be at least 2 hours.
- The home infusion agency staff must be trained in basic life support (cardiopulmonary resuscitation [CPR]), and should have a process for requesting additional emergency services, if needed.
- Home infusion agency must keep source documentation of the infusion, including documentation of any AEs. Home infusion agency must be amenable to providing specific source documentation to the Sponsor and agree to be monitored.

The Principal Investigator (PI) is responsible for approving a patient's initiation with home infusions and is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company during this clinical study.

It is the PI's responsibility to guide staff on the clinical management of the patient in case of IARs or hypersensitivity or anaphylactic reactions. The PI will be the point of contact for home infusion agency staff in case of questions or emergency situations.

Infusions given in the home setting versus in the clinic will be captured through the electronic case report form (eCRF) forms for AEs and exposure.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

This study is an open-label design.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is an open-label study without randomization. Patients who comply with all inclusion/exclusion criteria will be enrolled in the study. Each patient will receive 20 mg/kg qow.

The patient will retain the same patient number from the initial study.

8.5 PACKAGING AND LABELING

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

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

It is recommended that the reconstituted product be used immediately after reconstitution. Additional stability data are provided in the pharmacy manual.

8.7 RESPONSIBILITIES

The Investigator, the clinical site pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (eg, deficiency in condition, appearance, pertaining documentation, labeling, expiration date) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP provided by the Sponsor to a third party, allow the IMP provided by the Sponsor to be used other than as directed by this clinical trial protocol, or dispose of IMP provided by the Sponsor in any other manner.

8.7.1 Treatment accountability and compliance

Administration of the IMP is performed in collaboration with qualified study personnel, and under the responsibility of the Investigator or the subinvestigator.

- IMP accountability:
  - The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records include the date and number of treatment units received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor,
  - The person responsible for drug administration to the patient will record precisely the date, time of the drug administration, and number of treatment units used for administration,
  - The Investigator records the dosing information on the appropriate page(s) of the eCRF,
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and IMP records.

The patient's compliance with the treatment regimen will be monitored in terms of the patient receiving the study drug infusion every other week within a ±7-day window from the previous infusion date. Missed, delayed, or incomplete infusions will be clearly documented and considered in the analysis. Missed doses of study treatment due to sickness, safety concerns, or for medical reasons are not protocol deviations, but must be documented for analysis and potential impact on the study results.

8.7.2 Return and/or destruction of treatments

Reconciliation of the IMP must be performed at the site by the Investigator and the monitoring team using the appropriate accountability log and documented on the appropriate accountability log countersigned by the Investigator and the monitoring team.

A written authorization for destruction will be given by the Sponsor once the reconciliation is achieved. This destruction can be performed at the site depending on local requirements; alternatively, the IMP can be returned to the Sponsor for destruction.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP. Medications and therapies taken by the patient during the period between the end of the prior avalglucosidase alfa study until prior to providing informed consent for the extension study, and during the course of the study, will be recorded in the eCRF. Similarly, pre-infusion medications (if allowed; see Section 8.8.1 and Section 8.8.2) and assistive devices will be recorded in the eCRF.

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

8.8.1 Pretreatment for patients with infusion-associated reactions

In clinical trials with alglucosidase alfa, some patients were pretreated with antihistamines, antipyretics, and/or corticosteroids. Infusion-associated reactions occurred in some patients after receiving antipyretics, antihistamines, or corticosteroids.

In general, the use of pretreatment in this study is at the discretion of the Investigator. The routine use of pretreatment is not recommended, especially in patients with previous IgE-mediated hypersensitivity reaction. Antihistamines can mask early symptoms of a hypersensitivity reaction (skin reaction), making it difficult for the infusion staff to recognize the initial signs of distress and the need to decrease the infusion rate and/or otherwise intervene.

8.8.2 Management of infusion-associated reactions

For management of mild IARs, infusion rate reductions (ie, reduced to half the rate) or temporary interruptions may mitigate the reaction.

Testing for moderate, severe, and recurrent mild IARs will include, if clinically indicated:

- Assessments for circulating immune complex detection; and IgE, serum tryptase, and complement activation, following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions.
- Skin testing if IARs are suggestive of a Type I hypersensitivity reaction (IgE-mediated) as appropriate.

For moderate to severe or recurrent IARs, the Investigator may consider the use of pretreatment medications (ie, antihistamines, antipyretics, and/or glucocorticoids), in addition to infusion rate reductions, interruptions, or even discontinuation, if necessary. Please refer to the Investigator Brochure for further guidance on the management of infusion-associated reactions.

If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of the infusion should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, IV fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis, epinephrine has been administered. Because of the potential for severe infusion reactions, appropriate medical support measures, including CPR equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available.

The Investigator will continue to monitor the patient until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Baseline demographic characteristics will consist of:

1. Age (years).
2. Gender.
3. Race.
4. Ethnicity.
5. Pompe disease history including GAA mutations and aspects of disability.
6. ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study).

9.1 PRIMARY ENDPOINT - SAFETY

The primary endpoint of this study is safety. The following safety assessments will be collected and analyzed:

- Assessment of AEs/TEAEs, including IARs and deaths.
- Physical examination.
- Clinical laboratory evaluations, including hematology, biochemistry, and urinalysis.
- Vital signs.
- Body weight.
- 12-lead ECG.
- Immunogenicity assessments.

A β-hCG urine test will be administered to females of child bearing potential at baseline and monthly thereafter throughout the duration of the study.

9.1.1 Adverse events

Adverse events, spontaneously reported by the patient or observed by the Investigator, will be monitored throughout the study. This includes the monitoring and reporting of IARs. The safety profile will be based on incidence, severity, and cumulative nature of TEAEs.
Treatment-emergent adverse events are defined as AEs that develop or worsen during the on-treatment period. For this study, the on-treatment period will be defined as the period from the time of first dose of IMP to at least 4 weeks after the last administration of the IMP. The on-treatment period may end earlier (ie, 2 weeks after the last administration of IMP) if the patient enrolls in another study or receives commercially available ERT. For the purposes of the study, status of ongoing and new AEs will be assessed 4 weeks after the last study infusion, or for patients who discontinue early, after their last completed study visit (Section 10.1.3.8). Any new AE or serious AE (SAE) that occurs during the 4-week follow-up period and is assessed as related to the drug or study procedures will be reported/collected in the clinical database.

Definitions of AEs, SAEs, and AEs of special interest (AESIs), including reporting procedures, can be found in Section 10.4 to Section 10.6.

At each study visit, patients will be evaluated for new AEs and the status of existing AEs. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications.

Adverse events will be summarized with respect to the type, frequency, severity, seriousness, and relatedness. Pretreatment and TEAEs will be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" using the Medical Dictionary for Regulatory Activities (MedDRA). All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

9.1.2 Physical examination

Physical examination will include, at a minimum, an assessment of the patient's general appearance; skin; head, eyes, ears, nose, and throat; examinations of lymph nodes, abdomen, extremities/joints, neurological and mental status; heart and respiratory auscultation; peripheral arterial pulse; and pupil, knee, Achilles, and plantar reflexes.

9.1.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology and biochemistry) and urinalysis. Clinical laboratory values will be analyzed by a central laboratory. These values will be analyzed after conversion into standard international units, and international units will be used in all listings and tables.

Blood samples should be drawn in fasting conditions for:

- 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: AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, total and conjugated 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, leucocytes, 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).

9.1.4 Vital signs

Vital signs will 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 the post-infusion observation period. Collection windows are ±15 minutes.

9.1.5 Body weight

Body weight will be measured in kilograms and collected in the eCRFs every 3 months throughout the duration of the study, as well as at the "end of study visit". More frequent weight may be obtained at the discretion of the Investigator.

9.1.6 Electrocardiogram variables

Standard 12-lead ECGs are recorded after at least 15 minutes in the supine position using an electrocardiographic device. The following will be assessed: heart rate, rhythm, interval between the peaks of successive QRS complexes (RR), interval from the beginning of the P wave until the beginning of the QRS complex (PR), interval from 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 (QTc) automatic correction 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.

Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

- A single 12-lead ECG (25 mm/s, 10 mm/mV) printout including date, time, initials, and number of the patient, signature of the research physician, and at least 3 complexes for each lead. The study site cardiologist's medical opinion and automatic values will be recorded in the eCRF. This printout will be retained at the site.
- A single digital file will be stored which enables manual reading when it is necessary (centralized reading of computerized ECGs); each digital file will be identified by theoretical time (day and time), real date and real time (recorder time), and patient number (eg, 3 digits) and initials (eg, 3 digits). The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory

requirements (ie, US Food and Drug Administration [FDA] Code of Federal Regulations, Title 21, Part 11).

The qualified Investigator or appropriate designee (qualified physician) should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In the event of any clinically significant abnormal findings that meet the definition of an AE (see Section 10.4.1 for definitions and reporting), the Investigator will continue to monitor the patient with additional ECGs until the ECG returns to baseline or the Investigator determines that follow-up is no longer necessary.

In case of abnormal findings by the qualified Investigator, the ECG should be provided to the study site cardiologist for further confirmation and description of findings.

All ECGs will also be collected and read centrally by a third-party independent reviewer.

9.1.7 Immunogenicity

Immunogenicity assessments will include the following:

- Samples will be collected from patients and evaluated for anti-avalglucosidase alfa antibodies every month during the first 6 months and then every 3 months throughout the duration of the study. ADA seropositive patient serum will be assessed for neutralizing antibodies to avalglucosidase alfa which may include inhibition of enzyme activity and uptake.
- Samples will be collected from patients who were previously treated with alglucosidase alfa and evaluated for anti-alglucosidase alfa IgG antibodies every 6 months for up to the first 6 years of the study.
- Samples will be collected from patients and evaluated for IgE, complement activation, serum tryptase following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions (Section 8.8.2).
- In the event a patient exhibits signs or symptoms suggestive of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa, serum samples are obtained for the evaluation of circulating immune complexes.
- Leftover antibody samples will be stored for further analysis as needed.
- See the study-specific laboratory manual as well as the Study Operations Manual (SOM) for guidelines on the collection and shipment of antibody and IAR samples and circulating immune complex samples.

9.2 PHARMACOKINETICS

9.2.1 Sampling times

Blood samples for evaluation of avalglucosidase alfa PK will be collected before, during, and after avalglucosidase alfa infusions at 6 months and then yearly thereafter for the first 6 years.

Sampling times are as follows: pre-dose (prior to infusion), at the end of the infusion, and at 1, 4, 8, 12, and 24 hours after infusion. The following PK blood samples are to be collected within 15 minutes of scheduled time: pre-dose and all samples immediately following the end of the infusion through 8 hours post infusion. Pharmacokinetic samples collected 12 hours through 24 hours post infusion are to be collected ±2 hours of the scheduled time.

9.2.2 Number of pharmacokinetic samples

The number of PK samples will vary by patient depending on the length of the patient's participation in the extension study.

9.2.3 Sample handling procedure

Special procedures for collection, storage, and shipment will be provided in the study- specific laboratory manual.

9.2.4 Bioanalytical methods

Plasma samples will be analyzed using validated, sensitive and specific bioanalytical methods, namely, a fluorometric assay using a 4-methylumbelliferyl-α-D-glucoside (4-MUG) substrate to detect avalglucosidase alfa activity.

9.2.5 Pharmacokinetic parameters

The following PK parameters will be calculated, using noncompartmental methods from plasma avalglucosidase alfa concentrations obtained after single and repeat dose administration. The parameters will include, but may not be limited to the following list in Table 4.

Table 4 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Matrix	Definition/Calculation
C_{max}	avalglucosidase alfa	Plasma	Maximum plasma concentration observed
AUC_{last}	avalglucosidase alfa	Plasma	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time
AUC	avalglucosidase alfa	Plasma	Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_Z}$ Values with a percentage of extrapolation >20% will not be taken into account in the descriptive statistics
t_{last}	avalglucosidase alfa	Plasma	Time corresponding to the last concentration above the limit of quantification, C_{last}
$t_{1/2z}$	avalglucosidase alfa	Plasma	Terminal half-life associated with the terminal slope (λz) determined according to the following equation: $t_{1/2Z} = \frac{0.693}{\lambda_z}$ where λz is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi-logarithmic scale. Half-life is calculated by taking the regression of at least 3 points.
CL	avalglucosidase alfa	Plasma	Apparent total body clearance of a drug from the plasma calculated using the following equation: $CL = \frac{Dose}{AUC}$
Vd	avalglucosidase alfa	Plasma	Apparent Volume of Distribution during the terminal (λz) phase calculated using the following equation: $V_z = \frac{CL}{\lambda_z}$

9.3 PHARMACODYNAMIC PARAMETERS

9.3.1 Skeletal muscle magnetic resonance imaging

Skeletal muscle MRI will be performed prior to the muscle needle or open biopsy procedure. Skeletal muscle MRI images obtained within LTS13769 study will be analyzed using muscle MRI images obtained as baseline from previous study. Magnetic resonance imaging will be processed and analyzed centrally. A protocol for MRI acquisition and analysis will be provided in the study-specific manual.

9.3.2 Skeletal muscle biopsy

Muscle biopsy is not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline. Needle or open biopsy of the lower extremity (quadriceps) muscle will be performed following the skeletal muscle MRI. 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.

Further instructions regarding the biopsy sampling and the collection and shipment of biopsy samples will be provided in the study-specific laboratory manual.

9.3.3 Urinary Hex4

Fasted urine samples for the assessment of urinary Hex4 concentrations will be collected prior to IMP infusion. Procedures for the collection, handling, and shipment of all urine samples will be included in the study-specific laboratory manual.

[redacted]

9.4 EXPLORATORY EFFICACY ASSESSMENTS

Avalglucosidase alfa efficacy will be evaluated in terms of functional capacity using the 6MWT and PFT.

9.4.1 Six-minute walk test

The 6MWT will be performed to assess ambulatory capacity in the study population. During the treatment period, the assessment will be completed before IMP infusion. See the study-specific laboratory manual for further details.

The measurement is the distance walked in 6 minutes, measured in meters; the percent of predicted distance and the amount of time walked (3) to quantify endurance (as all patients may not complete the full 6-minute walk) will also be recorded. In addition, data will be collected for pre- versus post-test changes in heart rate. Testing equipment and administration techniques will be standardized among investigational sites. The distance (in meters) will be recorded and the corresponding percent predicted value will be calculated.

9.4.2 Pulmonary function testing endpoints

Pulmonary function testing will be completed before IMP infusion.

The PFT administration protocol is standardized across sites in accordance with American Thoracic Society guidelines (4). Pulmonary function testing will include the assessment of FVC, FEV1, MIP, MEP, and PEF in the upright and supine positions.

9.5 PHARMACOGENETIC ASSESSMENT

Fasted pharmacogenetic samples will be collected. Refer to the study-specific laboratory manual for guidelines on the collection and shipment of whole blood samples.

9.5.1 Skeletal muscle RNA expression analysis

In patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content >5% or who show significant clinical decline, muscle tissue samples will be taken via biopsy of the lower extremity (quadriceps) muscle, as indicated in Section 9.3.2. An additional serum sample will be collected in connection with this analysis. These serum samples will be used to assess whether proteins for any of the mRNA targets that are identified in muscle are expressed in serum and therefore could be assessed as a serum-based marker of Pompe disease. Results will be used to inform on biomarker targets for future studies and will not be reported in the CSR.

[redacted]

9.6 SAMPLED BLOOD VOLUME

The total volume of sampled blood will vary depending on the patient's length of participation in this extension study.

9.7 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to Pompe disease and other diseases than those defined in the present protocol.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

Some samples may remain labeled with the same identifiers as the one used during the study (ie, subject ID). They may be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.1).

10 STUDY PROCEDURES

Section 1.2 summarizes the schedule of study events for all patients enrolled into this study. Specific details on the timing of study assessments are provided below. The individual evaluations are described in Section 9.

Medical/surgical history, and Pompe disease history, including GAA gene mutations, will be imported from the patient's prior avalglucosidase alfa study file in the database when possible.

Adverse event and concomitant medication collection will be performed at every visit throughout the study.

10.1 VISIT SCHEDULE

10.1.1 Baseline visit

Patients enrolled in the study will have the following procedures performed at baseline.

The patient will receive information on the study objectives and procedures from the Investigator. The patient will have to sign the informed consent prior to any action related to the study.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for inclusion in the study. Final inclusion will be performed just before the IMP administration at the first treatment visit.

- Informed consent.
- Inclusion/exclusion criteria.
- Urine pregnancy test (females only).
- ECG.
- Demographics.
- Medical/Surgical history.
- Pompe disease history, inclusive of GAA mutation and aspects of disability.
- ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study).
- Results of MRI baseline from previous avalglucosidase alfa study to be obtained.

10.1.2 Treatment phase

10.1.2.1 Biweekly

The following will be performed every 2 weeks starting at the date of the first infusion:

- Vital signs.

- Infusion of avalglucosidase alfa.

Information regarding the infusion of the IMP can be found in the pharmacy manual.

10.1.2.2 Monthly

The following assessments will be performed on a monthly basis:

- Urine pregnancy test (females only).
- Biochemistry (for first 3 years since enrollment).
- Anti-avalglucosidase alfa antibodies and neutralizing antibodies in antidrug-antibody (ADA) positive patients (for first 6 months).

10.1.2.3 Quarterly

The following assessments will be performed on a quarterly basis:

- Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients (after the first 6 months).
- Body weight.
- Biochemistry (after first 3 years since enrollment).

10.1.2.4 Every 6 months

The following assessments will be performed every 6 months:

- Physical examination.
- ECG.
- Hematology and urinalysis.
- 6MWT.
- PFT.
- Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa).

10.1.2.5 At 6 months and yearly thereafter

The following assessments will be performed at 6 months and yearly thereafter:

- Avalglucosidase alfa PK plasma sample collection.
- Urine Hex4 sample collection.

10.1.2.6 Every 2 years

The following assessments will be performed every 2 years:

- MRI.
- Skeletal muscle biopsy (not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline).
- Serum sample collection for skeletal muscle RNA expression analyses (not required in patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content <5% unless the patient shows significant clinical decline).

10.1.2.7 Re-baseline visit

The following assessments will be performed at the re-baseline visit after having obtained informed consent and before receiving the higher dose.

The "Re-baseline" will only apply to patients who have switched from 5 or 10 to 20 mg/kg. If the patient changes dose from 5 or 10 mg/kg to 20 mg/kg qow dose, the visit dates need to be adapted accordingly (see Section 1.2).

Results from selected previous assessments may be used and the assessment does not need to be repeated at the re-baseline visit depending on the last available assessment date:

- Physical examination (within 1 month).
- Urine pregnancy test (females only).
- Body weight.
- Vital signs.
- ECG (within 1 month).
- Hematology and urinalysis (within 1 month).
- Biochemistry.
- Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients.
- Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa).
- Avalglucosidase alfa PK plasma sample collection (within 6 months).
- MRI (within 6 months).
- In patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content >5% or who show significant clinical decline:
  - Skeletal muscle needle or open biopsy (within 6 months),
  - Serum sample collection for skeletal muscle RNA expression analyses (within 6 months).

- Urine Hex4 sample collection (within 1 month).
- [redacted]
- [redacted]
- 6MWT (within 1 month).
- PFT (within 1 month).
- [redacted]

10.1.2.8 Patient temporarily discontinued from study treatment while remaining in the study

- In case of temporary treatment discontinuation of study drug the visits and assessments will be adapted to the absence of infusion of avalglucosidase alfa until the patient resumes treatment within the study:
  - Study visits can be adapted to every 4 weeks or when laboratory and/or clinical testing are scheduled, as long as the assessment time windows in the study protocol are respected. Patients should adhere to original target infusion and visit schedule based on first infusion in LTS13769 or first infusion of 20 mg/kg in the LTS13769 study.
  - As no infusion of IMP will be performed, no assessment of infusion-associated vital signs, as well as no PK sampling is required while the participant is temporarily withdrawn from treatment.
- Reinitiation of treatment with IMP will be offered to the patient at the discretion of the Investigator and in agreement with the study participant, under close and appropriate clinical and/or laboratory monitoring.

10.1.3 Additional follow-up phase

An additional follow-up phase will begin after the patient has completed the 6-year study period, and will last until avalglucosidase alfa is approved in the patient's country, except in the UK, Germany and Denmark, where the duration of the additional follow-up phase will be up to the approval in the country or limited to a maximum of 2 years, whichever occurs first (ie, for patients in the UK, Germany and Denmark, the total study duration per patient is 8 years at the maximum including the initial 6-year and the additional 2-year follow-up) (refer to Appendix 1 [Section 17.1] for definition applicable for patients in the UK, Germany and Denmark).

10.1.3.1 Biweekly

The following will be performed every 2 weeks:

- Vital signs.
- Infusion of avalglucosidase alfa.

Information regarding the infusion of the IMP can be found in the pharmacy manual.

10.1.3.2 Monthly

The following assessments will be performed on a monthly basis:

- Urine pregnancy test (females only).

10.1.3.3 Quarterly

The following assessments will be performed on a quarterly basis:

- Body weight.

10.1.3.4 Every 6 months

The following assessments will be performed every 6 months:

- Physical examination.
- ECG.
- Hematology and urinalysis.
- Biochemistry.
- Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients.
- 6MWT.
- PFT.

10.1.3.5 Yearly

The following assessments will be performed at 6 months and yearly thereafter:

- [redacted]
- [redacted]
- [redacted]

10.1.3.6 Every 2 years

The following assessments will be performed every 2 years:

- MRI.

10.1.3.7 End of study visit

The following will be performed at the end of study visit:

- Physical examination.

- Urine pregnancy test (females only).
- Body weight.
- Vital signs.
- ECG.
- Hematology and urinalysis.
- Biochemistry.
- Anti-avalglucosidase alfa antibodies and neutralizing antibodies in ADA-positive patients.
- MRI.
- In patients in whom the prior muscle biopsy, obtained in a prior avalglucosidase alfa study, had a glycogen content >5%, or who show significant clinical decline:
  - Skeletal muscle needle or open biopsy (within 6 months),
- Urine Hex4 sample collection.
- [redacted]
- [redacted]
- 6MWT.
- PFT.
- [redacted]
- Infusion of avalglucosidase alfa.

10.1.3.8 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow-up the outcome of any AEs (eg, clinical signs, laboratory values or other) until the return to normal or consolidation of the patient's condition.
- All AEs documented at a previous visit/contact that are designated as ongoing will be reviewed by the Investigator at subsequent visits/contacts.
- In case of any SAE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has left the clinical trial and that additional investigations may be requested by the monitoring team. The Investigator will ensure that follow-up includes further investigations consistent with appropriate medical management and patient consent to elucidate the nature and/or causality of the AE.
- In case of any SAE or non-serious AE brought to the attention of the Investigator at any time after cessation of the IMP and considered by him/her to be caused by the IMP with a reasonable possibility, this should be reported to the monitoring team.

- The Investigator will provide follow-up information for any SAE to the Sponsor as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an SAE.
- For this study, the on-treatment period will be defined as the period from the time of first dose of IMP to at least 4 weeks after the last administration of the IMP. The on-treatment period may end earlier (ie, 2 weeks after the last administration of IMP) if the patient enrolls in another study or receives commercially available ERT. In this case the follow-up period may be reduced from 4 to 2 weeks. For the purposes of the study, status of ongoing and new AEs will be assessed 4 weeks after the last infusion, or for patients who discontinue early, after their last completed study visit. Any new AE or SAE that occurs during the 4-week follow-up period and is assessed as related to the drug or study procedures will be reported/collected in the clinical database.

10.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the eCRF must be supported by appropriately identified source documentation. The results of certain examinations or evaluations recorded in the eCRF may be considered to be source data.

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

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

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a patient from treatment:

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

The Investigator or the Sponsor (see Section 14.2) terminates the study.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or if the patient becomes pregnant. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate screens of the eCRF when considered as confirmed. Visit and assessment schedules will be adapted to the absence of infusion of IMP (refer to Section 1.2 and Section 10.1.2.8).

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 Criteria for permanent treatment discontinuation

At patient request, ie, withdrawal of the consent for treatment, the patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate screens of the eCRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. If possible, the patients should be assessed using the procedures defined above.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

If possible, the patients are assessed using the procedure normally planned for the end of study visit.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or:
  - Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Is a medically important event:
  - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

AESIs will include:

- Infusion-associated reactions:
  - IARs are defined as AESIs that occur during either the infusion or the observation period following the infusion which are deemed to be related or possibly related to the IMP. At the discretion of the Investigator, AEs occurring after completion of the post-infusion observation period that are assessed as related may also be considered IARs. Refer to Section 8.8.2 for additional testing in the event a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions and for suggested guidelines for the management of IARs.
- Pregnancy:
  - Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
  - Male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy is mandatory in a female participant or in a female partner of a male participant, 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, adjusted according to the tested drug.
- Clinical laboratory (change from baseline, ie, prior to the first dose of GZ402666 in any prior avalglucosidase alfa study):
  - 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).

In the event of an AESI, the Sponsor will be informed immediately (ie, within 24 hours), using the AE form together with the SAE complementary form to be entered in the eCRF.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding screen(s) of the eCRF.
- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
  - There is one exception to this rule. In instances where a patient experiences an IAR (refer to Section 8.8.2), allergic, or anaphylactic reaction, either during infusion or post observation period, each of the individual signs and/or symptoms comprising the reaction should be captured as individual AE terms.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- All further data updates should be recorded in the eCRF as appropriate within 24 hours of knowledge. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper case report form (CRF) process) is available and should be used when the eCRF system does not work. Please refer to the Study Operations Manual for further guidance.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

The needs for specific monitoring, documentation, and management of AESIs are described in this section.

For each defined AESI, consider carefully the need to collect additional specific information that would impact the study and/or the eCRF design, such as:

- Pre-existing related condition or lifestyle of interest for the AE (eg, habits, cardiovascular risk factor).
- Expected list of associated signs and symptoms.
- Corrective actions (eg, treatment discontinuation, concomitant treatment).
- Diagnostic actions (eg, test[s] or procedure[s] results).
- Additional descriptive factors.
- Sequelae.
- IARs:
  - Any pre-infusion medication(s) administered,
  - Infusion rate at which the IAR occurred,
  - Time to onset of IAR,
  - Any adjustments to infusion rate made,
  - Any medications and/or therapies administered,
  - Time to IAR resolution (de-challenge),
  - Re-challenge,
  - Relevant vital signs (including pre-infusion vital signs).

10.4.4.1 Reporting of adverse events of special interest with immediate notification

For AESIs with immediate notification, the Sponsor will be informed immediately (ie, within 24 hours), as per the SAE notification instructions described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages in the eCRF.

- ALT increase.

- IARs.
- Pregnancy.
- Overdose.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, institutional review boards (IRBs)/independent ethics committees (IECs) as appropriate, and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the health authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition. Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

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

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

All data collected in this study will be documented using summary tables, figures, and patient data listings.

All summary statistics will be computed and displayed overall and by treatment group and scheduled assessment time point. Summary statistics for continuous variables will include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Any changes to the statistical analysis will be delineated in the statistical analysis plan.

11.1 DETERMINATION OF SAMPLE SIZE

This is an ongoing extension study, and therefore, the number of patients will be determined by enrollment from other avalglucosidase alfa studies. Thus, no formal sample size calculations have been performed.

11.2 DISPOSITION OF PATIENTS

Disposition of patients will be depicted by intended dose level for both the patient study status and also for the patient analysis populations. For patient study status, the total number of patients for each one of the following categories will be presented in the clinical study report:

- Registered patients are patients who signed the informed consent and who are planned to receive the IMP.
- All treated population.
- Patients who completed the study treatment period as per protocol.
- Patients who discontinued study treatment and reasons for discontinuation.
- Pharmacokinetic population.
- Pharmacodynamic population.
- Efficacy population.

For all categories of patients, percentages will be calculated using the number of exposed patients (all treated population). Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by dose level.

Additionally, the analysis populations for safety, PK, pharmacodynamics, and efficacy will be summarized in a table by patient counts on the registered population.

11.2.1 Protocol deviations

During the review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment compliance, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock and documented as appropriate, including missing data and IMP discontinuations, and classified as minor, major, or critical. Protocol deviations discovered during the data reconciliation process will be tracked by the Sponsor or its designee.

Individual deviations to inclusion and exclusion criteria as reported by the Investigator will be listed.

If any, other deviations will be listed by patient and/or described in the body of the clinical study report.

11.3 ANALYSIS POPULATIONS

- **Full Analysis Set**: This analysis set consists of all patients who received at least 1 complete infusion of IMP.
- **Safety Analysis Set**: This analysis set consists of all patients who received any amount of IMP and will be used as the basis for all safety analyses.
- **PK/Pharmacodynamics/Efficacy Analysis Set:** All patients without any critical deviations related to IMP administration, and for whom any PK/pharmacodynamic/efficacy data are available, will be included in the PK/pharmacodynamic/efficacy population.

11.4 PATIENT DEMOGRAPHIC AND MEDICAL HISTORY

Medical/surgical history, and Pompe disease history, including GAA gene mutations, will be imported from the patient's prior avalglucosidase alfa study file in the database when possible. ECG, hematology, biochemistry, and urinalysis data from first day of avalglucosidase alfa infusion (ie, prior to first infusion in any prior avalglucosidase alfa study) will be entered by the study site into the database. These data will be summarized using summary statistics for continuous variables and frequency distribution for categorical variables. All data will be presented in by-patient listings.

11.5 SAFETY ANALYSIS

Descriptive statistics for actual values and changes from baseline will be generated by time point for selected safety parameters of interest. Data may also be plotted. For the purpose of analysis, baseline will be prior to the first dose of GZ402666 in a prior avalglucosidase alfa study.

11.5.1 Physical examination, vital signs, and body weight

Observed measurements and changes from baseline to study time points in physical examination findings, vital signs (including but not limited to blood pressure, heart rate, respiratory rate, and temperature), and body weights will be summarized. Listings of abnormal findings/values will be presented.

11.5.2 Clinical laboratory tests

Observed measurements and changes from baseline to study time points in hematology, biochemistry, and urinalysis will be descriptively summarized. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. All data will be presented in listings along with individual listings of patients with clinically significant abnormal laboratory values.

11.5.3 Adverse events

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

11.5.4 Electrocardiogram

Observed measurements and changes from baseline to study time points in ECG results (QTc, PR interval, etc) will be summarized. Listings of abnormal findings/values will be presented for each patient.

11.5.5 Anti-avalglucosidase alfa antibodies, neutralizing antibodies, and infusion-associated reactions

Percentage of patients who seroconverted to avalglucosidase alfa, time to seroconversion and

peak anti-avalglucosidase alfa antibody titer will be summarized using summary statistics. For patients who were previously treated with alglucosidase alfa only, the percentage of patients testing positive to alglucosidase alfa and IgG antibody titer data to alglucosidase alfa will be summarized using summary statistics as well. Antibody titer values will be summarized using summary statistics at each study visit. All data will be presented in listings for each patient. By-patient listings will also display results of neutralizing antibody.

For patients who have an IAR, by-patient listings will also display results of circulating immune complex, anti-avalglucosidase alfa IgE antibody, serum tryptase activity, complement activation, and skin testing performed.

Descriptive summaries may also be provided as appropriate.

11.6 ANALYSIS OF PHARMACOKINETIC DATA

11.6.1 Pharmacokinetic parameters

The list of PK parameters is listed in Section 9.2.5.

11.6.2 Statistical analysis

Individual assessments and descriptive statistics (mean, standard deviation [SD], median, minimum, maximum, geometric mean, and percent coefficient of variation) 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, pre-dose ADA and neutralizing antibody titers for each patient will be analyzed graphically with respect to clearance at 6 months and then yearly thereafter. If relationships are apparent, further quantitative/statistical analysis may be performed (eg, statistical significance, correlation coefficients).

11.7 PHARMACODYNAMIC [redacted] ANALYSIS

Pharmacodynamic endpoints as described in Section 9.3 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 a pharmacodynamic endpoint is observed, longitudinal model may be employed to model change from baseline over time. In addition, 95% confidence intervals (CI) of changes will be presented.

Evaluation of intact muscle and fatty replacement from MRI will be descriptive using a grading scale and, if feasible, quantitative using a numeric method of determining the degree (%) of overall fatty replacement of muscle from the skeletal muscle MRI and an individual (%) measure for the quadriceps. A correlative measure comparing the biopsied muscle and its MRI counterpart will also be performed.

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.

To explore the relationship between PK endpoints and urine Hex4 levels, scatter plots and linear mixed model may be used as appropriate.

To explore the relationship between glycogen content and biomarkers, correlational statistics (Spearman or Pearson) at each scheduled study visit will be used. In addition, scatter plots and linear regression analysis will be used to describe the relationship between glycogen content and each biomarker.

[redacted]

11.8 EXPLORATORY EFFICACY ANALYSIS

Observed measurements and changes from baseline to each study time point in 6MWT distance walked and PFT parameters (% predicted sitting and supine FVC, FEV1, MIP, MEP, and PEF) will be summarized using summary statistics. In addition, 95% CIs will be used to estimate the change from baseline at each study visit. Graphical displays showing data over time will be presented.

11.9 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Number of weeks in the study, the number of study infusions, and the dose received by patients will be summarized using summary statistics. Frequency and percentage of patients remaining on treatment will be summarized quarterly.

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

11.10 PRIOR/CONCOMITANT MEDICATION/THERAPY

Concomitant medication/therapy data will be coded using the World Health Organization Drug dictionary. Number and percentages of patients receiving each concomitant medication/therapy will be tabulated.

11.11 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.

12 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1 REGULATORY AND ETHICAL CONSIDERATIONS

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation (GDPR)).
- The protocol, protocol amendments, Informed Consent Form (ICF), IB , and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the European Union (EU) Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

12.2 INFORMED CONSENT PROCESS

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative [defined as parent(s) or guardian(s)] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

13 STUDY MONITORING

13.1 DATA QUALITY ASSURANCE

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.2 SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents include (but are not limited to): participant's medical file, appointment books, original laboratory records, functional outcome assessment source document.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

14 ADDITIONAL REQUIREMENTS

14.1 DATA PROTECTION

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Patient race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported) or ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown) will be collected in this study because these data are required by several regulatory authorities. In addition, it is unknown if race or ethnicity may have an impact on the Pompe disease ERT. It is now recognized that some drug metabolism are impacted by race (eg, warfarin [5]) and/or ethnicity (various drugs [6]).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole “drug development program”, ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (DPO) (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep

their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.

- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

14.2 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

14.3 CLINICAL TRIAL RESULTS AND DISSEMINATION OF CLINICAL STUDY DATA

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

A Coordinating Investigator will be designated to review and sign the completed clinical study report.

Analysis of [redacted] exploratory muscle biopsy and PK not included in the study report will be included in separate technical reports.

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable datasets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations”.

14.4 PUBLICATION POLICY

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor or prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC written approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology. 2007;68:99-109.

2. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med. 2010;362:1396-406.

3. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-7.

4. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166:518-624.

5. Schelleman H, Chen J, Chen Z, Christie J, Newcomb CW, Brensinger CM, et al. Dosing Algorithms to Predict Warfarin Maintenance Dose in Caucasians and African Americans. Clin Pharmacol Ther. 2008;84:332-9.

6. Yasuda SU, Zhang L, Huang SM. The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies. Clin Pharmacol Ther. 2008;84:417-3.

17 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

17.1 APPENDIX 1: COUNTRY-SPECIFIC REQUIREMENTS

France

The Sponsor is required by the French health authority to state in the protocol that the option for home infusion added in LTS13769 protocol amendment 04 does not apply in France, consistent with their position disallowing home infusion for all enzyme replacement therapies (ERT).

United Kingdom, Germany and Denmark

In order to comply with the UK, German and Danish Health Authority position regarding the protocol language, the duration of the additional follow-up phase will be defined as “up to the approval in the country or limited to a maximum of 2 years whichever occurs first (ie, for patients in the UK, Germany and Denmark, the total study duration per patient is 8 years at the maximum including the initial 6-year period and the additional 2-year follow-up).”

17.2 APPENDIX 2: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly after the cover page.

17.2.1 Amended protocol 01: 09 December 2013

This amended protocol (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

Change inclusion criteria to specific acceptable contraceptive methods

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, 7.1 Inclusion criteria	Change to inclusion criteria	To add contraceptive methods to I04
Clinical Trial Summary, 6.2.1 Duration of study participation for each patient, 6.2.2 Determination of end of clinical trial (all patients)	Change to study duration	Clarification
11.11 Interim analysis	Change to interim analysis	Clarification

17.2.2 Amended protocol 02: 25 July 2014

This amended protocol (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

Change to frequency and timing of assessments

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Graphical study design, 1.2 Study flow chart, 9.1.7 Immunogenicity, 10.1.2.2 Monthly, 10.1.2.3 Monthly for first 6 months and Quarterly visits thereafter and 10.1.2.4 Every 6 months	Change to frequency of antibody testing	To simplify by reducing frequency of sampling for antibody testing
1.2 Study flow chart	Addition of time window for study assessments and IP administration	To specify accepted time window for study assessments and IP administration from previous assessment date and previous IP administration date
1.1 Graphical study design, 1.2 Study flow chart, 9.1.5 Body weight, 10.1.2.3 Monthly for first 6 months and Quarterly visits thereafter and 10.1.2.4 Every 6 months	Change to the frequency of assessment of body weight	To harmonize frequency of assessment of body weight with recommendations from the Pharmacy Manual
Throughout	Clarifications	Not summarized

17.2.3 Amended protocol 03: 29 January 2016

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

Change the dose regimen for all patients to 20 mg/kg qow and change to the visit schedule for patients switching from 5 mg/kg qow or 10 mg/kg qow to 20 mg/kg qow

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, 8.1 Investigational medicinal products and 8.4 Methods of assigning patients to treatment group	20 mg/kg body weight qow was selected as the final avalglucosidase alfa dose for the extension study.	Avalglucosidase alfa was generally safe and well tolerated at all dose levels in TDR12857. The doses were differentiated by improvement in FVC with avalglucosidase alfa 20 mg/kg qow in the treatment naïve patients (Group 1) versus stabilization with 5 mg/kg.
1.1 Graphical study design, 1.2 Study flow chart and 10.1.2.7 Re-baseline visit	Change to the visit schedule for patients switching from 5 mg/kg qow or 10 mg/kg qow to 20 mg/kg qow	To include a re-baseline visit for assessments before receiving the higher dose, from which point forward the patient will follow the new visit schedule
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

17.2.4 Amended protocol 04: 27 November 2017

This amended protocol (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

Added option for home infusion of IMP

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
8.1 Investigational medicinal products	Added option of home infusion of IMP for patients meeting all eligibility requirements in regions where home infusion is deemed appropriate	To allow collection of data on home infusion of IMP in a clinical setting under GCP and to enhance patient retention and collection of long-term safety data
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

17.2.5 Amended protocol 05: 18 July 2018

This amended protocol (amendment 05) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

To comply with the requirement of the French health authority to state in the protocol that the option for home infusion added in LTS13769 protocol amendment 04 does not apply in France, consistent with their position disallowing home infusion for all enzyme replacement therapies (ERT).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	Document formatting revision	To combine the protocol amendment into a consolidated amended protocol
8.1 Investigational medicinal products	Added reference to Section 17.1 specific for France	Provide detail on regional requirements for home infusion in France
17 Supporting documentation and operational considerations	Document formatting revision	Add a new section for appendices
17.1 Appendix 1: Country-specific requirements	Added requirement specific for France	Home infusion of ERT is not allowed in France
17.2 Appendix 2: Protocol amendment history	Document formatting revision	To provide a summary of all changes to original protocol in one place

17.2.6 Amended protocol 06: 06 September 2019

This amended protocol (amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

The overall rationale for this amendment is as follows:

- To comply with the DMC recommendation with regards to home infusions.
- To reference the Investigator's Brochure (IB) in the protocol.
- To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country.
- To comply with the United Kingdom (UK) position regarding the protocol language with regards to the study follow-up period duration.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	Document formatting revision	To combine the protocol amendment into a consolidated amended protocol
Clinical trial summary (Duration of study)	Text added regarding an additional follow-up phase for all patients and UK patients.	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country. To comply with the UK position regarding the protocol language with regards to study follow-up period duration.
	mRNA analysis was removed from the pharmacogenetics endpoints	This test will no longer be performed.
1.1 Graphical study design	Text added regarding follow-up phase for all patients and UK patients	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country. To comply with the UK position regarding the protocol language with regards to study follow-up period duration.
	mRNA analysis was removed from the "At 6 months", "Re-baseline", and "EOS" visits.	This test will no longer be performed.
1.2.1 and 1.2.2 Study flow charts	End of study visit and follow-up visit deleted and the columns for these visits and the procedures were moved to the new study flow chart in Section 1.2.3; footnote "b" updated	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country.
	mRNA analysis removed from pharmacogenetics assessments	This test will no longer be performed.
1.2.3 Study flow chart	Added study flow chart for additional follow-up phase	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country. The study flow chart was added to denote the study procedures required for the additional follow-up period.
4.1.2 Absorption, distribution, metabolism, and excretion data	Added reference to the Investigator's Brochure	To reference the IB in the protocol.
4.2.2.4 Pharmacogenomics	Text deleted/updated; sampling for mRNA was removed.	To reflect the amendment-specific changes
6.2.1 Duration of study participation for each patient	Text updated regarding study duration and text added regarding the follow-up phase for all patients and reference added to Appendix 1, Section 17.1 specific for the UK	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country. To comply with the UK position regarding the protocol language with regards to the study follow-up period duration.

Section # and Name	Description of Change	Brief Rationale
8.1 Investigational medicinal products (Home infusion)	Deleted the requirement for a signed "Patient Registration Form". Clarification for home infusion personnel regarding training of basic life support	To comply with the DMC recommendation with regards to the home infusions procedure.
9.1.7 Immunogenicity	Text updated for the sample collection period for patients who were previously treated with alglucosidase alfa Text updated to specify IAR and circulating immune complex samples must be collected and shipped per the study-specific laboratory manual and the Study Operations Manual	Clarification.
9.2.1 Sampling times	Text updated for the blood sample collection period	Clarification.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
10.1.2.5 At 6 months and yearly thereafter	Plasma sample collection for mRNA analysis removed	This test will no longer be performed.
10.1.2.7 Re-baseline visit	Plasma sample collection for mRNA analysis removed	This test will no longer be performed.
10.1.3 Additional follow-up phase	New section and subsections (Sections 10.1.3.1 through 10.1.3.6) with corresponding text added regarding procedures in the additional follow-up phase	To extend the additional follow-up period until avalglucosidase alfa is approved in the patient's country.
10.1.3.7 End of study visit	Restructured EOS visit section (this section was previously Section 10.1.2.8) and deleted the following assessments:	
	Anti-alglucosidase alfa IgG antibodies (only patients who were previously treated with alglucosidase alfa).	As patients have not received alglucosidase for 6 years, anti-GAA ADA assessments are not performed during the additional follow-up phase.
	NeoGAA PK plasma sample collection.	This test will no longer be performed.
	Serum sample collection for skeletal muscle RNA expression analyses (within 6 months).	This test will no longer be performed.
	mRNA assessment.	This test will no longer be performed.

Section # and Name	Description of Change	Brief Rationale
Throughout	"neoGAA" replaced with "avalglucosidase alfa"	To align with other protocols and overall development plan
17.1 Appendix 1: Country-specific requirements	Added requirements specific for the UK	To comply with the UK position regarding the protocol language with regards to study follow-up period duration.

17.2.7 Amended protocol 07: 21 January 2020

This amended protocol (amendment 07) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The overall rationale for this amendment is as follows:

- To clarify that study duration for each patient is initially 6 years to align protocol wording with other study documents (ICF in particular) and align between different sections of the protocol.
- To modify the wording on duration of the additional follow-up period after the 6-year study for patients in the UK and Germany as follows: the duration of the additional follow up period will be up to the approval in the country or limited to a maximum of 2 years, whichever occurs first (ie, for UK and German patients, the total study duration per patient is 8 years at the maximum including the initial 6-year and the additional 2-year follow-up).
- To correct typographical errors in the table footnote references in Section 1.2.3.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	Document formatting revision	To update document history and provide overall rationale for the amendment
Clinical trial summary (Duration of study)	Clarification that study duration for each patient is initially 6 years. Revised wording for study follow-up period duration specific for the UK and German patients.	To align protocol wording with other study documents (ICF in particular) and align between different sections of the protocol. To comply with the UK and German Health Authority position regarding the protocol language with regards to study follow-up period duration.

Section # and Name	Description of Change	Brief Rationale
1.1 Graphical study design	Revised wording for study follow-up period duration specific for the UK and German patients.	To comply with the UK and German Health Authority position regarding the protocol language with regards to study follow-up period duration.
1.2 Study flow chart	Deleted specifics regarding neutralizing antibody testing.	Details are provided in Section 9.1.7 Immunogenicity.
	Corrected footnote references.	To correct typographical errors in the study flow chart for the additional follow-up period.
6.2.1 Duration of study participation for each patient	Clarification that study duration for each patient is initially 6 years.	To align protocol wording with other study documents (ICF in particular) and align between different sections of the protocol.
	Revised wording for study follow-up period duration specific for the UK and German patients.	To comply with the UK and German Health Authority position regarding the protocol language with regards to study follow-up period duration.
9.1.7 Immunogenicity	Corrected typographical error regarding antibody testing.	To specify testing to be done for anti-avalglucosidase alfa antibodies.
	Modified wording regarding the type of testing for neutralizing antibodies to avalglucosidase alfa	To allow flexibility in case approval is obtained to end testing of inhibition of enzyme activity.
	Modified wording regarding duration of testing for anti-alglucosidase alfa IgG antibodies.	To allow testing of anti-alglucosidase alfa IgG antibodies to be stopped earlier than 6 years.
10.1.3 Additional follow-up phase	Revised wording for study follow-up period duration specific for the UK and German patients.	To comply with the UK and German Health Authority position regarding the protocol language with regards to study follow-up period duration.
17.1 Appendix 1: Country-specific requirements	Revised wording for study follow-up period duration specific for the UK and German patients.	To comply with the UK and German Health Authority position regarding the protocol language with regards to study follow-up period duration.
17.2.6 Appendix 2: Protocol amendment history	Added new section.	To incorporate the changes from amended protocol 05 to amended protocol 06.

17.2.8 Amended protocol 08: 30 September 2020

This amended protocol (Amendment 08) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact either the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment

The overall rationale for this amendment is as follows:

- To comply with the Danish Medicines Agency (DKMA) position regarding the protocol language with regards to the study follow-up period duration.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	Document formatting revision	To update document history and provide overall rationale for the amendment
Clinical trial summary (Duration of study)	Revised wording for study follow-up period duration specific for patients in the UK, Germany and Denmark.	To comply with the DKMA position regarding the protocol language with regards to study follow-up period duration.
1.1 Graphical study design (Additional Follow-up Phase)	Revised wording for study follow-up period duration specific for patients in the UK, Germany and Denmark.	To comply with the DKMA position regarding the protocol language with regards to study follow-up period duration.
6.2.1 Duration of study participation for each patient	Revised wording for study follow-up period duration specific for patients in the UK, Germany and Denmark.	To comply with the DKMA position regarding the protocol language with regards to study follow-up period duration.
10.1.3 Additional follow-up phase	Revised wording for study follow-up period duration specific for patients in the UK, Germany and Denmark.	To comply with the DKMA position regarding the protocol language with regards to study follow-up period duration.
17.1 Appendix 1: Country-specific requirements	Revised wording for study follow-up period duration specific for patients in the UK, Germany and Denmark.	To comply with the DKMA position regarding the protocol language with regards to study follow-up period duration.
17.2.6 Appendix 2: Protocol amendment history	Correction to description of amended protocol 06 changes consistent with designation as a substantial amended protocol.	To correct typographical error
17.2.7 Appendix 2: Protocol amendment history	Added new section.	To incorporate the changes from amended protocol 06 to amended protocol 07.

Signature Page for VV-CLIN-0049122 v9.0
lts13769-16-1-1-amended-protocol09

Approve & eSign	[redacted]	

Approve & eSign	[redacted]	

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

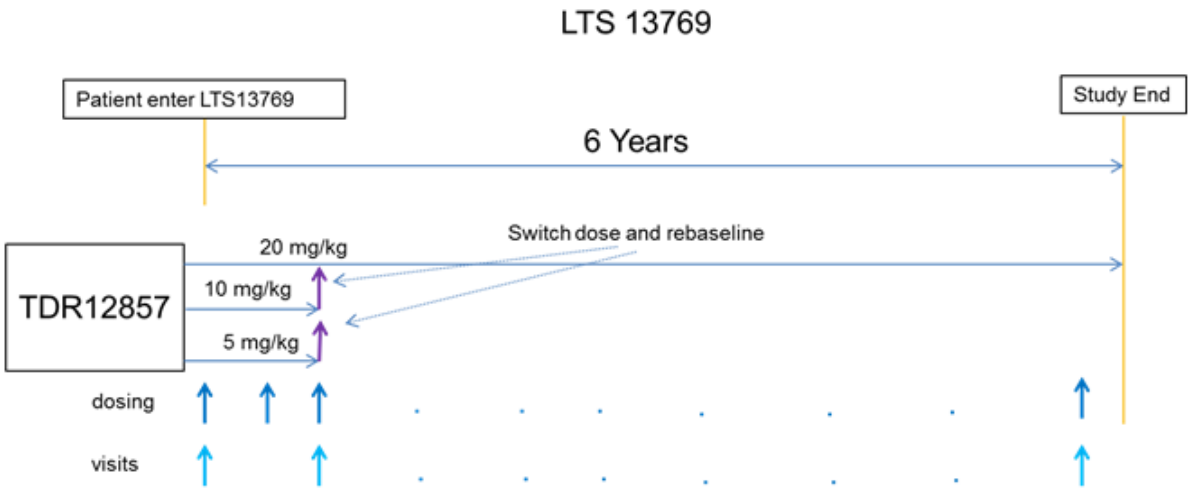
The secondary objectives of the LTS13769 study are to assess if the benefits of avalglucosidase alfa are maintained and the time course of response, by examining the long-term effect of avalglucosidase alfa on pharmacodynamic (PD) and exploratory efficacy variables.

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 VV-CLIN-0196357 v2.0

lts13769-16-1-9-sap

Approve & eSign	Meehyung Cho Clinical 26-Mar-2020 21:03:03 GMT+0000

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eTable 1 Number (%) of participants with study drug-related treatment-emergent adverse events by Medical Dictionary for Regulatory Activities (MedDRA) preferred term

	Participants with events, n (%)		
	Naïve Group (N=10)	**Switch Group (N=14)**	**Overall (N=24)**
MedDRA: Preferred term	Participants, n (%)	Participants, n (%)	Participants, n (%)
Any events	8 (80)	10 (71)	18 (75)
Headache	1 (10)	2 (14)	3 (13)
Nausea	2 (20)	1 (7)	3 (13)
Rash	1 (10)	2 (14)	3 (13)
Fatigue	2 (20)	1 (7)	3 (13)
Myalgia	1 (10)	1 (7)	2 (8)
Pruritus	1 (10)	1 (7)	2 (8)
Dizziness	1 (10)	1 (7)	2 (8)
Hypertension	1 (10)	1 (7)	2 (8)
Erythema	1 (10)	1 (7)	2 (8)
Dyspnea	1 (10)	1 (7)	2 (8)
Muscle spasms	1 (10)	1 (7)	2 (8)
Pain	0	1 (7)	1 (4)
Tremor	0	1 (7)	1 (4)
Flushing	1 (10)	0	1 (4)
Diarrhea	0	1 (7)	1 (4)
Lip swelling	0	1 (7)	1 (4)
Swollen tongue	0	1 (7)	1 (4)
Hyperhidrosis	0	1 (7)	1 (4)
Palmar erythema	0	1 (7)	1 (4)
Asthenia	0	1 (7)	1 (4)
Chills	1 (10)	0	1 (4)
Facial pain	0	1 (7)	1 (4)
Infusion site pain	0	1 (7)	1 (4)
Hypersensitivity	0	1 (7)	1 (4)
Dizziness postural	0	1 (7)	1 (4)
Paraesthesia	1 (10)	0	1 (4)
Somnolence	0	1 (7)	1 (4)
Eye pruritus	0	1 (7)	1 (4)
Lacrimation increased	0	1 (7)	1 (4)
Ventricular extrasystoles	0	1 (7)	1 (4)
Hypotension	0	1 (7)	1 (4)
Cough	1 (10)	0	1 (4)
Respiratory distress	1 (10)*	0	1 (4)
Abdominal pain	0	1 (7)	1 (4)
Gastroesophageal reflux disease	1 (10)	0	1 (4)
Flank pain	1 (10)	0	1 (4)
Balanoposthitis	0	1 (7)	1 (4)
Chest discomfort	1 (10)*	0	1 (4)
Infusion site reaction	0	1 (7)	1 (4)
Pyrexia	1 (10)	0	1 (4)
Blood creatinine increased	0	1 (7)	1 (4)
Breath sounds abnormal	0	1 (7)	1 (4)
Oxygen saturation increased	0	1 (7)	1 (4)
Pulmonary function test decreased	0	1 (7)†	1 (4)

*Naïve 5 mg/kg Group participant who discontinued NEO1 due to a serious adverse events (SAE) of respiratory distress and chest discomfort occurring during the 9th avalglucosidase alfa infusion; these SAEs were considered to be infusion-associated reactions and were not considered life-threatening

†Symptoms were recorded prior to study start

eTable 2 Change from Baseline over time in respiratory function parameters and 6MWT distance

Parameter	Group	Baseline mean ± SD (median) n	Change from Baseline Mean ± SD (median) n							
			Week 25	**Week 52**	**Week 78**	**Week 104**	**Week 156**	**Week 208**	**Week 260**	**Week 312**
Upright FVC, % predicted	**Naïve**	69.2±19.27 (58.7) n=10	2.6±6.77 (4.3) n=9	2.6±8.20 (4.4) n=8	2.6±7.01 (4.7) n=7	3.1±11.64 (4.8) n=7	0.1±10.44 (2.7) n=7	1.3±7.01 (0.0) n=7	−2.9±13.13 (−3.9) n=6	−0.04±11.51 (−0.04) n=2
	Switch	77.3±16.45 (75.9) n=14	−0.2±4.44 (−2.6) n=13	−2.5±6.01 (−2.0) n=11	−4.2±5.24 (−3.3) n=11	−3.8±5.41 (−2.4) n=11	−3.6±4.54 (−3.7) n=10	−1.7±5.29 (−1.6) n=10	−5.7±7.21 (−4.9) n=10	−6.3±4.58) (−8.8) n=3
Upright MIP, % predicted	**Naïve**	67.9±30.52 (56.3) n=9	8.7±9.01 (6.4) n=8	7.3±16.25 (9.0) n=7	7.8±14.93 (1.5) n=6	7.9±14.13 (0.8) n=6	10.4±20.63 (8.9) n=6	8.6±24.66 (3.3) n=6	2.7±22.39 (2.1) n=5	−5.7±7.88 (−5.7) n=2
	Switch	67.2±23.93 (80.0) n=13	4.7±9.12 (6.1) n=12	3.9±10.01 (5.5) n=10	−1.2±8.98 (−0.3) n=10	−3.0±9.77 (−2.6) n=10	−4.7±8.43 (−5.8) n=10	−2.1±8.03 (−4.2) n=9	−7.8±33.30 (−7.5) n=9	8.1±10.79 (7.9) n=3
Upright MEP, % predicted	**Naïve**	75.7±18.06 (76.1) n=9	13.1±6.06 (11.1) n=8	3.5±13.95 (6.0) n=7	10.4±15.34 (4.3) n=6	12.0±10.26 (9.3) n=6	15.7±15.80 (10.2) n=6	8.3±13.85 (6.4) n=6	4.5±14.84 (7.1) n=5	3.3±8.69 (3.3) n=2
	Switch	80.1±29.47 (87.7) n=13	5.6±23.17 (−4.9) n=12	9.9±17.27 (7.2) n=10	8.1±17.27 (7.4) n=10	7.5±22.24 (5.3) n=10	6.8±11.13 (5.4) n=10	6.1±21.61 (8.1) n=9	11.2±12.81 (10.3) n=9	6.7±9.23 (5.4) n=3
6MWT distance, meters	**Naïve**	449.2±118.4 (488.5) n=10	7.0±24.7 (1.0) n=9	17.0±62.9 (5.0) n=8	16.9±56.2 (15.0) n=8	42.7±106.8 (12.0) n=7	9.6±56.5 (−1.0) n=7	−12.8±64.6 (−13.0) n=6	−33.9±114.2 (−20.0) n=7	−46.5±4.9 (−46.5) n=2
	Switch	440.4±141.0 (439.0) n=14	−2.3±40.6 (5.0) n=13	−8.0±57.8 (18.0) n=11	−14.0±60.36 (−7.0) n=9	−39.5±110.4 (9.0) n=11	−16.2±85.4 (2.0) n=11	−22.6±87.2 (4.5) n=10	–44.5±107.0 (−12.5) n=10	−53.0±111.4 (−17.0) n=3

6MWT = 6-minute walk test; FVC = forced vital capacity; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure

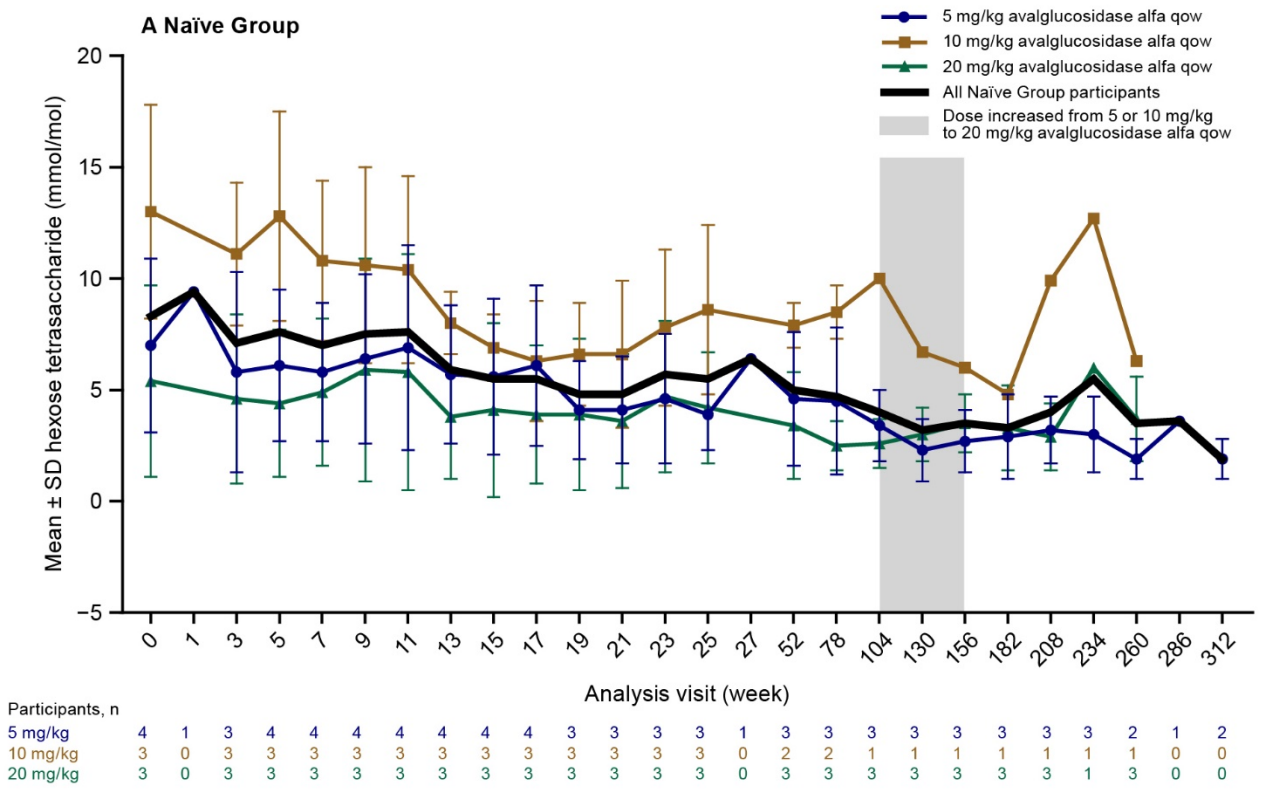
Note: Participants may not have completed all assessments at a given timepoint, therefore participant numbers may vary within that timepoint

eTable 3 IARs and ADA titers after up to 6.5 years in the 12 participants who had protocol-defined or algorithm-defined IARs

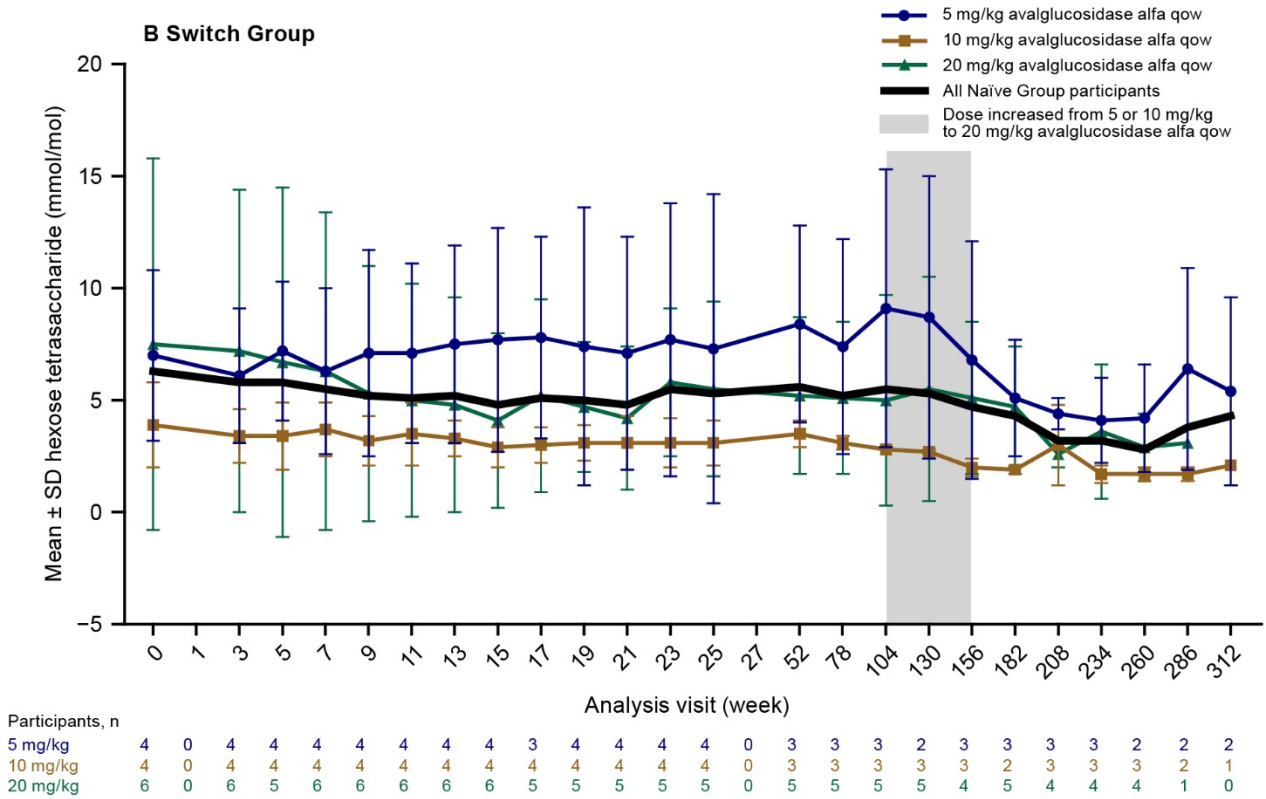
		NEO1		NEO-EXT		
		IAR	**ADA titer at time of IAR**	**IAR**	**ADA titer at time of IAR**	**Last available ADA titer**
Naïve Group	1	a. Rash b. Flushing, cough, dizziness, nausea and SAE of respiratory distress and chest discomfort	a. Negative b. 1,600–3,200	Not enrolled	Not enrolled	Not enrolled
	2	Erythema	Negative–400	None	NA	800
	3	Headache	Negative–800	None	NA	1,600
	4	Gastroesophageal reflux disease	Negative	None	NA	400
	5	None	NA	Pruritus	200	200
	6	None	NA	a. SAE of chills and pyrexia b. Chills and flank pain c. Hypertension	a. 12,800 b. 6,400 c. 3,200	3,200
Switch Group	7	None	NA	Headache	800	Negative
	8	Rash, pruritus, hypersensitivity	400	Erythema, abnormal breath sounds, ventricular extrasystoles, pruritus, lip and tongue swelling, oxygen saturation decreased	400	200
	9	a. Headache b. Dizziness, hypotension c. Headache	a. 1,600 b. 1,600–12,800 c. 12,800	a. Pain, nausea b. Pain, tremor, hyperhidrosis	3,200–6,400	3,200
	10	Infusion site reaction, infusion site pain	100	None	NA	Negative
	11	Myalgia	Negative	Not enrolled	Not enrolled	Not enrolled
	12	None	NA	Hypertension	Negative	Negative

ADA = anti-drug antibody; IAR = infusion-associated reaction; SAE = serious adverse event

eFigure 1 Mean±SD from Baseline over time in hexose tetrasaccharide. A Naïve Group. B. Switch Group. Normal range for Hex4: 0.194–3.36 mmol/mol cre (males and females, aged 13–18 years); 0.142–1.92 mmol/mol cre (males and females, aged >18 years).

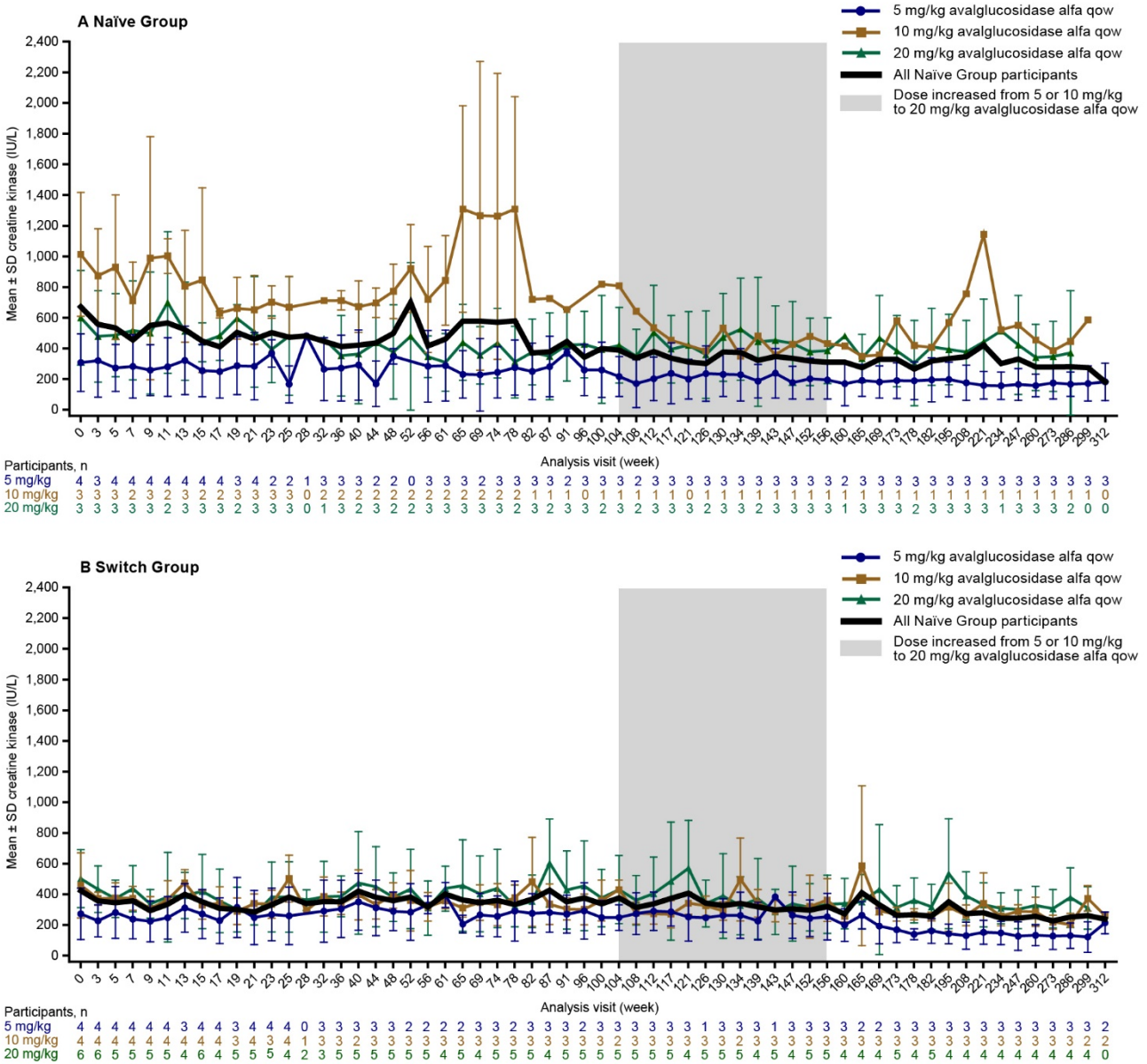


Participants, n																									
5 mg/kg	4	1	3	4	4	4	4	4	4	4	3	3	3	3	1	3	3	3	3	3	3	3	2	1	2
10 mg/kg	3	0	3	3	3	3	3	3	3	3	3	3	3	3	0	2	2	1	1	1	1	1	1	0	0
20 mg/kg	3	0	3	3	3	3	3	3	3	3	3	3	3	3	0	3	3	3	3	3	3	3	1	3	0	0

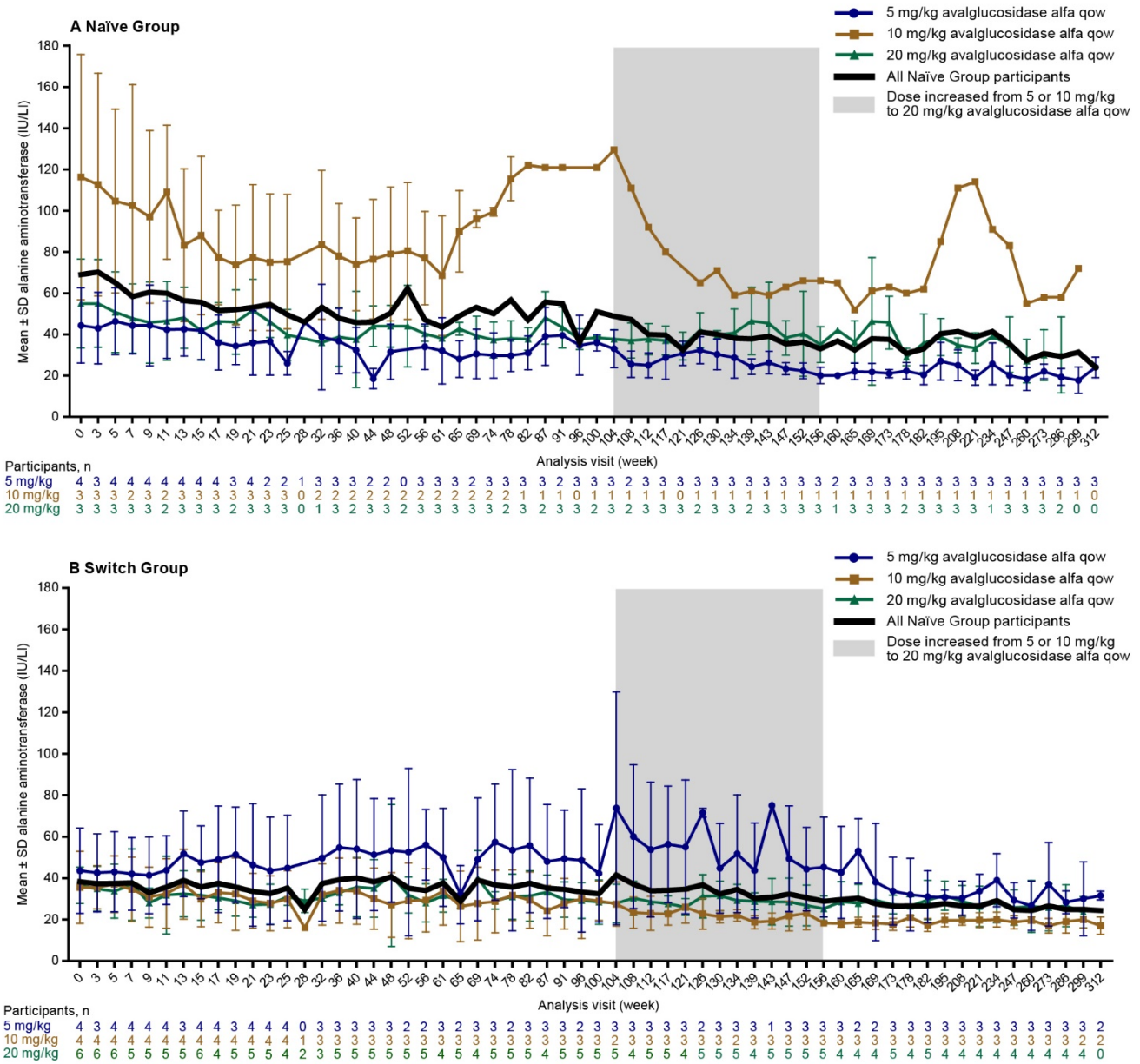


Participants, n																									
5 mg/kg	4	0	4	4	4	4	4	4	4	3	4	4	4	4	0	3	3	3	2	3	3	3	3	2	2	2
10 mg/kg	4	0	4	4	4	4	4	4	4	4	4	4	4	4	0	3	3	3	3	3	2	3	3	3	2	1
20 mg/kg	6	0	6	5	6	6	6	6	6	5	5	5	5	5	0	5	5	5	5	4	5	4	4	4	1	0

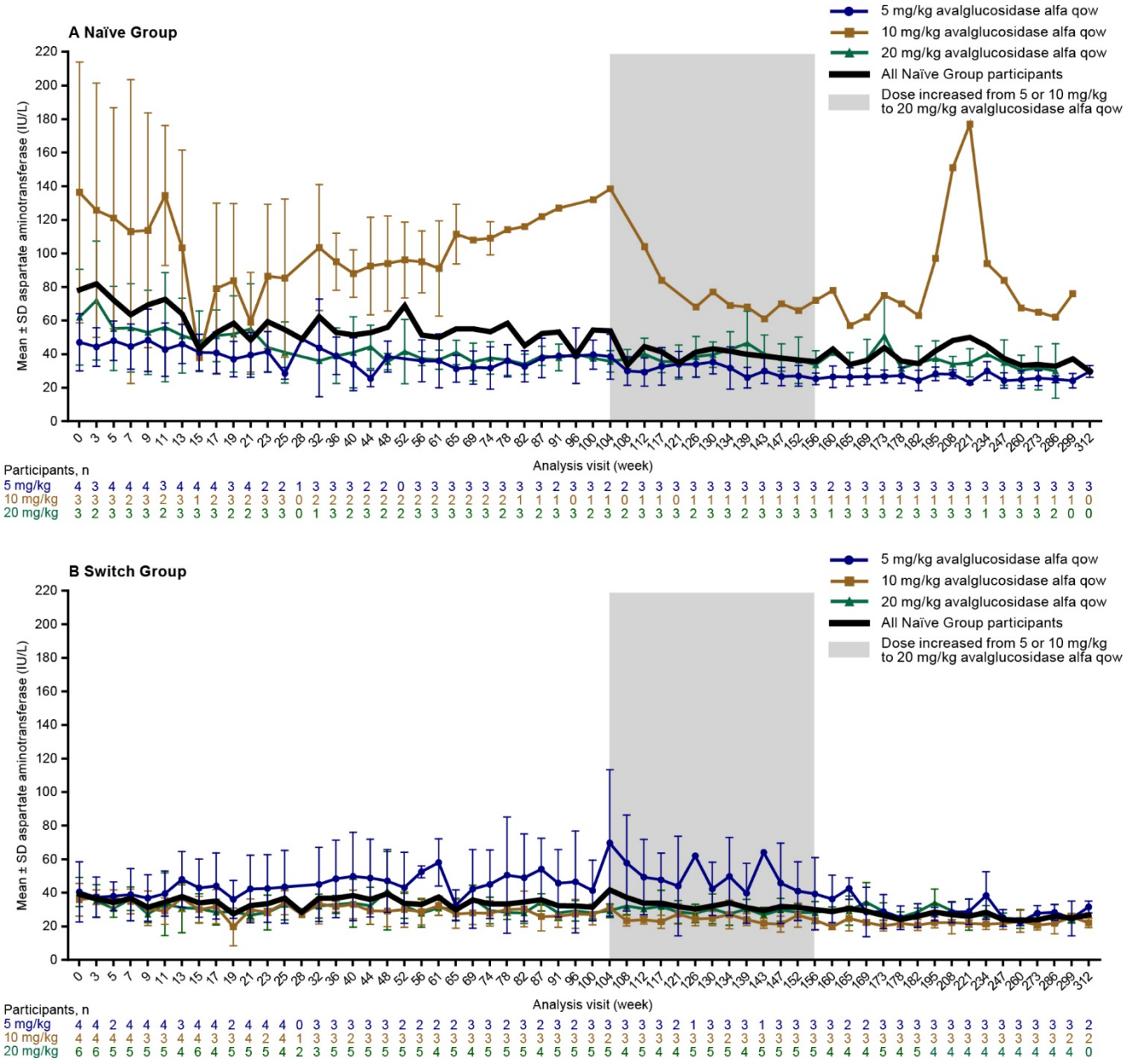
eFigure 2 Mean±SD from Baseline over time in creatine kinase. A Naïve Group. B. Switch Group. Normal range for CK: 18–169 IU/L for females; 18–198 IU/L for males.



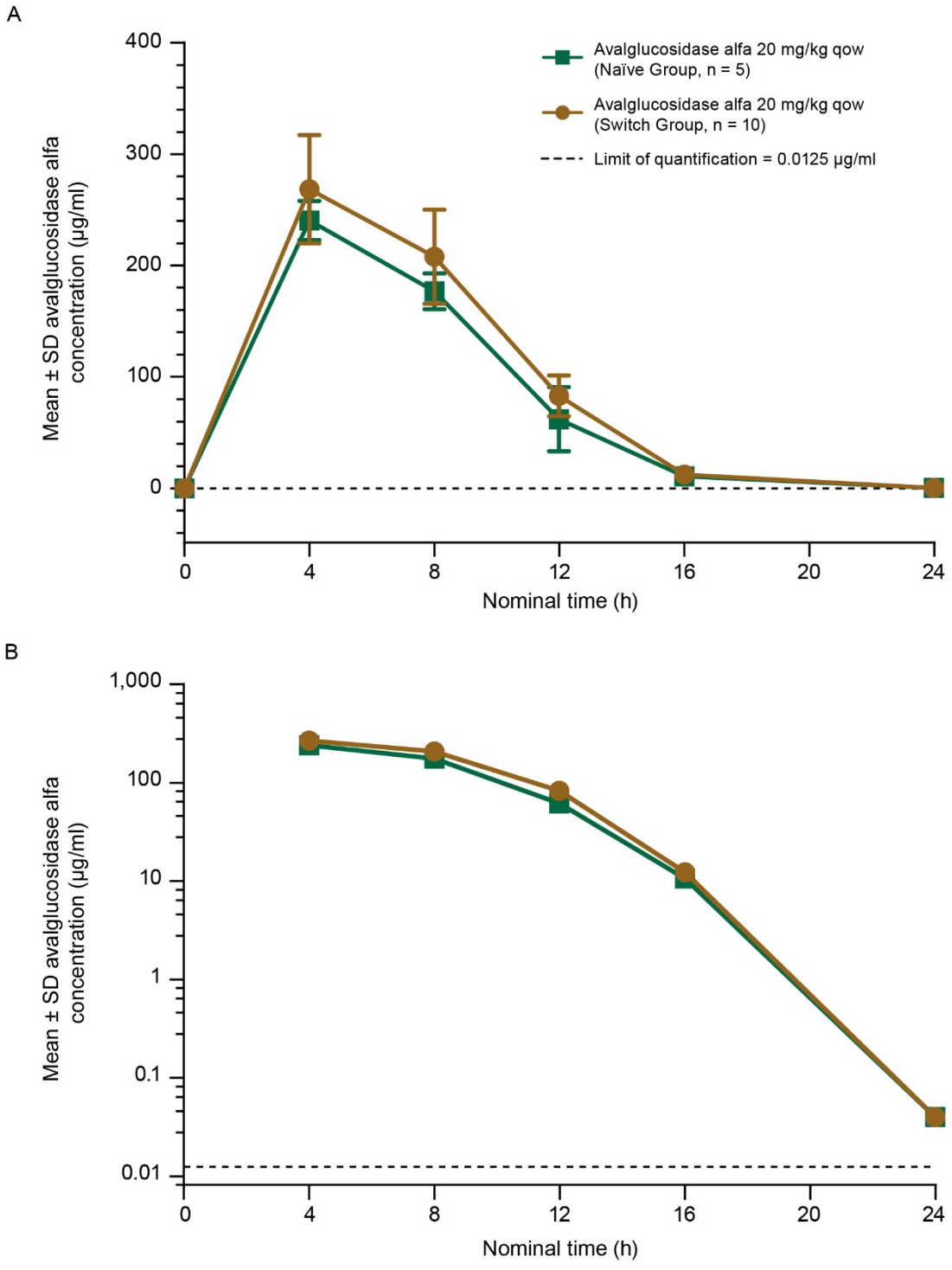
eFigure 3 Mean ± SD from Baseline over time in alanine aminotransferase. A Naïve Group. B. Switch Group.



eFigure 4 Mean ± SD from Baseline over time in aspartate aminotransferase. A Naïve Group. B. Switch Group.



eFigure 5 Plasma concentration of avalglucosidase alfa at Week 208 after 20 mg/kg qow for Switch and Naïve Groups. A. Linear scale; B. Semi-log scale.



eTable 4 Avalglucosidase alfa PK parameters over time

Parameter	**Week 26**			**Rebaseline at 20 mg/kg**	**Week 208**
Avalglucosidase alfa dose	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**	**20 mg/kg**	**20 mg/kg**
Participants, n	6	4	7	6	15
C_{max}, µg/mL, mean ± SD (geometric mean) [CV%]	90.9±32.0 (86.9) [35.2]	174±24.5 (173) [14.1]	371±276 (313) [74.4]	295±53.8 (290) [18.3]	259±42.4 (256) [16.4]
t_{max}, h, median (min − max)	1.8 (1.6 – 2.7)	2.3 (2.3 – 3.6)	3.8 (3.5 – 4.6)	3.9 (3.6 – 4.9)	3.9 (3.8 – 4.6)
AUC_{last} (µg•hr/mL), mean ± SD (geometric mean) [CV%]	308±113 (292) [36.9]	670±72.1 (667) [10.8]	1,660±868 (1,500) [52.3]	1,620±309 (1,590) [19.1]	1,350±266 (1,320) [19.7]
$t_{1/2z}$, h, mean ± SD (geometric mean) [CV%]	0.835±0.195 (0.817) [23.3]	0.975±0.535 (0.886) [54.9]	1.25±0.369 (1.21) [29.4]	1.37±0.425 (1.31) [31.1]	1.47±0.386 (1.41) [26.3]
CL_{ss}, mL/h, mean ± SD (geometric mean) [CV%]	1,170±398 (1,110) [34.1]	1,210±70.5 (1,200) [5.8]	1,010±257 (971) [25.5]	840±206 (816) [24.5]	1,140±233 (1,110) [20.6]
V_{ss}, L, mean ± SD (geometric mean) [CV%]	3.46±1.22 (3.25) [35.3]	4.43±0.291 (4.42) [6.6]	5.24±1.39 (5.01) [26.6]	4.52±1.24 (4.37) [27.5]	5.99±1.03 (5.91) [17.2]

AUC_{last} = area under the plasma concentration–time curve from time zero to the last measurable concentration; CLss = total body clearance from plasma at steady state; C_{max} = maximum plasma concentration observed; CV = coefficient of variation; PK = pharmacokinetic; $t_{1/2z}$ = terminal elimination half-life; t_{max} = time taken to reach C_{max}; V_{ss} = steady state volume of distribution