NCT02004704

STATISTICAL ANALYSIS PLAN

A long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency

GZ402665-LTS13632

STATISTICIAN: [redacted]

DATE OF ISSUE: 04-Nov-2019

Total number of pages: 58

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABAS-3:	Adaptive Behavior Assessment System, Third Edition
ADA:	anti-drug antibody
AESI:	adverse events of special interest
AP:	alkaline phosphatase
$AUC_{0\text{-}inf}$:	area under the concentration versus time curve from time 0 textraoplated to infinity
BMI:	body mass index
CL:	total body clearance
C_{max}:	maximum plasma concentration
CV:	coefficient of variation
DBP:	diastolic blood pressure
DBS:	dried blood spots
DP-3:	Developmental Profile 3
DXA:	dual-energy X-ray absorption
ECG:	electrocardiogram
e-CRF:	electronic case report form
FEV_1:	forced expiratory volume in the first 1 second
FVC:	forced vital capacity
HDL:	high-density lipoprotein
HR:	heart rate
LDL:	low-density lipoprotein
LLOQ:	lower limit of quantification
NE:	not evaluable
PCSA:	potentially clinically significant abnormality
PKDM:	pharmacokinetics, dynamics and metabolism
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SEM:	standard error of the mean
SMPD1:	acid sphingomyelinase gene
SOC:	system organ class
$t_{1/2z}$:	terminal half-life
t_{max}:	time to reach C_{max}
ULN:	upper limit of normal
VAS:	visual analogue scale
VLDL:	very low-density lipoprotein
V_{SS}:	volume of distribution at steady state.
WHO-DRUG:	World Health Organization-Drug Dictionary
WMW:	Wilcoxon-Mann-Whitney

1 OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical techniques to be used to analyze data from the study LTS13632 which is an extension study in the use of olipudase alfa in patients with acid sphingomyelinase deficiency (ASMD). It is based on Amended Clinical Trial Protocol 4, dated 31Jul2019. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multinational, multicenter, nonrandomized, open-label, long-term treatment study of approximately 25 patients who have previously participated in a study of olipudase alfa. 5 adult patients rolled over from study DFI13412 into LT13632 study and approximately 20 pediatric patients are expected to roll over from study DFI13803. Patients will be enrolled directly into this study from their previous study. Enrolled patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years, or marketing approval, whichever comes first. If marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's approval.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to obtain data regarding the safety of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa.

1.2.2 Secondary objectives

The secondary objectives of this study are to obtain data regarding the efficacy of olipudase alfa and to characterize olipudase alfa PD and PK following long-term administration.

1.3 DETERMINATION OF SAMPLE SIZE

Sample size is determined by the number of patients who complete the treatment phase of a previous clinical study of olipudase alfa, sign the informed consent form, and meet the eligibility criteria. The sample size is expected to be 17 – 5 from the adult study, 12 from the pediatric study.

1.4 STUDY PLAN

After completion of treatment period in the previous study, patients or their parents/legal guardians (pediatric patients) will sign informed consent to continue treatment in this extension study, at the dose the patient completed the previous study. Patients are expected to transition to the long term study without treatment interruptions. Circumstances where there may be a gap between trials are foreseen in the protocol and treatment administration guidance is provided accordingly (for details, see the protocol). During the treatment period, patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years (or marketing approval, whichever comes first). If marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's approval. Safety and efficacy assessments will occur at regular 3, 6, or 12 month intervals throughout the treatment period. Pharmacodynamic evaluations will occur every 3 months and PK evaluations will occur every 12 months. After treatment completion or premature withdrawal, an end-of treatment visit is scheduled in 2 weeks, and a safety follow-up phone call is scheduled in 30-37 days.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

In the section of statistical consideration of the Amended Clinical Trial Protocol 4 Section 11.6.3, treatment period is defined as time from first dose to the last dose of IMP +14 days. In this SAP, in order to incorporate the data from original study (ie, adult study DFI13412 or pediatric study DFI13803), the treatment period definition is changed to "the time from the first infusion of IMP (included) from original study to the end of the current study".

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The SAP Version 2 was based on Amended Clinical Trial Protocol 1. This SAP is based on Amended Clinical Trial Protocol 4 (dated 31July 2019).

- The post-treatment period has been removed from Section 2.1.3, since there is no pre-specified post-treatment period in the protocol.
- The paired t-test was used for testing change from baseline and/or percent change from baseline. Because the baseline value is highly correlated with change from baseline and/or percent change from baseline, the paired t-test has been changed to analysis of covariance with baseline included as covariates as indicated in Section 2.4.8.
- The definition of common TEAE, TEAE of infection, Hypersensitivity IARs and TEAE of bleeding are updated in Section 2.1.3.1.
- Analyses of adverse events by place of infusion was added to this SAP in Section 2.4.7.1.6.
- Subgroup analyses for efficacy endpoints was added to this SAP for patients from DFI13803 in Section 2.4.8.15.
- Patient narratives as described in Section 2.5 will be created, to replace various data listings.

- For Physician's global assessment of change, the 7 categories will be converted to numeric values and summarized, as described in Section 2.4.8.6.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the latest available value before the first infusion in the original study except for hematology parameters and ECG parameters; the definition of baseline for these parameters could be found in Section 2.6.1.

In addition to baseline parameters listed below, all baseline safety and efficacy parameters are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.7 and Section 2.4.8).

Demographic characteristics

Demographic variables are: gender (Male, Female); race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, Other, Not reported, Unknown); age in years prior to first olipudase infusion at original study; ethnicity (Hispanic, non-Hispanic), Ancestry (Arab, Jewish, Turkish, Mediterranean, Eastern European, Dutch, South American Native Indian, Other, Not reported, Unknown), sub-ancestry for Jewish (Askhenazi, Sephardic, Unspecified) and for Mediterranean (Moroccan, Tunisian, Algerian, Other). This data will be cross-checked against the original study and should match.

Medical history

Medical history at the time of entry into this extension study will be collected by body system regarding the presence or absence of any condition, and whether the condition is current or past. In addition, medical history of special interest, eg, pneumonia, bronchitis, etc, to ASMD will be collected regarding presence of any such history. Substance abuse (smoking and alcohol) data are also collected.

2.1.2 Prior or concomitant medications

Medications are carried over from the original study when the medication is continuing at the time of the signing of informed consent or taken 30 days prior to the informed consent. Medications used before 30 days of signing of informed consent may be entered in the database at the discretion of the investigator.

Concomitant medications will continue to be collected throughout the study until the final visit of the study.

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

All medications contained in the database of this study are considered concomitant medications since they are either continuing into or have started during this extension phase. During the study, certain antidepressants that may decrease olipudase alfa activity are prohibited; a detailed list is available in the study manual. This list is updated at least once a year with any change in WHO-DRUG versions. Cationic amphiphilic antihistamines, such as loratadine, desloratadine, astemizole, ebastine, terfenadine, and clemastine, may decrease olipudase alfa activity. Therefore, the need for their use in oral or IV administration should be carefully considered. For these medications, an exhaustive list cannot be provided, hence their use is left to the discretion of the investigator.

Due to scheduled liver biopsies in adult patients, certain medications and herbal supplements can be hepatotoxic or can cause or prolong bleeding, and should not be taken within 10 days before and 3 days after the biopsy procedure. Potentially hepatotoxic medications or herbal supplements include, but are not limited to, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, erythromycin, valproic acid, antidepressants, kava, and echinacea. Medications that may cause or prolong bleeding include, but are not limited to, anticoagulants, ibuprofen, aspirin, garlic supplements, ginkgo, and ginseng. For these two classes of medications, exhaustive lists cannot be provided, hence their use is left to the discretion of the investigator.

2.1.3 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG, etc.

Observation period

The observation period in this study is the **treatment** epoch, which is defined as from the first infusion of IMP (included) from the original study to the latest available date of data in the current study.

2.1.3.1 Adverse events

Adverse events are defined in the protocol, Section 10.5.1.1. All adverse events (including serious adverse events 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 database lock.

Adverse events are recorded from the time of informed consent until the end of study. Any AE that has been ongoing in the original study at the time of informed consent in this study will be copied over to this study's database and will be followed.

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

- Results in death, or
- Is life-threatening (**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), or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Is a medically important event.

Adverse events of special interest (AESI) include:

Protocol-defined IAR: Any AE that occur during the infusion or within up to 24 h after the start of the infusion and is considered related or possibly related to study treatment as judged by the investigator or the sponsor is defined as a protocol-defined IAR. An event occurring >=24 h after the start of an infusion may be judged an IAR at the discretion of the investigator or sponsor. Sponsor identification will reconcile with investigator identification of IAR before the database lock as much as possible. It is, however, possible that the sponsor identifies an AE as an IAR which the investigator did not agree to be an IAR.

Hypersensitivity IARs: A subset of protocol-defined IARs will also be defined programmatically by searching for preferred terms within Hypersensitivity SMQs (ie, SMQ code 20000214 Broad and Narrow scope).

Algorithm-defined IAR: All AEs that start between the start of infusion and the end of infusion plus 24 hours are defined as algorithm-defined IARs, irrespective of the perceived relation with study treatment. If an AE with missing time starts on the end of infusion date or on the following day, the AE will be considered an algorithm-defined IAR.

Pregnancy: Pregnancy of a female patient enrolled in the study as well as pregnancy occurring in female partner of a male patient enrolled in this study are captured as an AESI.

Symptomatic overdose: This is captured as an adverse event in this study. For details, please see Section 10.5.1.3.3 in the protocol.

Quantifiable Dose Limiting Toxicities (DLT) defined based on laboratory values: The following laboratory values and symptoms will be considered as Quantifiable Dose Limiting Toxicities:

- DLT1: Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to olipudase alfa therapy) and > ULN.
- DLT2: Any increase in total bilirubin or AP >1.5x baseline in the presence of AST or ALT > 2x ULN.

- DLT3: Any increase in ALT or AST >3x the ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN).

Adverse events of other interests include:

- Infections: TEAEs under the system organ class of Infections and Infestations
- Bleeding: TEAEs under the standard MedDRA queries (SMQs) of Hemorrhages (identified using SMQ code 20000038 broad and narrow scope).

2.1.3.2 Deaths

The death observation periods are defined below:

- Death on-treatment: deaths occurring during the treatment epoch.
- Death on-study: deaths occurring between informed consent date in this study and the end of the study.

2.1.3.3 Laboratory safety parameters

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be converted into standard international units, and both US conventional units and international units will be used in all displays for continuous variables.

The following clinical laboratory test results are assessed as part of safety profile:

- Clinical chemistry: Sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, total protein, albumin, glucose, phosphorus, and creatine kinase. These are scheduled for every 3 months.
- Liver function tests: ALT, AST, AP, gamma-glutamyl-transferase, total bilirubin, and direct bilirubin. These are scheduled for every 3 months.
- Hematology: Complete blood count with differential and platelet count, including hematocrit, hemoglobin, red blood cell, white blood cell, platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts. These are scheduled for every 3 months.
- Coagulation studies: Prothrombin time (Protime), partial thromboplastin time, international normalized ratio, and D-dimer. These are scheduled for every 3 months.
- Urinalysis: Dipstick for glucose, protein, hemoglobin, leukocytes, ketones, and bilirubin. These are scheduled for every 3 month visit in this study.
- Safety biomarkers: hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, ceramide in plasma and calcitonin. These are scheduled for every 3 month visit in this study.
- Immune response assessments: anti-olipudase alfa IgG antibodies. These are scheduled for every 3 month visit in this study.

- If an IAR is anticipated to be a hypersensitivity reaction, additional laboratory parameters will be evaluated as soon as possible: tryptase activity and complementation activation, IgG and IgE. A skin testing may also be performed.
- If an IAR is anticipated to be a cytokine release syndrome (CRS), additional laboratory parameters will be evaluated as soon as possible: IL-6, IL-8, calcitonin.

2.1.3.4 Vital signs

Vital signs are collected before and 1-hour after each infusion in this study; parameters include: heart rate, systolic and diastolic blood pressure, temperature and respiratory rate. Weight is collected before each infusion except in the case of home infusion, it is only collected in the previous site visit. Height is collected every six months of study treatment exposure for patients from DFI13803, and every 12 months into this study for patients from DFI13412.

2.1.3.5 Electrocardiogram

ECGs are manually read by an independent expert at the site. ECG parameters, including those related to QT intervals, are evaluated by a central laboratory. ECG is conducted for every 6 months of exposure to study treatment.

ECG parameters from the central laboratory will include interpretations related to:

- Sinus, supraventricular and ventricular rhythm.
- AV and intraventricular conduction.
- Axis and voltage.
- Chamber hypertrophy and enlargement.
- ST-T abnormalities.
- Ischemia and infarction.

2.1.3.6 Echocardiogram with Doppler

Echocardiogram with Doppler is scheduled for every 12 months (starting at 3 months in this study for pediatric patients). Examination will include, but not be limited to: ventricular cavity size, valve characterization, ejection fraction, ventricular wall thickness, regional wall motion, diastolic function, and pericardium characterization. Pulmonary blood pressure and blood flow will be determined by Doppler ultrasound.

2.1.3.7 Physical Examination

A complete physical examination is conducted for every 6 months (starting at 3 months in this study for pediatric patients), and an abbreviated physical examination (general appearance only) is performed pre- and post-infusion at 3-month visits that do not do complete exam.

2.1.3.8 Extended Neurological Examination

An extended neurological examination is conducted every 12 months (starting at 9 months in this study for pediatric patients).

2.1.3.9 Liver Biopsy (Patients from adult study DFI13412)

Liver biopsy is done at screening, Week 26 and Year 3 for patients who previously participated in the DFI13412 study. Liver biopsies are evaluated by a Sanofi Genzyme pathologist for liver fibrosis grading and for sphingomyelin accumulation. Fibrosis staging will be performed using the Lathe pathology reports. Liver biopsy report will not be stored in clinical database, but be received by clinical personnel at the site and kept in the patient local study file. Data of fibrosis staging will be recorded and transferred as external data. Sphingomyelin accumulation in liver tissue that is assessed from liver biopsy will be discussed under pharmacodynamic endpoints (Section 2.1.5).

2.1.3.10 Liver ultrasound Doppler (Patients from pediatric study DFI13803)

Liver ultrasound Doppler is performed for patients transitioning from DFI13803. Ultrasound is performed at Screening and Week 52 in the original study, then every 6 months (starting at 3 months in this study for pediatric patients) until 2 years, and yearly thereafter. This evaluation documents hepatic blood flow characteristics, principally portal vein pressure and blood flow direction. The structures to be examined include hepatic portal vein, the main hepatic artery and the main hepatic vein. Additional structures that may be examined include the network of intrahepatic portal veins, the main and intrahepatic arteries, the hepatic veins, the main and intrahepatic portal veins, the intrahepatic portion of the inferior vena cava, collateral venous pathways, and transjugular intrahepatic portosystemic shunts. Liver ultrasound Doppler will be performed using methods that are compatible with the standard institutional procedures of the investigational site.

2.1.4 Efficacy endpoints

Efficacy endpoints in this study are secondary endpoints. The schedule of data collection of these endpoints is described in the flow charts in Section 1.1 to 1.3 in the protocol.

2.1.4.1 Abdominal magnetic resonance imaging

Spleen and liver volumes will be assessed by abdominal MRI to quantify the degree of splenomegaly and hepatomegaly at approximately every 6 months for first 2 years in this study (starting at 3 months in this study for pediatric patients); for further details of timing, please refer to the protocol. The MRIs will be collected and read centrally by a third party blinded to patient number and study visit.

The vendor will provide spleen and liver volumes in the unit of cubic millimeters. This will be converted to the standard unit of cubic centimeters for reporting purposes, by dividing by 1000. The analysis will also use the unit of Multiples of Normal (MN), and the algorithm used is as follows:

Spleen Volume (MN) = Spleen volume (cm^3) / [2*weight (kg)]

Liver Volume (MN) = Liver volume (cm^3) / [25*weight (kg)]

where weight is the available value closest to the MRI scan date.

2.1.4.2 Pulmonary function tests

Pulmonary function tests (PFT) will be performed in patients ≥5 years old at screening in the original study to measure lung volumes, air flow, and gas exchange for evidence of interstitial lung disease (ILD) at approximately every 6 months for first 2 years in this study (starting at 3 months in this study for pediatric patients), and every 12 months thereafter; for further details of timing, please refer to the protocol. Completion of PFTs may depend on patient age or cooperation, or both.

Pulmonary function testing will include, but will not be limited to, assessment of forced vital capacity (FVC), forced expiratory volume in the first 1 second (FEV_1) of the FVC maneuver, and total lung capacity. Diffusing capacity of carbon monoxide (DL_{CO}) will be used to measure gas exchange across the alveolocapillary membrane. Observed values of PFT parameters and DLco will be reported. Percent predicted values will be computed based on following algorithm (height and hemoglobin values are from the available ones closest to the PFT evaluation date/time, and age is calculated at the PFT evaluation date):

Percent predicted values of FEV1 and FVC will use the Global Lung Initiative (GLI) 2012 reference equations (1).

Predicted TLC (Liters) will use the following formula for adults (2) and children (3)

Adults (≥18 years of age): = 0.0795*height(cm) + 0.0032*Age(years) – 7.333 for males
= 0.0590*height(cm) – 4.537 for females

Children (<18 years of age): exp(24.67 - 4.91*ln(Height(cm)) – 7.16*ln(Age(months) + 0.059*Sex + 1.47*ln(Height)*ln(Age))

Percent predicted TLC = 100*Observed TLC / Predicted TLC

Percent predicted DLco will be computed as follows: (2, 4) and children (3, 4):

Predicted DLco (adults), mL CO/min/mmHg:
= 0.416*Height(cm) - 0.219*Age(years) - 26.34 for males
= 0.256*Height(cm) - 0.144*Age(years) - 8.36 for females

Predicted Dlco (children), mmol/min/kPa (Sex: 0=female, 1=male):
= exp(34.80 - 6.89*ln(Height(cm)) – 8.66*ln(Age(months)) + 0.10*Sex + 1.79*ln(Height)*ln(Age))

Unit conversion: mL CO/min/mmHg = mmol/min/kPa*2.987

Hb-adjustment factor (to be applied to DLco in unit of mL CO/min/mmHg)
= 1.7*Hb(g/L) / [10.22 + Hb] for males, or children 15-18 yrs
= 1.7*Hb(g/L) / [9.38 + Hb] for females, or children <15 yrs

DLco adjusted for Hb = Observed DLco/HB-adj factor

Percent predicted (Hb-adjusted) DLco = 100*DLco adjusted for Hb / Predicted DLco

2.1.4.3 Pulmonary imaging - high resolution computed tomography (HRCT) and Chest X-rays

High-resolution computed tomography scans of the chest will be obtained at approximately every 12 months (starting at 9 months in this study for pediatric patients); for further details of timing, please refer to the protocol. This evaluation is meant to quantify the degree of possible interstitial lung disease (ILD).

Images will be collected centrally by a medical imaging core laboratory where they will be digitized and coded and read by a third party blinded to patient number and study visit. The mean density will be calculated at each lung level using standard HRCT software. The lung fields will be assessed by a central reader and scored subjectively for the degree of ILD (0=normal, 1=mild, 2=moderate, or 3=severe).

The bilateral lung boundaries are determined from the following 4 pre-defined levels on the HRCT images.

- Level 1 includes the aortic arch.
- Level 2 includes the carina.
- Level 3 is midway between the carina and 1 centimeter above the hemidiaphragm.
- Level 4 is 1 centimeter above the hemidiaphragm.

A qualitative assessment will be made of the ILD, ground glass appearance, reticular, nodular density, and pleura thickening of the right and left lungs for each pre-defined levels above according to the following criteria:

- 0 = No disease.
- 1 = Mild (affecting 1% to 25% of the lung volume).
- 2 = Moderate (affecting 26% to 50% of the lung volume).
- 3 = Severe (affecting 51% to 100% of the lung volume).
- NE = Not evaluable.

The mean scores at each scheduled visit for each of the 4 qualitative assessments are calculated as follows:

- Mean score across levels for left (or right) lung = Sum of scores for X levels for left (or right) lung / X

- Mean score across 4 levels and both lungs = (Mean score across X levels for left lung + Mean score across X levels for right lung)/2. Pulmonary imaging – chest X-ray

2.1.4.4 Pulmonary imaging - Chest X-rays

A chest X-ray (posterior-anterior and lateral views) will be performed at selected sites at approximately every 12 months (starting at 9 months in this study for pediatric patients); for further details of timing, please refer to the protocol.

Chest X-rays will be collected at the site and sent to a medical imaging core laboratory where they will be digitized (if not already done at the site), coded, and read by a third-party reader blinded to patient number and study visit. The lung fields will be scored subjectively for the degree of ILD - interstitial, reticular, nodular density, and pleura thickening of the right and left lungs separately for each pre-defined levels above according to the following criteria:

- 0 = No infiltrative lung disease.
- 1 = Mild (affecting 1% to 25% of the lung volume).
- 2 = Moderate (affecting 26% to 50% of the lung volume).
- 3 = Severe (affecting 51% to 100% of the lung volume).

Mean score across both lungs = Sum of 2 lung scores / 2Cycle Ergometry

Cycle ergometry is performed at every 6 months (starting at 3 months in this study for pediatric patients) for first 2 years in this study, and yearly thereafter; for details refer to the protocol. For patients transitioning from DFI13803, this assessment is not required during LTS in patients that are ≤6 years of age or <120 cm in height on Day 1/Week 0 in the original pediatric study, and is performed only in patients who have completed these assessments in DFI13803. Completion of the assessment may depend upon patient cooperation.

2.1.4.5 Cycle ergometry

Cycle ergometry assessments will include maximum workload (watts), maximum percent predicted workload (%), working time (min), maximum heart rate (breaths/min), maximum percent predicted heart rate (%), maximum O_2 saturation (%), maximum respiratory rate (breaths/min), maximum ventilation (L/min), maximum O_2 uptake (mL/min), maximum percent predicted O_2 uptake (%), maximum CO_2 output (mL/min), and maximum respiratory exchange ratio. maximum tidal volume (mL) and maximum percent predicted tidal volume (%) will be assessed for patients transitioning from study DFI13803.

2.1.4.6 Physician's global assessment

The physician's global assessment of the patient's progress will be evaluated every 6-months (starting at 3 months in this study for pediatric patients) for first 2 years in this study, yearly thereafter; for details, refer to the protocol. The investigator evaluates the patient's current clinical status compared with screening (baseline) by marking 1 of 7 categories: "marked improvement of

daily activities", "moderate improvement of daily activities", "mild improvement of daily activities", "no change", "mild worsening of daily activities", "moderate worsening of daily activities" or "marked worsening of daily activities".

2.1.4.7 Hematology

The clinical laboratory parameters of platelets and hemoglobin are considered as efficacy evaluations. Blood samples are collected for these evaluations at each scheduled clinic visit every 6 months (in addition to hematology sample of complete blood count).

2.1.4.8 Fasting lipids (including Lipoproteins of Interest)

Fasting lipids evaluations are done at each scheduled clinic visit at every 3 months for first 2 years in this study, every 12 months thereafter. The parameters include: total cholesterol, LDL, HDL, VLDL, triglycerides, apolipoprotein B, apolipoprotein A1, and lipoprotein [a].

2.1.4.9 Efficacy biomarkers

Serum chitotriosidase, ligand 18 (CCL-18), and ACE are evaluated every 3-months in the study.

2.1.4.10 Bone disease assessments (Patients from adult study DFI13412)

2.1.4.10.1 Bone marrow burden (BMB)

This is assessed only for patients who transition from DFI13412 at every 12 months into this study; this assessment is not done on patients who transition from the pediatric study DFI13803. An MRI of lumbar spine and bilateral femur is performed, and three parameters are evaluated for each region: T1 weighted score, T2 weighted score, extent of involvement - femur only, infiltration pattern - spine only. The scale of these results is as follows:

T1 score: 0=Slightly hyperintense or isointense, 1=Slightly hypointense, 2=Hypointense
T2 score: 0=Isointense, 1=Slightly hypointense or slightly hyperintense, 2=Hypointense or hyperintense, 3=Mixed type
Extent of Involvement: 0=No site involvement, 1=Diaphysi, 2=Proximal epiphysis/apophysis, 3=Distal epiphysis
Infiltration Pattern: 0=None, 1=Patchy, 2=Diffuse, 3= Fat surrounding the basivertebral vein

Total BMB score for each region is derived by adding up the three individual score. Total BMB score is derived by adding the total BMB score of two regions, and ranges from 0 to 16 [0 to 4: mild; 5 to 8: moderate; 9 to 16: marked to severe].

2.1.4.10.2 Dual-energy X-ray absorption (DXA) parameters)

This is assessed only for patients who transition from DFI13412 at every 12 months into this study; this assessment is not done on patients who rollover from the pediatric study DFI13803.

DXA of lumbar spine and bilateral femur is performed, and three parameters are evaluated for each region (and for left and right side separately for bilateral femur): Bone mineral density (BMD), T-score and Z-score. The scale of these results is as follows:

BMD: a numerical value in the unit of g/cm^2
T-score: [score >= -1] = Normal, [score > -2.5 to < -1] = Osteopenia, [score <= -2.5] = Osteoporosis
Z-score: [score > -2] = Normal, [score <= -2] = Below normal

A total score for bilateral femur is obtained by averaging the two side scores.

2.1.4.11 Bone biomarkers

Bone-specific Alkaline phosphatase and C-telopeptide levels are evaluated every 3-months in the study.

2.1.4.12 Bone age by hand X-ray (Patients from pediatric study DFI13803)

A hand X-ray is performed for patients who transition from DFI13803 study at Screening and Week 52 in the original study, and will continue every 6 months of exposure to olipudase alfa. Bone age will be provided by the central vendor - BioClinica; they will use calculations based on the Greulich & Pyle Atlas (5).

2.1.4.13 Tanner staging (Patients from pediatric study DFI13803)

Tanner stage for physical gender-related development is assessed for patients who transition from DFI13803 study. It is performed at Screening and every 3 months after first infusion until Week 52 in the original study, then continue every 6 months of exposure to olipudase alfa.

2.1.4.14 Height Z-score (Patients from pediatric study DFI13803)

This endpoint, reflecting failure to thrive, is specific to patients transitioning from pediatric study DFI13803. Patient height is collected at screening and within 24 hours prior to every infusion visit in the original study, then every 6 months in the extension study. Z-score is the normalized value when compared to mean and standard deviation of height of children considered to have normal growth, based on gender and age: [height – normal mean(height)]/normal SD (height). The normal levels are provided by World Health Organization list from 2007. Height z-score will be calculated and categorized using the number and percentage of patients in <= -4, > -4 to <= -3.5, > -3.5 to <= -3, > -3 to <= -2.5, > -2.5 to <= -2, > -2 to <= -1.5, > -1.5 to <= -1 and > -1.

2.1.5 Pharmacodynamic endpoints

The following parameters are evaluated every 3 months in this study:

- Ceramide levels in dried blood spot.
- Sphingomyelin levels in both plasma and DBS.
- Lyso-sphingomyelin levels in both plasma and DBS.

- Sphingosine-1-phosphate in both plasma and DBS.
- For patients from adult study DFI13412, Sphingomyelin accumulation is evaluated from liver tissue collected during liver biopsy at screening, Week 26 and Year 3.

2.1.6 Pharmacokinetic endpoints

Pharmacokinetic parameters will include C_{max}, t_{max}, and AUC0-T. If applicable, $t_{1/2z}$, CL, and V will be derived.

2.1.7 Health Outcome Measures

There are several health outcome questionnaires used in this study. The pediatric questionnaires are often age-specific, and may require response by parents (in addition to or in lieu of patient response). Pediatric patients transitioning to this extension study will start with the questionnaire appropriate for the age at entry, and will fill in questionnaire appropriate to the age at the time of completion of such questionnaire.

2.1.7.1 For patients from adult study DFI13412

These questionnaire data are collected every six months (at visits) since the original study DFI13412 until 2 years into this extension study, and yearly thereafter.

- The Brief Fatigue Inventory (BFI) is a validated, self-administered questionnaire to assess fatigue (originally developed for cancer patients), and uses numeric rating scales from 0 to 10 for 9 items in the scale. Patients are asked in 3 items to rate the severity of their fatigue at its worst, usual (these two with a recall period of 24 hours), and now; the response ranges from 0="No fatigue" to 10="Fatigue as bad as you can imagine". The extent that fatigue has interfered with different aspects of the patient's life (including general activity, mood, walking ability, normal work – both in and outside of home, interpersonal relationship, and enjoyment of life) is assessed in 6 items with a recall period of 24 hours.
  - The two parts are scored separately (6). A scale score is generated for fatigue severity as the average of individual questions in the scale. If 2 out of 3 items are available, the item scores are averaged to provide fatigue severity scale score; if less than 2 item scores are available, the scale score is left missing. A scale score is generated for the fatigue interference score as the average of individual questions in the scale as long as at least 4 out of 6 items have non-missing response; otherwise, this scale score for the patient is left as missing.
- The Brief Pain Inventory – Short Form (BPI-SF) is a validated, self-administered questionnaire designed to measure a patient's perceived level of pain. The BPI-SF measures the patient's intensity of pain (sensory dimension), the interference of pain in the patient's life (reactive dimension), and asks the patient about pain relief, pain quality, and the patient's perception of the cause of pain. The BPI-SF consists of 15 items.

- The scoring is based on 4 out of 8 questions in the pain severity domain, and 7 questions in the pain interference domain, which uses numeric scale (7). Pain severity questions ask for the experience of pain at its worst, at the least, on an average (all with a recall period of 24 hours) and right at the moment; the response ranges from 0="No pain" to 10="Pain as bad as you can imagine". Pain interference questions deal with general activity, mood, walking ability, normal work (both in and outside of home), interpersonal relationship, sleep and enjoyment of life – all with a recall period of 24 hours; the response ranges from 0="Does not interfere" to 10="Completely interferes". The two parts are scored separately. A scale score is generated for pain severity as the average of individual questions in the scale as long as 2 or more items in that scale has non-missing response; otherwise this scale score is left missing. A scale score is generated for pain interference as the average of individual questions in the scale as long as at least 50% of the questions (4 out of 7) have non-missing response; otherwise, this scale score for the patient is left as missing.
- The Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS) is a validated, self-administered questionnaire designed to evaluate health related quality of life in adult patients with chronic airflow limitation, chronic respiratory disease, and cystic fibrosis (8). The CRQ-SAS has 20 items and evaluates 4 dimensions of respiratory impairment, including dyspnea, fatigue, emotional function, and the patient's feeling of control over the disease (mastery). Each item is answered in a seven-point-scale, with 8 reserved for "not done".

DYSPNEA:	q's 1, 2, 3, 4, 5
FATIGUE:	q's 8, 11, 15, 17
EMOTIONAL FUNCTION:	q's 6, 9, 12, 14, 16, 18, 20
MASTERY:	q's 7, 10, 13, 19

  The scores for each question of each dimension are added and divided by the number of questions. Thus, using a seven-point scale for the responses, the minimum and maximum scores for each dimension is the same: 1 is the worst and 7 is the best. Only items that are answered will be scored. Therefore, items that are scored as "not done" (or left blank) will not be included in the summary (average) score. The average score of the completed items will be reported.
- The SF-36 is a 36-item, validated, multidimensional, generic health-related quality of life measure that has been validated for adults in numerous healthy and ill populations internationally. The SF-36 consists of 36 questions, 35 of which constitute 8 scales, including physical functioning, role physical, bodily pain, mental health, role emotional, social functioning, vitality, and general health. The questionnaire will also generate 2 summary measures known as physical health component score and mental health component score.
- SF-36 scale responses are numeric in value and is transformed to a 0-100 scale with higher number indicating better health-related quality of life (9). Q2 is not considered a part of 8 scales to be reported. Physical and mental health component scores are provided in a normalized form based on the normal population. The scoring of SF-36 will be contracted

out to its manufacturer Quality Metrics, which will provide the final scores of each domain for each patient at each time point.

Scale	Question #
Physical functioning	3a: vigorous activities
	3b: moderate activities
	3c: Lifting/carrying groceries
	3d: Climbing several flights of stairs
	3e: Climbing one flight of stairs
	3f: Bending/kneeling/ stooping
	3g: Walking >1 mile
	3h: Walking several hundred yards
	3i: Walking 100 yards
	3j: bathing/dressing
Role physical	4a: Cut down time on work/activity, physical
	4b: Accomplished less, physical
	4c: Limited in kind of work/activity, physical
	4d: Difficulty performing work/activity, physical
Bodily Pain	7: Pain intensity
	8: Pain interference
General health	1: health condition
	11a: Get sick easy
	11b: Heathy
	11c: Health get worse
	11d: Health excellent
Vitality	9a: Full of life
	9e: Lot of energy
	9g: Worn out
	9i: Tired
Social functioning	6: Extent with social interference
	10: Frequency with social interference
Role emotional	5a: Cut down time on work/activity
	5b: Accomplished less
	5c: Less careful with work/activity
Mental health	9b: Very nervous
	9c: Down in dumps
	9d: Calm/peaceful
	9f: Downhearted/depressed
	9h: Happy

- The Niemann-Pick B Health Assessment Questionnaire (NPB-HAQ), Version 2 is a disease-specific questionnaire that covers various aspects of fatigue, pain, respiratory, abdominal complaints, and quality of life, and questions specific to ASMD symptoms and physical activity. The questionnaire also includes items to gather information on patient utilization of care and caregiver support. This question has been developed internally by Genzyme (data on file).
- Three domains have been identified: resource utilization, physical activity and symptoms. Questions 9-13 (5 questions) have been identified to be included in the resource utilization domain; they ask about missed work days, hospital visits, hospital stay, medical device use, supplemental medical service use – all with a recall period of past one year. There are 17 different symptoms assumed common and bothersome to ASMD patients; a patient is to rate each symptom in a scale of 0-4 with 0="Not a problem" and 4 is the worst severity/bother. Physical activity domain consists of two questions – one asking for frequency of participation in sports or physical exercise in past one month, the other asking about the specific sports/physical activity the patients regularly participates in.

2.1.7.2 For patients from pediatric study DFI13803

These questionnaires are collected every 6 months for first 2 years in this study, yearly thereafter.

- The Pediatric Quality of Life (PedsQL) Generic Core scale is a brief, standardized, generic assessment instrument that systematically assesses patients' and parents' perceptions of health-related quality of life in pediatric patients with chronic health conditions (10). The PedsQL consists of a 23-item core measure including a self-report for children aged 5 to 18 years and for young adults aged 18 to 25 years. A report for parents of patients from birth to 25 years of age is also available. This data is collected at screening, then every 6 months until 2 years in this study, then yearly thereafter.

  In both patient and parent reports it measures four scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Psychosocial scale considers all questions in emotional, social and school functioning scales. The total scale considers all questions in the questionnaire, irrespective of individual scales. Each item in every scale uses the 4-point rating scale (0=never to 4=almost always). The algorithm of Scale Scores is as follows:

  1. The score is first reversed in a scale of 0-100: 0=100, 1=75, 2=50, 3=25, 4=0. A higher score indicates better Health-Related Quality of Life.
  2. If more than 50% of the items in the scale are missing, the Scale Score is not computed. If 50% or more of the items in the scale are completed, Scale Score is computed as the arithmetic average of the items answered.
- The PedsQL Multidimensional Fatigue Scale (10) consists of 18 questions, 6 regarding general fatigue, 6 regarding sleep/rest fatigue, and 6 regarding cognitive fatigue. It includes a self-report for children aged 5 to 18 years and for young adults aged 18 to 25 years. A report for parents of patients aged 2 to 25 years is also available. This data is collected at screening, then every 6 months until 2 years in this study, then yearly thereafter. Similar to

the PedsQL generic core scale, each item uses a scale of 0-4 for response, 0 indicating "never" and 4 indicating "almost always". The scale scores are computed using an algorithm.

- The PedsQL Pediatric Pain Questionnaire (10) consists of 3 questions that include a child self-report for patients aged 5 to18 years and a proxy report for parents of patients aged 5 to 18 years. These same questionnaires will be used for patients aged 18 to 25 years because questionnaires are not available for young adults. This data is collected at screening, then every 6 months until 2 years, then yearly thereafter.
- The first item is the degree of present pain, the second item is the degree of the worst pain, and the third item refers to the localization of pain and is not scored. The first two items will be scaled using visual analogue scales (VAS) from 0 (Not hurting/No discomfort/No pain) to 100 mm (Hurting a whole lot/Very uncomfortable/Severe pain). The present pain and worst pain are scored separately. The scores are based on line length to the nearest 5 mm. There is no imputation process since these are single item VAS scales.

2.1.8 Cognitive and adaptive function testing (Patients from pediatric study DFI13803)

Developmental Profile 3 (DP-3):

The Development profile questionnaire, Version 3 (DP-3) (11) is used for measuring cognitive function in patients age <6 years at entry into this study. The number of items to be answered on each content area of the DP-3 depends on the patient's age and functional level. For example, parents of patients who are ages 4 years to 6 years answer 23 items. For each content area (Physical, Adaptive Behavior, Social-Emotional, Cognitive, Communication), the raw score indicates the number of developmental items the subject is credited for being able to complete.

The DP-3 assessments are centrally scored to generate the General Development Score. For each content area and the General Development Score, standard scores, confidence intervals, descriptive categories, and percentile ranks are generated. For each content score, age-equivalence is generated.

This data is collected at screening of the original study, then every 6 months until 2 years into this study, then yearly thereafter until the patient turns 6 years of age.

Adaptive Behavior Assessment System, Third Edition (ABAS-3):

Adaptive behavior assessment system, version 3 (ABAS-3) (12) consists of several age-specific rating forms; for this study, the Parent/Primary Caregiver Form (Ages 0-5) and Parent Form (Ages 5-21) will be used. The ABAS-3 measures adaptive behavior at three different levels. At the highest level is the General Adaptive Composite, which is composed of all measured skill areas. The next level are three adaptive domains, each comprising multiple individual skill areas; these domains are Conceptual, Social, and Practical. At the third level are individual adaptive skill areas. For each adaptive skill area, the raw score is the sum of item behavior frequency ratings for all items.

The ABAS-3 assessments are centrally scored to generate scaled scores for each adaptive skill area. The scaled scores are utilized to generate a standard score, percentile rank, and confidence interval for the General Adaptive Composite and three adaptive domains (Conceptual, Social, and Practical).

This data is collected at screening of the original study, then every 6 months until 2 years into this study, then yearly thereafter until the patient turns 6 years of age.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for patient study status.

Enrolled patients are those who signed the informed consent for this study and met all enrollment criteria for this study. Number and percentage (calculated based on the number of patients who have completed the treatment period of the original study on schedule) of enrolled patients will be provided. Patients who have received one infusion of olipudase alfa in this extension phase, those who are continuing in the study at the time of reporting, those who completed the study and those who prematurely discontinued the study will be summarized; percentage will be calculated based on the number of enrolled patients. The reason for premature discontinuation will also be provided.

Protocol deviations

During the review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock and classified as minor, major or critical deviations, in consideration of whether this could potentially affect efficacy assessment endpoints. A listing of major or critical protocol deviations for all treated patients will be produced.

In addition to the above, the two conditions listed below will be evaluated:

Noncompliance: Missing 4 or more infusions for each 12 month period in this study, excluding for-cause missed infusions (such as when the missed infusions are required by the protocol due to a dose limiting toxicity), calculated over the extension phase only. Whether a missed infusion is for-cause or not will be reviewed and determined by the clinical team; the decision will be used in the determination of noncompliance. For details of calculations, please refer to Section 2.4.6.2.

Prohibited medications intake: The prohibited medications in this study have been defined in Section 2.1.2. The prohibited medication use that could potentially modify the effect of olipudase alfa (which includes, but not limited to, certain antidepressant) or could threaten the safety of olipudase alfa are major protocol deviations.

The protocol deviations identified by the review of the above two conditions will be listed for all treated patients as protocol deviations.

2.3 ANALYSIS POPULATIONS

2.3.1 Safety population

All subjects who were exposed to the study treatment, olipudase alfa, ie, who received at least one infusion of study treatment (total or partial), will be included in the safety population.

2.3.2 Pharmacokinetic population

The pharmacokinetic population includes all patients who receive at least 1 infusion of olipudase alfa and have evaluable pharmacokinetic data available post-baseline.

2.3.3 Pharmacodynamic population

Pharmacodynamic population includes all patients who are treated and have at least one evaluable pharmacodynamic measurement available post-baseline.

2.4 STATISTICAL METHODS

Data collected in this study will be presented using summary tables, figures, and data listings. Descriptive statistics for categorical variables will be provided using frequencies (n) and percentages (%). Descriptive statistics for continuous variables will be provided using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. All data used in tabular summaries or figures will be supported by listings of underlying data – raw and/or derived, and all figures will be supported by relevant summary information.

All summaries will be provided for the LTS population, along with separate subgroups in the population according to which original study the patient belonged to: DFI13412 (adult study, Phase 1B, 26 weeks, 5 patients), DFI13803 (pediatric study, Phase 1/2, 64 weeks, 12 patients). In addition, similar summaries will be produced by age cohort of adolescent, child, infant for the patients who transition from pediatric study DFI13803.

The scheduled visits in statistical displays will be labelled in months of total follow up time from the first infusion in the original study. For example, a 6-month visit in this study for a patient transitioning from the 26-week DFI13412 study will be identified as Month 12 exposure in the displays. The schedule of measurements for this study will be followed for display presentation with baseline derived from the original study. For patients in this study, the results from the original study visits will be included, unless specified otherwise, for the purpose of understanding the continuity of treatment effect during this extension phase; for details and descriptions of all results from the original study, please refer to the original study CSR. For parameters that are not collected in the extension phase will not be part of this SAP.

2.4.1 Demographics and baseline characteristics

Demographic and baseline characteristics, medical history and smoking/alcohol history from original study will be summarized using the safety population.

Genotype of acid sphingomyelinase gene (SMPD1), CHIT1, UGT1A1 will also be summarized with baseline disease characteristics, and be provided in data listings.

The SMPD1 variant type (ie, missense, frameshift, deletion, nonsense, etc) will be derived, if possible, from the SMPD1 amino-acid change.

For the classification of CHIT1 genotype, the following derivation will be applied:

- N = Wildtype (WT)/WT = Normal / 2 functional alleles
- H = WT/Duplication 24 (DUP24) = Heterozygous mutation / 1 functional allele
- M = DUP24/DUP24 = homozygous mutation / 2 non-functional alleles (no chito activity)

For the classification of UGT1A1 genotype, the following derivation will be applied:

- UGT1A1*1 = Fully functional allele = Not Gilbert variant
- UGT1A1*36 = Functional allele = Not Gilbert variant
- UGT1A1*28 = Gilbert syndrome allele = Gilbert variant
- UGT1A1*37 = Crigler-Najar syndrome type 2 allele (impaired UGT1A1) = Gilbert variant

Patients with 0 or 1 Gilbert variant alleles will be classified as “no Gilbert Syndrome”; patients with 2 Gilbert variants alleles will be classified as “Gilbert Syndrome”.

2.4.2 Baseline safety parameters

Baseline for safety parameters (weight, height, body mass index (BMI), physical exam, vital signs, echocardiograms, immune response assessments, and safety biomarkers) in general is defined as the last available non-missing value for the parameter before the first infusion in the original study. Most of the baseline values will thus be from the Day 1/Week 0 pre-infusion assessments in the original study, with the exception of hematology parameters and possibly electrocardiogram (ECG). Hematology samples are collected for pediatric patients twice at screening and twice on first infusion visit, once before and once after the first infusion; for adult patients, they are collected once at screening, twice before infusion on first infusion visit and one after the first infusion. The average of all measurements taken before the first infusion will serve as the baseline. Another exception may be the ECG parameters – Day 1/Week 0 (the first infusion visit in the original study) is to collect ECG in triplicate before the infusion; if 2 or more than 2 of these triplicate collections of ECG are before the first infusion, the average of these ECG parameter results will be considered as the baseline value; otherwise, the baseline value of ECG parameters will be taken from the latest observation before the first infusion.

Baseline safety data will be presented along with subsequent values assessed during or after olipudase alfa dosing using safety population.

2.4.3 Baseline efficacy parameters

Baseline for efficacy parameters (spleen/liver volume, pulmonary function, pulmonary imaging, cycle ergometry, efficacy biomarkers, height z-score, bone disease assessments, etc) is defined as the last available non-missing value for the parameter before the first infusion in the original study, except for the hematology parameters; for complete definition of baseline derivation, please refer to Section 2.6.1

2.4.4 Baseline pharmacodynamic parameters

Baseline values for sphingomyelin and sphingomyelin metabolites, including, but not limited to, ceramide in dried blood spots (DBS), lyso-sphingomyelin and sphingosine-1-phosphate in both plasma and DBS will be the last available value before first infusion in the original study; typically these will be the screening values from the original study.

Baseline pharmacodynamic data will be presented along with subsequent pharmacodynamic values assessed during or after olipudase alfa dosing using pharmacodynamic population.

2.4.5 Prior or concomitant medications

Concomitant medications have been defined in Section 2.1.2. In case the start/stop date of the medication is missing or incomplete preventing the unambiguous determination of the medication status, the medication will be categorized as concomitant.

Medication summaries will be presented by WHO-DRUG Anatomic Class and by WHO-DRUG Therapeutic Class using safety population. Tables will show all medications used during the study, sorted by most prevalent Anatomic Class and then by descending frequency of Therapeutic Class within Anatomic Class based on the prevalence within the overall column.

The prohibited medications in this study have been defined in Section 2.1.2. The list of prohibited antidepressant medications will be provided by the data management and will be merged with the concomitant medication data in the database to identify any use of it. For the cationic amphiphilic antihistaminics where an exhaustive list of drugs cannot be provided, clinical review performed before the database lock will determine whether their use constitutes a protocol deviation that interferes with assessment of effect of olipudase alfa. For the medications prohibited before and after the liver biopsies where an exhaustive list of drugs cannot be provided, clinical review performed before the database lock will determine whether their use constitutes a protocol deviation that interferes with assessment of the safety of olipudase alfa. A data listing of prohibited medication including antidepressant use, and any medication use identified in the clinical review as protocol deviation, will be provided, and will be identified with the respective category.

2.4.6 Extent of investigational medicinal product exposure and compliance

2.4.6.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed from the first infusion in the original study, and will be summarized using safety population. The duration of exposure is defined as the number of weeks between first infusion in the original study and disposition date in the study: (disposition date of the study [or the cutoff date for database lock if the patients are still ongoing] – first infusion date from original study + 1)/7. The number of infusions received and the duration of exposure will be summarized using safety population.

The distribution of weeks on study treatment (<12 weeks, >=12 weeks to <26 weeks, >=26 weeks to <38 weeks, >=38 weeks to <52 weeks, >=52 weeks to <64 weeks, etc) will be provided using number and percentage of patients by age group cohorts and overall. The total number of patient-years of exposure will also be provided.

Any overdose will be captured as an AE, and will be reported as such.

2.4.6.2 Compliance

Compliance to the treatment regimen will be monitored in terms of the percentage of scheduled infusions the patient receives during the treatment period, including exposure from the original study. A patient is considered noncompliant if the patient missed 4 or more infusions (excluding for-cause missed infusions, such as when the missed infusions are required by the protocol due to a dose limiting toxicity) every 12-month period in the extension study. Whether a missed infusion is for-cause or not will be reviewed and determined by the clinical team; the decision will be used in the analysis of compliance.

Overall Compliance = 100% x Total number of infusions received / Total number of expected infusions

where total number of expected infusions refers to the number of infusions expected between the first infusion in this study and the date of withdrawal or date of completion. It is calculated as the integer part of (Date of withdrawal/completion – Date of the first infusion in the extension study)/14. For interim calculations, date of withdrawal/completion will be substituted by the date of the database extraction used.

Compliance excluding for-cause = 100% x Total number of infusions received / (Total number of expected infusions – total number of for-cause missed infusion)

where the denominator is calculated as the integer part of [(Date of withdrawal/completion – Date of the first infusion in the extension study)/14] – number of for-cause missed infusions. For interim calculations, date of withdrawal/completion will be substituted by the date of the database extraction used.

Overall compliance and compliance excluding for-cause will be summarized descriptively as quantitative variable using safety population. The numbers and percentages of patients whose compliance are <80%, >=80% to <90%, >=90% to <100% and >=100% will be provided. Number and percentage of patients will be presented for missing 4 or more scheduled infusions, by every 12 months of treatment exposure.

Any interruption during infusion will be captured and provided in data listing. Any irregularities in dosing (such as does change or dose interruption) due to an AE will be captured with AE details, and will be provided with AE reports.

2.4.7 Analyses of safety data

The safety results will be presented using the safety population. Unless specified otherwise, the displays will include the original study data along with data collected in this study. Patients will be summarized and displayed by original study identifier, age cohort and overall. Safety data will be reported up to and including the time of treatment withdrawal, and follow-up for AEs, where applicable. The baseline value is the last available value before the first infusion of olipudase alfa in the original study, except for hematology parameters and possibly ECG parameters. For complete definition of baseline, refer to Section 2.6.1.

For all safety data, the observation period in this study is the **on-treatment period**, which is defined as the time from the first infusion of IMP (included) from original study to the end of the current study

The following definitions regarding potentially clinically significant abnormality (PCSA) will be applied to laboratory parameters, vital signs and ECG:

- The 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. These values are provided in Appendix A.
- PCSA criteria will determine which patients had at least 1 PCSA taking into account all evaluations performed, including unscheduled or repeated evaluations.
- Before determining a value as PCSA, the value will be rounded to the precision that the PCSA criterion is defined.

2.4.7.1 Analyses of adverse events

2.4.7.1.1 Definitions

Adverse events continuing from the original study into the entry into this extension study will be identified, and will be reported as one AE avoiding duplication of the same AE in two database. Adverse event summaries will include the number of events (N), number (n) and percentage (%) of patients experiencing an adverse event. The denominator for computation of percentages is the safety population. Sorting order will follow the internationally agreed MedDRA system organ

class (SOC) order, and further by decreasing number of events overall in preferred terms (PTs) within SOCs. When more than one PT has same number of events within the same SOC, the order of presentation will be alphabetical in PTs.

Treatment-emergent adverse events (TEAEs) will be defined as AEs that started during the on-treatment period – either in this study or in the original study.

If an AE date/time of onset is incomplete, an imputation algorithm will be used to classify the adverse event within the appropriate adverse event period. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine otherwise. Details on classification of AEs with missing or partial onset dates are provided in Section 2.6.2. If an AE worsens in severity, only the worst severity is captured on the AE log page in the e-CRF.

The AE log page in the e-CRF captures the date when the event become serious. If and when this date is non-missing, it indicates that the AE started as non-serious and became serious at a later date. To account for non-serious and serious parts of the AE collected in one AE log page, this AE will be split into two AEs - one non-serious, and one serious AE - with the same AE number, with the following modifications in data for these two AEs:

- Non-serious AE: AE end date, AE outcome, date of death or hospitalization, autopsy information, criterion for serious adverse event (SAE) will be blank.
- Serious AE: AE start date will use the date the event became serious.
- Action taken towards study drug and action taken (toward AE) will be considered in relation to the date the event became serious, the last infusion date and dosing information, and a determination will be made, in consultation with safety monitor of the trial, as to whether the recorded fields belong to non-serious AE or serious AE; then the decision will be implemented in analysis. Any such decision will be rationalized in the CSR.

For treatment-emergent AEs, separate listing of AEs, SAEs and IARs that started only after the first infusion in this extension study will be provided.

Start day of treatment emergent AE relative to first infusion = Start date of AE – first infusion date + 1

Start day of treatment emergent AE relative to last infusion = Start date of AE – last infusion date + 1

Total patient year for each group will be calculated and displayed on selected AE tables.

2.4.7.1.2 Treatment-emergent adverse events

An overview of TEAEs will be provided to include (potentially related is defined as either “related” or “possibly related” as assessed by the investigator):

- TEAEs
- TEAEs excluding original study
- TEAEs potentially related to study treatment

- TEAEs by the worst severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to study withdrawal
- TEAEs leading to dose reduction
- TEAEs leading to study treatment interruption
- Protocol-defined IARs
- Algorithm-defined IARs
- Treatment-emergent serious adverse events
- Treatment-emergent serious adverse events potentially related to study treatment
- TEAEs with fatal outcome (Deaths)
- Treatment-emergent pregnancies
- TEAEs which are considered symptomatic overdose
- Dose-limiting toxicities (collected in the adverse event log page in e-CRF, see protocol Section 8.1.6 for details)

The following summaries will be produced by primary SOC and PT:

- TEAEs
- TEAEs by the worst severity (ie, mild, moderate, or severe)
- TEAEs potentially related to study treatment
- TEAEs potentially related to study treatment, by the worst severity (ie, mild, moderate, or severe)

The most common TEAEs will be summarized by SOC and PT for patients from pediatric study DFI13803 and for patients from adult study DFI13412in separate tables. The criteria of most common TEAEs are the following, which will be applied to the two populations separately:

- the number of events of a preferred term is more than or equal to 2% of the number of all TEAEs in the population, AND
- the number of patients who had this event is more than or equal to 2.

For the above summary for or patients from pediatric study, it will be summarized by age cohort and overall.

TEAEs by the latest infusion dose immediately preceding the start of AE will be provided by SOC and PT.

2.4.7.1.3 Adverse events of special interest

Protocol-defined IAR: The following summaries will be produced by primary SOC and PT:

- Protocol-defined IARs
- Protocol-defined IARs by the worst severity
- Protocol-defined IARs started during infusion
- Protocol-defined IARs started between 0 hours (exclusive) and 3 hours (exclusive) post end of infusion
- Protocol-defined IARs started between 3 hours (inclusive) and 24 hours (inclusive) post end of infusion
- Protocol-defined IARs started between 24 hours (exclusive) and 72 hours (inclusive) post end of infusion
- Protocol-defined IARs started after 72 hours post end of infusion

Additionally, Hypersensitivity IARs will be summarized by primary SOC and PT.

In case there are IARs identified by the sponsor (before database lock) that the investigator did not agree to be an IAR, sponsor-identified IARs may be added to the list of investigator-identified IARs to define the protocol-defined IARs, and additional summaries may be produced.

Algorithm-defined IAR: The summary of algorithm-defined IARs by primary SOC and PT will be provided.

Pregnancy: Pregnancies will be provided as part of patient narrative.

Symptomatic overdose: The symptomatic overdose data will be provided as part of patient narrative.

Quantifiable Dose Limiting Toxicities defined based on laboratory values: As defined in Section 2.1.3.1, the Quantifiable Dose Limiting Toxicities will be provided in a data listing.

2.4.7.1.4 Adverse events of other interest

Infections: TEAEs of infections are defined under the system organ class of Infections and Infestations.

Bleeding: TEAEs of bleeding are defined under the standard MedDRA queries (SMQs) of Hemorrhages (identified using SMQ code 20000038 broad and narrow scope). Bleeding AE data will be summarized by SOC and PT for each age cohort.

2.4.7.1.5 Serious adverse events

Summary of Treatment-emergent serious adverse events will be provided by primary SOC and PT.

2.4.7.1.6 Analyses of adverse events by place of infusion

To assess the comparability between site infusion and home infusion, the following adverse events will be analyzed, pooling patients of different age cohorts. Only adverse events that occurred after the date when the first patient in the study received his/her first home infusion will be included in these analyses.

- Overview of treatment-emergent adverse events
- Treatment-emergent adverse events by SOC and PT
- Treatment-emergent adverse events by severity, and by SOC and PT
- Treatment-emergent adverse events by the latest infusion dose, and by SOC and PT
- Treatment-emergent serious adverse events by SOC and PT
- Protocol defined IARs by SOC and PT
- Protocol defined IARs by severity, and by SOC and PT
- Protocol-defined IARs started during infusion by SOC and PT
- Protocol-defined IARs started between 0 hours (exclusive) and 3 hours (exclusive) post end of infusion
- Protocol-defined IARs started between 3 hours (inclusive) and 24 hours (inclusive) post end of infusion
- Protocol-defined IARs started between 24 hours (exclusive) and 72 hours (inclusive) post end of infusion
- Protocol-defined IARs started after 72 hours post end of infusion
- Algorithm-defined IARs

2.4.7.2 Clinical laboratory evaluations

For parameters that are reported as BQL (below the quantification limit), the results often convey a clinically meaningful change. Therefore, a numerical value is necessary to be imputed for including these in descriptive statistics calculations as well as plotting them in by-patient graphs. For all these parameters the lower limit of quantification (LLOQ) is available in the database. The imputed value for BQL will observe the same precision as reported values, but will be lower than the LLOQ by the minimum of that precision. For example, if a parameter is reported to two decimal places, and its LLOQ is X, then the imputed value of BLQ is (X-0.01). On the other hand, if a parameter is reported to one decimal place, and its LLOQ is X, then the imputed value of BLQ is (X-0.1). Listing will provide data as BQL and <LLOQ where LLOQ will be populated.

Observed values, change from baseline and percent change from baseline to scheduled study time points will be summarized in separate groups of hematology (excluding hemoglobin and platelets which are considered efficacy parameter, hence the analyses have been described in Section 2.4.8.7), liver function tests, lipids, coagulation, etc. as described in Section 2.1.3.3. By patient plots of WBC, ALT, AST, total bilirubin will be provided. Summary plots over time will also be provided as needed.

Laboratory values will be classified as normal, above normal, or below normal based on normal ranges when provided by the laboratory. Shifts from baseline to scheduled time points, any time during the on-treatment period and the last available value, in the abnormality of any parameters will be provided.

PCSA values for hematology and liver function tests (provided in Appendix A) during the study (from first infusion in the original study to last available observation) will be summarized. PCSA values for hematology, liver function test and clinical chemistry parameters will be provided in separate listings.

2.4.7.3 Vital signs

Vital signs will include heart rate (HR, beats/minute), systolic and diastolic blood pressure (SBP/DBP, mmHg), respiratory rate and body temperature (°F or °C). Each vital sign parameter will be summarized as observed parameter value and change from baseline at each scheduled time point.

PCSA values during the study (from first infusion start to last available observation) will be summarized.

2.4.7.4 Electrocardiogram

For ECG parameters, the observed data and change from baseline will be summarized at each scheduled time point.

PCSA values will be summarized during the study (from first infusion start to last available observation).

2.4.7.5 Echocardiogram with Doppler

Shift tables will be created for valve characterization (including aortic regurgitation, mitral regurgitation, pulmonic regurgitation, tricuspid regurgitation). Summary of change from baseline in ejection fraction (%) and pulmonary artery systolic pressure will be provided. By-patient plots of left ventricular calculated ejection fraction (%) will be provided.

2.4.7.6 Physical examinations

Complete physical examination (except overall neurological exam - please see Section 2.4.7.7) will be classified as normal or abnormal. Shift tables will be provided. A listing of the abbreviated physical examination data will be provided.

Observed values and change from baseline for weight, height and BMI will be summarized for all scheduled time points.

For patients from the pediatric study DFI1303, the age-appropriate growth in height is a matter of efficacy; please see Section 2.4.8.14 for analysis of height z-scores.

2.4.7.7 Extended neurological examinations

This data will be summarized and listed. The overall evaluation of neurological exam collected in eCRF under physical exam will be included in this section.

2.4.7.8 Liver biopsy (Patients from adult study DFI13412)

Liver biopsy data will be received as external data.

The fibrosis stage will be summarized with number of patients and percentage for each stage at each visit. Cirrhosis and liver failure could be interpreted from this data. Change from baseline in Sphingomyelin from Liver biopsy will be summarized under pharmacodynamics (Section 2.4.9.1). Any other data from liver biopsies in the clinical database will be provided in a data listing.

2.4.7.9 Liver ultrasound Doppler (Patients from pediatric study DFI13803)

Liver ultrasound Doppler data will be provided in a data listing.

2.4.7.10 Safety biomarkers

Observed values and change from baseline will be summarized at each scheduled time point. Summary plots for observed values and/or by-patient plots over time will also be presented as appropriate.

2.4.7.11 Immune response assessments

Data listings will be provided to display results of anti-olipudase IgG antibody, neutralizing antibody, anti-olipudase alfa IgE antibody, serum tryptase activity, complement activation, and skin testing performed. If IgG antibody titer value is reported as <xx, the numeric value will be imputed as xx, the minimum required dilution (MRD), and used for summary purposes, Listing will provide results as reported as well as results as imputed.

A patient with at least one anti-drug antibody (ADA) response available in the database is considered evaluable.

A patient whose ADA status is positive at baseline is considered to have pre-existing ADA.

A patient whose ADA status is positive anytime post-baseline and is negative or missing at baseline is considered to have treatment-induced ADA.

A patient whose ADA status is positive at baseline (pre-existing ADA) and the ADA titer level anytime post-baseline is significantly higher than that at baseline is considered to have treatment-boosted ADA. A difference in titer values between 2 samples representing greater than or equal to twice the dilution level is considered significant. In other words, the post-baseline titer value divided by the baseline titer value will be greater than or equal to 4 to be considered significant. For example, if baseline titer value is 50, the post-baseline titer value has to be >=200.

For patients with treatment-induced ADA, the following 3 ADA responses are defined.

Transient ADA response is defined as:

- Treatment-induced ADA detected only at one sampling time point post-baseline (excluding the last sampling time point).
- Treatment-induced ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA response is defined as:

- Treatment-induced ADA detected at two or more sampling time points post-baseline, where the first and the last ADA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks.
- Treatment-induced ADA detected in the last two sampling time points, irrespective of the time period in between.

The following subclassifications for persistent ADA response will be considered as well. Since this study is ongoing, the final assessment will be the final assessment at the time of data cutoff date for initial BLA submission.

- Low response - if a patient's peak titer ≤400 and positive at final assessment. This represents the first titer that is greater than a 4-fold increase from the assay minimum required dilution (MRD). Titers within this range would be considered as Low response.
- Intermediate response - if a patient had persistent ADA response but peak titer is >400 and positive at final assessment.
- Tolerized - if a patient had persistent ADA response, but negative at the final assessment.

Indeterminate ADA response is defined as:

- Only the last sampling time point is positive and all previous samples are negative.

Pre-existing ADA = 100*(Number of patients with pre-existing ADA at baseline)/number of evaluable patients

ADA Incidence = 100*(treatment-boosted + treatment-induced ADA positive patients)/number of evaluable patients

The following information will be provided:

- Number of ADA evaluable patients
- Number (%) of patients with ADA positive/negative at baseline

- Number (%) of patients that never develop ADA at any time (ie, ADA is always negative during baseline and post-baseline visits)
- Number (%) of patients with treatment-boosted ADA
- Number (%) of patients with treatment-induced ADA
- Treatment emergent ADA: Number (%) of patients with treatment-boosted/treatment-induced ADA
- Duration of ADA response: Number (%) of patients with transient/persistent/indeterminate ADA response (each category separately)
- Number (%) of patients within persistent ADA response subclassifications: low response, intermediate response, tolerized (each category separately)
- Patients with treatment-induced ADA will be further characterized
  - Peak ADA titer: Median and $25^{th}/75^{th}$ quantiles (min, max) of the ADA titer for peak ADA titer of treatment-induced ADA positive patients
  - Last ADA titer (final assessment): Median and $25^{th}/75^{th}$ quantiles (min, max) of the last ADA titer of treatment induced ADA positive patients
- Number (%) of patients with positive neutralizing antibody (NAb)
  - NAb Inhibition of catalytic activity
  - NAb inhibition of cellular uptake

The assessment of ADA incidence and characterization by manufacturing process B compared with Process C will be conducted through pooled analyses and presented in the integrated summary of immunogenicity. The assessment of immunogenicity and safety by Processes will be presented in the integrated summary of safety (ISS).

2.4.8 Analyses of efficacy endpoints

All efficacy analyses to assess changes in organomegaly (spleen and liver), infiltrative lung disease, pulmonary function, cycle ergometry endpoints, physician's global assessment, hemoglobin/platelet, efficacy biomarkers, lipid profile, bone biomarkers, health outcome questionnaires, will be performed using the safety population. Additional endpoints for pediatric patients include: linear growth (height z-score), bone age, tanner staging and cognitive and adaptive functioning (up to the age of 6 years only).

Baseline for efficacy parameters will be defined as the last non-missing value before the first infusion in the original study, except for hemoglobin and platelet; for complete definition of baseline values, please refer to Section 2.6.1.

2.4.8.1 Spleen and liver volumes

For timing of MRI measuring spleen and liver volume, and the formula for calculating the volumes in multiples of normal (MN), refer to Section 2.1.4.1.

Change from baseline and percent change from baseline for both cm^3 and MN units, in addition to observed values, will be calculated and summarized for all scheduled visits. The analysis of covariance method (including baseline as covariate) and Wilcoxon-Mann-Whitney (WMW) test p-values (and 95% confidence interval) for the change from baseline and percent change from baseline will be provided in the summary tables for spleen/liver volumes in MN unit. Box plots of observed values for spleen and liver volumes in MN unit will be provided.

The correlation between spleen and liver volumes with other efficacy/safety/pharmacodynamic parameters may be explored graphically.

Analysis of covariance will be used to explore difference among different age cohorts for patients from pediatric study DFI13803, using the following model:

Percent change from baseline = age cohort + baseline

2.4.8.2 Pulmonary function testing

The parameters evaluated are DLco (mL/min/mmHg), FVC (L), FEV_1(L), TLC (L). Since the local sites use different equations to calculate percent predicted values, the calculation is standardized internally by using the formula provided in Section 2.1.4.2; the percent predicted values calculated at site will remain in the database but will neither be listed nor summarized. The observed values used in analyses are provided by local sites for original study, and will be used for calculation of percent predicted values. The patients transitioning from the pediatric study will continue to use children formula used during the original study even if the age limit prescribed for that formula is crossed during the extension phase.

For all 4 tests, percent (%) predicted values will be summarized for observed values, change from baseline and percent change from baseline using the safety population at scheduled study visit. The analysis of covariance method (including baseline as covariate) and WMW test p-values for the change from baseline and percent change from baseline will be provided in the summary tables for all 4 tests. Box plots of observed values, percent change from baseline for these 4 tests will be provided for the safety population. By-patient plots for all 4 tests over time will be provided.

Analysis of covariance will be used to explore difference among different age cohorts for patients from pediatric study DFI13803, using the following model:

Percent change in percent predicted PFT from baseline = age cohort + baseline percent predicted PFT

For patients from adult study DFI13412, a binary measure of responder (yes vs no) will be derived based on the change from baseline in % predicted DLco at each post-baseline visit. A patient is a responder at the visit, if the patient has change from baseline in % predicted DLco >=15. This binary measure of % predicted DLco will be included in data listing.

2.4.8.3 Pulmonary imaging - high resolution computed tomography

A qualitative assessment will be made for the following features: interstitial lung disease (reticular pattern), ground glass appearance, reticulo-nodular density (nodular densities) and pleural thickening of the right and left lungs based on a scale 0-3 as explained in Section 2.1.4.3.

For all 4 features, the mean and standard deviation will be provided for observed values and change from baseline by each side at each level. The mean scores at each scheduled visit are calculated as follows:

Mean score across 4 levels for left (or right) lung = Sum of scores for 4 levels / 4

Mean score across 4 levels and both lungs = (Mean score across 4 levels for left lung + Mean score across 4 levels for right lung) / 2

Summary of the above two types of mean scores and change from baseline for each feature will be provided at scheduled visits. A bar chart for the mean scores across 4 levels and both lungs of each feature will be provided.

2.4.8.4 Pulmonary imaging - Chest X-ray

The lung features (interstitial (overall ILD)), reticular, nodular, consolidation and pleura) will be scored subjectively for the degree of diffuse lung disease (infiltrative lung disease) in a scale of 0-3 as explained in Section 2.1.4.4.

For chest x-ray imaging, interstitial provides an overall assessment of interstitial lung disease with reticular and nodular may provide more supportive information on type of interstitial involvement. Consolidation provides a measure of air space disease and is assessed in addition to interstitial involvement. As HRCT provides a more robust characterization of the diffuse lung disease, only interstitial (overall ILD) of the chest X-ray will be analyzed; however data for all features will be provided in data listings.

Summary of mean scores and change from baseline for interstitial will be provided by scheduled visits.

2.4.8.5 Cycle ergometry

The parameters of cycle ergometry assessments are noted in Section 2.1.4.5. Percent predicted values (or observed values) will be summarized by scheduled visits along with change from baseline.

2.4.8.6 Physician's global assessment of change

Frequency shift table for physician's global assessment of disease severity (mild, moderate, severe) from the baseline will be provided at each scheduled post-baseline visit. Frequencies and percentages of patients at each clinical status will be provided at each scheduled post-baseline visit. Seven categories of Clinical Status in Physician's global assessment of change as detailed in Section 2.1.4.6 will be converted to numeric values as follows:

- "Marked improvement of daily activities" = 3.
- "Moderate improvement of daily activities" = 2.
- "Mild improvement of daily activities" = 1.
- "No change" = 0.
- "Mild worsening of daily activities" = -1.
- "Moderate worsening of daily activities" = -2.
- "Marked worsening of daily activities" = -3.

Observed numeric values at each post-baseline visits will be analyzed using analysis of covariance (ANCOVA) model with baseline as covariate. The baseline value will be Physician's global assessment of disease severity at screening with value of 1=mild, 2=moderate, 3=severe.

2.4.8.7 Hematology

Platelet and hemoglobin are efficacy parameters. At every six month clinic visit these two parameters are evaluated from two blood samples - one for complete blood count, one for hemogram. The average of these two values will be used for efficacy analysis. If and when two values are not available, the single available value will be used.

Observed values, change from baseline and percent change from baseline will be summarized at each scheduled time point. Summary plots of pre-infusion values over time will be provided. By-patient plots over time will also be provided.

For platelet and hemoglobin, analysis of covariance will be used to explore difference among different age cohorts for patients from pediatric study DFI13803, using the following model:

Percent change from baseline in platelets = age cohort + baseline

2.4.8.8 Fasting lipids (including lipoproteins of interest)

Observed values and change from baseline values will be summarized at each scheduled time point. Summary plots of pre-infusion values over time for each lipid parameters will be provided.

2.4.8.9 Efficacy biomarkers

Chitotriosidase values will be normalized prior to study analyses based on the patient's chitotriosidase genotype:

Chitotriosidase genotype	Normalization of chitotriosidase activity
Normal	Reported value to be used
Heterozygous	Value multiplied by 2
Homozygous mutation	Value set to “no value”

Observed values, change from baseline and percent change from baseline for efficacy biomarkers will be summarized at each time point. Summary plots of observed values and change from baseline over time for each efficacy biomarker will be provided.

Chitotriosidase genotype and normalized chitotriosidase activity will be listed.

2.4.8.10 Bone disease assessments (Patients from adult study DFI13412)

Bone marrow burden

Observed values and change from baseline values will be summarized at each scheduled time point for total BMB score, total femur score and total spine score separately. Summary plots as well as by-patient plot of observed values over time will be provided.

DXA parameters

Observed values and change from baseline values will be summarized at each scheduled time point for BMD, T-score and Z-score by the region of femur and spine separately.

2.4.8.11 Bone biomarkers

Observed values and change from baseline will be summarized at each scheduled time point. Summary plots of observed values and change from baseline over time for each bone biomarkers will be provided.

2.4.8.12 Bone age by hand X-ray (Patients from pediatric study DFI13803)

For each patient at each scheduled baseline and post-baseline visits, the difference between the bone age and actual age at that visit will be calculated. Then the change from baseline in the bone age and actual age difference will be analyzed with analysis of covariance (ANCOVA) model with baseline bone age and actual age difference as covariate.

2.4.8.13 Tanner staging (Patients from pediatric study DFI13803)

This data will be provided in a data listing.

2.4.8.14 Height z-score (Patients from pediatric study DFI13803)

The height z-score categories will be summarized for all scheduled visits. Change from baseline in height z-score will be analyzed with analysis of covariance (ANCOVA) model with baseline height z-score as covariate.

2.4.8.15 Subgroup analyses for efficacy (Patients from pediatric study DFI13803)

For Patients from pediatric study DFI13803, below subgroup analyses will be performed.

To assess persistence of efficacy in patients with different baseline disease severity, the following subgroup analysis will be conducted:

- Spleen volume (MN) by baseline spleen volume severity (severe vs not severe). Severe patients is defined as baseline spleen volume >15 multiple of normal (MN).
- % predicted DLco by baseline % predicted DLco severity (severe vs not severe). Severe patients is defined by baseline % predicted DLco <40%.

To assess the impact of immunogenicity on efficacy, descriptive summaries for spleen volume and platelet count will be conducted for the following two groups of patients treated with olipudase alfa:

- Patients with treatment emergent anti-drug antibody (ADA) positive defined as either treatment induced or treatment boosted ADA positive at any time during olipudase alfa treatment.
- Patients with ADA negative defined as neither treatment induced or treatment boosted ADA positive at all time during olipudase alfa treatment.

For all the above subgroup analyses, within each subgroup, the change or percent change from baseline at each longitudinal time point will be summarized and analyzed with the analysis of covariance (ANCOVA) approach with baseline as covariate.

The efficacy measures (spleen volume and platelet count) will also be compared between manufacturing Process B, Process C ([redacted]) and Process C ([redacted]) as described below.

- To compare Process B and Process C ([redacted]), descriptive summaries for above efficacy measures will be created for the patients who started on Process C ([redacted]) only (patients never on Process B) versus patients who started on Process B and then switched to Process C ([redacted]) (Patients who were ever on Process B). In this analysis, the data when patients were exposed to Process C ([redacted]) will be excluded.
- Descriptive summaries for above efficacy measures will be created for the patients who did not switch to Process C ([redacted]) yet (patients never on Process C ([redacted])) versus patients who switched to Process C ([redacted]) (Patients ever on Process C ([redacted])).
- For patients who switched to Process C([redacted]) and patients who switched to Process C ([redacted]) separately, the individual patient plot of observed values at each time point for above efficacy measures will be created with time point for start of each process (B, C ([redacted]) and C ([redacted])) added on the plot.

2.4.9 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.9.1 Pharmacodynamic analysis

Pharmacodynamic endpoints include sphingomyelin and its metabolites, including sphingomyelin accumulation in liver tissue, along with ceramide in DBS. These endpoints will be analyzed using pharmacodynamics population. Observed and change from baseline values will be summarized at scheduled visits. Summary plots over time for pre-infusion values will be provided.

2.4.9.2 Pharmacokinetic analysis

Plasma concentration-time data will be analyzed by non-compartmental methods, or nonlinear mixed effects modeling, based upon patient age and data suitability. Values will be reported for individual patient and summarized by age group cohorts, dose level, manufacturing process and study week as appropriate.

For ease of presentation, mean values will be arithmetic mean unless specified. Concentration values below the plasma assay limit will be treated as zero in calculating mean values. Mean values below Lower Limit of Quantification (LLOQ) will be reported as LLOQ in the tables and not plotted in the figures if after C_{max}. Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers displayed in the tables. Values expressed in all tables will be for ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

Pharmacokinetic parameters of olipudase alfa may be summarized using descriptive statistics such as arithmetic mean, geometric mean, SD, standard error of the mean (SEM), coefficient of variation (CV [%]), minimum, median, maximum, and number of observations for each study visit, dose level and age group cohort under the responsibility of Pharmacokinetics, Dynamics and Metabolism (PKDM) using Phoenix WinNonlin Professional, Version 8.1, or NONMEM (VII or above) running on a Linux cluster.

Associations between ADA variables (eg, ADA status) and PK of olipudase alfa (eg, AUC) will be explored for olipudase alfa at selected PK visits. If applicable, plot of olipudase alfa PK (eg, AUC) versus the selected PK visit may be provided by ADA classifications for the olipudase alfa treatment group. Nab data may be explored as appropriate.

2.4.10 Analyses of health outcome questionnaires and cognitive and adaptive function

Patients from adult study DFI13412 fill out different questionnaires from the patients from the pediatric study DFI13803, hence these will be analyzed separately.

2.4.10.1 For patients from adult study DFI13412

Brief Fatigue Scale (BFI)

The severity and interference of fatigue as measured by BFI (individual questions as well as scale score) will be summarized separately, along with change from baseline, at each scheduled time point.

Brief Pain Scale (BFI) - SF

The severity and interference of pain as measured by BPI-SF (individual questions as well as scale score) will be summarized separately, along with change from baseline, at each scheduled time point.

Chronic Respiratory Disease Questionnaire (CRQ-SAS)

The 4 dimensions of CRQ-SAS - dyspnea, fatigue, emotional function, and the patient's feeling of control over the disease (mastery) - will be summarized separately, along with change from baseline, at each scheduled time point.

SF-36

The 8 scales measured by SF-36 - physical functioning, role physical, bodily pain, mental health, role emotional, social functioning, vitality, and general health - as well as the 2 summary measures of physical health (PCS) and mental health (MCS) will be summarized separately, along with change from baseline, at each scheduled time point.

Niemann-Pick B Health Assessment Questionnaire (NPB-HAQ)

Three domains of NPB-HAQ - resource utilization, symptoms and physical activity – will be summarized separately with each question at each scheduled time point.

- For resource utilization in the past year of each scheduled time point, the following measures will be summarized: the total nights spent in the hospital, the number of emergency room or urgent care visits.
- For symptom in the past month of each scheduled time point, frequency and level of bothersome of each symptom will be listed.
- For physical activity in each scheduled time point, the number and percentage of patients at each frequency of physical activities will be summarized.

2.4.10.2 For patients from pediatric study DFI13803

The patient transitioning from the pediatric study will use the age-appropriate questionnaires at the entry to the extension study. As the study progresses if the patients crosses the threshold of the questionnaire, the new age appropriate questionnaire will be used, until the maximal age range (young adult). Since the baseline of the original study may use a different questionnaire than what

is used in the extension study, the change from baseline summaries will not be produced; however, when the same questionnaire is used for baseline and post-baseline visit, summary of change from baseline will be provided.

PedsQL Generic Core Scales

Individual scale scores, Psychosocial Health Summary Score, Physical Health Summary Score and the Total Scale Score will be calculated based on the 0-100 scale scores. Their computed values will be summarized at each scheduled time point.

PedsQL Multidimensional Fatigue Scale

Individual scale scores and the Total Scale Score will be calculated based on the 0-100 scale scores. Their computed values will be summarized at each scheduled time point.

PedsQL Pediatric Pain Questionnaire

Only the first two items out of 3 items are scored based on the 100 mm VAS. The observed values will be summarized at each scheduled time point.

Developmental Profile (DP-3) and Adaptive Behavior Assessment System (ABAS-3)

A listing of DP-3 and ABAS-3 raw and generated scores will be provided.

For the DP-3, by-patient bar graphs will be generated to demonstrate subject's performance over time using percentile rank and standard score for each content area (Physical, Adaptive Behavior, Social-Emotional, Cognitive, Communication) and General Development Score at all scheduled visits.

For the ABAS-3, by-patient bar graphs will be generated to demonstrate subject's performance over time using percentile rank and standard scores for the General Adaptive Composite and three adaptive domains (Conceptual, Social, and Practical) at all scheduled visits.

In addition, to illustrate patient's performance on the DP-3 and ABAS-3 collectively, group graphs by patient age will be developed showing tool standard scores of patients over time. One graph for the ABAS-3 General Adaptive Composite Standard Score and one graph for the DP-3 General Development Score Standard Score.

2.5 PATIENT NARRATIVES

Patient narratives criteria for this study are as follows:

- Deaths
- Serious adverse event
- Adverse Events leading to permanent treatment discontinuation

- Adverse events of special interest including the followings:
  - Protocol defined IARs (as specified in Section 2.1.3.1)
  - Pregnancy of female patient or partner of a male patient
  - Symptomatic overdose of study drug
  - Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to olipudase alfa therapy) and > ULN
  - Any increase in total bilirubin or AP >1.5x baseline in the presence of AST or ALT >2x ULN
  - Any increase in ALT or AST >3x the ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness (for adults only), fever, rash, or eosinophilia (> ULN)
  - Patients from pediatric study DFI13803: asymptomatic overdose of study drug

Patients who meet these criteria will be listed and provided to the medical writer.

2.6 DATA HANDLING CONVENTIONS

2.6.1 General conventions

In general, the baseline value is defined as latest value prior to the start of first infusion of original study, except for hematology parameters and possibly ECG parameters. For hematology parameters, the baseline value is defined as the average of all available values before the start of first infusion from original study. Other exception may be the ECG parameters - Day 1/Week 0 (the first infusion visit) collects ECG in triplicate before the infusion; if 2 or more than 2 of these triplicate collections of ECG are before the first infusion, the average of these ECG parameter results from original study will be considered as the baseline value; otherwise, the baseline value of ECG parameters will be taken from the latest observation before the first infusion from original study.

Age at ASMD diagnosis = number of years between the date of birth and the date of ASMD diagnosis.

2.6.2 Missing data

In general, no imputation is planned for missing data. The following approaches are default methods for missing data handling. Some exploratory analyses can be planned with different strategies for treating missing outcomes.

- Categorical data at baseline will be summarized for each age group cohort using counts (n) and percentages (%). The number of patients with missing data may be mentioned, but will not be included in the denominator for the calculation of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

- 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 study treatment is reported on the last infusion page in e-CRF.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior to the start of first infusion or concomitantly with study, it will be considered a prior as well as a concomitant medication.

Handling of adverse events with missing data

- If the AE is missing start date and/or time, the treatment-emergent adverse event will be determined by the following conservative principle: An adverse event will be considered a treatment-emergent adverse event if it cannot be confirmed that the event is not a Treatment-emergent adverse event due to missing data.
- If the timing of AE with respect to infusion start and/or end time could not be determined unambiguously, the AE will be assumed to be an algorithm-defined IAR.
- If the assessment of the relationship is missing, then the relationship of possibly related is assumed for the summary table, but no imputation will be done at the data level.
- If the worst severity grade is missing, a missing category will be added in the summary table.

2.6.3 Windows for time points

Statistical analysis will be based on the nominal visit which should follow schedule defined in protocol Section 1. Visits will not be windowed for analysis purposes, except for unscheduled visits in some cases as described in Section 2.6.4.

2.6.4 Unscheduled visits

In general, unscheduled visit measurements will not be included in the by-visit summaries, but will be used for computation of baseline and/or summaries of “any time” or “end of study” time points. If a scheduled post-baseline visit measurement of an efficacy parameter is missing, but an unscheduled visit value for the same parameter is available within 3 months (91 days) of scheduled 6-month or 12-month visit, the unscheduled visit value will be used to substitute the missing scheduled visit value. If the parameter is scheduled for evaluation every 3 months, a 45 day window will be used instead of 91 days. If two unscheduled visits qualify for missing scheduled visit value, the one closest in date to target visit date will be used. Laboratory, vital signs, ECG and PD parameters are collected at several times during a visit with respect to the infusion time, therefore a window for an unscheduled visit to substitute missing schedule values will not be considered.

3 INTERIM ANALYSIS

No formal interim analysis is planned for this study. A formal summary of data or interim CSR may be produced to support regulatory approval(s) and/or other application/submission requirement(s). However, due to the nature of the open label study, this analysis will have no impact on primary and secondary objectives of this study.

4 DATABASE LOCK

The database is planned to be locked at about 30 days after the last patient last visit. A formal database lock may be performed to produce summary of data or interim CSR that may be needed to support regulatory approval(s) and/or other submission/application requirement(s).

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Version 9.0 or higher. The exact version used will be documented in the clinical study report.

6 REFERENCES

1. Global Lung Initiative (GLI) reference [Online]. [cited 2019 Nov 05]. Available from: URL:http://www.ers-education.org/guidelines/global-lung-function-initiative.aspx

2. Crapo RO, Morris AH. Standardized Single breath normal values for carbon Monoxide Diffusing Capacity. Am Rev Respir Dis. 1981;123:185-9.

3. Koopman M, Zanen P, Kruitwagen CL, van der Ent CK, Arets HG. Corrigendum to "Reference values for paediatric pulmonary function testing: The Utrecht dataset". Respir Med. 2011;105:1970-1.

4. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720-35.

5. Greulich, WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Standford, Calif.: Standford University Press; 1959.

6. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. Cancer. 1999;85:1186-96.

7. Cleeland, CS. The brief pain inventory. MD Anderson, TX. Copyright: 2009.

8. The self-administered chronic respiratory questionnaire standardized (CRQ_SAS) and individualized verison (CRQ-SAI) - background information and interviewing suggestions (version: 07 Jul 2015). McMaster University, Canada. Copyright: 2001.

9. Maruish ME. User's Manual for the SF-36v2 Health Survey. 3rd ed. Lincoln, RI: QualityMetric, Inc; 2011.

10. PedsQL Generic Core Scales scoring algorithm [Online]. [cited 2019 Nov 05]. Available from: URL:http://www.pedsql.org/

11. Aplern, GD. Developmental Profile 3 (DP-3). Los Angeles, CA: Western Psychological Services. 2007.

12. Harrison P, Oakland T. Adaptive behavior assessment system, Third Edition (ABAS-3). Los Angeles, CA: Western Psychological Services. 2015.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix A Potentially clinically significant abnormalities (PCSA) criteria

Measures	Adult criteria	Pediatric criteria
Liver function tests		
ALT	>3 * ULN >5 * ULN >10 * ULN >20 * ULN	Same as adult
AST	>3 * ULN >5 * ULN >10 * ULN >20 * ULN	Same as adult
Alkaline Phosphatase	>1.5 * ULN	Same as adult
Total Bilirubin	>1.5 * ULN >2 * ULN	≥1.3 ULN
ALT and Total Bilirubin	ALT >3 * ULN and Total Bilirubin >2 * ULN	Same as adult
Hematology		
WBC	<3.0 GIGA/L (non-Black), <2.0 GIGA/L (Black), ≥16.0 GIGA/L	12 years or above, but less than 18 years by age: <4.5 GIGA/L >13.5 GIGA/L 6 years or above, but less than 12 years by age: <5.0 GIGA/L >17.0 GIGA/L 2 years or above, but less than 6 years by age: <3.0 GIGA/L >16.0 GIGA/L 28 days/1 month to 23 months old <4.0 GIGA/L >20.0 GIGA/L

Measures	Adult criteria	Pediatric criteria
Lymphocytes	>4.0 GIGA/L	12 years or above, but less than 18 years by age: <0.6 GIGA/L >6.0 GIGA/L 6 years or above, but less than 12 years by age: <1.0 GIGA/L >8.0 GIGA/L 2 years or above, but less than 6 years by age: <1.0 GIGA/L >9.5 GIGA/L 28 days/1 month to 23 months old <2.0 GIGA/L >13.5 GIGA/L
Neutrophils	<1.5 GIGA/L (non-Black) <1.0 GIGA/L (Black)	2 years or above, but less than 18 years by age: <1.2 GIGA/L >1.0 ULN 28 days/1 month to 23 months old <1.0 GIGA/L (1-3 months) <1.2 GIGA/L (3-24 months) >1 ULN
Monocytes	>0.7 GIGA/L	N/A
Basophils	>0.1 GIGA/L	N/A
Eosinophils	>0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA /L	Same as adult
Hemoglobin	Males: ≤115 g/L (≤7.14 mmol/L) and 20% decrease from baseline; ≥185 g/L (≥11.48 mmol/L) Females: ≤95 g/L (≤5.9 mmol/L) and 20% decrease from baseline; ≥165 g/L (≥10.24 mmol/L) Decrease from Baseline ≥20 g/L (1.24 mmol/L)	24 months/2 years to <16/18 years old: <10.0 g/dL and 20% decrease from baseline, or decrease from baseline >=2 g/dL 28 days/1 month to 23 months old (Infants): <9.0 g/dL and 20% decrease from baseline, or decrease from baseline >=2 g/dL
Hematocrit	Males: ≤0.37 v/v and 20% decrease from baseline; ≥0.55 v/v Females: ≤0.32 v/v and 20% decrease from baseline; ≥0.5 v/v	2 years or above, but less than 18 years by age: <0.32 l/l or 32% >0.47 l/l or 47% 28 days/1 month to 23 months old <0.29 l/l or 29% >0.42 l/l or 42%
RBC	18 years or above by age ≥6 TERA/L	N/A
Platelets	<100 GIGA/L and 20% decrease from baseline ≥700 GIGA/L	Same as adult

Measures	Adult criteria	Pediatric criteria
Electrocardiogram		
HR	<=50 bpm and decrease from baseline >=20 bpm >=120 bpm and increase from baseline >=20 bpm	28 days/1 month to 23 months old (Infants) ≤80 bpm and decrease from 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
PR	>=200 ms and increase from baseline >=20 ms	12 years or above, but less than 18 years by age: >=180 ms 6 years or above, but less than 12 years by age: >=170 ms 2 years or above, but less than 6 years by age: >=160 ms 28 days/1 month to 23 months old (Infants) >=140 ms
QRS	>=120 ms	12 years or above, but less than 18 years by age: >=110 ms 6 years or above, but less than 12 years by age: >=100 ms 2 years or above, but less than 6 years by age: >=95 ms 28 days/1 month to 23 months old (Infants): >=85 ms
QTc	Absolute values (ms) Males Females Borderline 431-450 ms 451-470 ms Prolonged >450 ms >470 ms Additional ≥500 ms ≥500 ms Increase from baseline (all ages, all gender) Borderline: 30-60 ms Prolonged: >60 ms	12 years or above by age: Males Females Borderline 431-450 ms 451-470 ms Prolonged >450 ms >470 ms Additional ≥500 ms ≥500 ms Birth/0 to <12 years old: Borderline 431-450 ms Prolonged >450 ms Additional ≥500 ms Increase from baseline (all ages) Borderline: 30-60 ms Prolonged: >60 ms

Measures	Adult criteria	Pediatric criteria
Clinical chemistry		
Creatinine	>=150 µmol/L >=30% change from baseline >=100% change from baseline	12 years or above, but less than 18 years by age: >=132 µmol/L or 1.5 mg/dL 6 years or above, but less than 12 years by age: >=90 µmol/L or 1.1 mg/dL Birth/0 to <6 years old (Neonates, Infants, Children): >53 µmol/L or 0.6 mg/dL
Blood Urea Nitrogen (BUN)	>=17 mmol/L	28 days/1 month to Less than 18 years by age: >=6.4 mmol/L
Chloride	<80 mmol/L >115 mmol/L	Same as adult
Sodium	<=129 mmol/L >=160 mmol/L	<=129 mmol/L >=150 mmol/L
Potassium	<3 mmol/L >= 5.5 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		
Hypoglycaemia	18 years or above by age: <=3.9 mmol/L and <LLN	Less than 18 years by age: <2.7 mmol/L
Hyperglycaemia	18 years or above by age: >=11.1 mmol/L (unfasted), >7 mmol/L (fasted)	Less than 18 years by age: >=10.0 mmol/L (unfasted), >=7 mmol/L (fasted)
Albumin	18 years or above by age: <=25 g/L	N/A
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 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 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

Measures	Adult criteria	Pediatric criteria
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	12 years or above, but less than 18 years by age: <=90 mmHg and decrease from baseline >=20 mmHg >=119 mmHg and increase from baseline >=20 mmHg 6 years or above, but less than 12 years by age: <=80 mmHg and decrease from baseline >=20 mmHg >=108 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 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
DBP	<=45 mmHg and decrease from baseline>=10 mmHg >=110 mmHg and increase from baseline >=10 mmHg	12 years or above, but less than 18 years by age: <=54 mmHg and decrease from baseline >=10 mmHg >=78 mmHg and increase from baseline >=10 mmHg 6 years or above, but less than 12 years by age: <=48 mmHg and decrease from baseline >=10 mmHg >=72 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 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
Urinalysis		
pH	18 years or above by age: ≤4.6, ≥8	N/A

Signature Page for VV-CLIN-0239885 v3.0
lts13632-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	