NCT03019406

AMENDED CLINICAL TRIAL PROTOCOL NO. 03

COMPOUND: AVALGLUCOSIDASE ALFA/GZ402666

An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response

STUDY NUMBER: ACT14132

STUDY NAME: Pediatric open-label, ascending dose cohort study (Mini-COMET)

VERSION DATE / STATUS: 05-Jan-2021 / Approved

Version Number:	1	EudraCT	2016-003475-21
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		WHO universal trial number:	U1111-1179-4616
Date:	05-Jan-2021	Total number of pages:	141

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NAMES AND ADDRESSES OF

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03 (Global)	All	05-Jan-2021, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 02 (Global)	All	24-Mar-2020, version 01 (electronic 4.0)
Protocol Amendment 03	All	27-Jul-2018, version 01 (electronic 2.0)
Amended Clinical Trial Protocol 01 (DE)	Germany only	04-Oct-2017, version 01 (electronic 1.0)
Protocol Amendment 02 (DE)	Germany only	04-Oct-2017, version 01 (electronic 1.0)
Protocol Amendment 01 (GB)	UK only	02-Feb-2017, version 01 (electronic 1.0)
Clinical Trial Protocol		19-Oct-2016, version 01 (electronic 1.0)

Amended protocol 03 (05 January 2021)

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

- 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 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 the Sections 8.1 and 8.9 (home infusion), to harmonize 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
Section 1.2 Flow chart;. 1.2.1 Treatment period; 1.2.2 Extension period (Week 27 to Week 35) including details for Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa; 1.2.3 Extension period (Week 37 to Week 145); 1.2.4 Extended long-term treatment period	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 performed at study site or infusion center was shortened or skipped for patient's safety reasons. Also to lighten this period after the end of pandemic and in order to get information in case this observation period is not performed, the observation time after the end of infusion is reduced to 1 hour.
Section 8.1 Investigational medicinal product(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 adverse event occurred during the observational period."	Due to Covid-19 pandemic restrictions, the observation period after the infusions performed at 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 get information in case this observation period is not performed, the observation time after the end of infusion is reduced to 1 hour.
Section 8.9.1 Home infusion for patients receiving alglucosidase alfa	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 (ie, after 6 months free of IARs instead of 12 months) or to resume home infusion quicker after interruption for IAR during home infusion. Some text is also updated to harmonize across the different studies included in the avalglucosidase alfa development program.

Section # and Name	Description and Change	Brief Rationale
Section 8.9.2 Home infusion for patients receiving avalglucosidase alfa	The text was updated to harmonize with other studies included in the avalglucosidase alfa development program. One of the bullet points was updated from: "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 no such IARs are present for at least 3 months." To "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."	The home infusion text is amended to allow patients to benefit from home infusion sooner (ie, after 6 months free of IARs instead of 12 months) or to resume home infusion quicker after interruption for IAR during home infusion. Some text is also updated to harmonize across the different studies included in the avalglucosidase alfa development program.
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.	To clarify that pregnancy is a reason for temporary treatment discontinuation and not permanent discontinuation.
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 the recent Sanofi procedures, the direct sending of source documents to the Sponsor (except to Pharmacovigilance department) is no more recommended.
Section 11.4.2 Analyses of safety data	Definition of baseline value was updated.	Clarification
Sections 12 Regulatory, ethical, and study oversight considerations, Section 13 Study monitoring, and Section 14 Additional requirements	Subsections and corresponding text in Sections 12, 13, and 14 were revised and updated to reflect practices, including monitoring techniques, as outlined in the current protocol template,.	To align with the current protocol template
Section 17.4: Appendix D (Protocol amendment history)	Added new Section 17.4.2.	To incorporate the changes from amended protocol 02 to amended protocol 03
Throughout	"2-hour post-infusion observation period" changed to "post-infusion observation period"	To reflect the amendment specific changes
Throughout	Typos have been corrected where necessary. Minor editorial and document formatting revisions	Clarifications

CLINICAL TRIAL SUMMARY

COMPOUND: GZ402666	**STUDY No.: ACT14132** **STUDY NAME: Pediatric open-label, ascending dose cohort study (Mini-COMET)**
TITLE	An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	2
STUDY OBJECTIVE(S)	**Primary objective:** To evaluate the safety profile of avalglucosidase alfa in patients with infantile-onset Pompe disease (IOPD) previously treated with alglucosidase alfa. **Secondary objectives:** To characterize the pharmacokinetic (PK) profile of avalglucosidase alfa and to evaluate the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. **Other objectives:** To determine [redacted], and effect of avalglucosidase alfa treatment on functional endurance, respiratory function, health-related quality of life (HRQOL), pain, developmental disability, and hearing in patients with IOPD.
STUDY DESIGN	Multi-stage, phase 2, open-label, multicenter, multinational, ascending dose cohort, repeated intravenous (IV) infusion study of avalglucosidase alfa in pediatric patients with IOPD who have been previously treated with alglucosidase alfa and demonstrated clinical decline (Stage 1) or sub-optimal clinical response (Stage 2) in specified respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis. <u>Stage 1</u> • Cohort 1 – at least 5 IOPD patients will receive avalglucosidase alfa at 20 mg/kg once every other week (qow) for 6 months. • Cohort 2 – at least 5 IOPD patients will receive avalglucosidase alfa at 40 mg/kg qow for 6 months. <u>Stage 2</u> • Cohort 3 – at least 10 IOPD patients will be randomized 1:1 to receive avalglucosidase alfa at the highest tolerated avalglucosidase alfa dose in Stage 1 (20 mg/kg qow or 40 mg/kg qow) or alglucosidase alfa treatment at current stable dose (defined by dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry) for 6 months. The randomization will be stratified on gender. If determined safe by an independent data monitoring committee (DMC) after the 3rd patient in the 20 mg/kg qow group (Cohort 1) has received the 3rd infusion of avalglucosidase alfa, and after 5 patients have started treatment in Cohort 1, the next cohort of avalglucosidase alfa at higher dose (40 mg/kg

	qow) will be initiated (Cohort 2). Cohort 3 will be initiated after determination of the highest tolerated avalglucosidase alfa dose in Cohort 1 and Cohort 2 after at least 5 patients in Cohort 1 and at least 5 patients in Cohort 2 have received the 7th dose of avalglucosidase alfa (or completed Week 13 with a minimum of 6 infusions). After completion of treatment for 6 months (Week 25) and data collection for the primary analysis, the patients will continue on long-term avalglucosidase alfa treatment and follow-up in the Extension Period for up to a total of 7 years in the study. Cohort 3 patients receiving alglucosidase alfa will have the option to switch to treatment with avalglucosidase alfa in the extension period or discontinue the study. The data cut-off for the primary analysis will be after the last patient in Cohort 3 has completed 6 months of treatment (Week 25). Safety, efficacy, PK and [redacted] will be performed at scheduled visits throughout the study treatment period. Ventilator use, adverse events (AEs) and concomitant and pre-infusion medications/therapies will be monitored continuously throughout the study. If a patient in Cohort 1, receiving 20 mg/kg qow avalglucosidase alfa, experiences further clinical decline at or after Week 25 when compared to prior to enrollment in ACT14132, and as defined by more rapid worsening of criteria of clinical decline, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator, which may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation) or increasing the avalglucosidase alfa dose to 40 mg/kg qow (once this dose is considered acceptable after the end-of-cohort 2 DMC meeting) or maximum tolerated dose (MTD) (once established) while being enrolled in the extension period of the study. If a patient in Cohort 2 or 3 experiences further clinical decline at or after Week 25 as defined by more rapid worsening of criteria of clinical decline than prior to study start, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator. This may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation). Patients must have completed the 25-week treatment period of the study before dose increase of avalglucosidase alfa (or start of avalglucosidase alfa for patients receiving alglucosidase alfa in Cohort 3) will be considered.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** The patient must have a documented acid α-glucosidase (GAA) deficiency from blood, skin or muscle tissue. The patient is aged <18 years old, has cardiac involvement at the time of Pompe disease diagnosis, has been receiving a stable dose of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry, and has documented (at least 2 recent and consecutive assessments prior to study entry, not less than 2 weeks apart) evidence of clinical decline or sub-optimal clinical response in at least 1 of the following parameters related to Pompe disease and NOT related to intercurrent illness as assessed by the Investigator, in addition to at least 1 previous assessment prior to onset of decline: For patients entering Stage 1 - clinical decline in at least 1 of the following parameters: respiratory function, motor skills, and/or cardiac parameters. For patients entering Stage 2 - sub-optimal clinical response in at least 1 of the following parameters: respiratory function, motor skills, and/or new onset of ptosis.

	Exclusion criteria: The patient has persistent high antibody titers, has a high risk for a severe allergic reaction to avalglucosidase alfa, is concurrently participating in another clinical study using investigational treatment for Pompe disease, previous treatment in any cohort of the ACT14132 study, has known clinically significant organ disease, or requires any prohibited concomitant medications.
Total expected number of patients	Approximately 20 patients
STUDY TREATMENT(s) **Investigational medicinal product(s)** **Formulation:** **Route(s) of administration:** **Dose regimen:**	 • avalglucosidase alfa (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan) • alglucosidase alfa Sterile lyophilized powder administered following reconstitution and dilution. Intravenous (IV) infusion <u>Stage 1</u> Cohort 1: avalglucosidase alfa 20 mg/kg qow Cohort 2: avalglucosidase alfa 40 mg/kg qow <u>Stage 2</u> Cohort 3: highest tolerated avalglucosidase alfa dose in Stage 1 or current stable dose of alglucosidase alfa. In the extension period, all patients will receive avalglucosidase alfa (20 mg/kg qow or 40 mg/kg qow or MTD once established).
ENDPOINT(S)	**Primary endpoint:** Data pertaining to the safety and tolerability of avalglucosidase alfa: • Assessment of AEs/treatment-emergent adverse events (TEAEs), including infusion-associated reactions (IARs) • Physical examinations including weight, height, and head circumference • Clinical laboratory evaluations including biochemistry, hematology, and urinalysis • Vital sign measurements • 12-lead electrocardiogram (ECG) • Immunogenicity assessments **Secondary endpoint(s):** Pharmacokinetics: • Plasma parameters include maximum plasma concentration observed (C_{max}), time to achieve maximum plasma concentration (t_{max}), area under the curve from time 0 to time of the last quantifiable concentration ($AUC_{0\text{-}last}$), terminal half-life ($t_{1/2z}$), clearance (CL), and volume of distribution (Vd) Change in the following parameters at 6 months: Efficacy: • Gross Motor Function Measure-88 (GMFM-88) and Gross Motor Function Classification System – Expanded and Revised (GMFCS-E&R) • Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI) Functional Skills Scale: Mobility Domain

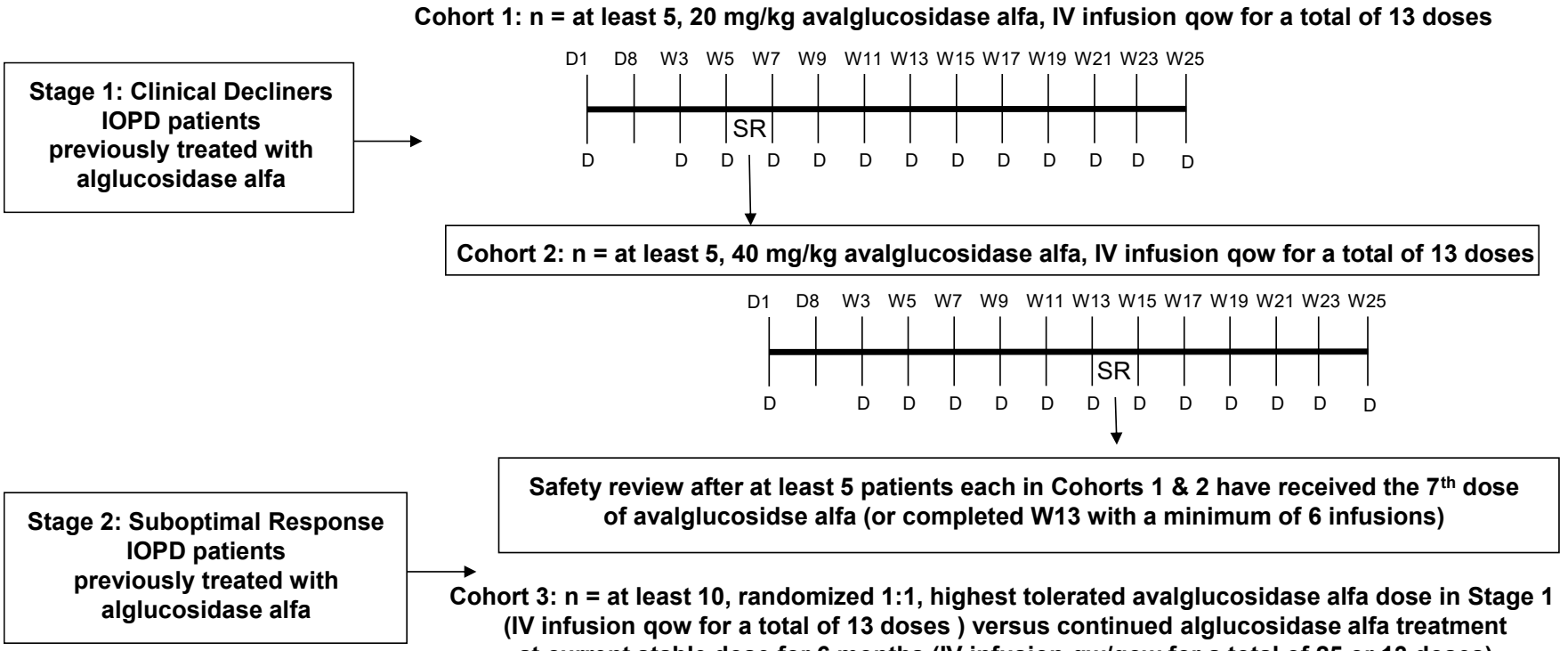
	• Quick Motor Function Test [QMFT] • Echocardiography (ECHO) endpoints: left ventricular mass index (LVMI) and left ventricular mass (LVM) Z-score • Eyelid position measurements: Interpalpebral fissure distance (IPFD), margin reflex distance (MRD-1), margin pupil distance (MPD) • Creatine kinase (CK) **Other endpoint(s):** Pharmacogenetics: • [redacted] • Optional stored DNA Pharmacodynamics: • Urinary Hex4 and [redacted] • Muscle biopsy (optional) Tertiary endpoints: • 6-minute walk test (6MWT) distance walked in patients who are able to ambulate at least 40 meters (approximately 130 feet) without stopping and without an assistive device • Pulmonary function testing (PFT) endpoints: percent predicted forced vital capacity (FVC), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in patients who can reliably undergo testing and/or who are not invasively ventilated • Hours of ventilator use/day (Ventilator use diary) • PedsQL Generic Core Scale (≥24 months of age) • PedsQL Pediatric Pain Questionnaire (>5 years of age) • Pain visual analog scale (VAS) • Bayley-III (1-42 months of age or in case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment) • Leiter-3 (≥42 months of age) • Hearing Testing • Motor Skills Checklist
ASSESSMENT SCHEDULE	The treatment period will comprise 15 visits including the screening visit (V1: Day -14 to Day -1, may be extended to up to 4 weeks in pre-specified situations [refer to Section 10.1.1]) and V2 (Day 1) through V15 (Week 25) occurring every 1 to 2 weeks for study drug infusion, safety assessment, PK, PD, and efficacy evaluations. The extension period will include study drug infusion, safety assessment, efficacy, and PD evaluations at selected visits from V16 (Week 27) through V76 (Week 145). An additional extended long-term treatment period of up to 226 weeks or until avalglucosidase alfa is approved in the patient's country, whichever comes first; (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients) will include biweekly visits (study drug infusion, 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, an up to 4-week post-treatment observation period will close the patient's participation. For all patients, all visits following V2 (Day 1) are calculated from the day of first infusion of investigational medicinal product (IMP) in 14-day increments with a window of ±7 days (in Cohort 3 participants, 7-day increments with a

	window of ± 3 days for weekly (qw) alglucosidase alfa treatment) for infusions and safety assessments and ±14 days for all other assessments. (If one visit date is changed, the next visit should take place according to the original schedule). Note: Patients who prematurely discontinue treatment should be followed as scheduled.
STATISTICAL CONSIDERATIONS	**Sample size determination:** No formal sample size calculations have been performed. Sample size for this study was based upon empirical considerations. **Analysis population:** The primary analysis population for Stage 1 and the overall study is the safety population, which is defined as all patients who received at least 1 infusion (partial or total) in the study. The primary analysis population for Stage 2 (Cohort 3) is the modified intent-to-treat (mITT) population, defined as all randomized patients in Cohort 3 who received at least 1 infusion and with evaluable baseline efficacy assessment. **Analysis of safety:** Safety analyses will be performed using the safety 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, preferred term (PT), and 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 within a considered period. The denominator for computation of percentages is the safety population. 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, and all AEs with fatal outcome will be summarized descriptively. Additional safety data including clinical laboratory tests, vital signs, ECG, and immunogenicity will be summarized descriptively. Safety data will be summarized by cohort/treatment arm within each stage, as well as by avalglucosidase alfa dose levels (20 mg/kg, 40 mg/kg). **Analysis of pharmacokinetics and preliminary efficacy:** PK parameters will be summarized for each visit and dose level using descriptive statistics. For each of the preliminary efficacy parameters, observed measurements and changes over time from pretreatment to post-baseline visit will be summarized by dose cohort/treatment arm within each stage and study visit using descriptive statistics. For those efficacy parameters that are used to identify patients who have sub-optimal response or clinical decline as part of inclusion criteria, patient profile (in terms of change over time) will be generated for those parameters where each patient will serve as his/her own control. Within Cohort 3, the effect of switching from alglucosidase alfa to avalglucosidase alfa will be assessed descriptively within each cohort/treatment arm using a composite score based on changes from pre-study to post 6 months avalglucosidase alfa treatment collected during the study. The control arm (alglucosidase alfa treatment) in Stage 2 will serve as a reference. The preliminary efficacy analysis will be performed within Cohort 3, based on

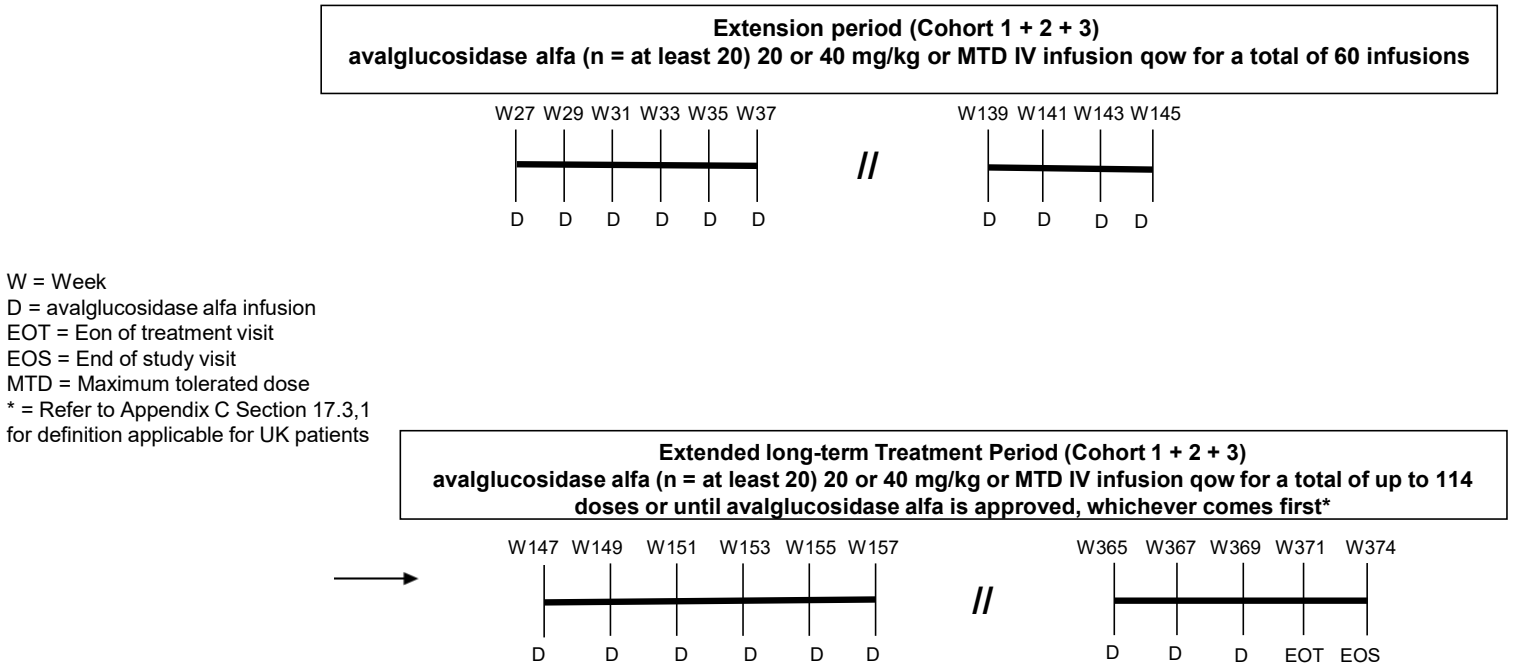
	the modified ITT population. Additional efficacy data will be summarized descriptively in the safety population.
DURATION OF STUDY PERIOD (per patient)	The duration of the study for each patient will be at least 7 years. After the initial period of 145 weeks, an additional period of up to 226 weeks or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients), including: • An up to 14-day screening period (may be extended to up to 4 weeks in pre-specified situations [refer to Section 10.1.1]); • A 25-week treatment period (primary analysis period [PAP]); • A 120-week extension period; • An up to 226 week extended long-term treatment period or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients), and; • An up to 4-week post-treatment observation period will close the patient's participation.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



W = Week
D = avalglucosidase alfa or alglucosidase alfa infusion
SR = Safety review by an independent Data Monitoring Committee (DMC)
IOPD=infantile onset Pompe disease; IC=intravenous; qow=every other week; qw=weekly
Cohort 2 will be initiated if avalglucosidase alfa is determined safe by the DMC after the 3rd patient in Cohort 1 has received the 3rd infusion of avalglucosidase alfa.
Stage 2 will be initiated after the highest tolerated dose in Stage 1 is determined.
Cohort 3 continue current stable dose of alglucosidase alfa (qw/qow) or switch to avalglucosidase alfa qow


Extension period (Cohort 1 + 2 + 3)
avalglucosidase alfa (n = at least 20) 20 or 40 mg/kg or MTD IV infusion qow for a total of 60 infusions
W27 W29 W31 W33 W35 W37
D D D D D D
//
W139 W141 W143 W145
D D D D
W = Week
D = avalglucosidase alfa infusion
EOT = Eon of treatment visit
EOS = End of study visit
MTD = Maximum tolerated dose
* = Refer to Appendix C Section 17.3,1 for definition applicable for UK patients
Extended long-term Treatment Period (Cohort 1 + 2 + 3)
avalglucosidase alfa (n = at least 20) 20 or 40 mg/kg or MTD IV infusion qow for a total of up to 114 doses or until avalglucosidase alfa is approved, whichever comes first*
W147 W149 W151 W153 W155 W157
D D D D D D
//
W365 W367 W369 W371 W374
D D D EOT EOS

1.2 STUDY FLOW CHART

Please refer to Section 10 for details.

1.2.1 Treatment period

Period	Screening/Baseline	Treatment Period													
Day(D) or Week (W)	**Day -14 to Day -1**	**D1**	**D8**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**W25**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Informed consent/assent	X														
Visit at clinical site[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X													
Demographics and baseline characteristics	X														
Medical/surgical history/Pompe history	X														
GAA activity[b]	X														
GAA mutation analysis[c]	X														
CRIM status[d]	X														
Prior/concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Retrospective chart review[e]	X														
IRT contact (Screening, Enrollment/Randomization/Dispensing)	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration															
avalglucosidase alfa/alglucosidase alfa infusion[g]		X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X
Safety															
β-hCG pregnancy test[h]	X	X			X		X		X		X		X		X
Physical examination[i]	X	X			X		X		X						X
Height/body length/head circumference[j]	X	X							X						X
Body weight	X	X			X		X		X		X		X		X
Vital signs[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[l]		X[m]			X				X						X
Hematology, biochemistry[n], urinalysis	X		X[o]		X[o]		X[o]		X		X[o]		X[o]		X
Anti-avalglucosidase alfa antibodies (with testing for neutralizing antibodies in anti-avalglucosidase alfa antibody positive patients)[p]	X		X		X		X		X		X		X		X
Anti-alglucosidase alfa antibodies (with	X		X						X						X

Period	Screening/Baseline	Treatment Period													
Day(D) or Week (W)	Day -14 to Day -1	D1	D8	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
testing for neutralizing antibodies in anti-alglucosidase alfa antibody positive patients)[p]															
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics[q]															
avalglucosidase alfa plasma samples		X							X						X
Pharmacodynamics															
Urine Hex4 samples[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Muscle biopsy (optional)[t]	X														X
Efficacy															
Ventilator use diary[u]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
GMFM-88, GMFCS-E&R[v]	X								X						X
Motor Skills Checklist[v]	X								X						X
QMFT	X								X						X
Pompe-PEDI, Functional Skills Scale: Mobility Domain[v]	X								X						X
Bayley-III/Leiter-3 scales[w]	X								X						X
Echocardiography[l]	X								X						X
Hearing testing[x]	X								X						X
Eyelid position measurements[y]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PedsQL Generic Core Scale questionnaire[z]	X								X						X
PedsQL Pediatric Pain Questionnaire[aa]	X								X						X
Pain VAS[aa]	X								X						X
PFT[bb]	X								X						X
6MWT[cc]	X								X						X
Pharmacogenetics															
[redacted]															
Stored DNA sample (optional)[s]	X														

Period	Screening/Baseline	Treatment Period													
Day(D) or Week (W)	Day -14 to Day -1	D1	D8	W3	W5	W7	W9	W11	W13	W15	W17	W19	W21	W23	W25
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
[redacted]															

6MWT = 6-minute walk test; [redacted]; BNP = brain natriuretic peptide; ADAs = anti-drug antibodies; β-hCG = beta-human chorionic gonadotropin; CK = creatine kinase; CRF = case report form; CRIM = cross-reactive immunologic material; D = Day; [redacted]; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EDTA = Ethylenediaminetetraacetic acid; EOS = end of study; GAA = acid α-glucosidase; GMFCS-E&R = Gross Motor Function Classification System – Expanded and Revised; GMFM-88 = Gross Motor Function Measure-88; IMP = investigational medicinal product; IRT = interactive response technology; PE = physical examination; PFT = pulmonary function testing; PedsQL = pediatric quality of life inventory; Pompe-PEDI = Pompe Pediatric Evaluation of Disability Inventory; PPT = plasma preparation tube; QMFT = Quick Motor Function Test; [redacted]; VAS = visual analog scale; W=week

a Clinic visit and/or visit by home infusion nurse for patients receiving alglucosidase alfa home infusion. 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 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, echocardiography, questionnaires) may be carried out over several days (refer to Section 10.1). 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 that no adverse event occurred during the observational period.

b If performed previously with historical results available, then the GAA activity does not need to be repeated, but result needs to be entered into the database.

c Gene mutation analysis is mandatory for all patients. If gene mutation analysis was conducted prior to signing the informed consent, these results may be utilized provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and parents give consent to utilize the results. Sample may be obtained at any other visit if not possible during screening due to blood volume limitation.

d Blood testing for CRIM status to be analyzed by central laboratory. If CRIM status was determined prior to enrollment and a report of the results is on file with the site, then the assessment does not need to be repeated, but result needs to be entered into the database. Results of CRIM status determined by the central laboratory from blood samples obtained for this study will not be provided to the site but will be uploaded to the Sanofi central repository through external data transfer.

e Retrospective chart review at screening/baseline to collect available data on clinical decline or sub-optimal clinical response as outlined in I 06 and I 07.

f Enrollment of patients in Cohorts 1 and 2 and randomization of patients in Cohort 3: IRT contact will be performed anytime during screening period for screening, prior to IMP administration for all other concerned visits and on or before Day 1 for enrollment/randomization.

g Biweekly administration or, for alglucosidase alfa in Cohort 3 only, weekly administration (current stable dose). For all patients, all visits following V2 (Day 1) are calculated from the day of first infusion of investigational medicinal product (IMP) in 14-day increments with a window of ±7 days (in Cohort 3 participants, 7 day increments with a window of ± 3 days for weekly (qw) alglucosidase alfa treatment) for infusions and safety assessments and ±14 days for all other assessments.

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

i Physical examination CRF will ask physician to record current muscle pain and cramps specifically at each PE assessment. Tanner stage will be assessed as part of the PE assessment at screening/baseline.

j To be measured at screening/baseline, every 3 months up to Week 73 and then every 6 months until Week 145/EOS in all patients.

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

l 12-lead ECG after at least 15 minutes in supine position (if supine is feasible for the patient). Review should be done at the site in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In addition, reading will be done by central reader for analyses purposes only.

m 12-lead ECG after at least 15 minutes in supine position (in triplicate predose 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 Biochemistry panel will include BNP and CK.

o Biochemistry assessments only for participants treated with avalglucosidase alfa. Sampling is not required for Stage 2 - Cohort 3 participants randomized to treatment with alglucosidase alfa.

p Serum samples are collected pre-infusion at each time point. Additional samples may be taken if clinically indicated in the event of IARs. Stage 2 Cohort 3 patients receiving alglucosidase alfa treatment do not require sampling of anti- avalglucosidase alfa antibodies and neutralizing antibodies in anti-avalglucosidase alfa antibody positive patients at Day 8, Week 5, Week 9, Week 13, Week 17, Week 21.

q Pharmacokinetic sampling schedule: prior to infusion; at the end of infusion; and 2, 4, 6, and 8 hours after the end of infusion at Day 1 and Week 25 and prior to infusion and 2 hours after the end of infusion at Week 13; additionally in the 40 mg/kg dose cohort 12 to 16 hours after the end of infusion at Day 1 and Week 25. For Stage 2 - Cohort 3 participants randomized to treatment with alglucosidase alfa, sampling of

avalglucosidase alfa pharmacokinetics is not required at Day 1, Week 13 and Week 25. 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 [redacted]

s 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 labs (hematology, biochemistry, ADA) and PK [redacted]

t Time points are suggested time points.

u In the event patient requires ventilator support (invasive or non-invasive) at any time during study treatment the patient will be asked to complete a daily ventilator use diary. On a biweekly basis, the periods of ventilator use/day (daytime, nighttime, both) will be reported by the Investigator based on the ventilator use diary.

v Patients included in Cohort 3 on the basis of sub-optimal clinical response documented by motor scale and/or clinical development evaluation tools other than GMFM-88 or Pompe-PEDI will undergo assessment with those tools in combination with the prescribed/planned testing at screening/baseline and Week 25.

w The Bayley-III will be administered to patients from 1 month of age until the maximum score on each of the 3 administered scales has been obtained. Once the maximum score for a scale has been achieved, only the remaining scales will be administered. Bayley-III is to be discontinued when the patient reaches 42 months of age. Leiter-3 Scale assessment is to be performed at the last assessment of the Bayley-III Scales prior to the patient reaching 42 months of age. In case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment, the patients should be assessed by the Bayley-III regardless of the patient's age.

x Hearing testing includes audiogram and brainstem auditory evoked potentials.

y Separate informed consent will be sought to permit for the acquisition and use of photographs of the patient's eyes in order to allow for independent review of eyelid position measurements by central reader.

z PedsQL Generic Core Scales will be used in pediatric patients 2 years and older, using age appropriate reports

aa Pain will be assessed by PedsQL Pediatric Pain Questionnaire for patients >5 years of age. Observer reported Pain VAS will be recorded in patients of all ages.

bb Pulmonary function tests are not required for patients unable to reliably undergo testing or for patients who are invasively ventilated; reading will be done by central reader.

cc 6MWT in patients who are able to ambulate at least 40 meters (approximately 130 feet) without stopping and without an assistive device.

1.2.2 Extension period (Week 27 to Week 35) including details for Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa

Period	Extension Period					
Day(D) or Week (W)	**W27**	**W28**	**W29**	**W31**	**W33**	**W35**
Visit	**V16**	**V17**[a]	**V18**	**V19**	**V20**	**V21**
Visit at clinical site[b]	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X
IRT contact (Dispensing)	X		X	X	X	X
Study treatment administration						
avalglucosidase alfa	X		X	X	X	X
Safety						
Urine pregnancy test[c]			X		X	
Physical examination[d]			X[a]		X[a]	
Body weight	X[a]		X		X	
Vital signs[e]	X		X	X	X	X
ECG[f]			X[a]			
Biochemistry[g]		X	X		X	
Anti-avalglucosidase alfa antibodies(with testing for neutralizing antibodies in anti-avalglucosidase alfa antibody positive patients)[h]		X	X[a]		X[a]	
Adverse event collection	X	X	X	X	X	X
Pharmacokinetics[i]						
avalglucosidase alfa plasma samples	X[a]					
Efficacy						
Ventilator use diary[j]	X		X	X	X	X

AE = adverse event; BNP = brain natriuretic peptide; β-hCG = beta-human chorionic gonadotropin; CK = creatine kinase; CRF = case report form; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; IRT = interactive response technology

a Visit/assessment is only required for the avalglucosidase alfa switch patients.

b In case of temporary treatment discontinuation, visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in 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, echocardiography, questionnaires) may be carried out over several days (refer to Section 10.1). 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 that no adverse event occurred during the observational period.

c Female patients of childbearing potential only will have a urine β-hCG test.

d Physical examination CRF will ask physician to record current muscle pain and cramps specifically at each PE assessment.

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

f 12-lead ECG after at least 15 minutes in supine position (if supine is feasible for the patient). Review should be done at the site in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In addition, reading will be done by central reader for analyses purposes only.

g Biochemistry panel will include BNP and CK.

h Serum samples are collected pre-infusion at each time point. Additional samples may be taken if clinically indicated in the event of IARs.

i For patients participating in Cohort 3 and switching to avalglucosidase alfa at Week 27, pharmacokinetic sampling will be performed prior to infusion; at the end of infusion; and 2, 4, 6, and 8 hours after the end of infusion at Week 27 and prior to infusion and 2 hours after the end of infusion at Week 37; additionally in the 40 mg/kg dose cohort 12 to 16 hours after the end of infusion at Week 27.

j In the event patient requires ventilator support (invasive or non-invasive) at any time during study treatment the patient will be asked to complete a daily ventilator use diary. On a biweekly basis, the periods of ventilator use/day (daytime, nighttime, both) will be reported by the Investigator based on the ventilator use diary.

1.2.3 Extension period (Week 37 to Week 145)

Period	Extension Period									
Timing	**9 Month (Week 37)**	**12 Month (Week 49)**	**15 Month (Week 61)**	**18 Month (Week 73)**	**21 Month (Week 85)**	**24 Month (Week 97)**	**27 Month (Week 109)**	**30 Month (Week 121)**	**33 Month (Week 133)**	**36 Month (Week 145)**
Visit[a]	**V22**	**V28**	**V34**	**V40**	**V46**	**V52**	**V58**	**V64**	**V70**	**V76**
Visit at clinical site	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X
Study treatment administration										
IRT contact (Dispensing)	X	X	X	X	X	X	X	X	X	X
avalglucosidase alfa infusion[b]	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X
Safety										
Urine pregnancy test[d,e]	X	X	X	X	X	X	X	X	X	X
Physical examination[f]	X	X	X[g]	X[g]		X		X		X
Height/body length/head circumference[h]	X	X	X	X		X		X		X
Body weight[e]	X	X	X	X	X	X	X	X	X	X
ECG[i]	X[g]	X		X		X		X		X
Hematology, urinalysis		X		X		X		X		X
Biochemistry[j]	X[k]	X[k]	X[k]	X[k]	X	X	X	X	X	X
Anti-avalglucosidase alfa antibodies (with testing for neutralizing antibodies in anti-avalglucosidase alfa antibody positive patients)[l]	X[m]	X[m]	X	X	X	X	X	X	X	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics[n]										
avalglucosidase alfa plasma samples	X	X								
Pharmacodynamics										
Urine Hex4 samples[o]		X		X		X		X		X
[redacted]										
Muscle biopsy (optional)[q]		X[g]								X
Efficacy										
Ventilator use diary[r]	X	X	X	X	X	X	X	X	X	X
GMFM-88, GMFCS-E&R		X		X		X		X		X
Motor Skills Checklist		X		X		X		X		X
QMFT		X		X		X		X		X
Pompe-PEDI, Functional Skills Scale: Mobility Domain		X		X		X		X		X
Bayley-III / Leiter-3 scales[s]		X		X		X		X		X
Echocardiography[i]		X		X		X		X		X
Hearing testing[t]		X		X		X		X		X
Eyelid position measurements[u]		X		X		X		X		X
PedsQL Generic Core Scale		X		X		X		X		X

Period	Extension Period									
Timing	9 Month (Week 37)	12 Month (Week 49)	15 Month (Week 61)	18 Month (Week 73)	21 Month (Week 85)	24 Month (Week 97)	27 Month (Week 109)	30 Month (Week 121)	33 Month (Week 133)	36 Month (Week 145)
Visit[a]	V22	V28	V34	V40	V46	V52	V58	V64	V70	V76
questionnaire[v]										
Pediatric Pain Questionnaire[w]		X		X		X		X		X
Pain VAS[w]		X		X		X		X		X
PFT[x]		X		X		X		X		X
6MWT[y]		X		X		X		X		X
Pharmacogenetics										
[redacted]										

6MWT = 6-minute walk test; ADA = anti-drug antibodies; β-hCG = beta-human chorionic gonadotropin; BNP = brain natriuretic peptide; CK = creatine kinase; CRF = case report form; [redacted]; ECG = electrocardiogram; EDTA = Ethylenediaminetetraacetic acid; EOS = end of study; ERT = enzyme replacement therapy; GMFCS-E&R = Gross Motor Function Classification System – Expanded and Revised; GMFM-88 = Gross Motor Function Measure-88; IRT = interactive response technology; PedsQL = pediatric quality of life inventory; Pompe-PEDI = Pompe Pediatric Evaluation of Disability Inventory; PE = physical examination; PFT = pulmonary function testing; QMFT = Quick Motor Function Test; [redacted]; VAS = visual analog scale

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, echocardiography, questionnaires) may be carried out over several days (refer to Section 10.1). 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 that no adverse event occurred during the observational period. For patients undergoing home infusion (as per conditions and instructions provided in Section 8.9.2) visit at clinical site is not required for infusion only visits. Refer to Section 10.1.3 for the concerned weeks details. If avalglucosidase alfa is approved in the patient's country before the patient reaches Week 145, the Week 145 visit will be performed as the end of treatment visit.

b Avalglucosidase alfa to be administered at study site every other week. As per conditions and instructions provided in Section 8.1.2, avalglucosidase alfa infusion may occur at home.

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

d Female patients of childbearing potential only will have a urine β-hCG test.

e Monthly.

f Physical examination CRF will ask physician to record current muscle pain and cramps specifically at each PE assessment. Tanner stage will be assessed as part of the PE assessment at Week 49, Week 97 and Week 145.

g For Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa only.

h To be measured at screening/baseline, every 3 months up to Week 73 and then every 6 months until Week 145/EOS in all patients.

i 12-lead ECG after at least 15 minutes in supine position (if supine is feasible for the patient). Review should be done at the site in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In addition, reading will be done by central reader for analyses purposes only.

j Biochemistry panel will include BNP and CK.

k Biochemistry in all patients will additionally be collected monthly for the first 6 months of the extension period (Week 29, Week 33, Week 37, Week 41, Week 45, and Week 49) and for patients who switch to avalglucosidase alfa in Stage 2 – Cohort 3 for 6 more months (Week 53, Week 57, Week 61, Week 65, Week 69, Week 73).

l Serum samples are collected pre-infusion at each time point. Additional samples may be taken if clinically indicated in the event of IARs.

m Anti-avalglucosidase alfa antibodies (with testing for neutralizing antibodies for avalglucosidase alfa antibody positive patients) in Stage 2 - Cohort 3 avalglucosidase alfa switch patients will be collected monthly for the first 6 months of the extension period (Week 29, Week 33, Week 37, Week 41, Week 45, Week 49).

n For patients participating in Cohort 3 and switching to avalglucosidase alfa at Week 27, pharmacokinetic sampling will be performed prior to infusion; at the end of infusion; and 2, 4, 6, and 8 hours after the end of infusion at Week 49 and prior to infusion and 2 hours after the end of infusion at Week 37; additionally in the 40 mg/kg dose cohort 12 to 16 hours after the end of infusion at Week 49.

o [redacted]

p 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 labs (hematology, biochemistry, ADA) and PK and [redacted].

q Time points are suggested time points.

r In the event patient requires ventilator support (invasive or non-invasive) at any time during study treatment the patient will be asked to complete a daily ventilator use diary. On a biweekly basis (including for patients receiving home infusions, see Section 8.9.2), the periods of ventilator use/day (daytime, nighttime, both) will be reported by the Investigator based on the ventilator use diary.

s The Bayley-III will be administered to patients from 1 month of age until the maximum score on each of the 3 administered scales has been obtained. Once the maximum score for a scale has been achieved, only the remaining scales will be administered. Bayley-III is to be discontinued when the patient reaches 42 months of age. Leiter-3 Scale assessment is to be performed at the last assessment of the Bayley-III Scales prior to the patient reaching 42 months of age. In case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment, the patients should be assessed by the Bayley-III regardless of the patient's age.

t Hearing testing includes audiogram and brainstem auditory evoked potentials.

u Separate informed consent will be sought to permit for the acquisition and use of photographs of the patient's eyes in order to allow for independent review of eyelid position measurements by a central reader.

v PedsQL Generic Core Scales will be used in pediatric patients 2 years and older, using age appropriate reports

w Pain will be assessed by PedsQL Pediatric Pain Questionnaire for patients >5 years of age. Observer reported Pain VAS will be recorded in patients of all ages.

x Pulmonary function tests are not required for patients unable to reliably undergo testing or for patients who are invasively ventilated.

y 6MWT in patients who are able to ambulate at least 40 meters (approximately 130 feet) without stopping and without an assistive device.

1.2.4 Extended long-term treatment period

Period	Extended long-term treatment period					
Timing[a]	Biweekly[b]	Every 4 weeks (Monthly)	Every 12 weeks (Quarterly)	Every 24 weeks (Every 6 Months)	Every 48 weeks (Yearly)	End of treatment Visit[c, a]
Visit at clinical site[c]	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X
Study treatment administration						
IRT contact (Dispensing)	X	X	X	X	X	X
avalglucosidase alfa infusion[d]	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X	X
Safety						
Urine pregnancy test[f]		X	X	X	X	X
Physical examination[g]				X	X	X
Height/body length/head circumference				X	X	X
Body weight		X	X	X	X	X
ECG[h]					X	X
Hematology[i], urinalysis				X	X	X
Biochemistry[i,l, k]				X	X	X
Anti-avalglucosidase alfa antibodies (with testing for neutralizing antibodies in anti-avalglucosidase alfa antibody positive patients) [j,i]			X	X	X	X
Adverse event collection	X	X	X	X	X	X
Efficacy						
Ventilator use diary[m]	X	X	X	X	X	X
GMFM-88, GMFCS-E&R					X	X
Motor Skills Checklist					X	X
QMFT					X	X
Pompe-PEDI, Functional Skills Scale: Mobility Domain					X	X
Leiter-3 scales (Bayley-III scale)[n]					X	X
Echocardiography[h]					X	X
Hearing testing[o]					X	X
Eyelid position measurements[p]				X	X	X
PedsQL Generic Core Scale questionnaire[q]					X	X
PFT[s]					X	X
6MWT[t]					X	X

6MWT = 6-minute walk test; β-hCG = beta-human chorionic gonadotropin; BNP = brain natriuretic peptide; CK = creatine kinase; CRF = case report form; ECG = electrocardiogram; GMFCS-E&R = Gross Motor Function Classification System – Expanded and Revised; GMFM-88 = Gross Motor Function Measure-88; IRT = interactive response technology; PE = physical examination; PFT = pulmonary function testing; PedsQL = pediatric quality of life inventory; Pompe-PEDI = Pompe Pediatric Evaluation of Disability Inventory; QMFT = Quick Motor Function Test; VAS = visual analog scale

a Refer to Section 10.1.4 for the concerned weeks details. Patients who permanently discontinue the study treatment prior to the scheduled end of treatment during the extended long-term treatment period will have assessments corresponding to the end of treatment visit. If the end of treatment visit occurs at the same time as a yearly visit, the yearly visit will not be performed.

b In case of temporary treatment discontinuation, visit and assessment schedules will be adapted to the absence of infusion of avalglucosidase alfa as outlined in 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, echocardiography, questionnaires) may be carried out over several days (refer to Section 10.1).

c For patients undergoing home infusion (as per conditions and instructions provided in Section 8.9) visit at clinical site is not required for infusion only visits.

d Avalglucosidase alfa to be administered at study site every other week. 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 that no adverse event occurred during the observational period. As per conditions and instructions provided in Section 8.1.2, avalglucosidase alfa infusion may occur at home.

e At every infusion. Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation and 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. Collection windows are ±15 minutes.

f Female patients of childbearing potential only will have a urine β-hCG test.

g Physical examination CRF will ask physician to record current muscle pain and cramps specifically at each PE assessment. Tanner stage will be assessed as part of the PE assessment.

h 12-lead ECG after at least 15 minutes in supine position (if supine is feasible for the patient). Review should be done at the site in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In addition, reading will be done by central reader for analyses purposes only. Echocardiography can be performed on a more frequent basis upon need of abnormality follow-up.

i 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.

j Serum samples are collected pre-infusion at each time point. Additional samples may be taken if clinically indicated in the event of IARs.

k Fasted sample, prior to IMP infusion.

l Biochemistry panel will include BNP and CK.

m In the event patient requires ventilator support (invasive or non-invasive) at any time during study treatment the patient will be asked to complete a daily ventilator use diary. On a biweekly basis (including for patients receiving home infusions, see Section 8.9.2), the periods of ventilator use/day (daytime, nighttime, both) will be reported by the Investigator based on the ventilator use diary.

n Leiter-3 Scale assessment is to be performed at the last assessment of the Bayley-III Scales prior to the patient reaching 42 months of age. In case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment, the patients should be assessed by the Bayley-III regardless of the patient's age.

o Hearing testing includes audiogram and brainstem auditory evoked potentials.

p Separate informed consent will be sought to permit for the acquisition and use of photographs of the patient's eyes in order to allow for independent review of eyelid position measurements by a central reader.

q PedsQL Generic Core Scales will be used in pediatric patients 2 years and older, using age appropriate reports.

r Pain will be assessed by PedsQL Pediatric Pain Questionnaire for patients >5 years of age. Observer reported Pain VAS will be recorded in patients of all ages.

s Pulmonary function tests are not required for patients unable to reliably undergo testing or for patients who are invasively ventilated.

t 6MWT in patients who are able to ambulate at least 40 meters (approximately 130 feet) without stopping and without an assistive device.

1.2.5 End of study

Period	End of Study Visit/Contact[a]
Day (D) or Week (W)	**4 weeks after the last IMP infusion**
Visit	**EOS**
Concomitant medications/therapies	X
AE collection	X

AE = adverse event; EOS = end of study; ERT = enzyme replacement therapy; IMP = investigational medicinal product.

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.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

Not applicable.

3 LIST OF ABBREVIATIONS

4-MUG: 4-methylumbelliferyl-α-D glucoside
6MWT: 6-minute walk test
[redacted] [redacted]
ADA: anti-drug antibody
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ATS: American Thoracic Society
$AUC_{0\text{-last}}$: area under the curve from time 0 to time of the last quantifiable concentration
BAEPs/BAERs: Brainstem auditory evoked potentials/responses
BfArM: Federal Institute for Drugs and Medical Devices
bis-M6P: bis-mannose-6-phosphate
BNP: brain natriuretic peptide
CDMS: clinical data management system
CFR: Code of Federal Regulations
CIOMS: Council for International Organizations of Medical Sciences
CK: creatine kinase
CL: total body clearance of a drug from plasma
C_{max}: maximum plasma concentration observed
COVID-19: Coronavirus disease 2019
CRF: case report form
CRIM: cross-reactive immunologic material
[redacted] [redacted]
DMC: data monitoring committee
ECG: electrocardiogram
ECHO: echocardiography
e-CRF: electronic case report form
EDTA: ethylenediaminetetraacetic acid
EOS: end of study
ERT: enzyme replacement therapy
FDA: US Food and Drug Administration
FVC: forced vital capacity
GAA: acid α-glucosidase
GCP: Good Clinical Practice
GDPR: General Data Protection Regulation
GMFCS-E&R: Gross Motor Function Classification System - Expanded and Revised
GMFM-88: Gross Motor Function Measure-88
GSD: glycogen storage disorder
HIPAA: Health Insurance Portability and Accountability Act
HRQOL: health-related quality of life

IAR:	infusion-associated reaction
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	independent ethics committee
Ig:	immunoglobulin
IgE:	immunoglobulin E
IMP:	investigational medicinal product
IOPD:	infantile-onset Pompe disease
IPFD:	interpalpebral fissure distance
IRB:	institutional review board
IRT:	interactive response technology
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IV:	intravenous
LLOQ:	lower limit of quantitation
LOPD:	late-onset Pompe disease
LVM:	left ventricular mass
LVMI:	left ventricular mass index
M6P:	mannose-6-phosphate
MedDRA:	Medical Dictionary for Regulatory Activities
MEP:	maximal expiratory pressure
MHRA:	Medicines and Healthcare products Regulatory Agency
MIP:	maximal inspiratory pressure
mITT:	modified intent to treat
MPD:	margin pupil distance
MPS-I:	mucopolysaccharidosis type-I
MRD-1:	margin reflex distance
MTD:	maximum tolerated dose
PAP:	primary analysis period
PCR:	polymerase chain reaction
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic(s)
PE:	physical examination
PFT:	pulmonary function test
PK:	pharmacokinetic(s)
Pompe-PEDI:	Pompe Pediatric Evaluation of Disability Inventory
PPT:	plasma preparation tube
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

qw:	weekly
rhGAA:	recombinant human acid α-glucosidase
RR:	interval between the peaks of successive QRS complexes
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
$t_{1/2z}$:	terminal half-life
TEAE:	treatment-emergent adverse event
t_{max}:	time to achieve maximum plasma concentration
ULN:	upper limit of normal
VAS:	visual analog scale
VAS-OBS:	Observational Visual Analogue Score
Vd:	volume of distribution
WOCBP:	women of childbearing potential
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

Pompe disease (also known as acid maltase deficiency or glycogen storage disorder (GSD) type II) is a rare, autosomal recessive genetic disorder caused by the deficiency of lysosomal acid α-glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells leading to a variety of symptoms, clinical decline and ultimately death. In addition to being a lysosomal storage disorder, Pompe disease is also considered a neuromuscular disease, a metabolic myopathy, and a GSD. The estimated global incidence of Pompe disease is 1:40,000, with variations in incidence reported between different ethnic groups (1, 2, 3, 4).

All presentations of Pompe disease are caused by the same underlying deficiency of lysosomal GAA. However, there is significant heterogeneity in the clinical presentation of Pompe disease, and the disease manifests as a broad clinical spectrum with a continuum of clinical signs and symptoms (4, 5, 6, 7). Pompe disease has been classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form of the disease to a more slowly progressive late-onset form (with symptom onset any time after infancy through adulthood), although there is considerable variability and overlap between these 2 extremes. The majority of patients with Pompe disease are classified with the late-onset subtype.

The most significant clinical manifestations of infantile-onset Pompe disease (IOPD) include cardiac abnormalities and muscle weakness leading to respiratory insufficiency (4). Infant patients present with cardiomegaly and cardiomyopathy leading to arrhythmias and cardiac failure (8). General muscle weakness causes a “floppy baby” appearance and impacts respiratory muscle function, commonly resulting in frequent infections and the requirement of assisted ventilation by six months of age (9). Further, infants with Pompe disease fail to meet early developmental milestones, like rolling and sitting, or experience regression if a skill is acquired (6). They also, experience difficulty in feeding, failure to thrive, hypotonia, and hepatomegaly (6, 10). In a natural history study of 168 infants, the ventilator-free survival rate was 16.9% at 12 months, 8.5% at 18 months, and 4.9% at 24 months (9). Death typically occurs due to respiratory or cardiac failure before one year of age (6).

Sanofi Genzyme has developed alglucosidase alfa, which contains the active ingredient recombinant human acid α-glucosidase (rhGAA), as long-term enzyme replacement therapy (ERT) for patients with a confirmed diagnosis of Pompe disease. Alglucosidase alfa treatment is globally approved (tradenames Myozyme® and Lumizyme®) for the treatment of Pompe disease based on its efficacy to prolong invasive ventilator free survival in infants (11, 12) and its ability to stabilize respiratory function in children and adults with the disease (13). To achieve these benefits alglucosidase alfa is administered at a dose of 20 mg/kg every other week. Echocardiography measurements demonstrate that alglucosidase alfa works well in cardiac muscle. There is a more variable response to treatment in skeletal muscle. This is thought to be, at least in part, due to the relative low level of bis-mannose-6-phosphate (bis-M6P) on alglucosidase alfa. Therefore, increasing the level of bis-M6P on alglucosidase alfa may provide a mechanism to drive uptake into the skeletal muscle.

Treatment of patients with IOPD with alglucosidase alfa has shown to be effective, especially if initiated shortly after birth. However, an unmet medical need exists in a proportion of IOPD patients treated with alglucosidase alfa at 20 mg/kg qow, who demonstrate sub-optimal treatment response, more precisely residual myopathy, and who may benefit from more potent treatment (14, 15, 16). Recent publications of clinical experience in IOPD patients receiving alglucosidase alfa doses greater or at higher frequency than the label dose of 20 mg/kg qow reflect generally good tolerance and safety experience of alternate dosing regimens (14, 17).

Sanofi Genzyme is investigating a second generation ERT for Pompe disease called avalglucosidase alfa (rhGAA [alglucosidase alfa] conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan); alglucosidase alfa 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 two 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).

The benefits and risks assessment of avalglucosidase alfa for the Phase 2 ACT14132 study is based upon the nonclinical studies of avalglucosidase alfa in 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 late-onset Pompe disease [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; adverse events (AEs) and infusion-associated reactions (IARs) are mostly nonserious 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.

A risk of acute cardiorespiratory failure requiring intubation and inotropic support after infusion in IOPD patients with underlying cardiac hypertrophy is considered based on experience with alglucosidase alfa and due to fluid overload. Appropriate medical support and monitoring measures should be readily available during avalglucosidase alfa infusion, and infants with cardiac dysfunction may require prolonged observation times that should be individualized based on the needs of the patient. Caution should be taken with fluid volume infusion.

The ACT14132 study will be the first exposure of avalglucosidase alfa in the IOPD population. The primary objective of this phase 2, open-label ascending dose cohort study is the assessment of safety and tolerability of administering avalglucosidase alfa in male and female pediatric patients with IOPD, who have been previously treated with alglucosidase alfa and demonstrated clinical decline or sub-optimal clinical response in specified respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis. The proposed starting dose is aligned with the adult dosing in the completed open-label ascending dose study of repeated biweekly infusions of avalglucosidase alfa (TDR12857), in which safety and generally good tolerability was shown at all dose levels (5 mg/kg qow, 10 mg/kg qow and 20 mg/kg qow) in adult LOPD patients, who

were both treatment-naïve and previously treated with alglucosidase alfa, is also based on experience with alglucosidase alfa treatment, including similar alglucosidase alfa PK profile in pediatric and adult patients (Genzyme Study AGLU01602 and Genzyme Study AGLU02704). The 40 mg/kg qow dose is based on previous experience of overall good tolerance of alglucosidase alfa administration at 40 mg/kg in both clinical practice and clinical trial settings and is consistent with what is observed in clinical practice when IOPD patients do not respond to 20 mg/kg qow dose of alglucosidase alfa and then receive 40 mg/kg of alglucosidase alfa (14, 17, 18, Clinical Trials AGLU01602, AGLU01702, AGLU09411). In the present study avalglucosidase alfa doses are planned to be administered in an ascending manner between the first and second cohorts, supported by the monitoring of potential safety signals by an independent data monitoring committee (DMC). See Appendix C (Section 17.3.2) for an addendum to this section for Germany only.

The first patients (at least 5) will be enrolled in the 20 mg/kg qow dose cohort. A decision to proceed from the 20 mg/kg qow dose to 40 mg/kg qow will be made by the Sponsor following a formal review by the DMC of Cohort 1 safety data after the third patient receives their third infusion of avalglucosidase alfa at 20 mg/kg qow.

The relevant data for this decision should be, at a minimum, AEs including IARs, biochemistry results, electrocardiogram (ECG), blood pressure, and heart rate and any available immunology results as applicable.

Depending on the tolerability profile observed in the dose level cohort of 20 mg/kg qow, one of the following decisions will be taken for the dose level cohort of 40 mg/kg qow:

- Dose escalation may continue as scheduled.
- The same dose may be administered in an additional cohort.
- A higher intermediate dose between the current dose of 20 mg/kg qow and the next planned dose of 40 mg/kg qow may be administered to the next cohort.
- A dose lower than current dose of 20 mg/kg qow may be administered to the next cohort, including the possibility of administering a lower dose than the starting dose.
- ACT14132 may be stopped.

For the purpose of this study, criteria as outlined in Section 10.3.1, Section 10.3.2, and Section 10.3.3, should be considered as guidance for the decision to stop avalglucosidase alfa administration to a patient or to stop the trial.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to evaluate the safety profile of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa.

5.2 SECONDARY

Secondary objectives are to characterize the pharmacokinetic (PK) profile of avalglucosidase alfa and to evaluate the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa.

5.3 OTHER

Additional objectives are to determine [redacted] effect of avalglucosidase alfa treatment on functional endurance, respiratory function, health-related quality of life (HRQOL), pain, developmental disability, and hearing in patients with IOPD.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

ACT14132 is a multi-stage, phase 2, open-label, multicenter, multinational, ascending dose cohort, repeated intravenous (IV) infusion study of avalglucosidase alfa in pediatric patients with IOPD who have been previously treated with alglucosidase alfa and demonstrated clinical decline (Stage 1) or sub-optimal clinical response (Stage 2) in specified respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis.

Stage 1

- Cohort 1 – at least 5 IOPD patients will receive avalglucosidase alfa at 20 mg/kg qow for 6 months.
- Cohort 2 – at least 5 IOPD patients will receive avalglucosidase alfa at 40 mg/kg qow for 6 months.

Stage 2

- Cohort 3 – at least 10 IOPD patients will be randomized 1:1 to receive avalglucosidase alfa at the highest tolerated avalglucosidase alfa dose in Stage 1 (20 mg/kg qow or 40 mg/kg qow) or alglucosidase alfa treatment at current stable dose (defined by dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry) for 6 months. The randomization will be stratified on gender.

The first 5 patients will be enrolled in the 20 mg/kg qow dose cohort. If determined safe by an independent DMC after the 3rd patient in the 20 mg/kg qow group (Cohort 1) has received the 3rd infusion of avalglucosidase alfa and after 5 patients have started treatment in Cohort 1, the next cohort of avalglucosidase alfa at higher dose (40 mg/kg qow) will be initiated (Cohort 2). Cohort 3 will be initiated after determination of the highest tolerated avalglucosidase alfa dose in Cohort 1 and Cohort 2 after at least 5 patients in Cohort 1 and at least 5 patients in Cohort 2 have received the 7th dose of avalglucosidase alfa (or completed Week 13 with a minimum of 6 infusions).

After completion of treatment for 6 months (Week 25) and data collection for the principal analysis, the patients will continue on long-term avalglucosidase alfa treatment and follow-up in the Extension Period for up to a total of 7 years in the study. Cohort 3 patients receiving alglucosidase alfa will have the option to switch to treatment with avalglucosidase alfa in the extension period or discontinue the study. The data cut-off for the primary analysis will be after the last patient in Cohort 3 has completed 6 months of treatment (Week 25).

Safety, efficacy, PK and [redacted] will be performed at scheduled visits throughout the study treatment period. Ventilator use, AEs and concomitant and pre-infusion medications/therapies will be monitored continuously throughout the study.

If a patient in Cohort 1, receiving 20 mg/kg qow avalglucosidase alfa, experiences further clinical decline at or after Week 25 when compared to prior to enrollment in ACT14132, and as defined by more rapid worsening of criteria of clinical decline, which is sustained on repeated study

assessments, the patient may be managed per the discretion of the Investigator, which may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation) or increasing the avalglucosidase alfa dose to 40 mg/kg qow (once this dose is considered acceptable after the end-of-cohort 2 DMC meeting) or maximum tolerated dose (MTD) (once established) while being enrolled in the extension period of the study.

If a patient in Cohort 2 or 3 experiences further clinical decline at or after Week 25 as defined by more rapid worsening of criteria of clinical decline than prior to study start, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator. This may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation).

Patients must have completed the 25-week treatment period of the study before dose increase of avalglucosidase alfa (or start of avalglucosidase alfa for patients receiving alglucosidase alfa in Cohort 3) will be considered.

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 7 years, including:

- An up to 14-day screening period (may be extended to up to 4 weeks in pre-specified situations [refer to Section 10.1.1]);
- A 25-week treatment period (primary analysis period [PAP]);
- A 120-week extension period.
- An up to 226-week extended long-term treatment period or until avalglucosidase alfa is approved in the patient's country, whichever comes first; (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients)
- 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

While all patients will be followed for up to 7 years during the study, the primary analysis for the study will be performed when all Cohort 3 patients have completed the 6-month primary analysis period (PAP). In addition, safety analyses will be performed in multiple time points by the DMC (see Section 6.4.1) to determine the dose for next cohort and the MTD.

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

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

An independent DMC, appointed by the Sponsor, will review 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, formal safety review will be performed by the DMC:

- After the third avalglucosidase alfa infusion for the third patient in Cohort 1 at a dose level of 20 mg/kg qow;
- After at least 5 patients in Cohort 1 and at least 5 patients in Cohort 2 have received their seventh avalglucosidase alfa infusion or completed Week 13 with a minimum of 6 infusions at dose levels of 20 mg/kg qow and 40 mg/kg qow (if considered safe in Cohort 1), respectively;
- Bi-annually, including at the time of the end of the PAP (all patients have been treated with avalglucosidase alfa or alglucosidase alfa for at least 6 months) and at the end of the study.

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 an allergist/immunologist, who could be a member of the DMC. 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).

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. The patient who has reached legal age of majority as defined by local regulation or the patient's legal guardian(s) must provide signed informed consent prior to any study-related procedures being performed. If the patient is legally minor per local regulations, assent shall be obtained from the patient, if applicable.

I 02. The patient must have a documented GAA deficiency from blood, skin or muscle tissue for confirmation of diagnosis of IOPD.

I 03. The patient is aged <18 years old.

I 04. The patient has cardiomyopathy at the time of diagnosis: ie, left ventricular mass index (LVMI) equivalent to mean age specific LVMI plus 2 standard deviations as published by Vogel (19).

I 05. The patient has been receiving a stable dose of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry.

For patients participating in Stage 1: Clinical Decliners Dose Cohort 1 & 2

I 06. The patient has evidence of clinical decline in at least 1 of the following parameters related to Pompe Disease and NOT related to intercurrent illness as assessed by the Investigator. To document decline, at least 2 recent and consecutive assessments prior to study entry, not less than 2 weeks apart, are required, in addition to at least 1 previous assessment prior to onset of decline:

- *Respiratory Function*
  New development or worsening of respiratory failure requiring the use or increased use of ventilatory assistance (invasive or non-invasive). Ventilatory assistance must have been required for at least 4 weeks prior to study enrollment,

  OR

- *Motor Skills*
  For patients ≤2 years of age at study entry, failure to acquire at least 2 new age appropriate gross motor milestones at least 6 months prior to study enrollment, eg:
  - Turning head side to side (supine)
  - Grasping small objects with hands
  - Transferring objects from hand to hand
  - Holding head upright with body supported
  - Rolling (supine to prone or prone to supine)

- Sitting (supported or unsupported)
- Transition in and out of sitting (lying to sitting, sitting to quadruped)
- Crawling
- Pull to stand
- Walking (with support, ie, cruising, or independently)
- Squatting (stand to squat, squat to stand),
- Walking up stairs (with assistance or independently)

OR

For patients >2 years of age at study entry, documented worsening of muscle weakness demonstrated by a loss of one of the following:

- Independent ring
- Independent ascending and descending stairs
- Independent walking
- Walking with an assistive device
- Transitions from the floor to standing
- Crawling
- Independent sitting
- Transitioning in and out of sitting
- Holding head up in sitting
- Functional use of upper extremities

OR

- Cardiac Parameters

  Left ventricular mass (LVM) Z-score ≥ 6 or LVMI ≥ 150 g/m^2.

For patients participating in Stage 2: Sub-optimal Responders Dose Cohort 3

I 07. The patient has evidence of sub-optimal clinical response in at least 1 of the following parameters related to Pompe Disease and NOT related to intercurrent illness as assessed by the Investigator. To document sub-optimal response, at least 2 recent and consecutive assessments prior to study entry, not less than 2 weeks apart, are required in addition to at least 1 previous assessment prior to onset of decline:

- *Respiratory Function*
  Documented sustained decline in relative % predicted forced vital capacity (FVC) change ≥15% or new onset of non-invasive ventilator assistance. Ventilatory assistance must have been required for at least 4 weeks prior to study enrollment,

OR

- *Motor Skills*
  Documented worsening of muscle strength demonstrated by a developmental plateau or

decrease on the Gross Motor Function Measure-88 (GMFM-88) and/or in scaled score of the Pompe-Pediatric Evaluation of Disability Inventory (Pompe-PEDI), Functional Skills Scale: Mobility Domain, or in other motor scale and/or clinical developmental evaluation tools,

OR

- *New onset of ptosis*
  The occurrence of ptosis (drooping eyelids), confirmed by at least 2 sequential assessments.

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 three subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. The patient has high antibody titer (anti-alglucosidase alfa antibody titer ≥1:25600) at 2 consecutive time points not less than 1 month apart.

E 02. The patient is concurrently participating in another clinical study using investigational treatment or has taken other investigational drugs within 30 days or 5 elimination half-lives of the investigational drugs from screening or randomization, whichever is longer.

E 03. The patient has previously been treated in any cohort of the ACT14132 study.

E 04. 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, and which may be reflected in corresponding abnormal laboratory parameters, that, in the opinion of the Investigator, precludes participation in the study or potentially decreases survival.

E 05. The patient has a high risk for a severe allergic reaction to avalglucosidase alfa (ie, previous moderate to severe anaphylactic reaction to alglucosidase alfa and/or patient has immunoglobulin E [IgE] antibodies to alglucosidase alfa, and/or a history of high sustained immunoglobulin G [IgG] antibody titers to alglucosidase alfa that in the opinion of the Investigator suggest a high risk for an allergic reaction to avalglucosidase alfa).

E 06. The patient, in the opinion of the Investigator, requires any prohibited concomitant medications (eg, immune modulatory treatment) for the duration of the study.

E 07. The patient and/or their parent/legal guardian, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

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 compound

E 08. Pregnant or breast-feeding female patient.

E 09. 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 serum 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.

E 10. 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]).

Note: Sexually active female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or to use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device (IUD), 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 subjects (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]).

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

E 11. Patient who has withdrawn consent before enrollment/randomization (starting from signed ICF).

E 12. 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 13. Any country-related specific regulation that would prevent the subject from entering the study.

If a patient does not meet all inclusion criteria or meets one or more exclusion criterion during the screening period, the patient may rescreen for the study once. The rescreening must be at least 14 days after the initial screening failure.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Avalglucosidase alfa will be supplied as a sterile, nonpyrogenic, lyophilized product in single-use vial containing approximately 100 mg of avalglucosidase alfa. Alglucosidase alfa 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.

Quantity of vials required for each infusion will be calculated by IRT based on the patient`s weight. The total amount of investigational product administered may be adjusted as needed to account for changes in body weight. Most recent body weight should be used for dose calculation; weight obtained at a previous infusion visit may be used for preparation of IMP, if obtained within a timeframe of 1 month. 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. For alglucosidase alfa only, the diluted solution should be filtered through a 0.2 – 0.22 micron, low protein-binding, in-line filter during administration to remove any visible particles. 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 alglucosidase alfa as outlined in Section 8.9.1, conditions and instructions provided in Section 8.9.2 for patients who receive home infusion of avalglucosidase alfa) 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 inform the DMC of any dose change related to AEs. For avalglucosidase alfa, no dose increase above the MTD of 20 mg/kg qow or 40 mg/kg qow (once determined) 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 Section 8.9.2 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.

Patients in the alglucosidase alfa arm in Stage 2 (Cohort 3) have the option to switch to avalglucosidase alfa treatment after the 6-month treatment period or discontinue the study.

For qow infusions, a time frame of ±7 days is acceptable using Day 1 as reference. For alglucosidase alfa weekly (qw) infusions, a time frame of ±3 days is acceptable using Day 1 as reference (If one visit date is changed, the next visit should take place according to the original schedule).

The study includes 2 main periods, the 25-week treatment period and the up to 346-week extension period.

8.1.1 Treatment period: Day 1 to Week 25 (Month 6)

Stage 1 (Cohort 1 and Cohort 2)

Cohort 1: At least 5 patients will receive avalglucosidase alfa by IV infusion following reconstitution and dilution at a dose of 20 mg/kg body weight every other week (qow) starting at V2/Day 1 continuing up to V15/W25 for a total of 13 doses (6 months).

Cohort 2: If determined safe by an independent DMC after the 3rd patient in the 20 mg/kg qow group (Cohort 1) has received the 3rd infusion of avalglucosidase alfa, the next cohort of avalglucosidase alfa at higher dose (40 mg/kg qow) will be initiated (Cohort 2) after at least 5 patients have started treatment in Cohort 1.

At least five patients in Cohort 2 will receive avalglucosidase alfa by IV infusion following reconstitution and dilution at a dose of 40 mg/kg body weight every other week (qow) starting at V2/Day 1 continuing up to V15/W25 for a total of 13 doses (6 months).

Stage 2 (Cohort 3)

Cohort 3: This cohort will be initiated after determination of the highest tolerated avalglucosidase alfa dose in Cohort 1 and Cohort 2 after at least 5 patients in Cohort 1 and at least 5 patients in Cohort 2 have received the 7th dose of avalglucosidase alfa (or completed Week 13 with a minimum of 6 infusions). At least 10 patients will be randomized 1:1 in an open-label manner in Cohort 3 to receive avalglucosidase alfa at the highest tolerated dose determined in Stage 1 or alglucosidase alfa treatment at current stable dose (defined by dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry) for the treatment duration of 6 months.

- Patients randomized into avalglucosidase alfa arm will receive avalglucosidase alfa by IV infusion following reconstitution and dilution every other week (qow) at the highest tolerated dose determined in Stage 1, starting at V2/Day 1 continuing up to V15/W25 for a total of 13 doses (6 months).
- Patients randomized into alglucosidase alfa arm will continue to receive alglucosidase alfa by IV infusion following reconstitution and dilution at their current stable dose (defined by the dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry) for the duration of 6 months.

After completion of treatment for 6 months (Week 25) and data collection for the principal analysis, the patients will continue on long-term avalglucosidase alfa treatment and follow-up for up to a total of 7 years in the study.

Cohort 3 patients receiving alglucosidase alfa during the treatment period (Day 1 to Week 25 [Month 6]) will have the option to switch to treatment with avalglucosidase alfa in the extension period or discontinue the study.

8.1.2 Extension period: Week 27 to Week 145 (Month 36) and additional extension period from Week 147 onwards

All patients (from Cohorts 1, 2 and 3) will receive avalglucosidase alfa administered by IV infusion qow starting at V16/W27 continuing up to V76/W145 for a total of up to 60 doses. 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 226 weeks or until avalglucosidase alfa is approved in the patient's country, whichever comes first; (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients) in which the patients will receive avalglucosidase alfa administered by IV infusion qow for up to an additional 72 doses.

- Participants in Cohort 1 will receive avalglucosidase alfa at a dose of 20 mg/kg qow. If a patient in Cohort 1, receiving 20 mg/kg qow avalglucosidase alfa, experiences further clinical decline at or after Week 25 when compared to prior to enrollment in ACT14132, and as defined by more rapid worsening of criteria of clinical decline, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator, which may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation) or increasing the avalglucosidase alfa dose to 40 mg/kg qow (once this dose is considered acceptable after the end-of-cohort 2 DMC meeting) or MTD (once established) while being enrolled in the extension period of the study.
- Participants in Cohort 2 will receive avalglucosidase alfa at 40 mg/kg qow or MTD (once established).
- Participants in Cohort 3 will receive the MTD of avalglucosidase alfa as determined based on safety data from both dose levels in Cohort 1 and Cohort 2.

If a patient in Cohort 2 or 3 experiences further clinical decline at or after Week 25 as defined by more rapid worsening of criteria of clinical decline than prior to study start, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator. This may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation).

Patients must have completed the 25-week treatment period of the study before dose increase of avalglucosidase alfa (or start of avalglucosidase alfa for patients receiving alglucosidase alfa in Cohort 3) will be considered.

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.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

This study is an open-label design.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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, in Stage 2 of the study (Cohort 3), at least 10 eligible IOPD patients will be randomized 1:1 to receive avalglucosidase alfa at the highest tolerated avalglucosidase alfa dose in Stage 1 or alglucosidase alfa treatment at current stable dose for 6 months (defined by dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry). The randomization will be stratified on gender.

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. 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 pharmacist or for Cohort 3 patients in the alglucosidase alfa arm already receiving home infusions, the Investigator or the Subinvestigator.

IMP accountability:

- Pharmacist or designee will record precisely the date, time of the drug administration and number of treatment units used for administration in the corresponding logs.
- The pharmacist or designee records the lot number of the treatment assigned by the central treatment allocation system/IRT at each visit in the appropriate log.
- The 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 (or ±3-day window if the participant receives alglucosidase alfa qw in the treatment period as part of Cohort 3) from the scheduled infusion date based on V2 (Day 1). 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.

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 by the monitor and written authorization has been provided by the Sponsor.

IMP reconciliation must be performed at the site by the pharmacist or designee and monitor using Treatment Log forms. A written authorization for destruction of used and unused IMP vials 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 AND THERAPY

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-CRFs). 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 log.

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

8.9 HOME INFUSION

8.9.1 Home infusion for patients receiving alglucosidase alfa

Patients who meet the specific criteria below may have the option for home infusion of alglucosidase alfa in countries where home infusion is available according to applicable regional regulations. 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 following criteria must be documented in the patient's medical record:

- For patients who are not receiving home infusions of alglucosidase alfa at study start: the patient must be clinically stable with no history of moderate or severe IARs or serious adverse events (SAEs) prior to study participation and have received at least 4 infusions during study participation with infusions monitored in a hospital or an infusion center prior to planned transition to home infusions.
- For patients who are receiving home infusions of alglucosidase alfa prior to study entry: the patient must be clinically stable with no history of moderate or severe IARs or SAEs prior to study participation and have received at least 2 infusions during study participation with infusions monitored in a hospital or infusion center prior to resuming home infusions.
- The patient must have no ongoing SAEs that, in the opinion of the Investigator, may impact the patient's ability to tolerate infusion.
- For patients receiving home infusions: the Home Infusion Agency staff must be trained by the Investigator prior to beginning home infusions. Any new staff member must be trained by the Investigator prior to resuming home infusions. The Investigator must confirm that the Home Infusion Agency staff has received training at least equivalent to that provided to new staff members.
- 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.
- If recurrent IARs or hypersensitivity/anaphylactic reactions occur, the Investigator should assess whether or not it is safe for the patient 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).
- The Home Infusion Agency must keep source documentation of the infusion, including documentation of any AEs. The Home Infusion Agency must be amenable to providing specific source documentation to the Sponsor and agree to be monitored. The Investigator is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company.

The Investigator is responsible for approving a patient's initiation with home infusions and is ultimately responsible for the safety of the patient during this clinical study. Refer to the home infusion guidance manual and pharmacy manual for further details regarding home infusions.

8.9.2 Home infusion for patients receiving avalglucosidase alfa

Home infusion may be possible in the 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 and their legal guardian(s) must be willing and able to comply with home infusion procedures.
- The patient or their legal guardian(s) has been informed and agreed on home infusion process by a dedicated home infusion staff.
- 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, such as 2020 Coronavirus disease 2019 (COVID-19) outbreak, with DMC agreement, the required period of 12 months with no history of moderate or severe IAR may be reduced to 6 months, to allow home infusion to be started sooner.
- If this reduced required period from at least 12 to at least 6 months is considered safe and after confirmation with the DMC as they did for COVID-19 outbreak, it will be considered as a permanent criterion after the unexpected event is resolved.
- No infusion rate increases higher than the highest rate infused at the clinical site or dose increase will be allowed while a patient is receiving home infusions. In case of dose increase while being infused at home will return to the study site for their following infusion and will continue to receive infusions at the site for at least 6 months. If no IARs have occurred during this 6-month period, home infusion may be resumed.
- 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 17.3.3] 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.
- The Home Infusion Agency must keep source documentation of the infusion, including documentation of any AEs and patient's body weight measured as per study flow chart. The Home Infusion Agency must be amenable to providing specific source documentation to the Sponsor, in agreed upon timeframe, and agree to be monitored. The Investigator 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.
- The periods of ventilator use/day (daytime, nighttime, both) will be reported to the Investigator by the Home infusion Agency based on the ventilator use diary. The Investigator will then report them in the case report form (CRF).
- It is the Investigator's responsibility to guide staff on the clinical management of the patient in case of IARs or hypersensitivity or anaphylactic reactions. The Investigator 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 e-CRF for AEs and exposure.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Safety endpoints

9.1.1.1 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 and therapies.

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 adverse events of special interest (AESIs), 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.

9.1.1.2 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 (CK), CK with MB fraction, lactate dehydrogenase,
  - Brain natriuretic peptide (BNP).

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

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

9.1.1.3 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 that is considered as first infusion rate change), at the end of the infusion, and at the end of the post-infusion observation period. Collection windows are ±15 minutes.

9.1.1.4 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 Subject ID, 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 collected. 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 with a date, time, and Subject ID. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (such as US Food and Drug Administration [FDA] Code of Federal Regulations [CFR], Title 21, Part 11).

The Investigator who reads the ECG or appropriate designee (non-investigator physician who reads the ECG) 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 ECG 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.

9.1.1.5 Physical examination

Physical examination (PE) 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. Physical examination CRF will ask physician to record current muscle pain and cramps specifically at each PE assessment. Tanner stage of sexual maturation will be assessed as part of the PE assessment at baseline and yearly thereafter. Details can be found in the study manual.

9.1.1.6 Body weight, height/length, and head circumference

Body weight will be measured in kilograms and collected monthly throughout the duration of the study. More frequent weight may be obtained at the discretion of the Investigator.

Standing height or body length will be measured at baseline and every 3 months up to Week 73 and then every 6 months and at the end of study (EOS). 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. Standing height is preferred, but if not possible due to patient's age or physical condition, body length is to be measured in the same position throughout the study. Head circumference will be measured at the same time points.

9.1.1.7 Immunogenicity

Immunogenicity assessments will include the following:

- During the treatment period, pre-infusion samples from patients receiving avalglucosidase alfa will be collected at baseline and then every month for evaluation of anti-avalglucosidase alfa anti-drug antibody (ADA) and at baseline and every 3 months (V9 [Week 13], and V15 [Week 25]) for evaluation of anti-alglucosidase alfa ADA. In addition, samples will be collected at V3 (Day 8) to monitor for an early antibody response (for both anti-avalglucosidase alfa ADA and anti-alglucosidase alfa ADA). Pre-infusion samples from patients receiving alglucosidase alfa will be collected at baseline, V3 (Day 8), V9 (Week 13), and V15 (Week 25) for evaluation of anti-alglucosidase alfa ADA and at baseline and V15 (Week 25) for evaluation of anti-avalglucosidase alfa ADA.
- During the extension period, pre-infusion samples from patients receiving avalglucosidase alfa since the start of the study will be collected every 3 months for evaluation of

anti-avalglucosidase alfa ADA. Samples from patients in Cohort 3 switching to avalglucosidase alfa will be collected at V17 (Week 28), V18 (Week 29), and V20 (Week 33) to monitor for an early antibody response (for avalglucosidase alfa), followed by collection every month for 6 months and then every 3 months for evaluation of anti-avalglucosidase alfa ADA.

- 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.

Leftover antibody samples will be stored for further analysis as needed.

See the study-specific laboratory manual as well as the study manual for guidelines on the collection and shipment of the samples.

9.2 SECONDARY ENDPOINTS

9.2.1 Pharmacokinetics

9.2.1.1 Sampling time

Blood samples for full evaluation of avalglucosidase alfa PK will be collected before and after infusions on V2 (Day 1) and V15 (Week 25) for participants who are treated with avalglucosidase alfa starting at Day 1. For participants in Stage 2 – Cohort 3 who are randomized to receive treatment with alglucosidase alfa at current stable dose during the Treatment Period and who switch to avalglucosidase alfa in the Extension Period, full PK profiles will be sampled on V16 (Week 27) and V28 (Week 49). Sampling times are as follows: predose (prior to infusion); at the end of the infusion; and at 2, 4, 6, and 8 hours after the end of infusion. PK samples will also be taken prior to infusion and at 2 hours after the end of infusion at V9 (Week 13), or at V22 (Week 37) for the avalglucosidase alfa switch patients. For patients in the 40 mg/kg dose cohorts, additional blood samples will be collected at 12 to 16 hours after infusions on V2 (Day 1) and V15 (Week 25), or on V16 (Week 27) and V28 (Week 49) for the avalglucosidase alfa switch patients (see Table 1).

Table 1 – PK sampling time

Visit	Cohort 1 patients	Cohort 2 patients	Cohort 3 patients randomized to avalglucosidase alfa	Cohort 3 patients randomized to alglucosidase alfa and switching to avalglucosidase alfa in the extension period
V2 (D1)	Predose; end of infusion; 2, 4, 6 and 8 h after end of infusion	Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion	Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion[a]	
V9 (W13)	Predose and 2 h after end of infusion	Predose and 2 h after end of infusion	Predose and 2 h after end of infusion	
V15 (W25)	Predose; end of infusion; 2, 4, 6 and 8 h after end of infusion	Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion	Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion[a]	
V16 (W27)				Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion[a]
V22 (W37)				Predose and 2 h after end of infusion
V28 (W49)				Predose; end of infusion; 2, 4, 6, 8 and 12-16 h after end of infusion[a]

a If the cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, the 12-16 hours after the end of infusion sample will not be taken.

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 (12 to 16 hours after infusions in the 40 mg/kg dose cohort).

9.2.1.2 Pharmacokinetics handling procedure

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

9.2.1.3 Bioanalytical method

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

The lower limit of quantitation (LLOQ) is 12.0 ng/mL or 0.0120 µg/mL.

9.2.1.4 Pharmacokinetics parameters

The following PK parameters will be determined for avalglucosidase alfa based on non-compartmental analysis. The parameters will include maximum plasma concentration observed (C_{max}), time to achieve maximum plasma concentration (t_{max}), area under the curve from time 0 to time of the last quantifiable concentration ($AUC_{0\text{-}last}$), and terminal half-life ($t_{1/2z}$). If data permit, other parameters including total body clearance of a drug from plasma (CL) and volume of distribution (Vd) will be included. The definitions of the PK parameters are presented in Table 2.

Table 2 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Matrix	Definition/Calculation
C_{max}	avalglucosidase alfa	Plasma	Maximum plasma concentration observed
t_{max}	avalglucosidase alfa	Plasma	Time to achieve maximum plasma concentration
$AUC_{0\text{-}last}$	avalglucosidase alfa	Plasma	Area under the plasma concentration versus time curve from time 0 to time of the last quantifiable concentration
$t_{1/2z}$	avalglucosidase alfa	Plasma	terminal half-life
CL	avalglucosidase alfa	Plasma	Total body clearance of a drug from the plasma
Vd	avalglucosidase alfa	Plasma	Volume of distribution

9.2.2 Secondary efficacy endpoints

9.2.2.1 Gross Motor Function Measure-88 (GMFM-88), Gross Motor Function Classification System - Expanded and Revised (GMFCS-E&R)

The GMFM-88 (20) 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. The GMFM-88 consists of 88 items organized into 5 dimensions:

- Lying and rolling (17 items)
- Sitting (20 items)
- Crawling and kneeling (14 items)
- Standing (13 items)
- Walking, running and 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.

While not originally validated for children with diagnoses other than cerebral palsy, the GMFM-88 has been used for other children with motor difficulties including children with osteogenesis imperfecta (21) and acute lymphoblastic leukemia (22). The GMFM-88 has been used to evaluate children and adults with Pompe disease (23) and was appropriate for use in this study because it measured change in motor performance over time secondary to an improvement or decline in muscle strength.

This assessment will include the expanded and revised Gross Motor Function Classification System for the GMFM-88 (GMFCS-E&R) (24). The GMFCS-E&R emphasizes concepts in the World Health Organization's International Classification of Functioning, Disability and Health. Emphasis is on usual performance in home, work and community settings without judgments about quality of movement or prognosis for improvement. The GMFCS-E&R is a 5 level classification system for specific age ranges 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 (24).

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 functional outcome manual for further details.

9.2.2.2 Quick Motor Function Test

The Quick Motor Function Test (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 (25). 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 10-15 minutes. Refer to the study-specific functional outcome manual for instructions on test administration.

9.2.2.3 Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI)

A disease-specific version of the PEDI was developed to assess functional capabilities and performance in children with Pompe disease from 2 months through adolescence (26, 27, 28, 29). The Pompe-PEDI is comprised of a Functional Skills Scale and Caregiver Assistance Scale; both scales have three domains: Self Care, Mobility, and Social Function. The Pompe-PEDI includes all items from the original PEDI, as well as additional items in the Functional Skills Mobility and Self-Care domains to reflect clinically relevant functional skills for children with Pompe disease. Norm-based scoring was developed for these new items and scoring algorithms for the PEDI have been adjusted to reflect the additional normative data collected for the Pompe-PEDI.

A trained assessor will administer the Pompe-PEDI, Functional Skills Scale: Mobility Domain to the patient or patient's legal guardian. This domain was selected to measure change in mobility secondary to changes in muscle strength; the domain consists of 160 mobility items that a patient or legal guardian reports if the patient is capable or unable of performing. Test administration requires approximately 15 minutes. The Pompe-PEDI will be centrally scored. Results are reported as raw score, normative standard score (with standard error) and scaled score (with standard error).

See the study-specific functional outcome manual for further details.

9.2.2.4 Echocardiography

Two-dimensional and M-mode echocardiography (ECHO) will be performed at the time points specified in Section 1.2 and a specified medium (eg, videotape or digital) will be sent to the core central cardiology laboratory for interpretation. A central cardiologist will review all ECHOs. This person will be blinded to the patient and study time point. The primary cardiac outcome assessments (measured and derived) to be recorded using off-line review include: left ventricle long axis, cross sectional area, end diastolic volume, end systolic volume, internal diameter, Septal wall diameter, Posterior wall diameter, Ejection Fraction, Left Ventricle sphericity, Left Ventricle thickness: dimension ratio, and LVM:volume ratio. M-mode parameters include: Left Ventricle Internal Dimension, Posterior Wall, Left Ventricle Internal Dimension, and Shortening Fraction. Systolic, Diastolic, and mean blood pressure will be determined. The following Tricuspid Valve/Mitral Valve parameters will also be assessed: Right Ventricular Pressure (by TR jet), TR gradient, Mitral Valve peak E, Mitral Valve peak A, E:A Ratio, and Mitral Valve deceleration time.

The ECHOs will be performed according to the developed protocol as outlined in the core cardiology laboratory manual. The study site cardiologist will review the ECHO in a timely manner for clinical management of the patient as central laboratory results will not be given to sites.

Any abnormal findings that meet the definition of an AE per Section 10.4.1.1 (eg, that result in an alteration in medical care, diagnostic or therapeutic) will be collected. All AEs will be recorded and followed as described in Section 10.4.2.

9.2.2.5 Eyelid position measurements

Ptosis (drooping eyelids) has been shown to occur in Pompe disease amongst other ophthalmologic findings (30, 31).

Separate informed consent will be sought to permit for the acquisition and use of photographs of the patient's eyes in order to allow for independent review of eyelid position measurements by central reader.

Study participants will have images taken of their eyes while wearing a pair of empty eyeglass frames with rulers attached as a standardized measurement tool at the time points specified in Section 1.2. The following eyelid position measurements will be performed by the central reader:

- Interpalpebral fissure distance (IPFD)
- Margin reflex distance-1 (MRD-1)
- Margin pupil distance (MPD)

Refer to the study manual for specific details on eyelid position measurements.

9.3 OTHER ENDPOINTS

9.3.1 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. Except for the genotyping of human GAA performed after 01-Jul-2018, the genetic results obtained from this study are not diagnostic and will be used for research purposes only.

9.3.1.1 GAA activity testing

If performed previously and historical results are available, then the GAA activity does not need to be repeated, but results and method will be collected. If results are not available, blood spot collection will be conducted at screening for standardized GAA activity testing.

Collection techniques, processing instructions, and shipping instructions are included in the study manual.

9.3.1.2 Cross-reactive Immunologic Material

Cross-reactive immunologic material (CRIM) analysis (32) will be conducted at screening by obtaining blood sample only if previous written results are not available; if patients have prior results, the testing does not need to be repeated. Results will be collected.

Results of CRIM status determined by the central laboratory from blood samples obtained for this study will not be provided to the site but will be uploaded to the Sanofi central repository through external data transfer.

Information for the collection and handling of these samples can be found in the study manual.

9.3.1.3 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 sent to another central laboratory where it will be amplified by polymerase chain reaction (PCR) using gene specific primers and the resulting PCR products will be sequenced for the identification of IOPD disease-associated variants within the GAA gene.

[redacted]

9.3.1.6 Optional stored DNA sample

For those patients who signed the optional pharmacogenetic ICF, 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 Subject ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by Subject 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 Subject 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.

9.3.2 Pharmacodynamic variables

9.3.2.1 Urine Hex4 levels

Fasting urine samples for the assessment of urinary 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.

[redacted]

9.3.2.3 Optional muscle biopsy

Optional muscle biopsy (for patients having signed [or for whom legal guardian(s) has(have) signed] the specific informed consent) when applicable may be performed at the suggested time points described in Section 1.2. If a baseline biopsy is obtained at baseline/screening or Week 25 (for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period), every effort should be made to obtain a follow-up biopsy as well.

Needle or open biopsy of the lower extremity (quadriceps) muscle will be performed. Glycogen content will be measured by histomorphometric analysis or severity grading to determine how effectively IMP is able to remove glycogen from muscle.

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

9.3.3 Tertiary endpoints

9.3.3.1 Pulmonary function testing (PFT)

Pulmonary function testing will be performed at the time points specified in Section 1.2. The PFT administration protocol is standardized across sites in accordance with the American Thoracic Society (ATS) guidelines (33). The PFT will include the assessment of FVC, forced expiratory volume in the first second of the FVC maneuver, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow in the upright and supine positions. Pulmonary function tests are not required for young patients unable to reliably undergo testing or for patients who are invasively ventilated, but missing assessments must be documented for analysis and potential impact on the study results.

9.3.3.2 Six-minute walk test

The 6MWT (34) will be performed at the time points specified in Section 1.2 to assess functional capacity for patients that are ambulatory, defined as the ability to ambulate 40m (approximately 130 feet) without stopping and without an assistive device. The 6MWT was originally developed as a global assessment of cardiac, respiratory, circulatory, and muscular capacity for adults (34). The 6MWT utilization has been expanded to neuromuscular disease research with adults and children, including studies of laronidase in mucopolysaccharidosis type-I (MPS-I) (35), idursulfase in mucopolysaccharidosis type II (36), and has proved safe, reliable and feasible in Duchenne muscular dystrophy (37). For administration to children, the guidelines proposed by the ATS have been modified to include accommodation to children's instructional needs, strategies for ensuring motivation, and techniques for promoting safety (37). Testing equipment and administration techniques will be standardized among investigational sites.

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 or there is a change in device use during the trial, this must be recorded in the e-CRF.

During the treatment period, the assessment will be completed before IMP infusion. The distance (in meters) will be recorded and the corresponding percent predicted value will be calculated (38). In addition, data will be collected for pre- versus post-test changes in heart rate.

See the study-specific functional outcome manual for further details.

9.3.3.3 Ventilator use diary

The Investigator will provide a respiratory diary to the patient (and/or the patient's parent[s]/legal guardian[s]) to record the daily use (if any) of mechanical ventilation (including both invasive and non-invasive) at daytime and nighttime. The date the patient first became dependent on invasive ventilator, as well as the reasons for first ventilator use will be collected and results will be recorded in the e-CRF. If the patient requires mechanical invasive or non-invasive ventilator support during the study, the start date, stop date, and reasons for each episode of continuous mechanical ventilator support will be collected. Invasive ventilation is defined as mechanical ventilatory support applied with the use of an endotracheal tube or tracheostomy, and non-invasive ventilation is defined as ventilatory support applied without the use of an endotracheal tube, ie, no invasion of the airway (39). On a biweekly basis, the periods of ventilator use/day (daytime, nighttime, both) will be reported by the Investigator based on the ventilator use diary and data recorded until (1) ventilator support is no longer needed; (2) patient death; or (3) end of study (whichever occurs first) . The date and reason that ventilator use is no longer needed will be recorded. The daily ventilator use diary is only required to be completed for patients using ventilator support.

If the patient requires any invasive or non-invasive mechanical ventilation (excluding planned ventilatory support less than 3 days duration for a planned surgical procedure), the Investigator will describe the events leading up to the mechanical ventilation using the ventilator use form/log in the e-CRF. Refer to Section 10.4.1.2, Section 10.4.2 and Section 10.4.3 for details regarding recording and reporting events of new invasive ventilatory support (excluding planned ventilatory support less than 3 days duration for a planned surgical procedure).

9.3.3.4 PedsQL Generic Core Scale questionnaire

The PedsQL Generic Core Scales is a general HRQOL tool and will be completed at the time points specified in Section 1.2. 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 Generic Core Scale encompasses 4 subscales including a patient's health and activities, feelings, problems with school, and how the patient gets along with others (40). 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 collected.

The 4 Multidimensional Scales and 3 Summary Scores are:

- Scales
  - Physical Functioning (8 items)
  - Emotional Functioning (5 items)
  - Social Functioning (5 items)
  - School Functioning (5 items)
- Summary Score
  - Total Scale Score (23 items)
  - Physical Health Summary Score (8 items)
  - Psychosocial Health Summary Score (15 items)

Items are reverse scored and linearly transformed to a 0 –100 scale, so that higher scores indicate better HRQOL. To reverse score, transform the scale items to 0 – 100 as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0. To create scale scores, the mean is computed by totaling the item scores and dividing by the number of items answered. This direct linear transformation does not affect the measurement properties of the scales, and is computed for ease of interpretation so that scores near 0 indicate poorer HRQOL and scores near 100 indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale score is not computed.

When examining the total scale, scores of 4.4 and 4.5 are considered to be minimal clinically meaningful differences on the child self-report and parent-proxy report, respectively (41).

Parents, children (ages 8 – 12 years), and adolescents (ages 13–18 years) may self-administer the PedsQL Generic Core Scale after instructions from the administrator. For younger children (ages 5–7 years) or if the child or adolescent is unable to self-administer the PedsQL Generic Core Scale (eg, due to illness, fatigue, reading difficulties), the measure should be read aloud.

The PedsQL Infant Scales version consists of the following 5 domains: (1) physical functioning, (2) physical symptoms, (3) emotional functioning, (4) social functioning, and (5) cognitive functioning. It includes formats for typically developing children 1 to 24 months old (parent-proxy report). The format, instructions, response scale, and scoring methods of the Infant Scales are identical to those of the Generic Core Scales.

9.3.3.5 Assessment of Pain (PedsQL Pediatric Pain Questionnaire and Observer reported pain visual analogue scale [VAS])

Pain will be assessed in patients at the time points specified in Section 1.2 using the following scales and questionnaire:

9.3.3.5.1 PedsQL Pediatric Pain Questionnaire

The 3-item PedsQL Pediatric Pain Questionnaire (42) comprises:

- Present Pain
- Worst Pain
- The third item refers to the localization of pain and is not scored

10 cm visual analog scales (VASs) from 0 (Not hurting / No discomfort / No pain) to 10 (Hurting a whole lot / Very uncomfortable / Severe pain)

The format, instructions, Likert response scale, and scoring method are identical to the PedsQL 4.0 Generic Core Scales, with higher scores indicating higher pain intensity. Present pain and worst pain are scored separately. The score is based on line length to the nearest 0.5 cm. There is no imputation process since these are single item VAS scales. The instructions for the standard version ask how much of a problem each item has been during the past one month. In this study, the PedsQL Pediatric pain Questionnaire will be applied to participants >5 years of age.

9.3.3.5.2 Observer reported pain visual analogue scale (VAS)

The Observational Visual Analogue Score (VAS-OBS, range 0-10) is a tool developed to measure subjective phenomena like pain. It consists of a 10-cm line in this study, either vertical or horizontal, anchored at the ends by labels such as “no pain” and “worst possible pain.” Observers estimate the level of perceived pain by putting a mark on the line. An observer uses the VAS to rate the intensity of the pain experienced by children (43). In this study, the VAS-OBS will be applied to all participants.

9.3.3.6 Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III)

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age (44). For this study, the Cognitive Scale and Motor Scale will be utilized. The Cognitive Scale assesses how a child thinks, responds and learns about the world. The Motor Scale is comprised of two subtests: the Fine Motor subtest and the Gross Motor subtest. The Fine Motor subtest assesses how well a child can use his or her hands and fingers to perform activities. The Gross Motor subscale assesses how well a child can move his or her body. Normative data are available for the Bayley-III from 1 month to 42 months of age and were derived from a sample of US infants and children in 2004. Data were also collected from 668 children with specific clinical diagnoses, including Down syndrome, prematurity, cerebral palsy, language impairment, pervasive developmental disorder and fetal alcohol exposure. Raw scores and scaled scores will be reported for the Cognitive, Fine Motor, and Gross Motor subtests. Composite scores with percentile rank

and confidence intervals will be reported for the Cognitive Scale and the Motor Scale (a composite of the Fine Motor and Gross Motor subtests).

The Bayley-III will be administered to patients from 1 month of age up to 42 months of age or until the maximum score on each of the 3 administered scales has been obtained according to the time points specified in Section 1.2. Once the maximum score for a scale has been achieved, only the remaining scales will be administered. Test administration takes approximately 90 minutes. Test results will be centrally scored by a trained assessor.

See the study-specific functional outcome manual for further details.

9.3.3.7 Leiter International Performance Scale, Third Edition (Leiter-3)

The Leiter-3 (45) will be administered by a trained assessor to assess intellectual ability. The Leiter Scale was designed as a nonverbal measure of intellectual function, memory and attention for individuals who could not be validly assessed with standard intelligence tests. Special populations for whom the Leiter Scale was intended include those with communication disorders, hearing impairments, motor impairments, and certain types of learning disabilities.

The Leiter-3, published in 2013, is an updated version of the Leiter-R. The Leiter-3 consists of two groups of subtests, the Cognitive Battery and the Attention/Memory Battery. Nonverbal Intelligence will be used in this study to estimate global intellectual ability. The first four subtests of the Cognitive Battery are compiled to assess Nonverbal Intelligence with a Nonverbal IQ Composite score. These subtests are: Figure Ground, Form Completion, Sequential Order, and Classification-Analogies. The fifth subtest (Visual Patterns) is an optional subtest, which may be administered if one of the four subtests is compromised. Raw and scaled scores will be reported for each administered subtest in addition to the Nonverbal IQ Composite score.

The Leiter-3 will be administered to patients starting at the last assessment of the Bayley-III Cognitive Scale prior to the patient reaching 42 months of age and then, as specified in Section 1.2. Test administration takes approximately 60 minutes. Test results will be centrally scored by a trained assessor.

In case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment, the patients should be assessed by the Bayley-III regardless of the patient's age.

See the study-specific functional outcome manual for further details.

9.3.3.8 Hearing testing

Hearing loss has been reported in patients with GSDs (46, 47). Furthermore, cochlear involvement has been demonstrated in a mouse model of Pompe disease, and hearing loss found in patients with IOPD (48).

Hearing will be assessed at the time points specified in Section 1.2 using both Audiogram and Brainstem auditory evoked potentials/responses (BAEPs/BAERs). Refer to the study manual for specific details on hearing testing procedures.

9.3.3.8.1 Audiogram

Refer to Table 3 for a list of commonly available hearing tests appropriate for infants and children of various ages. Abnormal hearing tests should be confirmed by more than one method, and should be correlated with the presence or absence of middle ear effusion. Results of the hearing testing will be collected. Refer to the study manual for specific details on hearing testing procedures.

Table 3 - Hearing assessments appropriate for age

Auditory test	Developmental age of child
Otoacoustic emission testing	all ages
Conditioned-oriented responses	9 months to 2.5 years
Visual reinforcement audiometry	9 months to 2.5 years
Play audiometry	2.5 years to 4 years
Conventional audiometry	4 years and older

Source: Cunningham, 2003 (49)

9.3.3.8.2 Brainstem auditory evoked potentials/responses

Brainstem auditory evoked potentials/responses will be recorded at the time points specified in Section 1.2 in order to measure the functioning of the auditory nerve and auditory pathways in the brainstem, thus aiding in the assessment of potential hearing loss in study participants. Since recording of BAEPs/BAERs may require sedation in young children which could pose unacceptable risks to patients who have significant cardiopulmonary compromise, BAEPs/BAERs should only be performed at the discretion of the Investigator. Missing assessments must be documented for analysis and potential impact on the study results.

If clinically significant changes in hearing as compared to baseline results are noted, the changes will be documented as AEs. Clinical significance is defined as any variation in hearing tests that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.3.3.9 Motor Skills Checklist

The GMFCS-E&R is accompanied by the Motor Skills Checklist. The Motor Skills Checklist includes functional tasks included in GMFCS-E&R classifications. Trained assessors indicate skills that are descriptors of the child or youth's current function in order to identify areas of change within each GMFCS-E&R level. The Motor Skills Checklist will be reviewed by a central scorer who assigns a classification of the Pompe Functional Classification Levels (Walker, Supported Walker, Supported Stander, Sitter, or Restricted Antigravity Movement) (50). See the study-specific functional outcome manual for further details.

9.4 FUTURE USE OF SAMPLES

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

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

These samples will remain labelled with the same identifiers used during the study (ie, subject 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 subject 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

Despite the significant impact of alglucosidase alfa on (ventilator-free) survival in patients who have been diagnosed at birth through neonatal screening programs and treated shortly thereafter, some patients exhibit slow declines in gross motor function and mobility starting at 18-24 months of age. This unmet need has only recently been revealed in these patients (14, 16, 51).

The primary objective of the ACT14132 study is the assessment of safety and tolerability of administering avalglucosidase alfa in male and female patients with IOPD, who have been previously treated with alglucosidase alfa and demonstrated clinical decline or sub-optimal clinical response in specified respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis. The PAP will be a 6-month period from start of study treatment. The primary endpoint will be data pertaining to the safety and tolerability of avalglucosidase alfa.

The secondary objectives are to characterize the PK profile of avalglucosidase alfa and to evaluate the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. Efficacy endpoints in ACT14132 include motor function, respiratory function, quality of life, pain, cardiac function, eyelid measurements, and cognitive and auditory function. These endpoints represent systems affected by Pompe disease and where clinical decline or sub-optimal response to alglucosidase alfa has been observed (14, 16, 51).

As a consequence of the evolution in the course of Pompe disease, demonstration of therapeutic activity that stabilizes or improves the long-term decline of specific clinical symptoms, such as gross motor function and mobility in alglucosidase alfa-treated IOPD patients will provide sufficient evidence of a treatment effect that is at least similar to alglucosidase alfa and could support an indication in all IOPD patients. In the context of availability of an existing treatment, assessment of these endpoints is important to assure that these patients can be safely switched from alglucosidase alfa to avalglucosidase alfa with potential stabilization of clinical symptoms.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

Visits that are longer due to multiple assessments or procedures (eg, motor assessments, echocardiography, questionnaires) may be carried out over up to 5 days (not necessarily consecutively), starting at least 7 days after the last IMP infusion, in order to accommodate the patients and their care-takers. In case several assessments/procedures are performed during the same day, it is recommended that they are performed in the following order, if applicable. It is not necessary to complete all assessment/procedures of the same category (eg, motor assessments) on the same day. IRT contact for enrollment/randomization or dispensing can be performed at any time but before IMP administration. In any case, IMP administration, including vital signs and PK sampling when applicable, will be the last procedure of the last day and the appropriate time needed for post-infusion surveillance will be taken into account (refer to Section 8.1).

1. Patient-reported outcomes and questionnaires (Ventilator use diary, PedsQL Generic Core Scale questionnaire, PedsQL pediatric pain questionnaire, Pain VAS, when applicable: no preferred order)
2. Physical examination (including height/body length, body weight, head circumference, Tanner stage) and patient/legal guardian standard interview (global health status, AE, medication)
3. Procedures:
    - Echocardiography, ECG, hearing testing, eyelid position measure (for patients having signed [or for whom legal guardian(s) has(have) signed] the specific informed consent): no preferred order
    - PFT
4. Motor assessments (preferred order, not leading to protocol deviation if order is different based on patient needs and assessor availability): GMFM-88/QMFT, then Bayley-III/Leiter-3 scales, Pompe-PEDI (Functional Skills Scale, Mobility Domain), GMFCS-E&R, with Motor Skills Checklist and 6MWT.
5. All laboratory assessments (blood, urine) and muscle biopsy (for patients having signed [or for whom legal guardian(s) has(have) signed] the specific informed consent) when applicable
6. IMP administration including vital signs and PK sampling when applicable

10.1.1 Screening/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 performing any study-related procedure.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for inclusion in the study. For participants in Cohort 3, randomization will be performed prior to IMP administration.

The recommended duration of the screening period is up to 14 days but may be extended to a maximum of 4 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.
- A concurrent acute disease or event occurred during the screening period, which does not meet an exclusion criterion (see Section 7.2).
- The study or the IMP administration is temporarily put on hold due to a Sponsor decision (see Section 10.3.1).

If a patient does not meet all inclusion criteria or meets one or more exclusion criterion during the screening period, the patient may rescreen for the study once. The rescreening must be at least 14 days after the initial screening failure.

In case of rescreening, the patient will be first screened failed in the IRT, will sign a new written ICF and a new patient number will be provided. All screening assessments/procedures will have to be performed again, except GAA and [redacted] genotyping and CRIM status.

For screening failures, the following data obtained during screening will be collected: patient's demographic data, inclusion and exclusion criteria, relevant medical, surgical and Pompe disease history (if available), previous and concomitant medications (if available), AE data (if available) and reason for failure.

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

- Informed consent/assent;
- Inclusion/exclusion criteria;
- Demographics and baseline characteristics:
  - Age (years);
  - Gender;
  - Race;
  - Ethnicity;
- Medical/Surgical history;
- Pompe disease history, inclusive of GAA mutation, CRIM status, GAA activity, and aspects of disability;
- Retrospective chart review to collect available assessments prior to study entry documenting clinical decline or sub-optimal clinical response as outlined in I 06 and I 07 (refer to Section 7.1);
- Physical examination (inclusive of Tanner stage);

- Body weight;
- Height/body length;
- Head circumference;
- Lab:
  - Serum β-HCG pregnancy test (females of childbearing potential only);
  - Safety sampling:
    - Hematology, biochemistry (including BNP and CK), and urinalysis;
    - Anti-drug antibodies (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa and anti-alglucosidase alfa antibodies;
  - Biomarkers:
    - Urine Hex4 sample collection;
    - [redacted]
  - [redacted]
  - GAA mutation analysis (if historical results are not available; may be obtained at any other visit if not possible during screening due to blood volume limitation)
  - Stored DNA sample (optional; may be obtained at any other visit if not possible during screening due to blood volume limitation);
  - 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 labs (hematology, biochemistry, ADA) and PK and [redacted].
- Muscle biopsy (optional);
- Ventilator use diary;
- PFT (in patients who can reliably undergo testing and/or who are not invasively ventilated);
- 6MWT (in patients who are able to ambulate at least 40 meters [approximately 130 feet] without stopping and without an assistive device);
- GMFM-88/GMFCS-E&R
- Motor Skills Checklist;
- QMFT;
- Pompe-PEDI, Functional Skills Scale: Mobility Domain;
- Bayley-III/Leiter-3 scales;
- Echocardiography;
- Hearing testing;
- Eyelid position measurements;

- PedsQL Generic Core Scale questionnaire (≥24 months of age);
- PedsQL Pediatric Pain Questionnaire (>5 years of age);
- Pain VAS;
- AE collection;
- Prior/concomitant medications/therapies;
- IRT contact for notification of screening.

10.1.2 Treatment period

Patients enrolled in the study will have the following procedures performed starting at Day 1. Day of first infusion should occur within 1 to 14 days of consent. All subsequent numbered 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 (7 day increments with a window of ±3 days for qw alglucosidase alfa treatment in Stage 2 – Cohort 3 participants randomized to alglucosidase alfa treatment at current stable dose) and ±14 days for all other assessments.

10.1.2.1 Day of first infusion (Day 1)

The following will be performed on the day of first infusion (Day 1):

- Inclusion/exclusion criteria;
- IRT contact to confirm patient enrollment (Stage 1 patients, Cohorts 1 and 2) and randomization (Stage 2, Cohort 3 only);
- Physical examination;
- Body weight;
- 12-lead ECG (triplicate);
- Vital signs (before, during, and following infusion: see Section 1.2);
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);
  - Biomarkers:
    - Urine Hex4 sample collection;
    - [redacted]
    - [redacted]
    - [redacted]
    - Avalglucosidase alfa plasma PK sample collection (before and following infusion) in patients receiving avalglucosidase alfa:
      - For Cohort 1 and 2 patients and for Cohort 3 patients who are randomized in the avalglucosidase alfa group, this visit requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion.

- For Cohort 2 patients and for Cohort 3 patients who are randomized in the avalglucosidase alfa group, another sample will be taken 12 to 16 hours after the end of IMP infusion. If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken. 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 labs (hematology, biochemistry, ADA) and PK and [redacted]

- Ventilator use diary;
- Eyelid position measurements;
- Infusion of IMP;
- AE collection;
- Concomitant medications/therapies.

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

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

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

- Lab
  - Safety:
    - Biochemistry in patients receiving avalglucosidase alfa;
    - ADAs (with neutralizing antibodies in ADA positive patients) for anti-avalglucosidase alfa and anti-alglucosidase alfa antibodies for patients receiving avalglucosidase alfa;
    - ADAs (with neutralizing antibodies in ADA positive patients) for anti-alglucosidase alfa antibodies for patients receiving alglucosidase alfa;
  - Biomarkers:
    - Urine Hex4 sample collection;
  - 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 labs (hematology, biochemistry, ADA) and PK and [redacted]
- AE collection;
- Concomitant medications/therapies.

10.1.2.3 Weekly (alglucosidase alfa only)

The following will be performed every week starting at the date of the first infusion for patients in Stage 2 – Cohort 3, who are randomized to receive alglucosidase alfa treatment at current stable dose and who have been receiving weekly infusions of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry:

- Vital signs (before, during, and following infusion: see Section 1.2);
- Infusion of IMP;
- AE collection;
- Concomitant medications/therapies.

10.1.2.4 Biweekly

The following will be performed every 2 weeks (W3, W5, W7, W9, W11, W13, W15, W17, W19, W21, W23, and W25):

- Lab:
  - Biomarkers:
    - Urine Hex4 sample collection;
- Ventilator use diary;
- Eyelid position measurements;
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of IMP;
- AE collection;
- Prior/concomitant medications/therapies.

10.1.2.5 Monthly

The following assessments will be performed on a monthly basis (W5, W9, W13, W17, W21, and W25):

- Lab:
  - Biomarkers:
    - Urine Hex4 sample collection;
  - Urine β-HCG pregnancy test (females of childbearing potential only);
  - Safety:
    - Biochemistry in patients receiving avalglucosidase alfa;

    - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies for patients receiving avalglucosidase alfa;
- Ventilator use diary;
- Eyelid position measurements;
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of IMP;
- ECG (at Week 5);
- Body weight;
- Physical examination (at Week 5, Week 9, and Week 13);
- AE collection;
- Prior/concomitant medications/therapies.

10.1.2.6 Every 3 months

The following assessments will be performed at quarterly visits (W13 and W25):

- Physical examination;
- Body weight;
- Height/body length/head circumference;
- Lab:
    - Urine β-HCG pregnancy test (females of childbearing potential only);
    - Safety:
        - Hematology, biochemistry, and urinalysis;
        - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa and anti-alglucosidase alfa antibodies for patients receiving avalglucosidase alfa, and anti-alglucosidase alfa antibodies only for patients in Stage 2-Cohort 3, who are randomized to receive alglucosidase alfa treatment at current stable dose (W13 only);
        - ADAs (with neutralizing antibodies in ADA positive patients) for anti-avalglucosidase alfa and anti-alglucosidase alfa antibodies (W25 only);
    - Biomarkers:
        - [redacted]
        - [redacted]
        - [redacted]
        - Urine Hex4 sample collection;

- Avalglucosidase alfa plasma PK sample collection (before and following infusion) in patients receiving avalglucosidase alfa;
  - For Cohort 1 and 2 patients and for Cohort 3 patients who are randomized in the avalglucosidase alfa group, this visit requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion (Week 25 only).
  - For Cohort 2 patients and for Cohort 3 patients who are randomized in the avalglucosidase alfa group, another sample will be taken 12 to 16 hours after the end of IMP infusion (Week 25 only). If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken.
- 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 labs (hematology, biochemistry, ADA) and PK and [redacted]

- ECG;
- Vital signs (before, during, and following infusion: see Section 1.2);
- Muscle biopsy (optional) at Week 25 only;
- Ventilator use diary;
- PFT (in patients who can reliably undergo testing and/or who are not invasively ventilated);
- 6MWT (in patients who are able to ambulate at least 40 meters [approximately 130 feet] without stopping and without an assistive device);
- GMFM-88/GMFCS-E&R
- Motor Skills Checklist;
- QMFT;
- Pompe-PEDI, Functional Skills Scale: Mobility Domain;
- Bayley-III/Leiter-3 scales;
- Echocardiography;
- Hearing testing;
- Eyelid position measurements;
- PedsQL Generic Core Scale questionnaire (≥24 months of age);
- PedsQL Pediatric Pain Questionnaire (>5 years of age);
- Pain VAS;
- IRT contact for IMP resupply;
- Infusion of IMP;

- AE collection;
- Concomitant medications/therapies.

10.1.3 Extension period (Week 27 to Week 145)

10.1.3.1 Day of first infusion within the extension period (W27)

- Lab:
  - avalglucosidase alfa plasma PK sample collection (before and following infusion) for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period. For these patients this visit requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion. Another sample will be taken 12 to 16 hours after the end of IMP infusion. If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken;
- Body weight for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period;
- Ventilator use diary;
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.2 One week following first infusion within the extension period

The following will be performed one week following the date of the first infusion of the extension period for patients in Stage 2 – Cohort 3 switching to avalglucosidase alfa (W28):

- Biochemistry;
- ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.3 Two weeks following first infusion within the extension period (Week 29)

- Body weight;
- Physical examination for patients in Stage 2 - Cohort 3 switching to avalglucosidase alfa in the extension period;
- Ventilator use diary;
- Lab:

- Urine β-HCG pregnancy test (females of childbearing potential only);
- Safety:
  - Biochemistry;
  - ADAs (with neutralizing antibodies in ADA positive patients) for anti-avalglucosidase alfa antibodies in Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period;

- ECG in Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period;
- Vital signs (before, during, and following infusion (see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.4 Every 2 weeks (Biweekly)

The following will be performed every 2 weeks (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, 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):

- Ventilator use diary;
- Vital signs (before, during, and following infusion (see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.5 Every 4 weeks (Monthly)

The following assessments will be performed on a monthly basis (W29, W33, W37, W41, W45, W49, 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):

- Body weight;
- Physical examination for patients in Stage 2 – Cohort 3 switching to avalglucosidase alfa in the extension period up to Week 37;
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);

- Safety:
  - Biochemistry (monthly for the first 6 months of the extension period in all subjects, up to Week 73 for patients in Stage 2 – Cohort 3 switching to avalglucosidase alfa in the extension period, and then every 3 months);
  - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies through Week 49 in Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period and then every 3 months;
- Ventilator use diary;
- Vital signs (before, during, and following infusion);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.6 Every 12 weeks (Quarterly)

The following assessments will be performed every 3 months (W37, W49, W61, W73, W85, W97, W109, W121, W133, and W145):

- Physical examination (up to Week 49 for all subjects, up to Week 73 for patients in Stage 2 – Cohort 3 switching to avalglucosidase alfa in the extension period, and then every 6 months);
- Body weight;
- Height/body length/head circumference (up to Week 73 and then every 6 months);
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);
  - Safety:
    - Biochemistry;
    - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies;
  - Avalglucosidase alfa plasma PK sample collection (before and following infusion) for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period: at W37 and W49. For these patients the W49 visit (V28) requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion. Another sample will be taken 12 to 16 hours after the end of IMP infusion. If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken;
  - 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 labs (hematology, biochemistry, ADA) and PK and [redacted]

[redacted]

- ECG in Stage 2 - Cohort3 patients switching to avalglucosidase alfa in the extension period up to Week 37;
- Ventilator use diary;
- Vital signs (before, during, and following infusion (see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.3.7 Every 24 weeks (Every 6 months)

The following assessments will be performed every 6 months (W49, W73, W97, W121, and W145):

- Physical examination (inclusive of Tanner stage at W49, W97, and W145);
- Body weight;
- Height/body length/head circumference;
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);
  - Safety:
    - Hematology, biochemistry, and urinalysis;
    - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa;
  - Avalglucosidase alfa plasma PK sample collection (before and following infusion) for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period: at W37 and W49. For these patients the W49 visit (V28) requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion. Another sample will be taken 12 to 16 hours after the end of IMP infusion. If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken;
  - Biomarkers:
    - [redacted]
    - [redacted]
    - [redacted]
    - Urine Hex4 sample collection;

- 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 labs (hematology, biochemistry, ADA) and PK and [redacted]

- ECG;
- Ventilator use diary;
- Vital signs (before, during, and following infusion (see Section 1.2);
- Muscle biopsy (optional) at Week 49 in Stage 2 – Cohort 3 switching to avalglucosidase alfa in the extension period, and Week145 in all patients;
- PFT (in patients who can reliably undergo testing and/or who are not invasively ventilated);
- 6MWT (in patients who are able to ambulate at least 40 meters [approximately 130 feet] without stopping and without an assistive device);
- GMFM-88/GMFCS-E&R
- Motor Skills Checklist;
- QMFT;
- Pompe-PEDI, Functional Skills Scale: Mobility Domain;
- Bayley-III/Leiter-3 scales;
- Echocardiography;
- Hearing testing;
- Eyelid position measurements;
- PedsQL Generic Core Scale questionnaire (≥24 months of age);
- PedsQL Pediatric Pain Questionnaire (>5 years of age);
- Pain VAS;
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.4 Extended long-term treatment period (From Week 147 onwards)

10.1.4.1 Biweekly

The following assessments will be performed every 2 weeks, starting at Week 147 and up to an additional 226 weeks after Week 145 (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, W291, W293, W295, W297, W299, W301, W303, W305, W307, W309, W311, W313, W315, W317, W319, W321, W323, W325, W327, W329, W331, W333, W335, W337, W339, W341, W343, W345, W347, W349, W351, W353, W357, W359, W361, W363, W365, W367, W369, and W371) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients):

- Ventilator use diary (for patients receiving home infusion: the ventilator use diary will be checked at site visits);
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.4.2 Every 4 weeks (Monthly)

The following assessments will be performed every 4 weeks, starting at Week 149 and up to an additional 226 weeks after Week 145 (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, W293, W297, W301, W305, W309, W313, W317, W321, W325, W329, W333, W337, W341, W345, W349, W353, W357, W361, W365, and W369) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients):

- Body weight;
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);
- Ventilator use diary (for patients receiving home infusion: the ventilator use diary will be checked at site visits);
- Vital signs (before, during, and following infusion: see Section 1.2);

- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.4.3 Every 12 weeks (Quarterly)

The following assessments will be performed every 12 weeks, starting at Week 157 and up to an additional 226 weeks after Week 145 (W157, W169, W181, W193, W205, W217, W229, W241, W253, W265, W277, W289, W301, W313, W325, W337, W349, and W361) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients):

- Body weight;
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);
  - Safety:
    - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies;
- Ventilator use diary (for patients receiving home infusion: the ventilator use diary will be checked at site visits);
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.4.4 Every 24 weeks (Every 6 months)

The following assessments will be performed every 24 weeks, starting at Week 169 and up to an additional 226 weeks after Week 145 (W169, W193, W217, W241, W265, W289, W313, W337, and W361) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients):

- Physical examination (inclusive of Tanner stage);
- Height/body length/head circumference;
- Body weight;
- Lab:
  - Urine β-HCG pregnancy test (females of childbearing potential only);

    - Safety:
        - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies;
        - Hematology, biochemistry, and urinalysis;
- Ventilator use diary (for patients receiving home infusion: the ventilator use diary will be checked at site visits);
- Eyelid position measurements;
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply;
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.4.5 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 an additional 226 weeks after Week 145 (W193, W241, W289, W337 or end of treatment) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients):

- ECG;
- Physical examination (inclusive of Tanner stage);
- Height/body length/head circumference;
- Body weight;
- Lab:
    - Urine β-HCG pregnancy test (females of childbearing potential only);
    - Safety:
        - ADAs (with neutralizing antibodies in ADA-positive patients) for anti-avalglucosidase alfa antibodies;
        - Hematology, biochemistry, and urinalysis;
- Ventilator use diary;
- GMFM-88/GMFCS-E&R
- Motor Skills Checklist;
- QMFT;
- Pompe-PEDI, Functional Skills Scale: Mobility Domain;
- Leiter-3 scale (Bayley-III scale in case the developmental level of an individual patient is below the level required for the Leiter-3 Scale assessment);

- Echocardiography (can be performed on a more frequent basis upon need of abnormality follow-up);
- Hearing testing;
- Eyelid position measurements;
- PedsQL Generic Core Scale questionnaire (≥24 months of age);
- PFT (in patients who can reliably undergo testing and/or who are not invasively ventilated);
- 6MWT (in patients who are able to ambulate at least 40 meters [approximately 130 feet] without stopping and without an assistive device);
- Vital signs (before, during, and following infusion: see Section 1.2);
- IRT contact for IMP resupply (or end of treatment call for end of treatment visit);
- Infusion of avalglucosidase alfa;
- AE collection;
- Concomitant medications/therapies.

10.1.5 End of study

The following assessments will be performed at follow-up visit/contact (two to four weeks after last infusion):

- AE collection;
- Concomitant medications/therapies.

10.1.6 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, V22/Week 37, V28/Week 49, V40/Week 73, V52/Week 97, V64/Week 121, and V76/Week 145 or any every 24 or 48 weeks visit [depending on the assessment, see Section 1.2.4] of the extended long-term treatment period), 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. In these instances, this will not be considered a deviation but should be clearly documented in the patient's file.

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

- In case of temporary treatment discontinuation of study drug, the visits and assessments will be adapted to the absence of infusion of avalglucosidase alfa until the patient resumes treatment within the study:
  - Study visits can be adapted to every 4 weeks or when laboratory and/or clinical testing are scheduled, as long as the assessment time windows in the study protocol are respected. Patients should adhere to original target infusion and visit schedule based on first infusion in the ACT14132 study.
  - As no infusion of IMP will be performed, no assessment of infusion-associated vital signs, as well as no PK sampling is required while the participant is temporarily withdrawn from treatment.
  - A patient who will be enrolled but will not receive the first infusion due to a concurrent reason or event not related to the study, will be considered as being temporarily discontinued from the study drug and the rules described above will apply.

- Reinitiation of treatment with IMP will be offered to the patient at the discretion of the Investigator and in agreement with the study participant, under close and appropriate clinical and/or laboratory monitoring.

Patients who permanently discontinue the study treatment prior to the scheduled Week 25 or after Week 25, but prior to the scheduled Week 145 visit, will have assessments corresponding respectively to Week 25 or Week 145 performed prior to or in combination with the safety assessment after last infusion (refer to Section 10.1.4). Patients who permanently discontinue the study treatment prior to the scheduled end of treatment during the extended long-term treatment period will have assessments corresponding to the end of treatment visit.

10.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the e-CRF must be supported by appropriately identified source documentation.

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.
- Magnetic resonance imaging (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 treatment 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 10.1.7).

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

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 >3× the baseline value, except if the increased value is still within the normal range.

- Any increase in ALT or AST >3× the upper limit of normal (ULN), in the presence of total bilirubin >2× 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 will immediately decide to discontinue study drug dosing in all clinical trial patients and to not dose new patients, prior to receipt of DMC recommendation. This applies to a decision on dose escalation, as outlined in Section 4 as well. 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 10.1.1).

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 in the source documents and in the e-CRF.

If a patient experiences further clinical decline at or after Week 25 as defined by more rapid worsening of criteria of clinical decline than prior to study start, which is sustained on repeated study assessments, the patient may be managed per the discretion of the Investigator. This may include return to treatment with commercially available alglucosidase alfa (and termination of trial participation).

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

10.3.4 Handling of patients after permanent treatment discontinuation

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

Patients are encouraged to continue their regular scheduled study visits during the PAP (6 months). At the minimum, a discontinuation visit should be scheduled after the premature permanent discontinuation of treatment, if occurred prior to week 25, where the patients will be assessed using the procedure normally planned for the final study visit (Week 25) including a PK sample, if appropriate. This full assessment visit can be combined with the 4-week safety follow-up if necessary.

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 ICF) 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 treatment phase (Week 25) including a PK sample, if appropriate; or if the patient withdraws from the study after the scheduled Week 25 visit, using the procedures normally planned for the Week 145 visit including a PK sample, if not performed previously in participants in Cohort 3 switching to avalglucosidase alfa at Week 27 of the extension period. 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 10.1.4).

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 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 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 re-randomized/reallocated (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 **adverse event** (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

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- 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 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × 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;
- Any new invasive ventilatory support (excluding planned ventilatory support less than 3 days duration for a planned surgical procedure).

10.4.1.3 Adverse event of special interest

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

  Of note, asymptomatic overdose has to be reported as a standard AE, and is not considered an AESI.

- Clinical laboratory (change from baseline)
  - ALT or AST increase of ≥3 × ULN if baseline is <ULN, or ALT or AST increase ≥2 × the baseline value if baseline is ≥ULN;
  - A maximum ALT value of ≥400 IU/L (except if baseline value is ≥400 IU/L) or AST value of ≥500 IU/L (except if baseline value is ≥500 IU) or an increase in direct, indirect, or total bilirubin of ≥2 × ULN;
  - Serum creatinine increase of >1.5 × 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 ICF until the end of the study as defined by the protocol for that patient, are to be recorded on 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 one 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 post observation period, each of the individual signs and/or symptoms comprising the reaction should be captured as individual AE terms.

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.

Instructions for AE reporting are summarized in Table 4.

See Appendix C (Section 17.3.2) for an addendum to this section for Germany only.

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 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 pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in Table 4.

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 4 - 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 (except if baseline value ≥ 400 IU/L) or AST ≥500 IU/L (except if baseline value ≥ 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

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

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, ie, any 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 and the patient's guardian(s), such a procedure may be initiated as per guidelines in the pharmacy manual.

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

No formal sample size calculations have been performed. Sample size for this study was based upon empirical considerations.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the ICF.

For Cohort 3, randomized patients consist of all patients who have been allocated a treatment kit based on the randomization process for participants. 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

Safety population: all patients who received at least 1 infusion (partial or total) in the study.

Modified intent-to-treat (mITT) population: all randomized patients in Cohort 3 who received at least 1 infusion and with evaluable baseline efficacy assessment, analyzed according to the treatment group allocated by randomization.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

Duration of study drug exposure is defined below:

For the PAP

- Duration of IMP exposure is defined as the first dose date in the extension period (or 14 days after the last dose date in PAP if the patient is not continuing in extension period) minus (–) first dose date in the treatment period, regardless of unplanned intermittent discontinuations.

For the extension period,

- Duration of IMP exposure is defined as 14 days after the last dose in the extension period minus (–) the first dose date in the extension period, regardless of unplanned intermittent discontinuations. This is defined only for Cohort 3 alglucosidase alfa patients who are switched to avalglucosidase alfa and treated in the extension period.

For the overall treatment duration,

- Duration of avalglucosidase alfa total exposure is defined as 14 days after last avalglucosidase alfa dose in study minus (–) first avalglucosidase alfa dose date in the study. This is defined for all patients other than the Cohort 3 alglucosidase alfa patients.

The duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum), as well as categorical variable (eg, <2 months, 2-4 months, 4-6 months for the PAP).

The cumulative dose information for the considered period (PAP or overall treatment period) will be assessed by the total number of infusions received in the considered period, as well as total amount of IMP in mL (if this information is available from the database) received in the considered period. These data will be summarized descriptively.

For Cohorts 1 and 2, and Cohort 3 avalglucosidase alfa patients, both duration of IMP exposure and cumulative dose will be summarized for the PAP, as well as the overall treatment period. For Cohort 3 alglucosidase alfa patients, both duration of IMP exposure and cumulative dose will be summarized for the PAP; in addition, duration of IMP exposure will be summarized for the extension period after switching to avalglucosidase alfa.

11.4.1.1 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. Compliance to the treatment regimen will be monitored by site personnel during the study.

Treatment compliance for the PAP and the extension period respectively will be summarized descriptively as quantitative variable using the safety population. The number and percentage of patients with noncompliance (missed 2 or more consecutive infusions not for safety cause, or missed ≥20% of total doses in the treatment or extension period) will be provided.

11.4.2 Analyses of safety data

In general, for the PAP, the summary of safety results will be presented by study cohort/treatment arm within each stage, as well as by dose levels among the avalglucosidase alfa-treated patients. For the overall avalglucosidase alfa treatment period, the summary of safety results will be presented by dose levels among avalglucosidase alfa patients. All safety results that have been collected at the time of the analysis will be included for the overall treatment period summaries. For Cohort 3 alglucosidase alfa patients, the summary of safety results for the extension period will be presented separately. Safety endpoints are presented in Section 9.1.1.

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

The baseline value is defined as the last non-missing value prior to first IMP intake. Further details will be provided in the SAP.

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 pre-defined 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.

11.4.2.1 Adverse events

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse event incidence tables will be presented by system organ class (SOC) sorted by internationally agreed order, preferred term (PT), and 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 within a considered period. The denominator for computation of percentages is the safety population.

AE observation period:

- Pretreatment 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 pretreatment, on-treatment, and post-treatment period. Treatment-emergent adverse events (TEAEs) for analysis purpose will include all On-treatment AEs.

Unless otherwise specified, the primary analysis of AE will be based on TEAEs with onset date within the first 25 weeks PAP. Similar descriptive summaries will be performed for the long-term extension period (after 25 weeks) separately based on those TEAEs with onset date beyond 25 weeks of treatment phase. A pooled AE 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 one occurrence of the same AE with different reported severities. Relationship of the AE to treatment will be categorized as related/not 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 study cohort and treatment group, as well as by dose levels among avalglucosidase alfa patients, 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).

11.4.2.2 Clinical laboratory tests

Observed measurements and changes from baseline to study time points in biochemistry, hematology, and urinalysis will be descriptively summarized by study cohort and treatment group, as well as by dose levels among avalglucosidase alfa-treated patients. 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.

11.4.2.3 Physical examination, vital signs, and electrocardiogram

Potentially clinically significant findings observed during the on-treatment 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 study cohort and treatment group, as well as by dose levels among avalglucosidase alfa-treated patients. Listings of abnormal findings/values from these data as well as from PE assessment inclusive of body weight and height, as well as head circumference and Tanner stage, will be presented.

11.4.2.4 Anti-avalglucosidase alfa and anti-alglucosidase 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 using summary statistics.

Anti-avalglucosidase alfa and anti-alglucosidase 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.

11.4.3 Analyses of efficacy endpoints

Efficacy endpoints are presented in Section 9.2.2.

To evaluate the effect of switching to avalglucosidase alfa after having received alglucosidase alfa at current stable dose, comparative assessment on a composite score and several other efficacy endpoints will be conducted using the mITT population in Cohort 3.

The composite score will be constructed considering 3 domains: GMFM-88 and GMFCS-E&R, ptosis, and respiratory function (the use of respiratory device). Within each domain, the change from baseline to Week 25 will be classified into improvement, unchanged, and worsening with respect to pre-defined minimally important difference in each domain. The corresponding score will be determined based on both the baseline status and the change from baseline to Week 25.

The difference in average composite scores between avalglucosidase alfa and alglucosidase alfa patients will be used as the test statistic. Due to the small sample size, statistical inference will be derived based on the re-randomization approach instead of the asymptotic approximation. Specifically, all possible randomization sequences that are consistent with the selected randomization design (matched pairs design with 5 pairs or stratified randomization stratifying on gender) will be generated, the test statistics will be calculated for all randomization sequences, and the statistical significance level will be calculated as the proportion of more or equally extreme scenarios than the observed one, among all possible scenarios.

The composite score will also be summarized descriptively by treatment group in Cohort 3.

For those efficacy parameters that are used to identify patients who have sub-optimal response or decline as part of inclusion criteria, patient profile (in terms of change over time) will be generated for those parameters where each patient will serve as his/her own control. Effect of switching from alglucosidase alfa to avalglucosidase alfa will be assessed descriptively within each cohort/treatment arm based on changes from pre-study (collected by retrospective chart review at screening/baseline) to 6 months post-avalglucosidase alfa treatment collected during the study. The control arm (alglucosidase alfa treatment) in Stage 2 will serve as a reference.

Efficacy will also be summarized for all cohorts based on the safety population (all treated patients). For each of the efficacy parameters, observed measurements and changes over time from baseline to each post-baseline visit will be summarized by study cohort and treatment arm within each stage using descriptive statistics. Continuous data will be summarized using the number of available observations, mean, standard deviation (SD), median, minimum, and maximum in each study cohort/treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each study cohort/treatment group. Denominators

for the percentages will be based on the safety population with evaluable data on the corresponding endpoint.

11.4.3.1 Multiplicity considerations

Multiplicity adjustment is not needed as there is only one hypothesis test for the composite score defined above between avalglucosidase alfa and alglucosidase alfa groups in Cohort 3.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

The list of PK parameters is listed in Section 9.2.1.4.

PK exposures (C_{max}, $AUC_{0\text{-last}}$ and $t_{1/2z}$) for avalglucosidase alfa may be determined using non-compartmental analysis. If data allow, total body clearance of a drug (CL) and Vd 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 subjects and summarized using descriptive statistics by study week as appropriate.

To evaluate the effect of immunogenicity on the PK of avalglucosidase alfa, predose IgG and neutralizing antibody titers for each patient will be analyzed graphically with respect to PK parameter. If relationships are apparent, further quantitative/statistical analysis may be performed (eg, statistical significance, correlation coefficients).

Pharmacodynamic endpoints as described in Section 9.3.2 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.

[redacted]

11.4.5 Analyses of tertiary endpoints

Tertiary endpoints are presented in Section 9.3.3.

For each of the tertiary endpoints, observed measurements and changes over time from baseline to each post-baseline visit will be summarized by study cohort and treatment arm within each stage using descriptive statistics. Continuous data will be summarized using the number of available observations, mean, standard deviation (SD), median, minimum, and maximum in each dose cohort/treatment group. Categorical and ordinal data will be summarized using the number and

percentage of patients in each dose cohort/treatment group. Denominators for the percentages will be based on the safety population with evaluable data on the corresponding endpoint.

11.5 INTERIM ANALYSIS

While all patients will be followed for up to 7 years during the study, the primary analysis for the study will be performed when all Cohort 3 patients have completed the 6-month PAP. In addition, safety analyses will be performed in multiple time points by DMC (see Section 6.4.1) to determine the dose for next cohort and the MTD.

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

Since there is only one hypothesis test for the composite score to be performed at the end of the PAP, no adjustment is needed for the interim analyses.

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.
- 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 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), 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 participant or his/her legally authorized representative and answer all questions regarding 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, 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). When participants are no longer in the study, teams in charge of the amendment must define if those participants must re-consent or not 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 the participant's 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 electronic 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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)
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.
- 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 e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents include (but are not limited to): participant's medical file, appointment books, original laboratory records, functional outcome assessment source document.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). 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 [52]) and/or ethnicity (various drugs [53]).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; 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 local data protection law. 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- 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 result.

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 used by/communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies.
- 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 agency's 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 European Economic 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 subject and should assure appropriate subject 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. The Coordinating Investigator will be designated based upon patient participation in the study.

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

Study participants

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

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable 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 where applicable before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF 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 (WOCBP)

A woman is considered of reproductive potential (WOCBPWOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male and Female Subjects

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If*

not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
• 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 drug. 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 subject.)*
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 subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 28 days after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. 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 subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, 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.

For the purpose of this study 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 (please refer to Section 10.4.1.2).

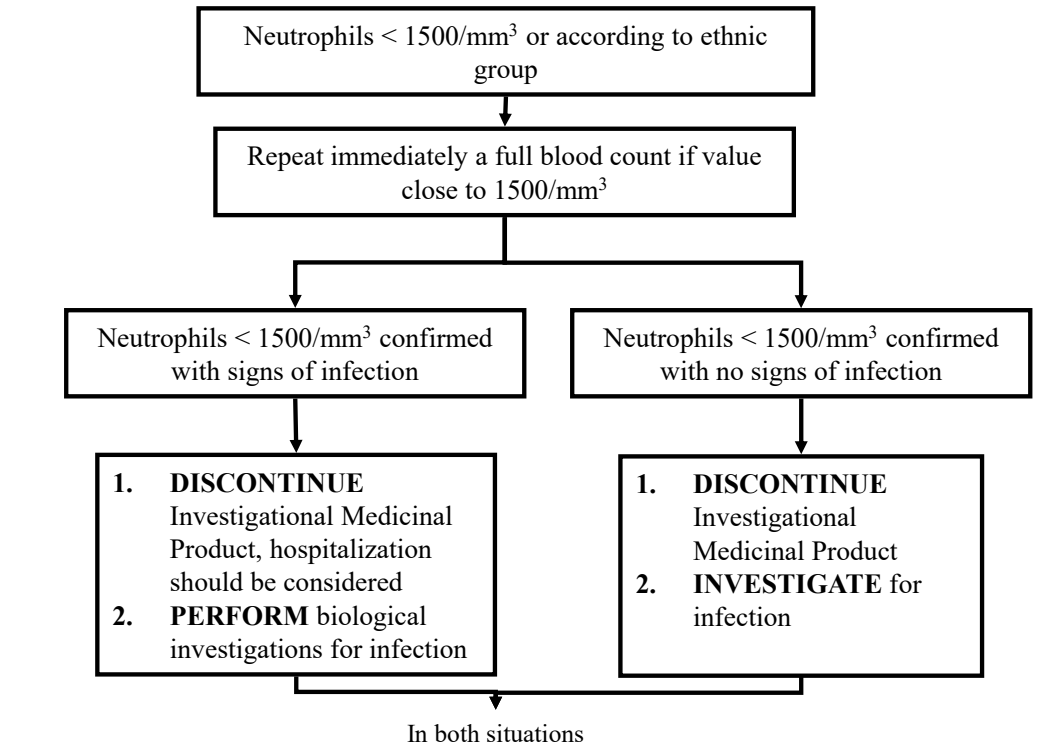
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.1.6. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

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

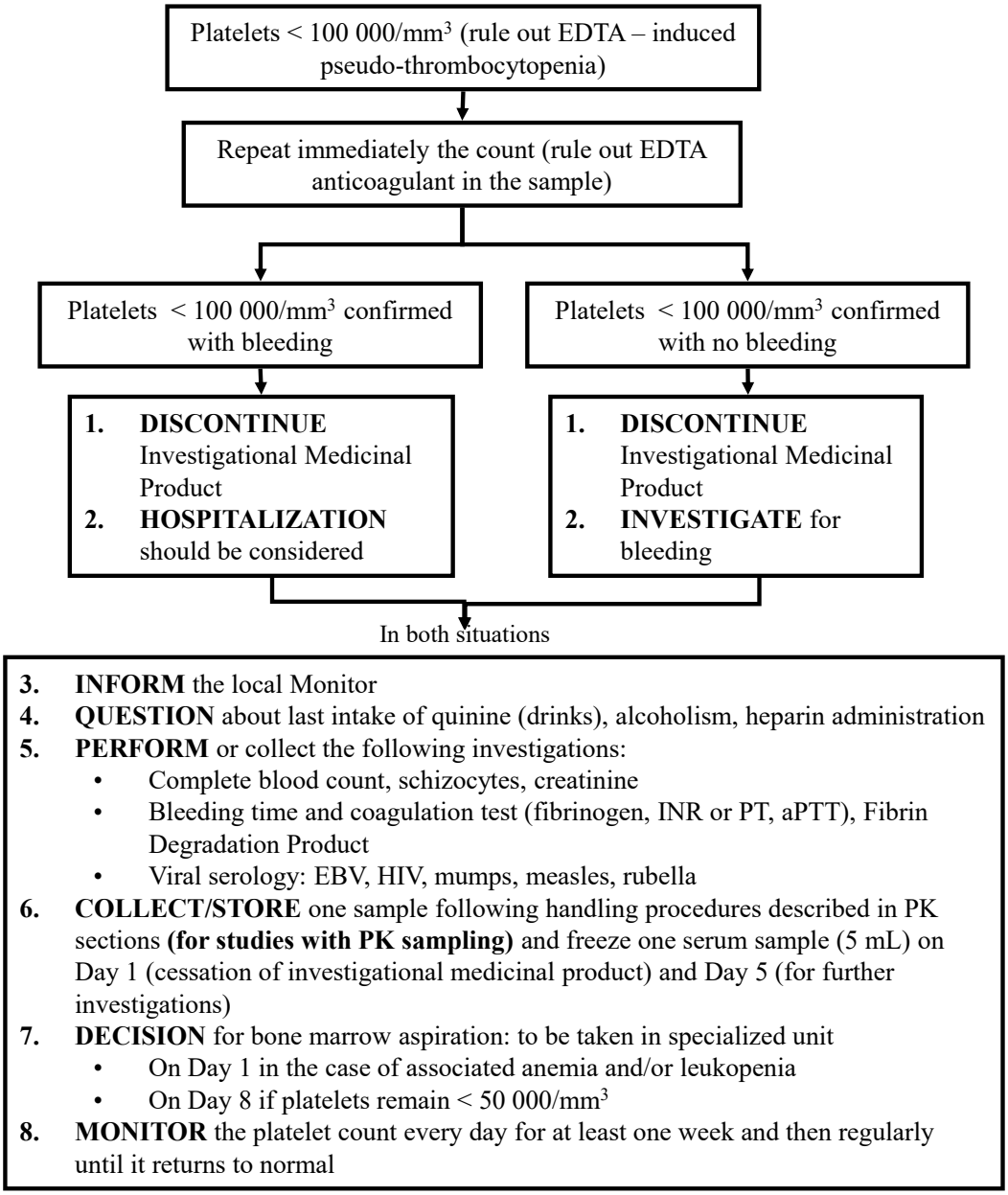


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

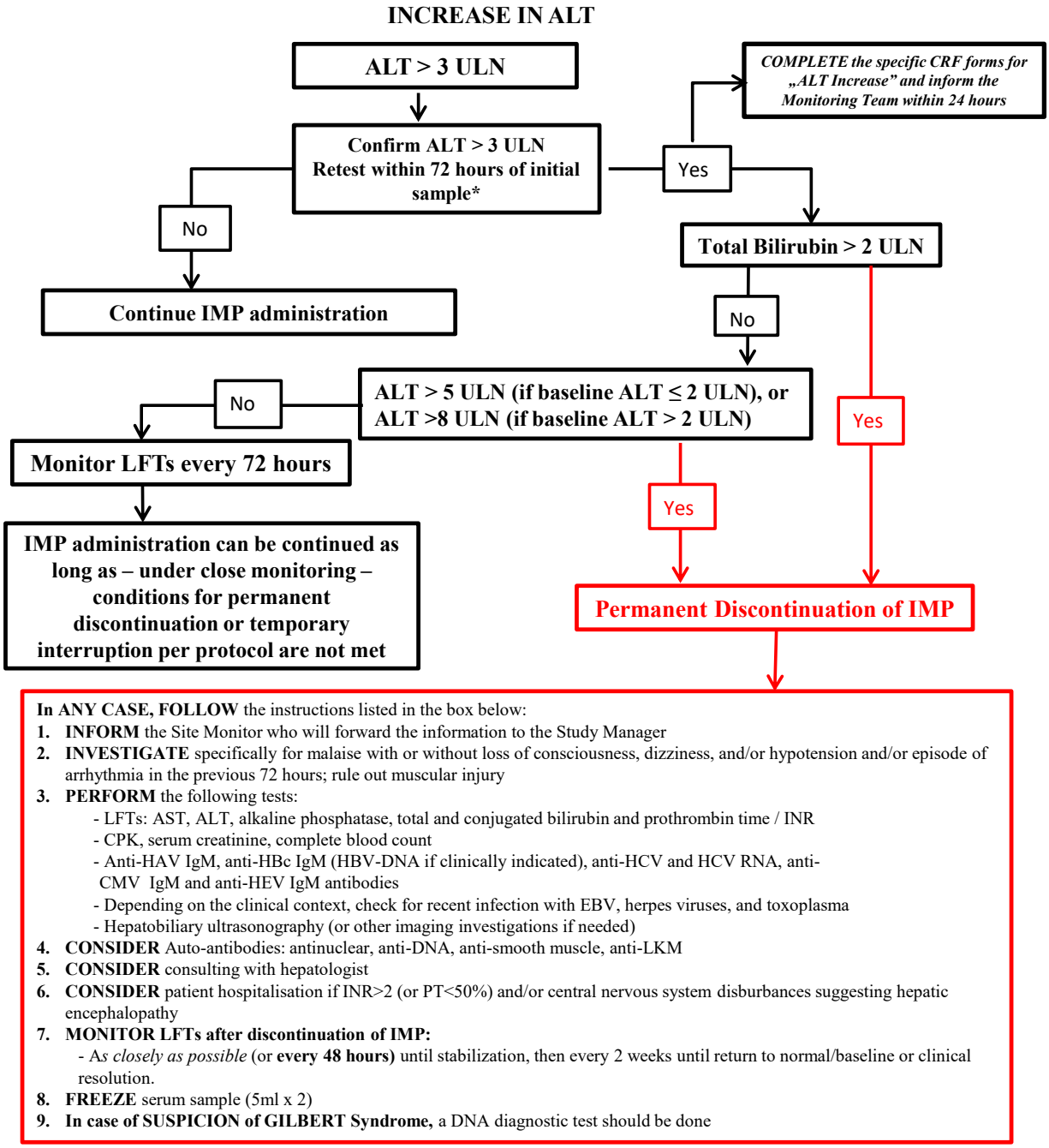
Neutropenia is to be recorded as AE only if at least 1 of the criteria listed in Section 10.4.3 is met guidelines for reporting AE in Section 10.4.2 is met.

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.

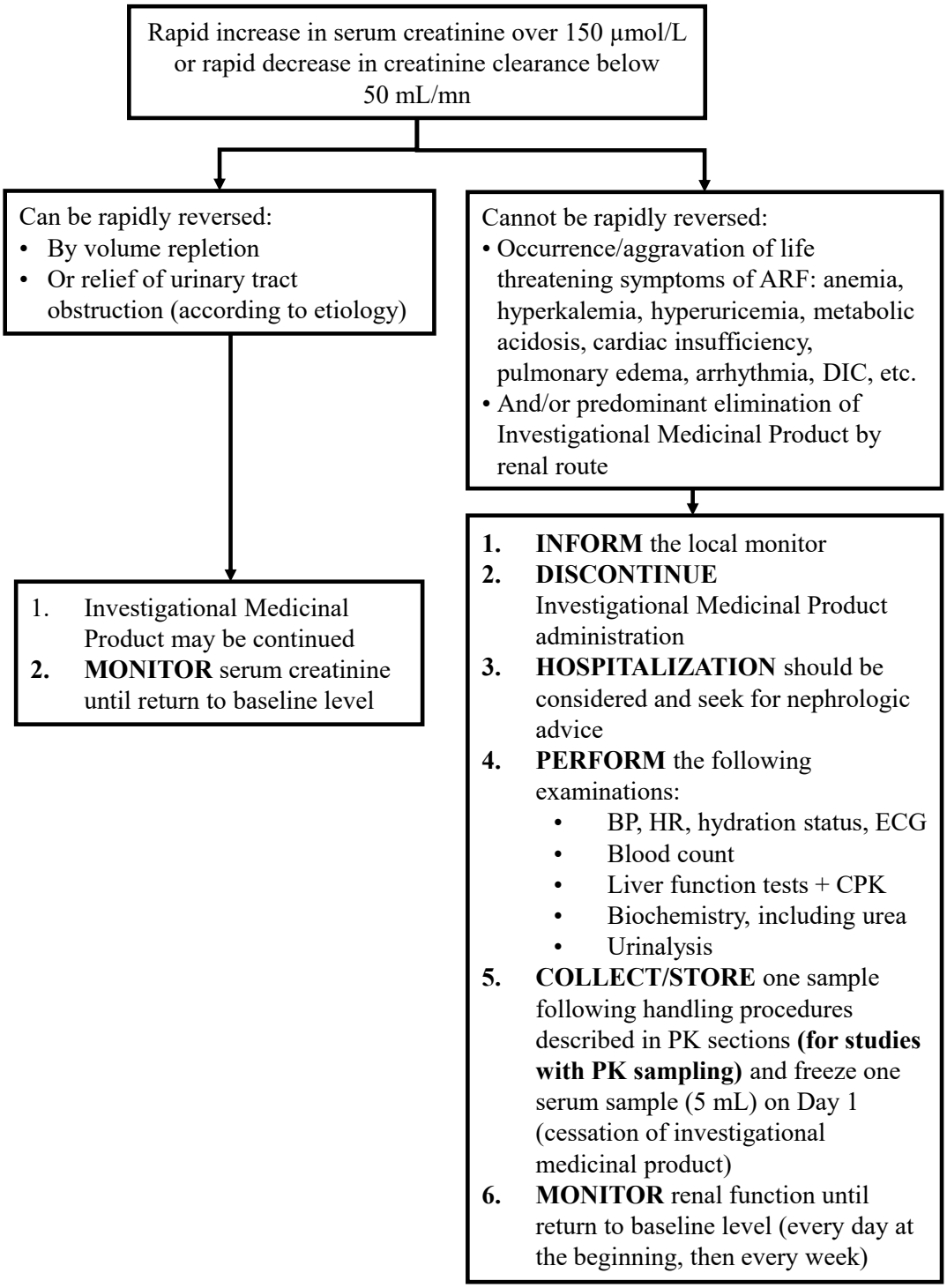
Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.



*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 AE only if at least one of the criteria listed in Section 10.4.3 is met

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 United Kingdom

17.3.1.1 Requirement for local protocol amendment dated 02 Feb 2017

An amendment to the protocol applicable in the United Kingdom was written in response to a request by the Medicines and Healthcare products Regulatory Agency (MHRA) medical reviewer. In alignment with requirements from the MHRA, the last paragraph of Section 10.3.1 underlines that final decisions regarding discontinuation of study drug for all or selected clinical trial patients will be made by the Sponsor. In the event a significant safety concern arises, this decision may be made prior to receipt of the Data Monitoring Committee (DMC) recommendation.

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

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

The following text:

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 DMC recommendations

Is replaced with:

In the event a significant safety concern arises, the Sponsor ~~may~~ **will** immediately decide to discontinue study drug dosing in all clinical trial patients and to not dose new patients, prior to receipt of DMC recommendations. This applies to a decision on dose escalation, as outlined in Section 4 as well.

17.3.1.2 Requirement for amended protocol dated 23 Mar 2020

In order to comply with the UK position regarding the protocol language, the duration of the additional follow-up phase will be defined as ‘up to 144 weeks after the last patient has been enrolled in the study’.

17.3.2 Germany

17.3.2.1 Requirement for local protocol amendment dated 04 Oct 2017

- Provide an amendment to the protocol applicable only in Germany in response to a request by the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices [BfArM])

In section(s): 10.4.2

Rationale: In principle, all changes in laboratory values, vital signs and electrocardiograms which occur within a clinical trial and which the study investigator assesses as clinically relevant must be documented as adverse events.

In alignment with requirements from the BfArM the following update is added as a local protocol amendment for Germany.

In section(s):

10.4.2 General guidelines for reporting adverse events

The following text:

- 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.

Is replaced with:

- 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, and/or
  - Otherwise deemed by the Investigator to be clinically significant.

17.3.3 France

Consistent with the French Health Authority position disallowing home infusion for all ERTs, the option for home infusion added in ACT14132 amended protocol 02 does not apply in France.

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: 27 Jul 2018

Major changes (eg, substantial changes according to European Clinical Trial Applications guidance) for modifying the Final Version of the Protocol were made as part of this protocol amendment.

- **Change to the sample size**

  In section(s): tabulated clinical trial summary, Sections 1.1, 4, 6.1, 6.4.1, 8.1.1 and 8.4 of the protocol

  Rationale:

  - Cap of 5 patients per cohort in Stage 1, Cohort 1 and Cohort 2, has been removed to alleviate constraints in conduct of the study and maximize the collection of data in pediatric patients. At least 10 patients will be included in Cohort 3.

- **Change to endpoints**

  In section(s): tabulated clinical trial summary, Sections 1.2.1, 1.2.3, 9.3.3.5, 9.3.3.5.2, 10.1.1, 10.1.2.6, 10.1.3.7, and 16 of the protocol

  Rationale:

  - FLACC assessment has been removed from the protocol to reduce patient and investigational staff burden due to the limited expected value of the assessment.

- **Change to sampling for pharmacodynamic variables**

  In section(s): tabulated clinical trial summary, Sections 1.2.1, 1.2.3, 2, 3, 9.3.2.2, 10.1.2.1, 10.1.2.6, 10.1.3.6, 10.1.3.7 and 14.9 of the protocol

  [redacted]

- **Change to inclusion/exclusion criteria**

In section(s): Sections 7.2.1 and 8.8.2 of the protocol

Rationale:

- **E 06.** Beta-blockers are no longer a prohibited concomitant medication as they are considered standard of care in this IOPD patient population.

Globally, reference to the investigational medicinal product (product code GZ402666) has been changed from neoGAA to its recently approved International Nonproprietary Name, avalglucosidase alfa.

17.4.2 Amended protocol 02: 24 Mar 2020

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 has been extended to an additional period of up to 226 weeks (Week 371) or until avalglucosidase alfa is approved in the patient's country, whichever comes first (refer to Appendix C [Section 17.3.1] for definition applicable for UK patients).
- In countries where it is permitted, home infusion of avalglucosidase alfa in the extension period may be allowed (refer to Appendix C [Section 17.3.3] for France]).
- Clarifications were given regarding the conditions for temporary IMP discontinuation with DMC consultation.
- Clarifications were given regarding AESI related to LFT values that can fluctuate as part of the underlying Pompe disease.
- Clarification was given in the tertiary endpoints that the Motor Skills Checklist is completed in concert with the Gross Motor Function Classification System, Expanded and Revised.
- Clarification was given in the description of some tertiary endpoints.
- Clarification was given regarding the possibility of additional interim analysis for regulatory purpose during the extension period.
- Clarification was given regarding the order of motor assessments.
- As patients are no longer treated with alglucosidase alfa after Week 25 when entering the extension period, the collection of samples for analysis of anti-alglucosidase alfa antibodies was removed from the follow-up after primary analysis period (PAP).
- Sections 12, 13, and 14 were updated to reflect practices as outlined in the current protocol template.

France-specific requirement

- The option for home infusion added in this amended protocol 02 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

- To comply with the United Kingdom (UK) position regarding the protocol language with regards to the study follow-up period duration.

Protocol amendment summary of changes table

Section # and Name	Description and Change	Brief Rationale
Clinical trial summary (Secondary endpoints) Section 9.2.1.4 (Pharmacokinetics parameters) Section 11.4.4 (Analyses of pharmacokinetic and pharmacodynamic variables)	Terminal half-life ($t_{1/2z}$) was added as an additional PK parameter	Although tested, this parameter was not presented in the protocol. It is then added.
Clinical trial summary (Tertiary endpoints) Section 9.3.3.9 (Motor Skills Checklist)	Motor Skills Checklist was added under tertiary endpoints	Although tested, this parameter was not included as an endpoint. Since this evaluation is complementary to other motor evaluations it is then added under tertiary endpoints.
Clinical trial summary (Assessment schedule, Duration of study period), Section 6.2.1 (Duration of study participation for each patient), Section 8.1.2 (Extension period: Week 27 to Week 145 (Month 36) and additional extension period from Week 147 onwards)	An additional extended follow-up period of up to 226 weeks and corresponding text was added including text to comply with the United Kingdom (UK) position regarding the protocol language with regards to the study follow-up period duration.	To allow study participants to continue to receive the investigational medicinal product (IMP) after Week 145.
Clinical trial summary (Assessment schedule) Section 10.1.2 (Treatment period)	Language for time window for visits is updated	Clarification and consistency with other studies of the program
Section 1.2.1 (Treatment period)-Efficacy	Motor Skills Checklist was added.	To comply with the addition of this parameter in the tertiary endpoints.
Section 1.2.1 (Treatment period)-Footnote “a”	Additional text was added in case of temporary discontinuation	Clarification
Section 1.2.1 (Treatment period)-Footnote “g”	The footnote was edited to adopt the amendment-specific change	Clarification and consistency with other studies of the program
Section 1.2.1 (Treatment period)-Footnote “u”	The footnote was edited regarding use and reporting of ventilator diary	Clarification
Section 1.2.2 (Extension period (Week 27 to Week 35) including details for Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa) Safety	Deleted anti-alglucosidase alfa antibodies assessments post primary analysis period (PAP)	As patients are no longer treated with alglucosidase alfa in ETP, the measurement of anti-alglucosidase alfa after PAP is no longer needed.
Section 1.2.2 (Extension period (Week 27 to Week 35) including details for Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa) Footnote “b”	Additional text was added in case of temporary discontinuation	Clarification
Section 1.2.2 (Extension period (Week 27 to Week 35) including details for Stage 2 - Cohort 3 for patients switching to avalglucosidase alfa) Footnote “j”	The footnote was edited regarding use and reporting of ventilator diary	Clarification

Section # and Name	Description and Change	Brief Rationale
Section 1.2.3 (Extension period (Week 37 to Week 145)	• Section heading was updated from Week 149 to Week 145 • The column for the 4-week follow-up visit/contact and 37 Month (Week 149) was deleted • Deleted anti-alglucosidase alfa antibodies assessments post PAP • Efficacy: Motor Skills Checklist was added. • Footnote “a”: Additional text was added regarding temporary discontinuation and instruction was added regarding home infusion • Footnote “b”: Additional text added regarding possibility of home infusion of avalglucosidase alfa • Footnote “r”: The footnote was edited regarding use and reporting of ventilator diary	To reflect the amendment specific changes and including additional extended follow-up period
Section 1.2.4 (Extended long-term treatment period)	New schedule of assessment regarding extended long-term treatment period was added.	To reflect the amendment-specific changes
Section 1.2.5 (End of study)	New schedule of assessment regarding end of study was added.	To reflect the amendment-specific changes
Section 6.3 (Interim analysis) and Section 11.5 (Interim analysis)	New text was added regarding possibility of additional interim analysis for regulatory purpose during the extension period	Clarification
Section 8.1 (Investigational medicinal product(s))	• Clarification that the use of an in-line filter is for alglucosidase alfa infusions only • The following text was added: “The Sponsor will inform the DMC of any dose change related to AEs” • Extension period of “120-week” changed to “up to 346-week”	Clarification
Section 8.9 (Home infusion) Section 8.9.1 (Home infusion for patients receiving alglucosidase alfa)	New section for home infusion details including the re-numbered section on home infusion for alglucosidase alfa and the new section on home infusion for avalglucosidase alfa	Implementation of home infusion of avalglucosidase alfa as an option, where allowed.
Section 8.9.2 (Home infusion for patients receiving avalglucosidase alfa)	New section and corresponding text regarding home infusion for patients receiving avalglucosidase alfa was added.	To reflect the amendment-specific changes
Section 9.1.1.3 (Vital signs)	Text updated to clarify what is included in the definition of infusion rate change	Clarification

Section # and Name	Description and Change	Brief Rationale
Section 9.1.1.7 (Immunogenicity)	Updated anti-avalglucosidase alfa assessment period and deleted anti-alglucosidase alfa assessments.	As patients are no longer treated with alglucosidase alfa in ETP, the measurement of anti-alglucosidase alfa after PAP is no longer needed.
Section 9.2.1.3 (Bioanalytical method)	Updated lower limit of quantification from 12.50 ng/mL (or 0.0130 ng/mL) to 12.0 ng/mL (or 0.0120 ng/mL)	Clarification
Section 9.2.2.4 (Echocardiography)	Text is updated to clarify that M-mode is also performed	Clarification
Section 9.3.3.3 (Ventilator use diary)	Text was updated regarding reporting of periods for ventilator use/day	Clarification
Section 9.3.3.9 (Motor Skills Checklist)	New section for Motor Skills Checklist and corresponding text was added.	To reflect the amendment-specific changes
Section 10.1 (Visit schedule)	The order for evaluating motor assessments was edited, the Motor Skills Checklist was added, and GSGC scale was deleted.	Clarification
Section 10.1.1 (Screening/baseline visit)	Motor Skills Checklist was added for GMFCS-E&R	To comply with the addition of this parameter in the tertiary endpoints.
Section 10.1.2.2 (One week following first infusion (Week 2 [Day 8]))	Added text for anti-alglucosidase alfa anti-drug antibodies (ADA) assessments.	Clarification
Section 10.1.2.5 (Monthly)	The following bullet points were added: • Biomarkers: ○ Urine Hex4 sample collection • Ventilator use diary; • Eyelid position measurements; • Vital signs (before, during, and following infusion: see Section 1.2); • IRT contact for IMP resupply; • Infusion of IMP;	Clarification for visit exhaustivity
Section 10.1.2.6 (Every 3 months)	• Motor Skills Checklist was added for GMFCS-E&R • New bullet list as “IRT contact for IMP resupply” was added	To reflect the amendment-specific changes and clarification for visit exhaustivity
Section 10.1.3 (Extension period)	Section heading was adjusted to “Extension period (Week 27 to Week 145)”	Clarification.
Section 10.1.3.2 (One week following first infusion within the extension period)	Deleted assessments for anti-alglucosidase alfa antibodies	As patients are no longer treated with alglucosidase alfa in ETP, the measurement of anti-alglucosidase alfa after PAP is no longer needed.
Section 10.1.3.3 (Two weeks following first infusion within the extension period (Week 29))	• New bullet list as “IRT contact for IMP resupply” was added	Clarification for visit exhaustivity

Section # and Name	Description and Change	Brief Rationale
Section 10.1.3.4 (Every 2 weeks (Biweekly))	• Section heading updated and added "Every 2 weeks" • "W147" removed from list of time points	Clarification
Section 10.1.3.5 (Every 4 weeks (Monthly))	• Section heading updated and added "Every 4 weeks" • New bullet list as "ventilator use diary" was added • New bullet list as "IRT contact for IMP resupply" was added	Clarification for visit exhaustivity
Section 10.1.3.6 (Every 12 weeks (Quarterly))	• Section heading changed from "Every 3 months" to "Every 12 weeks (Quarterly)" • Deleted assessments for anti-alglucosidase alfa antibodies • New bullet list as "ventilator use diary" was added • New bullet list as "IRT contact for IMP resupply" was added	Clarification for visit exhaustivity. As patients are no longer treated with alglucosidase alfa in ETP, the measurement of anti-alglucosidase alfa after PAP is no longer needed.
Section 10.1.3.7 (Every 24 weeks (every 6 months))	• Updated section heading and added "Every 24 weeks" • Deleted assessments for anti-alglucosidase alfa antibodies • The following text was added: "Avalglucosidase alfa plasma PK sample collection (before and following infusion) for Stage 2 – Cohort 3 patients switching to avalglucosidase alfa in the extension period: at W37 and W49. For these patients the W49 visit (V28) requires a stay at the site prior to and for at least 8 hours following the end of IMP infusion. Another sample will be taken 12 to 16 hours after the end of IMP infusion. If the Cohort 3 dose of avalglucosidase alfa is 20 mg/kg qow, this additional sample will not be taken;" • Motor Skills Checklist was added The following bullet points were added: • IRT contact for IMP resupply; • Infusion of avalglucosidase alfa; • AE collection; • Concomitant medications/therapies.	Clarification for visit exhaustivity. As patients are no longer treated with alglucosidase alfa in ETP, the measurement of anti-alglucosidase alfa after PAP is no longer needed.

Section # and Name	Description and Change	Brief Rationale
Section 10.1.4 (Extended long-term treatment period (From Week 147 onwards)	New section and corresponding text was added for extended long-term treatment period	To reflect the amendment-specific changes
Section 10.1.6 (Follow-up)	Text was updated in case of missed visit where efficacy assessments/procedures to be performed	Clarification
Section 10.1.7 (Follow-up for patients who temporarily or permanently discontinued the study treatment)	The following text was added: "Patients who permanently discontinue the study treatment prior to the scheduled end of treatment during the extended long-term treatment period will have assessments corresponding to the end of treatment visit."	Clarification
Section 10.3.1 (Temporary treatment discontinuation with investigational medicinal product(s))	The bulleted list was changed from: "Any increase in ALT, AST, total bilirubin, or alkaline phosphatase >3x the baseline value" to "Any increase in ALT, AST, total bilirubin, or alkaline phosphatase >3 × the baseline value, except if the increased value is still within the normal range."	Clarification
Section 10.4.1.3 (Adverse event of special interest) and Table 4 (Summary of adverse event reporting instructions)	The criteria was changed from: "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" to "A maximum ALT value of ≥400 IU/L (except if baseline value is ≥400 IU/L) or AST value of ≥500 IU/L (except if baseline value is ≥500 IU) or an increase in direct, indirect, or total bilirubin of ≥2 x ULN"	Clarification
Section 10.6 (Safety instructions)	The following text was added: "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 and the patient's guardian(s), such a procedure may be initiated as per guidelines in the pharmacy manual."	Text added for IAR evaluation by DMC with the possibility of desensitization procedure
Section 11.4.1.1 (Compliance)	Updated the compliance text.	Clarification
Section 11.4.2.4 (Anti-avalglucosidase alfa and anti-alglucosidase alfa antibodies, neutralizing antibodies, and other immunogenicity testing)	Updated the text pertaining to summarization of anti-avalglucosidase alfa and anti-alglucosidase alfa titer.	Clarification
Section 11.4.3 (Analyses of efficacy endpoints)	Updated the text for composite score.	Clarification

Section # and Name	Description and Change	Brief Rationale
Section 12 (Regulatory, ethical, and study oversight considerations), Section 13 (Study monitoring) Section 14 (Additional requirements)	The sections were updated to reflect the current protocol template-specific text.	To align with current protocol template
Section 16 (Bibliographic references)	New reference #50 was added and subsequent references were renumbered.	Reference to new text added.
Section 17.3: Appendix C (Country-specific requirements)	The section was updated to include UK- and France-specific amendment text	Administrative update.
Section 17.4: Appendix D (Protocol amendment history)	New section and corresponding text was added	Administrative update.
Throughout	Typos have been corrected where necessary.	Clarifications
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Signature Page for VV-CLIN-0211221 v5.0
act14132-16-1-1-amended-protocol03

Approve & eSign	[redacted]

Approve & eSign	[redacted]