SANOFI GENZYME

NCT02782741

AMENDED CLINICAL TRIAL PROTOCOL 06

COMPOUND: GZ402666

A Phase 3 randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late onset Pompe disease

STUDY NUMBER: EFC14028

STUDY NAME: COMparative Enzyme replacement Trial with neoGAA versus rhGAA (COMET)

VERSION DATE / STATUS: 04-Feb-2022/Final

Version Number:	1	EudraCT IND Number(s) WHO universal trial number:	2016-000942-77 109569 UTN U1111-1178-4806
Date:	04-Feb-2022	Total number of pages:	156

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: Email:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: Email:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 06	UK only	04-Feb-2022, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 05	Canada only	18-Nov-2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04 (Global)	All	21-Dec-2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03 (Global)	All	10-Apr-2019, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02 (Global)	All	18-Jul-2017, version 1 (electronic 2.0)
Protocol Amendment 03	All	18-Jul-2017, version 1 (electronic 1.0)
Protocol Amendment 02 (SE)	Sweden only	03-Aug-2016, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (Global)	All	03-Aug-2016, version 1 (electronic 1.0)
Protocol Amendment 01	All	03-Aug-2016, version 1 (electronic 1.0)
Clinical Trial Protocol		30-Mar-2016, version 1 (electronic 3.0)

Amended protocol 06 (04 February 2022)

This amended protocol 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.

OVERALL RATIONALE FOR THE AMENDMENT

Under the current EFC14028 protocol applicable for patients in the UK (Amended protocol 04) the duration of the extended open-label avalglucosidase alfa long-term follow-up period is defined as ‘up to 144 weeks after the last patient has been enrolled in the study’. Last enrolled patient was a pediatric patient enrolled in the open-label period in August 2020. The 144-week period leads to May 2023. This date is inconsistent with the maximum period allowed per protocol, which is 289 weeks of treatment, because all patients in the UK will reach Week 289 earlier than May 2023. In order to correct this discrepancy, the duration of the extended open-label avalglucosidase alfa long-term follow-up period will be defined as ‘up to the approval in the country or to the maximal duration planned in the study (ie, end of treatment at Week 289), whichever occurs first’.

Protocol amendment summary of changes table

Section # and Name	Description and Change	Brief Rationale
Protocol Amendment Summary of Changes	Document formatting revision.	To update document history and provide overall rationale for the amendment and summary of changes table.
Section 17.3 Appendix C: Country-specific requirements	Revised text in Section 17.3.4 United Kingdom to state the following: In the UK, the duration of the extended open-label avalglucosidase alfa long-term follow-up period will be defined as 'up to the approval in the country or to the maximal duration planned in the study (ie, end of treatment at Week 289), whichever occurs first'.	To correct a discrepancy in the definition of duration of the extended open-label avalglucosidase alfa long-term follow-up period in the UK to not exceed the maximal planned 289-week duration of treatment in the study.
Section 17.4 Appendix D: Protocol amendment history	Added new section (Section 17.4.5).	To incorporate the changes from amended protocol 05 to the amended protocol 06.

CLINICAL TRIAL SUMMARY

COMPOUND: GZ402666

STUDY No.: EFC14028
STUDY NAME: COMparative Enzyme replacement Trial with neoGAA versus rhGAA (COMET)

TITLE	A Phase 3 randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late-onset Pompe disease (LOPD)
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective:** The primary objective of the study is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by Forced Vital Capacity (FVC) % predicted in the upright position, as compared to alglucosidase alfa. **Secondary objectives:** Secondary objectives are to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6-minute walk test [6MWT]), inspiratory muscle strength (maximum inspiratory pressure [MIP]), expiratory muscle strength (maximum expiratory pressure [MEP]), lower extremity muscle strength (hand-held dynamometry [HHD]), motor function (Quick Motor Function Test [QMFT]), and health-related quality of life (Short Form-12 [SF-12]). **Other Objectives**: Additional objectives are to determine the pharmacokinetics (PK), exploratory pharmacodynamics (PD), pharmacogenetics and effect of avalglucosidase alfa treatment on motor function (Gross Motor Function Measure-88 [GMFM-88] and Gait, Stair, Gower's Maneuver, and Chair [GSGC]), upper extremity muscle strength (HHD), health-related quality of life (EuroQoL in 5 dimensions [EQ-5D-5L] and Pediatric Quality of Life Inventory [PedsQL] Generic Core Scale), and patient reported outcomes (Pompe Disease Symptom Scale [PDSS], Pompe Disease Impact Scale [PDIS], Rasch-built Pompe-specific Activity scale [R-PAct], and Patient Global Impression of Change [PGIC]).
STUDY DESIGN	A Phase 3 multicenter, multinational, randomized, double-blinded study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa (Myozyme®/Lumizyme®) in treatment-naïve patients with LOPD. The study includes 2 main periods: the blinded treatment period and the open-label avalglucosidase alfa long-term follow-up phase. Patients in the alglucosidase alfa arm will be switched to avalglucosidase alfa treatment after 12 months. Patients will remain blinded to the randomized treatment until after database is locked. Randomization will be in a 1:1 ratio with stratification factors based on baseline FVC, gender, age, and country (Japan or ex-Japan).

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** The patient has confirmed acid alpha-glucosidase (GAA) enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations. **Exclusion criteria:** The patient is <3 years of age, has known Pompe specific cardiac hypertrophy, is wheelchair dependent, is not able to ambulate 40 meters (approximately 130 feet) without stopping and without an assistive device, requires invasive-ventilation (non-invasive ventilation is allowed), is not able to successfully perform repeated FVC measurements in upright position of ≥30% predicted and ≤85% predicted, or has had previous treatment with immunomodulation, alglucosidase alfa, or any investigational therapy for Pompe disease.
Total expected number of patients	Approximately 96 patients
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Avalglucosidase alfa Alglucosidase alfa
Formulation:	Avalglucosidase alfa and alglucosidase alfa will be supplied as sterile lyophilized powder, administered following reconstitution and dilution
Route(s) of administration:	Avalglucosidase alfa and alglucosidase alfa will be administered by intravenous (IV) infusion
Dose regimen:	Avalglucosidase alfa and alglucosidase alfa, at a dose of 20 mg/kg of body weight every other week (qow)
ENDPOINT(S)	**Primary endpoint:** Change in FVC% predicted in the upright position from baseline to 12 months (Week 49). **Secondary endpoint(s):** Change in the following parameters from baseline to 12 months (Week 49): Efficacy: • 6MWT distance walked; • MIP and MEP (% predicted); • Lower extremity muscle strength (HHD); • Motor function (QMFT), and • Health-related quality of life (SF-12). Safety: • Assessment of adverse events (AEs)/treatment-emergent adverse events (TEAEs), including infusion-associated reactions (IARs); • Clinical laboratory evaluations including hematology, biochemistry, urinalysis; • Physical examination; • Vital signs, height, body weight

	• 12-lead electrocardiogram (ECG); • Immunogenicity assessments. **Other endpoints:** Tertiary endpoints: • Motor function (GMFM-88 and GSGC); • Upper extremity muscle strength (HHD), and • Health-related quality of life (EQ-5D-5L and PedsQL). • Pharmacokinetics, pharmacogenetics, and pharmacodynamics Exploratory endpoints for patient reported outcomes: • PDSS/PDIS; • R-PAct; • PGIC.
ASSESSMENT SCHEDULE	The study will comprise up to 76 visits including the Screening Visit (V1: Day -14 to Day -1); V2 (Day 1/Day 2) through V27 (Week 49) occurring every 1 to 2 weeks for study drug infusion, PK, safety assessment, and efficacy evaluations in the blinded treatment period; V28 (Week 51) through V76 (Week 145) for study drug infusion, safety assessment, and efficacy evaluations in the open-label avalglucosidase alfa long-term follow-up phase; an additional extended open-label avalglucosidase alfa long-term follow-up period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients) will include bi-weekly visits (study drug infusion, adverse events check and vital signs) as well as less frequent visits for other assessments (every 4 weeks, 12 weeks, 24 weeks and 48 weeks). At the end of this period, the end of study visit/contact will be performed. If at the end of the recruitment, <4 pediatric patients aged 3 to <18 years are enrolled, up to 2 additional pediatric patients will be enrolled directly in the open-label avalglucosidase alfa long-term follow-up phase where they will receive avalglucosidase alfa. For this subgroup of pediatric patients, the study will comprise 52 visits including the Screening Visit (V1: Day -14 to Day -1) and the Enrollment Visit V2 (Day 1/Day 2); V3 (1 week after V2) through V52 (Week 97) for study drug infusion, PK, safety assessment, and efficacy evaluations in the open-label avalglucosidase alfa long-term follow-up phase (refer to study flow chart Section 1.2.5.1 for V29 details); an additional extended open-label avalglucosidase alfa long-term follow-up period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) will include bi-weekly visits (study drug infusion, AEs checks and vital signs) as well as less frequent visits for other assessments (every 4 weeks, 12 weeks, 24 weeks and 48 weeks). At the end of this period, the end of study visit/contact will be performed. For all patients, all visits following V2 are calculated from day of first infusion of investigational medicinal product (IMP) in 14-day increments with a window of ±7 days for infusions and safety assessments and ±14 days for all other assessments.

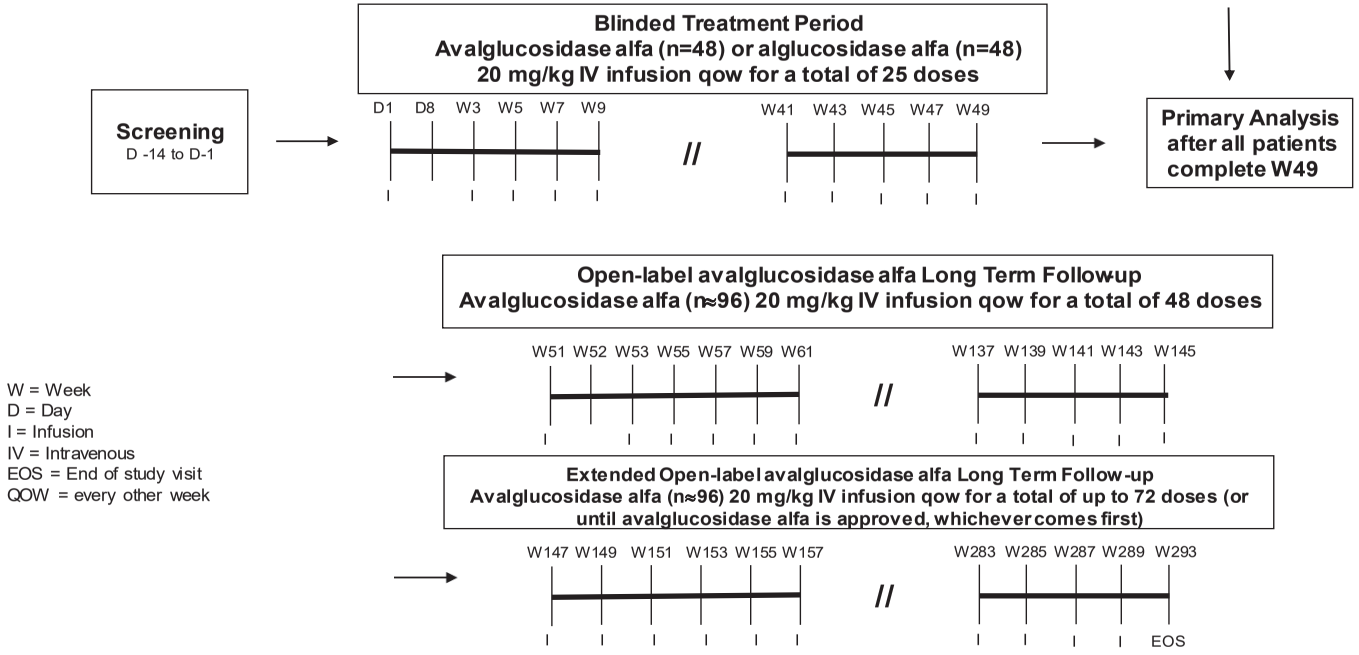
STATISTICAL CONSIDERATIONS	**Sample size determination:** Sample size calculation is based on a comparison of FVC (% predicted) change from baseline at 12 months (Week 49). The study will be tested for non-inferiority (NI) first (with an NI margin of 1.1%), followed by superiority testing if NI is achieved. A sample size of 96 (1:1 randomization ratio) will provide 80% power to demonstrate NI of avalglucosidase alfa versus alglucosidase alfa with 2-sided 5% significance level. The power calculation was based on 2-sample t-test. The following assumptions were made based on the alglucosidase alfa pivotal study for LOPD (LOTS) and the completed avalglucosidase alfa Phase 1/2 study (TDR12857): • Common standard deviation of 5.1%; • Mean treatment difference (avalglucosidase alfa – alglucosidase alfa) of 2.0%; • Percent of patients with missing data to be 10%. **Analysis population:** The modified intent-to-treat (mITT) population is defined as all randomized patients who received at least 1 infusion (partial or total). The mITT population is the primary analysis population for all efficacy endpoints. Patients will be analyzed in the treatment group to which they were randomized. The per protocol (PP) population is defined as a subset of the mITT population that excludes patients with major protocol deviations that potentially impact the primary efficacy endpoint. The criteria for exclusion of patients from the PP population will be determined and documented prior to database lock. The PP population will be used for sensitivity analysis purposes. The safety population is defined as all patients who received at least 1 infusion (partial or total). All safety analyses will be performed on the safety population. Patients will be summarized based on the treatment they received. **Analysis of efficacy:** The primary efficacy endpoint is the change from baseline to Week 49 in FVC (% predicted) in upright position. The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) with change from baseline as outcome variable. The MMRM model will include the baseline FVC (% predicted) as a continuous variable, and gender, age, treatment group, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance matrix shared across treatment groups will be used to model the within-patient error, the Kenward-Roger approximation will be used to estimate the degrees of freedom, and the model will be fit using restricted maximum likelihood. This analysis will include all post-baseline assessments up to Week 49, regardless of treatment discontinuation status; missing data will not be imputed and will be assumed to be missing-at-random (MAR). Sensitivity analyses will be performed to assess the impact of missing data. The primary comparison of interest is the difference in least-square means between groups at the Week 49 visit. A US Food and Drug Administration (FDA)-specific primary analysis will be conducted using the method described above for those patients

	in the mITT population 8 years of age or older in order to match the lower age range of patients in the LOTS trial of alglucosidase alfa. **Analysis of safety:** Safety analyses will be performed using the safety population and the "as treated" population. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event incidence tables will be presented by system organ class (SOC) sorted by internationally agreed order and preferred term (PT) sorted alphabetically for each treatment arm, by the number and percentage of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment arm. All TEAEs, all TEAEs potentially related to study drug, all TEAEs leading to treatment discontinuation, all TEAEs that are IARs, all treatment-emergent serious adverse events (SAEs) (including treatment-related SAEs), all AEs with fatal outcome, and adverse event of special interest (AESI)s will be summarized descriptively by treatment groups. Additional safety data including clinical laboratory tests, vital signs, ECG, and immunogenicity will be summarized descriptively by treatment groups.
DURATION OF STUDY PERIOD (per patient)	After the initial period (blinded treatment period and open-label avalglucosidase alfa long-term follow-up period), an additional period of up to 144 weeks (or until avalglucosidase alfa is approved in patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients), including: Blinded treatment period: • An up to 14-day screening period (may be extended to up to 8 weeks in pre-specified situations [refer to Section 10.1.2]); • A 49-week blinded treatment period (Primary Analysis Period [PAP]), except for the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase. Open-label avalglucosidase alfa long-term follow-up period: • An up to 96-week open-label treatment period (open-label avalglucosidase alfa long-term follow-up phase) for all patients regardless of prior randomization group; Extended open-label avalglucosidase alfa long-term follow-up period: • An up to 144 week (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients) extended open-label treatment period (extended open-label avalglucosidase alfa long-term follow-up phase) for all patients and • An up to 4-week post-treatment observation period.

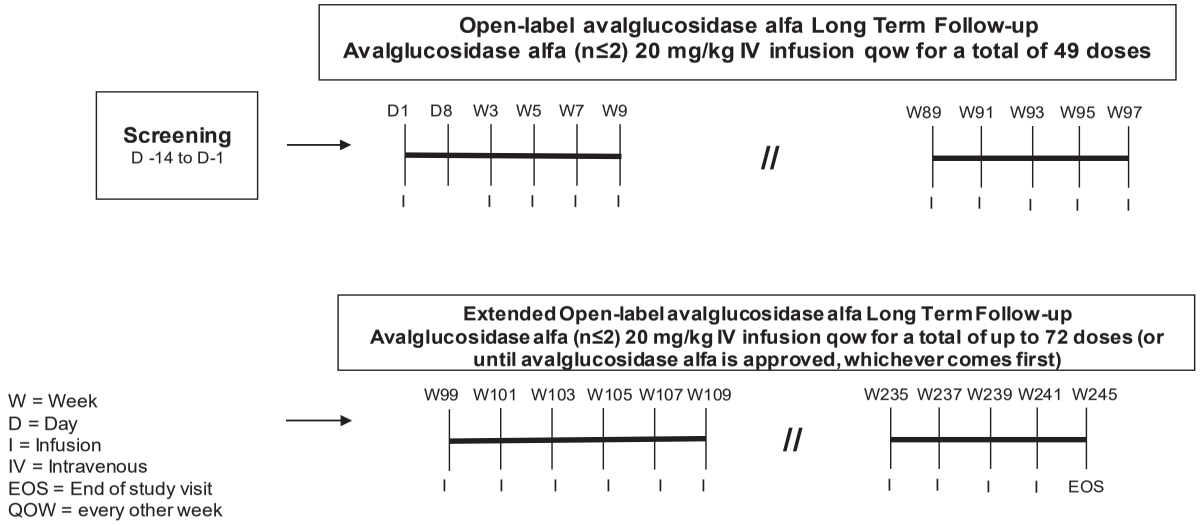
1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

1.1.1 General Graphical Study Design



1.1.2 Graphical study design for pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase



1.2 STUDY FLOW CHART

Please refer to Section 10 for details.

1.2.1 Blinded treatment period

Phase	Screening/ Baseline[a]	Blinded treatment period														
Day(D) or Week (W)	Day -14 to Day -1[b]	D1/D2[c, d]		D8 (W2)	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit[e]	V1	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
		Pre-randomization	Post randomization													
Informed consent	X															
Visit at clinical site	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X														
Demographics and baseline characteristics[g]	X															
Medical/surgical history/Pompe history	X															
Prior/concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
Study treatment administration																
Avalglucosidase alfa/alglucosidase alfa infusion[f]			X		X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X[a]		X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																
PFT[h]	X									X						X
6MWT	X									X						X
HHD	X									X						X
GMFM-88/GMFCS	X									X						X
QMFT	X									X						X
GSGC	X									X						X
SF-12[i]	X									X						X
EQ-5D-5L[i]	X									X						X
PedsQL[j]	X									X						X
PDSS/PDIS[i]	X[i]	X[i]								X						X

Phase	Screening/ Baseline[a]	Blinded treatment period														
Day(D) or Week (W)	Day -14 to Day -1[b]	D1/D2[c, d]		D8 (W2)	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit[e]	V1	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
		Pre-randomization	Post randomization													
R-PAct[i, k]	X									X						X
Safety																
Physical examination	X[m]									X						X
Height	X[n]									X[n]						X[n]
β-HCG pregnancy test[o]	X	X				X		X		X		X		X		X
Body weight	X	X				X[p]		X[p]		X		X[p]		X[p]		X
Vitals[q]		X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG[r]		X								X						X
Hematology, biochemistry (fasting), urinalysis[s, z]	X			X[t]		X[t]		X[t]		X		X[t]		X[t]		X
ADA (with neutralizing antibodies in ADA-positive patients)[s, u]	X			X		X		X		X		X		X		X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK																
PK plasma samples[s, v]			X							X						X
Pharmacodynamics																
Urine Hex4 samples[w]	X	X								X						X
Exploratory biomarker plasma and DBS samples[s, w]		X								X						X
Exploratory biomarker urine samples[w]	X	X								X						X
Pharmacogenetics																
GAA[x] and ACE genotyping[s]	X															
microRNA plasma samples[s, w]		X								X						X
Stored DNA sample (optional)[s]	X															

Phase	Blinded treatment period											
Day(D) or Week (W)	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49
Visit	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27
Visit at clinical site	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration												
Avalglucosidase alfa/alglucosidase alfa infusion[f]	X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy												
PFT[h]						X						X
6MWT						X						X
HHD						X						X
GMFM-88/GMFCS						X						X
QMFT						X						X
GSGC						X						X
SF-12[i]						X						X
EQ-5D-5L[i]						X						X
PedsQL[j]						X						X
PDSS/PDIS[i]						X						X
R-PAct[i, k]						X						X
PGIC[l]												X
Safety												
Physical examination						X						X[m]
Height						X[n]						X[n]
Urine pregnancy test[o]		X		X		X		X		X		X
Body weight		X[p]		X[p]		X		X[p]		X[p]		X
Vitals[q]	X	X	X	X	X	X	X	X	X	X	X	X
ECG						X						X
Hematology, biochemistry (fasting), urinalysis[s, z]		X[t]		X[t]		X		X[t]		X[t]		X
ADA (with neutralizing antibodies in ADA-positive patients)[s, u]		X		X		X		X		X		X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X
PK												
PK plasma samples[s, v]						X						X

Phase	Blinded treatment period											
Day(D) or Week (W)	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49
Visit	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27
Pharmacodynamics												
Urine Hex4 samples[w]						X						X
Exploratory biomarker plasma and DBS samples[s, w]						X						X
Exploratory biomarker urine samples[w]						X						X
Pharmacogenetics												
microRNA plasma samples[s, w]						X						X

a Pre-study IRT contact to inform identification of potential patient and initiation of IMP shipment (refer to IRT quick reference document for details).

b See Section 10.3.1.

c Visits at Day 1/Day 2 and Week 49 require that the patients remain in the hospital or infusion center prior to and for at least 8 hours following IMP infusion, as an in-patient or out-patient, as per hospital/center procedure. A patient card will be provided to the patient once the patient is randomized.

d All procedures are to be performed on the day of randomization (Day 1), or day following randomization (Day 2) to allow preparation of the IMP for infusion.

e In case of temporary or permanent treatment discontinuation, patients will be asked to perform visit and assessment schedules as outlined in protocol Section 10.1.9. Procedures and assessments are not presented in the chronological order in the flow chart. Refer to Section 10.1 for the recommended order of procedures and assessments. Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days.

f Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each 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 or their legally authorized representative (for pediatric patients) to ensure no adverse event occurred during the observational period.

g Demographic characteristics: age, gender, race, ethnicity

h FVC, MIP, and MEP (Additional parameters of respiratory function may be obtained and analyzed as appropriate). Ventilator use status and any change thereof will be recorded on the eCRF by authorized site personnel.

i SF-12, EQ-5D-5L, R-PAct (during visit) and PDSS/PDIS (via an e-diary daily for 2 weeks between visits/24 hours recall only) are to be conducted for patients who are ≥18 years of age at screening/baseline. The PDSS and PDIS will also be administered during the screening period 24-hour recall version administered during the screening period. Then the 7-day recall version administered one time prior to first infusion (ie, at Day -1, Day 1, or Day 2).

j PedsQL to be conducted for patients who are <18 years of age at screening/baseline.

k For selected countries (eg, UK, USA, Canada, Belgium and The Netherlands; for those patients whose first language is English or Dutch).

l PGIC: Patients who are ≥18 years of age at the date of the concerned visit will complete this assessment at Week 49, Week 97, and Week 145.

m Head circumference and Tanner stage are assessed as part of the physical examination in pediatric patients at baseline, Week 49, Week 97, and Week 145.

n Height will be measured annually in all patients (ie, at baseline, Week 49, Week 97, and Week 145) and in pediatric patients every 3 months up to Week 73 and then every 6 months (ie, at Week 97, Week 121, and Week 145).

o Female patients of childbearing potential only will have serum test for pregnancy at Screening, a urine β-hCG test up to 24 hours before first infusion (ie, D1/D2) and every 4 weeks thereafter.

p Monthly body weight assessment for pediatric patients only.

q Vital signs (including heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, ie, a total of 7 assessments. Collection windows are ±15 minutes.

r 12-lead ECG after at least 15 minutes in supine position (in triplicate at Day 1 only) and prior to receiving IMP: 3 ECGs within 5 minutes will be performed with at least 1 minute between 2 replicates.

s For pediatric patients, blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of <7 mL/kg over an 8-week period. Sampling is prioritized for safety laboratory tests (hematology, biochemistry, ADA) and PK and then exploratory tests. ACE genotyping and optional DNA storage samples may be obtained at any other visit if not possible during screening due to blood volume limitation. If no plasma sample or no DBS for exploratory biomarkers or microRNA can be taken at D1 for a given patient due to blood volume limitation, the corresponding samples (ie, DBS, plasma [EDTA] or plasma [PPT, microRNA]) will not be taken during the study for this patient.

t Biochemistry assessments only at Week 29, Week 33, Week 41, Week 45.

u Additional samples may be taken if clinically indicated in the event of IARs. During the blinded treatment period, patients in the avalglucosidase alfa treatment arm will be tested for anti-avalglucosidase alfa antibodies and patients in the alglucosidase alfa arm will be tested for anti-alglucosidase alfa antibodies; in addition, patients in the alglucosidase alfa treatment arm will also be tested for anti-avalglucosidase alfa antibodies at V27/W49 to get their baseline value.

v PK samples are to be collected prior to infusion; at the end of infusion; and 2, 4, 6, and 8 hours after the end of infusion at Day 1/Day 2 and Week 49 and prior to infusion and 2 hours after the end of infusion at Week 13, Week 25, and Week 37. PK parameters to include C_{max}, $AUC_{0\text{-last}}$, CL, and Vss where appropriate. Pharmacokinetic blood samples are to be collected within 15 minutes of scheduled time: predose and all samples immediately following the end of the infusion through 8 hours post infusion.

w Fasted urine or plasma sample. As blood volume permits (see footnote [S]), it is preferred to get DBS + plasma (EDTA) + plasma (PPT, microRNA), or DBS + plasma (EDTA), or DBS alone.

x GAA genotyping only if historical results not available. (Gene mutation analysis is mandatory for all patients. Blood sample results for patient gene mutation analysis must be obtained during screening/baseline in order to assess patient for study eligibility. If gene mutation analysis was conducted prior to signing the informed consent, these results may be collected provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and patients/legally authorized guardians give consent to utilize the results. If interpretation of GAA genotyping is inconclusive for the diagnosis of Pompe disease, or if only 1 mutation has been reported, then GAA enzyme activity level, normal laboratory ranges and tissue source need to be provided in the interpretation field of the GAA genotyping e-CRF page for the purpose of confirming Pompe Disease. GAA enzyme activity level measured on a Dried Blood Spot sample is not considered as sufficient to confirm eligibility in this study; GAA enzyme activity level from another source (skin fibroblast, peripheral blood leukocyte or muscle biopsy sample) will be needed).

y This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).

z For visits where urine dipstick is required refer to Section 9.2.2.2 for conditions requiring sending a urine sample to central laboratory.

Abbreviations: 6MWT = 6-minute walk test; ACE = angiotensin converting enzyme; ADA = anti-drug antibody; AE = adverse event; β-HCG = beta-human chorionic gonadotropin; DBS = dried blood spot; DNA = deoxyribonucleic acid; ECG = electrocardiogram; e-CRF = electronic case report form; EDTA = ethylene diamine tetraacetic acid; EQ-5D-5L = EuroQoL in 5 dimensions; GAA = acid α-glucosidase; GMFCS = Gross Motor Function Classification System; GMFM-88 = Gross Motor Function Measure-88; GSGC = Gait, Stair, Gower's Maneuver, and Chair; Hex4 = glucose tetrasaccharide; HHD = hand-held dynamometer; IAR = infusion associated reaction; ; IMP = investigational medicinal product; IRT = interactive response technology; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PDSS/PDIS = Pompe Disease Symptom Scale and Pompe Disease Impact Scale; PedsQL = Pediatric Quality of Life Inventory; PFT = pulmonary function testing; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; QMFT = Quick Motor Function Test, RNA = ribonucleic acid; R-PAct = Rasch-built Pompe-specific Activity scale; SF-12 = Short Form-12.

1.2.2 Open-label avalglucosidase alfa long-term follow-up phase[a]

Phase	Open-label avalglucosidase alfa long-term follow-up phase						
Day(D) or Week (W)	W51	W52	W53	W55	W57	W59	W61
Visit	V28	V29	V30	V31	V32	V33	V34
Visit at clinical site[t]	X	X	X	X	X	X	X
Prior/concomitant medications[s]	X	X	X	X	X	X	X
Study treatment administration							
Avalglucosidase alfa infusion[b]	X		X	X	X	X	X
IRT contact for treatment kits allocation	X		X	X	X	X	X
Efficacy							
PFT[c]							X
6MWT							X
HHD							X
GMFM-88/GMFCS							X
QMFT							X
GSGC							X
SF-12[d]							X
EQ-5D-5L[d]							X
PedsQL[e]							X
PDSS/PDIS[d]							X
R-PAct[d, f]							X
Safety							
Physical examination							X
Height							X[h]
Urine pregnancy test[i]			X		X		X
Body weight			X[j]		X[j]		X
Vitals[k]	X		X	X	X	X	X
ECG[m]							X
Hematology, biochemistry (fasting), urinalysis[l, u]		X[n]	X[n]		X[n]		X
ADA (with neutralizing antibodies in ADA-positive patients) [l, o]		X	X		X		X
AE collection	X	X	X	X	X	X	X

Phase	Open-label avalglucosidase alfa long-term follow-up phase						
Day(D) or Week (W)	W51	W52	W53	W55	W57	W59	W61
Visit	V28	V29	V30	V31	V32	V33	V34
Pharmacodynamics							
Urine Hex4 samples[p]							X
Exploratory biomarker plasma and DBS samples[l, p]							X
Exploratory biomarker urine samples[p]							X
Pharmacogenetics							
microRNA plasma samples[l, p]							X

Phase	Open-label avalglucosidase alfa long-term follow-up phase														
Day (D) or Week (W)	**W63**	**W65**	**W67**	**W69**	**W71**	**W73**	**W75**	**W77**	**W79**	**W81**	**W83**	**W85**	**W87**	**W89**	**W91**
Visit	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**
Visit at clinical site[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration															
Avalglucosidase alfa infusion[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety															
Physical examination						X									
Height						X[h]									
Urine pregnancy test[i]		X		X		X		X		X		X		X	
Body weight		X[j]		X[j]		X		X[j]		X[j]		X		X[j]	
Vitals[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[m]						X									
Hematology, biochemistry (fasting), urinalysis[l, u]		X[n]		X[n]		X		X[n]		X[n]		X[n]		X[n]	
ADA (with neutralizing antibodies in ADA-positive patients)[l, o]		X		X		X						X			
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics															
Urine Hex4 samples[p]						X									
Exploratory biomarker plasma and DBS samples[l, p]						X									
Exploratory biomarker urine samples[p]						X									
Efficacy															
PFT[c]						X									
6MWT						X									
HHD						X									
GMFM-88/GMFCS						X									
QMFT						X									

Phase	Open-label avalglucosidase alfa long-term follow-up phase														
Day (D) or Week (W)	**W63**	**W65**	**W67**	**W69**	**W71**	**W73**	**W75**	**W77**	**W79**	**W81**	**W83**	**W85**	**W87**	**W89**	**W91**
Visit	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**
GSGC						X									
SF-12[d]						X									
EQ-5D-5L[d]						X									
PedsQL[e]						X									
PDSS/PDIS[d]						X									
R-PAct[d, f]						X									
Pharmacogenetics															
microRNA plasma samples[l, p]						X									

Phase	Open-label avalglucosidase alfa long-term follow-up phase													
Day (D) or Week (W)	**W93**	**W95**	**W97**	**W99**	**W101**	**W103**	**W105**	**W107**	**W109**	**W111**	**W113**	**W115**	**W117**	**W119**
Visit	**V50**	**V51**	**V52**	**V53**	**V54**	**V55**	**V56**	**V57**	**V58**	**V59**	**V60**	**V61**	**V62**	**V63**
Visit at clinical site[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration														
Avalglucosidase alfa infusion[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety														
Physical examination			X[q]											
Height			X[h]											
Urine pregnancy test[i]	X		X		X		X		X		X		X	
Body weight	X[j]		X		X[j]		X[j]		X		X[j]		X[j]	
Vitals[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[m]			X											
Hematology, biochemistry (fasting), urinalysis[l, u]	X[n]		X		X[n]		X[n]		X[n]		X[n]		X[n]	
ADA (with neutralizing antibodies in ADA-positive patients) [l, o]			X						X					
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics														
Urine Hex4 samples[p]			X											
Exploratory biomarker plasma and DBS samples[l, p]			X											
Exploratory biomarker urine samples[p]			X											
Efficacy														
PFT[c]			X											
6MWT			X											
HHD			X											
GMFM-88/GMFCS			X											

Phase	Open-label avalglucosidase alfa long-term follow-up phase													
Day (D) or Week (W)	W93	W95	W97	W99	W101	W103	W105	W107	W109	W111	W113	W115	W117	W119
Visit	V50	V51	V52	V53	V54	V55	V56	V57	V58	V59	V60	V61	V62	V63
QMFT			X											
GSGC			X											
SF-12[d]			X											
EQ-5D-5L[d]			X											
PedsQL[e]			X											
PDSS/PDIS[d]			X											
R-PAct[d, f]			X											
PGIC[g]			X											
Pharmacogenetics														
microRNA plasma samples[l, p]			X											

Phase	Open-label avalglucosidase alfa long-term follow-up phase												
Day (D) or Week (W)	**W121**	**W123**	**W125**	**W127**	**W129**	**W131**	**W133**	**W135**	**W137**	**W139**	**W141**	**W143**	**W145**
Visit	**V64**	**V65**	**V66**	**V67**	**V68**	**V69**	**V70**	**V71**	**V72**	**V73**	**V74**	**V75**	**V76**
Visit at clinical site[t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[s]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration													
Avalglucosidase alfa infusion[a]	X	X	X	X	X	X	X	X	X	X	X	X	X[r]
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety													
Physical examination	X												X[q]
Height	X[h]												X[h]
Urine pregnancy test[i]	X		X		X		X		X		X		X
Body weight	X		X[j]		X[j]		X		X[j]		X[j]		X
Vitals[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[m]	X												X
Hematology, biochemistry (fasting), urinalysis[l,u]	X		X[n]		X[n]		X[n]		X[n]		X[n]		X
ADA (with neutralizing antibodies in ADA-positive patients) [l, o]	X						X						X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics													
Urine Hex4 samples[p]	X												X
Exploratory biomarker plasma and DBS samples[l, p]	X												X
Exploratory biomarker urine samples[p]	X												X

Phase	Open-label avalglucosidase alfa long-term follow-up phase												
Day (D) or Week (W)	W121	W123	W125	W127	W129	W131	W133	W135	W137	W139	W141	W143	W145
Visit	V64	V65	V66	V67	V68	V69	V70	V71	V72	V73	V74	V75	V76
Efficacy													
PFT[c]	X												X
6MWT	X												X
HHD	X												X
GMFM-88/GMFCS	X												X
QMFT	X												X
GSGC	X												X
SF-12[d]	X												X
EQ-5D-5L[d]	X												X
PedsQL[e]	X												X
PDSS/PDIS[d]	X												X
R-PAct[d, f]	X												X
PGIC[g]													X
Pharmacogenetics													
microRNA plasma samples[l, p]	X												X

a Pediatric patients directly enrolled in the open-label avalglucosidase alfa long-term follow-up phase, see Section 1.2.5.

b Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each 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 or their legally authorized representative (for pediatric patients) to ensure no adverse event occurred during the observational period. As per conditions and instructions provided in Section 8.1, avalglucosidase alfa infusion may occur at home.

c FVC, MIP, and MEP (Additional parameters of respiratory function may be obtained and analyzed as appropriate). Ventilator use status and any change thereof will be recorded on the e-CRF by authorized site personnel.

d SF-12, EQ-5D-5L, R-PAct (during visit) and PDSS/PDIS (via an e-diary daily for 2 weeks between visits/24 hours recall only) are to be conducted for patients who are ≥18 years of age at screening/baseline.

e PedsQL to be conducted for patients who are <18 years of age at screening/baseline.

f For selected countries (eg, UK, USA, Canada, Belgium and The Netherlands, for those patients whose first language is English or Dutch).

g PGIC: Patients who are ≥18 years of age at the date of the concerned visit will complete this assessment at Week 49, Week 97 and Week 145. PGIC will be administered annually in follow-up during the extension period.

h Height will be measured annually in all patients (ie, at baseline, Week 49, Week 97, and Week 145) and in pediatric patients every 3 months up to Week 73 and then every 6 months (ie, at Week 97, Week 121, and Week 145).

i Female patients of childbearing potential only.

j Monthly body weight assessment for pediatric patients only.

k Vital signs (including heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, ie, a total of 7 assessments. Collection windows are ±15 minutes.

l For pediatric patients, blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of <7 mL/kg over an 8-week period. Sampling is prioritized for safety laboratory tests (hematology, biochemistry, ADA) and then exploratory tests. If no plasma sample or no DBS for exploratory biomarkers or microRNA can be taken at D1 for a given patient due to blood volume limitation, the corresponding samples (ie, DBS, plasma [EDTA] or plasma [PPT, microRNA]) will not be taken during the study for this patient.

m 12-lead ECG after at least 15 minutes in supine position and prior to receiving IMP.

n Biochemistry assessments only.

o Additional samples may be taken if clinically indicated in the event of IARs.

p Fasted urine or plasma sample. As blood volume permits (see footnote *l*), it is preferred to get DBS + plasma (EDTA) + plasma (PPT, microRNA), or DBS + plasma (EDTA), or DBS alone.

q Head circumference and Tanner stage are assessed as part of the physical examination in pediatric patients at baseline, Week 49, Week 97, and Week 145.

r End of treatment IRT contact after completion of last infusion.

s This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).

t Procedures and assessments are not presented in the chronological order in the flow chart. Refer to Section 10.1 for the recommended order of procedures and assessments. Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days.

u For visits where urine dipstick is required refer to Section 9.2.2.2 for conditions requiring sending a urine sample to central laboratory.

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; DBS = dried blood spot; ; e-CRF = electronic case report form; ECG = electrocardiogram; EDTA = ethylene diamine tetraacetic acid; EQ-5D-5L = EuroQoL in 5 dimensions; FVC = forced vital capacity; GMFCS = Gross Motor Function Classification System; GMFM-88 = Gross Motor Function Measure-88; GSGC = Gait, Stair, Gower's Maneuver, and Chair; Hex4 = glucose tetrasaccharide; HHD = hand-held dynamometry; IAR = infusion associated reaction; IRT = interactive response technology; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PDSS/PDIS = Pompe Disease Symptom Scale and Pompe Disease Impact Scale; PedsQL = Pediatric Quality of Life Inventory; PFT = pulmonary function testing; PGIC = Patient Global Impression of Change; QMFT = Quick Motor Function Test; R-PAct = Rasch-built Pompe-specific Activity scale; SF-12 = Short Form-12.

1.2.3 Extended open-label avalglucosidase alfa long-term follow-up phase

Phase	Extended open-label avalglucosidase alfa long-term follow-up phase					
Timing	**Biweekly[a]**	**Every 4 weeks (Monthly)**	**Every 12 weeks(Quarterly)**	**Every 24 weeks (Every 6 Months)**	**Every 48 weeks (Yearly)**	**End of treatment Visit**
Visit at clinical site	X[b]	X	X	X	X	X
Prior/concomitant medications[c]	X	X	X	X	X	X
Study treatment administration						
Avalglucosidase alfa infusion[d]	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X
Safety						
Physical examination					X	X
Height[e]				X	X	X
Urine pregnancy test[f]		X	X	X	X	X
Body weight		X[p]	X	X	X	X
Vitals[g]	X	X	X	X	X	X
ECG[o]					X	X
Hematology, biochemistry (fasting), urinalysis[h, i]				X	X	X
ADA (with neutralizing antibodies in ADA-positive patients)[j]			X	X	X	X
AE collection	X	X	X	X	X	X
Efficacy						
PFT[k]				X	X	X
6MWT				X	X	X
SF-12[l]				X	X	X
EQ-5D-5L[l]				X	X	X
PDSS/PDIS[l]				X	X	X
R-PAct[l, m]				X	X	X
PGIC[n]					X	X

a In case of temporary treatment discontinuation, visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in Section 10.1.7. Procedures and assessments are not presented in the chronological order in the flow chart. Refer to Section 10.1 for the recommended order of procedures and assessments. Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days.

b For patients undergoing home infusion (as per conditions and instructions provided in Section 8.1) visit at clinical site is not required for infusion only visits.

c This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).

d Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each 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 or their legally authorized representative (for pediatric patients) to ensure no adverse event occurred during the observational period. As per conditions and instructions provided in Section 8.1, avalglucosidase alfa infusion may occur at home.

e Height will be measured every 6 months in pediatric patients only.

f Female patients of childbearing potential only.

g Vital signs (including heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, i.e., a total of 7 assessments. Collection windows are ±15 minutes.

h For pediatric patients, blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of <7 mL/kg over an 8-week period. Sampling is prioritized for safety laboratory tests and then exploratory tests.

i For visits where urine dipstick is required refer to Section 9.2.2.2 for conditions requiring sending a urine sample to central laboratory.

j Additional samples may be taken if clinically indicated in the event of IARs. ADA against avalglucosidase alfa only.

k FVC, MIP, and MEP (Additional parameters of respiratory function may be obtained and analyzed as appropriate). Ventilator use status and any change thereof will be recorded on the e-CRF by authorized site personnel.

l SF-12, EQ-5D-5L, R-PAct (during visit) and PDSS/PDIS (via an e diary daily for 2 weeks between visits) are to be conducted for patients who are ≥18 years of age at screening/baseline.

m For selected countries (eg, UK, USA, Canada, Belgium and The Netherlands, to patients whose first language is English or Dutch).

n PGIC: Patients who are ≥18 years of age at the date of the concerned visit will complete this assessment annually.

o 12-lead ECG after at least 15 minutes in supine position and prior to receiving IMP.

p Weight will be measured every 4 weeks in pediatric patients only

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; e-CRF = electronic case report form; ECG = electrocardiogram; EQ-5D-5L = EuroQoL in 5 dimensions; FVC = forced vital capacity; IAR = infusion associated reaction; IRT = interactive response technology; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PDSS/PDIS = Pompe Disease Symptom Scale and Pompe Disease Impact Scale; PedsQL = Pediatric Quality of Life Inventory; PFT = pulmonary function testing; PGIC = Patient Global Impression of Change; R-PAct = Rasch-built Pompe-specific Activity scale; SF-12 = Short Form-12.

1.2.4 End of study

Phase	End of Study Visit/Contact[a]
Day (D) or Week (W)	4 weeks after the last IMP infusion
Visit	EOS
Prior/concomitant medications[b]	X
AE collection	X

a If the patient enrolls in another study or receives commercially available ERT, the follow-up period may be reduced from 4 to 2 weeks.
b This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).
Abbreviations: AE = adverse event; EOS = end of study; ERT = enzyme replacement therapy; IMP = investigational medicinal product.

1.2.5 Pediatric patients aged 3 to <18 years entering directly in the open-label avalglucosidase alfa long-term follow-up phase

1.2.5.1 Screening and open-label avalglucosidase alfa long-term follow-up phase

Phase	Screening/ Baseline[a]	open-label avalglucosidase alfa long-term follow-up phase														
Day(D) or Week (W)	Day -14 to Day -1[b]	D1/D2[c, d]		D8 (W2)	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit[e]	V1	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
		Pre-enrollment	Post enrollment													
Informed consent	X															
Visit at clinical site	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X														
Demographics and baseline characteristics[f]	X															
Medical/surgical history/Pompe history	X															
Prior/concomitant medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment		X														
Study treatment administration																
Avalglucosidase alfa infusion[h]			X		X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X[a]		X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																
PFT[i]	X									X						X
6MWT	X									X						X
HHD	X									X						X
GMFM-88/GMFCS	X									X						X
QMFT	X									X						X
GSGC	X									X						X
PedsQL	X									X						X
Safety																
Physical examination	X[j]									X						X
Height	X									X						X
β-HCG pregnancy test[k]	X	X				X		X		X		X		X		X
Body weight	X	X				X		X		X		X		X		X
Vitals[l]		X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG[m]		X								X						X

Phase	Screening/ Baseline[a]	open-label avalglucosidase alfa long-term follow-up phase														
Day(D) or Week (W)	Day -14 to Day -1[b]	D1/D2[c, d]		D8 (W2)	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit[e]	V1	V2		V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
		Pre-enrollment	Post enrollment													
Hematology, biochemistry (fasting), urinalysis[n, v]	X			X[o]		X[o]		X[o]		X		X[o]		X[o]		X
ADA (with neutralizing antibodies in ADA-positive patients)[n, p]	X			X		X		X		X		X		X		X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK																
PK plasma sample[n, q]			X							X						X
Pharmacodynamics																
Urine Hex4 samples[r]	X	X								X						X
Exploratory biomarker plasma and DBS samples[n, r]		X								X						X
Exploratory biomarker urine samples[r]	X	X								X						X
Pharmacogenetics																
GAA[s] and ACE genotyping[n]	X															
microRNA plasma samples[n, r]		X								X						X
Stored DNA sample (optional)[n]	X															

Phase	open-label avalglucosidase alfa long-term follow-up phase																	
Day(D) or Week (W)	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W52	W53	W55	W57	W59	W61
Visit	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29[u]	V30	V31	V32	V33	V34
Visit at clinical site[e]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Prior/concomitant medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Study treatment administration																			
Avalglucosidase alfa infusion[h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Efficacy																			
PFT[i]						X						X							X
6MWT						X						X							X
HHD						X						X							X
GMFM-88/GMFCS						X						X							X
QMFT						X						X							X
GSGC						X						X							X
PedsQL						X						X							X
PGIC[t]												X							
Safety																			
Physical examination						X						X[j]							X
Height						X						X							X
Urine pregnancy test[k]		X		X		X		X		X		X			X		X		X
Body weight		X		X		X		X		X		X			X		X		X
Vitals[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
ECG[m]						X						X							X
Hematology, biochemistry (fasting), urinalysis[n, v]		X[o]		X[o]		X		X[o]		X[o]		X			X[o]		X[o]		X
ADA (with neutralizing antibodies in ADA-positive patients)[n, p]		X		X		X		X		X		X			X		X		X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
PK																			
PK plasma samples[n, q]						X						X							
Pharmacodynamics																			
Urine Hex4 samples[r]						X						X							X
Exploratory biomarker plasma and DBS samples[n, r]						X						X							X

Phase	open-label avalglucosidase alfa long-term follow-up phase																		
Day(D) or Week (W)	W27	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W52	W53	W55	W57	W59	W61
Visit	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29[u]	V30	V31	V32	V33	V34
Exploratory biomarker urine samples[r]						X						X							X
Pharmacogenetics																			
microRNA plasma samples[n, r]						X						X							X

Phase	Open-label avalglucosidase alfa long-term follow-up phase																	
Day(D) or Week (W)	W63	W65	W67	W69	W71	W73	W75	W77	W79	W81	W83	W85	W87	W89	W91	W93	W95	W97
Visit	V35	V36	V37	V38	V39	V40	V41	V42	V43	V44	V45	V46	V47	V48	V49	V50	V51	V52
Visit at clinical site[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration																		
Avalglucosidase alfa infusion[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
PFT[i]						X												X
6MWT						X												X
HHD						X												X
GMFM-88/GMFCS						X												X
QMFT						X												X
GSGC						X												X
PedsQL						X												X
PGIC[t]																		X
Safety																		
Physical examination						X												X[j]
Height						X												X
Urine pregnancy test[k]		X		X		X		X		X		X		X		X		X
Body weight		X		X[j]		X[j]		X		X[j]		X[j]		X		X[j]		X[j]
Vitals[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[m]						X												X
Hematology, biochemistry (fasting), urinalysis[n, v]		X[o]		X[o]		X		X[o]		X[o]		X[o]		X[o]		X[o]		X
ADA (with neutralizing antibodies in ADA-positive patients) [n, p]		X		X		X						X						X
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics																		
Urine Hex4 samples[r]						X												X
Exploratory biomarker plasma and DBS samples[n, r]						X												X
Exploratory biomarker urine samples[r]						X												X
Pharmacogenetics																		
microRNA plasma samples[n, r]						X												X

a Pre study IRT contact to inform identification of potential patient and initiation of IMP shipment (refer to IRT quick reference document for details).

b See Section 10.3.1.

c Visits at Day 1/Day 2 and Week 49 require that the patients remain in the hospital or infusion center prior to and for at least 8 hours following IMP infusion, as an in-patient or out-patient, as per hospital/center procedure. A patient card will be provided to the patient once the patient is enrolled.

d All procedures are to be performed on the day of enrollment (Day 1), or day following enrollment (Day 2) to allow preparation of the IMP for infusion.

e In case of temporary or permanent treatment discontinuation, patients will be asked to perform visit and assessment schedules as outlined in protocol Section 10.1.7. Procedures and assessments are not presented in the chronological order in the flow chart. Refer to Section 10.1 for the recommended order of procedures and assessments. Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days. For patients undergoing home infusion (as per conditions and instructions provided in Section 8.1) visit at clinical site is not required for infusion only visits.

f Demographic characteristics: age, gender, race, ethnicity

g This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).

h Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each 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 or their legally authorized representative (for pediatric patients) to ensure no adverse event occurred during the observational period. As per conditions and instructions provided in Section 8.1, avalglucosidase alfa infusion may occur at home.

i FVC, MIP, and MEP (Additional parameters of respiratory function may be obtained and analyzed as appropriate). Ventilator use status and any change thereof will be recorded on the e-CRF by authorized site personnel.

j Head circumference and Tanner stage are assessed as part of the physical examination in pediatric patients at baseline, Week 49 and Week 97.

k Female patients of childbearing potential only will have serum test for pregnancy at Screening, a urine beta hCG test up to 24 hours before first infusion (ie, D1/D2) and every 4 weeks thereafter.

l Vital signs (including heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, ie, a total of 7 assessments. Collection windows are ±15 minutes.

m 12-lead ECG after at least 15 minutes in supine position (in triplicate at Day 1 only) and prior to receiving IMP: 3 ECGs within 5 minutes will be performed with at least 1 minute between 2 replicates.

n Blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of <7 mL/kg over an 8-week period. Sampling is prioritized for safety laboratory tests (hematology, biochemistry, ADA) and PK and then exploratory tests. ACE genotyping and optional DNA storage samples may be obtained at any other visit if not possible during screening due to blood volume limitation. If no plasma sample or no DBS for exploratory biomarkers or microRNA can be taken at D1 for a given patient due to blood volume limitation, the corresponding samples (ie, DBS, plasma [EDTA] or plasma [PPT, microRNA]) will not be taken during the study for this patient.

o Biochemistry assessments only.

p Additional samples may be taken if clinically indicated in the event of IARs.

q Pharmacokinetic samples are to be collected prior to infusion; at the end of infusion; and 2, 4, 6, and 8 hours after the end of infusion at Day 1/Day 2 and Week 49 and prior to infusion and 2 hours after the end of infusion at Week 13, Week 25, and Week 37. Pharmacokinetic parameters to include C_{max}, $AUC_{0\text{-}last}$, CL, and V_{ss} where appropriate. Pharmacokinetic blood samples are to be collected within 15 minutes of scheduled time: predose and all samples immediately following the end of the infusion through 8 hours post infusion.

r Fasted urine or plasma sample. As blood volume permits (see footnote *n*), it is preferred to get DBS + plasma (EDTA) + plasma (PPT, microRNA), or DBS + plasma (EDTA), or DBS alone.

s GAA genotyping only if historical results not available. (Gene mutation analysis is mandatory for all patients. Blood sample results for patient gene mutation analysis must be obtained during screening/baseline in order to assess patient for study eligibility. If gene mutation analysis was conducted prior to signing the informed consent, these results may be collected provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and patients/legally authorized guardians give consent to utilize the results. If interpretation of GAA genotyping is inconclusive for the diagnosis of Pompe disease, or if only 1 mutation has been reported, then GAA enzyme activity level, normal laboratory ranges and tissue source need to be provided in the interpretation field of the GAA genotyping e-CRF page for the purpose of confirming Pompe Disease). GAA enzyme activity level measured on a Dried Blood Spot sample is not considered as sufficient to confirm eligibility in this study; GAA enzyme activity level from another source (skin fibroblast, peripheral blood leukocyte or muscle biopsy sample) will be needed).

t PGIC: Patients who are ≥18 years of age at the date of the concerned visit will complete this assessment at Week 49 & Week 97

u Visit not performed for these patients but indicated for consistency with the global population.

v For visits where urine dipstick is required, refer to Section 9.2.2.2 for conditions requiring sending a urine sample to central laboratory.

Abbreviations: 6MWT = 6-minute walk test; ACE = angiotensin converting enzyme; ADA = anti-drug antibody; AE = adverse event; DBS = dried blood spot; DNA = deoxyribonucleic acid; ECG = electrocardiogram; e-CRF = electronic case report form; EDTA = ethylene diamine tetraacetic acid; EQ-5D-5L = EuroQoL in 5 dimensions; Hex4 = glucose tetrasaccharide; IAR = infusion associated reaction; IRT = interactive response technology; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PDSS/PDIS = Pompe Disease Symptom Scale and Pompe Disease Impact Scale; PedsQL = Pediatric Quality of Life Inventory; PFT = pulmonary function testing; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; R-PAct = Rasch-built Pompe-specific Activity scale; SF-12 = Short Form-12.

1.2.5.2 *Extended open-label avalglucosidase alfa long-term follow-up phase (pediatric patients enrolling directly in open-label follow-up phase)*

Phase	extended open-label avalglucosidase alfa long-term follow-up phase					
Timing	**Biweekly[a]**	**Every 4 weeks (Monthly)**	**Every 12 weeks (Quarterly)**	**Every 24 weeks (Every 6 Months)**	**Every 48 weeks (Yearly)**	**End of treatment Visit**
Visit at clinical site[b]	X	X	X	X	X	X
Prior/concomitant medications[c]	X	X	X	X	X	X
Study treatment administration						
Avalglucosidase alfa infusion[b, d]	X	X	X	X	X	X
IRT contact for treatment kits allocation	X	X	X	X	X	X
Safety						
Physical examination					X	X
Height				X	X	X
Urine pregnancy test[e]		X	X	X	X	X
Body weight		X	X	X	X	X
Vitals[f]	X	X	X	X	X	X
ECG[k]					X	X
Hematology, biochemistry (fasting), urinalysis[g, l]				X	X	X
ADA (with neutralizing antibodies in ADA-positive patients)[h]			X	X	X	X
AE collection	X	X	X	X	X	X
Efficacy						
PFT[i]				X	X	X
6MWT				X	X	X
PGIC[j]					X	X

a In case of temporary treatment discontinuation, visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in Section 10.1.7. Procedures and assessments are not presented in the chronological order in the flow chart. Refer to Section 10.1 for the recommended order of procedures and assessments. Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days.

b For patients undergoing home infusion (as per conditions and instructions provided in Section 8.1) visit at clinical site is not required for infusion only visits.

c This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches).

d Patients will be required to remain in the hospital or the infusion center for observation of AEs for 1 hour after each 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 or their legally authorized representative (for pediatric patients) to ensure no adverse event occurred during the observational period. As per conditions and instructions provided in Section 8.1, avalglucosidase alfa infusion may occur at home.

e Female patients of childbearing potential only.

f Vital signs (including heart rate, blood pressure, respiratory rate, temperature and oxygen saturation) are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, ie, a total of 7 assessments. Collection windows are ±15 minutes.

g Blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of <7 mL/kg over an 8-week period. Sampling is prioritized for safety laboratory tests and then exploratory tests.

h Additional samples may be taken if clinically indicated in the event of IARs.

i FVC, MIP, and MEP (Additional parameters of respiratory function may be obtained and analyzed as appropriate). Ventilator use status and any change thereof will be recorded on the e-CRF by authorized site personnel.

j PGIC: Patients who are ≥18 years of age at the date of the concerned visit will complete this assessment annually.

k 12-lead ECG after at least 15 minutes in supine position and prior to receiving IMP.

l For visits where urine dipstick is required, refer to Section 9.2.2.2 for conditions requiring sending a urine sample to central laboratory.

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; e-CRF = electronic case report form; IAR = infusion associated reaction; IRT = interactive response technology; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PedsQL = Pediatric Quality of Life Inventory; PFT = pulmonary function testing; PGIC = Patient Global Impression of Change

1.2.5.3 End of study (pediatric patients enrolling directly in open-label follow-up phase)

Phase	**End of Study Visit/Contact**[a]
Week (W)	**4 weeks after the last IMP infusion**
Visit	**EOS**
Prior/concomitant medications[b]	X
AE collection	X

a If the patient enrolls in another study or receives commercially available ERT, the follow-up period may be reduced from 4 to 2 weeks.
b This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (eg, walker, cane, crutches)
AE = adverse event; EOS = end of study; ERT = enzyme replacement therapy; IMP = investigational medicinal product.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

6MWT:	6-minute walk test
ACE:	angiotensin converting enzyme
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATS/ERS:	American Thoracic Society/European Respiratory Society
AUC:	area under the plasma concentration versus time curve from time 0 to time of last quantifiable concentration
CDMS:	clinical data management system
CL:	clearance
C_{max}:	maximum plasma concentration
CRF:	case report form
DBS:	dried blood spot
DMC:	data monitoring committee
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
e-CRF:	electronic case report forms
EQ-5D-5L:	EuroQoL in 5 dimensions
ERT:	enzyme replacement therapy
FDA:	Food and Drug Administration
FEV_1:	forced expiratory volume in the 1st second of the FVC maneuver
FVC:	forced vital capacity
GAA:	acid alpha-glucosidase
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GLI:	global lung initiative
GMFCS-E&R:	Gross Motor Function Classification System - Expanded and Revised
GMFM-88:	Gross Motor Function Measure-88
GSD:	glycogen storage disease
GSGC:	Gait, Stair, Gower's maneuver, and Chair
Hex4:	glucose tetrasaccharide
HHD:	hand-held dynamometry
HLGT:	high level group term
HLT:	high level term
IAR:	infusion-associated reaction
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee

IgE:	immunoglobulin E
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
IV:	intravenous
LLOQ:	lower limit of quantitation
LOPD:	late onset Pompe disease
M6P:	mannose-6-phosphate
MAR:	missing-at-random
MCS:	mental component summary
MedDRA:	Medical Dictionary for Regulatory Activity
MEP:	maximum expiratory pressure
MIP:	maximum inspiratory pressure
mITT:	modified intent-to-treat
MMRM:	mixed model for repeated measure
NI:	non-inferiority
PAP:	primary analysis period
PCR:	polymerase chain reaction
PCS:	physical component summary
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PDIS:	Pompe Disease Impact Scale
PDSS:	Pompe Disease Symptom Scale
PedsQL:	Pediatric Quality of Life Inventory
PEF:	peak expiratory flow
PFT:	pulmonary function testing
PGIC:	Patient Global Impression of Change
PI:	Principal Investigator
PK:	pharmacokinetic(s)
PP:	per protocol
PR:	interval from the beginning of the P wave until the beginning of the QRS complex
PT:	preferred term
QMFT:	quick motor function test
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
RNA:	ribonucleic acid
R-PAct:	Rasch-built Pompe-specific Activity scale
RR:	interval between the peaks of successive QRS complexes
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SF-12:	Short Form-12
SOC:	system organ class

SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
Vss:	volume of distribution at steady state
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

Sanofi Genzyme is investigating an enzyme replacement therapy (ERT) for Pompe disease called avalglucosidase alfa (rhGAA conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan); rhGAA is produced in a mammalian cell line (Chinese hamster Ovary) using recombinant DNA technology. Avalglucosidase alfa is a modification of alglucosidase alfa that results in the conjugation of a number of hexamannose structures containing 2 terminal mannose-6-phosphate (M6P) moieties to oxidized sialic acid residues on alglucosidase alfa, thereby increasing bis-M6P levels on the compound. More detailed information on the compound is provided in the Investigator's Brochure (IB).

A proportion of patients with LOPD treated with alglucosidase alfa demonstrate suboptimal treatment response, in particular in respiratory function, and may benefit from a potentially more potent treatment (avalglucosidase alfa) (1). The efficacy and safety of avalglucosidase alfa in treatment-naïve LOPD has not been evaluated in a controlled study. As there are no data on the safety and efficacy of avalglucosidase alfa in treatment-naïve pediatric LOPD patients 3 years and older, this study will be also conducted to evaluate treatment response in that population.

The benefits and risks assessment of avalglucosidase alfa for the Phase 3 EFC14028 study is based upon the nonclinical studies of avalglucosidase alfa in acid α-glucosidase (GAA) knockout mice, CD-1 mice and cynomolgus monkey studies, as well as on the results from the clinical Phase 1/2 TDR12857 study (in adult treatment-naïve LOPD patients and adult LOPD patients who had been treated with alglucosidase alfa prior to their study participation) and previous experience with alglucosidase alfa. In nonclinical studies, avalglucosidase alfa was more successful in reducing glycogen in muscle tissue compared to alglucosidase alfa. The safety profile of avalglucosidase alfa in both nonclinical and clinical studies has shown avalglucosidase alfa to be well-tolerated; AEs and IARs are mostly non-serious and usually manageable (see IB Section 7 for detailed discussion of risks). The potential benefits of avalglucosidase alfa, balanced against its known risks, support further investigation of the safety and efficacy of avalglucosidase alfa across the broad spectrum of Pompe disease, including both pediatric and adult patients.

The overall objective of this study is to evaluate the efficacy and safety of avalglucosidase alfa in treatment-naïve patients with LOPD as compared to alglucosidase alfa. The primary objective of the study is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position. Additional secondary objectives are to evaluate the safety profile of avalglucosidase alfa in treatment-naïve patients with LOPD and to determine the effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12 in patients ≥18 years of age). Other objectives are to determine the PK, exploratory PD, pharmacogenetics and effect of avalglucosidase alfa treatment on motor function (GMFM-88 and GSGC), upper extremity muscle strength (HHD), health-related quality of life (EQ-5D-5L and PedsQL Generic Core Scale), and patient reported outcomes (Pompe Disease Symptom Scale [PDSS], Pompe Disease Impact Scale [PDIS], Rasch-built Pompe-specific Activity scale [R-Pact], and Patient Global Impression of Change [PGIC]).

The screening phase (time from signing of informed consent form to start of study treatment) should not exceed 14 days, but could be extended to a maximum of 8 weeks in pre-specified situations (refer to Section 10.1.2). Patients will be observed in a 12-month blinded treatment phase, in which patients will receive an IV infusion of 20 mg/kg avalglucosidase alfa or alglucosidase alfa biweekly (qow). This dose regimen is supported by data from a Phase 1/2 study showing a potential avalglucosidase alfa dose response after treatment for 6 months in previously untreated patients, with doses differentiated by improvement in FVC with avalglucosidase alfa 20 mg/kg qow versus stabilization with 5 mg/kg qow. Following the 12-month treatment period, patients will continue in the study in an open-label treatment period, in which all patients will receive an IV infusion of 20 mg/kg avalglucosidase alfa qow for long-term follow-up.

The primary and secondary endpoint assessments selected for this study have been used in previous studies in patients with LOPD.

Exclusion criteria limiting the study population to LOPD patients who are able to ambulate 40 meters (approximately 130 feet) without stopping and without an assistive device, do not require invasive-ventilation, and have an FVC in upright position of ≥30% predicted and ≤85% predicted are intended to assure that patients can reliably and safely perform the required test procedures.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position, as compared to alglucosidase alfa.

5.2 SECONDARY

Secondary objectives are to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12).

For the Canada-specific requirement regarding HHD, refer to Appendix C Section 17.3.3.

5.3 OTHER

Other objectives are to determine the PK, exploratory PD, pharmacogenetics and effect of avalglucosidase alfa treatment on motor function (GMFM-88 and GSGC), upper extremity muscle strength (HHD), health-related quality of life (EQ-5D-5L and PedsQL Generic Core Scale), and patient reported outcomes (PDSS/PDIS, R-PAct, and PGIC).

For the Canada-specific requirement regarding HHD, refer to Appendix C Section 17.3.3.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

EFC14028 is a Phase 3, multicenter, multinational, randomized, double-blind, 12-month PAP study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa (both at 20 mg/kg qow) in treatment-naïve patients with LOPD ages 3 and above. The study includes an open-label avalglucosidase alfa long-term follow-up phase for all patients, in which patients in the alglucosidase alfa arm will be switched to avalglucosidase alfa treatment after 12 months. Patients will remain blinded to the randomized treatment until after database is locked. Randomization will be in a 1:1 ratio with stratification factors based on baseline FVC, gender, age, and country (Japan or ex-Japan).

At the end of the recruitment, if <4 pediatric patients aged 3 to <18 years are enrolled, in order to comply with Health Authority requirements to enroll a certain number of pediatric patients, up to 2 additional pediatric patients will be screened and enrolled directly in the open-label avalglucosidase alfa long-term follow-up phase where they will receive avalglucosidase alfa.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The duration of the study for each patient will be at least up to approximately 3 years (151 weeks) (or 2 years [99 weeks] for the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase), including:

- An up to 14-day screening period (refer to Section 10.1.2 for extended duration in pre-specified situations);
- A 49-week blinded treatment period (PAP), except for the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase;
- An up to 96-week open-label treatment period (open-label avalglucosidase alfa long-term follow-up phase) for all patients regardless of prior randomization group;

An extended open-label avalglucosidase alfa long-term follow-up period will last up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients) for all patients (extended open-label avalglucosidase alfa long-term follow-up phase).

An up to 4-week post-treatment observation period will close the patient's participation.

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/contact.

6.3 INTERIM ANALYSIS

No interim analysis is planned during the double-blinded PAP (refer to Section 6.2.1 for the details of the different periods). Note that the primary analysis for the study is performed at the end of PAP, when the database will be locked and a study report will be produced for regulatory submission. The study will continue for additional 2 years (open-label long-term extension) and with an additional extension period of up to 144 additional weeks or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients). A final database lock will occur at the end of extension period, with a corresponding final study report generated.

After the primary analysis for PAP, interim analyses may be performed during the open-label extension period to provide additional information for regulatory purpose.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

An independent data monitoring committee (DMC), appointed by the Sponsor, will review unblinded data as outlined in the DMC charter, which is maintained separately from the study protocol. The DMC procedures will be detailed in the DMC charter and will have to be approved by the DMC members.

During the course of the study, bi-annual reviews of safety data will be performed by the DMC. In addition, the DMC will review safety data on an ad hoc basis as outlined in the DMC charter. IARs and other events which could require consultation of allergist/immunologist will be reviewed by the DMC member who is an allergist/immunologist. Should any major safety issues arise, final decisions regarding the study will be made by the Sponsor, taking into consideration the DMC opinion (as applicable).

An independent statistical center will be used to provide unblinded data to the DMC through a completely confidential process, and act as liaison between the Sponsor biostatistician and the DMC.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

Study EFC14028 is being conducted as a Phase 3 multicenter, multinational, randomized, double-blinded study to minimize bias.

EFC14028 is a head-to-head study design to compare avalglucosidase alfa directly to alglucosidase alfa, which is the only available ERT for LOPD. The study will be conducted at a

dose of 20 mg/kg qow, which is the recommended labeled dose for alglucosidase alfa and is supported based on results from nonclinical studies and the safety and exploratory efficacy results from the Phase 1 TDR12857 clinical study as being likely to result in greater glycogen depletion in skeletal muscles and clinical efficacy than alglucosidase alfa without new safety concerns.

Because avalglucosidase alfa is expected to be at least as efficacious as alglucosidase alfa, it is considered appropriate to test first for NI and then for superiority.

The primary endpoint of the EFC14028 study is % predicted FVC in the upright position, which is one of the same primary endpoints used in the AGLU02704 (LOTS) trial, which was the basis for the approval of alglucosidase alfa in LOPD. FVC is an established measure of lung capacity, and respiratory insufficiency is a major source of morbidity and death in this patient population.

A 12-month duration for the PAP should be sufficient to see a treatment difference compared to alglucosidase alfa and to collect safety data, including the development of anti-drug antibody (ADA).

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. The patient must provide signed, informed consent prior to performing any study-related procedures. Consent of a legally authorized guardian(s) is (are) required for legally minor patients as defined by local regulation. If the patient is legally minor, signed written consent shall be obtained from parent(s)/legal guardian and assent obtained from patients, if applicable.

I 02. The patient has confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations.

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 which are sorted and numbered in the following 5 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. The patient is <3 years of age.

E 02. The patient has known Pompe specific cardiac hypertrophy.

E 03. The patient is wheelchair dependent.

E 04. The patient is not able to ambulate 40 meters (approximately 130 feet) without stopping and without an assistive device. Use of assistive device for community ambulation is appropriate.

E 05. The patient requires invasive-ventilation (non-invasive ventilation is allowed).

E 06. The patient is not able to successfully perform repeated FVC measurements in upright position of ≥30% predicted and ≤85% predicted.

E 07. The patient has had previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease.

E 08. The patient (and patient's legal guardian if patient is legally minor as defined by local regulation) is (are) not able to comply with the clinical protocol.

E 09. The patient is concurrently participating in another clinical study using investigational treatment or has taken other investigational drugs or prohibited concomitant medications within 30 days or 5 half-lives from screening or randomization, whichever is longer.

E 10. The patient has known history of drug or alcohol abuse within 6 months prior to the time of screening.

E 11. The patient has clinically significant organic disease (with the exception of symptoms relating to Pompe disease), including clinically significant cardiovascular, hepatobiliary, 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.

E 12. Patient with prior or current use of immune tolerance induction therapy.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

None.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi Genzyme compound

E 13. Pregnant or breastfeeding female patient

E 14. Female patient of childbearing potential not protected by highly effective contraceptive method of birth control and/or who is unwilling or unable to be tested for pregnancy. The patient, if female and of childbearing potential, must have a negative pregnancy test (beta-human chorionic gonadotropin [β-HCG]) at screening/baseline. Pregnancy tests may be performed more frequently in some countries due to local legislations related to female patient of childbearing potential participating in clinical trials. For patients in Sweden, refer to Appendix C (Section 17.3.1).

Male participant with a female partner of childbearing potential not protected by highly effective method(s) of birth control (see Appendix A Section 17.1). For patients in Sweden, refer to Appendix C (Section 17.3.1).

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 2 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 and for at least 28 days after receiving the last study drug dose. Sterilized or infertile patients (defined as having undergone surgical sterilization, ie, vasectomy/bilateral tubectomy, hysterectomy and bilateral ovariectomy or as being postmenopausal, defined as at least 12 months of amenorrhea prior to enrollment) will be exempted from the requirements to use contraception in this study (see contraceptive guidance in Appendix A Section 17.1 or refer to Appendix C Section 17.3.1 for patients in Sweden).

7.2.4 Additional exclusion criteria during or at the end of screening or run-in phase before randomization

E 15. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form)

E 16. Despite screening of the patient, enrollment/randomization is stopped at the study level

7.2.5 Additional exclusion criteria related to country-specific requirements

E 17. Any country-related specific regulation that would prevent the patient from entering the study

Note: FVC% predicted may be repeated up to 3 times during the screening period if American Thoracic Society/European Respiratory Society (ATS/ERS) quality criteria have not been met as assessed by the central laboratory. Repeat tests should not occur on the same day in order to allow the patient to rest.

Patients may be re-screened if their clinical condition changes. Patients who were screen failed because their FVC% predicted was >85% may be rescreened only if a clinically relevant worsening respiratory condition related to Pompe Disease and not related to intercurrent illness as assessed by the Investigator occurs.

In case of re-screening, the patient will be first screened failed in the interactive voice/web response system (IXRS), will sign a new written informed consent form and a new patient number will be provided. All screening assessments/procedures will have to be performed again, except GAA and angiotensin converting enzyme (ACE) genotyping.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Avalglucosidase alfa, the IMP, will be supplied as a sterile, nonpyrogenic, lyophilized product in single-use vial containing approximately 100 mg of avalglucosidase alfa. Alglucosidase alfa (IMP) is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder in a single-use vial containing 50 mg of alglucosidase alfa.

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

Quantity of vials required for each infusion will be calculated based on the patient`s weight. The total amount of IMP administered may be adjusted as needed to account for changes in body weight. Most recent body weight should be used for dose calculation; weight obtained at a previous infusion visit may be used for preparation of IMP, if obtained within a timeframe of 1 month for pediatric patients and 3 months in adult patients. Each 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, preparation, and administration of the investigational product 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. The Sponsor will consult the DMC for any dose change related to AE. 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 or their legally authorized representative (for pediatric patients) to ensure that no adverse event occurred during the observational period.

The study includes 2 main periods: the blinded treatment period and the open-label avalglucosidase alfa long-term follow-up phase.

In the blinded treatment period avalglucosidase alfa or alglucosidase alfa will be administered by IV infusion every 2 weeks starting at Randomization Visit (Visit 2, Day 1/Day 2) continuing up to V27/W49 for a total of 25 doses.

Patients in the alglucosidase alfa arm will be switched to avalglucosidase alfa treatment after 12 months.

In the open-label avalglucosidase alfa long-term follow-up phase, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at V28/W51 continuing up to V76/W145 for a total of 48 doses.

In the extended open-label avalglucosidase alfa extension period, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at V77/W147 and continuing up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients) for up to 72 additional doses.

For pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at Randomization Visit (Visit 2, Day 1/Day 2) continuing up to V52/W97 for a total of 49 doses. For these patients, in the extended open-label avalglucosidase alfa extension period, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at V53/W99 and continuing up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) for up to 72 additional doses.

For all patients, all visits following V2 are calculated from day of first infusion of IMP in 14 days increments with a window of ±7 days for infusions and safety assessments and ±14 days for all other assessments. There should not be less than 7 days between 2 IMP infusions.

Patients who prematurely discontinue treatment should be followed as scheduled.

Home infusion

Home infusion may be possible in the open-label extension period, 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 while receiving avalglucosidase alfa 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 at least 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 the 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 regulations (see Appendix C Section 17.3.2 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 10.6).
- 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) 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, in agreed upon timeframe, 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 case report form (CRF) forms for AEs and exposure.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Refer to Section 10.5 for suspected unexpected adverse drug reaction requiring unblinding by the Sponsor.

In the double-blinded period of the study, avalglucosidase alfa and alglucosidase alfa will be provided as open-label supplies.

For blinding purposes, the on-site preparation of avalglucosidase alfa and/or alglucosidase alfa will therefore be performed by an independent unblinded pharmacist or an independent unblinded designee at the investigational site. The unblinded pharmacist or the unblinded designee should not be involved in activities that could be biased by the knowledge of the treatment assignment (eg, AE assessments, access to PD data) and will not disclose any information to anyone and ensure to maintain blinding condition of the study.

Each treatment kit will be labeled with a number generated by a computer program according to Sanofi procedure. The treatment numbers will be obtained by the unblinded pharmacist or the

unblinded designee at the time of patient randomization and subsequent patients' visits scheduled via centralized treatment allocation system (interactive response technology [IRT]).

In accordance with the double-blind design of the first blinded treatment period, study patients, Investigators and study site personnel, except for the unblinded pharmacist or the unblinded designee, will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2. The unblinded pharmacist or the unblinded designee is not allowed to disclose any unblinded information to the blinded study site team and therefore should not take part to any discussion regarding AE assessments for the patients, except to give information in a blinded manner on the preparation of the IMP (eg, preparation steps order well followed, confirmation of the usual visual aspect of the IMP once diluted).

Additional measures will be taken to ensure blinding of the patients (see pharmacy manual for details).

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking.

The code-breaking can also be performed by contacting the "24-hour alert system". A patient card, including the relevant "24-hour alert system" telephone number will be provided to every patient who will participate in the study.

If the code is broken, the patient must withdraw from IMP administration. Please refer to Section 10.3 of the protocol for details on handling of patient treatment discontinuation.

At the facilities where the systemic drug concentration measurements, ADAs and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team. One programmer may be unblinded to prepare the dataset for population PK analysis. The procedure detailing the process to maintain blind beyond the programmer is described in a separate Sanofi quality document.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Upon confirmation by the Investigator or Subinvestigator (if appropriately delegated) that the patient meets all eligibility criteria and completion of the screening and baseline assessments, eligible patients will be randomized as described below.

Treatment assignment and randomization will be performed using a centralized treatment allocation system/IRT. During the double-blind period, approximately 96 patients will be randomly assigned across sites to 1 of 2 treatment arms, avalglucosidase alfa or alglucosidase alfa at 20 mg/kg qow in a 1:1 ratio. Randomization will be performed within each of the following 6 strata:

A) Age <18,

B) Age ≥18, all genders and FVC (% predicted), Japan,

C) Age ≥18, male and FVC (% predicted) <55%, ex-Japan,

D) Age ≥18, female and FVC (% predicted) <55%, ex-Japan,

E) Age ≥18, male and FVC (% predicted) ≥55%, ex-Japan,

F) Age ≥18, female and FVC (% predicted) ≥55%, ex-Japan.

To control the number of patients with high baseline FVC (% predicted), the percent of enrolled patients with baseline FVC (% predicted) of 80% to 85% will be capped at 15% of the total population.

The treatment kit number lists are generated centrally by the Sponsor. The IMPs (avalglucosidase alfa or alglucosidase alfa in blinded treatment period; avalglucosidase alfa in open-label long-term follow-up period and in additional extension open-label follow-up) are packaged in accordance with the lists.

The IRT (centralized treatment allocation system) generates the patient randomization list and allocates the treatment number and the corresponding treatment kits to the patients accordingly. Investigator and assigned study site personnel will have access to blinded IRT menu/reports, whereas the unblinded pharmacist or unblinded designee will have access to unblinded reports.

The treatment kits will be allocated using a centralized treatment allocation system (IRT) every 2 weeks starting at Visit 2 (Day 1/Day 2). Multiple treatment kits will be required to be used for each IMP administration.

The number of vials of avalglucosidase alfa/alglucosidase alfa to be used for each infusion will be calculated using the latest available body weight data. Body weight will be measured at the time points specified in Section 1.2.

Before randomizing a patient, the Investigator or designee will have to contact the centralized treatment allocation system/IRT.

The pediatric patients aged 3 to <18 years enrolling directly in the in the open-label long-term follow-up phase, avalglucosidase alfa will not be randomized as they will be assigned to avalglucosidase alfa.

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.

8.7 RESPONSIBILITIES

The Investigator, the hospital 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 (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor designee. 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 the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP 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 unblinded pharmacist or the unblinded designee.

IMP accountability:

- Unblinded pharmacist or unblinded designee will maintain records of the precise date, time of the drug administration and number of treatment units used for administration. This information can be available only to the unblinded pharmacist or unblinded designee at the site and unblinded monitor.

- The unblinded pharmacist or the unblinded designee will maintain records of the treatment numbers assigned by the central treatment allocation system/IRT at each visit.
- The unblinded monitor assigned to the study will perform reconciliation.

The patient's compliance with the treatment regimen will be monitored in terms of the patient receiving the study drug infusion qow within a ±7-day window from the scheduled infusion date based on V2 (Day 1/Day 2). Missed, delayed, or incomplete infusions will be clearly documented. 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. Refer to Section 10.1.7 if the missed infusion is due to a missed visit.

8.7.2 Return and/or destruction of treatments

Destruction of IMP kits (ie, used, unused or expired) can be performed during the course of the study as well as at the end of the study once reconciliation has occurred.

Used vials must be kept in their original secondary packaging (box) unless unique treatment number is printed on the vial which will allow reconciliation to be performed by site and Sponsor representative.

In some specific cases described in the monitoring plans (blinded and unblinded), reconciliation may be performed by blinded monitor, as long as the blinding is maintained as per conditions detailed in the monitoring plan.

Reconciliation of IMP kits allocated during patient's double-blind period must be performed at the site by the unblinded pharmacist or the unblinded designee and unblinded monitor using treatment log forms and documented on-site IMP inventory countersigned by the unblinded pharmacist or the unblinded designee and unblinded monitor. A written authorization for destruction of used and unused IMP must be provided by the Sponsor once the IMP reconciliation is achieved.

Destruction at the site is strongly encouraged and can be performed provided that the following requirements are met:

- Site has appropriate facilities to destroy IMP;
- Site has procedures to allow traceability of the batches and quantities destroyed, and delivers the corresponding destruction documentation/certificate; and
- Sponsor has provided written authorization to destroy IMP.

In case the above requirements are not satisfied and the site cannot destroy IMP, the kits will be returned to Sponsor for destruction.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Medications and therapies taken by the patient during the 30-day period prior to the

Screening/Baseline Evaluation Visit and during the course of the study will be recorded in the electronic Case Report Forms (e-CRF). Similarly, pre-infusion medications (if allowed; see Section 8.8.1) and assistive devices (eg, walker, cane, crutches) will be recorded in the e-CRF. The use (if any) of mechanical ventilation (including both invasive and noninvasive) will be recorded on the e-CRF ventilator use form.

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 and avalglucosidase alfa, some patients were pretreated with antihistamines, antipyretics, and/or corticosteroids. Infusion-associated reactions occurred in some patients even 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 immunoglobulin E (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.

Refer to Section 10.6 for IAR management recommendations including pretreatments.

8.8.2 Prohibited concomitant medications

Use of immunomodulation treatments (eg, methotrexate, rituximab, immunoglobulins, and other immunosuppressants), either alone or in combination, that would interfere with the evaluation of the immunogenic potential of avalglucosidase alfa, is not allowed during participation in the study. In the case of administration of a prohibited treatment, the Sponsor must be notified, the treatment with IMP will be discontinued, and the patient will be asked to continue study assessments to the extent possible prior to study withdrawal.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

Pulmonary function testing (PFT) will be performed locally at the time points specified in Section 1.2 and measured by a central laboratory. During the treatment period, the assessment will be completed before IMP infusion. Assessment should continue to be collected for at least up to Week 49, end of PAP, if the patient discontinues the treatment earlier.

The PFT administration protocol is standardized across sites in accordance with ATS/ERS guidelines (2). Per ATS/ERS 2005 quality standards, an adequate test requires a minimum of 3 acceptable FVC maneuvers and acceptable repeatability needs to be met for the largest and next-largest FVC and forced expiratory volume in the 1st second of the FVC maneuver (FEV_1) as outlined in the study manual. Patients may repeat the PFT assessment up to 3 times within the Screening Visit time window in case of failed quality as determined by the central laboratory (refer to Section 7 for details on screening and re-screening conditions). For each PFT assessment, up to 8 efforts may be performed. Patients are not allowed to use noninvasive ventilation during this assessment. The primary efficacy endpoint is the change from baseline to Week 49 in FVC (% predicted) in upright position. FVC will be reported in liters and percent of predicted normal values based on age, gender, race, and height. Global Lung Initiative (GLI) 2012 reference equations will be used for this study (3).

Postbaseline PFT should meet the ATS/ERS 2005 quality standards. However, if no acceptable efforts can be recorded during the upright position PFT with up to 8 efforts, an additional PFT may be scheduled as soon as possible no later than 45 days after this failed planned test, if this is feasible for the patient. The highest acceptable effort will be kept in the database.

In addition, if the patient did not perform the PFT at a planned visit, the patient should be reminded to perform the PFT as soon as possible no later than 45 days after the missed test, if it is feasible for patient to perform the test within this period.

Refer to the study specific manual for instructions on test administration.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

9.2.1.1 Six-minute walk test

The 6MWT (4) will be performed at the times specified in Section 1.2 to assess functional capacity in the late-onset Pompe population. During the treatment period, the assessment will be completed before IMP infusion. See the study specific functional outcome assessment manual for further details.

The primary measurement is the distance walked in 6 minutes, measured in meters; the amount of time walked (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. Reference equations for the prediction of total distance walked applicable to the study population will be used (5, 6).

For the purpose of stabilization and if deemed necessary by the Investigator, the participant may use a walking device, such as cane or walker during the assessment. If such a device is used during the assessment, this must be recorded in the e-CRF. Also, if there is a change in device use during the trial, this must be recorded in the e-CRF.

9.2.1.2 Pulmonary function testing

Refer to Section 9.1.1 on the primary efficacy endpoint for information on PFT administration.

Secondary efficacy endpoints measured by PFT will include the assessment of MIP and MEP in the upright position. Additional parameters of respiratory function collected may be analyzed as appropriate, including the assessment of FVC, MIP, and MEP in the supine position and (FEV_1) and peak expiratory flow (PEF) in the upright and supine positions.

9.2.1.3 Hand-held dynamometry (lower extremity muscle strength)

Hand-held dynamometry using the make technique will be performed at the time points specified in Section 1.2 (7). Equipment will be standardized across sites. During the treatment period, the assessment will be completed before IMP infusion. Stabilization procedures for all muscles groups will be followed to avoid use of compensatory muscles. To complete a make test the examiner holds the dynamometer stationary while the patient exerts a maximal force against the dynamometer. The patient makes a gradual increase in force and then completes an isometric hold for 4 to 5 seconds.

Lower extremity strength in the muscle groups detailed below will be tested by the same physical therapist or trained assessor.

- Hip Flexion;
- Hip Extension;
- Hip Abduction;
- Hip Adduction;
- Knee Flexion;
- Knee Extension;
- Ankle Dorsiflexion;
- Ankle Plantar Flexion.

The limb tests will be completed bilaterally to account for differences in the generated force for the dominant and nondominant limb. Every muscle group will be measured 2 times and the highest value will be reported in the e-CRF. Patients may use noninvasive ventilation during the dynamometry assessment. Refer to the study specific manual for instructions on test administration.

For the Canada-specific requirement regarding HHD refer to Appendix C Section 17.3.3.

9.2.1.4 Quick Motor Function Test

The QMFT will be administered at the time points specified in Section 1.2 to evaluate changes in motor function concurrently with the GMFM-88. During the treatment period, the assessment will be completed before IMP infusion.

The QMFT is an observer administered test comprising 16 items specifically difficult for patients with Pompe disease (8). The items are scored separately on a 5-point ordinal scale (ranging from 0 to 4) with a total score of all items ranging between 0 and 64 points. The test was validated in 91 Pompe patients, aged 5 to 76 years, with different levels of disease severity. Test administration takes approximately 10 to 15 minutes. Refer to the study specific manual for instructions on test administration.

9.2.1.5 12-Item Short-Form Health Survey (SF-12)

The SF-12 Version 2.0 will be administered at the time points specified in Section 1.2. During the treatment period, the assessment will be completed before IMP infusion if possible. The SF-12 is comprised of a subset of 12 items from the SF-36 to reproduce the physical component summary (PCS) and mental component summary (MCS) scales (9). The SF-12 will be administered to assess health-related quality of life in patients ≥18 years of age at screening/baseline. The data from the questionnaire will be entered into the e-CRF by the site personnel.

9.2.2 Safety endpoints

9.2.2.1 Adverse events

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 spontaneously reported by the patient or observed by the Investigator, will be monitored throughout the study. This includes the monitoring and reporting of IARs.

Definitions of AEs, SAEs, and AESI, including reporting procedures, can be found in Section 10.4 to Section 10.7.

Refer to the appropriate study documentation for guidelines on the evaluation of AEs, including relationship to study treatment, severity grading, outcome, and action taken regarding the IMP.

9.2.2.2 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: aspartate aminotransferase (AST), alanine aminotransferase (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). A urine sample will be sent to the central laboratory for that purpose.

9.2.2.3 Vital signs

Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation. Vital signs are to be assessed prior to infusion, with each infusion rate change (including the start of infusion which is considered as first infusion rate change), at the end of the infusion and at the end of the post-infusion observation period, ie, a total of 7 assessments. Collection windows are ±15 minutes.

9.2.2.4 Electrocardiogram variables

Standard 12-lead ECGs are recorded at the time points specified in Section 1.2 after at least 15 minutes in the supine position using an electrocardiographic device. The following will be assessed: heart rate, rhythm, interval from start of the Q wave to the end of the S wave (QRS),

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 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, left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, repolarization charges, and overall cardiac impression for each patient. For Day 1 only, and prior to receiving IMP, 3 ECGs within 5 minutes will be performed with at least 1 minute between 2 replicates.

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, 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 e-CRF. 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). The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (such as US FDA Code of Federal Regulations, Title 21, Part 11 or EU regulation Eudralex volume 4 annex 11).

The Investigator who reads the ECGs or appropriate designee (noninvestigator physician who reads the ECGs) 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 Investigator who reads the ECGs or appropriate designee, 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 for analysis purposes and not for clinical management of the patient.

9.2.2.5 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. Head circumference and Tanner stage of sexual maturation will be assessed as part of the physical examination in pediatric patients at baseline and yearly thereafter. Details can be found in the study manual.

9.2.2.6 Body weight and height

Body weight will be measured in kilograms and collected in the e-CRFs monthly for pediatric patients and every 3 months throughout the duration of the study for adults. More frequent weight may be obtained at the discretion of the Investigator.

Standing height will be measured in all patients at baseline and annually thereafter, and in pediatric patients additionally every 3 months up to Week 73 and then every 6 months. If possible, height will be measured in the morning of the study visit day, prior to the PFT, and by using the same stadiometer for all measurements.

9.2.2.7 Immunogenicity

Immunogenicity assessments will include the following:

- Samples will be collected from patients for evaluation of ADA every month up to Week 73 and then every 3 months throughout the duration of the study. In addition, samples will be collected from all patients at Week 2 (Day 8) and Week 52 (1 week after the first possible avalglucosidase alfa infusion in patients who received alglucosidase alfa during the blinded treatment period) to monitor for an early antibody response in avalglucosidase alfa-treated patients.
  - Patients in the avalglucosidase alfa treatment arm will be tested for anti-avalglucosidase alfa antibodies and patients in the alglucosidase alfa treatment arm will be tested for anti-alglucosidase alfa antibodies; in addition, patients in the alglucosidase alfa treatment arm will also be tested for anti-avalglucosidase alfa antibodies at V27/W49 to get their baseline value. In the open-label follow-up phase, patients from the alglucosidase alfa treatment arm who have switched to avalglucosidase alfa will be tested for both anti-alglucosidase alfa antibodies and anti-avalglucosidase alfa antibodies. In these patients, ADA against alglucosidase alfa will no longer be tested in the extended open-label follow-up phase (ie, after Week 145). Patients who remain on avalglucosidase alfa treatment will continue to be tested for anti-avalglucosidase alfa antibodies. Patients who are positive for anti-avalglucosidase alfa antibodies will be tested to determine if the antibodies cross-react with alglucosidase alfa.
  - ADA seropositive patient serum will be assessed for neutralizing antibodies to avalglucosidase alfa and/or alglucosidase alfa, as appropriate, including inhibition of enzyme activity and uptake.
  - Samples may be collected from patients and evaluated for IgE, complement activation, serum tryptase following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions (Section 10.6).
- In the event a patient exhibits signs or symptoms suggestive of systemic immune-mediated reactions involving skin and other organs, serum samples are obtained for the evaluation of circulating immune complexes.

- See the study specific laboratory manual as well as the study manual for guidelines on the collection and shipment of antibody samples and for details on circulating immune complex testing.

9.3 OTHER ENDPOINTS

9.3.1 Tertiary efficacy endpoints

9.3.1.1 Gait, Stair, Gower's Maneuver, and Chair composite functional assessment

Functional performance will be measured using the GSGC score at the time points specified in Section 1.2. During the treatment period, the assessment will be completed before IMP infusion. The GSGC total score can be obtained by adding the item scores of the 4 functional tests; item scores range from 1 to 7 for 3 items and 1 to 6 for 1 item (Arising from a chair). Total scores can vary from a minimum of 4 representing normal performance to a maximum of 27 representing the poorest functional score. The GSGC performance test has been validated for use with glycogen storage disease (GSD) type II patients and patients with Duchenne muscular dystrophy (10). Each of the functional items is also evaluated according to the time required to complete the task.

- Time to walk 10 meters (Gait);
- Time to climb 4 stairs (Stair);
- Time to stand from sitting on the floor (Gower's Maneuver);
- Time to stand from sitting position in a chair (Chair).

See the study specific manual for further details.

9.3.1.2 Gross Motor Function Measure

The GMFM-88 (11) will be administered at the time points specified in Section 1.2 to evaluate changes in motor function. During the treatment period, the assessment will be completed before IMP infusion. The GMFM-88 was developed specifically to detect quantitative changes in gross motor function. There is no age cut-off for the GMFM-88.

Of the 5 dimensions to the GMFM-88, 2 will be evaluated in this study:

- Standing (13 items);
- Walking, Running & Jumping (24 items).

Items were selected to represent motor functions typically performed by children without motor impairments by 5 years of age. Each item is scored on a 4-point Likert scale (ie, 0 = cannot do; 1 = initiates [<10% of the task]; 2 = partially completes [10% to <100% of the task]; 3 = task completion). The score for each dimension is expressed as a percentage of the maximum score for that dimension. Total score is obtained by adding the percentage scores for each dimension and

dividing the sum by the total number of dimensions. Therefore, each dimension contributes equally to the total score.

This assessment will include the expanded and revised Gross Motor Function Classification System for the GMFM-88 (GMFCS-E&R) adapted for adults (12). The GMFCS emphasizes concepts in the World Health Organization's International Classification of Functioning, Disability and Health. Emphasis is on performance in home, work and community settings without judgments about quality of movement or prognosis for improvement. The GMFCS is a 5-level classification system consisting of Levels I to V based on self-initiated movement, with emphasis on sitting, transfers, and mobility. The distinctions between levels are based on functional limitations, the need for assistive mobility devices, and to a much lesser extent, quality of movement, and are designed to be meaningful in daily life (12).

The general headings for the 5 levels are:

- Level I Walks without limitations
- Level II Walks with limitations
- Level III Walks using a hand-held mobility device
- Level IV Self-mobility with limitations; may use powered mobility
- Level V Transported in a manual wheelchair

See the study specific manual for further details.

9.3.1.3 Hand-held dynamometry (upper extremity muscle strength)

Hand-held dynamometry using the make technique will be performed at the time points specified in Section 1.2 (7, 13). Equipment will be standardized across sites. During the treatment period, the assessment will be completed before IMP infusion. Stabilization procedures for all muscles groups will be followed to avoid use of compensatory muscles. To complete a make test, the examiner holds the dynamometer stationary while the patient exerts a maximal force against the dynamometer. The patient makes a gradual increase in force and then completes an isometric hold for 4 to 5 seconds.

Upper extremity strength in the muscle groups detailed below will be tested by the same physical therapist or trained assessor.

- Shoulder Flexion;
- Shoulder Extension;
- Shoulder Abduction;
- Shoulder Adduction;
- Elbow Flexion;
- Elbow Extension;
- Grip Strength.

The limb tests will be completed bilaterally to account for differences in the generated force for the dominant and nondominant limb. Every muscle group will be measured 2 times and the highest value will be reported in the e-CRF. Patients may use noninvasive ventilation during the dynamometry assessment. See the study specific manual for further details.

For the Canada-specific requirement regarding HHD, refer to Appendix C Section 17.3.3.

9.3.1.4 5-Level EuroQoL in 5 dimensions

The EQ-5D-5L survey will be completed at the time points specified in Section 1.2. During the treatment period, the assessment will be completed before IMP infusion if possible. The EQ-5D-L is a standardized instrument for use as a measure of health outcome (14). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L descriptive system comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and is rated according to 5 levels of health/ability (either no problem, slight problem, moderate problem, severe problem; or unable to perform activity or no, slight, moderate, severe, or extreme). The EQ VAS records the respondents' self-rated health status on a vertical graduated (0-100) visual analogue scale. Patients who are ≥18 years of age at screening/baseline will complete this assessment. The data from the questionnaire will be entered into the e-CRF by the site personnel.

9.3.1.5 Pediatric Quality of Life Inventory

The PedsQL Generic Core Scales is a general health-related quality of life tool and will be completed at the time points specified in Section 1.2 by patients who are <18 years of age at screening/baseline. If patients are unable to complete this assessment, a parent proxy form will be used. During the treatment period, the assessment will be completed before IMP infusion if possible, and the patients will continue on the age-specific assessment they first completed at screening/baseline, even if they exceed the age range for that specific tool over the trial duration. The 23-item PedsQL encompasses 4 subscales including a patient's health and activities, feelings, problems with school, and how the patient gets along with others (15). Items are evaluated on a 5-point Likert scale with 0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = almost always, and the data from the questionnaire will be entered into the e-CRF by the site personnel.

9.3.2 Pharmacokinetics

9.3.2.1 Sampling time

Blood samples for full evaluation of avalglucosidase alfa and alglucosidase alfa PK will be collected before and after infusions on Visit 2 (Day 1/Day 2) and Visit 27 (Week 49). Sampling times are as follows: pre-dose (prior to infusion), at the end of the infusion, and at 2, 4, 6, and 8 hours after the end of infusion. In addition, sparse blood samples will be collected predose (prior to infusion) and at 2 hours after the end of infusion at Week 13, Week 25, and Week 37.

Pharmacokinetic blood samples are to be collected within 15 minutes of scheduled time: predose and all samples immediately following the end of the infusion through 8 hours post-infusion.

9.3.2.2 Pharmacokinetics handling procedure

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

9.3.2.3 Bioanalytical method

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

The lower limit of quantitation (LLOQ) is 12 ng/mL or 0.012 µg/mL for avalglucosidase alfa.

9.3.2.4 Pharmacokinetics parameters

The following pharmacokinetic parameters will be determined for avalglucosidase alfa and alglucosidase alfa based on non-compartmental analysis. The parameters will include C_{max} and $AUC_{0\text{-last}}$. If data permit, other parameters including clearance (CL) and volume of distribution at steady state (Vss) will be included. The definitions of the pharmacokinetic parameters are presented in Table 1.

Table 1 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Matrix	Definition/Calculation
C_{max}	avalglucosidase alfa/alglucosidase alfa	Plasma	Maximum plasma concentration observed
$AUC_{0\text{-last}}$	avalglucosidase alfa/alglucosidase alfa	Plasma	Area under the plasma concentration versus time curve from time 0 to time of the last quantifiable concentration
CL	avalglucosidase alfa/alglucosidase alfa	Plasma	Total body CL of a drug from the plasma
Vss	avalglucosidase alfa/alglucosidase alfa	Plasma	Volume of distribution at steady state

9.3.3 Pharmacogenetic assessment

Pharmacogenetic samples will be collected at the time points specified in Section 1.2. Refer to the study specific laboratory manual for guidelines on the collection and shipment of whole blood samples.

9.3.3.1 Genotyping of human acid α-glucosidase gene

If historical results are not available, a blood sample will be collected as specified in Section 1.2 and sent to a centralized laboratory where it will be extracted to yield DNA. The DNA will be amplified by polymerase chain reaction (PCR) using gene specific primers and the resulting PCR products will be sequenced for the identification of mutations and genetic variation (polymorphisms and associated haplotypes) within the GAA gene.

Gene mutation analysis is mandatory for all patients but GAA genotyping is only to be performed if historical results are not available. Blood sample results for patient gene mutation analysis must

be obtained prior to screening/baseline in order to assess patient for study eligibility. However, results from the central laboratory may be used if performed during the screening period but should be obtained before the baseline visit to confirm eligibility. If gene mutation analysis was conducted prior to signing the informed consent, these results may be collected provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and patient and/or legal guardian gives consent to utilize the results. If interpretation of GAA genotyping is inconclusive for the diagnosis of Pompe disease, or if only 1 mutation has been reported, then GAA enzyme activity level, normal laboratory ranges and tissue source needs to be provided in the interpretation field of the GAA genotyping e-CRF page for the purpose of confirming Pompe Disease.

9.3.3.2 Angiotensin converting enzyme marker allele status

DNA samples will also be collected as specified in Section 1.2 for an exploratory assessment of ACE (also known as DCP1) gene polymorphisms involving the absence (deletion, D allele) or presence (insertion, I allele) of a 287 base pair alu-repeat fragment located in intron 16 of the ACE gene. The ACE allele genotype status will be identified by PCR.

9.3.3.3 Exploratory assessment of circulating microRNA in plasma

Plasma samples will be collected as specified in Section 1.2 and assessed for circulating microRNA concentrations on both the whole-genome and individual gene levels.

9.3.3.4 Optional stored DNA sample

For those patients who signed the optional pharmacogenetic informed consent form, a blood sample will be collected at the study visit as specified in Section 1.2 and this sample will be stored.

This sample may be used to determine a possible relationship between genes and response to treatment with avalglucosidase alfa or alglucosidase alfa and possible side effects to the same.

This blood sample will be transferred to a site that will, on behalf of Sanofi, extract DNA from the sample and that is managed by a contractor which can be located outside of your country, within or outside of the European Union.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (deidentification code) that is different from the Patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by Patient ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored in the USA for up to 15 years from the completion of the clinical study report, after which the samples will be destroyed.

Special procedures for storage and shipping of pharmacogenetic samples are described in detail in the study specific laboratory manual.

9.3.4 Pharmacodynamic variables

9.3.4.1 Urine Hex4 levels

Fasted urine samples for the assessment of urinary glucose tetrasaccharide (Hex4) concentrations will be collected prior to IMP infusion as specified in Section 1.2. Procedures for the collection, handling and shipment of all urine samples will be included in the study specific laboratory manual.

9.3.4.2 Exploratory urine, DBS, and plasma biomarkers

Fasted DBS, plasma and urine will be collected prior to IMP infusion at the times specified in Section 1.2 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.

9.3.5 Quality of life/health economic variables/other endpoints

9.3.5.1 Pompe Disease Symptom and Impact Scales

The PDSS and PDIS will be completed as both a 24-hour recall PDSS (version 1.1) and PDIS (version 1.2), as well as a 7-day recall PDSS (version 1.7) and PDIS (version 1.27). After training by the site staff at screening/baseline, patients will complete the 24-hour version of the PDSS and PDIS daily throughout the entire screening period. The patients will also complete a one-time administered, 7-day recall version prior to first infusion (ie, at Day -1, Day 1, or Day 2). During the trial, patients will complete the 24-hour recall version of the scales daily via an e-diary for 2 weeks between visits at the time points specified in Section 1.2. Patients ≥18 years of age at screening/baseline will complete this assessment. The PDSS and PDIS are both self-administered questionnaires specifically designed to capture the symptoms and impacts pertinent to patients with LOPD. The PDSS contains 12 questions on a scale from 0 (none) to 10 (as bad as I can imagine), while the PDIS contains 15 questions with varying scales implemented depending on question type. The data from these scales will be analyzed both separately and together as a composite. Since these are recall questionnaires, they can be completed by the patient anytime, but preferably at the same time of the day. In case of unavailability of the e-diary (eg, device dysfunction or deficiency), a paper version of the scale(s) will be used and the data will be transferred into the database.

9.3.5.2 Rasch-built Pompe-specific Activity scale

The R-PAct scale will be completed at the time points specified in Section 1.2 in selected countries (eg, UK, USA, Canada, Belgium and The Netherlands). Patients whose first language is English or Dutch and who are ≥18 years of age at screening/baseline will complete this

assessment. During the treatment period, the assessment will be completed before IMP infusion if possible. The R-PAct is a self-administered questionnaire specifically suited to quantify the effects of Pompe disease on patient's ability to carry out daily activities and their social participation. It consists of 18 items suited to quantify activity limitations, ranging from unable to perform daily life activities (0) to able to perform without difficulty (2) in patients with Pompe disease (16). The data from this questionnaire will be entered into the e-CRF by the site personnel.

9.3.5.3 Patient Global Impression of Change

The PGIC items will be completed at Week 49 (PAP patients and 2 additional pediatric patients in open-label period) and will be administered annually in follow-up during the extension period. Patients who are ≥18 years of age at the concerned visit will complete this assessment at Week 49, Week 97 and Week 145 (pediatric patients in open-label period will complete this assessment at Week 49 and Week 97). The PGIC items consist of 4 questions pertaining to overall disease-related symptoms, activities of daily living, as well as mobility and respiratory issues. The items range from -3 (a great deal worse) to 0 (no change) to 3 (a great deal better). The data from this scale will be used to support and validate additional endpoints in the trial.

9.4 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 patient s 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.

These samples will remain labelled with the same identifiers used during the study (ie, Patient ID). They will 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 patient confidentiality and personal data (see Section 14.1). The samples may be stored or used for as long as they last or are needed for research.

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary objective of the EFC14028 study is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC % predicted in the upright position, as compared to alglucosidase alfa in approximately 96 patients with LOPD, male or female, aged from 3 years, and previously not treated with ERT. The PAP will be a 12-month phase from start of study treatment. The primary endpoint will be change in % predicted FVC from baseline to 12 months (49 weeks).

The consensus of a survey of treaters conducted by Sanofi Genzyme highlighted respiratory function improvement as an ongoing unmet need in Pompe disease. In LOPD patients,

alglucosidase alfa leads to improvement in 6MWT and muscle function with stabilization of decline in respiratory function. The most common cause of death in Pompe disease is respiratory complications of long-term decline in respiratory function.

In previous alglucosidase alfa experience from the AGLU02704 double-blind placebo-controlled trial in late-onset patients, the patients from the alglucosidase alfa treated arm had a mean (±standard deviation [SD]) change from baseline in % predicted FVC of 1.56 ±4.3 at 6 months, demonstrating stabilization. In a subsequent study of alglucosidase alfa in 18 late-onset patients (AGLU07310), there was an average improvement of 1.8 % in FVC. More recently, a Phase 1/2 trial (TDR12857) with avalglucosidase alfa in an LOPD population similar to AGLU07310 was completed, in which the mean (SD) change from baseline in % predicted FVC was 6.2 (3.15) in the 3 patients previously naïve to treatment dosed with 20 mg/kg avalglucosidase alfa or 5.2 when looking at the 6 patients from the 10 and 20 mg/kg treatment-naïve group. Replication of this preliminary clinical evidence of superiority of avalglucosidase alfa over the existing treatment of alglucosidase alfa with respect to pulmonary function should correlate to a clinically meaningful benefit in the context of the known long-term respiratory complications seen in Pompe disease.

The secondary objectives are to determine the effect of avalglucosidase alfa on change in 6MWT distance walked, MIP and MEP % predicted, muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12). In the context of availability of an existing treatment, assessment of these endpoints is important to assure that the new treatment is not less effective.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

It is recommended that assessments/procedures at a site visit are performed in the following order, if applicable:

1. Patient-reported outcomes and other questionnaires
2. Physical examination (including height, body weight, head circumference, Tanner stage) and patient interview
3. Procedures:
   - ECG
   - PFT
4. Motor assessments
5. Safety and laboratory assessments
6. IMP administration

Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days, consecutive or not. In any case, IMP administration will be the last procedure and the appropriate time needed for post-infusion surveillance will be taken into account.

10.1.1 Prestudy IRT contact

- IRT contact to inform identification of potential patient and initiation of IMP shipment for each patient

Information regarding the prestudy IRT contact can be found in the IRT manual.

10.1.2 Screening period/baseline visit

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

Patients who have signed their written informed consent will have the following procedures performed at screening/baseline.

- Informed consent;
- Inclusion/exclusion criteria;
- Demographics and baseline characteristics:
  - Age (years);

  - Gender;
  - Race;
  - Ethnicity;
- Medical/Surgical history;
- Pompe disease history, inclusive of GAA mutation and aspects of disability;
- Physical examination (inclusive of head circumference and Tanner stage for pediatric patients only);
- β-HCG pregnancy test (females of childbearing potential only);
- Body weight;
- Height;
- Hematology, biochemistry, and urinalysis;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- Urine Hex4 sample collection;
- Exploratory biomarker urine sample collection;
- GAA genotyping (if historical results are not available);
- ACE genotyping;
- Stored DNA sample (optional);
- SF-12 (patients ≥18 years of age);
- EQ-5D-5L (patients ≥18 years of age);
- PedsQL (patients <18 years of age);
- PDSS/PDIS (patients ≥18 years of age, 24-hour recall version daily [ie, during screening] via an e-diary, as well as 7-day recall version prior to first infusion [ie, at Day -1, Day 1, or Day 2]);
- R-PAct (patients ≥18 years of age);
- PFT;
- 6MWT;
- GSGC;
- GMFM-88/GMFCS;
- QMFT;
- HHD (not applicable for Canadian sites, see Appendix C Section 17.3.3);
- AE collection;
- Prior/concomitant medications;

- IRT contact for notification of screening.

The recommended duration of the screening period is up to 14 days but may be extended to a maximum of 8 weeks in the following pre-specified situations:

- One or more of the assessments/procedures were not properly conducted or results were flawed because of a proven and tracked device deficiency (eg, spirometer) or a proven and tracked vendor deficiency (eg, courier vendor responsible for transferring samples from investigating site to central laboratory). In this case, the test(s) will be repeated.
- An intercurrent acute disease or event occurred during the screening period, which does not meet an exclusion criterion (see Section 7.2).
- Up to 4 PFTs (original plus 3 repeat tests) may be required to meet ATS/ERS quality criteria.
- The study or the IMP administration is temporarily put on hold due to a Sponsor decision (see Section 10.3.1).

FVC% predicted may be repeated up to 3 times during the screening period if ATS/ERS quality criteria have not been met as assessed by the central laboratory. Repeat tests should not occur on the same day in order to allow the patient to rest.

Re-screening may be allowed as described in Section 7.2.5.

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

For the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase, an IRT call for enrollment will replace the randomization call and will be performed just before the IMP administration at the first treatment visit. Postscreening schedule for this subgroup of pediatric patients is detailed in Section 10.1.7.

10.1.3 Blinded treatment period

Patients enrolled in the study will have the following procedures performed starting at Day of first infusion. Day of first infusion should occur within 1 to 14 days after Screening/Baseline. All subsequent visits are calculated from day of first infusion of IMP in 14-day increments with a window of ±7 days for infusions and safety assessments and ±14 days for all other assessments.

A patient card will be provided to the patient once the patient is randomized (see study manual for details).

10.1.3.1 Day of first infusion (Day 1/Day 2)

The following will be performed on the day of randomization (Day 1), or day following randomization (Day 2) to allow preparation of the IMP for infusion:

- Inclusion/exclusion criteria;
- Urine pregnancy test (females of childbearing potential only);
- Body weight;
- 12-lead ECG (triplicate);
- Vital signs (before, during, and following infusion);
- Urine Hex4 sample collection;
- Exploratory biomarker urine sample collection;
- Exploratory biomarker DBS and plasma sample collection;
- Plasma sample collection for microRNA analyses;
- IRT contact to confirm patient randomization and treatment kits allocation;
- PK plasma sample collection (before and following infusion);
- Infusion of IMP;
- AE collection;
- Prior/concomitant medications;
- PDSS and PDIS (patients ≥18 years of age at screening/baseline: 7-day recall version administered prior to first infusion (ie, at Day 1 or Day 2).

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

This visit requires a stay at the site prior to and for at least 8 hours following IMP infusion as an in-patient or out-patient, as per hospital/center procedure.

10.1.3.2 One week following first infusion (Week 2 [Day 8])

The following will be performed 1 week following the date of the first infusion:

- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications.

10.1.3.3 Biweekly

The following will be performed every 2 weeks starting at the date of the first infusion (W3, W5, W7, W9, W11, W13, W15, W17, W19, W21, W23, W25, W27, W29, W31, W33, W35, W37, W39, W41, W43, W45, W47 and W49):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);

- Infusion of IMP;
- AE collection;
- Prior/concomitant medications.

10.1.3.4 Every 4 weeks

The following assessments will be performed on a monthly basis (W5, W9, W13, W17, W21, W25, W29, W33, W37, W41, W45 and W49):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of IMP;
- Urine pregnancy test (females of childbearing potential only);
- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- Body weight (for pediatric patients only);
- AE collection;
- Prior/concomitant medications.

10.1.3.5 Every 12 weeks

The following assessments will be performed at quarterly visits (Week 13, Week 25, Week 37, and Week 49):

- Physical examination (inclusive of head circumference and Tanner stage for pediatric patients only at Week 49);
- Urine pregnancy test (females of childbearing potential only);
- Body weight;
- IRT contact for treatment kits allocation;
- Height (for pediatric patients only and adult patients only at Week 49);
- Hematology, biochemistry, and urinalysis;
- ECG;
- Vital signs (before, during, and following infusion);
- PK plasma sample collection (before and following infusion);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- Exploratory biomarker urine sample collection;

- Exploratory biomarker DBS and plasma sample collection;
- Plasma sample collection for microRNA analyses;
- Urine Hex4 sample collection;
- SF-12 (patients ≥18 years of age at screening/baseline);
- EQ-5D-5L (patients ≥18 years of age at screening/baseline);
- PedsQL (patients <18 years of age at screening/baseline);
- PDSS/PDIS (patients ≥18 years of age at screening/baseline, via an e-diary daily for 2 weeks between visits);
- R-PAct (patients ≥18 years of age at screening/baseline);
- PGIC (patients ≥18 years of age at screening/baseline, at Week 49 only);
- PFT;
- 6MWT;
- GSGC;
- GMFM-88/GMFCS;
- QMFT;
- HHD (not applicable for Canadian sites, see Appendix C Section 17.3.3);
- Infusion of IMP;
- AE collection;
- Prior/concomitant medications.

Week 49/Visit 27 requires a stay at the site prior to and for at least 8 hours following IMP infusion.

10.1.4 Open-label avalglucosidase alfa long-term follow-up phase

10.1.4.1 Every 2 weeks (Biweekly)

The following will be performed every 2 weeks starting at the date of the first infusion of the follow-up phase (Week 51 and then W53, W55, W57, W59, W61, W63, W65, W67, W69, W71, W73, W75, W77, W79, W81, W83, W85, W87, W89, W91, W93, W95, W97, W99, W101, W103, W105, W107, W109, W111, W113, W115, W117, W119, W121, W123, W125, W127, W129, W131, W133, W135, W137, W139, W141, W143 and W145):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;

- AE collection;
- Prior/concomitant medications.

10.1.4.2 One week following first infusion in open-label phase (Week 52)

The following will be performed 1 week following the date of the first infusion of the follow-up phase:

- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications.

10.1.4.3 Every 4 weeks

The following assessments will be performed every 4 weeks (W53, W57, W61, W65, W69, W73, W77, W81, W85, W89, W93, W97, W101, W105, W109, W113, W117, W121, W125, W129, W133, W137, W141 and W145):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight (for pediatric patients only);
- Urine pregnancy test (females of childbearing potential only);
- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients) (monthly through Week 73);
- AE collection;
- Prior/concomitant medications.

10.1.4.4 Every 12 weeks

The following assessments will be performed every 3 months (W61, W73, W85, W97, W109, W121, W133 and W145):

- Urine pregnancy test (females of childbearing potential only);
- Body weight;
- IRT contact for treatment kits allocation;
- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients);

- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications.

10.1.4.5 At 12 weeks, 24 weeks, and then every 24 weeks

The following assessments will be performed at Week 61, Week 73, Week 97, Week 121, and Week 145:

- Physical examination (inclusive of head circumference and Tanner stage for pediatric patients only at Week 97, Week 145);
- Urine pregnancy test (females of childbearing potential only);
- Body weight;
- IRT contact for treatment kits allocation;
- Height (for pediatric patients only and for adult patients only at Week 97 and Week 145);
- Hematology, biochemistry, and urinalysis;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- ECG;
- Vital signs (before, during, and following infusion);
- Exploratory biomarker urine sample collection;
- Exploratory biomarker DBS and plasma sample collection;
- Plasma sample collection for microRNA analyses;
- Urine Hex4 sample collection;
- SF-12 (patients ≥18 years of age at screening/baseline);
- EQ-5D-5L (patients ≥18 years of age at screening/baseline);
- PedsQL (patients <18 years of age at screening/baseline);
- PDSS/PDIS (patients ≥18 years of age at screening/baseline, via an e-diary daily for 2 weeks between visits);
- R-PAct (patients ≥18 years of age at screening/baseline);
- PGIC (patients ≥18 years of age at the concerned visit, annually);
- PFT;
- 6MWT;
- GSGC;

- GMFM-88/GMFCS;
- QMFT;
- HHD (not applicable for Canadian sites, see Appendix C Section 17.3.3);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications;
- IRT call for end of treatment (Week 145 for patients not entering the extended open-label avalglucosidase alfa long-term follow-up phase only).

10.1.5 Extended open-label avalglucosidase alfa long-term follow-up phase

10.1.5.1 Biweekly

The following assessments will be performed every 2 weeks, starting at Week 147 and up to 144 additional weeks (W147, W149, W151, W153, W155, W157, W159, W161, W163, W165, W167, W169, W171, W173, W175, W177, W179, W181, W183, W185, W187, W189, W191, W193, W195, W197, W199, W201, W203, W205, W207, W209, W211, W213, W215, W217, W219, W221, W223, W225, W227, W229, W231, W233, W235, W237, W239, W241, W243, W245, W247, W249, W251, W253, W255, W257, W259, W261, W263, W265, W267, W269, W271, W273, W275, W277, W279, W281, W283, W285, W287, W289) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications.

10.1.5.2 Every 4 weeks (Monthly)

The following assessments will be performed every 4 weeks, starting at Week 149 and up to 144 additional weeks (W149, W153, W157, W161,W165, W169, W173, W177, W181, W185, W189, W193, W197, W201, W205, W209, W213, W217, W221, W225, W229, W233, W237, W241, W245, W249, W253, W257, W261, W265, W269, W273, W277, W281, W285, W289) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;

- Vital signs (before, during, and following infusion);
- Body weight (for pediatric patients only);
- Infusion of avalglucosidase alfa;
- Urine pregnancy test (females of childbearing potential only);
- AE collection;
- Prior/concomitant medications.

10.1.5.3 Every 12 weeks (Quarterly)

The following assessments will be performed every 12 weeks, starting at Week 157 and up to 144 additional weeks (W157, W169, W181, W193, W205, W217, W229, W241, W253, W265, W277, W289) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications.

10.1.5.4 Every 24 weeks (every 6 months)

The following assessments will be performed every 24 weeks, starting at Week 169 and up to 144 additional weeks (W169, W193, W217, W241, W265, W289) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;

- Prior/concomitant medications;
- Height (in pediatric patients only);
- Hematology, biochemistry, and urinalysis;
- PFT;
- 6MWT;
- SF-12 (patients ≥18 years of age at screening/baseline);
- EQ-5D-5L (patients ≥18 years of age at screening/baseline);
- PDSS/PDIS (patients ≥18 years of age at screening/baseline, via an e-diary daily for 2 weeks between visits);
- R-PAct (patients ≥18 years of age at screening/baseline).

10.1.5.5 Every 48 weeks (Yearly) and end of treatment visit

The following assessments will be performed every 48 weeks, starting at Week 193 and up to 144 additional weeks after Week 145 (W193, W241, W289) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications;
- Height;
- Hematology, biochemistry, and urinalysis;
- ECG;
- PFT;
- 6MWT;
- SF-12 (patients ≥18 years of age at screening/baseline);
- EQ-5D-5L (patients ≥18 years of age at screening/baseline);
- PedsQL (patients <18 years of age at screening/baseline);
- PDSS/PDIS (patients ≥18 years of age at screening/baseline, via an e-diary daily for 2 weeks between visits);

- R-PAct (patients ≥18 years of age at screening/baseline);
- PGIC (patients ≥18 years of age at the concerned visit).

10.1.6 End of study

The following assessments will be performed at the end of study visit/contact (2 to 4 weeks after last infusion):

- AE collection;
- Prior/concomitant medications.

10.1.7 Visit schedule for pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase (starting after screening period)

Pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase will have the following procedures performed starting at Day of first infusion. Day of first infusion should occur within 1 to 14-day after screening/baseline. All subsequent visits are calculated from day of first infusion of IMP in 14-day increments with a window of ±7 days for infusions and safety assessments, and ±14 days for all other assessments.

- IRT contact to inform identification of potential patient and initiation of IMP shipment for each patient

Information regarding the pre-study IRT contact can be found in the IRT manual.

10.1.7.1 Day of first infusion (Day 1/Day 2) (pediatric patients enrolling directly in the open-label follow-up phase)

The following will be performed on the day of randomization (Day 1), or day following randomization (Day 2) to allow preparation of the IMP for infusion:

- Inclusion/exclusion criteria;
- Urine pregnancy test (females of childbearing potential only);
- Body weight;
- 12-lead ECG (triplicate);
- Vital signs (before, during, and following infusion);
- Urine Hex4 sample collection;
- Exploratory biomarker urine sample collection;
- Exploratory biomarker DBS and plasma sample collection;
- Plasma sample collection for microRNA analyses;
- IRT contact to confirm patient enrollment and treatment kits allocation;
- PK plasma sample collection (before and following infusion);

- Infusion of IMP;
- AE collection;
- Prior/concomitant medications.

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

This visit requires a stay at the site prior to and for at least 8 hours following IMP infusion as an in-patient or out-patient, as per hospital/center procedure. A patient card will be provided to the patient once the patient is enrolled (see study manual for details).

10.1.7.2 Open-label avalglucosidase alfa long-term follow-up phase (pediatric patients enrolling directly in the open-label follow-up phase)

10.1.7.2.1 One week following first infusion (Week 2)

The following will be performed 1 week following the date of the first infusion:

- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications.

10.1.7.2.2 Every 2 weeks (Biweekly)

The following will be performed every 2 weeks starting at Week 3 (W3, W5, W7, W9, W11, W13, W15, W17, W19, W21, W23, W25, W27, W29, W31, W33, W35, W37, W39, W41, W43, W45, W47, W49, W51, W53, W55, W57, W59, W61, W63, W65, W67, W69, W71, W73, W75, W77, W79, W81, W83, W85, W87, W89, W91, W93, W95 & W97):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications.

10.1.7.2.3 Every 4 weeks

The following assessments will be performed every 4 weeks (W5, W9, W13, W17, W21, W25, W29, W33, W37, W41, W45, W49, W53, W57, W61, W65, W69, W73, W77, W81, W85, W89, W93 & W97):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);

- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients) (monthly through Week 73, then at W97 only).

10.1.7.2.4 Every 12 weeks until W73 and at W97

The following assessments will be performed every 12 weeks until W73 and at W97 (W13, W25, W37, W49, W61, W73 & W97):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- Hematology, biochemistry, and urinalysis;
- ADAs (with neutralizing antibodies in ADA-positive patients);
- Physical examination (inclusive of head circumference and Tanner stage at W49 & W97);
- Height;
- ECG;
- Exploratory biomarker urine sample collection;
- Exploratory biomarker DBS and plasma sample collection;
- Plasma sample collection for microRNA analyses;
- Urine Hex4 sample collection;
- PedsQL;
- PGIC (patients ≥18 years of age at the concerned visit, at W49 and W97 only);
- PFT;
- 6MWT;

- GSGC;
- GMFM-88/GMFCS;
- QMFT;
- HHD;
- IRT call for end of treatment (Week 97 for patients not entering the extended open-label avalglucosidase alfa long-term follow-up phase only).

10.1.7.3 Extended open-label avalglucosidase alfa long -term follow-up phase (pediatric patients enrolling directly in open-label follow-up phase)

10.1.7.3.1 Biweekly

The following assessments will be performed every 2 weeks, starting at W99 and up to 144 additional weeks (W99, W101, W103, W105, W107, W109, W111, W113, W115, W117, W119, W121, W123, W125, W127, W129, W131, W133, W135, W137, W139, W141, W143, W145, W147, W149, W151, W153, W155, W157, W159, W161, W163, W165, W167, W169, W171, W173, W175, W177, W179, W181, W183, W185, W187, W189, W191, W193, W195, W197, W199, W201, W203, W205, W207, W209, W211, W213, W215, W217, W219, W221, W223, W225, W227, W229, W231, W233, W235, W237, W239, W241) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- AE collection;
- Prior/concomitant medications.

10.1.7.3.2 Every 4 weeks (Monthly)

The following assessments will be performed every 4 weeks, starting at W101 and up to 144 additional weeks (W101, W105, W109, W113, W117, W121, W125, W129, W133, W137, W141, W145, W149, W153, W157, W161, W165, W169, W173, W177, W181, W185, W189, W193, W197, W201, W205, W209, W213, W217, W221, W225, W229, W233, W237, W241) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Body weight (for pediatric patients only);
- Infusion of avalglucosidase alfa;

- Urine pregnancy test (females of childbearing potential only);
- AE collection;
- Prior/concomitant medications.

10.1.7.3.3 Every 12 weeks (Quarterly)

The following assessments will be performed every 12 weeks, starting at W109 and up to 144 additional weeks (W109, W121, W133, W145, W157, W169, W181, W193, W205, W217, W229, W241) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications.

10.1.7.3.4 Every 24 weeks (every 6 months)

The following assessments will be performed every 24 weeks, starting at W123 and up to 144 additional weeks (W123, W145, W169, W193, W217, W241) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications;
- Height;
- Hematology, biochemistry, and urinalysis;

- PFT;
- 6MWT.

10.1.7.3.5 Every 48 weeks (Yearly) and end of treatment visit

The following assessments will be performed every 48 weeks, starting at W147 and up to 144 additional weeks (W147, W193, W241) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C Section 17.3.4 for definition applicable for UK patients):

- IRT contact for treatment kits allocation;
- Vital signs (before, during, and following infusion);
- Infusion of avalglucosidase alfa;
- Body weight;
- Urine pregnancy test (females of childbearing potential only);
- ADAs (with neutralizing antibodies in ADA-positive patients);
- AE collection;
- Prior/concomitant medications;
- Height;
- Hematology, biochemistry, and urinalysis;
- ECG;
- PFT;
- 6MWT;
- PGIC (patients ≥18 years of age at the concerned visit).

10.1.7.4 End of study (pediatric patients enrolling directly in the open-label follow-up phase)

The following assessments will be performed at the end of study visit/contact (2 to 4 weeks after last infusion):

- AE collection;
- Prior/concomitant medications.

10.1.8 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 will be reported/collected in the clinical database.
- In exceptional circumstances, if a visit is missed during the course of the study, the following should be followed:
  - If safety assessments/procedures should have been performed during that missed visit, they will be performed at the next visit, even if none was planned, using unscheduled lab kits for any lab samples.
  - If efficacy assessments/procedures should have been performed during that missed visit (ie, V9/Week 13, V15/Week 25, V21/Week 37, V27/Week 49, V34/Week 61, V40/Week 73, V52/Week 97, V64/Week 121 [not applicable for pediatric patients aged 3 to <18 directly enrolled in the open-label long-term follow-up phase], V76/Week 145 [not applicable for pediatric patients aged 3 to <18 directly enrolled in the open-label long-term follow-up phase], or any every 24 weeks visit of the extended open-label long-term follow-up phase), they will be performed at the earliest possible date (which might exceed the authorized window) and will still be associated with the visit that was missed (see CRF completion guidelines for details regarding the CRF completion in this case). In these instances, this will not be considered a deviation but should be clearly documented in the patient's file. Refer to Section 9.1.1 for details on PFT when missed.
- Visits that are longer due to multiple assessments or procedures (eg, motor assessments and multiple questionnaires) may be carried out over 2 days. In any case, IMP

administration should be the last procedure and the appropriate time needed for post-infusion surveillance will be taken into account.

- Postbaseline PFT should meet the ATS/ERS 2005 quality standards. However, if no acceptable efforts can be recorded during the upright position PFT with up to 8 efforts, an additional PFT may be scheduled as soon as possible no later than 45 days after this failed planned test, if this is feasible for the patient. The highest acceptable effort will be kept in the database.
- In addition, if the patient did not perform the PFT at a planned visit, the patient should be reminded to perform the PFT test as soon as possible no later than 45 days after the missed test, if it is feasible for the patient to perform the test within this period.

10.1.9 Follow-up for patients who temporarily or permanently discontinued the study treatment

- For those patients who discontinued treatment prior to the scheduled Week 49 visit, assessments related to the primary and secondary efficacy and safety endpoints will be performed every 3 months (ie, at Week 13, 25, 37, 49) if not done previously based on original protocol schedule (ie, PFT, 6MWT, SF-12, HHD, QMFT, AE, prior/concomitant medications, ECG, vital signs, laboratory tests [Urine pregnancy test (females of childbearing potential only), hematology, biochemistry, urinalysis, ADAs (with neutralizing antibodies in ADA-positive patients), exploratory biomarker urine sample collection, exploratory biomarker DBS and plasma sample collection, plasma sample collection for microRNA analyses, urine Hex4 sample collection], physical examination, body weight and height) (refer to Section 10.1.3.5).
- For those patients who discontinued treatment after the scheduled Week 49 visit but before Week 145 visit:
  - In case of permanent discontinuation: assessments corresponding to Week 145 as outlined in Section 10.1.4.5 will be performed if possible.
  - In case of temporary discontinuation: study visits can be adapted to visits when laboratory and/or clinical testing are scheduled, as much as possible, as long as the assessment time windows in the study protocol are respected.
- For those patients who discontinued treatment during the extended open-label avalglucosidase alfa long-term follow-up phase:
  - In case of permanent discontinuation: assessments corresponding to the end of treatment visit as outlined in Section 10.1.5.5 and Section 10.1.7.3.5 will be performed if possible.
  - In case of temporary discontinuation, 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 and the patient come to visits when laboratory and/or clinical testing are scheduled, as much as possible, as long as the assessment time windows in the study protocol are respected.

- 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 or permanently withdrawn from treatment.
- Patients need to be assessed 4 weeks post last infusion. However, this 4-weeks post-infusion safety assessment may be combined with the regular scheduled visits indicated here (refer to Section 10.1.5 and Section 10.1.7).
- For patients permanently discontinued from study treatment, Investigator must perform end of treatment call to IRT.
- For further guidance on handling of patient discontinuation, refer to Section 10.3.

10.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the e-CRF must be supported by appropriately identified source documentation. The results of certain examinations or evaluations recorded in the e-CRF 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 or equivalent IMP room 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 e-CRF. 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;
- 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 (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(s) 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 pages of the e-CRF. Visit and assessment schedules will be adapted to the absence of infusion of IMP (refer to Section 1.2 and Section 10.1.9).

Temporary treatment discontinuation decided by the Investigator corresponds to 1 or more doses not administered to the patient.

All efforts should be made to continue to follow the patients for primary and key secondary endpoints, after the temporary treatment discontinuation.

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 AE not related to the patient's underlying condition.
- More than 1 AE rated severe, not related to the patient's underlying condition, for which the relationship to treatment cannot be reasonably excluded.

- Any increase in ALT, AST, total bilirubin, or alkaline phosphatase >3x the baseline value, except if the increased value is still in the normal range.
- Any increase in ALT or AST >3x the upper limit of normal (ULN), in the presence of total bilirubin >2x ULN.
- Any AE that, in the opinion of the Investigator or Sponsor, raises significant concerns regarding the safety of the IMP administered dose.

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 IMP related death.

After consideration of DMC recommendations, final decisions for discontinuation of study drug for all or selected clinical trial patients and for not dosing new 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 and to not dose new patients prior to receipt of a DMC recommendation. Investigational sites will be notified within 24 hours of the Sponsor's notification of the event(s).

If a temporary discontinuation of study drug occurs while one or more patient is currently in their screening period, this screening period might be extended (see Section 10.1.2).

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 List of criteria for permanent treatment discontinuation

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 reason(s) for treatment discontinuation and this should be documented in the e-CRF.

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.

Any code-breaking requested by the Investigator will lead to a permanent treatment discontinuation of the patient for whom the code was broken (see Section 8.3.2).

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol (see Section 10.1.9), or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Since the primary study comparison is based on intent-to-treat principle using all randomized patients with any study treatment, missing data, especially the key study assessments during the PAP (Week 49) may potentially lead to biased results and challenges in assessing the treatment effect of the study drug. Therefore, all efforts should be made to continue to follow the patients for primary and key secondary endpoints, after a permanent discontinuation of treatment, in addition to the 4-weeks post-treatment safety follow-up. At the minimum, patients should be assessed at their regularly scheduled Week 49 visit (or as close as possible to Week 49 even if it may be outside of visit window) if treatment discontinuation occurred prior to that visit.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed by documenting the reason(s) for treatment discontinuation.

Patients who permanently discontinue study treatment and who will be switched to commercial alglucosidase alfa will be withdrawn from the study.

In the event that a patient dies, permission will be sought (through a separate informed consent form) for a research autopsy or post mortem research biopsy. Samples collected from these procedures will be used for research purposes only and data will not be included in any study analyses.

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 without any effect on their care. Discontinuation of study 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. Therefore, if patients no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining visits (see Section 10.3.4). The value of critical study data collected during their continued involvement will be emphasized as important to the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the last visit of the PAP (Week 49) including a PK sample, if appropriate, or if the patient withdraws from the study after the scheduled Week 49 visit, using the procedures normally planned for the last dosing day with the IMP (Week 145 in the open-label avalglucosidase alfa long-term follow-up phase or end of treatment visit in the extended open-label avalglucosidase alfa long-term follow-up phase). Patients need to be assessed 4 weeks post last infusion. However, this 4 weeks post-infusion safety assessment may be combined with the regular scheduled visits indicated here (refer to Section 10.1.6).

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.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review 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 (SAP) 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 rerandomized (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 in-patient 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 medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

10.4.1.3 Adverse event of special interest

An AE of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

AESIs will include:

- IARs:

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 10.6 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.

- Symptomatic overdose (serious or nonserious) with IMP:
  - 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 protocol-defined therapeutic interval (see Section 8.1), adjusted according to the tested drug.
    Of note, asymptomatic overdose has to be reported as a standard AE.
- Clinical laboratory (change from baseline):
  - ALT or AST increase of ≥3 x 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 and within 24 hours, using the AE form together with the SAE complementary form to be entered in the e-CRF.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, 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 page(s) or screen(s) of the e-CRF.
- 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 study treatment, 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 study treatment or by the study procedure(s).
- If the Investigator assesses the AE related to study treatment and the Investigator cannot reasonably explain the AE by other factors (such as clinical state, concomitant therapy, and /or other interventions) or if the cause of the AE is unknown by the Investigator, the relationship to study treatment must be checked “Related” by the Investigator.

- The Investigator should check “Not Related” when there is a clear alternative cause to the event other than the study treatment according to the Investigator.

There is 1 exception to this rule. In instances where a patient experiences an IAR (refer to Section 10.6), allergic, or anaphylactic reaction, either during infusion or postobservation 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 PP, 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

Instructions for AE reporting are summarized in Table 2.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- All further data updates should be recorded in the e-CRF as appropriate within 24 hours of knowledge of the SAE. 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 is available and should be used when the e-CRF 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

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF. Instructions for AE reporting are summarized in Table 2.

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, 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).

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix B (Section 17.2).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia,
- Thrombocytopenia,

- ALT increase,
- Acute renal insufficiency.

Refer to Section 10.4.1.3 for specific laboratory abnormalities that are identified as AESIs.

Table 2 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
AE (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
SAE (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
		Death	Yes	Yes	Yes
AESI	Expedited (within 24 hours)	IAR	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	Yes
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT≥ULN)	Yes	Yes	Yes
		AST≥3 ULN (if baseline AST<ULN) and AST≥2 x baseline (if baseline AST≥ULN)	Yes	Yes	No
		ALT ≥400 IU/L or AST ≥500 IU/L, or increase in direct, indirect, or total bilirubin ≥2 x ULN	Yes	Yes	Yes
		Serum creatinine >1.5 x baseline (if final creatinine >ULN)	Yes	Yes	No

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AST = aspartate aminotransferase; ALT = alanine aminotransferase; IAR = infusion-associated reaction; IU/L = international units per liter; SAE = serious adverse event; ULN = upper limit of normal.

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 regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Adverse events that are considered expected will be specified by the reference safety information (IB for avalglucosidase alfa and label for alglucosidase alfa).

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

10.6 SAFETY INSTRUCTIONS

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 IB (Sections 7.1.2 and 7.1.3) for further guidance on the management of IARs.

Moderate, severe, and recurrent mild IARs will be discussed with the DMC. If the DMC recommends or suggests that a desensitization procedure to the IMP could be proposed to the patient, in agreement with the Investigator, such a procedure may be initiated as per pharmacy manual guidelines. Depending on the phase of the study the patient will be in at the time of the desensitization procedure, this one may be blinded (if the procedure is started when the patient is still in the double-blind phase) or unblinded (if the procedure is started when the patient is in one of the open-label phases).

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 cardiopulmonary resuscitation 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.

10.7 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

11.1 DETERMINATION OF SAMPLE SIZE

Sample size calculations are based on the primary efficacy endpoint of change from baseline to Week 49 in FVC (% predicted) upright position, with the following assumptions:

- Normal distribution for the endpoint with a common SD of 5.1% predicted, which is estimated based on the data from previous trials (AGLU02704-LOTS),
- Mean treatment difference (avalglucosidase alfa – alglucosidase alfa) of 2.0% predicted, assumed based on a conservative estimate when comparing studies AGLU02704-LOTS and TDR12857,
- A 2-sided 5% significance level,
- Expected percent of missing data = 10%,
- An NI margin of 1.1%, which is based on the estimated alglucosidase alfa effect from the placebo-controlled study (AGLU02704-LOTS). The proposed margin represents approximately 50% of the lower bound of the 80% confidence interval for the alglucosidase alfa versus placebo treatment effect.

A total sample size of 96 (1:1 randomization ratio) will provide approximately 80% power to demonstrate NI of avalglucosidase alfa versus alglucosidase alfa, when the true difference (avalglucosidase alfa – alglucosidase alfa) is 2.0% predicted. If the NI criterion is met, a test for superiority will be performed. If the true difference between avalglucosidase alfa and alglucosidase alfa is 3.5% predicted (as suggested based on cross-study comparisons between AGLU02704-LOTS and TDR12857), the study will have at least 85% power to demonstrate superiority of avalglucosidase alfa to alglucosidase alfa.

Calculations were made using East 6.3 software.

11.2 DISPOSITION OF PATIENTS

Screened patients will be defined as any patient who has signed the informed consent form. Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

11.3 ANALYSIS POPULATIONS

The randomized population will include any patient who had been allocated to a randomized treatment arm regardless if study drug was administered.

11.3.1 Efficacy populations

The **mITT population** will include randomized patients who receive at least 1 infusion (partial or total). The mITT population will be used for all efficacy analyses unless otherwise specified. Analyses using the mITT population will be performed according to the treatment arm allocated by randomization and not actual treatment received.

The **PP population** will be a subset of the mITT population who have no major protocol deviations that are expected to interfere with assessments of the primary efficacy endpoint. This population will be used for sensitivity analyses and described with more detail in the SAP.

11.3.2 Safety population

The **safety population** will include patients who receive at least 1 infusion (partial or total). The safety population will be analyzed according to which treatment was received, unless otherwise specified.

11.3.3 Extension treatment population

The **extension treatment population** will consist of patients who receive at least 1 avalglucosidase alfa dose (partial or total) during the extension treatment period.

11.4 STATISTICAL METHODS

Unless otherwise specified, efficacy analyses will use the mITT population, where patients will be considered to be in the treatment group to which they were randomized. Safety analyses will use the safety population, where patients will be considered to be in the treatment group of the treatment they actually received.

For all analyses, the avalglucosidase alfa treatment group will be compared to the alglucosidase alfa group. While the primary comparison of interest is at 12 months (49 weeks), all summary statistics will be computed and displayed by treatment group and each scheduled assessment time as well. Summary statistics for continuous variables will minimally include n, mean, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Unless otherwise specified, all baseline values will be defined as the last non-missing value prior to randomization.

11.4.1 Extent of study treatment exposure and compliance

11.4.1.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure and compliance will be assessed and summarized within the first 12-month double-blind period for the safety population.

Duration of IMP exposure is defined as the last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, mean, SD, median, min, and max). The percentage of patients with compliance is <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be provided.

Treatment exposure beyond the 12-month double-blind period will be summarized separately.

11.4.2 Analyses of efficacy endpoints

Efficacy endpoints and assessments are provided in Section 9.

11.4.2.1 Analysis of primary efficacy endpoints

Refer to Section 9.1.1 for details on this endpoint.

The primary efficacy endpoint of change from baseline in FVC (% predicted) in upright position to Week 49 will be analyzed in the mITT population using an MMRM with change from baseline as outcome variable. The MMRM model will include the baseline FVC (% predicted) and age (both as continuous variables), gender (male, female), treatment group, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance matrix shared across treatment groups will be used to model the within-patient error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The model will be fitted using restricted maximum likelihood. The difference between treatment groups will be estimated based on least-square means at the Week 49 visit within the MMRM model.

The primary analyses will be performed after all mITT patients have been followed for at least 12 months after randomization. This analysis will include all post-baseline assessments up to Week 49, regardless of treatment discontinuation status; missing data will not be imputed and will be assumed to be missing-at-random (MAR).

The primary statistical objective is to test the NI of avalglucosidase alfa versus alglucosidase alfa at 5% level of significance. The null and alternative hypotheses based on an NI margin of 1.1 are described as H_{01} and H_{a1} below:

- H_{01}: avalglucosidase alfa – alglucosidase alfa $\leq$-1.1 versus H_{a1}: avalglucosidase alfa – alglucosidase alfa >-1.1

The study will be considered to have met its primary statistical objective if the NI null hypothesis (H_{01}) is rejected, or the lower bound of the 2-sided 95% confidence interval for the least square mean difference of avalglucosidase alfa – alglucosidase alfa is >-1.1.

After NI is demonstrated, a test for superiority of avalglucosidase alfa versus alglucosidase alfa will be performed with an overall 5% level of significance.

If the superiority null hypothesis of no difference between avalglucosidase alfa and alglucosidase alfa is rejected, and the point estimate for the difference favors avalglucosidase alfa, the statistical superiority of avalglucosidase alfa versus alglucosidase alfa can be claimed.

The same analysis as described above will be performed for the PP population to assess the robustness of the study outcome.

A US FDA-specific primary analysis will be conducted using the method described above for those patients in the mITT population 8 years of age or older in order to match the lower age range of patients in the LOTS trial of alglucosidase alfa.

Sensitivity analyses will be performed to assess the impact of missing data.

Additional supportive analyses for the primary efficacy endpoint will be performed, including subgroup analyses based on age, gender, and baseline FVC.

11.4.2.2 Analyses of secondary efficacy endpoints

Refer to Section 9.2.1 for details on these endpoints.

The secondary efficacy endpoints are change from baseline at week 49 for the following parameters:

- 6MWT distance walked (in meters);
- MIP and MEP% predicted;
- Lower extremity muscle strength (HHD);
- Motor function as assessed by QMFT;
- Health-related quality of life as assessed by SF-12.

Each of the secondary endpoints will be analyzed based on the MMRM model, similar to that described for the primary endpoint (the model will be further adjusted by baseline score of corresponding parameter), using the mITT population (with the exception of SF-12, which will be analyzed for a subset of mITT patients with age ≥18). The difference between treatment group will be assessed with least square mean difference at Week 49 estimated within the framework of MMRM model. P-value and corresponding 2-sided 95% CI will be provided.

For 6MWT endpoint, the statistical objective is to demonstrate the superiority of avalglucosidase alfa versus alglucosidase alfa.

For MIP and MEP, the primary analysis will be based on % predicted value in upright position.

For HHD, the primary analysis is based on the lower extremity summary score. For QMFT, the primary analysis is based on the total score, while each individual item score will be summarized descriptively. For SF-12, the PCS and MCS scales will be analyzed separately.

See Section 11.4.2.3 for consideration of multiplicity.

For the Canada-specific requirement regarding HHD refer to Appendix C Section 17.3.3.

11.4.2.3 Multiplicity considerations

The primary efficacy endpoint (FVC% predicted change from baseline) will be tested for NI of avalglucosidase alfa versus alglucosidase alfa first. After the NI is demonstrated, the superiority of the avalglucosidase alfa versus alglucosidase alfa will be tested with the same overall 5% significance level.

After the superiority of avalglucosidase alfa versus alglucosidase alfa is demonstrated on the primary efficacy endpoint, the hypothesis testing for the secondary efficacy endpoints will proceed in a hierarchical fashion using the closed testing principle, and will stop if significance level of 5% is not achieved. Testing will proceed according to the following sequence:

1. 6MWT change from baseline to Week 49 (superiority test),
2. % predicted change from baseline to Week 49 for MIP (superiority test),
3. % predicted change from baseline to Week 49 for MEP (superiority test),
4. HHD (lower extremity summary score) change from baseline to Week 49 (superiority test).

Analysis of additional secondary endpoints will be considered for supportive purposes.

For the Canada-specific requirement regarding HHD, refer to Appendix C Section 17.3.1.

11.4.3 Open-label avalglucosidase alfa long-term follow-up phase

Efficacy data during the extension treatment phase will be summarized descriptively for each of the efficacy parameters through the last visit (up to the end of the extended open-label avalglucosidase alfa long-term follow-up phase). For the primary efficacy endpoint, the effect of switching treatment will be assessed for those patients who switched from alglucosidase alfa to avalglucosidase alfa during the extension period. For patients who receive avalglucosidase alfa throughout the blinded treatment phase, as well as the long-term follow-up phase, long-term effect of avalglucosidase alfa will be assessed.

11.4.4 Analyses of safety data

Refer to Section 9.2.2 for details on these endpoints.

The summary of safety results will be presented by treatment group.

All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before randomization.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

Unless otherwise specified, primary safety analyses will be based on first 12 months of PAP for comparability of treatment effect. Data during the open-label period (beyond 12 months) will be summarized separately (by original treatment group as well as combined).

In addition, for patients who receive avalglucosidase alfa throughout the blinded treatment phase, as well as the long-term follow-up phase, long-term safety will be assessed using all data during the 2 periods.

11.4.4.1 Adverse events

All AEs will be coded using the most recent version of the MedDRA.

Adverse event observation period:

- Pre-treatment AEs are defined as those AEs that developed or worsened prior to the 1st study treatment.
- On-treatment AEs are defined as those AEs that developed or worsened between the 1st study treatment date to the last study treatment date + 4 weeks.
- Post-treatment AEs are defined as those AEs that developed or worsened after the on-treatment period.

On-study period will include pre-treatment, on-treatment, and post-treatment period. Treatment-emergent AEs for analysis purpose will include all on-treatment AEs.

Unless otherwise specified, the primary analysis of AEs will be based on TEAEs with onset date within the first 12 months PAP. Similar descriptive summaries will be performed for the

long-term follow-up period (after 12 months) separately based on those TEAEs with onset date beyond 12 months of double-blind period. A pooled AEs summary using all TEAEs during the avalglucosidase alfa exposure period will be provided as well.

Post-treatment AEs will be summarized separately.

The incidence of TEAEs, AESI (including IARs), will also be tabulated (frequencies and percentages) 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 1 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, IARs, and AESIs for all patients will be provided, which will include severity and relationship to treatment, as well as actions taken regarding treatment, and patient outcome.

The incidence of AEs leading to study discontinuations will also be summarized by treatment group, with details provided in the listing.

Death: The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) by primary SOC, high level group term (HLGT), high level term (HLT) and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.4.2 Clinical laboratory tests

Observed measurements and changes from baseline to study time points in biochemistry, hematology, 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. Individual listings of patients with potentially clinically significant abnormalities will be presented.

11.4.4.3 Physical examination, vital signs, and electrocardiogram

Potentially clinically significant findings observed during the TEAE observation period for vital signs (including but not limited to blood pressure, heart rate, respiratory rate, etc) and ECG (QTc, PR interval, etc) will be summarized by treatment group. Listings of abnormal findings/values from these data as well as from physical examination inclusive of body weight and height, as well as head circumference and Tanner stage in pediatric patients, will be presented.

11.4.4.4 Anti-avalglucosidase alfa antibodies, neutralizing antibodies, and other immunogenicity testing

Percentage of patients who seroconverted to avalglucosidase alfa, time to seroconversion and peak anti-avalglucosidase alfa antibody titer will be summarized by treatment group using summary statistics. Anti-avalglucosidase alfa 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, 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.

11.4.5 Analyses of pharmacokinetic and pharmacodynamic variables

The list of PK parameters is listed in Section 9.3.2.4.

Pharmacokinetic exposures (C_{max} and $AUC_{0\text{-}last}$) for avalglucosidase alfa and alglucosidase alfa may be determined using non-compartmental analysis. If data allows, total body clearance of a drug (CL), and Vss will be determined. If data do not lend to non-compartmental analysis, model-based approaches such as nonlinear mixed effects modeling may be used. Values will be reported for individual patient s and summarized using descriptive statistics by study week as appropriate.

To evaluate the effect of immunogenicity on the PK of avalglucosidase alfa, pre-dose immunoglobulin G (IgG) and neutralizing antibody titers for each patient will be analyzed graphically with respect to PK parameter for Week 1 (Day 1/Day 2), Week 13, Week 25, Week 37, and Week 49. If relationships are apparent, further quantitative/statistical analysis may be performed (eg, statistical significance, correlation coefficients).

Pharmacodynamic endpoints as described in Section 9.3.4 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 PD endpoint is observed, longitudinal model may be employed to model change from baseline over time. In addition, 95% confidence intervals of changes will be presented.

Urine Hex4 levels normalized by creatinine 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% confidence intervals of changes will be presented.

Correlation between PK endpoints and Hex4 levels may be explored as appropriate.

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

11.4.6 Analyses of patient reported outcomes (health-related quality of life/health economics variables and Patient Global Impression of Change [PGIC])

Refer to Section 9.3.5 for details on these endpoints.

The 18 questions for the R-PAct will be scored according to the 0 (unable to perform) to 2 (able to perform without difficulty) Likert scale and will have a descriptive analysis by treatment group.

Scores for the PDSS and PDIS will be calculated separately for each questionnaire, as well as a composite score for both questionnaires together. The analysis will be descriptive and separated by treatment group.

Further details on the scoring algorithms will be provided in the SAP.

PGIC total score will be summarized descriptively by treatment group at each of the scheduled visits. Correlation of PGIC and primary and key secondary endpoints will be explored.

11.5 INTERIM ANALYSIS

No interim analysis is planned during the double-blinded PAP (refer to Section 6.2.1 for the details of the different periods). Note that the primary analysis for the study is performed at the end of PAP, when the database will be locked and a study report will be produced for regulatory submission. The study will continue for additional 2 years (open label long-term extension) and an additional extension period of up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.3 for patients in Canada and Section 17.3.4 for definition applicable for UK patients) and a final database lock will occur at the end of extension period, with a corresponding final study report generated.

After the primary analysis for PAP is completed, interim analyses may be performed during the open-label extension period to provide additional information for regulatory purpose. However, those additional analyses after PAP will be considered for supportive purpose and no significance level will be allocated to for analyses after the completion of PAP.

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 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 e-CRF 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 eCRF.

- 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 [17]) and/or ethnicity (various drugs [18]).

- 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 (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 data sets 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 to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of Health Authorities (competent regulatory authority) of an amendment, as required by local regulation, 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 case of substantial amendment to the clinical trial protocol, approval from the Health Authorities (competent regulatory authority) will be sought before implementation.

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

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17 APPENDICES

17.1 APPENDIX A: GUIDANCE ON CONTRACEPTIVE METHODS AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS

Woman of childbearing potential (WOCB)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

CONTRACEPTIVE GUIDANCE

Male patients

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 6.2):
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 3 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame)
- Refrain from donating sperm for the duration of the study and for 1 month after the last dose of study treatment
- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 3.

Table 3 - Female Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
Oral[b]
Intravaginal
Transdermal
Progestogen-only hormone contraception associated with inhibition of ovulation
Oral[b]
Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. *b* Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, TWO highly effective methods of contraception should be utilized during the treatment period and for at least 1 month, corresponding to time needed to eliminate study treatment after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male patients with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. This applies only to patients who receive study treatment. After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record

pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

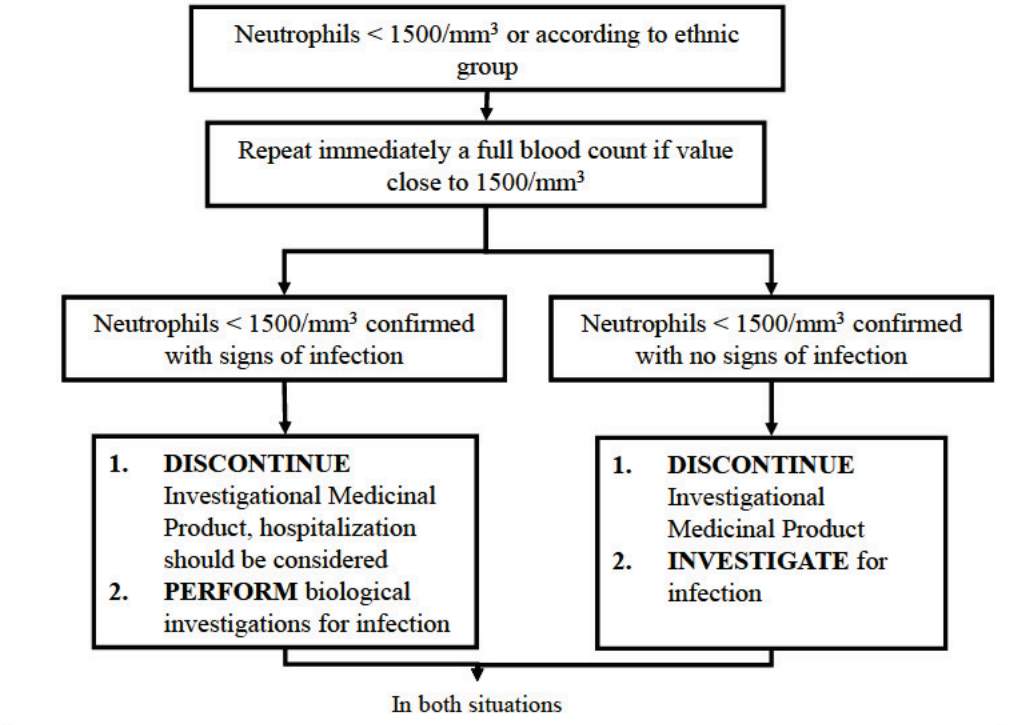
Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any SAE occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.3. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will temporarily discontinue study treatment.

17.2 APPENDIX B: GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI

Note: A final decision regarding permanent discontinuation of IMP will be made by the Sponsor after consideration of DMC recommendations.

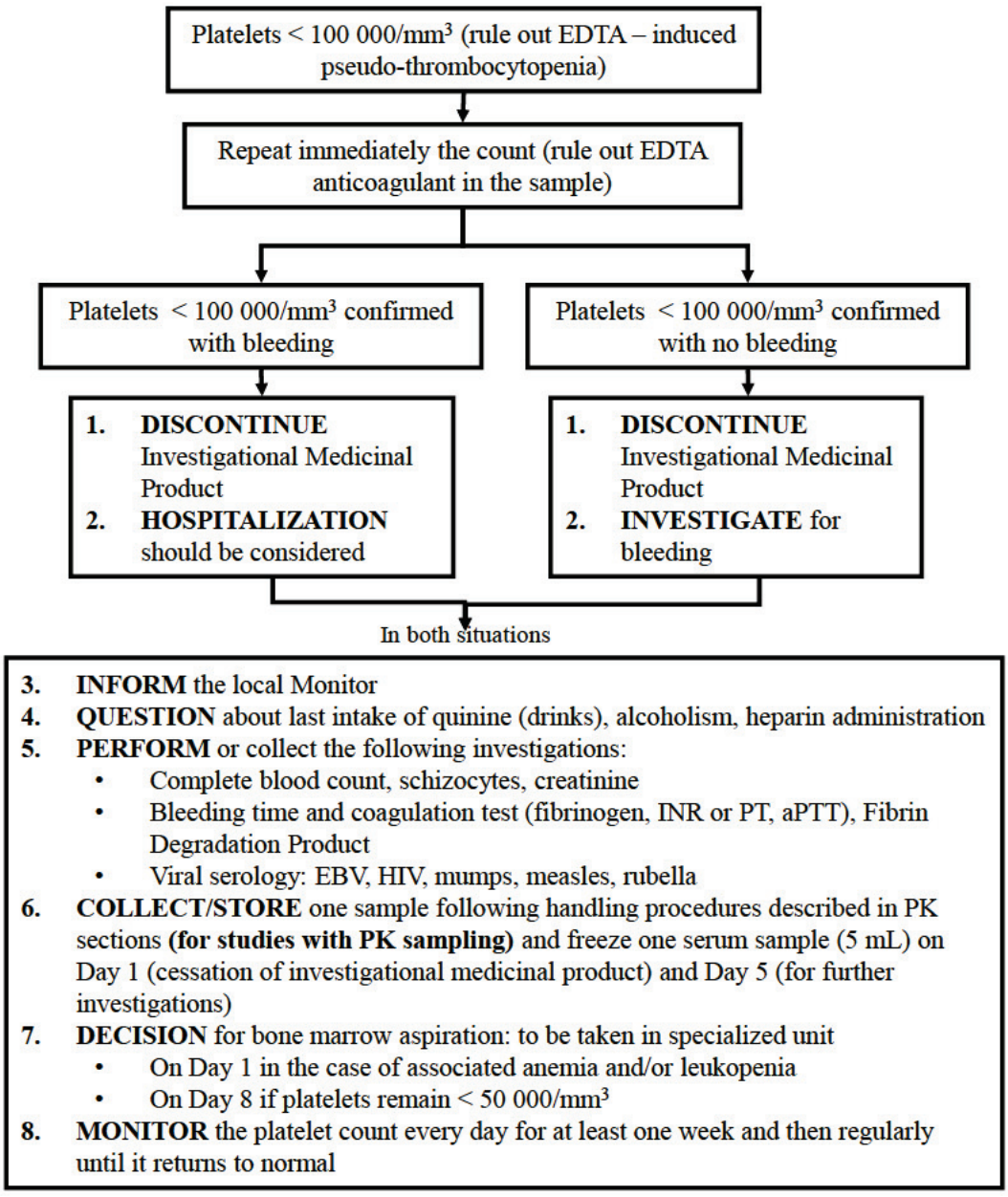
NEUTROPENIA



Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

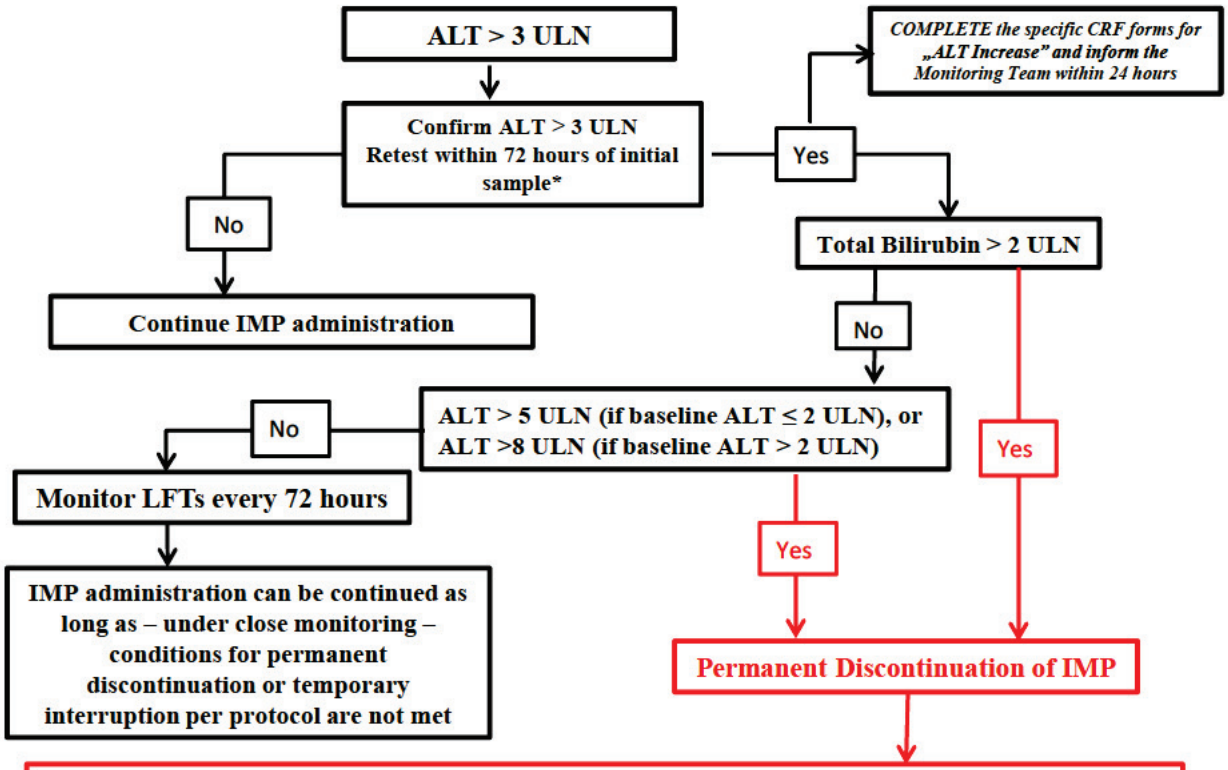
THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

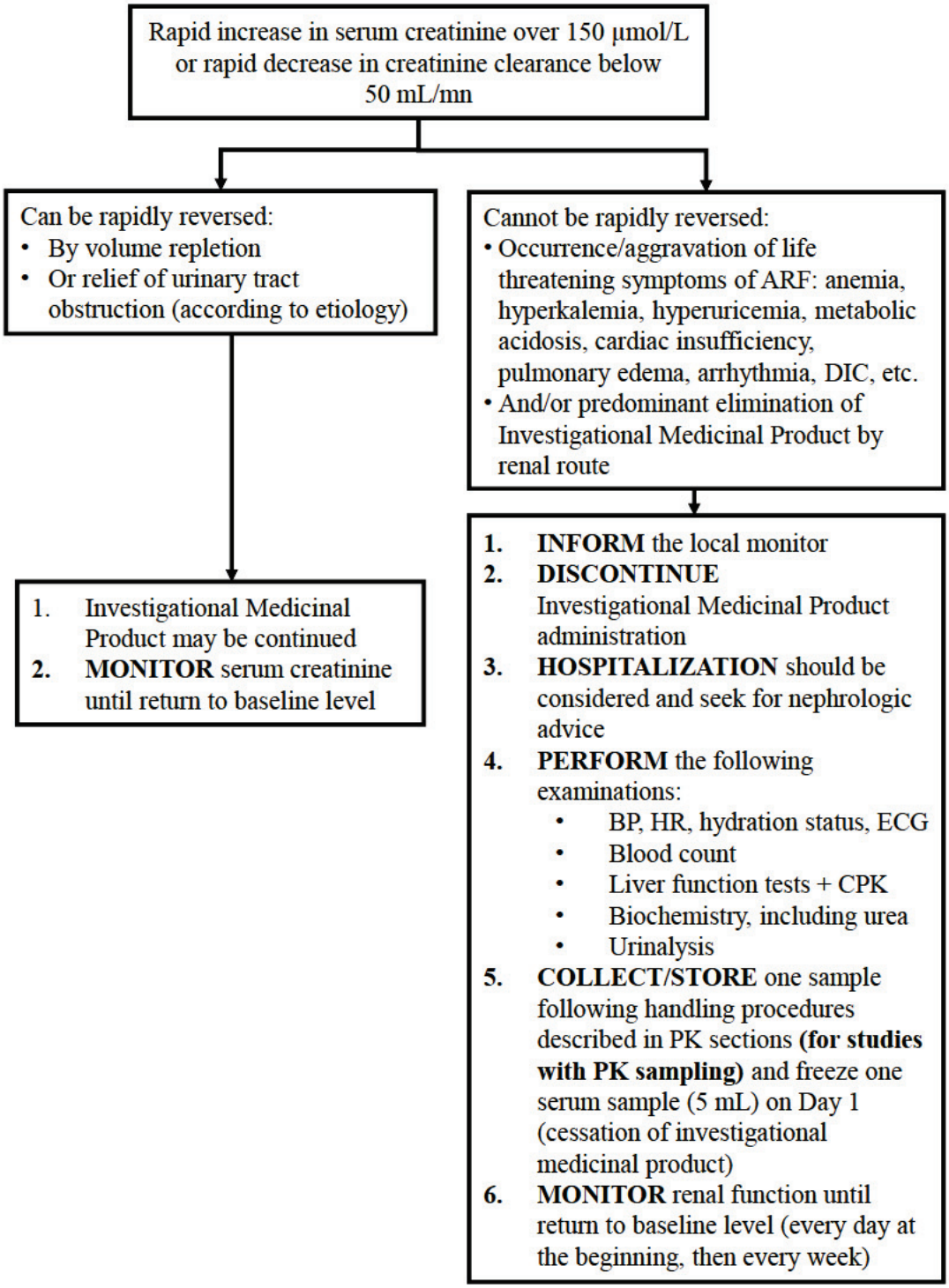
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours**) until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

17.3 APPENDIX C: COUNTRY-SPECIFIC REQUIREMENTS

17.3.1 Sweden

Provided an addendum to the protocol applicable only in Sweden with recommendations related to contraception and pregnancy testing in line with the Clinical Trial Facilitation Group (CTFG) guidance 2014.

www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

The aim of this document was to supplement as part of the protocol the definitions of women of childbearing potential and fertile men and the list of birth control methods which may be considered as highly effective.

Definition of Women of Childbearing Potential and of Fertile Men

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Birth Control Methods Which May Be Considered As Highly Effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (1):
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation (1):
  - oral

  - injectable
  - implantable (2)
- intrauterine device (IUD) (2)
- intrauterine hormone-releasing system (IUS) (2)
- bilateral tubal occlusion (2)
- vasectomized partner (2,3)
- sexual abstinence (4)

1. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3 in the CTFG guidance).
2. Contraception methods that in the context of this guidance are considered to have low user dependency.
3. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
4. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

17.3.2 France

Consistent with the French Health Authority position disallowing home infusion for all ERTs, the option for home infusion added in EFC14028 amended protocol 03 does not apply in France.

17.3.3 Canada

Due to operational challenges with the use of the HHD in Canada, several measures assessed with this device will be missing. Therefore, these assessments (HHD in lower extremity muscle strength [see Section 9.2.1.3] and HHD in upper extremity muscle strength [see Section 9.3.1.3]) will no longer be required in study participants in Canadian sites.

For enrolled patients wishing to start commercial treatment with avalglucosidase alfa in Canada after their participation in the EFC14028 study, and to avoid a treatment gap between the end of treatment visit of the EFC14028 study and the possibility to start commercial treatment with avalglucosidase alfa, the duration of study participation of patients in Canada is defined as follows:

An extended open-label avalglucosidase alfa long-term follow-up period will last up to 144 additional weeks (or until avalglucosidase alfa is commercially available in Canada, whichever comes first) for all enrolled patients in Canada (extended open-label avalglucosidase alfa long-term follow-up phase).

17.3.4 United Kingdom

In the UK, the duration of the extended open-label avalglucosidase alfa long-term follow-up period will be defined as ‘up to the approval in the country or to the maximal duration planned in the study (ie, end of treatment at Week 289), whichever occurs first’.

17.4 APPENDIX D: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes for the current amendment is located directly before the Clinical Trial Summary.

17.4.1 Amended protocol 01: 03 Aug 2016

Major changes specific to this global amendment include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, Sections 4, 7.1, and 7.2.1	Change to the inclusion/exclusion criteria. Inclusion criteria I01 and exclusion criteria E08 were reworded and E06 was modified.	I01. and E08. were reworded in order to comply with local requirements regarding age of minors and adults. E06. was modified to allow more severely compromised patients into the study by reducing the lower cutoff for % predicted FVC from 40% to 30%.
Clinical Trial Summary, Sections 1.1, 8.4, and 11.1	Change to the sample size; sample size was increased from approximately 86 to approximately 96.	Sample size was increased from approximately 86 to approximately 96 as a result of modification to the exclusion criteria for % predicted FVC (the primary efficacy endpoint) and using a more conservative 10% estimate for missing data.
Throughout	Minor editorial changes to spelling, punctuation, grammar, and syntax.	Minor, therefore have not been summarized.

17.4.2 Amended protocol 02: 18 Jul 2017

No substantial changes were made to the protocol. Throughout the protocol, following changes were included:

- Minor editorial changes to spelling, punctuation, grammar, and syntax.
- Table of contents was updated.
- Flow charts were updated to reflect the study procedures in Section 10 and to clarify that AEs and concomitant medication use information are to be collected at each visit to assure that information is kept up to date.
- Sections, table footnotes and citations, and references were renumbered.
- Tables were reformatted.
- Abbreviations were updated in text, Section 3 (Abbreviations), and table footnotes.
- References were updated.

- Screening period was extended: The screening phase (time from signing of informed consent form to start of study treatment) should not exceed 14 days, but could be extended to a maximum of 8 weeks in pre-specified situations (refer to Section 10.1.2).
- Added details of re-screening: Patients may be re-screened once if their clinical condition changes. Patients who were screen failed because their FVC% predicted was >85% may be re-screened only if a clinically relevant worsening respiratory condition related to Pompe Disease and not related to intercurrent illness as assessed by the Investigator occurs. In case of re-screening, the patient will be first screened failed in the IXRS, will sign a new written informed consent form and a new patient number will be provided. All screening assessments/procedures will have to be performed again, except GAA and ACE genotyping.
- PFT details updated: Patients may repeat the assessment once up to three times within the Screening Visit time window in case of failed quality as determined by the central laboratory.
- Clarification in the ADA tests was provided: Patients in the neoGAA treatment arm will be tested for anti-neoGAA antibodies and patients in the alglucosidase alfa treatment arm will be tested for anti-alglucosidase alfa antibodies. In the open label follow-up phase, patients from the alglucosidase alfa treatment arm who have switched to neoGAA will be tested for both anti-alglucosidase alfa antibodies and anti-neoGAA antibodies. Patients who remain on neoGAA treatment will continue to be tested for anti-neoGAA antibodies. Patients who are positive for anti-neoGAA antibodies will be tested to determine if the antibodies cross-react with alglucosidase alfa.

17.4.3 Amended protocol 03: 10 Apr 2019

This amended protocol 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.

Overall Rationale for the Amendment

Global changes

- In order to allow study participants to continue to receive the investigational medicinal product (IMP) after Week 145, the study is extended to an additional period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients).
- Enrollment of patients aged 3 to <18 years in the study has been challenging, mainly due to exclusion criterion related to respiratory function (requirements that FVC% predicted ≤85%). At the end of the recruitment, if <4 patients aged 3 to <18 years are enrolled, in order to comply with Health Authority requirements to enroll a certain number of pediatric patients, up to 2 additional pediatric patients will be enrolled directly in the open-label avalglucosidase alfa long-term follow-up phase where they will receive avalglucosidase alfa.

- In countries where it is permitted, home infusion of avalglucosidase alfa in the extension period may be allowed.
- Language is added in the 'randomization code-breaking during the study' section, to document that an unblinded programmer will prepare the dataset for population PK analysis.
- The statistical section is updated. Removed non-inferiority test of 6MWT from the testing order and used superiority instead for secondary endpoint of 6MWT in accordance with feedback from regulatory agency. Also, added superiority test of MEP to the hierarchical testing and updated definition of safety population.
- The mRNA test is removed since this test is not performed.
- Clarifications are given regarding the conditions for temporary IMP discontinuation with DMC consultation (eg, in case of abnormal liver function test).
- Collection of dry blood spot has been added for determination of exploratory biomarkers in addition to samples of urine and plasma to develop alternative assays and potentially reduce blood volume needed for testing in future.

Canadian-specific requirement

- Due to operational challenges with the use of the hand-held dynamometers (HHD) in Canada, several measures assessed with these devices will be missing. Therefore, these assessments (HHD in lower extremity muscle strength, HHD in upper extremity muscle strength) will no longer be required in study participants in Canadian sites.

France-specific requirement

- The option for home infusion added in this amended protocol 03 does not apply in France to be consistent with the French Health Authority position disallowing home infusion for all enzyme replacement therapies (ERT).

United Kingdom-specific requirement

- In the UK, the duration of the extended open-label avalglucosidase alfa long-term follow-up period will be defined as 'up to 144 weeks after the last patient has been enrolled in the study' to comply with the UK position regarding the protocol language to be used for study extensions.

Protocol amendment summary of changes table

Section # and Name	Description and Change	Brief Rationale
Clinical Trial Summary	Added the following description 'an additional extension period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) will include bi-weekly visits (study drug infusion, adverse events (AEs) check and vital signs) as well as less frequent visits for other assessments (every 4 weeks, 12 weeks, 24 weeks and 48 weeks). At the end of this period, the end of study visit/contact will be performed. If at the end of the recruitment, <4 pediatric patients aged 3 to <18 years are enrolled, up to 2 additional pediatric patients will be enrolled directly in the open-label avalglucosidase alfa long-term follow-up phase where they will receive avalglucosidase alfa. For this subgroup of pediatric patients, the study will comprise 52 visits including the Screening Visit (V1: Day -14 to Day -1) and the Enrollment Visit V2 (Day 1/Day 2); V3 (1 week after V2) through V52 for study drug infusion, PK, safety assessment, and efficacy evaluations in the open-label avalglucosidase alfa long-term follow-up phase; an additional extension period of up to 144 weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) will include bi-weekly visits (study drug infusion, AE checks and vital signs) as well as less frequent visits for other assessments (every 4 weeks, 12 weeks, 24 weeks and 48 weeks). At the end of this period, the end of study visit/contact will be performed. For all patients, all visits following V2 are calculated from day of first infusion of IMP in 14-day increments with a window of ±7 days for infusions and safety assessments and ±14 days for all other assessments.'	To maintain internal consistency with other sections of the protocol corresponding to the potential enrollment of pediatric patients aged 3 to <18 years directly in the open-label avalglucosidase alfa long-term follow-up phase.
Clinical Trial Summary Section 6.2.1 Duration of study participation for each patient	Added following texts: For overall duration: '(or 2 years [99 weeks] for the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase)' For 49-week blinded treatment period: 'except for the subgroup of pediatric patients aged 3 to	In order to clarify the updated study periods and durations corresponding to the potential enrollment of pediatric patients aged 3 to <18 years directly in the open-label avalglucosidase alfa long-term follow-up phase.

Section # and Name	Description and Change	Brief Rationale
	<18 years enrolling directly in the open-label long-term follow-up phase' For extended open-label long-term follow-up period: 'An extended open-label avalglucosidase alfa long-term follow-up period will last up to 144 additional weeks (or until avalglucosidase alfa is approved whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) for all patients (extended open-label avalglucosidase alfa long-term follow-up phase).'	
Section 1.2.1 Blinded treatment period Section 1.2.2 Open-label avalglucosidase alfa long-term follow-up phase Section 1.2.5.1 Screening and open-label avalglucosidase alfa long-term follow-up phase	Pharmacogenetics assessment of mRNA has been removed from schedule.	This test is not performed.
Section 1.2.1 Blinded treatment period Section 1.2.2 Open-label avalglucosidase alfa long-term follow-up phase Section 1.2.5.1 Screening and open-label avalglucosidase alfa Long-term Follow-up Phase	Collection of dry blood spot has been added for determination of exploratory biomarkers in addition to samples of urine and plasma. Corresponding footnotes in study flow charts has been updated.	To develop alternative assays and potentially reduce blood volume needed for testing in future.
Section 1.2.2 Open-label avalglucosidase alfa long-term follow-up phase Section 8.1 Investigational medicinal product(s)	Footnote "a" added and updated footnote "b" to add following details. 'As per conditions and instructions provided in Section 8.1, avalglucosidase alfa infusion may occur at home.' Added eligibility criteria for home infusion during the open-label extension period. The subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase will be eligible for home infusion after remaining stable on avalglucosidase alfa administration for at least 12 months.	In countries where it is permitted, home infusion of avalglucosidase alfa in the extension period may be allowed.
Section 1.2.3 Extended open-label avalglucosidase alfa long-term follow-up phase Section 10.1.5 Extended open-label avalglucosidase alfa long-term follow-up phase	Added the table and corresponding list of assessments for 'Extended open-label avalglucosidase alfa long-term follow-up phase'	Added the assessments for this newly added phase.
Section 1.2.5 Pediatric patients aged 3 to less than 18 years entering directly in the open-label avalglucosidase alfa	Added the table and corresponding list of assessments for 'Screening and open-label avalglucosidase alfa long-term follow-up phase' and 'Extended open-label avalglucosidase alfa	Added the assessments for the pediatric patients aged 3 to <18 years enrolling directly in the open-label avalglucosidase alfa long-term follow-up.

Section # and Name	Description and Change	Brief Rationale
long-term follow-up Section 10.1.7 Visit schedule for pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase (starting after screening period)	long-term follow-up phase' and 'End of study'	
Section 5 Study objectives Section 9.2.1.3 Hand-held dynamometry (lower extremity muscle strength) Section 9.3.1.3 Hand-held dynamometry (upper extremity muscle strength) Section 11.4.2.2 Analyses of secondary efficacy endpoints Section 11.4.2.3 Multiplicity considerations	Added the following text under secondary and other objectives: 'For the Canada-specific requirement regarding HHD, refer to Appendix C Section 17.3.3.'	For clarifying regarding the country-specific requirements.
Section 6.1 Description of the study	Added following description: 'At the end of the recruitment, if <4 pediatric patients aged 3 to <18 years are enrolled, in order to comply with Health Authority requirements to enroll a certain number of pediatric patients, up to 2 additional pediatric patients will be screened and enrolled directly in the open-label avalglucosidase alfa long-term follow-up phase where they will receive avalglucosidase alfa.	Added clarification regarding enrollment of the patients aged 3 to <18 years of age.
Section 6.3 Interim analysis Section 11.5 Interim analysis	Added the following text: 'and an additional extension period of up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients)'	To cover the extended open-label long-term follow-up period.
Section 7. Selection of patients	Re-screening is no longer limited to only one re-screening possibility.	Removal of this limitation in order to re-screen pediatric patients who were screen failed twice because their FVC% predicted was >85% both times.
Section 8.1 Investigational medicinal product(s)	Added the following text: 'In the extended open-label avalglucosidase extension period, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at V77/W147 and continuing up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) for an additional up to 72 doses. For pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase, avalglucosidase alfa will be	Added the description regarding the visit schedule during the additional open-label extension period.

Section # and Name	Description and Change	Brief Rationale
	administered by IV infusion every 2 weeks starting at Randomization Visit (Visit 2, Day 1/Day 2) continuing up to V52/W97 for a total of 49 doses. For these patients, in the extended open-label avalglucosidase alfa extension period, avalglucosidase alfa will be administered by IV infusion every 2 weeks starting at V53/W99 and continuing up to 144 additional weeks (or until avalglucosidase alfa is approved in the patient's country, whichever comes first; refer to Appendix C Section 17.3.4 for definition applicable for UK patients) for up to 72 additional doses. For all patients, all visits following V2 are calculated from day of first infusion of IMP in 14-day increments with a window of ±7 days for infusions and safety assessments, and ±14 days for all other assessments. There should not be less than 7 days between 2 IMP infusions.'	
Section 8.3.2 Randomization code breaking during the study	Added following text 'One programmer may be unblinded to prepare the dataset for population PK analysis. The procedure detailing the process to maintain blind beyond the programmer is described in a separate Sanofi quality document.'	Language is added in the 'randomization code breaking during the study' section, to document that an unblinded programmer will prepare the dataset for population PK analysis.
Section 8.7.2 Return and/or destruction of treatments	Added following text: 'In some specific cases described in the monitoring plans (blinded and unblinded), reconciliation may be performed by blinded monitor, as long as the blinding is maintained as per conditions detailed in the monitoring plan.'	Language added for reconciliation of IMP in specific cases.
Section 9.1.1 Primary efficacy endpoint	Added the following text 'For each PFT assessment, up to 8 efforts may be performed.'	Clarification added for primary efficacy endpoint assessment.
Section 9.2.2.2 Laboratory safety variables	Added following text: 'A urine sample will be sent to the central laboratory for that purpose'	Clarification provided that quantitative measurement of urine will be performed at central laboratory.
Section 9.2.2.3 Vital signs	Added the following clarification regarding infusion rate change '(including the start of infusion which is considered as first infusion rate change)', and added following text regarding number of assessments 'ie, a total of 7 assessments'	Clarification added regarding infusion rate change and number vital signs assessments.
Section 9.2.2.7 Immunogenicity	Added following text: 'In these patients, ADA against alglucosidase alfa will no longer be tested in the extended open-label follow-up phase (ie, after Week 145).'	Clarification provided for performing ADA test against alglucosidase alfa during extended open-label follow-up phase.
Section 9.3.2.3 Bioanalytical method	Updated the LLOQ from '12.5 ng/mL or 0.013 µg/mL' to '12 ng/mL or 0.012 µg/mL'.	Updated the LLOQ of the method for avalglucosidase alfa.

Section # and Name	Description and Change	Brief Rationale
Section 1.2.1 Blinded treatment period Section 1.2.5.1 Screening and Open-label avalglucosidase alfa Long-term Follow-up Phase	Added following text in table footnote 'x' of Section 1.2.1 and table footnote 's' of Section 1.2.5.1: 'GAA enzyme activity level measured on a Dried Blood Spot sample is not considered as sufficient to confirm eligibility in this study; GAA enzyme activity level from another source (skin fibroblast, peripheral blood leukocyte or muscle biopsy sample) will be needed).'	Clarification added for genotyping and for biochemical diagnosis of Pompe disease if required.
Section 9.3.3.1 Genotyping of human acid α-glucosidase gene	Added the following texts: 'However, results from the central laboratory may be used if performed during the screening period but should be obtained before the Baseline Visit to confirm eligibility.'	
Section 10.1.2 Screening period/baseline visit	Added following text: 'For the subgroup of pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase, an interactive response technology (IRT) call for enrollment will replace the randomization call and will be performed just before the IMP administration at the first treatment visit. Post screening schedule for this subgroup of pediatric patients is detailed in Section 10.1.7.'	Clarification added for patients enrolling directly in the open-label long-term follow-up phase.
Section 10.1.7 Visit schedule for pediatric patients	Added section 10.1.7 and subsections of visit schedule for pediatric patients aged 3 to <18 years enrolling directly in the open-label long-term follow-up phase (starting after screening period).	Clarification for visit schedule added for pediatric patients enrolling directly in the open-label long-term follow-up phase.
Section 10.1.8 Follow-up	Following clarification added for V64/Week 121: '[not applicable for pediatric patients aged 3 to <18 directly enrolled in the open-label long-term follow-up phase]' Following clarification added for V76/Week 145 '[not applicable for pediatric patients aged 3 to <18 directly enrolled in the open-label long-term follow-up phase], or any every 24 weeks visit of the extended open-label long-term follow-up phase'	Clarification added regarding assessments on V64/Week 121 and V76/Week 145.
Section 10.1.9 Follow-up for patients who temporarily or permanently discontinued the study treatment	Added the following text: 'For those patients who discontinued treatment during the extended open-label avalglucosidase alfa long-term follow-up phase, assessments corresponding to the End of Treatment Visit as outlined in Section 10.1.7.3.5 will be performed if possible'.	Clarification added for patients who discontinued treatment during extended long-term follow-up phase.
Section 10.3.1 Temporary treatment discontinuation with investigational medicinal	Temporary IMP discontinuation criteria have been updated in case an AE occurs: • Any life-threatening AE: deleted NCI and	CTCAE reference is removed since it relates to oncology terminology.

Section # and Name	Description and Change	Brief Rationale
product(s)	CTCAE 'Grade 4' More than 1 AE: deleted CTCAE 'Grade 3 or Greater'	
Section 10.6 Safety instructions	Added the following text: 'Moderate, severe, and recurrent mild IARs will be discussed with the DMC. If the DMC recommends or suggests that a desensitization procedure to the IMP could be proposed to the patient, in agreement with the Investigator, such a procedure may be initiated as per pharmacy manual guidelines. Depending on the phase of the study the patient will be in at the time of the desensitization procedure, this one may be blinded (if the procedure is started when the patient is still in the double-blind phase) or unblinded (if the procedure is started when the patient is in one of the open-label phases)'.	Text added for IAR evaluation at DMC and possibility of desensitization procedure.
Section 11.3 Analysis populations	Definition of safety population has been updated.	Clarification added regarding the patients enrolled directly in open-label long-term follow-up period.
Section 11.4 Statistical methods	Deleted the following text 'In the case that NI of FVC (% predicted) is demonstrated and the superiority of the primary efficacy endpoint is not achieved, additional supportive data on 6MWT will be needed to demonstrate the clinical meaningfulness of the NI for the primary endpoint.' The statistical section is updated: • Primary endpoint FVC (% predicted): removed non-inferiority test of 6MWT from the testing order. • Secondary endpoint (6MWT): the primary statistical objective changed from non-inferiority to superiority of avalglucosidase alfa versus alglucosidase alfa. • Added following superiority test to the hierarchical testing '% predicted change from baseline to Week 49 for MEP'.	Updated in accordance with the feedback received from Regulatory Agency.
Section 14.2 Record retention in study sites Section 14.5 Data protection	Administrative changes made.	Clarifications added in line with other sections.
Section 17.3 Appendix C: Country-specific requirements	Added country-specific requirements for France.	Clarified that home infusion is not allowed in France.
	Added country-specific requirements for Canada.	Added due to operational challenges with the use of the HHD in Canada, several measures assessed with this device will be missing. Therefore, these assessments (HHD in lower extremity muscle strength,

Section # and Name	Description and Change	Brief Rationale
		HHD in upper extremity muscle strength) will no more be required in study participants in Canadian sites.
	Added country specific requirements for UK.	The duration of the extended open-label avalglucosidase alfa long-term follow-up period will be defined as 'up to 144 weeks after the last patient has been enrolled in the study' in the UK. Hence, this wordings added to comply with the UK position regarding the protocol language to be used for study extensions.
Throughout	Added generic name of the investigational drug in addition to compound code. Minor editorial, typo error corrections, and document formatting revisions.	Minor, therefore have not been summarized.

17.4.4 Amended protocol 04: 21 December 2020

This amended protocol 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.

Overall Rationale for the Amendment

- To include in this amendment the recommendations that were developed for the COVID-19 pandemic period and 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 most updated wordings that are compliant with general guidance, including monitoring techniques.
- To update Section 8.1 for details regarding home infusion, to harmonize this text across the different studies included in the avalglucosidase alfa development program.

Protocol amendment summary of changes table

Section # and Name	Description and 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; Section 6.1 Description of the Study	Requirement for a patient to remain blinded to the randomized treatment in the study is updated from 'after database is locked and the primary analysis completed' to just 'after database is locked'.	To update the text related to blinding.
Section 1.2 - Flow chart: 1.2.1 Blinded treatment period; 1.2.2 Open-label avalglucosidase alfa long-term follow-up phase; 1.2.3 Extended open-label avalglucosidase alfa long-term follow-up phase. For pediatric patients enrolling directly in open-label period: 1.2.5.1 Screening and open-label avalglucosidase alfa long-term follow-up phase: 1.2.5.2 Extended open-label avalglucosidase alfa long-term follow-up phase	The footnote related to the 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 with the following text:: *"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* or their legally authorized representative (for pediatric patients) *to ensure that no adverse event occurred during the observational 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 1.2.1 Blinded treatment period; Section 9.2.2.7 Immunogenicity	Information related to the assessment related to ADA (with neutralizing antibodies in ADA-positive patients)[s, u] was revised to add the following information: *"In addition, patients in the alglucosidase alfa treatment arm will also be tested for anti-avalglucosidase alfa antibodies at V27/W49 to get their baseline value".*	To get the same level of information from patients receiving alglucosidase alfa treatment as compared with patients receiving avalglucosidase alfa treatment during the blinded treatment period.
Section 8.1 Investigational medicinal product(s)	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* or their legally authorized representative (for pediatric patients) *to ensure that no AE 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 # and Name	Description and Change	Brief Rationale
Section 8.1 Investigational medicinal product(s)	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 (i.e. after at least 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 10.1.9 Follow-up for patients who temporarily or permanently discontinued the study treatment	Text related to permanent and temporary discontinuation was updated.	This change was made to avoid unnecessary clinic visits.
Section 10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)	Text was updated to clarify that temporary treatment discontinuation may be considered if patient becomes pregnant. Text was also updated to clarify that 'visit and assessment schedules will be adapted to the absence of infusion of IMP'.	To clarify that pregnancy is a reason for temporary treatment discontinuation and not permanent discontinuation. Also, to clarify that 'visit and assessment requirements will be changed in the absence of IMP.
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 17.4 Appendix D: Protocol amendment history	Added new section (Section 17.4.3).	To incorporate the changes from amended protocol 03 to the amended protocol 04.
Throughout	Minor editorial, document formatting, and typographical correction are made.	Clarification.

17.4.5 Amended protocol 05: 18 November 2021

This amended protocol 05 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.

Overall Rationale for the Amendment

Under the current EFC14028 protocol (Amended protocol 04) patients will complete the study on Week 289 visit or upon approval of avalglucosidase alfa, whichever comes first. For enrolled

patients wishing to start commercial treatment with avalglucosidase alfa in Canada after their participation in the EFC14028 study, there might be a treatment gap between the end of treatment visit of the EFC14028 study (if based on approval of avalglucosidase alfa in Canada) and the time to being able to receive avalglucosidase alfa as a commercial treatment. In order to cover this gap, the patients' participation in the open label phase of the study is extended until the Week 289 visit or availability of commercial avalglucosidase alfa, whichever comes first for enrolled patients in Canada.

Protocol amendment summary of changes table

Section # and Name	Description and Change	Brief Rationale
Protocol Amendment Summary of Changes	Document formatting revision.	To update document history and provide overall rationale for the amendment and summary of changes table.
Clinical trial summary: Assessment schedule, Duration of study period (per patient) Section 6.2.1 Duration of study participation for each patient Section 6.3 Interim analysis Section 8.1 Investigational medicinal product(s) Section 10.1.5.1 Biweekly to Section 10.1.5.5 Every 48 weeks (Yearly) and end of treatment visit Section 11.5 Interim analysis	Added reference to Section 17.3.3 Canada.	To allow the 2 enrolled adult patients in Canada to continue the study according to the planned schedule of assessments after approval of the product in Canada until the product is made commercially available in Canada.
Section 17.3 Appendix C: Country-specific requirements	New text added to Section 17.3.3 Canada to state the following: For enrolled patients wishing to start commercial treatment with avalglucosidase alfa in Canada after their participation in the EFC14028 study, and to avoid a treatment gap between the end of treatment visit of the EFC14028 study and the possibility to start commercial treatment with avalglucosidase alfa, the duration of study participation of patients in Canada is defined as follows: An extended open-label avalglucosidase alfa long-term follow-up period will last up to 144 additional weeks (or until avalglucosidase alfa is commercially available in Canada, whichever comes first) for all enrolled patients in Canada (extended open-label avalglucosidase alfa long-term follow-up phase).	To allow the 2 enrolled adult patients in Canada to continue the study according to the planned schedule of assessments after approval of the product in Canada until the product is made commercially available in Canada.
Section 17.4 Appendix D: Protocol amendment history	Added new section (Section 17.4.4).	To incorporate the changes from amended protocol 04 to the amended protocol 05.

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