NCT02032524

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

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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. Exploratory plasma and urine biomarkers. **Pharmacogenetics** Serum skeletal muscle ribonucleic acid (RNA) expression analysis. Plasma circulating microRNA analyses.

	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 • Exploratory biomarker urine sample collection • Exploratory biomarker plasma sample collection • microRNA plasma sample collection	• 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) • Exploratory biomarker urine sample collection (within 1 month) • Exploratory biomarker plasma sample collection (within 1 month)	• 6MWT (within 1 month) • PFT (within 1 month) • microRNA plasma sample collection (within 1 month) • 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 • Exploratory biomarker urine sample collection • Exploratory biomarker plasma sample collection	• 6MWT • PFT • microRNA plasma sample collection • 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	
Exploratory biomarker plasma samples[h]						X	
Exploratory biomarker urine samples[h]						X	
Efficacy[f]	within a ±14-day window[e]						
6MWT					X		
PFT					X		
Pharmacogenetics[f]	within a ±14-day window[e]						
Plasma samples for circulating microRNA analyses[h]						X	
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 blood, urine, or plasma 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	
Exploratory biomarker plasma samples[h]	X					X	
Exploratory biomarker urine samples[h]	X					X	
Efficacy[f]	within a ±14-day window[e]						
6MWT	X				X		
PFT	X				X		
Pharmacogenetics[f]	within a ±14-day window[e]						
Plasma samples for circulating microRNA analyses[h]	X					X	
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 blood, urine, or plasma 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	
Exploratory biomarker plasma samples[g]					X		X	
Exploratory biomarker urine samples[g]					X		X	
Efficacy[e]	within a ±14-day window[d]							
6MWT				X			X	
PFT				X			X	
Pharmacogenetics[e]	within a ±14-day window[d]							
Plasma samples for circulating microRNA analyses[g]					X		X	

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 blood, urine, or plasma 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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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 and exploratory biomarkers 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.

Fasted plasma samples and fasted urine samples will be taken for exploration of potential biomarkers of disease severity or response to avalglucosidase alfa.

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. If feasible, circulating RNA measurement could provide a minimally invasive biomarker for disease progression and severity. Therefore, plasma samples will also be collected and assessed for circulating microRNA concentrations on both the whole-genome and individual gene levels.

When a muscle biopsy is available, skeletal muscle tissue samples, taken by needle or open biopsy, will be evaluated for exploratory RNA expression. 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.

9.3.4 Exploratory plasma and urine biomarkers

Fasted plasma and urine samples will be collected prior to IMP infusion for the assessment of exploratory biomarkers. Procedures for the collection, handling, and shipment of all samples will be included in the study-specific laboratory manual. Results will be used to inform on biomarker targets for future studies and will not be reported in the CSR.

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.

9.5.2 Circulating microRNA analysis

Plasma samples will be collected and assessed for circulating microRNA concentrations on both the whole-genome and individual gene levels. Results will be used to inform on biomarker targets for future studies and will not be reported in the CSR.

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.
- Exploratory biomarker urine sample collection.
- Exploratory biomarker plasma sample collection.
- Plasma sample collection for microRNA analyses.

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).
- Exploratory biomarker urine sample collection (within 1 month).
- Exploratory biomarker plasma sample collection (within 1 month).
- 6MWT (within 1 month).
- PFT (within 1 month).
- Plasma sample collection for microRNA analyses (within 1 month).

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:

- Exploratory biomarker urine sample collection.
- Exploratory biomarker plasma sample collection.
- Plasma sample collection for microRNA analyses.

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.
- Exploratory biomarker urine sample collection.
- Exploratory biomarker plasma sample collection.
- 6MWT.
- PFT.
- Plasma sample collection for microRNA analyses.
- 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 AND EXPLORATORY BIOMARKER 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.

Similar analyses will be carried out to explore the relationship between other pharmacodynamic endpoints, exploratory biomarkers, and exploratory efficacy assessments.

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 DBS, plasma and urine biomarkers, pharmacogenetic biomarkers, exploratory immunogenicity assessments, 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.
9.3.4 Exploratory plasma and urine biomarkers	Text added regarding biomarker results and reporting	Clarification.
9.5.1 Skeletal muscle RNA expression analysis	Text added regarding biomarker results and reporting	Clarification.
9.5.2 Circulating microRNA analysis	Heading updated (sampling for mRNA was removed) and text added regarding biomarker results and reporting	Clarification.
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

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AMENDED CLINICAL TRIAL PROTOCOL 09 ERRATUM

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

Amended Clinical Trial Protocol 09		Version number: 1 (electronic 9.0)	Date: 21-Dec-2020
Version Number:	1	EudraCT IND Number(s) WHO universal trial number	2013-003321-28 109569 U1111-1147-3439
Date of Erratum:	25-Nov-2023	Total number of pages:	4

REASON FOR ERRATUM:

In the Clinical Trial Summary table (page 5) and in section 5.2 (page 33), exploratory efficacy variables are wrongly listed as secondary endpoints.

In the LTS13769 study protocol (Amended Clinical Trial Protocol 09, page 6), exploratory plasma and urine biomarkers and pharmacogenetics assessments are wrongly listed as secondary endpoints. These assessments are clearly exploratory in nature and are not reported in the Clinical Study Report, as also described in the study protocol:

- Amended Clinical Trial Protocol 09, page 50

9.3.4 Exploratory plasma and urine biomarkers

Fasted plasma and urine samples will be collected prior to IMP infusion for the assessment of exploratory biomarkers. Procedures for the collection, handling, and shipment of all samples will be included in the study-specific laboratory manual. Results will be used to inform on biomarker targets for future studies and will not be reported in the CSR.

- Amended Clinical Trial Protocol 09, page 51

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.

9.5.2 Circulating microRNA analysis

Plasma samples will be collected and assessed for circulating microRNA concentrations on both the whole-genome and individual gene levels. Results will be used to inform on biomarker targets for future studies and will not be reported in the CSR.

DESCRIPTION OF CHANGE AND WHAT IS BEING CHANGED:

CLINICAL TRIAL SUMMARY

The following text on page 5:

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.

Is replaced with:

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.

The following text beginning on page 6:

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. Exploratory plasma and urine biomarkers. **Pharmacogenetics** Serum skeletal muscle ribonucleic acid (RNA) expression analysis. Plasma circulating microRNA analyses. **Exploratory Endpoints:** **Efficacy** 6-minute walk test (6MWT). Pulmonary function testing (PFT) endpoints.

Is replaced with:

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. ~~Exploratory plasma and urine biomarkers.~~ ~~**Pharmacogenetics**~~ ~~Serum skeletal muscle ribonucleic acid (RNA) expression analysis.~~ ~~Plasma circulating microRNA analyses.~~ **Exploratory Endpoints:** **Efficacy** 6-minute walk test (6MWT). Pulmonary function testing (PFT) endpoints. **Pharmacodynamics** Exploratory plasma and urine biomarkers. **Pharmacogenetics** Serum skeletal muscle ribonucleic acid (RNA) expression analysis. Plasma circulating microRNA analyses.

5.2 SECONDARY

The following text on page 33:

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.

Is replaced with:

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.

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lts13769-16-1-1-amended-protocol09-erratum-25-nov-2023

Approve & eSign	[redacted]
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