NCT03019406

STATISTICAL ANALYSIS PLAN

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

GZ402666-ACT14132

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

6MWT:	six-minute walk test
%:	percentage
[redacted]	[redacted]
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	area under the curve
Bayley-III:	Bayley Scale of Infant and Toddler Development, Third Edition
BAEPs/BAERs:	Brainstem auditory evoked potentials/responses
BMI:	body mass index
BMS:	Biomedical System
BNP:	brain natriuretic peptide
CK:	creatine kinase
CL:	clearance
CSR:	clinical study report
CRIM:	cross-reactive immunologic material
DBL:	database lock
DMC:	Data Monitoring Committee
e-CRF:	electronic case report form
ECG:	electrocardiogram
ECHO:	echocardiography
ERT:	enzyme replacement therapy
ETP:	extension treatment period
FEV1:	forced expiratory volume in the first second of the FVC maneuver
FVC:	forced vital capacity
GAA:	lysosomal acid α-glucosidase
GLI:	global lung initiative
GMFCS-E&R:	Gross Motor Function Classification System - Expanded and Revised
GMFM-88:	Gross Motor Function Measure-88
HLGT:	high-level group term
HLT:	high-level term
HRQOL:	health-related quality of life
IAR:	infusion associated reaction
IMP:	investigational medicinal product
IOPD:	infantile-onset Pompe disease
IPFD:	interpalpebral fissure distance
IRT:	interactive response technology
IV:	introvenous

LLT:	lower-level term
Leiter-3:	Leiter International Performance Scale, Third Edition
LVM:	left ventricular mass
LVMI:	left ventricular mass index
MedDRA:	medical dictionary for regulatory activity
MEP:	maximum expiratory pressure
MIP:	maximum inspiratory pressure
mITT:	modified intent-to-treat
MPD:	margin pupil distance
MRD:	minimal required dilution
MRD-1:	margin reflex distance-1
MTD:	maximum tolerated dose
n:	number
NAb:	neutralizing antibody
NYHA:	the New York Heart Association
PAP:	primary analysis period
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PDIS:	Pompe disease impact scale
PDSS:	Pompe disease symptom scale
PE:	physical examination
PEDI:	Pediatric Evaluation of Disability Inventory
PFT:	Pulmonary Function Test
PK:	pharmacokinetics
PP:	per protocol
PR:	interval from the beginning of the P wave until the beginning of the QRS complex
PT:	preferred term
PY:	patient year
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
RR:	interval between the peaks of successive QRS complex
SAE:	serious adverse event
SD:	standard deviation
SMQ:	standard MedDRA query
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
VAS:	Visual Analogue Scale
Vd:	volume of distribution
WHO-DD:	World Health Organization-Drug Dictionary
Z-score:	standard score

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

ACT14132 is a multi-stage phase 2 open-label, multicenter, multinational, ascending dose cohort, repeated intravenous infusion study of avalglucosidase alfa in pediatric patients with infantile-onset Pompe disease (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 presence of ptosis.

Stage 1:

- Cohort 1 – at least 5 IOPD patients will receive avalglucosidase alfa at 20 mg/kg 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.

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.

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).

Upon confirmation by the Investigator or sub-Investigator (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.

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 3 years in the study. Cohort 3 patients receiving alglucosidase alfa will have the option to switch to treatment with avalglucosidase alfa maximum tolerated dose (MTD) as determined based on safety data from both dose levels in Cohort 1 and Cohort 2 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) and analysis will be conducted on all data available by then.

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 study participation) or increasing the avalglucosidase alfa dose to 40 mg/kg qow or 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 study 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.

1.2 OBJECTIVES

1.2.1 Primary objectives

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

1.2.2 Secondary objectives

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.

1.2.3 Other objectives

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.

1.3 DETERMINATION OF SAMPLE SIZE

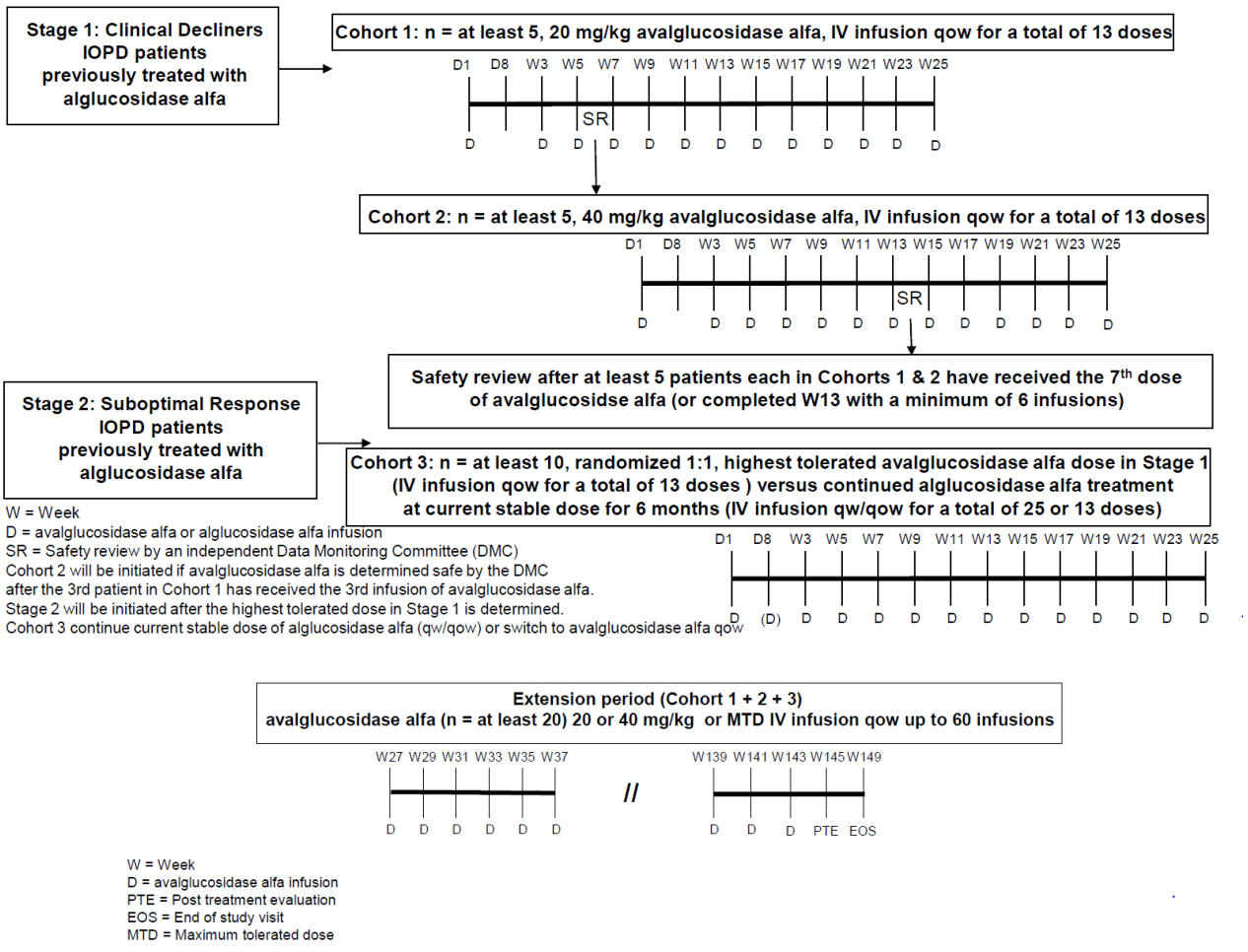
No formal sample size calculations have been performed. Sample size for this study was based upon empirical considerations.

1.4 STUDY PLAN

For each patient who signs the informed consent, the study consists of:

- An up to 14-day screening period (may be extended to up to 4 weeks in pre-specified situations [refer to protocol Section 10.1.1]);
- A 25-week treatment period (Primary Analysis Period [PAP]);
- An up to 120-week Extension Treatment Period (ETP);
- An up to 4-week post-treatment observation period.

Figure 1 – Graphical Study Design



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The current SAP is based on Protocol Amendment 03 Version 1 (dated 27 July 2018). This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled on 26 October, 2017). The listing below gives the rationale and key details of major changes (e.g., substantial changes according to European Clinical Trial Applications guidance) to the protocol statistical section.

- Change to the sample size: 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: FLACC assessment has been removed from the protocol to reduce patient and investigational staff burden due to the limited expected value of the assessment.
- The baseline value is defined as the last non-missing value prior to first investigational medicinal product (IMP) intake, unless otherwise specified. This is true for PAP. However, in the ETP analyses, the ETP baseline value is defined as:
  - The last non-missing value prior to first IMP intake in PAP for patients receiving avalglucosidase alfa from the beginning of this study;
  - The last non-missing value prior to first IMP intake in ETP for patients switching to avalglucosidase alfa from alglucosidase alfa.
- The composite score constructed considering 3 domains: Gross Motor Function Measure-88 (GMFM-88) and Gross Motor Function Classification System - Expanded and Revised (GMFCS-E&R), Ptosis, and Respiratory Function serves as an exploratory endpoint.

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

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The listing below gives the rationale and key details of major changes to Statistical Analysis Plan Version 1.0.

- In retrospective Chart Review, update “new onset of ptosis” to “presence of ptosis”.
- Update part of the definition of transient ADA response from “treatment induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the patient’s last sample time point is ADA-negative” to “the last sample time point is positive and separated by <16 weeks from the first positive result”.
- Treatment-boosted ADAs are excluded from the analysis of ADA kinetics. If many patients have preexisting ADAs, kinetics of boosting will be described separately.
- The assessment of NAb response is simplified.

- Expand the composite score from cohort 3 to all population in Table 1
- Update the wording on re-randomization test for efficacy endpoints besides to composite score
- Update PCSA following ISS

2 STATISTICAL AND ANALYTICAL PROCEDURES

The interim analysis will be performed when all Cohort 3 patients have completed the 6-month (25 weeks) primary analysis period and will include a formal database lock and analyses of safety (including adverse events, physical examinations and growth, clinical laboratory evaluations, electrocardiogram [ECG], vital signs and immunogenicity), PK, efficacy(including GMFM-88, GMFCS-E&R, Pompe-Pediatric Evaluation of Disability Inventory [PEDI] mobility, Quick Motor Function Test [QMFT], echocardiography [ECHO], Eyelid position measurements including Interpalpebral fissure distance [IPFD], Margin reflex distance-1 [MRD-1], Margin pupil distance [MPD], total creatine kinase [CK], CK with MB fraction, and Composite Score Constructed Considering 3 Domains: GMFM-88 and GMFCS-E&R, Ptosis, and Respiratory Function), PD (urinary Hex4 level), and exploratory effect of avalglucosidase alfa treatment on functional endurance, six-minute walk test (6MWT), respiratory function (including Pulmonary Function Testing [PFT] and ventilator use diary), PedsQL Generic Core Scales, HRQOL, pain (including PedsQL Pediatric Pain Questionnaire and Visual Analogue Scale [VAS]), developmental disability (including Bayley Scale of Infant and Toddler Development, Third Edition [Bayley-III] and Leiter International Performance Scale, Third Edition [Leiter-3]), and hearing testing in patients with IOPD. A Clinical study report (CSR) will be prepared after the PAP analysis.

After the completion of primary analysis when all Cohort 3 patients have completed the 6-month (25 weeks) primary analysis period, interim analyses may be performed in ETP to provide additional information for regulatory purpose.

The final ETP analyses will be performed after all patients completed ETP. A final DBL will occur and a final CSR will be prepared after the ETP analyses.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The PAP baseline value is defined as the last non-missing value prior to first investigational medicinal product (IMP) intake, unless otherwise specified.

The ETP baseline value is defined as:

- The last non-missing value prior to first IMP intake in PAP for patients receiving avalglucosidase alfa from the beginning of this study;
- The last non-missing value prior to first IMP intake in ETP for patients switching to avalglucosidase alfa from alglucosidase alfa.

Demographic characteristics

Demographic variables are age at study entry (year), gender (Male, Female), race (American Indian or Alaska Native, Asian, Black or Africa American, Native Hawaiian or other Pacific Islander, White, Not Reported), ethnicity (Hispanic, non-Hispanic, Unknown, Not Reported).

Medical or surgical history

Medical or surgical history includes prior or existing condition in different body systems as well as prior or existing medical conditions/surgical procedures of specific interest.

Disease characteristics at baseline

Pompe disease history includes acid α-glucosidase (GAA) genotyping, CRIM (cross-reactive immunologic material) status, GAA enzyme activity, [redacted], aspects of disability (Pompe medical history, ventilator and assistive mobility device use), age at first symptoms of Pompe disease, age at diagnosis of Pompe disease, age at first treatment with alglucosidase alfa, time from Pompe disease diagnosis to first infusion of study drug, time from first symptoms of Pompe disease to first infusion of study drug.

Pompe medical history includes:

- Cardiovascular history (evidence of cardiac involvement, current NYHA (the New York Heart Association) heart failure classification, congestive heart failure),
- Ears, nose, throat medical history (enlarged tongue, hearing loss),
- Gastrointestinal (hepatomegaly, gastroesophageal reflux),
- Respiratory history (pneumonia, tracheostomy, sleep disturbances, sleep apnea),
- Musculoskeletal history (muscle weakness in upper extremities, muscle weakness in lower extremities, scoliosis, joint contractures, and current ambulatory status, assisted walking device and wheelchair use).

Family history of Pompe disease history includes confirmed Pompe disease in other family members.

Retrospective Chart Review

Retrospective review of available assessments prior to study entry documents clinical decline or suboptimal clinical response. It may include the following assessments:

- Respiratory function evaluation:
  - FVC (% predicted),
  - use of ventilator support.
- Motor function evaluation:
  - gross motor milestone,
  - GMFM-88 composite score,
  - Pompe-PEDI mobility,
  - QMFT,
  - GMFCS-E&R,

  - other test or assessment, if any.
- Cardiac Function Evaluation:
  - Left ventricular mass (LVM) standard score (Z-score);
  - Left ventricular mass index (LVMI; g/m^2);
- Other Evaluation:
  - Presence of ptosis.

The above assessments have documented (at least 2 recent and consecutive assessments prior to study entry, not less than 2 weeks apart) evidence of clinical decline or suboptimal 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 - suboptimal clinical response in at least 1 of the following parameters: respiratory function, motor skills, and/or presence of ptosis.

Growth parameters at baseline

Weight (kg), height/total body length (cm), body mass index (BMI, kg/m^2), head circumference (cm) and Tanner stage of sexual maturation.

Vital signs

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation. The baseline values for vital signs are the last non-missing assessment prior to the first study treatment by comparing the infusion time and measurement time.

Immunogenicity status

The immunogenicity evaluation at baseline includes antibody status (positive or negative) and magnitude (titer) of the anti-drug antibodies (ADA).

2.1.2 Prior or concomitant medications

Medications and therapies taken by the patient during the 30-day period prior to the Screening/Baseline evaluation visit and during the course of the study will be recorded in the electronic Case Report Forms (e-CRF).

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at Sanofi at the time of DBL.

- Prior medications are those that are taken in the 30 days prior to first IMP intake as well as pre-study alglucosidase alfa medication for at least the 6 months prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from first study treatment to the end of treatment + 28 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.3).
- Post-treatment medications are those the patient took in the period running from the 28 days after last IMP intake up to the end of the study.

2.1.3 Safety endpoints

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, ECG, physical examination (PE), weight, height, head circumference and immunogenicity.

Observation period

The observation period will be divided into the following epochs:

- The **pre-screening epoch** is defined as the time before the signed informed consent date.
- The **screening epoch** is defined as the time from the signed informed consent date up to first administration of IMP.
- The **treatment epoch for PAP** is defined as the time from the first administration of the study drug to,
  - The time just prior to the first administration of the study drug in ETP, or,
  - Four weeks (28 days) after the last infusion date if the patient does not go to ETP. If the patient enrolls in another study or receives commercially available enzyme replacement therapy (ERT), the follow-up period maybe reduced from 4 to 2 weeks.
- The **treatment epoch for ETP** is defined as the time from the first administration of the study drug in ETP to the last administration of the study drug + 4 weeks (28 days). If the patient enrolls in another study or receives commercially available ERT, the follow-up period maybe reduced from 4 to 2 weeks.
- The **post-treatment epoch for PAP** is defined as the time beyond the treatment epoch in PAP through the last study assessment; this epoch is defined only for patients who do not receive any infusion in ETP.
- The **post-treatment epoch for ETP** is defined as the time beyond the treatment epoch in ETP through the last study assessment, defined only for patients who receive any infusion in ETP.

The on-study observation period comprises of screening, treatment and post-treatment epochs. The overall avalglucosidase alfa treatment period is from the first administration of avalglucosidase alfa to the last administration + 4 weeks (28 days). If the patient enrolls in another study or receives commercially available ERT, the follow-up period maybe reduced from 4 to 2 weeks.

2.1.3.1 Adverse events variables

Adverse event observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the screening epoch.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the treatment epoch.
- Post-treatment AEs in PAP are AEs that developed or worsened or became serious during post-treatment epoch in PAP and could only be observed in patients who do not get an infusion in ETP.
- Post-treatment AEs in ETP are AEs that developed or worsened or became serious during the post-treatment epoch for ETP and could only be observed for patients who receive at least one infusion in ETP.

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

Serious adverse events

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

- results in death, or,
- is life-threatening, or,
  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization, or,
- results in persistent or significant disability/incapacity, or,
- is a congenital anomaly/birth defect, 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 (i.e., 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 (i.e., agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
  - convulsions (seizures, epilepsy, epileptic fit, absence, etc.) ;
- Development of drug dependence or drug abuse;
- Alanine aminotransferase (ALT) >3 × upper limit of normal (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-day's duration for a planned surgical procedure).

Adverse event of special interest

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

AESIs will include:

- Infusion-associated reactions (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. See more detailed definition in Section 2.1.4.
- Pregnancy:
  - Pregnancy might occur in a female patient included in the clinical 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.

- 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.
- Clinical laboratory (change from baseline):
  - ALT or aspartate aminotransferase (AST) increase of ≥3 × the 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 or AST value of ≥500 IU/L 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).

2.1.3.2 Deaths

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

- On-study: deaths occurring during the on-study observation period (for PAP and ETP respectively);
- Treatment: deaths occurring during the treatment epoch (for PAP and ETP respectively);
- Post-treatment: deaths occurring during the post-treatment epoch (for PAP and ETP respectively).

2.1.3.3 Laboratory safety variables

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

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

- Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets.
- Biochemistry:
  - Plasma/serum electrolytes: sodium, potassium, chloride, calcium;

- Liver function: AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, total and direct bilirubin;
- Renal function: creatinine, blood urea nitrogen, uric acid;
- Metabolic panel: glucose, albumin, total proteins, total cholesterol, triglycerides;
- Potential muscle toxicity: CK, CK with MB fraction, lactate dehydrogenase;
- Brain natriuretic peptide (BNP).

- Urinalysis will include urine color, appearance, specific gravity, proteins, glucose, erythrocytes, leukocytes, ketone bodies, and pH to be assessed:
  - Qualitatively: A dipstick is to be performed on a freshly voided specimen for qualitative detection using a reagent strip;
  - Quantitatively: A quantitative measurement for protein, erythrocytes, and leukocytes count will be required in the event that the urine sample test is positive for any of the above parameters by urine dipstick (e.g., to confirm any positive dipstick parameter by a quantitative measurement).

2.1.3.4 Vital signs

Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation.

2.1.3.5 Electrocardiogram variables

Standard 12-lead ECGs are recorded after at least 15 minutes in the supine position using an electrocardiographic device. The following will be assessed: heart rate, rhythm, interval 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 (both Fredericia and Bazett corrections 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.

2.1.3.6 Physical examination

Physical examination parameters include assessments 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 grasp reflexes. Physical examination e-CRF also asks 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.

2.1.3.7 Body weight, height/total body 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 total 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. 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, total body length is to be measured in the same position throughout the study.

BMI will be calculated as the body weight divided by the square of the body height.

Head circumference will be measured at the same time points.

2.1.3.8 Immunogenicity

Immunogenicity assessments will include the following:

- During the 25-week treatment period, pre-infusion samples from patients receiving avalglucosidase alfa will be collected every month for evaluation of anti-avalglucosidase alfa ADA and every 3 months for evaluation of anti-alglucosidase alfa ADA. In addition, samples will be collected at Visit 3 (Day 8) to monitor for an early antibody response using both assays. For patients receiving alglucosidase alfa, only anti-alglucosidase alfa ADA will be evaluated.
- During the 120-week extension period, pre-infusion samples from all patients will be collected every 3 months for evaluation of anti-avalglucosidase alfa ADA and every 6 months for evaluation of anti-alglucosidase alfa ADA. In addition, participants in Cohort 3 switching to avalglucosidase alfa will have samples collected at Visit 17 (Week 28) to monitor for an early antibody response using both assays, 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 (NAbs) 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 anti-drug IgE, complement activation, serum tryptase following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions.

In the event a patient exhibits signs or symptoms suggestive of systemic immune complex mediated reactions involving skin and other organs, serum samples are obtained for the evaluation of circulating immune complexes.

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

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

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

The ADA attributes will be determined by the following conditions:

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

The following kinetics of the ADAs will be analyzed:

- Onset of ADA is defined as the time period (in days) between the first study drug administration and the first instance of treatment induced ADAs.
- Duration of ADA will be calculated as the date of last treatment induced ADA sample minus the date of first treatment induced or boosted ADA sample + 1.
- Persistent ADA response is defined as,
  - Treatment induced ADAs detected at two or more sample time points during the treatment, where the first and last ADA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks.

- Transient ADA response is defined as,
  - Treatment induced ADA detected only at one sampling time point during the treatment, followed by an ADA-negative value; Or,
  - Treatment induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the patient's last sample time point is ADA-negative.
- Indeterminate ADA response is defined as,
  - Only the last sample time point is positive; Or
  - The last sample time point is positive and separated by <16 weeks from the first positive result.

Treatment-boosted ADAs are excluded from the analysis of ADA kinetics. If many patients have preexisting ADAs, kinetics of boosting will be described separately.

For the assessment of NAb response, the qualitative sample status will be assessed and be categorized into the following classes:

- NAb-negative sample: a sample is considered negative if NAbs are not detected.
- NAb-positive sample: sample in which NAb is detected.

2.1.4 Infusion associated reactions

Protocol-defined IARs

IARs are defined as AESIs that occur during either the infusion or the observation period following the infusion which are deemed to be related or possibly related to the IMP. At the discretion of the Investigator, AEs occurring after completion of the post-infusion observation period that are assessed as related or possibly related may also be considered IARs. AESIs defined in protocol only include the protocol-defined IARs.

Algorithm-defined IARs

An alternative definition of IAR is defined as any treatment-emergent AE meeting one of the following criteria:

- Event occurs from the start of infusion to the end of infusion plus 24 hours window, and considered related study drug;
- If AE start date is non-missing but time component is missing, compare AE Start date with infusion start date (date component only) and infusion end date (date component only). If AE Start date is between infusion start date and infusion end date plus one day, consider such AE as algorithm-defined IAR if AE is related to study drug.

The algorithm-defined IAR will be summarized as supplementary to the protocol-defined IARs for the safety review.

2.1.5 Pharmacokinetic endpoints

Pharmacokinetic variables include C_{max}, t_{max}, area under the curve ($AUC_{0\text{-}last}$), clearance (CL), and volume of distribution (Vd).

2.1.6 Efficacy endpoints

The baseline value for efficacy endpoints is the same as the baseline definition in Section 2.1.1.

Efficacy endpoints include the following:

Gross Motor Function Measure-88 and Gross Motor Function Classification System - Expanded and Revised

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 raw score and a percent score, which is the percentage of the maximum score for that dimension. Total raw score is obtained by adding the raw score from each dimension. Total percentage 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. The total raw score weights each item, not each dimension, equally.

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. Level I represents high functioning; Level V represents low functioning.

Pompe Pediatric Evaluation of Disability Inventory

A disease-specific version of PEDI was developed to assess functional capabilities and performance in children with Pompe disease from 2 months through adolescence. 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. An increase in raw score of 1 point indicates the acquisition of 1 new skill. 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).

Quick Motor Function Test

QMFT will be used to evaluate changes in motor function concurrently with the GMFM-88.

The QMFT is an observer administered test comprising 16 items specifically difficult for patients with Pompe disease. 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.

A higher QMFT score represents better outcome. If any of the 16 items comprising QMFT is missing, the total score of the QMFT will be considered as missing. QMFT total score is the sum of all item scores. QMFT percentage score is the QMFT total score divided by the maximum score of 64.

Echocardiography

Two-dimensional and M-mode ECHO will be performed 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 ECHO. This person will be blinded to the patient and study time point. The primary cardiac outcome assessments (measured and derived by an external vendor Biomedical Systems) to be recorded using off-line review include: LVMI, LVM Z-score, 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 Left Ventricle mass: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.

Eyelid position measurements

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

Protocol Amendment 03 Version 1 Section 1.2. The following eyelid position measurements will be performed by the central reader:

- IPFD,
- MRD-1,
- MPD.

Creatine kinase

CK measurements will come from the central lab, including both total CK and CK with MB fraction.

Composite Score Constructed Considering 3 Domains: GMFM-88 and GMFCS-E&R, Ptosis, and Respiratory Function

The exploratory composite score will be constructed considering 3 domains: GMFM-88 and GMFCS-E&R, ptosis, and respiratory function (measured by the use of respiratory device). Within each domain, the change from baseline to Week 25 will be classified into improvement, unchanged, and worsening (Appendix A), and then receives a domain score which is determined by the baseline status and the change category according to Table 1. The composite score is the sum of the 3 domain scores.

Table 1- Composite Score Constructed Considering 3 Domains: GMFM-88 and GMFCS-E&R, Ptosis, and Respiratory Function

Domain	Population	Change from Baseline at the End of PAP		
		Improvement	Unchanged	Worsening
Respiratory	Suboptimal clinical response/decline [a]	2	1	0
	No suboptimal clinical response/decline	1	0	-1
Motor skills	Suboptimal clinical response/decline [b]	2	1	0
	No suboptimal clinical response/decline	1	0	-1
Ptosis	Suboptimal clinical response[c]	2	1	0
	No suboptimal clinical response	1	0	-1

a. Suboptimal clinical response is documented sustained decline in percent predicted FVC ≥15% or new onset of non-invasive ventilator assistance (acquired for at least 4 weeks prior to study enrollment). If a patient is not old enough to perform PFT properly, assign a score of 0. Clinical decline is 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,

b. Suboptimal clinical response is documented worsening of muscle strength demonstrated by a developmental plateau or decrease in GMFM-88 Total Score and/or in scaled scores of Pompe-PEDI scale or in other motor scale and/or clinical developmental evaluation tools. Use GMFM-88 only if the patient entered the cohort due to suboptimal clinical response on Pompe PEDI. Clinical decline for patients ≤2 years of age at study entry, is failure to acquire at least 2 new age appropriate gross motor milestones at least 6 months prior to study enrollment; for patients >2 years of age at study entry, documented worsening of muscle weakness.

c. Suboptimal clinical response is new onset of ptosis.

If a patient does not have any suboptimal response/decline at baseline for a domain (respiratory, motor skills, or ptosis), a score of 1, 0, or -1 is assigned if a patient improves, remains the same, or declines, respectively, with the exception of improvement for ptosis (which is not possible). Otherwise, if a patient has a suboptimal clinical response/decline at baseline for a domain (respiratory, motor skills, or ptosis), a score of 2, 1, or 0 is assigned if a patient improves, remains the same, or declines. It is under the rationale that stopping a declining trend shall be credited with a higher score.

2.1.7 Pharmacodynamics endpoint

PD endpoint includes the urinary Hex4 level.

2.1.8 Pharmacogenetics endpoints

Pharmacogenetics endpoints will be based on baseline characteristics (Section 2.1.1).

2.1.9 Tertiary endpoints

Tertiary endpoints include:

Six-minute walk test

The 6MWT will be performed to assess functional capacity for patients who are ambulatory, defined as the ability to ambulate 40 m (approximately 130 feet) without stopping and without an assistive mobility device. The primary outcome measure of the 6MWT is the distance walked in 6 minutes recorded in meters. Test equipment and administration techniques will be standardized among the investigational sites. The percent (%) predicted value will be calculated based on the normal reference equations from Table 2 (3) (4), which cover the age range in this study. A similar approach was used by Montes et al (5). For analysis purposes, the age at each assessment will be calculated based on (assessment date - birth date + 1)/365.25. Height (which is to be assessed annually for patients with age ≥18 years and every 3 months for patients with age <18 years) will be based on the most recent valid value at or prior to the assessment date.

Table 2 - Equations for calculating reference value for percent predicted total distance walked in 6MWT

Reference	Age at baseline	Gender	Equation
(3)	≥18 years	Male and Female	868.8 - 2.99 * age - 74.7*sex
(4)	<18 years	Male	196.72 + 39.81 * age – 1.36 * age2 + 132.28 * height
	<18 years	Female	188.61 + 51.50 * age – 1.86 * age2 + 86.10 * height

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

Additional information, including the amount of time walked (to quantify endurance, as all patients may not complete the full 6-minute walk), as well as the use and change from baseline in

assistive mobility devices (including straight cane, wide-based cane, one crutch, two crutches, standard walker, rolling walker, orthotics and other) will also be reported.

Pulmonary function testing

The PFT will include the assessment of FVC, forced expiratory volume in the first second of the FVC maneuver (FEV1), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow 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.

FVC will be reported in absolute value in liters. The FVC (% predicted) value is defined as 100*(actual FVC measurement/predicted value of FVC). The Quanjer GLI-2012 regression equations and lookup tables (1) are used to calculate predicted values of FVC. Predicted values of FVC are functions of sex, age in years (3-95 years), height in cm, and ethnic group (Whites, African Americans, South East Asians, North East Asians and for Other ethnic groups or people of mixed descent). FVC is predicted according to the following equation:

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

Where

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

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

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

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

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

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

For the analysis purpose, the age will be calculated based on (assessment date - birth date + 1)/365.25. Height will be based on the most recent valid value at or prior to the assessment date.

The percent predicted values for MIP and MEP will be calculated (6, 7). The normal reference values used for percent predicted calculation will be dependent on each patient's age, gender, and weight (Table 3). For each patient, the same equations used for the baseline will be used to calculate the predicted values (eg, if a patient started at ≤17 years of age and turns 18 during the study, he/she will still use the pediatric formula after turning to 18). For analysis purposes, the age will be calculated based on (assessment date - birth date + 1)/365.25. Weight for age <18 will be based on the most recent valid value at or prior to the assessment date. The percent predicted value is defined as (absolute measurement/normal reference value) * 100. Since the reference

values will be available only for patients of age 7 years or older, the percent predicted MIP and MEP will not be derived for patients aged <7.

Table 3 - Reference equations for predicted value of MEP and MIP

Test/Age at baseline	Male	Female
MEP		
≥18 years old (6)	174 – 0.83 * age	131 – 0.86 * age
7–17 years old (7)	35 + 5.5 * age	24 + 4.8 * age
MIP		
≥18 years old (6)	120 – 0.41 * age	108 – 0.61 * age
7–17 years old (7)	44.5 + 0.75 * weight	40 + 0.57 * weight

Age in years; weight in kg.

All PFTs will be reported centrally from Biomedical Systems (BMS) following pulmonary software specification and user requirement (2).

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 noninvasive ventilation is defined as ventilatory support applied without the use of an endotracheal tube, i.e., no invasion of the airway. On a bi-weekly basis, the average number of hours of ventilator use/day will be calculated 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.

PedsQL Generic Core Scale questionnaire

The PedsQL Generic Core Scales is a general HRQOL tool. 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 study 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. 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.

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.

PedsQL Pediatric Pain Questionnaire

The 3-item PedsQL Pediatric Pain Questionnaire comprises:

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

10 cm (100 mm) VAS scales from 0 (Not hurting/No discomfort/No pain) to 10 (100) (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 (5 mm). 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.

Observer reported pain visual analogue scale

The Observational Visual Analogue Score (VAS-OBS, range 0-10) is a tool developed to measure subjective phenomena like pain. It usually consists of a 10-cm line, 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. In this study, the VAS-OBS will be applied to all participants.

Bayley Scale of Infant and Toddler Development, Third Edition

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. 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. Raw scores, scaled scores, and age equivalent 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). Test results will be centrally scored by a trained assessor.

Leiter International Performance Scale, Third Edition

The Leiter-3 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.

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, corresponding percentile rank, and 95% Confidence Interval.

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 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.

Hearing Testing

Hearing will be assessed using both Audiogram and Brainstem auditory evoked potentials/responses (BAEPs/BAERs).

- Audiogram: Table 4 summarizes 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.

Table 4 - Hearing assessments appropriate for age Auditory test Developmental age of child

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)

- BAEPs/BAERs will be recorded 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.

2.2 DISPOSITION OF PATIENTS

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

Screened patients will be defined as any patient who has signed the informed consent form.

Randomized patients consist of all Cohort 3 patients who have had a treatment kit number allocated and recorded in the interactive response technology (IRT) database, regardless of whether the treatment kit was used.

For cohort 3, patients treated without being randomized, if any, will not be considered as randomized and will not be included in any efficacy population.

For patient study status, the total number of patients in each of the following categories will be presented using a summary table:

- Screened patients,
- Screen failure patients and reasons for screen failure (if data is available),
- Treated patients (Stage 1),
- Randomized patients (Stage 2),
- Nonrandomized but treated patients (Stage 2),
- Randomized and treated patients (Stage 2),
- Randomized but not treated patients (Stage 2),
- Number and percentage of patients who completed the treatment epoch for PAP,
- Number and percentage of patients who did not complete the treatment epoch for PAP, with corresponding reasons.
- Patients who continued into ETP,
- Patients who completed ETP,
- Number and percentage of patients who did not complete the ETP treatment, with corresponding reasons,
- Number and percentage of patients who did not complete the ETP follow-up, with corresponding reasons (will be included in final study report only).
- Number and percentage of patients who received increased or decrease dose, i.e. increase from 20 mg/kg qow to 40 mg/kg qow (Cohort 1), or decrease from 40 mg/kg qow to 20 mg/kg qow.

For all categories of patients (except for the screened and randomized/nonrandomized categories), the summaries will be provided by study cohort and randomized treatment, and percentages will be calculated using the number of safety patients (Stage 1) or randomized patients (Stage 2) as the denominator.

A listing of patients who received increased or decrease dose will also be provided.

All critical or major deviations potentially impacting efficacy analyses, randomization (Cohort 3), and drug-dispensing irregularities, and other major or critical deviations will be listed by patient for all enrolled patients and also summarized in tables giving numbers and percentages of deviations by study cohort and randomized treatment.

Additionally, the analysis populations for safety, PK and efficacy (Section 2.3) will be summarized in a table by number of patients in the randomized population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error; OR
- A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

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

All randomization and drug-dispensing irregularities will be documented in the CSR. Whether any of these constitute a major protocol deviation is deferred to the decision by the clinical team before the DBL. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will also be described.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site
Patient nonrandomized but treated

2.3 ANALYSIS POPULATIONS

2.3.1 Safety population

The safety population is the primary population for Stage 1 and the overall study safety analysis.

The safety population will include patients who receive at least 1 infusion (partial or total). The safety population will be analyzed according to treatment received. For PAP, safety population includes patients who receive at least 1 infusion in PAP. For ETP, safety population includes patients who receive at least 1 infusion in ETP. Overall safety of avalglucosidase alfa will be based on patients who receive at least 1 infusion during either PAP or ETP.

For Cohort 1 and Cohort 2, patients for whom it is unclear whether IMP was administered will be included in the safety population. For cohort 3, randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.

For Cohort 3, nonrandomized but treated patients, if any, will not be part of the safety population in PAP; however, their safety data will be presented separately in PAP.

2.3.2 Efficacy populations

For Cohort 3, patients treated without being randomized, if any, will not be considered randomized and will not be included in any efficacy population.

The modified intent-to-treat (mITT) population is defined as all randomized patients in Cohort 3 who received at least 1 infusion and with evaluable baseline efficacy assessment. Patients will be analyzed in the treatment group to which they are randomized.

The mITT population is the primary population for Cohort 3 (Stage 2) efficacy analysis.

2.3.3 Additional analysis populations

The ETP population will consist of safety patients who receive at least one avalglucosidase alfa dose during ETP.

The PK population will consist of patients from the safety population in PAP who have evaluable drug concentration data. PK analysis for cohort 3 patients who switch to avalglucosidase alfa during the ETP will be reported in the final CSR.

For Cohort 1 and Cohort 2, the PD or pharmacogenetic analysis population for the parameter of interest will consist of safety patients who have evaluable PD or pharmacogenetic data for the parameter of interest. For cohort 3, the PD or pharmacogenetic analysis population for the parameter of interest will consist of mITT patients who have evaluable PD or pharmacogenetic data for the parameter of interest.

The ADA evaluable population will consist of patients from safety population who have at least one ADA sample taken post-baseline after drug administration that is appropriate for ADA testing with a reportable result. Patients with missing or non-reportable baseline samples and reportable post-baseline samples will be considered as evaluable.

2.4 STATISTICAL METHODS

Unless otherwise specified, safety analyses will use the safety population, where patients who receive at least one infusion of avalglucosidase alfa in PAP will be assigned to the avalglucosidase alfa arm for the PAP safety analysis purposes. Efficacy analyses will use the mITT population, where patients will be considered to be in the treatment group to which they were randomized. In addition, efficacy will also be summarized for all cohorts based on the safety population.

In general, all summary statistics will be computed and displayed by study cohort and treatment arm. Summary statistics for continuous variables will minimally include the number of available data (n), mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, n and percentages will be presented and denominators for the percentages will be based on the analysis population used. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

2.4.1 Demographics and baseline characteristics

Demographics and baseline characteristics parameters described in Section 2.1.1 and physical examination parameters described in Section 2.1.3.6 will be analyzed by study cohort and treatment arm among patients who received at least one dose of avalglucosidase alfa in either PAP and/or ETP, using summary statistics, based on the safety population and also in the mITT population. Denominators for the percentages will be based on the analysis population used, unless otherwise specified.

Medical history will be summarized by body system and preferred term in the safety population.

Z-scores for weight, height/total body length, BMI and head circumference will be also summarized according to the clinical growth charts of Centers for Disease Control and Prevention for applicable patients (8).

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

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

2.4.2 Prior or concomitant medications

Prior medications and concomitant medications are defined in Section 2.1.2. If a drug is started before first IMP intake but continues after the first infusion of the study drug, it is considered prior as well as concomitant.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the Anatomical Therapeutic Chemical (ATC) classification and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication. Prior and concomitant mediations will be summarized separately using safety population.

Prior and concomitant medications will be summarized by study cohort and treatment arm in the treatment epoch for PAP among patients who receive at least one dose of avalglucosidase alfa in PAP. The summary of concomitant medications will be repeated for the treatment epoch for ETP, as well as for the overall avalglucosidase alfa treatment period among patients who receive at least one dose of avalglucosidase alfa in ETP.

2.4.3 Extent of investigational medicinal product exposure and compliance

2.4.3.1 Extent of investigational medicinal product exposure

The extent of study drug exposure will be assessed by the duration of study drug exposure (weeks), number of infusions, amount of dose received and total duration of study drug exposure (patient × years). The extent of study drug exposure will be summarized in the safety population.

Duration of study drug exposure is defined below:

For PAP,

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

For ETP,

- Duration of IMP exposure is defined as 14 days after last dose in ETP minus (–) the first dose date in ETP, regardless of unplanned intermittent discontinuations.

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 continuous variable, as well as a categorical variable (e.g., <12 weeks, 12 to <24 weeks, ≥24 weeks for PAP).

The cumulative dose information for the considered period (PAP, ETP, or the 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 PAP, ETP, 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 PAP; in addition, duration of IMP exposure will be summarized for ETP after switching to avalglucosidase alfa.

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

Treatment compliance for ETP and overall study period will be summarized similarly.

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

2.4.4 Analyses of safety data

In general, for PAP, the summary of safety results will be presented by study cohort and treatment arm. For the overall avalglucosidase alfa treatment period, the summary of safety results will be presented by initial planned dose levels among avalglucosidase alfa patients. For Cohort 3 alglucosidase alfa patients, the summary of safety results for ETP will be presented in separate tables.

In the PAP analysis, the safety analyses will be carried out with patients by the actual treatment received, irrespective of the treatment the patient has been randomized to. The actual treatment received is defined as:

- avalglucosidase alfa if the patient receives at least one infusion with this drug in PAP;
- alglucosidase alfa if the patient only receives alglucosidase alfa in PAP.

In the ETP analysis and/or overall evaluation of avalglucosidase alfa safety, the safety analyses will be carried out by the following 3 groups:

- AVAL/AVAL in ETP includes data in ETP among patients who received avalglucosidase alfa in PAP and ETP;
- ALGLU/AVAL in ETP includes data in ETP among patients who received alglucosidase alfa in PAP and received avalglucosidase alfa in ETP;
- AVAL/AVAL and ALGLU/AVAL in overall avalglucosidase alfa treatment period includes data in PAP and/or ETP among patients who received avalglucosidase alfa in that period.

General rules

All safety analyses will be performed on the safety population as defined in Section 2.3.1, unless otherwise specified, using the following common rules:

- The safety baseline value is defined the same as the baseline definition in Section 2.1.1.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated January 2014 [Appendix B]).
  - PCSA criteria will determine which patients had at least 1 PCSA during the treatment epoch (for PAP and ETP respectively), taking into account all evaluations performed during this period, including nonscheduled or repeated evaluations.
  - The number of all such patients will be the numerator for the on-treatment PCSA percentage; the denominator will be the number of patients assessed for that given parameter in the treatment epoch by treatment group on the safety population.
- For the overall evaluation of avalglucosidase alfa safety, selected analysis will be repeated by dose levels among avalglucosidase alfa patients
- The analysis of the safety variables will be essentially descriptive and no inferential testing is planned.

2.4.4.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pre-treatment AEs and post-treatment AEs will be described separately.

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

AE summaries will include number (n) and percentage of patients experiencing an AE by study cohort and treatment group. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the number of patients in the specific population within each study cohort or treatment group. The number of different AE events will be included in some summaries as well whenever appropriate.

Unless otherwise specified, sorting order will follow the internationally agreed SOC order, and further by decreasing number of events in PTs within SOCs in the avalglucosidase alfa arm. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Analysis of TEAE(s) in PAP

The following TEAE summaries will be generated for the safety population.

- An overview of TEAEs in PAP, including:
  - TEAEs,
  - TEAEs potentially related to study drug,
  - Serious TEAEs,
  - Serious TEAEs potentially related to study drug,
  - Severe TEAEs,
  - Severe TEAEs potentially related to study drug
  - TEAEs leading to permanent treatment discontinuation,
  - TEAEs leading to death,
  - TEAEs leading to death potentially related to study drug
  - Protocol-defined IARs,
  - Algorithm-defined IARs.
- All TEAEs during PAP by primary SOC, HLGT, HLT, and PT, showing n and % of patients with at least one TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs during PAP by primary SOC and PT sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC for the avalglucosidase alfa arm.
- All TEAEs during PAP presented by PT, sorted by decreasing incidence of PT in the avalglucosidase alfa arm.

- All TEAEs regardless of relationship and related to IMP during PAP by primary SOC, and PT.
- All TEAEs during PAP by maximal severity (i.e., mild, moderate, or severe), presented by primary SOC and PT.
- Most common TEAEs during PAP by primary SOC and PT sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. The most common TEAE are defined as those preferred terms occurring in ≥ 2 patients.
- Listing of TEAEs.

Analysis of treatment-emergent SAE(s) in PAP

- All treatment-emergent SAEs during PAP, by primary SOC and PT.
- All treatment-emergent SAEs regardless of relationship and related to IMP during PAP, by primary SOC and PT.
- Listing of treatment-emergent SAEs.

Analysis of TEAE(s) leading to treatment discontinuation in PAP

- TEAEs leading to permanent treatment discontinuation during PAP, by primary SOC and PT.
- TEAEs leading to permanent treatment discontinuation during PAP presented by PT, sorted by decreasing incidence of PT in the avalglucosidase alfa arm.
- Listing of TEAEs leading to permanent treatment discontinuation during PAP, including details on dose, severity, and relationship, etc.

Analysis of adverse events with AESIs in PAP

- Treatment-emergent AESIs during PAP, by primary SOC and PT, showing the n and % of patients, sorted by decreasing incidence of PT within the avalglucosidase alfa arm.
- Treatment-emergent protocol-defined IARs during PAP, by primary SOC and PT, presented by overall n and %, as well as by start time of IAR in relation to end of infusion time (during infusion, ≤2 hours, >2 to 24 hours, >24 to 72 hours, >72 hours).
- Treatment-emergent algorithm-defined IARs during PAP, by primary SOC and PT, presented by overall n and %, as well as by start time of IAR in relation to end of infusion time (during infusion, ≤2 hours, >2 to 24 hours, >24 to 72 hours, >72 hours).
- Treatment-emergent protocol-defined IARs during PAP, by PT and maximal severity, presented by overall n and %, as well as by start time of IAR in relation to end of infusion time (during infusion, ≤2 hours, >2 to 24 hours, >24 to 72 hours, >72 hours).
- Treatment-emergent algorithm-defined IARs during PAP, by PT and maximal severity, showing presented by overall n and %, as well as by start time of IAR in relation to end of infusion time (during infusion, ≤2 hours, >2 to 24 hours, >24 to 72 hours, >72 hours).
- Listing of AESIs during PAP.
- Listing of treatment-emergent protocol-defined IARs during PAP.

- Listing of treatment-emergent algorithm-defined IARs during PAP.

Analysis of TEAEs in ETP and overall avalglucosidase alfa treatment period

Selected PAP safety analyses will be performed for ETP and/or overall avalglucosidase alfa treatment period.

In addition, a summary table of Kaplan-Meier estimates of TEAEs by 6-month time intervals will be provided for patients who only receive avalglucosidase alfa during the overall avalglucosidase alfa treatment period (no analysis if denominator < 5).

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT.
- All AEs with onset during the post-treatment epoch for PAP or ETP by primary SOC and PT.
- All post-treatment SAEs with onset during the post-treatment epoch for PAP or ETP by primary SOC and PT.
- Listing of pre-treatment AEs.
- Listing of post-treatment AEs.

Anaphylactic/hypersensitivity reactions and potential immune-mediated reactions

A comprehensive programming search of AEs which meet the Standard MedDRA Query (SMQ) (Broad + Narrow combined and Narrow alone) criteria for hypersensitivity and anaphylactic reaction will be used to identify AEs that potentially are associated with symptoms of anaphylactic and hypersensitivity reaction. Results of this search will be provided in summary tables and in a by patient listing by group. The most recent version of MedDRA SMQ will be used at the time of analysis. A medical review of these cases will be performed.

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

2.4.4.2 Deaths

A listing of deaths will be provided. If there are more than 4 deaths in total, the following summaries of deaths will be generated for the safety population:

- N and % of patients who died by study period (on-study, treatment epoch for PAP or ETP, post-treatment epoch for PAP or ETP) and reasons for death.

- TEAEs leading to death (death as an outcome on the AE case report form page as reported by the Investigator) by primary SOC, and PT. Corresponding listing will be provided as well.

2.4.4.3 Analyses of laboratory variables

Observed measurements and changes from baseline to study time points in biochemistry, hematology, and urinalysis will be descriptively summarized for each visit or study assessment (baseline and each post-baseline time point), by study cohort and treatment arm, as well as by dose levels among avalglucosidase alfa treated patients for the overall avalglucosidase alfa treatment period. This section will be organized by biological functions.

All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. The n and % of patients with the following selected laboratory abnormalities of all laboratory variables, when applicable, will be summarized for each visit or study assessment.

- Blood chemistry:
  - Plasma/serum electrolytes: sodium, potassium,
  - Liver function: AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, indirect bilirubin, direct bilirubin,
  - Renal function: creatinine,
  - Metabolic panel: glucose, albumin, protein, cholesterol, triglycerides,
  - Potential muscle toxicity: CK, CK with MB fraction,
  - Brain natriuretic peptide (BNP).
- Hematology: hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets.

Comparisons of the worst laboratory abnormalities with the baseline will be presented for each laboratory parameter listed above, when applicable. This analysis will be conducted for PAP and for the overall avalglucosidase alfa treatment period.

Individual listings of patients with potentially clinically significant abnormalities will be presented.

The incidence of PCSAs (list provided in Appendix B) at any time during the treatment-emergent adverse event period will be summarized by biological functions and treatment groups. The PCSA analyses will be conducted for PAP primarily. Similar analyses will be conducted for the overall avalglucosidase alfa treatment period.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The following analyses will be performed:

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

2.4.4.4 Analyses of vital sign variables

The summary statistics of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each scheduled visit or study assessment (baseline, each post-baseline time point) by study cohort and treatment group.

The incidence of PCSAs (list provided in Appendix B) based on worst value at any time during the treatment-emergent adverse event period will be summarized by study cohort and treatment groups.

The PCSA analyses will be conducted for both PAP and ETP separately. Similar analyses will be conducted for the overall avalglucosidase alfa treatment period.

2.4.4.5 Analyses of electrocardiogram variables

The summary statistics of all ECG variables (laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point) by study cohort and treatment group.

A listing of ECG measurements will be provided.

The incidence of PCSAs (list provided in Appendix B) based on worst value at any time during the treatment-emergent adverse event period will be summarized by treatment groups.

The PCSA analyses will be conducted for both PAP and ETP separately. Similar analyses will be conducted for the overall avalglucosidase alfa treatment period.

2.4.4.6 Analyses of physical examinations

All physical examination variables will be listed by visits and summarized descriptive by study cohort and treatment group, as well as by dose levels among avalglucosidase alfa treated patients.

2.4.4.7 Analyses of immunogenicity parameters

Percentage of patients who seroconverted to avalglucosidase alfa and time to seroconversion will be summarized using summary statistics, by study cohort and treatment group, as well as by dose levels among avalglucosidase alfa treated patients for the overall avalglucosidase alfa treatment period.

Anti-avalglucosidase alfa and anti-alglucosidase alfa antibody titer values will be summarized using summary statistics at each study visit by study cohort and treatment group, as well as by dose levels among avalglucosidase alfa treated patients for the overall avalglucosidase alfa treatment period. Median and quartiles Q1 and Q3 titer values will be reported. All data will be presented in listings for each patient.

By patient listings will also display results of NAb, as well as results testing for IARs if clinically indicated (i.e., circulating immune complex, anti-avalglucosidase alfa IgE antibody, serum tryptase activity, complement activation, and skin testing). Descriptive summaries may also be provided as appropriate.

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

- ADA prevalence rate, defined as

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

- ADA incidence rate, defined as

  100 × (number of patients with treatment-boosted + treatment- induced ADA)/(number of evaluable patients);

- Treatment induced ADA incidence rate, defined as,

  100 × (number of patients with treatment induced ADA)/(number of evaluable patients with ADA negative at baseline);

- Treatment boosted ADA incidence rate, defined as

  100 × (number of patients with treatment boosted ADA)/(number of evaluable patients with ADA positive at baseline);

- Incidence rate of NAbs (for inhibition of uptake, inhibition of activity and both, respectively), defined as

  100 × (number of patients positive for NAbs)/(number of evaluable patients)

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

- Onset time of ADA will be analyzed descriptively using summary statistics including median and quartiles Q1 and Q3.
- Duration of ADA will be analyzed descriptively using summary statistics including median and quartiles Q1 and Q3. It will only be calculated for the patients with at least two ADA positive samples.
- The n and % of persistent ADA response will be summarized descriptively. This will be performed for the patients with at least two post baseline samples which are separated by at least 16 weeks.
- The n and % of transient ADA response will be summarized descriptively. This will be performed for the patients with at least two post baseline samples where the last sampling time point is negative.
- The n and % of indeterminate ADA response will be summarized descriptively. This will be performed for the patients with at least one post baseline sample.

ADA peak titer, last titer, and geometric mean titer will be summarized. Graphs of ADA titer over time and boxplots of the highest post-baseline ADA titer will be provided. The analyses will be performed for PAP, ETP and the overall avalglucosidase alfa treatment periods.

2.4.5 Association of ADA with selected efficacy endpoints

Scatter plots will be used to display the correlations of immunogenicity (ADA titers and NAb) and change from baseline at week 25 for selected efficacy endpoints including 6MWT (total distance walked in meter), FVC (% predicted) upright, FVC (% predicted) supine, MIP (% predicted) upright, MEP (% predicted) upright, GMFM-88, QMFT, Pompe-PEDI Functional Skills Scale: Mobility Domain, CK, LVM Z-score, LVMI, Hex4, GAA genotyping, CRIM status, GAA enzyme activity and [redacted].

2.4.6 Association of ADA with safety

Selected safety parameters (AEs, SAEs, IARs and potential immune complex mediated reactions) will be summarized by ADA and NAb response categories.

2.4.7 Analyses of pharmacokinetic variables

PK exposures (C_{max} and $AUC_{0\text{-}last}$) for avalglucosidase alfa will be determined using non-compartmental analysis. If data allow, total body clearance of a drug (CL), and V_{ss} 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 patients and summarized using descriptive statistics by study week and time point as appropriate.

The results will be presented by dose levels among avalglucosidase alfa patients in the PK population.

PK parameters for individual patients will be derived from population PK analysis using the data from this study pooled with other studies if necessary. The population PK results will be documented in a separate report.

To evaluate the effect of immunogenicity on the pharmacokinetics of avalglucosidase alfa, pre-dose IgG titer for each patient will be presented graphically with respect to PK parameter.

2.4.8 Analyses of efficacy endpoints

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.

All efficacy endpoints defined in Section 2.1.6 will be summarized descriptive by dose cohort and treatment group. For 6MWT results, descriptive summary will only be provided for those complete the 6 minutes walk test.

The mean composite scores between avalglucosidase alfa and alglucosidase alfa patients will be compared. The difference in average composite scores between avalglucosidase alfa and alglucosidase alfa patients will be used as the test statistic, and calculate a p-value. The null and alternative hypotheses for the primary efficacy endpoint are described as H_0 and H_a below:

H_0: Mean Composite Score for avalglucosidase alfa = Mean Composite Score for alglucosidase alfa; versus
H_a: Mean Composite Score for avalglucosidase alfa ≠ Mean Composite Score for alglucosidase alfa

The difference in average composite scores between avalglucosidase alfa and alglucosidase alfa patients will be used as the test statistic.

The control arm (alglucosidase alfa treatment) in Cohort 3 will serve as a reference. If deemed appropriate, these analysis might be repeated using Cohort 2 and/or Cohort 1 patients combined with Cohort 3 avalglucosidase alfa treated patients.

Statistical inference will be performed based on the re-randomization approach. Specifically, all possible randomization sequences that are consistent with the selected randomization design (i.e., 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. Due to the small sample size and open-label nature, p-values will serve as references only and any interpretations should be made with caution.

Similar re-randomization test might be performed for other efficacy endpoints.

Patient profile (in terms of change over time starting from baseline) will be generated for all efficacy 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 study cohort and treatment arm based on changes from pre-study (collected by retrospective chart review at screening/baseline) to 6 months (Week 25) post-avalglucosidase alfa treatment using descriptive statistics. Denominators for the percentages will be based on the safety population with evaluable data on the corresponding endpoint.

2.4.8.1 Multiplicity issues

This phase 2 study is not considered as a confirmatory clinical study. P-values will be presented without multiplicity adjustment.

2.4.8.2 Subgroup analyses

Due to the limited power in these subpopulations, selected subgroup analyses, if appropriate, may be explored using descriptive statistics or graphically by treatment group for the overall avalglucosidase alfa treatment period only.

The following baseline factors may be explored to assess their impact on efficacy with exploratory analysis: prior alglucosidase treatment duration, duration of disease, age at first alglucosidase infusion, age at first infusion of avalglucosidase alfa, gender, race, ethnicity, baseline status on invasive ventilatory support, baseline use of noninvasive ventilatory support, baseline status on assistive device use, baseline LVM Z-score, baseline GMFCS level, GAA genotyping, CRIM status, [redacted], quartiles of peak IgG antibody titer and status of inhibitory antibody.

2.4.9 Analyses of pharmacodynamics variables

Creatinine-normalized urine Hex4 levels (mmol/mol) will be summarized using descriptive statistics at each scheduled study visit in PD population. Observed measurements as well as the 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 urine Hex4 levels will be explored as appropriate.

[redacted]

2.4.10 Analyses of tertiary endpoints

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. Denominators for the percentages will be based on the safety population with evaluable data on the corresponding endpoint. Graphical displays may be provided as appropriate.

2.4.10.1 Correlation of efficacy endpoints

In order to identify the relationship between outcomes, correlation analysis for the following efficacy endpoints (at baseline, at Week 25 and change from baseline to Week 25) might be explored graphically for all enrolled patients, regardless of cohorts or treatment arms. Corresponding summary tables may be generated as appropriate.

- GMFM-88: total raw score, total % score
- Pompe PEDI Functional Skills Scale: Mobility Domain: raw score, normative standard score, scaled score,
- QMFT: total score
- ECHO: LVM-Z score and LVMI
- CK
- Hex4
- 6MWT: distance walked
- Pulmonary function testing: FVC (% predicted) upright, MIP (% predicted) upright, MEP (% predicted) upright
- Use of ventilator
- PedsQL generic core scale score
- PedsQL pediatric pain questionnaire score
- Pain visual analog scale
- Bayley-III Composite score
- Leiter-3 Nonverbal IQ Composite score

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

In general, the baseline value is defined as latest non-missing value prior to the start of first infusion in PAP or ETP (Section 2.1.1). In the case an assessment performed on the same date as the first infusion date, but it is impossible to determine the evaluation time relative to first infusion start time, the evaluation time will be assumed to follow the protocol-defined schedule.

2.5.2 Missing data handling in data presentation

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized for each treatment group using n and %. Denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.

- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only.

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

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on drug exposure e-CRF page. If this date is missing, then the duration is missing.

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

Handling of missing/partial dates for adverse events or concomitant medications

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the treatment-emergent adverse event period, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

No imputation for medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of missing or partial birth date for calculation of age

Complete missing of birth date is not expected for the study. However, there could be rare situations in which the birth day or month is not provided for the patient due to confidentiality. In this case, the missing day will be imputed as 15th of the month, and missing month will be imputed as June as default. The adjustment may be needed in the case of conflicting with study dates. These adjustments should be very rare and will be documented in the data specification document.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.

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

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP in the frequency tables is considered as possibly related, but no imputation should be done at the data level.

Handling of missing severity of adverse events

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

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline".

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSA is >0.5 GIGA/L or > ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling of ADA titer with missing or non-numerical values

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

Handling of missing domains for the composite score

If any of the 3 domains including GMFM-88 and GMFCS-E&R, ptosis, and respiratory function, has missing data at baseline, the domain score of change from baseline at the end of PAP will be 0.

If data is missing at Week 25, the score measured at precedent visit (Week 13) will be used.

2.5.3 Study day calculation

Based on study protocol, study Day 1 is the date of first study infusion (i.e., Week1 Day 1).

Study day for a given assessment is defined as the assessment date - date of first study infusion + 1 if the assessment date is on or after Day 1, or assessment date - date of first study infusion if the assessment date is before Day 1.

For cohort 3 patients, if a randomized patient is not treated (first infusion date is missing), study Day 1 is the date of randomization.

2.5.4 Windows for time points

The visit windows for efficacy endpoints are defined in the following table. For analysis purpose, a larger window (as shown in the last column of Table 5) will be used. This will be applicable for those analyses requiring visit information.

The analysis visit will be defined by comparing the actual visit date with the nominal (or target) date and the corresponding analysis window from Table 5. If more than one non-missing value is assigned to the same visit, then the one closest to the target date will be used in the by-visit analysis. Multiple values on the same date will be averaged first. If two assessments are on different dates but equal distance from the target date, the later date will be used.

For the safety analyses (laboratory, ECG and vital signs), the nominal visit will be used for the by-visit type of analyses.

Table 5 - Study visit nominal visit days and windows for efficacy endpoints

Scheduled Visit	Visit window defined in protocol in study days	Visit window for analysis purpose in study days
Screening/Baseline	Day -14 to -1	-28 to -1 (or 1 if before 1st infusion)
Week 13	Day 85 ±14	Day 0 (or Day 2 if Screening/baseline on Day 1) to 85 + 41
Week 25	Day 169 ±14	Day 169- 42 to 169 + 41 and prior to any ETP treatment
Week 37	Day 253 ±14	Day 253- 42 to 253 + 41 and after the 1st ETP treatment
Week 49	Day 337 ±14	Day 337- 42 to 337 + 41
Week 61	Day 421 ±14	Day 421 - 42 to 421 + 41
Week 73	Day 505 ±14	Day 505 - 42 to 505 + 83
Week 97	Day 673 ±14	Day 673- 84 to 673 + 83
Week 121	Day 841 ±14	Day 841- 84 to 841 + 83
Week 145	Day 1009 ±14	Day 1009- 84 to 1009 + 83 ±84

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries, but will be used for computation of baseline, worst values, and summary of PCSAs.

2.5.6 Pooling of centers for statistical analyses

Not planned.

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

While all patients will be followed for up to 3 years during the study, the primary analysis for the study will be performed when all Cohort 3 patients have completed the 6-month PAP or discontinued from the study before completing PAP. In addition, safety analyses will be performed in multiple time points by the DMC to determine the dose for next cohort and the MTD. The DMC procedures are detailed in the DMC charter. Furthermore, an additional analysis might be performed for avalglucosidase alfa submission.

Since there is only one hypothesis test for the composite score to be performed at the end of the primary analysis period, no adjustment is needed for the interim analyses. Additional analyses after PAP will be considered for supportive purpose.

4 DATABASE LOCK

The DBL for the primary efficacy analyses is planned to be approximately 30 days after last patient last visit in PAP.

The final database lock for the study is planned to be approximately 30 days after the last patient last visit in ETP.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Classification of changes (including improvement, unchanged or worsening) from baseline to Week 25 for the 3 domains comprising the composite score

Appendix B Potentially clinically significant abnormalities (PCSA) criteria

Appendix A Classification of changes (including improvement, unchanged or worsening) from baseline to Week 25 for the 3 domains comprising the composite score (9).

Parameter		Week 25		
	Baseline	**Improvement**	**Unchanged**	**Worsening**
Respiratory	No use of any ventilation assistance	NA	No use of any ventilation assistance	Use of any ventilation assistance
	Use non-invasive ventilation assistance during daytime only or nighttime only	No use of any ventilation assistance	Use non-invasive ventilation assistance during daytime only or nighttime only	Use non-invasive ventilation assistance during both daytime and nighttime Use invasive ventilation assistance
	Use non-invasive ventilation assistance during both daytime and nighttime	No use of any ventilation assistance Use non-invasive ventilation assistance during daytime only or nighttime only	Use non-invasive ventilation assistance during both daytime and nighttime	Use invasive ventilation assistance
	Use invasive ventilation assistance during daytime only or nighttime only	No use of any ventilation assistance Use non-invasive ventilation assistance	Use invasive ventilation assistance during daytime only or nighttime only	Use invasive ventilation assistance during both daytime and nighttime
	Use invasive ventilation assistance during both daytime and nighttime	No use of any ventilation assistance Use non-invasive ventilation assistance Use invasive ventilation assistance <24 hrs/day	Use invasive ventilation assistance during both daytime and nighttime	NA
Motor Skills: GMFM-88 Total Score[a]	Level I Walker	Total Score increase ≥3.22	-3.22 < Total Score change <3.22	Total Score decrease ≥3.22
	Level II Supported walker	Total Score increase ≥2.76	-2.76 < Total Score change <2.76	Total Score decrease ≥2.76
	Level III Supported stander	Total Score increase ≥1.41	-1.41 < Total Score change <1.41	Total Score decrease ≥1.41
	Level IV Sitter	Total Score increase ≥1.65	-1.65 < Total Score change <1.65	Total Score decrease ≥1.65
	Level V Restricted antigravity movement	Total Score increase ≥0.8	-0.8 < Total Score change <0.8	Total Score decrease ≥0.8
Presence of Ptosis	No ptosis	NA	No ptosis	≥1 eye has ptosis
	1 eye only	No ptosis	1 eye only	Both eyes
	Both eyes	≤1 eye has ptosis	Both eyes	NA

a. - Total score is Total percent score of GMFM-88, and baseline of Level I-V are GMFCS Levels

Appendix B Potentially clinically significant abnormalities criteria

Measures	Adult Criteria	Pediatric Criteria
Liver function tests		
ALT	>3 x ULN	≥3 x ULN
	>5 x ULN	≥5 x ULN
	>10 x ULN	≥10 x ULN
	>20 x ULN	≥20 x ULN
AST	>3 x ULN	≥3 x ULN
	>5 x ULN	≥5 x ULN
	>10 x ULN	≥10 x ULN
	>20 x ULN	≥20 x ULN
Alkaline Phosphatase	>1.5 x ULN	≥1.5 x ULN
Total Bilirubin	>1.5 x ULN	≥1.3 x ULN
	>2 x ULN	
ALT and Total Bilirubin	ALT >3 x ULN and Total Bilirubin >2 x ULN	ALT ≥3 x ULN and Total Bilirubin ≥ 2 x ULN
Hematology		

White Blood Cell (WBC)	<3.0 GIGA/L (non-Black), <2.0 GIGA/L (Black), ≥16.0 GIGA/L	Birth/0 to 27 days old (Neonates) <4.0 GIGA/L >25.0 GIGA/L 28 days/1 month to 23 months old (Infants) <4.0 GIGA/L >20.0 GIGA/L 24 months/2 years to <6 years old (Children) >3.0 GIGA/L >16.0 GIA/L 6 to <12 years old (Children) <5.0 GIGA/L >17.0 GIGA/L 12 to 16/18 years old (Adolescents) <4.5 GIGA/L >13.5 GIGA/L
Lymphocytes	>4.0 GIGA/L	Birth/0 to 27 days old (Neonates) <1.2 GIGA/L >17.0 GIGA/L 28 days/1 month to 23 months old (Infants) <2.0 GIGA/L >13.5 GIGA/L 24 months/2 years to <6 years old (Children) <1.0 GIGA/L >9.5 GIGA/L 6 to <12 years old (Children) <1.0 GIGA/L >8.0 GIGA/L 12 to 16/18 years old (Adolescents) <0.6 GIGA/L >6.0 GIGA/L

Neutrophils	<1.5 GIGA/L (non-Black) <1.0 GIGA/L (Black)	Birth/0 to 27 days old (Neonates) <4.0 GIGA/L (1 day old) <1.5 GIGA/L (2 – 7 days old) <1.25 GIGA/L (>7 day – 1 month old) >1 ULN 28 days/1 month to 23 months old (Infants) <1.0 GIGA/L (1 – 3 months) <1.2 GIGA/L (3 – 24 months) >1 ULN 24 months/2 years to <6 years old (Children) <1.2 GIGA/L >1 ULN 6 to <12 years old (Children) <1.2 GIGA/L >1 ULN 12 to 16/18 years old (Adolescents) <1.2 GIGA/L >1 ULN
Monocytes	>0.7 GIGA/L	
Basophils	>0.1 GIGA/L	
Eosinophils	>0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA /L	>0.5 GIGA/L Or >ULN if ULN >0.5 GIGA/L
Hemoglobin	Males: ≤115 g/L (≤7.14 mmol/L), ≥185 g/L (≥11.48 mmol/L) Females: ≤95 g/L (5.9 mmol/L), ≥165 g/L (10.24 mmol/L) Decrease from Baseline ≥ 20 g/L (1.24 mmol/L)	Birth/0 to 27 days old (Neonates) <86 mmol/L or 12.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL 28 days/1 month to 23 months old (Infants) <1.40 mmol/L or 9.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL 24 months/2 years to <16/18 years old (Children, Adolescents) <1.55 mmol/L or 10.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL

Hematocrit	Males : ≤0.37 v/v, ≥0.55 v/v Females : ≤0.32 v/v, ≥0.5 v/v	Birth/0 to 27 days old (Neonates) <0.39 l/l or 40% >0.61 l/l or 47% 28 days/1 month to 23 months old (Infants) <0.29 l/l or 29% >0.42 l/l or 42% 24 months/2 years to <16/18 years old (Children, Adolescents) <0.32 l/l or 32% >0.47 l/l or 47%
RBC	≥6 TERA/L	
Platelets	<100 GIGA/L and 20% decrease from baseline ≥ 700 GIGA/L is missing	<100 GIGA/L >700 GIGA/L

ECG – PCSA criteria

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

QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Birth/0 to 27 days old (Neonates) ≥85 ms 28 days/1 month to 23 months old (Infants) ≥85 ms 24 months/2 years to <6 years old (Children) ≥95 ms 6 to <12 years old (Children) ≥100 ms 12 to 16/18 years old (Adolescents) ≥110 ms
QTc (either QTcF or QTcB)	Absolute values (ms >450 ms >480 ms >500 ms Increase from baseline 30-60 ms >60 ms	Birth/0 to <12 years old (Neonates, Infants, Children) Absolute values (ms) Borderline: 431 – 450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30 – 60 ms Prolonged*: Increase from baseline >60 ms 12 to 16/18 years old (Adolescents) Absolute values (ms) Borderline: 431 – 450 ms (Boys);451 – 470 ms (Girls) Prolonged*: >450 ms (Boys);>470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline30 – 60 ms Prolonged*: Increase from baseline >60 ms

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

Clinical chemistry

Creatinine	≥150 µmol/L (Adults) ≥30% increase from baseline ≥100% increase from baseline	Birth/0 to <6 years old (Neonates, Infants, Children) >53 µmol/L or 0.6 mg/dL 6 years to <12 years old (Children) ≥90 µmol/L or 1.1 mg/dL 12 years to 16/18 years old (Adolescents) ≥132 µmol/L or 1.5 mg/dL

Blood Urea Nitrogen	≥17 mmol/L	Birth/0 to 27 days old (Neonates) ≥4.3 mmol/L or 12 mg/dl 28 days/1 month to 16/18 years old (Infants, Children, Adolescents) ≥6.4 mmol/L or 18 mg/dl
Chloride	<80 mmol/L >115 mmol/L	≤80 mmol/L ≥115 mmol/L
Sodium	≤129 mmol/L ≥160 mmol/L	≤129 mmol/L ≥150 mmol/L
Potassium	<3 mmol/L ≥5.5 mmol/L	Birth/0 to 27 days old (Neonates) ≤3.0 mmol/L ≥7.0 mmol/L 28 days/1 month to 23 months old (Infants) ≤3.5 mmol/L ≥6.0 mmol/L 24 months/2 years to 16/18 years old (Children, Adolescents) ≤3.5 mmol/L ≥5.5 mmol/L
Glucose		
Hypoglycemia	≤3.9 mmol/L and <LLN	<2.7 mmol/L
Hyperglycemia	≥11.1 mmol/L (unfasted); ≥ 7 mmol/L (fasted)	≥7 mmol/L (fasted after >12 hours of fast); ≥10.0 mmol/L (unfasted)
Albumin	≤25 g/L	
Vital signs		

Heart rate	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	Birth/0 to 27 days old (Neonates) ≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm 28 days/1 month to 23 months old (Infants) ≤80 bpm and decrease form baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm 24 months/2 years to <6 years old (Children) ≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm 6 to <12 years old (Children) ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm 12 to 16/18 years old (Adolescents) ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
Systolic BP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	Birth/0 to 27 days old (Neonates) ≤60 mmHg and decrease from baseline ≥20 mmHg ≥85 mmHg and increase from baseline ≥20 mmHg 28 days/1 month to 23 months old (Infants) ≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg 24 months/2 years to <6 years old (Children) ≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old (Children) ≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old (Adolescents) ≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg

Diastolic BP	≤45 mmHg and decrease from baseline ≥10 mmHg	Birth/0 to 27 days old (Neonates)
	≥110 mmHg and increase from baseline ≥10 mmHg	≤34 mmHg and decrease from baseline ≥10 mmHg
		≥50 mmHg and increase from baseline ≥10 mmHg
		28 days/1 month to 23 months old (Infants)
		≤34 mmHg and decrease from baseline ≥10 mmHg
		≥54 mmHg and increase from baseline ≥10 mmHg
		24 months/2 years to <6 years old (Children)
		≤34 mmHg and decrease from baseline ≥10 mmHg
		≥59 mmHg and increase from baseline ≥10 mmHg
		6 to <12 years old (Children)
		≤48 mmHg and decrease from baseline ≥10 mmHg
		≥72 mmHg and increase from baseline ≥10 mmHg
		12 to 16/18 years old (Adolescents)
		≤54 mmHg and decrease from baseline ≥10 mmHg
		≥78 mmHg and increase from baseline ≥10 mmHg

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