NCT02004704

AMENDED CLINICAL TRIAL PROTOCOL NO. 07

COMPOUND: olipudase alfa / GZ402665

A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency

STUDY NUMBER: LTS13632

VERSION DATE / STATUS: 15-Apr-2022 / Final

CLINICAL STUDY DIRECTOR: [redacted]

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, Version
Amended Clinical Trial Protocol 07	All	15-Apr-2022, Version 1 (electronic 10.0)
Amended Clinical Trial Protocol 06	All	29-Jan-2021, Version 1 (electronic 9.0)
Amended Clinical Trial Protocol 05	All	18-Aug-2020, Version 1 (electronic 8.0)
Amended Clinical Trial Protocol 04	All	31-Jul-2019, Version 1 (electronic 6.0)
Amended Clinical Trial Protocol 03	All	25-Apr-2018, Version 1 (electronic 5.0)
Protocol Amendment 03	All	25-Apr-2018, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	All	25-Apr-2017, Version 1 (electronic 4.0)
Protocol Amendment 02	All	25-Apr-2017, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	23-Mar-2016, Version 1 (electronic 3.0)
Protocol Amendment 01	All	23-Mar-2016, Version 2 (electronic 3.0)
Clinical Trial Protocol	All	02-Apr-2013, Version 1 (electronic 1.0)

Amended Clinical Trial Protocol 07 (15-Apr-2022)

This amended protocol (07) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment are described below:

- To allow the continuity of treatment with olipudase alfa in the time frame between local Regulatory approval and commercial accessibility by clarifying the duration of study treatment.
- To comply with the requirements agreed in the olipudase alfa Pediatric Investigational Plan (PIP).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary - Study Design	Language updated: • Patients will receive olipudase alfa every 2 weeks for 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This duration will ensure a maximum 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated with olipudase alfa in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.	• To allow the continuity of treatment with olipudase alfa in the time frame between local Regulatory approval and commercial accessibility • To comply with the agreed PIP
Clinical Trial Summary - Duration of Study Period (Per Patient)	Language updated: • The maximum study duration per patient is 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between the local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with	• To allow the continuity of treatment with olipudase alfa in the time frame between Regulatory approval and commercial accessibility • To comply with the agreed PIP

Section # and Name	Description of Change	Brief Rationale
	olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa. An EOT visit after the last administered dose of study treatment and a safety follow-up phone call 30 to 37 days after the last administered dose of study treatment will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.	
Section 4.2 Study Rationale	Language updated and order of paragraphs rearranged for readability: • The current study is an open-label, long-term treatment study planned for 9 years, or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years to comply with the agreed PIP. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.	• To allow the continuity of treatment with olipudase alfa in the time frame between Regulatory approval and commercial accessibility. • To comply with the agreed PIP
Section 6 Study Design	Language updated and sub-headers (Treatment Period and DMC) added for readabillity: • Enrolled patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years, or until	• To allow the continuity of treatment with olipudase alfa in the time frame between Regulatory approval

Section # and Name	Description of Change	Brief Rationale
	olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.	and commercial accessibility. • To comply with the agreed PIP
Section 6.1.1 Treatment period	Language updated and sub-headers (Treatment Period and Schedule of Assessments) added for readability: • During the treatment period, patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.	• To allow the continuity of treatment with olipudase alfa in the time frame between Regulatory approval and commercial accessibility. • To comply with the agreed PIP

Section # and Name	Description of Change	Brief Rationale
Section 6.1.2 Post treatment period	Language updated: For patients completing or discontinuing/withdrawing from the study, there will be a post-treatment period consisting of an end of treatment (EOT) visit 2 weeks (±7 days) after the last administered dose of study treatment and a safety follow-up phone call 30 to 37 days after the last administered dose of study treatment. An end-of-treatment visit and a safety follow up phone call will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.	To reflect amendment-specific changes.
Section 6.3 Duration of Study Participation	Language updated: • Treatment period of 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years.	• To allow the continuity of treatment with olipudase alfa in the time frame between Regulatory approval and commercial accessibility. • To comply with the agreed PIP
Section 6.3 Duration of Study Participation	Language updated for clarification: Follow up period concluded with a safety follow up phone call 30 to 37 days after the patient's last infusion in the LTS13632 study. A safety follow-up phone call will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.	To reflect amendment-specific changes.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary – Study Design and Duration Of Study Period (per patient); Section 6 Study Design; Section 6.1.1 Treatment Period; Section 6.3 Duration of study participation	Removal of the following text: If marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's approval, in accordance with local regulations.	Olipudase alfa is in the process of being submitted worldwide, so the statement regarding marketing approval not being available is no longer applicable.
Section 4.2 Study Rationale	Removal of the following text: If marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's and health authorities' approval, in accordance with local regulations.	Olipudase alfa is in the process of being submitted worldwide, so the statement regarding marketing approval not being available is no longer applicable.
Section 11.1.1	Section number has been updated.	Formatting
Section 17.2 - Appendix B Protocol Amendment History	The numbering of this section has been updated. Due to addition of amendment history for Amended Clinical Trial Protocol 06 (29-Jan-2021) as sub-section 17.2.1, all further sub-sections were re-numbered accordingly.	To conform with the usual process for amendment history.

CLINICAL TRIAL SUMMARY

COMPOUND: olipudase alfa (recombinant human acid sphingomyelinase / GZ402665)	**STUDY No:** GZ402665 (LTS13632)
TITLE	A long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency
INVESTIGATOR/TRIAL LOCATION	Multinational, multicenter
PHASE OF DEVELOPMENT	2
STUDY OBJECTIVE(S)	Primary objective The primary objective of this study is to obtain data regarding the safety of olipudase alfa in patients with acid sphingomyelinase deficiency (ASMD) who are exposed to long-term treatment with olipudase alfa. Secondary objective(s) The secondary objectives of this study are to obtain data regarding the efficacy of olipudase alfa and to characterize olipudase alfa pharmacodynamics (PD) and pharmacokinetics (PK) following long-term administration.
STUDY DESIGN	This is a multinational, multicenter, nonrandomized, open-label, long-term treatment study of patients who have previously participated in a study of olipudase alfa. • Patients will receive olipudase alfa every 2 weeks for 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term “commercially accessible” is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa. Patients will start this study at the same dose they were receiving at the end of their primary study, provided that they have not missed more than 1 biweekly dose between studies. During the study, for pediatric patients who will reach adult age (18 years old) will receive the adult infusion volume.

STUDY POPULATION Main selection criteria	Inclusion criteria To enter this study, patients must have fulfilled the following criteria: • The patient completed the treatment period of a previous study of olipudase alfa with an acceptable safety profile in the opinion of the investigator and sponsor. • The patient and/or the patient's parent(s)/legal guardian(s) is willing and able to provide signed written informed consent. • The patient who is female and of childbearing potential must have a negative urine pregnancy test for beta human chorionic gonadotropin (β-HCG). • Female patients of childbearing potential and sexually mature male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle or use 2 acceptable effective methods of contraception up to 15 days following their last dose of study drug.
	Exclusion criteria Exclusion criteria related to study methodology: • The patient has any new condition or worsening of an existing condition which in the opinion of the investigator would make the patient unsuitable for enrollment or could interfere with the patient participating in or completing the study. • The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study. • The patient is unwilling or unable to abstain from the use of alcohol for 1 day prior to and 3 days after each olipudase alfa infusion for the duration of the treatment period. • The patient is unwilling or unable to avoid, for 10 days before and 3 days after liver biopsies, medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, antidepressants, kava, echinacea) or may cause or prolong bleeding (eg, anticoagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng) (only patients who previously participated in the DFI13412 study). Exclusion criteria related to the current knowledge of the compound and condition: • The patient requires medication(s) that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, desipramine]).
Total expected number of patients	Approximately 25 patients. 5 adult patients rolled over from study DFI13412 and approximately 20 pediatric patients expected to roll over from study DFI13803
STUDY TREATMENT(s)	
Investigational medicinal product(s) Formulation	Olipudase alfa (recombinant human acid sphingomyelinase; GZ402665) Sterile lyophilized powder administered by intravenous (IV) infusion following reconstitution and dilution. During clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process. The different processes are referred to as Process B, C([redacted]) and C([redacted]).

Route(s) of administration	IV infusion.
Dose regimen	Patients will receive an IV infusion of olipudase alfa every 2 weeks (± 3 days). Home infusion may be possible. Patients must meet specific eligibility requirements. In addition, the investigator and the sponsor must agree that home infusion is appropriate. Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home.Patients will continue their current dose if they have not missed more than 1 dose between studies. Dose reintroduction regimens may be required for patients who have missed more than 1 dose between studies or during this study, depending on their usual dose. For patients receiving home infusions who have missed 2 or fewer doses, the investigator can decide whether reintroduction should occur at the hospital/study site or via home infusion. For patients who have missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the hospital/study site. If the site visit is not possible, During a regional or national emergency declared by a governmental agency, such as the COVID-19 pandemic, due to site closure or extenuating circumstances that prevent an in-person site visit, reintroduction may be done via home infusion in compliance with applicable country-specific regulations.
ENDPOINT(S)	Primary endpoints Data pertaining to the safety and tolerability of olipudase alfa • Assessment of adverse events (AEs)/treatment-emergent adverse events (TEAEs), including infusion-associated reactions (IARs) and Adverse Events of Special Interest (AESI). • Complete Physical examinations. • Extended Neurologic examinations. • Abbreviated Physical Exam • Weight. • Height (pediatric patients only). • Vital sign measurements. • Clinical laboratory tests. • Electrocardiograms (ECGs). • Doppler echocardiography. • Safety biomarkers. • Liver biopsy (only patients who previously participated in the DFI13412 study). • Liver ultrasound with Doppler (only patients who previously participated in DFI13803). • Immune response assessments. Secondary endpoints (efficacy) • Abdominal magnetic resonance imaging (MRI) to evaluate improvements in spleen and liver volume. • Pulmonary imaging (high-resolution computed tomography [HRCT]. and chest X-ray [at selected sites]). • Pulmonary function test.

	• Hematology (hemoglobin and platelet count). • Lipid profile. • Health outcome questionnaires (adult and Pediatric). • Hand X-ray for bone age and bone maturation (pediatric patients). • Linear patient growth by height Z-score (pediatric patients). Other endpoints • Physician's global assessment of change. • Cognitive and adaptive function (pediatric patients who performed the assessments in DFI13803) • Cycle ergometry. • Efficacy biomarkers. • Bone disease assessments (only patients who previously participated in the DFI13412 study). • Bone biomarkers. • Tanner staging (pediatric patients). • Photographs (optional). Pharmacokinetics Plasma parameters, including Cmax, AUClast, AUC0-∞, t1/2z, CL and Vss. Pharmacodynamics • Sphingomyelin in liver tissue (only in adults) and plasma. • Metabolites levels in plasma and dried blood spot (DBS).
ASSESSMENT SCHEDULE	Patients will be enrolled directly from their previous study. (Note: The term "pediatric patients only" means patients coming from the original pediatric trial, DFI13803. Some of these patients will reach adult age [18 years old] while in this study. These patients will be adults by age, but they will remain part of the "pediatric patient" cohort.) In case of more than 3 infusions missed between trials, assessments (eg, efficacy biomarkers, sphingomyelin and metabolites) may be repeated at study entry. Patients who require dose reintroduction will have these assessments at each infusion until reaching their usual dose of olipudase alfa: • Before infusion: vital sign measurements, liver function tests (LFTs), hematology, and safety biomarkers. • Immediately after infusion: vital sign measurements. • 24 hours after infusion: vital sign measurements, LFTs, and safety biomarkers. • 48 hours after infusion: vital sign measurements, LFTs and safety biomarkers. The 48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for regulatory submissions in 2021. During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is >2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can

	be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment. Baseline is defined as the following: • For initial dose escalation: last values prior to first dose of olipudase alfa • For dose re-escalation: last values prior to the first re-escalation dose Safety will be monitored continuously. Safety and efficacy assessments will occur regularly every 3, 6, 9, and 12 months. In the first 5 years, pharmacodynamic (PD) evaluations will occur every 3 months then every 6 months after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. After 5 years, PD evaluations will occur every 12 months. PK evaluation will occur every 12 months only in the first 5 years and upon introduction of Process C(■) or Process C(■) at any time during the study. For patients completing or discontinuing/withdrawing from the study, there will be a post treatment period consisting of an end-of-treatment (EOT) visit 2 weeks (±7 days) after the last administered dose of olipudase alfa and a safety follow-up phone call 30 to 37 days after the last administered dose.
STATISTICAL CONSIDERATIONS	**Sample size determination** 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 of the LTS13632 study, and meet the eligibility criteria. It is expected that the sample size for this study will be approximately 25. **Analysis populations** The safety set will include all enrolled patients who received at least 1 dose (partial or total) of olipudase alfa in the current study. **Analysis of safety** Safety analyses will include a summary of treatment duration, the total number of infusions received, and the total amount of olipudase alfa received. Frequencies (number and percentage) of patients with 1 or more treatment-emergent AEs will be summarized by the Medical Dictionary for Regulatory Activities System Organ Class (SOC) and preferred term (PT). All treatment-emergent AEs, all treatment-emergent AEs potentially related to olipudase alfa, all treatment-emergent AEs leading to treatment discontinuation and study discontinuation, all treatment-emergent AEs that are infusion-associated reactions, all treatment--emergent serious adverse events (SAEs) (including treatment-related SAEs), and all AEs with fatal outcomes (including fatal treatment-emergent AEs) will be summarized. Other safety variables, including laboratory parameters and vital sign measurements, will be summarized by study visit and by dose. The PK analysis will include all patients who receive at least 1 infusion of study drug after PK analysis informed consent and have evaluable PK data. Other analysis populations, such as for pharmacogenomics, if any, will be defined in the SAP.

	Analysis of secondary endpoints Summary statistics for the values, nominal change from baseline, and percent change from baseline will be presented for efficacy assessments at various study time points. The association between changes in efficacy parameters and total amount of drug received will be examined. Plasma concentration-time data will be analyzed using actual dosing and sampling times by noncompartmental methods. Pharmacokinetic parameters will be calculated for each patient and summarized by dose level and study week. As data permit, PK parameters may also be evaluated across dose level at each manufacturing scale. Metabolite levels will be summarized by dose level and time point using descriptive statistics.
DURATION OF STUDY PERIOD (per patient)	• The maximum study duration per patient is 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible. • The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days. • This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment. • Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years. • The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa. An EOT visit after the last administered dose of study treatment and a safety follow-up phone call 30 to 37 days after the last administered dose of study treatment will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.
STUDY COMMITTEES	Independent data monitoring committee (DMC).

1 STUDY FLOW CHARTS

Table 1 and Table 3 are the study flow charts for adult patients coming from study DFI13412, corresponding to the period Year 1 to Year 5 and beyond Year 5, respectively. Complementary flow charts have been added for the changes to be effective after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (Table 2 and Table 4). Table 5, Table 7, and Table 9 are the study flow charts for pediatric patients coming from the pediatric study DFI13803 and correspond to Year 1, Year 2 through Year 5, and beyond Year 5, respectively. Complementary flow charts have been added for the changes to be effective after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (Table 6, and Table 10). Table 11 and Table 12 are the pharmacokinetic (PK) sampling schedules for adults and pediatric patients, respectively.

Patients will be enrolled directly from their previous study after providing informed consent.

In case of more than 3 infusions missed between trials, assessments (eg, efficacy biomarkers, sphingomyelin and metabolites) may be repeated at study entry. The investigator, after discussion with the sponsor, may order individualized assessments before the patient receives the first infusion in this study.

Dose reintroduction regimens may be required for patients who have missed more than 1 dose between studies or during this study (LTS13632), depending on their usual dose. For patients receiving home infusions who have missed 2 or fewer doses, the investigator can decide whether reintroduction should occur at the hospital/study site or via home infusion. For patients who miss 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the study site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, reintroduction can occur via home infusion in compliance with applicable country-specific regulations.

Patients who require dose reintroduction will have these assessments at each infusion until reaching their usual dose of olipudase alfa:

- Before infusion: vital sign measurements, liver function tests (LFTs), hematology, and safety biomarkers.
- Immediately after infusion: vital sign measurements.
- 24 hours after infusion: vital sign measurements, LFTs, hematology, and safety biomarkers.
- 48 hours after infusion: vital sign measurements, LFTs, hematology, and safety biomarkers.
  The 48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is >2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment.

Baseline is defined as the following:

- For initial dose escalation: last values prior to first dose of olipudase alfa
- For dose re-escalation: last values prior to the first re-escalation dose

For a new manufacturing scale, if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion under the new manufacturing scale. For introduction of drug product from Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). If introduction of Process C([redacted]) occurs, sample collection of anti olipudase alfa antibody (IgG) will be monthly for the first 6 months after introducing the drug product from Process C([redacted]) then quarterly after that.

If a PK or IgG sample collection for the planned introduction of drug product from Process C([redacted]) was erroneously taken, the future sample collection will be adjusted to the blood volume per each age cohort in order to avoid excessive blood withdrawal. For specific details, please refer to Study Manual. See Section 9.3.8 for time points and additional information.

1.1 FLOW CHART FOR ADULTS: YEAR 1 THROUGH YEAR 5

Table 1 - Study flow chart for former patients from the DFI13412 study - Year 1 through Year 5 - only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination			X		X	X	
Extended neurological examination					X	X	
Abbreviated physical examination	X	X		X			
	Before and after each infusion						
Weight[d]	Before each infusion					X	
Height					X	X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[e]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X	X	X	X	X	
Hemoglobin level and platelet count[f]			X		X	X	
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[e, g]			X		X	X	
Doppler echocardiography					X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin, plasma ceramide)		X	X	X	X	X	
Abdominal MRI (liver and spleen volumes)			X (first 2 years)[h]		X	X	
Chest HRCT					X	X	
Chest X-ray[i]					X	X	
Pulmonary function tests (FVC,FEV_1,DL_{CO},TLC)[j]			X (first 2 years)[h]		X	X	
Cycle ergometry[j]			X (first 2 years)		X	X	
Physician global assessment			X (first 2 years)		X	X	
Efficacy biomarkers (serum chitotriosidase, CCL18)		X	X	X	X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)		X	X	X	X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X (first 2 years)	X	X (first 2 years)	X	X	
Metabolite levels in plasma		X	X	X	X	X	
Metabolite levels in dried blood spot		X	X	X	X	X	
Patient photographs (optional)					X		
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Lumbar spine and bilateral femur MRI					X	X	
Lumbar spine and bilateral femur DXA					X	X	
Adult health outcome questionnaires (BFI, BPI-SF, SFCRQ-SAS, SF-36, NPB-HAQv2)			X (first 2 years)		X	X	
Pharmacokinetics[e, k]					X		
	See Section 1.6 and Table 11						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Sphingomyelin in liver tissue (liver biopsy)	A liver biopsy will be performed after at least 3 years in the study for patients who previously participated in the DFI13412 study						
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after starting the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, NPB HAQ, abdominal MRI, HRCT, chest X-ray, pulmonary function tests, cycle ergometry, and Doppler echocardiography will not be repeated if they had been done within 3 months prior. DXA and bone MRI will not be repeated if they were done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d Weight at previous onsite visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

e At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).
f As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests.
g Patients must rest in the supine position for 510 minutes prior to and during all electrocardiograms.
h During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), an abdominal MRI and pulmonary function tests (PFTs) will be performed at the first 6-month visit after the change, but only if that 6-month visit is not a 12-month visit at which the assessment is already scheduled.
i Only at selected sites.
j Assessments should be performed at the same time (±2 hours) to ensure consistency.
k Pharmacokinetic testing will only occur yearly and during the study period, for the switch from Process B to Process C or from Process C([redacted]) to the updated manufacturing process C([redacted]). For introduction of process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion of Process C([redacted]) IMP. In case reintroduction of olipudase alfa coincides with introduction of Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under Process C([redacted]). For schedule of PK assessment in adults, see Section 1.6, Table 11.

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; BFI=Brief Fatigue Inventory; BPI-SF=Brief Pain Inventory- Short Form; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DXA=dual-energy X-ray absorptiometry; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; NPB-HAQv2=Niemann-Pick B Health Assessment Questionnaire, version 2; SF=short form; SFCRQ-SAS=Chronic Respiratory Disease Questionnaire Self-administered Standardized; TLC=total lung capacity; VLDL=very low-density lipoprotein.

Table 2 - Study flow chart for former patients from the DFI13412 study - Year 1 through Year 5 - only applicable after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination			X		X	X	
Extended neurological examination					X	X	
Abbreviated physical examination	X	X		X			
	Before and after each infusion						
Weight[d]	Before each infusion					X	
Height					X	X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[e]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X	X	X	X	X	
Hemoglobin level and platelet count[f]			X		X	X	
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[e, g]			X		X	X	
Doppler echocardiography					X	X	
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin)		X	X	X	X	X	
Abdominal MRI (liver and spleen volumes)			X		X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
			(first 2 years)[h]				
Chest HRCT					X	X	
Chest X-ray[i]					X	X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[j]			X (first 2 years)[h]		X	X	
Cycle ergometry[j]			X (first 2 years)		X	X	
Physician global assessment			X (first 2 years)		X	X	
Efficacy biomarkers (serum chitotriosidase, CCL18)			X		X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)			X		X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X (first 2 years)	X	X (first 2 years)	X	X	
Metabolite levels in plasma (ceramide, lyso-sphingomyelin)			X		X	X	
Patient photographs (optional)					X		
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Lumbar spine and bilateral femur MRI					X	X	
Lumbar spine and bilateral femur DXA					X	X	
Adult health outcome questionnaires (BFI, BPI-SF, SFCRQ-SAS, SF-36, NPB-HAQv2)			X (first 2 years)		X	X	
Pharmacokinetics[k]					X		
	See Section 1.6 and Table 11						
Sphingomyelin in liver tissue (liver biopsy)	A liver biopsy will be performed after at least 3 years in the study for patients who previously participated in the DFI13412 study						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after starting the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; BFI=Brief Fatigue Inventory; BPI-SF=Brief Pain Inventory- Short Form; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DXA=dual-energy X-ray absorptiometry; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; NPB-HAQv2=Niemann-Pick B Health Assessment Questionnaire, version 2; SF=short form; SFCRQ-SAS=Chronic Respiratory Disease Questionnaire Self-administered Standardized; TLC=total lung capacity; VLDL=very low-density lipoprotein.

a Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, NPB HAQ, abdominal MRI, HRCT, chest X-ray, pulmonary function tests, cycle ergometry, and Doppler echocardiography will not be repeated if they had been done within 3 months prior. DXA and bone MRI will not be repeated if they were done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

e At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).

f As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests.

g Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

h Upon a manufacturing scale change, an abdominal MRI and pulmonary function tests (PFTs) will be performed at the first 6-month visit after the change, but only if that 6-month visit is not a 12-month visit at which the assessment is already scheduled.

i Only at selected sites.

j Assessments should be performed at the same time (±2 hours) to ensure consistency.

k Pharmacokinetic testing will only occur yearly and upon introduction of Process C([redacted]) or Process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion under Process C([redacted]). For the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under [redacted] In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under Process C([redacted]) or Process C([redacted]). For schedule of PK assessment in adults, see Section 1.6, Table 11.

1.2 FLOWCHART FOR ADULTS: BEYOND YEAR 5

Table 3 - Study flow chart for former patients from DFI13412 - beyond Year 5 - only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination					X	X	
Extended neurological examination					X	X	
Abbreviated physical examination	X						
	Before and after each infusion						
Weight[d]		X	X	X	X	X	
Height					X	X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[e]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)			X		X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Hematology, Hemoglobin level and platelet count	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), 2 samples will be taken during an infusion 3 months after introducing the new process, one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.						
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[e, f]					X	X	
Safety biomarkers (hsCRP, iron, ferritin, calcitonin, plasma ceramide)			X		X	X	
Abdominal MRI (liver and spleen volumes)					X	X	
Chest HRCT					X	X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[g]					X	X	
Physician global assessment					X	X	
Efficacy biomarkers (serum chitotriosidase, CCL18)					X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])					X	X	
Metabolite levels in plasma					X	X	
Patient photographs (optional)					X		
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Olipudase alfa infusion	X	X	X	X	X		
Adult health outcome questionnaires (BFI, BPI SF, SFCRQ SAS, SF-36)					X	X	
Pharmacokinetics[h]							
Immune response assessments							
Anti olipudase alfa antibody (IgG)	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after introducing the new process and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific

regulations.

b All patients will have a visit 2 weeks (±3 days) after the last dose of study treatment. For the end of study/early discontinuation visit, all "beyond Year 5" assessments will not be repeated if they had been done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

e At time points when multiple assessments are scheduled, the order will be: vital sign measurements then electrocardiogram.

f Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

g Assessments should be performed at the same time (±2 hours) to ensure consistency.

h Beyond 5 years, pharmacokinetic testing will only occur upon introduction of Process C([redacted]) or Process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under Process B and at the first infusion under Process C([redacted]). For the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in adults, see Section 1.6, Table 11.

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; BFI=Brief Fatigue Inventory; BPI-SF=Brief Pain Inventory- Short Form; DL_{CO}=diffusing capacity of the lung for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; SF=short form; SFCRQ-SAS=Chronic Respiratory Disease Questionnaire Self-administered Standardized; TLC=total lung capacity; VLDL=very low-density lipoprotein.

Table 4 - Study flow chart for former patients from DFI13412 - beyond Year 5 - only applicable after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination					X	X	
Extended neurological examination					X	X	
Abbreviated physical examination	X						
	Before and after each infusion						
Weight[d]		X	X	X	X	X	
Height					X	X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[e]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)			X		X	X	
Hematology, hemoglobin level and platelet count	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), 2 samples will be taken during an infusion 3 months after introducing Process C([redacted]) or Process C([redacted]), one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[e, f]					X	X	
Safety biomarkers (hsCRP, iron, ferritin, calcitonin, plasma)			X		X	X	
Abdominal MRI (liver and spleen volumes)					X	X	
Chest HRCT					X	X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[g]					X	X	
Physician global assessment					X	X	
serum chitotriosidase, CCL18					X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])					X	X	
Metabolite levels in plasma (ceramide, lyso-sphingomyelin)					X	X	
Patient photographs (optional)					X		
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Adult health outcome questionnaires (BFI, BPI SF, SFCRQ SAS, SF-36)					X	X	
Pharmacokinetics[h]							

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2-week visit (±3 days)[a]**	**Every 3-month visit (±14 days)[a]**	**Every 6-month visit (±14 days)[a]**	**Every 9-month visit (±14 days)[a]**	**Every 12 month visit (±14 days)[a]**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Immune response assessments							
Anti olipudase alfa antibody (IgG)	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), Collection will be monthly for the first 6 months after introducing the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; BFI=Brief Fatigue Inventory; BPI-SF=Brief Pain Inventory- Short Form; DL_{CO}=diffusing capacity of the lung for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; SF=short form; SFCRQ-SAS=Chronic Respiratory Disease Questionnaire Self-administered Standardized; TLC=total lung capacity; VLDL=very low-density lipoprotein.

a Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±3 days) after the last dose of study treatment. For the end of study/early discontinuation visit, all "beyond Year 5" assessments will not be repeated if

they had been done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

e At time points when multiple assessments are scheduled, the order will be: vital sign measurements then electrocardiogram.

f Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

g Assessments should be performed at the same time (±2 hours) to ensure consistency.

h Beyond 5 years, upon introduction of Process C([redacted]) or Process C([redacted]), for Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the Process B and at the first infusion under Process C([redacted]). For the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in adults, see Section 1.6, Table 11.

1.3 FLOW CHART FOR PEDIATRIC (FORMER DFI13803) PATIENTS: YEAR 1

The term "pediatric patients" means patients coming from the original pediatric trial, DFI13803. Some of these patients will reach adult age (18 years old) while in this study. These patients will be adults by age, but they will remain part of the "pediatric patient" cohort.

Table 5 - Study flow chart for former DFI13803 patients - Year 1 - only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination		X		X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X		X		X		
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, LFTs, hematology, coagulation, urinalysis)		X	X	X	X	X	
Hemoglobin level and platelet count[g]		X		X		X	
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f, h]		X		X		X	
Doppler echocardiography				X		X	
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin, plasma ceramide)		X	X	X	X	X	
Abdominal MRI (liver and spleen volumes)		X		X		X	
Chest HRCT				X		X	
Chest X-ray[i]				X		X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[j, k]		X		X		X	
Physician global assessment		X		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Efficacy biomarkers (serum chitotriosidase, CCL18)		X	X	X	X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)[k]		X	X	X	X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X	X	X	X	X	
Metabolite levels in plasma		X	X	X	X	X	
Metabolite levels in dried blood spot[k]		X	X	X	X	X	
Patient photographs (optional)				X		X	
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.					X	
Olipudase alfa infusion	X	X	X	X	X		
Liver ultrasound with Doppler		X		X		X	
Hand X-ray for bone age		X		X		X	
Tanner staging		X		X		X	
Cognitive and adaptive function (for patients who performed the assessment in DFI13803 (DP-3 and ABAS)		X		X		X	
Linear patient growth by height Z-score		X		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)		X		X		X	
Pharmacokinetics[f, l]				X			
	See Section 1.6 and Table 12						
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after introducing the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an

acceptable alternative to site visits if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, abdominal MRI, HRCT, chest X-ray, pulmonary function tests (PFTs) , Doppler echocardiography, hand X-ray, and pediatric health outcome questionnaires will not be repeated if they had been done within the prior 3 months.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits. Body mass index (BMI) will be calculated.

f At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).

g As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests. If drug product from a manufacturing scale change or an updated manufacturing process is administered, 2 samples will be taken during an infusion 3 months after introducing the new scale or the updated manufactured process one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.

h Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

i Only at selected sites

j Assessments should be performed at the same time (±2 hours) to ensure consistency.

k Only for patients for whom it was done in DFI13803.

l Pharmacokinetic testing will only occur yearly and upon introduction of a manufacturing scale change from Process B to Process C([redacted]) or from Process C([redacted]) to the updated manufacturing process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under Process B and at the first infusion under Process C([redacted]). For the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in children, see Section 1.6, Table 12.

ABAS=Adaptive Behavior Assessment System; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DP-3=Development Profile-Third Edition; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

Table 6 - Study flow chart for former DFI13803 patients - Year 1 - only applicable after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Note: The informed consent form must be signed and the inclusion/exclusion criteria must be verified prior to the patient's first visit.							
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study. Concomitant medications that the patient is taking when the written informed consent is signed and up to 30 days prior should be reported in this study.						
Complete physical examination		X		X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X		X		X		
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, LFTs, hematology, coagulation, urinalysis)		X	X	X	X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Hemoglobin level and platelet count[g]		X		X		X	
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f, h]		X		X		X	
Doppler echocardiography				X		X	
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin,)		X	X	X	X	X	
Abdominal MRI (liver and spleen volumes)		X		X		X	
Chest HRCT				X		X	
Chest X-ray[i]				X		X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[j]		X		X		X	
Physician global assessment		X		X		X	
serum chitotriosidase, CCL18			X		X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)			X		X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X	X	X	X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Metabolite levels in plasma (ceramide, lyso-sphingomyelin)			X		X	X	
Patient photographs (optional)				X		X	
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.					X	
Olipudase alfa infusion	X	X	X	X	X		
Liver ultrasound with Doppler		X		X		X	
Hand X-ray for bone age		X		X		X	
Tanner staging		X		X		X	
Cognitive and adaptive function (for patients who performed the assessment in DFI13803 (DP-3 and ABAS)		X		X		X	
Linear patient growth by height Z-score		X		X		X	
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)		X		X		X	
Pharmacokinetics[f, k]				X			
	See Section 1.6 and Table 12						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**W14[a] QV (±14 days)**	**W26[a] QV (±14 days)**	**W38[a] QV (±14 days)**	**W52[a] QV (±14 days)**	**Study completion, patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after introducing the drug product from the new process and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. Patients will receive olipudase alfa every 2 weeks (±3 days). Quarterly visits will occur at the site If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, abdominal MRI, HRCT, chest X-ray, pulmonary function tests (PFTs) , Doppler echocardiography, hand X-ray, and pediatric health outcome questionnaires will not be repeated if they had been done within the prior 3 months.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits. Body mass index (BMI) will be calculated.
f At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).
g As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests. If drug product from a manufacturing scale change or an updated manufacturing process is administered, 2 samples will be taken during an infusion 3 months after introducing the new scale or the updated manufactured process one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.
h Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.
i Only at selected sites
j Assessments should be performed at the same time (±2 hours) to ensure consistency.
k Pharmacokinetic testing will only occur yearly and upon introduction of a manufacturing scale change from Process B to Process C([redacted]) or from Process C([redacted]) to the updated manufacturing process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under Process B and at the first infusion under Process C([redacted]). For the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in children, see Section 1.6, Table 12.

ABAS=Adaptive Behavior Assessment System; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DP-3=Development Profile-Third Edition; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

1.4 FLOW CHART FOR PEDIATRIC (FORMER DFI13803) PATIENTS: YEAR 2 THROUGH YEAR 5

The term "pediatric patients" means patients coming from the original pediatric trial, DFI13803. Some of these patients will reach adult age (18 years old) while in this study. These patients will be adults by age, but they will remain part of the "pediatric patient" cohort.

Table 7 - Study flow chart for former DFI13803 patients - Year 2 through Year 5 - only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study.						
Complete physical examination		X		X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X		X		X		
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X	X	X	X	X	
Hemoglobin level and platelet count[g]		X		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						Patient discontinuation, or withdrawal[b]	Safety follow-up phone call[c]
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f,h]		X		X		X	
Doppler echocardiography				X		X	
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin, plasma ceramide)		X	X	X	X	X	
Abdominal MRI (liver and spleen volumes)[i]		X (Year 2 only)		X		X	
Chest HRCT				X		X[i]	
Chest X-ray[j]				X		X[i]	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[i, k]		X (Year 2 only)		X		X	
Physician global assessment		X (Year 2 only)		X		X	
Efficacy biomarkers (serum chitotriosidase, CCL18)		X	X	X	X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)[l]		X	X	X	X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X	X (Year 2 only)	X	X (Year 2 only)	X	
Metabolite levels in plasma		X	X	X	X	X	
Metabolite levels in dried blood spot[l]		X	X	X	X	X	
Patient photographs (optional)				X			
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Olipudase alfa infusion	X	X	X	X	X		
Liver ultrasound with Doppler		X (Year 2 only)		X		X	
Hand X-ray for bone age		X		X		X	
Tanner staging		X		X		X	
Cognitive and adaptive function (for patients who performed the assessments in DFI13803) (DP-3 and ABAS)		X (Year 2 only)		X		X	
Linear patient growth by height Z-score		X		X		X	
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)		X (Year 2 only)		X		X	
Pharmacokinetics[f,m]				X			
	See Section 1.6 and Table 12						
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after introducing the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. All patients will have a visit 2 weeks (±3 days) after the last Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, abdominal MRI, HRCT, chest X-ray, pulmonary function tests (PFTs), Doppler echocardiography, hand X-ray, and pediatric health outcome questionnaires will not be repeated if they had been done within 3 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

f At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).

g As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests. If drug product from a manufacturing scale change or an updated manufacturing process is administered, 2 samples will be taken during an infusion 3 months after introducing the new scale or the updated manufactured process one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.

h Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

i Upon a manufacturing scale change that occurs beyond Year 2, an abdominal MRI and pulmonary function tests will be performed at the first 6-month visit after the change, but only if that 6-month visit is not a 12-month visit at which the assessment is already scheduled. Pulmonary function tests will be performed for patients who had a baseline assessment in the DFI13803

study.

j Only at selected sites.

k Assessments should be performed at the same time (±2 hours) to ensure consistency.

l Only for patients for whom it was done in DFI13803.

m Pharmacokinetic testing will only occur yearly and upon introduction of a manufacturing scale change from Process B to Process C(■) or from Process C(■) to the updated manufacturing process C(■),. For Process C(■), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under process B and at the first infusion under Process C(■). For the switch from Process C(■) to Process C(■), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C(■). In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C(■) or Process C(■), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in children, see Section 1.6, Table 12.

ABAS=Adaptive Behavior Assessment System; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DP-3=Development Profile-Third Edition; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

Table 8 - Study flow chart for former DFI13803 patients - Year 2 through Year 5 - only applicable after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study.						
Complete physical examination		X		X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X		X		X		
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X	X	X	X	X	
Hemoglobin level and platelet count[g]		X		X		X	
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f, h]		X		X		X	
Doppler echocardiography				X		X	
Safety biomarkers (hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, calcitonin, plasma ceramide)		X	X	X	X	X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						Patient discontinuation, or withdrawal[b]	Safety follow-up phone call[c]
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Abdominal MRI (liver and spleen volumes)[i]		X (Year 2 only)		X		X	
Chest HRCT				X		X[i]	
Chest X-ray[j]				X		X[i]	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[i, k]		X (Year 2 only)		X		X	
Physician global assessment		X (Year 2 only)		X		X	
Efficacy biomarkers (serum chitotriosidase, CCL18)			X		X	X	
Bone biomarkers (alkaline phosphatase, C-telopeptide)			X		X	X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])		X	X (Year 2 only)	X	X (Year 2 only)	X	
Metabolite levels in plasma (ceramide, lyso-sphingomyelin)			X		X	X	
Patient photographs (optional)				X			
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Liver ultrasound with Doppler		X (Year 2 only)		X		X	
Hand X-ray for bone age		X		X		X	
Tanner staging		X		X		X	
Cognitive and adaptive function (for patients who performed the assessments in DFI13803) (DP-3 and ABAS)		X (Year 2 only)		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.						**Patient discontinuation, or withdrawal[b]**	**Safety follow-up phone call[c]**
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**		
Year 2		**W66**	**W80**	**W92**	**W104**		
Year 3		**W118**	**W132**	**W144**	**W156**		
Year 4		**W170**	**W184**	**W196**	**W208**		
Year 5		**W222**	**W236**	**W248**	**W260**		
Linear patient growth by height Z-score		X		X		X	
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)		X (Year 2 only)		X		X	
Pharmacokinetics[l]				X			
	See Section 1.6 and Table 12						
Immune response assessments							
Anti-olipudase alfa antibody (IgG)	Quarterly During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), collection will be monthly for the first 6 months after introducing the new process, and quarterly after that.						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. All patients will have a visit 2 weeks (±3 days) after the last Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of

the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, abdominal MRI, HRCT, chest X-ray, pulmonary function tests (PFTs), Doppler echocardiography, hand X-ray, and pediatric health outcome questionnaires will not be repeated if they had been done within 3 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

f At time points when multiple assessments are scheduled, the order will be: vital sign measurements, electrocardiogram, pharmacokinetics (PK).

g As indicated, an additional sample will be collected for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests During the study period, for the switch from Process B to Process C(■) or from Process C(■) to the updated manufacturing process C(■) , 2 samples will be taken during an infusion 3 months after introducing Process C(■) or Process C(■), one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.

h Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

i During the study period, for the switch from Process B to Process C or from Process C(■) to the updated manufacturing process C(■), that occurs beyond Year 2, an abdominal MRI and pulmonary function tests will be performed at the first 6-month visit after the change, but only if that 6-month visit is not a 12-month visit at which the assessment is already scheduled. Pulmonary function tests will be performed for patients who had a baseline assessment in the DFI13803 study.

j Only at selected sites.

k Assessments should be performed at the same time (±2 hours) to ensure consistency.

l Pharmacokinetic testing will only occur yearly and upon introduction of a manufacturing scale change from Process B to Process C(■) or from Process C(■) to the updated manufacturing process C(■),. For Process C(■), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under process B and at the first infusion under Process C(■). For the switch from Process C(■) to Process C(■), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C(■). In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C(■) or Process C(■), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in children, see Section 1.6, Table 12.

ABAS=Adaptive Behavior Assessment System; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; CCL18=chemokine (CC-motif) ligand 18; DL_{CO}=diffusing capacity of the lung for carbon monoxide; DP-3=Development Profile-Third Edition; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

1.5 FLOW CHART FOR PEDIATRIC (FORMER DFI13803) PATIENTS: BEYOND YEAR 5

Table 9 - Study flow chart for former DFI13803 patients - Year 5 and beyond - only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**Study completion, patient discontinuation or withdrawal[b]**	**Safety follow-up phone call[c]**
Year 6		**W274**	**W288**	**W300**	**W312**		
Year 7		**W326**	**W340**	**W352**	**W364**		
Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study.						
Complete physical examination				X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X						
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X		X		X	
Hematology hemoglobin level and platelet count	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), 2 samples will be taken during an infusion 3 months after introducing the new process, one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart..						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**Study completion, patient discontinuation or withdrawal[b]**	**Safety follow-up phone call[c]**
Year 6		**W274**	**W288**	**W300**	**W312**		
Year 7		**W326**	**W340**	**W352**	**W364**		
Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f, g]				X		X	
Safety biomarkers (hsCRP, iron, ferritin, calcitonin, plasma ceramide)		X		X		X	
Abdominal MRI (liver and spleen volumes)[i]				X		X	
Chest HRCT				X		X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[h]				X		X	
Physician global assessment				X		X	
Efficacy biomarkers (serum chitotriosidase, CCL18)				X		X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])				X		X	
Metabolite levels in plasma				X		X	
Patient photographs (optional)				X			
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Hand X-ray for bone age				X		X	
Tanner staging				X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**Study completion, patient discontinuation or withdrawal[b]**	**Safety follow-up phone call[c]**
Year 6		**W274**	**W288**	**W300**	**W312**		
Year 7		**W326**	**W340**	**W352**	**W364**		
Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Linear patient growth by height Z score		X		X		X	
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)				X		X	
Pharmacokinetics[i]							
Immune response assessments							
Anti olipudase alfa antibody (IgG)	During the study period, for the switch from Process B to Process C(■) or from Process C(■) to Process C ■), collection will be monthly for the first 6 months after introducing new process						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. All patients will have a visit 2 weeks (±3 days). Quarterly visits will occur at the site If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site

closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, all "beyond Year 5" assessments will not be repeated if they had been done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

f At time points when multiple assessments are scheduled, the order will be: vital sign measurements then electrocardiogram.

g Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

h Assessments should be performed at the same time (±2 hours) to ensure consistency.

i Beyond 5 years, pharmacokinetic testing will only occur upon introduction of Process C([redacted]) or the Process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under Process B and at the first infusion under Process C([redacted]). During the study period, for the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in adults, see Section 1.6, Table 11.

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; DL_{CO}=diffusing capacity of the lung for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

Table 10 - Study flow chart for former DFI13803 patients - Year 5 and beyond - only applicable after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**Study completion, patient discontinuation or withdrawal[b]**	**Safety follow-up phone call[c]**
Year 6		**W274**	**W288**	**W300**	**W312**		
Year 7		**W326**	**W340**	**W352**	**W364**		
Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Adverse events	Collect continuously throughout the study. Adverse events that started during the previous study and are ongoing at the time the patient signs the written informed consent should be reported in this study.						
Concomitant medications	Collect continuously throughout the study.						
Complete physical examination				X		X	
Extended neurological examination[d]				X		X	
Abbreviated physical examination	X						
	Before and after each infusion						
Weight[e]	Before each infusion					X	
Height		X		X		X	
Vital sign measurements (blood pressure, heart rate, respiratory rate, temperature)[f]	Before and 1 hour (±10 minutes) after each infusion.					X	
Clinical laboratory tests (clinical chemistry, hematology, LFTs, coagulation, urinalysis)		X		X		X	
Hematology, hemoglobin level and platelet count	During the study period, for the switch from Process B to Process C([redacted]) or from Process C([redacted]) to Process C([redacted]), 2 samples will be taken during an infusion 3 months after introducing the new process, one for deferential hematology and the other for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart.						

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
Visit/timing	**Every 2 weeks (±3 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**QV[a] (±14 days)**	**Study completion, patient discontinuation or withdrawal[b]**	**Safety follow-up phone call[c]**
Year 6		**W274**	**W288**	**W300**	**W312**		
Year 7		**W326**	**W340**	**W352**	**W364**		
Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Urine β-HCG pregnancy test (only women of childbearing potential)	Every 4 weeks					X	
Electrocardiogram[f, g]				X		X	
Safety biomarkers (hsCRP, iron, ferritin, calcitonin)		X		X		X	
Abdominal MRI (liver and spleen volumes)				X		X	
Chest HRCT				X		X	
Pulmonary function tests (FVC, FEV_1, DL_{CO}, TLC)[h]				X		X	
Physician global assessment				X		X	
Efficacy biomarkers (serum chitotriosidase, CCL18)				X		X	
Fasting lipids (total cholesterol, HDL, LDL, VLDL, triglycerides, ApoB, ApoA1, lipoprotein[a])				X		X	
Metabolite levels in plasma (ceramide, lyso-sphingomyelin)				X		X	
Patient photographs (optional)				X			
	Photographs (eg, abdominal) will be taken on patients who volunteer to provide visual context of the disease.						
Olipudase alfa infusion	X	X	X	X	X		
Hand X-ray for bone age				X		X	
Tanner staging				X		X	
Linear patient growth by height Z score		X		X		X	

Study period	Treatment					Post treatment	
Note: The visit schedule is calculated in reference to the first infusion of the patient's previous study. The ±14 day window applies only to assessments not linked to the time of the infusion. For infusions and assessments closely linked to the time of the infusion (eg, abbreviated physical exams, vital signs), the Q2W visit window of ±3 days remains.							
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Year 8		**W378**	**W392**	**W404**	**W416**		
Year 9		**W430**	**W444**	**W456**	**W468**		
Pediatric health outcome questionnaires (PedsQL, PedsQL Multidimensional Fatigue Scale, PedsQL Pediatric Pain Questionnaire)				X		X	
Pharmacokinetics[i]							
Immune response assessments							
Anti olipudase alfa antibody (IgG)	If introduction of a drug product from Process C([redacted]) or Process C([redacted]) occurs, collection will be monthly for the first 6 months after introducing the drug product from the new process						
Neutralizing antibodies	In patients who develop anti-olipudase alfa antibody (IgG)						
IL-6, IL-8, and calcitonin	In case of suspected cytokine release syndrome						
Immune response assessment in case of IAR suggestive of hypersensitivity reaction							
Anti-olipudase alfa antibody (IgG)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
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Anti-olipudase alfa antibody (IgE)	At least 3 days after or prior to the next infusion in case of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Serum tryptase and complement activation	Within 1 to 3 hours of a moderate/severe or recurrent IAR suggestive of a hypersensitivity reaction						
Skin testing	If necessary						

a Patients from DFI13803 are to follow the pediatric schedule of events in the LTS13632 study. The pediatric schedule of events is based on pediatric patients receiving 64 weeks of treatment in the prior DFI13803 study. The adult schedule of events is based on adult patients receiving 26 weeks of treatment in the prior DFI13412 study. All patients will have a visit 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit

assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

b All patients will have a visit 2 weeks (±7 days) after the last dose of study treatment. For the end of study/early discontinuation visit, all "beyond Year 5" assessments will not be repeated if they had been done within 6 months prior.

c All patients will have a final safety follow-up phone call 30 to 37 days after the last dose of study treatment.

d If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803 study. If possible, the same neurologist should perform the neurological examination throughout the study.

e Weight at previous on-site visit may be used to calculate drug dosage at current visit. Weight is not required at home infusion visits unless quarterly visit occurs at home. Body mass index (BMI) will be calculated.

f At time points when multiple assessments are scheduled, the order will be: vital sign measurements then electrocardiogram.

g Patients must rest in the supine position for 5-10 minutes prior to and during all electrocardiograms.

h Assessments should be performed at the same time (±2 hours) to ensure consistency.

i Beyond 5 years, pharmacokinetic testing will only occur upon the introduction of a drug product from Process C([redacted]) or Process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under Process B and at the first infusion under Process C([redacted]). During the study period, for the switch from Process C([redacted]) to Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in adults, see Section 1.6, Table 11.

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; β-HCG=beta human chorionic gonadotropin; DL_{CO}=diffusing capacity of the lung for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IAR= infusion-associated reaction; Ig=immunoglobulin; IL=interleukin; LDL=low-density lipoprotein; LFT=liver function test; MRI=magnetic resonance imaging; PedsQL=Pediatric Quality of Life; TLC=total lung capacity; VLDL=very low-density lipoprotein.

1.6 STUDY FLOW CHART: PHARMACOKINETIC SAMPLING

For both adult and pediatric patients, PK testing will only occur yearly (up to 5 years) and upon the introduction of a drug product from Process C(■) or Process C(■) at any time during the study. For Process C(■), if treatment is not interrupted, PK collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion Process C(■). For introduction of drug product from Process C(■), if treatment is not interrupted, PK sample collection will take place at the second infusion under the Process C(■). In case reintroduction of olipudase alfa coincides with introduction of drug product from Process C(■) or Process C(■), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For introduction of drug product from Process C(■), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C(■).

If a PK sample collection for the planned introduction of drug product from an updated manufacturing process was erroneously taken, the future sample collection will be adjusted according to the blood volume allowed per each age cohort in order to avoid excessive blood withdrawal. For specific details, please refer to Study Manual.

Table 11 - Pharmacokinetic sampling in adults

Week	Before infusion[a]	End of infusion	Hours after infusion[b]					
			1	4	8	24	48	96
12-month visit (up to 5 years)	X	X	X	X	X	X	X	X
If a manufacturing scale change or an updated manufacturing process occurs	X	X	X	X	X	X	X	X

a Pre-infusion sample to be collected within 24 hours before infusion start.

b Sample collections are to be within ±10 minutes for those <8 hours from infusion end and ±3 hours for those ≥8 hours after infusion end.

Table 12 - Pharmacokinetic sampling in pediatric patients

Visit	Age	Time from end of infusion[a]						
12-month visit or if introduction of a drug product from a manufacturing scale change or an updated manufacturing process occurs	Adolescent	**Pre-infusion[b]**	**End of infusion**	**2 h**	**6 h**	**24 h**	**48 h**	**96 h**
		X	X	X	X	X	X	X
		Pre infusion[b]	**End of infusion**	**0-30 min**	**2-4 h**	**6-12 h**	**24-36 h**	**84-96 h**
	Child	X		X	X	X	X	X
	Infant/early child	X		X		X	X	X

a Sample collections are to be within ±10 minutes for those <8 hours from infusion end and ±3 hours for those ≥8 hours after infusion end.

b Pre-infusion sample to be collected within 24 hours before infusion start.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ABAS: Adaptive Behavior Assessment System
ACE: angiotensin converting enzyme
AE: adverse event
AP: alkaline phosphatase
Apo: apolipoprotein
APR: acute phase reaction
ASM: acid sphingomyelinase
ASMD: acid sphingomyelinase deficiency
ASMKO: acid sphingomyelinase knock out
$AUC_{0-\infty}$: area under the concentration-time curve from time 0 to infinity
AUC_{last}: area under the concentration-time curve
BFI: Brief Fatigue Inventory
BMD: bone mineral density
BMI: body mass index
BPI: Brief Pain Inventory
CCL-18: chemokine (CC-motif) ligand 18
C_{eoi}: concentration at the end of infusion
CL: apparent total body clearance
C_{max}: maximum concentration observed
CO_2: carbon dioxide
CRF: case report form
CRS: cytokine release syndrome
CS: clinically significant
DBS: dried blood spot
DL_{CO}: diffusing capacity of the lung for carbon monoxide
DMC: Data Monitoring Committee
DNA: deoxyribonucleic acid
DP-3: Development Profile-Third Edition
DXA: dual-energy X-ray absorptiometry
ECHO: echocardiogram
EOT: end of treatment
FEV_1: forced expiratory volume in the first 1 second
FVC: forced vital capacity
HDL: high-density lipoprotein
HRCT: high resolution computed tomography
IAR: infusion associated reaction
ICH: International Council on Harmonisation
IEC: independent ethics committee
IL: interleukin
ILD: interstitial lung disease
IMP: investigational medicinal product

IRB:	institutional review board
IV:	intravenous
LDL:	low-density lipoprotein
LFT:	liver function test
MIP:	macrophage inflammatory protein
MRI:	magnetic resonance imaging
NCS:	not clinically significant
NE:	not evaluable
NPB-HAQ:	Niemann-Pick B Health Assessment Questionnaire version 2
NPD:	Niemann-Pick disease
O_2:	oxygen
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PedsQL:	Pediatric Quality of Life
PFT:	pulmonary function test
PIP:	pediatric investigational plan
PK:	pharmacokinetic
PT:	preferred term
SAE:	serious adverse event
SF:	Short Form
SF-36:	Short Form-36
SFCRQ SAS:	Chronic Respiratory Disease Questionnaire Self-administered Standardized
SOC:	system organ class
$t_{1/2z}$:	terminal half-life associated with the terminal slope (λ_z)
t_{max}:	time to reach maximum concentration
VLDL:	very low-density lipoprotein
V_{ss}:	apparent volume of distribution at steady-state
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Human acid sphingomyelinase deficiency (ASMD) is a serious, rare, life threatening lysosomal storage disorder for which only palliative treatment exists. Patients with ASMD are unable to metabolize sphingomyelin properly due to mutations in SMPD1, the gene encoding acid sphingomyelinase (ASM), whose transcription and translation results in a defective (ASM) enzyme. Inactivity of ASM leads to the lysosomal accumulation of sphingomyelin and, secondarily, increases in cholesterol and other related lipids, mostly in the organs, such as the spleen, liver, lung, and bone marrow.

Historically, ASMD has been diagnosed as Niemann-Pick Disease (NPD) and of either Type A or Type B disease. Type A (NPD A) is characterized as the early-onset and acute neuropathic form of (NPD) and results in failure to thrive, hepatosplenomegaly, rapidly progressive neurological degeneration, and death, usually before the age of 3 years (1). Niemann-Pick disease Type B (NPD B) is a milder disease with little or no neurological involvement that may already have manifestations in childhood. The most common disease manifestation is hepatosplenomegaly. Other more variable features include liver dysfunction, pulmonary disease, retinal stigmata, and growth retardation. Niemann-Pick disease Type B is usually diagnosed in childhood after organomegaly is observed, typically after the age of 2 years. Most patients diagnosed with Type B disease live into adulthood. Being an autosomal recessive single gene disease, ASMD is acknowledged to generate a spectrum of phenotypes. Accordingly, cases classified as intermediate to the A and B extremes have been reported. Patients with this intermediate form (NPD A/B) may develop neurologic symptoms during childhood and have a chronic neurodegenerative disease course.

Sanofi Genzyme is developing a potential enzyme replacement therapy for ASMD with olipudase alfa, a recombinant human acid sphingomyelinase, for the treatment of the non-neurological manifestations of ASMD. This recombinantly-derived enzyme is expressed in Chinese hamster ovarian cells transfected with olipudase alfa complementary DNA that encodes a 627-residue peptide chain. The resulting gene product retains the enzymatic activity and lysosomal targeting of the native protein.

Proof of concept for olipudase alfa therapy has been demonstrated in the acid sphingomyelinase knock-out (ASMKO) mouse (2), which exhibits both systemic and neurological features of ASMD. Repeat intravenous (IV) bolus administration of olipudase alfa to ASMKO mice led to dose-dependent reductions of sphingomyelin in visceral organs and in the lungs to a lesser extent, but was unable to prevent neurologic decline and prolong survival (3, 4). However, chronic dosing in the ASMKO animal model is limited because the mice succumb to the neurologic disease resulting from the natural progression of complete ASMD in approximately 6 to 8 months.

Pharmacodynamic (PD), pharmacokinetic (PK), and toxicological studies conducted in the ASMKO mouse found significant reductions of sphingomyelin in the liver, lung, kidney, and spleen at olipudase alfa doses ranging from 0.1 to 5.0 mg/kg in a time-dependent manner;

however, toxicity was observed in ASMKO mice given single high-dose boluses of olipudase alfa (≥10 mg/kg). The same single, high doses did not cause toxic effects in normal mice, Sprague Dawley rats, or cynomolgus monkeys, suggesting that catabolites of sphingomyelin, and not olipudase alfa itself, were the cause of the toxic effects. Subsequent "debulking" studies in ASMKO mice demonstrated that a slow reduction in the sphingomyelin load over time using multiple low doses of olipudase alfa (4 doses of 3.0 mg/kg of olipudase alfa administered over 8 days) followed by a high dose (20 mg/kg 3 days later) prevented the toxicity associated with the single initial high doses. These findings suggest that the observed toxicity is related to the rate of substrate degradation and that step-wise removal of substrate likely mitigates toxicity. Furthermore, repeat high doses of olipudase alfa (30 mg/kg every 2 weeks for 7 doses) administered after a 7-day debulking period (3 mg/kg on Days 1, 3, 5, and 7) also did not cause toxicity.

During clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process. The different processes are referred to as Process B, C([redacted]) and C([redacted]).

In a completed Phase 1 study (5), the safety, PK, and PD profiles of single, ascending doses of olipudase alfa were evaluated. Single doses of 0.03, 0.1, 0.3, 0.6, and 1.0 mg/kg of olipudase alfa were infused sequentially by dose cohort in 11 adult patients with ASMD. Study results found dose-related increases in ceramide, bilirubin, high-sensitivity C-reactive protein (hsCRP), and other acute phase reactants in patients that peaked 24 to 48 hours postdose and resolved by Day 14. Reported adverse events (AEs) involving constitutional symptoms (pain, fever, nausea, and vomiting) were consistent with first-dose-related toxicity and occurred in a dose-dependent fashion as was previously observed in the ASMKO mouse. Serious adverse events (SAEs) related to olipudase alfa treatment were not reported. The sponsor terminated the study subsequent to a single patient dosed at 1.0 mg/kg of olipudase alfa presenting with hyperbilirubinemia and an acute-phase reaction (APR) with clinical symptoms. Of note, this patient was subsequently confirmed to have Gilbert's syndrome. Because there were no other signs of liver toxicity or hemolysis, the observed hyperbilirubinemia may have been secondary to specific inhibition of bilirubin uptake into hepatocytes and/or glucuronide conjugation of bilirubin within hepatocytes.

In a completed Phase 1b, open-label, multicenter ascending-dose study in 5 adult patients with ASMD, the safety and tolerability of olipudase alfa were evaluated during a 26-week treatment period (6). Patients received an initial IV dose of 0.1 mg/kg of olipudase alfa, then the dose was escalated in a stepwise manner to a final target IV dose of 3.0 mg/kg. All patients remained at 3.0 mg/kg for the remainder of the treatment period. Upon completion of the study, all patients enrolled into an open-label, long-term treatment study. Results from this trial demonstrated that the progressive, within-patient olipudase alfa dose escalation regimen was well tolerated in adult ASMD patients. No serious or severe AEs or deaths were reported in the study. Related AEs consisted predominantly of infusion-associated reactions (IARs), most of which were mild in severity with all patients recovering without sequelae. At the end of the 6-month treatment period, a positive response to treatment with olipudase alfa was observed in several individual efficacy parameters. This included mean decreases in spleen and liver volumes by 25.3% and 17.1%, respectively; decreased interstitial lung disease (ILD) scores; increased percent predicted diffusing capacity of the lung for carbon monoxide (DL_{CO}); reduction in serum chitotriosidase, chemokine (CC-motif) ligand 18 (CCL-18), and angiotensin-converting enzyme (ACE); a positive trend

towards a less proatherogenic lipid profile; and, trends for improvement in quality of life assessments for fatigue and pain.

Other clinical studies of olipudase alfa are planned or ongoing. These include:

- A Phase 1/2, multicenter, open-label, ascending-dose study to evaluate the safety, tolerability, PK, PD, and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with ASMD.
- A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled repeat-dose study to evaluate the efficacy, safety, PD, and PK of olipudase alfa in patients with ASMD.

A complete summary of nonclinical and clinical experience with olipudase alfa can be found in the investigator's brochure.

4.2 STUDY RATIONALE

Cumulative data from preclinical and human studies conducted to date with olipudase alfa demonstrate both the safety and tolerability of repeat dosing of olipudase alfa. This study will provide long-term data on olipudase alfa in pediatric and adult patients with ASMD.

This study is being conducted to allow patients with ASMD to continue the olipudase alfa treatment they were receiving at the end of their primary study after that study is completed. Individual dose adjustments are allowed in this study, but may also be recommended based on results from completed or ongoing studies of olipudase alfa. The primary objective of this study is to obtain safety data in pediatric and adult patients with ASMD who are exposed to long-term treatment with olipudase alfa. Secondary objectives are to obtain efficacy, PK, and PD data.

Treatment Period

- The current study is an open-label, long-term treatment study planned for 9 years, or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible.
- The term "commercially accessible" is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days.
- This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment.
- Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years to comply with the agreed PIP.
- The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.

5 STUDY OBJECTIVES

5.1 PRIMARY

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.

5.2 SECONDARY

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.

6 STUDY DESIGN

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 LTS13632 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.

Treatment Period

- Enrolled patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years, or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa commercially accessible.
- The term “commercially accessible” is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days.
- This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment.
- Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years.
- The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.

Data Monitoring Committee

A chartered, independent data monitoring committee (DMC) will provide ongoing expert, independent review of safety data to ensure the protection and safety of the patients, as described in Section 6.4.

6.1 DESCRIPTION OF THE PROTOCOL

The study consists of 2 periods, treatment and posttreatment.

6.1.1 Treatment period

Treatment Period

- During the treatment period, patients will receive an IV infusion of olipudase alfa every 2 weeks for 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible.
- The term “commercially accessible” is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days.
- Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years.
- The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.

In the first 5 years, safety and efficacy assessments will occur at regular 3, 6, or 12 month intervals then only selected assessments will occur every 6 or 12 months after 5 years.

Schedule of Assessments

In the first 5 years, pharmacodynamic (PD) evaluations will occur every 3 months then every 6 months after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. After 5 years, PD evaluations will occur every 12 months.

PK evaluations will occur every 12 months only in the first 5 years and upon introduction of Process C([redacted]) or Process C([redacted]) at any time during the study. Beyond 5 years, pharmacokinetic testing will only occur upon the introduction of Process C([redacted]) or Process C([redacted]). For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient’s last infusion under the current manufacturing scale and at the first infusion under Process C([redacted]). For introduction of Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new process. For schedule of PK assessment in adults, see Section 1.6, Table 11.

6.1.2 Post treatment period

For patients completing or discontinuing/withdrawing from the study, there will be a posttreatment period consisting of an end-of-treatment (EOT) visit 2 weeks (±7 days) after the last administered dose of study treatment and a safety follow-up phone call 30 to 37 days after the last administered dose of study treatment.

An EOT visit and a safety follow-up phone call will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.

6.2 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 submission/application requirement(s).

6.3 DURATION OF STUDY PARTICIPATION

The length of a patient's participation will be from the time the informed consent form is signed until the last planned assessment/visit. The approximate maximum study duration per patient is as follows:

- Treatment period of 9 years or until olipudase alfa becomes commercially accessible (see maximum duration below), whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa is commercially accessible.
- The term “commercially accessible” is defined as when olipudase alfa is commercially accessible to each patient on an individual basis (eg, reimbursement being in place). The duration of study treatment with olipudase alfa between local Regulatory approval and commercial accessibility should not exceed 90 days. Therefore, as described below, after local Regulatory approval, the patient can continue in the LTS13632 study for a maximum of 127 days.
- This will ensure 90 days of study treatment with olipudase alfa for patients after local Regulatory approval and a safety follow up phone call 30 to 37 days after the last dose of study treatment.
- The patient can switch immediately after the end of study treatment to commercial treatment without any gap in order to ensure continuity of treatment with olipudase alfa.
- Notwithstanding the above, every pediatric patient will be treated in the LTS13632 study for at least 3 years.
- Follow up period concluded with a safety follow up phone call 30 to 37 days after the patient’s last infusion in the LTS13632 study. A safety follow-up phone call will also apply in case the patient switches immediately after the end of study treatment to commercial treatment.

6.3.1 Determination of end of clinical trial (all patients)

The study will be considered to be complete when the last patient has his/her last contact with his/her study site.

6.4 STUDY COMMITTEES

An independent DMC, composed of members independent from the sponsor and the study investigators, is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study (ie, exposure to study drug). All activities and responsibilities of the DMC are described in the DMC charter in compliance with applicable guidance (7).

Data monitoring committee meetings will occur at regular intervals as outlined in the DMC charter specific to this study. The report of a potential dose-limiting toxicity to the sponsor or the occurrence of any safety-related issues identified by the sponsor's medical monitor or global safety officer that pose a medical concern, for example a fatal event, will result in the DMC holding an ad hoc review of the safety data and providing its recommendations to the sponsor regarding further patient treatment.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

To enter this study, patients must have fulfilled the following criteria:

I 01. The patient completed the treatment period of a previous study of olipudase alfa with an acceptable safety profile in the opinion of the investigator and sponsor.

I 02. The patient and the patient's parent(s)/legal guardian(s) is willing and able to provide signed written informed consent.

I 03. The patient who is female and of childbearing potential must have a negative urine pregnancy test for beta-human chorionic gonadotropin (β-HCG) (see Section 9.1.9).

I 04. Female patients of childbearing potential and sexually mature male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle or use 2 acceptable effective methods of contraception up to 15 days following their last dose of study drug (see Section 10.2.3.2).

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be assessed for the following exclusion criteria:

7.2.1 Exclusion criteria related to study methodology

E 01. The patient has any new condition or worsening of an existing condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

E 02. The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study.

E 03. The patient is unwilling or unable to abstain from the use of alcohol for 1 day prior to and 3 days after each olipudase alfa infusion for the duration of the treatment period.

E 04. The patient is unwilling or unable to avoid, for 10 days before and 3 days after liver biopsies, medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, erythromycin, valproic acid, antidepressants, kava, echinacea) or may cause or prolong bleeding (eg, anticoagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng) (only patients who previously participated in the DFI13412 study).

7.2.2 Exclusion criteria related to the current knowledge of the compound and condition

E 05. The patient requires medication(s) that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, desipramine]).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The study drug, olipudase alfa, is a sterile, white to off-white lyophilized cake supplied in single-use, 20 cc Type 1 glass vials. Each vial contains 20 milligrams of extractable olipudase alfa.

The study drug will be reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL of olipudase alfa. The study drug will be further diluted in 0.9% sodium chloride for injection solution to a specific volume based on dose.

Detailed instructions on olipudase alfa preparation, storage, and administration are provided in the corresponding manual.

Refer to Section 8.5 for product handling and complaints reporting.

8.1.1 Treatments administered

Patients will receive olipudase alfa every 2 weeks (±3 days). Home infusions may be possible. To be eligible for home infusions, patients must meet the criteria in Section 10.2.1.

Patients will start this study at the same dose they were receiving at the end of their primary study, provided that they have not missed more than 1 biweekly dose between studies.

All patients will have a visit 2 weeks (±3 days). Quarterly visits will occur at the site. If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic) and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments). Telehealth visits are an acceptable alternative to site visits, if site visits are not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, in accordance with institutional policy and with applicable country-specific regulations.

Dose reintroduction regimens may be required for patients who have missed more than 1 dose between studies or during this study (LTS13632), depending on their usual dose. For patients receiving home infusions who have missed 2 or fewer doses, the investigator can decide whether reintroduction should occur at the hospital/study site or via home infusion. For patients who have missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the hospital/study site. If the site visit is not possible during a regional or national emergency declared

by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, reintroduction may be done via home infusion.

Olipudase alfa reintroduction guidance will depend on the patient's usual dose and the number of missed infusions:

- If a patient misses 1 dose, continue at the dose previous to the missed dose.
- If a patient misses 2 doses:
  - If the previous dose was >0.6 mg/kg, the next dose must be 1 level below the last dose,
  - If the previous dose was ≤0.6 mg/kg, the next dose must be equal to the last dose.
- If a patient misses 3 or more doses:
  - If the previous dose was >0.6 mg/kg, the next dose must be 0.3 mg/kg (0.3 mg/kg should be repeated at the subsequent infusion, similar to dose escalation schedule in the original study). Details will be provided in the study manual
  - If the previous dose was ≤0.6 mg/kg, the next dose must be equal to the last dose,
  - If a patient has missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa for patients receiving infusions at home should occur at the hospital/study site.
  - If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, reintroduction may be done via home infusion, if the patient has previously been approved for home infusion.

8.1.2 Route and method of administration

Patients will receive IV olipudase alfa over the same time period as in their original study. The length of the infusion time may be adjusted based on the patient's tolerance of the infusion.

During the study, pediatric patients who reach adult age (18 years old) will receive the adult infusion volume.

See Section 8.1.5 for information on dose adjustments following dosing delays or missed doses.

8.1.3 Dosing considerations

Patients will receive the same olipudase alfa dose every 2 weeks, provided they have not missed more than 1 biweekly dose between studies.

Dosing will be based on an individual patient's mass (ie, weight) as outlined in Section 8.1.1. For patients who participated in the DFI13412 study and who had a body mass index (BMI) >30, the dose will be based on the mass (in kilograms) corresponding to a BMI of 30 given the specific patient's height.

8.1.4 Dose adjustments

Dose adjustments may also be considered at any time in consultation with the sponsor but may be recommended based on current safety or efficacy analysis results obtained from completed or ongoing studies of olipudase alfa.

8.1.5 Dosing delays or missed doses

Dose reintroduction regimens may be required for patients who have missed more than 1 dose between studies or during this study (LTS13632), depending on their usual dose. For patients receiving home infusions who have missed 2 or fewer doses, the investigator can decide whether reintroduction should occur at the hospital/study site via home infusion. For patients who have missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the hospital/study site. If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), reintroduction may be done via home infusion, if the patient has previously been approved for home infusion.

Patients who require dose reintroduction will have these assessments at each infusion until reaching their usual dose of olipudase alfa:

- Before infusion: vital sign measurements, liver function tests (LFTs), hematology tests and safety biomarkers.
- Immediately after infusion: vital sign measurements.
- 24 hours after infusion: vital sign measurements, LFTs, hematology and safety biomarkers
- 48 hours after infusion: vital sign measurements, LFTs and safety biomarkers.
  The 48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is >2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment.

Baseline is defined as the following:

- For initial dose escalation: last values prior to first dose of olipudase alfa
- For dose re-escalation: last values prior to the first re-escalation dose

8.1.6 Dose stopping criteria

If any of the following AEs occur, dosing will be temporarily stopped for the specific patient who experienced the AE:

- Any SAE, not related to the patient's underlying condition and considered related to the study treatment.
- Any increase in AST, ALT, total bilirubin, or alkaline phosphatase (AP) >3x baseline (prior to olipudase alfa therapy, ie, baseline value from the primary study) and > the upper limit of normal (ULN).
- Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT > 2 x ULN.
- Any increase in ALT or AST >3 x 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).
- Any AE that, in the opinion of the investigator or sponsor, raises significant concern regarding the safety of olipudase alfa at the administered dose.

8.1.7 Study interruption criteria

If either of these criteria are met,

- 2 patients develop the same severe AE that is not related to their underlying condition, or
- A death occurs that is assessed as related or possibly related to olipudase alfa, an ad hoc DMC meeting will be held to review the safety data and provide its recommendations to the sponsor regarding further patient treatment.

After consideration of DMC recommendations, final decisions regarding discontinuation of study drug for all or selected clinical trial patients will be made by the Sponsor.

In the event a significant safety concern arises, the Sponsor may immediately decide to discontinue study drug dosing in all clinical trial patients prior to receipt of DMC recommendation.

If the study is temporarily or permanently halted, the Sponsor will notify the health authorities of the halt by a substantial amendment in regions where this applies.

8.1.8 Treatment discontinuation

A patient's study treatment may be discontinued at any time at the patient's request or at the discretion of the investigator or sponsor. The following may be justifiable reasons for the investigator or sponsor to discontinue a patient from treatment:

- The patient was erroneously included in the study (ie, was found to not have met the inclusion/exclusion criterion).

- The patient is unable to comply with the requirements of the protocol.
- The patient participates in another interventional investigational study
- In the opinion of the investigator, the patient is no longer deriving clinical benefit.
- Pregnancy

Patients who received at least 1 dose of investigational product and who are withdrawn from the study will be asked to complete all discontinuation assessments prior to withdrawal (as detailed in Section 1.1 and Section 1.2 [adults] and Section 1.4 and Section 1.5 [pediatric patients]) and will receive a safety follow up telephone call from the study site 30 to 37 days after the final administration of olipudase alfa.

The investigator will document the reason(s) for treatment discontinuation/study withdrawal on the case report form (CRF).

8.2 BLINDING PROCEDURES

Not applicable. This is a single-arm, open-label study design.

8.3 PACKAGING AND LABELING

Olipudase alfa is packaged and labeled according to Good Manufacturing Practices and local regulatory specifications and requirements. Refer to the corresponding manual for additional details.

8.4 STORAGE CONDITIONS AND SHELF LIFE

All clinical trial material must be kept in a secure area with restricted access and be stored under adequate refrigerated temperature conditions (2°C to 8°C [36°F to 46°F]). Temperature excursions will be handled as described in the corresponding manual.

It is recommended that the reconstituted product be used immediately after reconstitution. Additional stability data are provided in the corresponding manual.

8.5 RESPONSIBILITIES

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense the investigational medicinal product (IMP) will be responsible for ensuring that the study drug used in the clinical trial is securely maintained as specified by the sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the investigator's prescription and it is the investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor in order to recall IMP and eliminate potential hazards.

Under no circumstances will the investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.5.1 Treatment accountability and compliance

Compliance to the treatment regimen will be monitored in terms of the percentage of scheduled infusions the patient receives through the treatment period. No infusions should be missed. Noncompliance is defined as missing 2 consecutive infusions or 4 total infusions per each 12-month period throughout the treatment period. As they are identified, the investigator should discuss noncompliant patients on a case by case basis with the sponsor's medical monitor (or designee).

8.5.2 Return and/or destruction of treatments

Reconciliation of study drug must be performed at the site by the investigator and the monitoring team using treatment log forms and documented on center study drug inventory countersigned by the investigator and the monitoring team.

If appropriate, a written authorization for destruction will be provided by the sponsor clinical trial team once the reconciliation is achieved. Investigational medicinal product destruction may be performed at the site depending on study drug specificities and local requirements; alternatively, study drug may be returned to the sponsor for destruction.

8.6 CONCOMITANT MEDICATION

Medications and therapeutic procedures received by the patient in the 30 days prior to their providing written and signed informed consent or assent until the final visit for this study will be recorded on the concomitant medication CRF, as appropriate.

Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary.

- Prior medications will be defined as medications that were taken prior to the first infusion of olipudase alfa.
- Concomitant medications will be defined as medications that are taken after providing informed consent in this study.

During the study, prohibited medications include those that may decrease olipudase alfa activity (eg, chlorpromazine, tricyclic anti-depressants [eg, imipramine or desipramine]). See the most recent version of the study manual for a list of concomitant medications that may decrease olipudase alfa activity.

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. There is no restriction on topical antihistamines.

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 (only patients who previously participated in the DFI13412 study). 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.

These lists of prohibited medications and herbal supplements may be incomplete. The investigator may also prohibit medications and products not listed here. Therefore, the investigator must review all medications and products for every patient. For more information on medications and herbal supplements that may decrease olipudase alfa activity or may be hepatotoxic, refer to the most recent version of the study manual.

Pretreatment in general is not recommended for prophylactic management of IARs. For patients who experience moderate to severe or recurrent IARs (as defined in Section 10.5.1.3.2) suggestive of hypersensitivity, pretreatment regimens (eg, antihistamines, antipyretics, glucocorticoids) may be prescribed by the investigator as per clinical judgment. In particular, the need for cationic amphiphilic antihistamines administered orally or IV should be carefully considered given the potential risk for functional inhibition of olipudase alfa activity by such drugs.

8.6.1 Treatment of infusion-associated reactions

For management of mild IARs, infusion rate reductions (eg, reduced to half the rate) or temporary interruptions may mitigate the reaction. For moderate to severe or recurrent IARs, the investigator may consider the use of pretreatment medications (eg, antihistamines, antipyretics, and/or glucocorticoids), if the symptoms are suggestive of hypersensitivity reaction, in addition to infusion rate reductions, interruptions, or discontinuation. In particular, the need for cationic amphiphilic antihistamines administered orally or IV should be carefully considered given the potential risk for functional inhibition of olipudase alfa activity by such drugs.

Patients experiencing symptoms suggestive of hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, during olipudase alfa infusion should be managed according to the general standards of care consistent with the treatment of such reactions. If anaphylaxis or other severe allergic reactions occur, immediate discontinuation of the infusion should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe IARs, appropriate medical personnel and equipment to perform resuscitation must be readily available in the event of a hypersensitivity reaction.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

The term “pediatric patients only” means patients coming from the original pediatric trial, DFI13803. Some of these patients will reach adult age (18 years old) while in this study. These patients will be adults by age, but they will remain part of the “pediatric patient” cohort.

9.1 ENDPOINTS

9.1.1 Primary endpoint

Primary safety endpoints pertaining to the safety and tolerability of olipudase alfa, as described in Section 9.1.4 through Section 9.1.15, include:

- Assessment of AEs/treatment-emergent AEs (TEAEs), including IARs (eg, cytokine release syndrome [CRS], APRs), and adverse events of special interest [AESIs]).
- Complete physical examinations.
- Extended neurological examinations.
- Abbreviated physical examinations.
- Weight.
- Height (pediatric patients only).
- Vital sign measurements.
- Clinical laboratory tests:
  - Clinical chemistry,
  - LFTs,
  - Hematology,
  - Coagulation studies,
  - Urinalysis,
  - Urine pregnancy test (women of childbearing potential only).
- ECGs.
- Echocardiogram with Doppler.
- Liver biopsy (only patients who previously participated in the DFI13412 study).
- Liver ultrasound with Doppler (only patients who previously participated in DFI13803).

- Safety biomarkers:
  - High-sensitivity C-reactive protein (hsCRP),
  - Iron,
  - Ferritin,
  - Cardiac troponin I,
  - Interleukin (IL) 6,
  - IL 8,
  - Calcitonin,
  - Plasma ceramide.
- Immune response assessments.

A site physician will assess safety findings as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Any abnormal findings that meet the definition of an AE per Section 10.5.1 will be recorded on the AE CRF.

The analysis of safety is described in Section 11.6.3.

9.1.2 Secondary endpoints (efficacy)

Secondary endpoints (efficacy), as described in Section 9.2.1 through Section 9.2.9 include:

- Abdominal magnetic resonance imaging (MRI) to evaluate improvements in spleen and liver volume.
- Pulmonary imaging:
  - High resolution computed tomography (HRCT),
  - Chest X-rays (at selected sites).
- Pulmonary function tests (PFTs).
- Hematology:
  - Hemoglobin,
  - Platelet count.
- Lipid profile:
  - Total cholesterol,
  - High-density lipoprotein (HDL),
  - Low-density lipoprotein (LDL),
  - Very low-density lipoprotein (VLDL),
  - Triglycerides,
  - Apolipoprotein B (ApoB),
  - Apo A,
  - Lipoprotein(a).
- Hand X-ray (pediatric patients only).

- Linear patient growth by height Z-score (pediatric patients only).
- Adult health outcome questionnaires:
  - Brief Fatigue Inventory (BFI),
  - Brief Pain Inventory Short Form (BPI-SF),
  - Chronic Respiratory Disease Questionnaire Self-administered Standardized (SFCRQ SAS),
  - Short Form 36 (SF-36),
  - Niemann-Pick B Health Assessment Questionnaire (NPB-HAQv2), version 2.
- Pediatric health outcome questionnaires:
  - Pediatric Quality of Life (PedsQL),
  - PedsQL Multidimensional fatigue scale,
  - PedsQL Pediatric Pain Questionnaire.
- An additional questionnaire about home infusion experience may be added for patients who received home infusion treatment for at least one year.

Efficacy analyses are described in Section 11.6.2.

9.1.3 Other endpoints

Other endpoints, as described in Section 9.3.1 through Section 9.3.9, include:

- Physician global assessment of change.
- Cognitive and adaptive function (for pediatric patients who performed the assessments in DFI13803):
  - Development Profile-Third Edition (DP-3),
  - Adaptive Behavior Assessment System (ABAS).
- Cycle ergometry to evaluate exercise capacity.
- Efficacy biomarkers, including, but not limited to:
  - Serum chitotriosidase,
  - CCL18
- Bone disease assessments (only patients who previously participated in the DFI13412 study):
  - Lumbar spine MRI for bone marrow burden score,
  - Bilateral femur MRI for bone marrow burden score,
  - Lumbar spine by dual-energy X-ray absorptiometry (DXA) for bone mineral density (BMD) T-score and Z-score,
  - Bilateral femurs by DXA for BMD T-score and Z-score.

- Bone biomarkers:
  - AP,
  - C-telopeptide levels.
- Tanner staging (pediatric study DFI13803 patients only).
- Photographs (optional).
- Pharmacokinetics.
- Pharmacodynamics (metabolite levels in plasma and/or dried blood spot (DBS) [eg, sphingomyelin, lysosphingomyelin]).
- Plasma ceramide.
- Sphingomyelin levels in liver tissue obtained by liver biopsy (only patients who previously participated in the DFI13412 study).

Efficacy analyses are described in Section 11.6.2.

Pharmacokinetic parameters and pharmacodynamics (PD) will be assessed as described in Section 9.3.8 and Section 9.3.9, respectively. Pharmacokinetic and PD analyses are described in Section 11.6.4.

9.1.4 Safety assessments

See Section 10.5.1 for more details about AEs.

9.1.5 Complete physical examination

A complete physical examination will be performed prior to infusion at the time points specified in Section 1.1 through Section 1.5. A complete physical examination will include assessment of the patient's general appearance, general neurological status, skin, head, eyes, ears, nose, throat, lymph nodes, heart, lungs, abdomen, and extremities/joints.

9.1.6 Extended neurological examination

9.1.6.1 Extended neurological examination in adults

The neurological examination in adults will include, but is not limited to, mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, coordination, and gait.

9.1.6.2 Extended neurological examination in pediatric patients

The neurological examination in pediatric patients will include, but is not limited to, mental status, posture, cranial nerves, motor system including muscle atrophy, tone and power, reflexes, sensory system, coordination, gait, and age-appropriate responses. If possible, the neurological examination should be performed by the same neurologist who performed it in the DFI13803

study. Also, if possible, the neurological examination should be performed by the same neurologist throughout the study.

9.1.7 Abbreviated physical examination

An abbreviated physical examination of the patient's general appearance only will be performed before and after infusion at the time points specified in Section 1.1 through Section 1.5 Patients will be assessed for body weight, height, and calculated BMI at the time points specified in Section 1.1 through Section 1.5.

9.1.8 Vital sign measurements

Vital sign measurements will be obtained before and after infusions at the time points specified in the flow charts in Section 1.1 through Section 1.5. Patients must be in a supine position for approximately 5 to 10 minutes before their vital signs are measured. Vital sign measurements will include systolic and diastolic blood pressure (mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°F or °C).

For patients who have a dose reintroduction, vital signs will be measured at each visit before (within 30 minutes) the infusion, immediately after the infusion, and at 24 and 48 hours postinfusion until the patients are back on their usual dose of olipudase alfa (Section 8.1.5).

9.1.9 Clinical laboratory tests

Pediatric patient blood volumes by age cohort are provided in Section 9.5.

The clinical laboratory data consist of blood analyses (clinical chemistry, LFTs, hematology, coagulation studies) urinalysis, and for women of childbearing potential only, a urine pregnancy test. Values will be converted into standard international units and then analyzed. International units will be used in all listings and tables.

Acute phase reactions and CRS are associated with changes in specific clinical laboratory parameters (Section 10.5.1.3.2).

The following clinical laboratory test results will be assessed by the site as specified in Section 1.1 through Section 1.5.

- Clinical chemistry: Sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, total protein, albumin, glucose, cholesterol, phosphorus, and creatine kinase.
- Liver function tests: ALT, AST, AP, gamma-glutamyl-transferase, total bilirubin, and direct bilirubin.
- Hematology: Complete blood count with differential and platelet count, including hematocrit, hemoglobin, and red blood cell, white blood cell, platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts.

- Coagulation studies: Prothrombin time (Protime), partial thromboplastin time, international normalized ratio, and D-dimer.
- Urinalysis: Dipstick for glucose, protein, hemoglobin, leukocytes, ketones, and bilirubin.
- Urine pregnancy test (women of childbearing potential only) (Note: If a urine pregnancy test is positive, study drug dosing should be withheld until results are confirmed with a serum β-hCG test.)

Laboratory reports will be made available to the investigator in a timely manner to ensure appropriate clinical review.

9.1.10 Electrocardiograms

Standard 12-lead, digitized electrocardiograms (ECGs) will be conducted as a singlet as specified in Section 1.1 through Section 1.5.

Electrocardiograms will be performed while the patient remains in a supine position for approximately 5 to 10 minutes prior to and while conducting the ECG. The following parameters will be assessed: heart rate; cardiac rhythm; respiratory rate; pulse rate; QRS, QT, and QTc intervals; QRS-axis; R-voltage V6; S-voltage V1; left ventricular hypertrophy criteria; right ventricular hypertrophy criteria; and, repolarization changes. Interpretation will include an assessment of heart rate, cardiac rhythm, intervals, axis, conduction defects, and overall cardiac impression for each patient.

A specialist trained in the interpretation of this test at each study site will review the ECGs according to site-specific procedures for safety. Where possible, the same examiner should perform all such reviews. Electrocardiograms of completed patients may be read by a central reviewer for data analysis.

Details for ECG procedures are provided in the corresponding manual.

9.1.11 Echocardiogram with Doppler

A standard 2-dimensional and M-mode echocardiogram (ECHO) with Doppler will be conducted at the time points specified in Section 1.1 through Section 1.5. The ECHO may be conducted up to 24 hours before the infusion.

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.

A specialist trained in the interpretation of this test at each study site will review the ECHOs according to site-specific procedures for safety. Where possible, the same examiner should perform all such reviews.

Details for ECHO procedures are provided in the corresponding manual.

9.1.12 Liver biopsy for sphingomyelin in liver tissue (only patients who previously participated in the DFI13412 study)

A liver biopsy will be performed after at least 3 years in the study.

Liver biopsy samples will be evaluated for sphingomyelin accumulation. Sphingomyelin accumulation in liver will be quantified by computer morphometry of high resolution light microscopy images. Sphingomyelin will also be quantified using liquid chromatography-tandem mass spectrometry (LC/MS/MS). Liver tissue samples will also be evaluated using histopathological methods.

Sample processing, storage, and shipment guidelines are provided in the corresponding manual.

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. Prohibited medications and products that are not to be taken within 10 days before and 3 days after the biopsy are discussed in Section 8.6.

9.1.13 Liver ultrasound with Doppler (only patients who previously participated in the DFI13803 study)

Liver ultrasound Doppler will be performed to document hepatic blood flow characteristics, principally portal vein pressure, and blood flow direction. The structures to be examined include the 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.

9.1.14 Safety biomarkers

Safety biomarkers including, but not limited to, hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, plasma ceramide and calcitonin will be assessed as specified in the study flow charts in Section 1.1 through Section 1.5. Ceramide is also a PD biomarker (Section 9.3.9.3).

The percent neutrophils (acute-phase reactants), total bilirubin, and direct bilirubin are considered safety biomarkers, although they are assessed as part of the routine clinical laboratory tests (Section 9.1.9).

9.1.15 Immune response assessments

Samples will be collected as specified in Section 1.1 through Section 1.5 for the evaluation of anti-olipudase alfa IgG antibodies. If introduction of a drug product from Process C([redacted]) or from Process C([redacted]) occurs, testing will occur monthly for the first 6 months after introducing the drug product from Process C([redacted]) or Process C([redacted]). If seroconversion occurs, patients will also be tested for neutralizing antibodies to olipudase alfa.

In the event that a patient reports an IAR that is suggestive of a hypersensitivity reaction (as described in Section 10.5.1.3.2.1) and is of:

- Moderate intensity,
- Severe intensity, or,
- Is recurrent (of any intensity grade), additional blood samples will be collected and sent to the sponsor for anti-olipudase alfa antibody (IgG and IgE), tryptase activity, and complement activation testing as described below. Skin testing may also be performed if a hypersensitivity reaction is suspected.
- For IgE anti-olipudase alfa antibody testing the same predose serum sample drawn for anti-olipudase alfa IgG testing may be used if the IAR occurs at that study visit. If a predose sample was not drawn on that day, the patient should return to the study site at least 3 days after the event for a serum sample to be drawn. Testing is conducted for research purposes to gain additional information as to individual patients' responses to study treatment and for aiding in the clinical management of patient safety.
- Blood samples will be drawn within 1 to 3 hours of an IAR for serum tryptase activity testing (serum) and complement activation testing (plasma), when clinically indicated.
- Refer to the corresponding manual for guidelines on the collection and shipping of samples.
- If necessary, following consultation between the investigator and the sponsor, skin testing may be performed in patients who experience an IAR that meets the following criteria:
  - The IAR has moderate or severe intensity or is recurrent, and,
  - The patient has persistent and intractable symptoms of hypersensitivity suggestive of an IgE-mediated hypersensitivity reaction as described in Section 10.5.1.3.2.1,
  - See also the corresponding manual for skin testing procedures.
- Cytokine release syndrome: If a patient experiences an AE of moderate or severe intensity that is suggestive of CRS (as described in Section 10.5.1.3.2.3, an additional blood sample for IL-6, IL-8, and calcitonin will be drawn immediately (if a sample has not already been obtained within the previous 30 minutes).

Refer to the corresponding manuals for comprehensive lists of panel tests and guidelines on the collection and shipment of samples.

9.2 EFFICACY ASSESSMENTS

The efficacy assessments (secondary endpoints) are described in Section 9.2.1 through Section 9.2.9. These include improvements in spleen and liver volume (as measured by abdominal MRI), pulmonary imaging by HRCT and chest X-ray (at selected sites) (for ILD scores), PFTs, hematology, lipid profiles, adult health outcome questionnaires, pediatric health outcome questionnaires, and for pediatric patients only, hand X-rays, Tanner staging, and linear growth by height Z-score.

Refer to the study flow charts in Section 1.1 through Section 1.6 for the timing of these assessments throughout the study. Efficacy analyses are described in Section 11.6.2.

9.2.1 Abdominal magnetic resonance imaging

Spleen and liver volumes will be assessed by abdominal MRI to quantify the degree of splenomegaly and hepatomegaly at the time points specified in Section 1.1 through Section 1.5.

Upon a manufacturing scale change, an abdominal MRI will be performed at the first 6-months visit after the change if that 6-months visit is not a 12-months visit where the assessment is already scheduled. Patients are required to fast from solid foods (liquids, such as water, milk, and juice, are allowed) for 6 hours prior to the MRI to reduce the effect of a meal.

The MRIs will be collected and read centrally by a third party blinded to patient number and study visit. Procedures for MRI are detailed in the corresponding manual.

9.2.2 Pulmonary imaging

9.2.2.1 High-resolution computed tomography

High-resolution computed tomography scans of the chest will be obtained as specified in Section 1.1 through Section 1.5 to quantify the degree of possible ILD.

High-resolution computed tomography will be performed using methods that are compatible with the standard institutional procedures of the investigational site. 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) (8).

The bilateral lung boundaries are determined from the following 4 pre-defined levels on the HRCT images (8).

- 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 level 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.

Procedures for HRCT scans are detailed in the corresponding manual.

9.2.2.2 Chest X ray

A chest X-ray (posterior-anterior and lateral views) will be performed at selected sites as indicated in Section 1.1 through Section 1.5.

A study site physician, such as the investigator, a pulmonologist, or a radiologist, should review the chest X-ray in a timely manner to determine whether there are any safety concerns and for clinical management of the patient. 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 (8):

- 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).

Procedures for chest X-ray scoring are detailed in the corresponding manual.

9.2.3 Pulmonary function tests

Pulmonary function tests will be performed in all patients previously enrolled in the DFI13412 study, and in patients for whom it was done in the DFI13803 study, to measure lung volumes, air flow, and gas exchange for evidence of ILD at the time points specified in the study flow charts in Section 1.1 through Section 1.5. Completion of PFTs may depend on patient age or cooperation, or both.

Upon a manufacturing scale change, PFTs will be performed at the first 6-month visit after the change if that 6-month visit is not a 12-month visit where the assessment is already scheduled. The pulmonary function test (PFT) administration protocol is standardized across sites in accordance with American Thoracic Society/European Respiratory Society guidelines (9, 10). 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. Pulmonary function tests should occur at the same time of day across study visits (±2 hours of the time of day of the first assessment).

Patients who routinely take bronchodilators must withhold bronchodilators before routine PFTs as follows:

- Short-acting inhaled or oral bronchodilators (eg, albuterol) - 8 hours.
- Medium-acting inhaled bronchodilators (eg, atrovent) - 12 hours.
- Long-acting inhaled or oral bronchodilators (eg, salmeterol) - 24 hours.

The equipment will be part of the institution's quality control/assurance program with regard to validation and calibration. The equipment is calibrated the day of the testing. A log will be kept and a copy will be submitted to the sponsor at the completion of the study. Where possible, the same equipment will be used for all measurements.

A specialist trained in the interpretation of this test should review the PFTs in a timely manner for clinical management of the patient.

9.2.4 Hematology

Hemoglobin and platelet counts will be assessed as safety and as efficacy parameters, as ASMD results in hematologic disorders. An additional blood sample will be obtained for hemoglobin and platelet count at least 24 hours and up to 2 weeks apart from the sample collected for clinical laboratory tests at the time points specified in Section 1.1 through Section 1.5.

9.2.5 Fasting lipid profile

A fasting lipid profile will be assessed as an efficacy parameter, as ASMD results in the progressive accumulation of lipids.

Blood will be collected prior to infusion for fasting lipids (including, but not limited to, total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), VLDL-cholesterol (VLDL-C), triglycerides, ApoB, apolipoprotein A1, and lipoprotein [a]) at the time points specified in Section 1.1 through Section 1.5.

9.2.6 Health outcome questionnaires

9.2.6.1 Adults

The following health-related quality of life instruments will be completed by patients according to the time points specified in Section 1.1 and Section 1.2.

- The BFI is a validated, self-administered questionnaire that was originally developed to assess fatigue severity in cancer patients (11). The BFI has 9 items and uses numeric

rating scales from 0 to 10. Patients are asked in 3 items to rate the severity of their fatigue at its worst, usual, and now during normal waking hours. The amount that fatigue has interfered with different aspects of the patient's life during the preceding 24 hours (including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life) is assessed in 6 items.

- The 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 (12, 13). The BPI-SF consists of 15 items that use a numeric rating scale to assess pain severity and pain interference in the past 24 hours.
- The Chronic Respiratory Disease Questionnaire Self-Administered Standardized (SFCRQ-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 (14). 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).
- 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 (15). The SF-36 consists of 8 scales, including physical functioning, role physical, bodily pain, mental health, role emotional, social functioning, vitality, and general health. The questionnaire also includes 2 summary measures of physical health and mental health derived from scale aggregates.
- The 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 (completed up to 5 years).

9.2.6.2 Pediatric patients

For pediatric patients, health outcome measures will be evaluated as specified in Section 1.3 through Section 1.5 using the assessment tools in Table 13 summarized by age range. Completion of questionnaires may depend on patient age or cooperation, or both.

Table 13 - Quality of life assessments

Assessment	Scale
Quality of life-general	**PedsQL Core Scales** Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age) Young adult (18-25 years of age) **Parent report for:** Infants (1-12 months of age) Infants (13-24 months of age) Toddlers (2-4 years of age) Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age) Young adult (18-25 years of age)
Fatigue	**PedsQL Multidimensional Fatigue Scale, Standard version for:** Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age) Young adult (18-25 years of age) **Parent report for**: Toddlers (2-4 years of age) Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age) Young adult (18-25 years of age)
Pain	**PedsQL Pediatric Pain Questionnaire**: Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age) **Parent report for:** Young child (5-7 years of age) Child (8-12 years of age) Teen (13-18 years of age)

PedsQL = Pediatric Quality of Life

The PedsQL 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 (16). 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.

The PedsQL Multidimensional Fatigue Scale consists of 18 questions, 6 regarding general fatigue, 6 regarding sleep/rest fatigue, and 6 regarding cognitive fatigue. It also 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.

The PedsQL Pediatric Pain Questionnaire 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.

Refer to the study operations manual for further details.

9.2.6.3 Additional questionnaires

A questionnaire about home infusion experience may be added at any time before the end of the study for patients who received home infusion treatment for at least one year.

9.2.7 Hand X-ray (only patients who previously participated in the DFI13803 study)

Patients will have an X-ray performed on their left hand, fingers, and wrist as indicated in Section 1.3 through Section 1.5.

The 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 blinded to patient number and study visit. Bone age (maturation) will be calculated using the Greulich & Pyle Atlas (17).

9.2.8 Tanner staging (only patients who previously participated in the DFI13803 study)

Patient puberty stage will be evaluated according to Tanner staging (18, 19). Tanner stage for genitals (male, stage I though V), breasts (females, stage I though V), and pubic hair (both genders, stage I through V) will be documented at the time points specified in Section 1.3 through Section 1.5.

9.2.9 Linear growth by height by Z-score (only patients who previously participated in the DFI13803 study)

Growth in pediatric patients will be assessed by height Z-scores.

9.3 OTHER ASSESSMENTS

Other assessments are described in Section 9.3.1 through Section 9.3.9. The assessments will include physician global assessment of change, cognitive and adaptive function (for pediatric patients who performed the assessments in the DFI13803 study), cycle ergometry, efficacy biomarkers, bone disease assessments, bone biomarkers, photographs (optional), PK, and PD. Pharmacokinetic parameters and PD will be assessed as described in Section 9.3.8 and Section 9.3.9, respectively.

Refer to the study flow chart in Section 1.1 through Section 1.6 for the timing of these assessments throughout the study.

9.3.1 Physician global assessment of change

The physician's global assessment of the patient's progress will be evaluated prior to infusion at the time points specified in the study flow chart in Section 1.1 through Section 1.5.

The investigator will evaluate the patient's current clinical status compared to baseline in the first study before the patient received the first dose of olipudase alfa by marking 1 of the following 7 categories: marked improvement, moderate improvement, mild improvement, no change, mild worsening, moderate worsening, or marked worsening.

9.3.2 Cognitive and adaptive function (for pediatric patients who performed the assessments in the DFI13803 study)

Cognitive function will be evaluated using the DP-3 assessment tool. Adaptive function will be evaluated using the ABAS. These assessments will be performed only for pediatric patients who performed the assessments in DFI13803. Completion of these assessments may depend on patient age or cooperation, or both.

Assessment time points are specified in Section 1.3 and Section 1.4. Refer to the study operations manual for further details.

9.3.3 Cycle ergometry

Cycle ergometry will be performed at the time points specified in Section 1.1. Completion of the assessment may depend upon patient cooperation.

Cardiopulmonary status will be assessed using a stationary 1-wheeled cycle as an ergometer to measure a person's work output under controlled conditions. Patients will be asked to ride the cycle at increasing workload levels until they can no longer proceed. Patients will breathe through a tube connected to a 1-way valve for continuous measurements of oxygen (O_2) uptake, carbon dioxide (CO_2) output, and tidal volume throughout the test. Heart rate, respiratory rate, and digital O_2 saturation will also be continuously monitored. Steady-state levels for each workload will be calculated for O_2 uptake, CO_2 output, tidal volume, ventilation, and respiratory exchange ratio. The maximum workload achieved will be recorded and expressed as percent predicted. In addition, percent predicted maximum will be calculated for O_2 uptake, heart rate, and tidal volume. Note that cycle ergometry assessments must occur at the same time for each assessment (ie, ±2 hours of the time of day of the first assessment).

Procedures for cycle ergometry assessments are detailed in the corresponding manual.

9.3.4 Efficacy biomarkers

Blood samples for efficacy biomarkers will be collected prior to infusion at the time points specified in Section 1.1 through Section 1.5. Biomarkers will include, but not be limited to, serum chitotriosidase, CCL-18.

Processing, storage, and shipment guidelines for samples to be sent to the sponsor are provided in the corresponding manual.

9.3.5 Bone disease assessments

Bone disease assessments will be obtained only for patients who previously participated in the DFI13412 study as specified in Section 1.1 through Section 1.5. Magnetic resonance imaging of the lumbar spine and both femurs will be used to determine bone marrow burden scores (20, 21). Dual-energy X-ray absorptiometry of the lumbar spine and both femurs will provide total BMD measurements, BMD T-scores, and Z-scores. The assessments may be performed on the same day as the spleen and liver volume MRIs.

All bone images will be sent to a central reviewer for blinded analysis of potential bone disease. See the corresponding manual for further details.

9.3.6 Bone biomarkers

Serum bone-specific alkaline phosphatase and C-telopeptide levels will be evaluated as indicated in Section 1.1 through Section 1.5.

9.3.7 Patient photographs

Photographs (eg, abdominal) will be taken as specified in Section 1.1 through Section 1.5 of patients who volunteer to provide visual context of the disease.

9.3.8 Pharmacokinetics

For both adult and pediatric patients, PK testing will only occur yearly for the first 5 years and upon the introduction of Process C([redacted]) or Process C([redacted]) at any time during the study. For Process C([redacted]), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion Process C([redacted]). For introduction of drug product from Process C([redacted]),if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C([redacted]). In case reintroduction of olipudase alfa coincides with introduction of a drug product from Process C([redacted]) or Process C([redacted]), PK samples will be collected at the infusions at which patients receive their usual dose of olipudase alfa under the new process.

Blood samples for pediatric patients are drawn at different intervals than samples in adult patients (Section 1.6, Table 12 and Table 11, respectively) and in different volumes (Section 9.5).

9.3.8.1 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment are provided in the corresponding manual.

9.3.8.2 Bioanalytical method

Plasma will be separated from blood samples and analyzed for plasma concentrations of olipudase alfa using a validated enzyme-linked immunosorbent method.

9.3.8.3 Pharmacokinetic sampling and parameters in adults

9.3.8.3.1 Sampling time in adults

Pharmacokinetic sampling will occur at the time points listed in Section 1.1 and Section 1.6. Specific time points are detailed in Table 11. If a patient receives only a partial infusion (eg, due to a safety concern), PK sampling will be repeated the next time the patient receives that dose. If a repeat is required, all PK time points will be repeated.

Windows around PK blood samples are ±10 minutes for collection times less than 8 hours and ±3 hours for collection times of 8 hours or longer post infusion.

Blood samples may be drawn for PK assessments using an indwelling catheter from an arm that is not used for dose administration. The exact time of dose administration (start and stop times of infusion), rate of infusion, and dose will be recorded along with exact sampling times.

If a manufacturing scale change occurs, serial blood samples for PK will be collected at all of the same time points with the last infusion of olipudase alfa produced at the original scale and with the first infusion of olipudase alfa produced at the new scale. For introduction of drug product from Process C([redacted]), PK sample collection will only take place at the second infusion under Process C([redacted]).

9.3.8.3.2 Number of pharmacokinetic samples in adults

Table 14 shows the approximate number of plasma samples in adults.

Table 14 - Approximate number of plasma samples in adult patients

Collection	Number of samples
Yearly collection (5 years)	8
Change in manufacturing scale	
Last infusion on old scale	8
First infusion on new scale	8
Updated manufacturing process	
Second infusion on updated process	8
Total by patient	64

9.3.8.3.3 Pharmacokinetics parameters in adults

The following PK parameters will be calculated using noncompartmental methods from plasma olipudase alfa concentrations. The parameters will include, but may not be limited to, those listed in Table 15.

Table 15 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Definition/Calculation
C_{max}	olipudase alfa	Maximum plasma concentration observed
Ceoi	olipudase alfa	Concentration at the end of infusion
t_{max}	olipudase alfa	Time to reach C_{max}
AUC_{last}	olipudase alfa	Area under the plasma concentration-versus-time curve calculated using the trapezoidal method from time zero to the real time
$AUC_{0-\infty}$	olipudase alfa	Area under the plasma concentration-versus-time curve extrapolated to infinity according to the following equation: $$AUC = AUC_{last} + \frac{C_{last}}{\lambda_z}$$ Values with a percentage of extrapolation > 20% will not be taken into account in the descriptive statistics
$t_{1/2z}$	olipudase alfa	Terminal half-life associated with the terminal slope (λ_z) determined according to the following equation: $$t_{1/2Z} = \frac{0.693}{\lambda_z}$$ where λ_z is the slope of the regression line of the terminal phase of the plasma concentration-versus-time curve, in semilogarithmic scale. Half-life is calculated by taking the regression of at least 3 points.
CL	olipudase alfa	Apparent total body clearance of a drug from the plasma calculated using the following equation: $$CL = \frac{Dose}{AUC}$$
V_{ss}	olipudase alfa	Apparent volume of distribution at steady state using the following equation: $$Vss = \frac{CL \times AUMC}{AUC}$$

Note: The analyte and matrix for all PK parameters are olipudase alfa and plasma, respectively.

9.3.8.4 Pharmacokinetic sampling and parameters in pediatric patients

9.3.8.4.1 Sampling time in pediatric patients

Pharmacokinetic sampling will occur at the time points listed in Section 1.3 through Section 1.6. Specific time points are detailed in Table 12 for each age group. To minimize the amount of blood drawn, post dose time points have been selected for sparse sampling of PK parameters.

If a patient receives only a partial infusion (eg, due to a safety concern), PK sampling will be repeated the next time the patient receives that dose. If a repeat is required, all PK time points will be repeated.

In adolescent patients, windows around PK blood samples are ±10 minutes for collection times <8 hours and ±3 hours for collection times ≥8 hours post infusion.

Depending on patient age, blood samples may be drawn for PK assessments using an indwelling catheter from an arm that is not used for olipudase alfa infusions. The exact time of olipudase alfa infusions (start and stop times of infusion), rate of infusion, time of infusion rate changes, and dose will be recorded along with exact sampling times.

9.3.8.4.2 Number of pharmacokinetic samples in pediatric patients

Table 16 shows the approximate number of plasma samples by age cohort.

Table 16 - Approximate number of plasma samples by pediatric age cohort

Collection	Adolescent cohort	Child cohort	Infant/early child cohort
Yearly collection (5 years)	7	6	5
	Change in manufacturing scale		
Last infusion on old scale	7	6	5
First infusion on new scale	7	6	5
	Updated manufacturing process		
Second infusion on updated process	7	6	5
Total by patient	56	48	40

9.3.8.4.3 Pharmacokinetics parameters in pediatric patients

Plasma concentration-time data will be analyzed by noncompartmental methods, nonlinear mixed effects modeling or by population-based analysis, based upon patient age and data suitability. Where appropriate, PK parameters calculated using noncompartmental methods from plasma olipudase alfa concentrations may include those listed in Table 15.

9.3.9 Pharmacodynamic assessments

Only patients who previously participated in the DFI13412 study will have PD assessments for clearance of sphingomyelin accumulation in liver tissue. All patients will be assessed for metabolite levels in plasma and/or DBS, as well as plasma ceramide.

9.3.9.1 Liver biopsy for sphingomyelin in liver tissue (only patients who previously participated in the DFI13412 study

Liver biopsy samples will be evaluated for sphingomyelin accumulation and liver pathology in the patients who previously participated in the DFI13412 study who were at least 18 years old when they entered in the study. Patients who were younger than 18 years old when they entered the study will not have liver biopsies. See Section 9.1.12 for details about liver biopsies.

9.3.9.2 Metabolite levels in plasma and dried blood spot (all patients)

Metabolite levels (eg, sphingomyelin, lyso-sphingomyelin) in plasma and/or DBS will be quantified by the sponsor (or designee) using samples collected as detailed in the study flow chart in Section 1.1 through Section 1.5. Procedure, preparation, and sample shipment guidelines for plasma and DBS sampling are provided in the corresponding manual.

9.3.9.3 Plasma ceramide (all patients)

Plasma ceramide will be quantified at the time points shown in the flow chart in Section 1.1 through Section 1.5. Plasma ceramide is also being tested as a safety biomarker.

9.4 APPROPRIATENESS OF MEASUREMENTS

The safety, efficacy, and PK/PD measurements in this trial are accepted methods for assessing patient safety and outcomes.

9.5 SAMPLED BLOOD VOLUME

For all pediatric patients, no more than 7 mL/kg of blood will be collected during any 8-week period. Additional blood samples may be collected at the investigator's discretion for patient safety monitoring.

If a PK or IgG sample collection for the planned introduction of drug product from Process C(■) was erroneously taken, the future sample collection will be adjusted according to the blood volume allowed per each age cohort in order to avoid excessive blood withdrawal. For specific details, please refer to Study Manual.

Table 17 shows the approximate sampled blood volume in patients ages 12 to <18 years old in the first 5 years.

Table 17 - Approximate sampled blood volume in patients ages 12 to <18 years in the first 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	5.0	4	20.0
Hematology	2.0	4	8.0
Coagulation	3.6	4	14.4
Safety biomarkers	6.5	4	26.0
Efficacy biomarkers	10.0	4	40.0
Serum bone-specific AP and C-telopeptide	2.5	4	10.0
Metabolites in plasma and/or DBS	3.2	4	12.8
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	3.5	4	14.0
Olipudase alfa pharmacokinetics	1.5	7	10.5
		Approximate total per year	155.7
		Approximate total per 5 years	778.5

AP=alkaline phosphatase

Table 18, Table 19 show the additional approximate sampled blood volume in patients ages 12 to <18 years old with an olipudase alfa manufacturing scale change or manufacturing process update respectively. Not all of the patients will be exposed to both changes; therefore, blood volume would be calculated individually. To avoid excessive blood volume withdrawn, if similar assessment is regularly scheduled (IgG, PK or hematology and coagulation) in the same month, priority is given to manufacturing scale or updated manufacturing process update assessments and the regular similar assessments may be canceled.

Table 18 - Additional approximate sampled blood volume in patients ages 12 to <18 years with an olipudase alfa manufacturing scale change

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	3.5	1 sample per month for 6 months	21.0
Olipudase alfa pharmacokinetics - prior to manufacturing scale change	1.5	7	10.5
Olipudase alfa pharmacokinetics - post manufacturing scale change	1.5	7	10.5
		Approximate additional volume per study	42.0

Table 19 - Additional approximate sampled blood volume in patients ages 12 to <18 years with the olipudase alfa updated manufacturing process

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	3.5	1 sample per month for 6 months	21.0
Olipudase alfa pharmacokinetics – Second infusion on updated process	1.5	7	10.5
Hematology samples 3 months after first infusion on updated process	2	1	2
Coagulation and platelet samples 3 months after first infusion on updated process	3.6	1	3.6
		Approximate additional volume per study	37.1

Table 20 shows the approximate sampled blood volume in patients ages 12 to <18 years old beyond 5 years.

Table 20 - Approximate sampled blood volume in patients ages 12 to <18 years beyond 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	5	2	10.0
Hematology	3.6	2	7.2
Safety biomarkers	6.5	2	13.0
Efficacy biomarkers	10	1	10.0
Metabolites in plasma and/or DBS	3.2	1	3.2

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Approximate total per year, beyond 5 years			43.4
Approximate total per 4 years, beyond 5 years			173.6

Table 21 shows the approximate sampled blood volume in the child cohort (6 to <12 years old) and in patients ages 3 to <6 years old in the first 5 years.

Table 21 - Approximate sampled blood volume in patients in the child cohort (6 to <12 years) and in patients ages 3 to <6 years in the first 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	4.0	4	16.0
Hematology	1.2	4	4.8
Coagulation	2.8	4	11.2
Safety biomarkers	6.2	4	24.8
Efficacy biomarkers	5.1	4	20.4
Serum bone-specific AP and C-telopeptide	2.2	4	8.8
Metabolites in plasma and/or DBS	1.5	4	6.0
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	1.1	4	4.4
Olipudase alfa pharmacokinetics	1.5	6	9.0
		Approximate total per year	105.4
		Approximate total per 5 years	527.0

AP=alkaline phosphatase

Table 22 and Table 23 show the additional approximate sampled blood volume in patients in the child cohort (6 to <12 years) and ages 3 to <6 years with an olipudase alfa manufacturing scale change to Process C([redacted]) or manufacturing process update to Process C([redacted]) respectively. Not all of the patients will be exposed to both changes; therefore blood volume would be calculated individually. To avoid excessive blood volume withdrawn, if similar assessment is regularly scheduled (IgG, PK or hematology and coagulation) in the same month, priority is given to manufacturing scale or updated manufacturing process update assessments and the regular assessment may be canceled.

Table 22 - Additional approximate sampled blood volume in patients in the child cohort (6 to <12 years) and ages 3 to <6 years with an olipudase alfa manufacturing scale change

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG positive patients	2.2	1 sample per month for 6 months	13.2
Olipudase alfa pharmacokinetics – prior to manufacturing scale change	1.5	6	9.0
Olipudase alfa pharmacokinetics – post manufacturing scale change	1.5	6	9.0
		Approximate additional volume per study	31.2

Table 23 - Additional approximate sampled blood volume in patients in the child cohort (6 to <12 years) and ages 3 to <6 years with an olipudase alfa manufacturing process update

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	2.2	1 sample per month for 6 months	13.2
Olipudase alfa pharmacokinetics – Second infusion on updated process	1.5	6	9.0
Hematology samples 3 months after first infusion on updated process	1.2	1	1.2
Coagulation and platelet samples 3 months after first infusion on updated process	2.8	1	2.8
		Approximate additional volume per study	26.2

Table 24 shows the approximate sampled blood volume in the child cohort (6 to <12 years old) and in patients ages 3 to <6 years old beyond 5 years.

Table 24 - Approximate sampled blood volume in patients in the child cohort (6 to <12 years) and in patients ages 3 to <6 years - beyond 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	4	2	8.0
Hematology	2.8	2	5.6
Safety biomarkers	6.2	2	12.4
Efficacy biomarkers	5.1	1	5.1
Metabolites in plasma and/or DBS	1.5	1	1.5

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Approximate total per year, beyond 5 years			32.6
Approximate total per 4 years, beyond 5 years			130.4

Table 25 shows the approximate sampled blood volume in patients from birth to ≤2 years old in the first 5 years.

Table 25 - Approximate sampled blood volume in patients from birth to ≤2 years of age in the first 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	4.0	4	16.0
Hematology	1.2	4	4.8
Coagulation	2.8	4	11.2
Safety biomarkers	4.0	4	16.0
Efficacy biomarkers	3.7	4	14.8
Serum bone-specific AP and C-telopeptide	2.2	4	8.8
Metabolites in plasma and/or DBS	1.5	4	6.0
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	1.1	4	4.4
Olipudase alfa pharmacokinetics	1.5	5	7.5
		Approximate total per year	89.5
		Approximate total per 5 years	447.5

AP=alkaline phosphatase

Table 26 and Table 27 show the additional approximate sampled blood volume in patients from birth to ≤2 years of age with an olipudase alfa manufacturing scale change or manufacturing process update respectively. Not all of the patients will be exposed to both changes; therefore blood volume would be calculated individually. To avoid excessive blood volume withdrawn, if similar assessment is regularly scheduled (IgG, PK or hematology and coagulation) in the same month, priority is given to manufacturing scale or updated manufacturing process update assessments and the regular assessment may be canceled.

Table 26 - Additional approximate sampled blood volume in patients from birth to ≤2 years of age with an olipudase alfa manufacturing scale change

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	1.1	1 sample per month for 6 months	6.6
Olipudase alfa pharmacokinetics – prior to manufacturing scale change	1.5	5	7.5
Olipudase alfa pharmacokinetics – post manufacturing scale change	1.5	5	7.5
		Approximate additional volume per study	21.6

Table 27 - Additional approximate sampled blood volume in patients from birth to ≤2 years of age with an olipudase alfa manufacturing process update

Assessment	Volume (mL) per sample	Number of samples	Total (mL)
Anti-olipudase alfa IgG and neutralizing antibodies in IgG-positive patients	1.1	1 sample per month for 6 months	6.6
Olipudase alfa pharmacokinetics – Second infusion on updated process	1.5	5	7.5
Hematology samples 3 months after first infusion on updated process	1.2	1	1.2
Coagulation and platelet samples 3 months after first infusion on updated process	2.8	1	2.8
		Approximate additional volume per study	18.1

Table 28 shows the approximate sampled blood volume in patients from birth to ≤2 years old beyond 5 years.

Table 28 - Approximate sampled blood volume in patients from birth to ≤2 years of age- beyond 5 years

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Liver function, clinical chemistry, and lipid profile	4	2	8
Hematology	2.8	2	5.6
Safety biomarkers	4	2	8
Efficacy biomarkers	3.7	1	3.7
Metabolites in plasma and/or DBS	1.5	1	1.5

Assessment	Volume (mL) per sample	Number of samples per year	Total (mL) per year
Approximate total per year, beyond 5 years			26.8
Approximate total per 4 years, beyond 5 years			107.2

Additional blood samples may be required for IgE, serum tryptase, and complement activation following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions. Additional blood volumes are provided in Table 29.

Table 29 - Approximate sampled blood volume per infusion following moderate, severe, or recurrent IARs suggestive of hypersensitivity reactions

Type	Volume (mL) per sample
IgE antibodies	3.5
Serum tryptase	3.5
Complement	2.0
Total per infusion	9.0

9.6 FUTURE USE OF SAMPLES

For patients who have consented to it, left over samples following testing may be used for other research purposes (excluding genetic analysis) related to ASMD. These samples will be stored for 15 years after end of the study in compliance with applicable country-specific regulations.

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

These samples will remain labeled with the same identifiers as the ones used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The sponsor has included safeguards for protecting subject confidentiality and personal data (Section 14.3 and Section 14.5, respectively).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

Section 1.1 through Section 1.5 summarize the schedules of study events for all patients enrolled into this study. Individual assessments are described in Section 9.

10.2 STUDY PROCEDURES

Infusions will take place at the study site, or for some patients, at home.

10.2.1 Home infusions

Home infusion may be possible. Patients must meet the eligibility requirements outlined below. In addition, the investigator and the sponsor must agree that home infusion is appropriate.
To receive home infusions, the following criteria must be met:

- The investigator must agree in writing that home infusion is appropriate for the patient.
- The patient, or the pediatric patient's parent(s) or legal guardian(s), must be willing and able to comply with home infusion procedures.
- The patient must, in the investigator's (or designee's) opinion, have been clinically stable with no history of moderate or severe IARs for at least 6 months, and must be on a stable olipudase alfa dose. No infusion rate increases will be allowed while a patient is receiving home infusions.
- The patient must have no ongoing (not yet recovered) SAEs that, in the opinion of the investigator, may affect the patient's ability to tolerate the infusion.
- Home infusion infrastructure, resources, and procedures must be established and available according to applicable regional regulations.
- For patients experiencing an IAR while being infused at home, the investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion or return to the study site for their following infusion and when the patient would be ready to resume home infusion. In case home infusion continues, the investigator will guide the home infusion staff on the measures to be followed for subsequent infusion to manage the IAR (eg, infusion interruption, premedication, change the infusion rate, etc. See Treatment of infusion-associated reactions in Section 8.6.1.
- If recurrent IARs or hypersensitivity reactions occur, the investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion.
- If a severe hypersensitivity reaction or an anaphylaxis reaction occurs, during an infusion given at home, treatment will be discontinued immediately, and appropriate medical treatment will be initiated. The patient will return to the study site for further management

until the investigator agrees with the sponsor that it is safe for the patient to continue to be treated via home infusion. See Section 8.6 for details on severe hypersensitivity and anaphylaxis management.

- For the switch from Process C(■) IMP to Process C(■) IMP, if the site visit is possible, the patient should receive the first infusion at the site. However, if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, the first infusion of the Process C(■) IMP is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations.
- Prior to beginning home infusions, the home infusion staff, including new staff members, must have been appropriately trained and/or licensed, if applicable, on proper procedures to prepare and administer infusions, monitor patients, document procedures, and report to site on a timely basis.
- The home infusion staff must have access to and be trained on proper use of safety equipment, including, but not limited to, cardiopulmonary resuscitation equipment.
- Home infusion staff must keep source documentation of the infusion, including documentation of any AEs. Home infusion staff must be amenable to providing specific source documentation to Sanofi Genzyme and agree to be monitored. The Principal Investigator is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company.
- An additional questionnaire about home infusion experience may be added any time before end of the study for patients who received home infusion treatment for total time of at least of one year.

10.2.2 Alcohol consumption

Patients must be willing to abstain from the use of alcohol for 1 day prior to and 3 days after each study drug infusion (see Section 7.2).

Patients will be counseled to limit alcohol consumption during the study:

- Male patients to a maximum of 30 grams of alcohol per day (2 drinks/day).
- Female patients to a maximum of 15 grams of alcohol per day (1 drink/day).

Patients who do not limit alcohol can be discontinued from the study according to investigator's discretion.

10.2.3 Pregnancy and contraception

Female patients of childbearing potential are required to have a negative urine β-HCG pregnancy test before enrolling in the trial and every 4 weeks prior to undergoing visit specific assessments and receiving olipudase alfa.

10.2.3.1 Pregnancy

Pregnancy will lead to treatment discontinuation in all cases. No studies of olipudase alfa have been conducted in pregnant women. To ensure patient safety for this study, all female patients of childbearing potential must have a negative urine β-HCG pregnancy test every 4 weeks.

Female patients of childbearing potential and sexually mature male patients must be willing to practice true abstinence, or use 2 acceptable, effective methods of contraception. Every effort will be made to prevent pregnancy during this study. In all cases, the sponsor must be notified of all terminations to treatment as soon as possible and, if applicable, the date of withdrawal from the study must be recorded in the CRF and in the patient's medical record. If possible, all tests and evaluations listed for the end of study visit will be carried out. If a patient fails to return for the necessary visits, then every effort must be made to contact the patient and determine the reason(s), which will be recorded on the CRF.

Female patients will be instructed to notify the investigator immediately if they discover they are pregnant. Male patients will be instructed to notify the investigator immediately if they discover that their sexual partner is pregnant.

If the investigator learns of a report of pregnancy at any time after signing the informed consent, the investigator should follow the instructions in Section 10.5.2.3.1 for female patients on the study to contact Global Pharmacovigilance and Epidemiology (GPE) within 24 hours. For female partners of male patients on the study, the pregnancy form will be used to report the pregnancy to Global Pharmacovigilance and Epidemiology (GPE) within 24 hours. Follow-up of the pregnancy is mandatory until the outcome has been determined. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The investigator will be asked to obtain follow-up information after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

If a female patient is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths are reported as SAEs, and the investigator should follow the instructions in Section 10.5.2.2.

10.2.3.2 Contraception

Female patients of childbearing potential and sexually mature male patients are required to practice true abstinence in line with their preferred and usual lifestyle or use 2 acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established nonbarrier method such as oral, injected, or implanted hormonal methods, an intrauterine device,

or an intrauterine system for the duration of the study, and for at least 15 days after the last dose of study drug.

Female patients will be considered capable of bearing children unless they have not yet had menarche, had a hysterectomy or bilateral oophorectomy, or have undergone menopause (ie, are ≥50 years old without menses for ≥1 year or are <50 years old with confirmed ovarian failure).

10.3 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (eg, hospital records, clinical and office charts, laboratory reports and notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided in the CRF.

All protocol-required information collected during the study must be recorded by the investigator or other study personnel in the source documentation for the study. The source documentation will be used to enter the protocol-required information into the CRF. No data should therefore be directly entered into the CRF.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the source and CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to treatment discontinuation in all cases. Sexually active female patients of childbearing potential and sexually active male patients who permanently discontinue must use 2 forms of contraception for at least 15 days after their last dose.

10.4.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation, decided by the investigator, corresponds to more than 1 dose not administered to the patient. Dose reintroduction regimens may be required for patients who have missed more than 1 dose between studies, depending on their usual dose.

For patients receiving home infusions who have missed 2 or fewer doses, the investigator can decide whether reintroduction should occur at the hospital/study site or via home infusion. For

patients who miss 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the hospital/study site. If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), reintroduction may be done via home infusion.

The investigator, in consultation with the sponsor, will determine whether the patient will be redosed. Reintroducing patients to olipudase alfa treatment will take into account the patient's usual dose, the number of missed infusions, and the patient's ability to tolerate the dose.

Upon reintroduction of treatment, certain assessments will be repeated at infusions (Section 8.1.5). The investigator will decide if additional specific assessments may be required before the patient can begin the reintroduction regimen.

Olipudase alfa reintroduction guidance is described in Section 8.1.1. Reintroduction of olipudase alfa treatment will be done with appropriate monitoring at the discretion of the investigator and confirmation that the patient still meets the study criteria (Section 7.1 and Section 7.2).

The duration of all temporary treatment discontinuations should be recorded by the investigator in the appropriate screens of the CRF.

10.4.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the investigator, sponsor, or the patient not to re-expose the patient to the IMP at any time.

10.4.3 List of criteria for permanent treatment discontinuation

Patients may withdraw from treatment at any time and irrespective of the reason. The investigator may also decide to withdraw a patient from treatment.

Patients should discontinue the IMP for the following reasons:

- Unacceptable toxicity.
- The need for intervention or therapy precluded by protocol, and determination by the investigator that it is medically necessary to do so.
- The patient was unable to comply with the requirements of the protocol.
- The patient wishes to be withdrawn from treatment.
- The patient was erroneously included in the study (failed to satisfy all study criteria in Section 7).
- The patient participated in another investigational study without the prior written authorization from the sponsor.
- The patient is no longer deriving clinical benefit, in the opinion of the investigator.
- Pregnancy.

In addition, the sponsor may decide to discontinue the trial prematurely for any other reason.

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

Patients who received at least 1 dose of study drug and who are withdrawn from the study will be asked to complete all discontinuation assessments before withdrawal (as detailed in Section 1.1, Section 1.2, Section 1.4 and Section 1.5). They will also receive a safety follow-up telephone call from the study site 30 to 37 days after the final administration of study drug. If a patient fails to return for the necessary visits, every effort must be made to contact the patient to determine the reason(s). The investigator will document the reason(s) for treatment discontinuation/study withdrawal on the CRF and in the patient's medical record. In all cases, the sponsor must be notified of all study terminations as soon as possible.

10.4.4 Handling of patients after permanent treatment discontinuation

Patients or parent/legal guardians who decide to discontinue participation in the study should be contacted by the study investigator in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs.

When possible, all tests and evaluations listed in Section 1.1, Section 1.2, Section 1.4 and Section 1.5 for the post treatment withdrawal visit should be carried out within 2 weeks of the last olipudase alfa infusion. If a patient fails to return for the necessary visits, every effort must be made to contact the patient and determine the reason(s) and record the reason(s) on the CRF.

In all cases, the sponsor must be notified of all study terminations as soon as possible and the reason for and date of withdrawal from the study must be recorded in the CRF and in the patient's medical record.

10.4.5 Procedure and consequence for patient withdrawal from study

Patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Preferably the patient should withdraw consent in writing and, if the patient refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

The reason for withdrawal should be captured. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Patients who withdraw should be asked to come back for the end of study visit and will receive the safety follow phone call.

For patients who fail to return to the site, the investigator should make the best effort to contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status.

Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

The investigator is the primary person responsible for making all clinically relevant decisions on safety issues.

Any abnormal findings that meet the definition of an AE per Section 10.5.1 will be recorded on the CRF. The investigator will continue to monitor the patient until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

All AEs (as described in Section 10.5.1) regardless of seriousness or relationship to study treatment will be collected from the time of written informed consent until the patient completes participation in the study as defined in Section 6.3.1. Adverse events that started during the previous study which are ongoing at the time the patient signs the written informed consent should be reported in this study.

All SAEs (as described in Section 10.5.1.2) and any AESI requiring immediate notification (as described in Section 10.5.2.3.1) including those ongoing at the time of study completion) will be monitored until resolution, stabilization of the condition, or until it is mutually agreed upon by both the investigator and the sponsor safety physician to discontinue.

If, at any time after the patient has completed participation in the study (as defined in Section 6.3.1), the investigator or study staff becomes aware of an SAE that they believe is possibly related or related to IMP, then the event and any known details should be reported promptly to the sponsor. Follow the reporting instructions in Section 10.5.2.2.

All AEs diagnosed by the investigator will be reported per applicable regulations and guidelines. Definitions for AEs, SAEs, AESI; and instructions for AE monitoring and reporting, are provided in Section 10.5 through Section 10.8. All AEs will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the time of the considered database lock.

The investigator is responsible for reviewing and signing all laboratory reports. Any abnormal findings that meet the definition of an AE per Section 10.5.1 will be recorded on the CRF. The investigator will continue to monitor the patient until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

10.5.1 Definitions of adverse events

10.5.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.5.1.2 Serious adverse event

An 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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

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

- Cancers diagnosed during the study.
- Chronic neurodegenerative diseases if newly diagnosed and not part of the ASMD spectrum.

10.5.1.3 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment. Reporting guidelines and follow-up instructions are provided below.

AESIs include pregnancy, IARs (hypersensitivity reactions, APRs, and CRSs).

10.5.1.3.1 Pregnancy

Pregnancy of a female patient entered in the study, and pregnancy occurring in a female partner of a male patient entered in this study. See Section 10.2.3.1 for details.

10.5.1.3.2 Infusion-associated reactions

Some AEs may be manifestations of IARs, including hypersensitivity reaction, APR, and CRS. However, original signs and symptoms must be reported as AEs. In the CRF, investigators are asked to identify whether a specific AE represents a clinical manifestation of the IAR.

Infusion-associated reactions are defined as AEs that occur during the infusion or within up to 24 hours after the start of infusion and are considered as related or possibly related to the study treatment by the investigator or the sponsor. An event occurring ≥24 hours after the start of an infusion may be judged an IAR at the discretion of the investigator or sponsor. For this study of olipudase alfa, IARs may present as different types of reactions, such as hypersensitivity reactions, APRs, and CRS.

10.5.1.3.2.1 Hypersensitivity reactions

Infusion-associated hypersensitivity reactions seen with other enzyme replacement therapies are typically immunoglobulin-mediated (IgG/IgE) and occur after sensitization. After subsequent exposure to the antigen typically early into or shortly after the infusion, a "sensitized" patient may experience a broad range of allergic reactions that can be mild to severe or life-threatening. Anaphylaxis (or anaphylactic reaction) is a serious, IgE mediated allergic reaction that is rapid in onset, and may cause death (22). Anaphylactoid, or non-immunologic anaphylaxis, reactions may present with similar serious clinical manifestations as anaphylaxis, but without prior exposure to the drug and are due to nonimmunologic-mediated mast cell degranulation. Although mechanistically different, anaphylactic and anaphylactoid reactions are treated similarly.

Common symptoms of hypersensitivity reactions seen with other enzyme replacement therapy include urticaria, rash, dyspnea, and less frequently, angioedema. Other symptoms of hypersensitivity IARs, APRs, and CRS include fever, hypotension, tachycardia, nausea, vomiting, pain, and headache.

There were no IARs suggestive of hypersensitivity in the Phase 1b trial (6).

10.5.1.3.2.2 Acute phase reactions

Acute phase reactions are considered a type of IAR. Acute phase reactions were observed in the Phase 1 single-dose study (5) and the Phase 1b repeat-dose study (6) in 2 patients during dose escalation. The patients successfully completed the trial. Typically, APRs occurred within 12 to 72 hours after olipudase alfa infusion and were indicative of an inflammatory response as they were associated with elevations in hsCRP and changes acute phase reactants including, but not limited to, neutrophils, iron, ferritin, fibrinogen, D-dimer, transferrin, albumin, prothrombin time, and partial thromboplastin time. Typical AEs that were reported by the patient included, but were not limited to, pyrexia, nausea, vomiting, fatigue, and pain; and were concurrent with the changes in specific laboratory parameters. Accordingly, APRs will be determined based on combined significant laboratory findings and clinical symptoms.

10.5.1.3.2.3 Cytokine release syndrome

Cytokine release syndrome is another type of IAR, attributed to the release of excessive amounts of cytokines shortly after the IV administration of certain therapeutic agents. The severe form of CRS is cytokine storm, which may be life threatening. Nonclinical studies of high-dose olipudase alfa have suggested the possibility of CRS. There were no events characterized as cytokine release syndrome in either the Phase 1 single- or the Phase 1b repeat-dose trials with olipudase alfa (5, 6). The Phase 1 single-dose study demonstrated increases in IL-8 and IL-6; macrophage inflammatory protein 1, alpha component (MIP-1α); macrophage inflammatory protein 1, beta component (MIP-1β); and other cytokines and biomarkers (based Myriad Rules-Based Medicine Human Multi-Analyte Profile® antigen panel) after a single dose of ≥ 0.3 mg/kg of olipudase alfa (5). In the Phase 1b trial, increases in mean IL-6 and IL-8 values were associated with the first administrations of olipudase alfa at doses 0.6 mg/kg through 2.0 mg/kg and tended to be concurrent with acute phase responses (6). Unlike immunoglobulin-mediated hypersensitivity reactions, no prior antigen exposure is required for the development of CRS. Symptoms of CRS develop soon after exposure, and range from mild to severe. Although CRS shares some symptoms with other IARs (ie, hypersensitivity reactions and APRs), symptoms typical of CRS include pyrexia, nausea, vomiting, fatigue, pain, myalgia, and in severe cases, multiorgan system dysfunction or failure, severe headache, and pulmonary edema. Cytokine release syndrome will be determined based on combined significant laboratory findings and clinical symptoms.

10.5.1.3.3 Symptomatic overdose (serious or nonserious) of study drug

An overdose (accidental or intentional) of study drug is defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half

the recommended duration of administration. An asymptomatic overdose will be reported as a standard AE.

10.5.1.3.4 Laboratory values

The following laboratory values and symptoms will be considered AESIs (see also dose stopping criteria in Section 8.1.6), as follows:

- 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, fever, rash, or eosinophilia (> ULN).

10.5.1.3.5 Other significant events

Any AE that, in the opinion of the investigator or sponsor, raises significant concern regarding the safety of olipudase alfa at the administered dose will be considered an AESI.

10.5.1.4 Definitions for criteria of adverse events

10.5.1.4.1 Relationship to study treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. This assessment is to be made in blinded studies and also for known comparators. For each AE/SAE the investigator is to determine whether there is a reasonable possibility demonstrated by evidence which suggests a causal relationship between the study treatment and the AE according to the categories below:

- Not related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A relationship to the investigational product must be assigned for each AE/SAE recorded, even if there is only limited information at the time. The investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

10.5.1.4.2 Severity of adverse event scoring

Note that "severity" is not the same as "seriousness," which is defined in Section 10.5.1.2.

Intensity:

- Mild = no modification of daily activities and does not require mandatory corrective/symptomatic treatment.
- Moderate = hinders normal daily activities and/or requires mandatory corrective/symptomatic treatment.
- Severe = prevents daily activities and requires mandatory corrective/symptomatic treatment.

10.5.1.4.3 Outcome

Outcome describes the status of the AE. The investigator will provide information regarding the patient outcome of each AE. Definitions for possible results of an AE include:

- Fatal: The termination of life as a result of an AE.
- Not recovered/not resolved: The patient has not recuperated, or the AE has not improved.
- Recovering/resolving: The patient is recuperating, or the AE is improving.
- Recovered/Resolved: The patient has recuperated, or the AE has resolved.
- Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.
- Unknown: Not known, not observed, not recorded, or refused.

10.5.1.4.4 Action taken regarding the investigational product

The investigator will be required to provide the action taken regarding investigational product (eg, active, comparator) in response to the AE. Options include:

- Dose increased: Increase in the frequency, strength, or amount of investigational product administered.
- Dose not changed: No change in administration of the investigational product.
- Dose reduced: Reduction in the frequency, strength, or amount of investigational product administered.
- Drug (investigational product) interrupted: Temporary interruption in administration of the investigational product.
- Drug (investigational product) withdrawn: Administration of the investigational product terminated (no further dosing).

- Not applicable: Determination of a value is not relevant in the current context. “Not applicable” can be used only if the:
  - AE occurred before the first IMP dose,
  - Patient has died; or,
  - AE occurred after the last scheduled infusion.
- Unknown: Not known, not observed, not recorded, or refused.

10.5.2 Guidelines for reporting adverse events

10.5.2.1 General guidelines

See Table 30 for an overview of AE reporting instructions.

- All AEs, regardless of seriousness or relationship to study treatment spanning from the signature of the informed consent form until the end of the study are to be recorded on the corresponding CRF.
- Except for IARs, whenever possible, diagnosis or single syndrome will be reported instead of symptoms. For IARs, all symptoms must be separately recorded.
- The investigator will specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- The investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients.
- Laboratory, vital sign measurements, or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic, and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI (Section 10.5.1.3).

10.5.2.2 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the CRF; the system will automatically send a notification to the monitoring team after approval of the investigator within the CRF or after a standard delay. If automatic notification is not available, paper SAE notifications must be sent manually to the local Pharmacovigilance and Epidemiology office.

- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the electronic CRF system does not work.

Any SAE brought to the attention of the investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility should be reported to the monitoring team.

10.5.2.3 Guidelines for reporting adverse events of special interest

10.5.2.3.1 Reporting of adverse events of special interest with immediate notification

For AESIs the sponsor will be informed within 24 hours as per the SAE notification instructions described in Section 10.5.2.2 even if not fulfilling a seriousness criterion, using the corresponding screens in the CRF.

- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria,
  - In the event of pregnancy, study drug should be discontinued,
  - Follow-up of the pregnancy is mandatory until the outcome has been determined.
- Infusion-associated reaction (see Section 10.5.1.3.2), which include:
  - Hypersensitivity reactions,
  - Acute-phase reaction,
  - Cytokine release syndrome.
- Symptomatic overdose with IMP:
  - No doses greater than 3.0 mg/kg every other week have been administered to patients. In the event of overdose, the infusion should be terminated immediately. The patient should be monitored closely for the development of IARs, including seizures (which may occur at high doses of polysorbate 80), and should be treated appropriately at the investigator’s discretion,

- **Note:** An overdose (accidental or intentional) of study drug is defined as an increase of at least 30% of the dose to be administered in the specified duration, or if the dose is administered in less than half the recommended duration of administration. The circumstances (ie, accidental or intentional) will be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms (Section 10.5.2.5).

- The following laboratory values and symptoms (see also dose stopping criteria in Section 8.1.6) as follows:
  - Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to olipudase alfa therapy, [ie, baseline in the previous study (DFI13412 or DFI13803)]) 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, fever, rash, or eosinophilia (>ULN).
- Any AE that, in the opinion of the investigator or sponsor, raises significant concern regarding the safety of olipudase alfa at the administered dose

10.5.2.3.2 Reporting of adverse events of special interest without immediate notification

- Asymptomatic overdose with IMP (see Section 10.5.2.3.1 for the definition of an overdose).

10.5.2.4 Guidelines for management of specific laboratory abnormalities

Not applicable.

10.5.2.5 Summary of adverse event reporting

Table 30 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety complementary form	Other specific forms
Adverse event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious adverse event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criteria per Section 10.5.1.2	Yes	Yes	No
Adverse event of special interest	Expedited (within 24 hours)	Symptomatic overdose	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Infusion associated reactions (IAR)/hypersensitivity reactions	Yes	Yes	No
		Laboratory values per Section 10.5.1.3 and Section 10.5.2.3			

Abbreviations: AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event; ULN=upper limit of normal

10.6 PREGNANCY REPORTING

Female patients will be instructed to notify the investigator immediately if they discover they are pregnant. Pregnant female patients will be discontinued from the study.

Male patients will be instructed to notify the investigator immediately if they discover that their sexual partner is pregnant.

If the investigator learns of a report of pregnancy at any time after signing the informed consent, the investigator should follow the instructions in Section 10.5.2.3.1 to contact the sponsor within 24 hours. The investigator will be asked to complete the AE form, the safety complementary form, and the pregnancy form. The patient will be followed until the outcome of the pregnancy is known. The investigator will be responsible for this follow-up.

If not otherwise established, the investigator will inform the patient that the sponsor is required to gather information regarding the course and outcome of the pregnancy after exposure to a study product. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information. Follow-up information may be requested at additional time points. All study-related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy is an AESI, not an AE or SAE. All information received will be assessed for any AEs and SAEs and processed per study guidelines. If the patient is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths are reported as SAEs.

10.7 OBLIGATIONS OF THE SPONSOR

During the course of the study, the sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction), to the health authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate, and to the investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the health authorities according to local regulations.

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

10.8 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations and will be included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

An SAP will be written and finalized prior to database lock to give guidance to the statistical analysis. It will be in compliance with the International Council on Harmonisation (ICH) and Food and Drug Administration's Guidance for Industry: Statistical Principles for Clinical Trials.

11.1 GENERAL CONSIDERATIONS

The sponsor or its designee will perform the statistical analysis of the data from this study. The analysis will be performed using the SAS® statistical software system Version 9.3 or higher.

Important CRF data, as well as any outcomes derived from the data, will be displayed in patient data listings. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using descriptive statistics (number of patients with observation, mean, standard deviation, median, minimum, and maximum).

11.1.1 Final analysis

The final analysis will be performed at the completion of the treatment period. This analysis will include safety, efficacy, PK, and PD data. Analyses of change will be based upon changes from baseline prior to olipudase alfa therapy (ie, baseline in the previous study [DFI13412 or DFI13803]) through study completion. The final statistical analyses will be performed when the entire database is locked and signed off, in accordance with the standard operating procedures of the sponsor or designee.

11.2 DETERMINATION OF SAMPLE SIZE

Sample size will be determined by the number of patients who complete the treatment phase of a previous clinical study of olipudase alfa, sign the informed consent form for the LTS13632 study, and meet the eligibility criteria. It is expected that the sample size for this study will be approximately 25.

11.3 DISPOSITION OF PATIENTS

Enrolled patients are defined as patients who signed informed consent forms.

Patient enrollment will be summarized for the enrolled patient set by study site, including frequency and percentage of patients who received at least 1 infusion (total or partial) of study treatment.

All patients who receive an infusion (total or partial) of olipudase alfa (safety population) will be included in the summary of patient disposition. The number and percentage of patients who either complete the study or withdraw from the study, and/or withdraw from treatment, along with the

reasons for their withdrawal, and who completed or discontinued the posttreatment safety follow up will be presented.

11.4 ANALYSIS POPULATIONS

The safety set will include all enrolled patients who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

The PK analysis includes all patients who receive at least 1 infusion of study drug after PK analysis informed consent and have evaluable PK data. Other analysis populations, such as for pharmacogenomics, if any, will be defined in the SAP.

Subgroup analyses may be conducted for safety and efficacy endpoints in subpopulations of the safety set. Subpopulations may be defined by parameters including, but not limited to, age, gender, genotype, exposure to study treatment, pre-dose (trough) plasma concentration of olipudase alfa, and concomitant therapies. Further details will be provided in the SAP.

Throughout the study, "baseline" refers to the baseline in the previous study (DFI13412 or DFI13803).

11.5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using descriptive statistics for the safety set.

11.6 STATISTICAL METHODS

All analysis will be done on the safety set unless specified otherwise.

11.6.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed and summary statistics will be presented.

11.6.2 Analyses of efficacy endpoints

Efficacy assessments are described in Section 9.2.

Summary statistics for the values, nominal change from baseline, and percent change from baseline will be presented for efficacy assessments at various study time points. The baseline value is defined to be the latest assessment value prior to the first dose of study treatment in the primary study. For selected parameters, the mean (95% confidence interval) or median (interquartile range) may be plotted over time. Categorical variables will be summarized using frequencies and percentages at various study time points.

The association between changes in efficacy parameters and total amount of drug received may be examined.

11.6.2.1 Multiplicity considerations

Not applicable.

11.6.3 Analyses of safety data

Safety assessments are described in Section 9.1.4 through Section 9.1.15. All safety analyses will be performed on the safety set (defined in Section 11.4). No formal inferential testing will be performed. Summaries will be descriptive in nature.

The following definitions will be applied to laboratory parameters, ECGs, and vital sign measurements.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests and vital signs.
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment period, taking into account all evaluations performed during the treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment PCSA percentage.
- Treatment period: the treatment period used for quantitative analysis is defined as the time from first dose to the last dose of IMP +14 Days.

11.6.3.1 Adverse events

The definitions in Section 10.5.1 will be used for AEs. Pretreatment AEs will be listed and presented separately from treatment-emergent AEs.

All AEs will be coded using the most recent version of the MedDRA. Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT) sorted in alphabetical order for each treatment group, and the number and percentage of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to olipudase alfa, all treatment-emergent AEs leading to treatment discontinuation and study discontinuation, all treatment-emergent AEs that are IARs, all treatment-emergent SAEs (including treatment-related SAEs), and all AEs with fatal outcomes (including fatal treatment-emergent AEs) will be summarized.

Detailed listings of AEs, SAEs, AESIs, related AEs, and discontinuations due to AEs will be provided. These will include the olipudase alfa dose of the infusion prior to or during the occurrence of the AE, where applicable.

For the overall analyses of AEs, the number of AEs and annualized rate, and the number and proportion of patients experiencing specific AEs will be tabulated according to the olipudase alfa dose level of the infusion prior to or during the occurrence of the AE.

Separate analyses of AEs will also be conducted by demographic characteristics (eg, age and sex). Adverse events of special interest, such as IARs, and SAEs will be analyzed similarly.

11.6.3.1.1 Adverse events of special interest

Detailed listings for AESIs, including IAR, APR, and CRS will be provided.

11.6.3.1.2 Deaths

The following deaths summary will be generated:

- Treatment-emergent AE leading to death (death as an outcome on the AE CRF page as reported by the investigator) by primary SOC and PT showing number and percent of patients sorted by internationally agreed order of SOC and alphabetic order of PT.

11.6.3.2 Laboratory data and vital sign measurements

11.6.3.2.1 Physical examinations, vital sign measurements, electrocardiograms, and echocardiograms

Observed values and changes from baseline (as applicable) will be summarized descriptively overall and by highest tolerated dose and/or by dose received prior to evaluation. Outlier summaries for the ECG parameters (eg, QTc) will be created for the safety set.

11.6.3.2.2 Clinical laboratory tests

Observed values and changes from baseline to study time points will be summarized descriptively overall and by highest tolerated dose and/or by dose received prior to evaluation. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Frequencies of CS abnormal values and shifts from baseline to study time points will be summarized. Patient listings of biomarkers will be provided.

11.6.3.3 Immune response assessments

Immune response assessments will be analyzed in the safety set. The presence, absence, and titers of serum anti-olipudase alfa IgG antibodies will be summarized. The data will be summarized over time overall and by the dose level of the infusion prior to or during the evaluation.

Levels of acute phase reactants, serum tryptase, complement activation, neutralizing antibodies, and anti-olipudase alfa antibodies (IgG and IgE) obtained in response to an IAR, and skin testing results (if available), will be presented in patient listings, if applicable.

11.6.4 Analyses of pharmacokinetic and pharmacodynamic variables

Plasma concentration-time data will be analyzed using actual dosing and sampling times by noncompartmental methods. Pharmacokinetic parameters will be calculated for each patient and summarized by dose level and study week. As data permit, PK parameters may also be evaluated across dose level at each manufacturing scale or manufacturing process. Metabolite levels will be summarized by dose level and time point using descriptive statistics.

11.6.5 Analyses of quality of life and cognitive variables

Scoring for the quality of life and cognitive assessments will be conducted as stated by the developers of the questionnaires. Differences with respect to the changes from baseline will be presented descriptively.

11.7 INTERIM ANALYSIS

No formal interim analysis is planned for this study; however a formal summary of data or interim CSR may be produced to support regulatory approval(s) and/or other application/ submission requirement(s).

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. See also Section 13.1.

12.3 INFORMED CONSENT

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, and under the investigator's responsibility, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC]). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the informed consent form should be signed, name filled in, and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion.

For patients who are less than 18 years old, the informed consent form should be signed, name filled in, and personally dated by the patient or the patient’s parents, or by the patient’s legally acceptable guardian, and by the person who conducted the informed consent discussion. If only 1 parent or guardian signs the consent form, the investigator must document the reason there is only 1 parent or guardian’s signature. A copy of the signed and dated written informed consent form will be provided to the patient.

Pediatric participants who can read the assent form will do so before writing their name and dating or signing and dating the form. Pediatric participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Pediatric participants who can understand, but who can neither write nor read, will have the assent form read to them in the presence of an impartial witness who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the investigator for obtaining the patient's informed consent must be reviewed and approved by the sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the investigator or the sponsor must submit this clinical trial protocol to the appropriate ethics committee (IRB/IEC) and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with ethics committee (IRB/IEC) composition.

The clinical trial (study number, clinical trial protocol title, and version number), the documents reviewed (clinical trial protocol, informed consent form, investigator's brochure, investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational medicinal product will not be released at the study site and the investigator will not start the study before the written and dated approval/favorable opinion is received by the investigator and the sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol must be submitted to the ethics committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the investigator's brochure will be sent to the ethics committee (IRB/IEC).

A progress report is sent to the ethics committee (IRB/IEC) at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The investigator(s) and delegated investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice, and the applicable regulatory requirements.

The investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the sponsor (including security rules). The investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, discrepancy resolution form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives. In particular, the Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Particular attention should be paid to the confidentiality of the patient's data to be transferred.

The investigator may appoint such other individuals as he/she may deem appropriate as subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators will be supervised by and work under the responsibility of the investigator. The investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded in the CRFs. Thus, the main duty of the monitoring team is to ensure the safety, well-being, and rights of all study subjects are observed, and to assist the investigator and the sponsor in maintaining a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted through monitoring visits, letters, or telephone calls by a representative of the monitoring team to ensure patient safety, well-being, and rights are observed, and to review study progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include, but not be limited to, review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records that support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection laws and rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the sponsor to record (according to sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the CRF.

The computerized handling of the data by the sponsor when available in the CRF may generate additional requests (discrepancy resolution form) to which the investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The following computerized systems may be used during the different steps of the study:

- For data management activities, Medidata RAVE.
- For PK activities, WinNonlin.
- For statistical activities, SAS.
- For pharmacovigilance activities, AWARE.

- For monitoring activities, IMPACT.
- For medical writing activities, VEEVA VAULT.
- For MRI activities, WebSend, BioPACS, and BioTrack.
- For IMP management, NASCA.
- For ECGs, CAMI7.
- For ECHO, Digiview.
- For central laboratory tests, Covance LabLink.

14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualifications, and training of each investigator and subinvestigator will be signed, dated, and provided to the sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The investigator must maintain confidentiality for all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The investigator should retain the study documents at least 25 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The investigator must notify the sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the CRFs, the investigator's brochure, and the results obtained during the course of the clinical trial is confidential prior to the publication of results. The investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committees (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The subinvestigators shall be bound by the same obligation as the investigator. The investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The investigator and the subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the investigator and the sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, investigators, and collaborators involved in the study.

14.4 PROPERTY RIGHTS

All information, documents, and IMP provided by the sponsor or its designee are and remain the sole property of the sponsor.

The investigator shall not mention any information or the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions that arise directly or indirectly from the clinical trial in any form shall be the immediate and exclusive property of the sponsor.

The sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the investigator and/or the subinvestigators shall provide all assistance required by the sponsor, at the sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the investigator and/or to the patients, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The sponsor also collects specific data regarding the investigator, as well as personal data from any person involved in the study, that may be included in the sponsor’s databases. The data shall be treated by both the sponsor and the investigator in compliance with all applicable laws and regulations.

Patient race will be collected in this study because these data are required by several health authorities, including the United States Federal Drug Administration. The following options will be listed for race on the CRF: American Indian or Alaska Native; Asian; Black; Native Hawaiian or Other Pacific Islander; White; Japanese; and the additional options of Not Reported and Unknown.

14.6 INSURANCE COMPENSATION

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not relieve the investigator and the collaborators from

maintaining their own liability insurance policy. An insurance certificate will be provided to the ethics committees (IECs/IRBs) or health authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice, and applicable regulatory requirements, the investigator should permit auditing by or on the behalf of the sponsor and inspection by regulatory authorities.

The investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such, will not disclose any personal identity or personal medical information.

The investigator must make every effort to assist with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the investigator is notified of a planned inspection by the authorities, he must inform the sponsor and authorize the sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities must be immediately communicated by the investigator to the sponsor.

The investigator must take appropriate measures required by the sponsor to take corrective actions for all issues identified during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 Decided by the sponsor

Decided by the sponsor in the following cases:

- If the information on the product leads to doubt as to the benefit/risk ratio.
- If the investigator has received from the sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the investigator of a fundamental obligation under this agreement, including but not limited to, breach of the clinical trial protocol, breach of the applicable laws and regulations, or breach of the ICH guidelines on Good Clinical Practice.
- If the total number of patients are included earlier than expected.

The sponsor reserves the right to stop the study or patient treatment at any time for any reason. In any case, the sponsor will notify the investigator of its decision by written notice.

14.8.2 Decided by the investigator

The investigator must notify (30 days prior notice) the sponsor of his/her decision and give the reason in writing.

In all cases (decided by the sponsor or by the investigator), the appropriate ethics committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The sponsor will be responsible for preparing a clinical study report and providing a summary of study results to the investigator.

The coordinating investigator who will sign off on the study report will be the investigator who first enrolled the largest number of patients in the trial.

14.10 PUBLICATIONS AND COMMUNICATIONS

The investigator agrees not to publish or release data or information pertaining to the study prior to the sponsor's written consent, being understood that the sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the sponsor agrees that, consistent with scientific standards, the first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred within 12 months of the completion of this study at all sites, the investigator shall have the right to publish or present independently the results of this study to the review procedure set forth herein. The investigator shall provide the sponsor with a copy of any such presentation or publication derived from the study for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other measures as the sponsor deems appropriate to establish and preserve its proprietary rights.

The investigator shall not use the name(s) of the sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the sponsor. The sponsor shall not use the name(s) of the investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The investigator should not implement any deviation from or changes to the clinical trial protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor, and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the ethics committee (IRB/IEC) and also by regulatory authorities if substantial prior to its implementation, unless there are overriding safety reasons.

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

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17 APPENDICES

17.1 APPENDIX A: COUNTRY SPECIFIC REQUIREMENTS

This section is not applicable.

17.2 APPENDIX B: PROTOCOL AMENDMENT HISTORY

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

17.2.1 Amended Clinical Trial Protocol 06 (29-Jan-2021)

This amended protocol (06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment are described below:

1. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic, to allow more flexibility with regard to additional options for monitoring techniques in compliance with applicable country-specific regulations.

2. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic that can lead to site closure or extenuating circumstances that prevent an in-person site visit, for the switch from Process C([redacted]) investigational medicinal product (IMP) to the updated manufacturing Process C([redacted]) IMP, adding the possibility to perform the first infusion at home for eligible patients in agreement between the Sponsor and the Investigator and in compliance with applicable country-specific regulations.

3. Liver function test (LFT) monitoring after infusion is already included in this protocol. However, review of the interim data from the clinical development program has identified "Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa" as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation have been added to the protocol.

Other important changes include:

1. In the context of this long-term study, the assessments have been streamlined to reduce patient burden. Assessments to ensure patient safety will be preserved. This change will be implemented

after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (the first cutoff date was on 10 December 2019).

2. During the study, pediatric patients who reach adult age (18 years old) will receive the adult infusion volume.

3. Other changes, omissions and corrections have also been addressed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary-Study design	Language added for clarification: During the study, pediatric patients who will reach adult age (18 years old) will receive the adult infusion volume.	Clarification on how to manage the IMP in patients reaching the adult age
Clinical Trial Summary-Study treatment	Language added for clarification: During clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process. The different processes are referred to as Process B, C(■) and C(■).	Clarification on the olipudase alfa manufacturing process changes
Clinical Trial Summary-Endpoint(s)	Sphingomyelin in plasma and metabolites in dried blood spot will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021	Analysis of sphingomyelin, ceramide and other metabolites (sphingosine-1- phosphate) in plasma or DBS through 52 weeks of treatment has been completed for all patients. Lyso-sphingomyelin and ceramide which represent the most informative readouts for pharmacodynamic response to treatment will be maintained throughout the study to continue to monitor levels of substrate and its metabolic product. In the context of this long-term study, these assessments will be streamlined to reduce patient burden. Assessments to ensure patient safety have been preserved.
Clinical Trial Summary-Assessment Schedule	Addition of: 48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is >2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment.	The assessments have been streamlined to reduce patient burden in the extension phase of this trial. Assessments to ensure patient safety have been preserved. The 48 hours post-infusion assessments no longer assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021; however, 24 hours post-infusion

Section # and Name	Description of Change	Brief Rationale
	Baseline is defined as the following: · For initial dose escalation: last values prior to first dose of olipudase alfa · For dose re-escalation: last values prior to the first re-escalation dose Below text is updated: In the first 5 years, pharmacodynamic (PD) evaluations will occur every 3 months then every 6 months after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. After 5 years, PD evaluations will occur every 12 months. PK evaluation will occur every 12 months only in the first 5 years and upon introduction of Process C(■) or Process C(■) at any time during the study.	assessments remain. Therefore, patient safety is not being compromised. Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa has been added as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation have been added to the protocol.
Section 1 - Study Flow Charts.	Updated manufacturing scale has been replaced by Process C(■). Updated manufacturing process has been replaced by Process C(■). Five new flowcharts (Tables 2, 4, 6, 8, and 10) have been added (resulting in table renumbering) describing assessments after cutoff for planned second database lock in 2021. Previous flow charts with the addition of: only applicable before the implementation of changes that will occur after the cutoff date of the second database lock For each of the flow charts initially presented in the protocol, complementary flow charts have been added to be effective after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. The following parameters will no longer been assessed: - Metabolites in plasma: ACE, sphingomyelin - Metabolites in dried blood spot - 48 hours after infusion: vital sign measurements, LFTs, hematology, and safety during dose re-escalation Timing changed from quarterly to every 6 months through Year 5 for the following parameters: - Metabolites in plasma: ceramide, lyso-sphingomyelin - Efficacy biomarkers: serum chitotriosidase, CCL18 - Bone biomarkers (alkaline phosphatase, C-telopeptide) if site visits are not possible (eg, during the COVID-19 pandemic) replaced by: If the site visit is not possible during a	Clarification on olipudase alfa manufacturing process changes In the context of this long-term study, some assessments will be streamlined to reduce patient burden. Given current knowledge about the study drug, assays can be replaced by targeted testing. Assessments to ensure patient safety will be preserved. This change will be implemented after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (the first cutoff date was on 10 December 2019): sites will be informed of the effective date. Analysis of sphingomyelin, ceramide and other metabolites (sphingosine-1- phosphate) in plasma or DBS through 52 weeks of treatment has been completed for all patients. Lyso-sphingomyelin and ceramide which represent the most informative readouts for pharmacodynamic response to treatment will be maintained throughout the study to continue to monitor levels of substrate and its metabolic product. Analysis of ACE through 52 weeks of treatment has been

Section # and Name	Description of Change	Brief Rationale
	regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit	completed for all patients. Initial objective to monitor for changes with treatment were achieved; no further longitudinal analysis is required. The other assessments have been streamlined to reduce patient burden in the extension phase of this trial. Assessments to ensure patient safety have been preserved.
Section 1.6 Study flow chart	Addition of: Switch from Process B to Process C for new manufacturing scale Switch from Process C([redacted]) to Process C([redacted]) for the updated manufacturing process	Clarification on the olipudase alfa manufacturing processes
Section 4.1 Introduction	Addition of: During clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process. The different processes are referred to as Process B, C([redacted]) and C([redacted]).	Clarification on the olipudase alfa manufacturing processes
Section 6.1.1 Treatment period	Below text is updated: PK evaluations will occur every 12 months only in the first 5 years and upon introduction of a drug product from Process B to the new manufacturing scale Process C or from Process C([redacted]) to the updated manufacturing Process C [redacted]) at any time during the study. In the first 5 years, pharmacodynamic (PD) evaluations will occur every 3 months then every 6 months after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. After 5 years, PD evaluations will occur every 12 months. PK evaluation will occur every 12 months only in the first 5 years and upon introduction of Process C([redacted]) or Process C([redacted]) at any time during the study.	Clarification on olipudase alfa manufacturing process changes
Section 8.1.1 Treatments administered	Added: If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit	Clarification when a site visit is not possible
Section 8.1.2 – Route and method of administration	Language updated*:* During the study, pediatric patients who reach adult age (18 years old) will receive the adult infusion volume.	Clarification on how to manage the IMP in patients reaching the adult age
Section 8.1.5 – Dosing delays or missed doses	48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021	The assessments have been streamlined to reduce patient burden in the extension phase of

Section # and Name	Description of Change	Brief Rationale
	During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is >2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment. Baseline is defined as the following: · For initial dose escalation: last values prior to first dose of olipudase alfa · For dose re-escalation: last values prior to the first re-escalation dose	this trial. Assessments to ensure patient safety have been preserved. The 48 hours post-infusion assessments no longer assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021; however, 24 hours post-infusion assessments remain. Therefore, patient safety is not being compromised. Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa has been added as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation have been added to the protocol.
Section 9.1.15 – Immune response assessments	Added: If introduction of a drug product from Process C(■) or from Process C(■) occurs, testing will occur monthly for the first 6 months after introducing the drug product from Process C(■) or Process C(■)	Clarification on olipudase alfa manufacturing process changes.
Section 9.3.8 Pharmacokinetics	PK testing will only occur yearly for the first 5 years and upon the introduction of Process C(■) or Process C(■) at any time during the study. For Process C(■), if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion Process C(■). For introduction of drug product from Process C(■),if treatment is not interrupted, PK sample collection will take place at the second infusion under Process C(■).	Clarification regarding olipudase alfa manufacturing process changes
Section 9.5 Sampled blood volume	Added: If a PK or IgG sample collection for the planned introduction of drug product from Process C(■) was erroneously taken	Clarification regarding olipudase alfa manufacturing process changes
Section 10.2.1 – Home infusions.	For the switch from Process C(■) IMP to the updated manufacturing Process C(■) IMP, if the site visit is possible, the patient should receive the first infusion at the site. However, if the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), the first infusion of Process C(■) is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations.	To facilitate treatment continuation via home infusion during the COVID-19 pandemic when site visit is not available for eligible patients. No safety risks are anticipated based on the following: 1. Process C(■) IMP is produced using an

Section # and Name	Description of Change	Brief Rationale
		updated manufacturing process; it is produced as per Good Manufacturing Process (GMP) requirements and is considered comparable to Process C(■) IMP. 2. There is clinical experience with the switch from Process C(■) to Process C(■). 3. There is appropriate selection of patients in home infusion setting with appropriate medical support.
Section 13.1 – Responsibilities of the Investigator (s).	Language added for clarification: In particular, the Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.	To further clarify the responsibilities of the Investigator(s).
Section 13.2 – Responsibilities of the Sponsor.	Language added: Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.	To include the possibility to perform remote monitoring during a regional or national emergency such as the current COVID-19 pandemic.
Section 17.2 - Appendix B Protocol Amendment History	Due to addition of amendment history for Amended Clinical Trial Protocol 05 (18-Aug-2020) as sub-section 17.2.1.1, all further sub-sections were re-numbered accordingly..	To conform with the usual process for amendment history.

17.2.2 Amended Clinical Trial Protocol 05 (18-Aug-2020)

This amended protocol (05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is mainly made to change the reintroduction dose to a lower dose for patients who missed 3 or more infusions and allow dose reintroduction and quarterly visits to be performed via home infusion for eligible patients if the site visit is not possible due to site closure

or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic). This amended protocol extended cognitive and adaptive function assessments, ABAS and DP-3, to all pediatric patients who have performed the assessment during the previous DFI13803 study. The amendment also provided guidance regarding assessments related to updated manufacturing process and home infusion. Other changes, omissions and corrections are addressed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary-Study design, Duration of Study Period (per patient); Sections 4.2 Study Rationale; 6 Study Design; 6.1.1 Treatment Period; 6.3 Duration of Study Participation	Add the highlighted text to the sentence: Patients will receive olipudase alfa every 2 weeks for 9 years or marketing approval, whichever comes first, unless the patient decides to enter another olipudase alfa clinical trial within the 9-year period prior to marketing approval.	To give patients in this study the opportunity to enroll in another olipudase clinical trial prior to marketing approval
Clinical Trial Summary-Study design; Sections 6 Study Design; 6.1.1 Treatment Period; 6.3 Duration of Study Participation	Add the highlighted text to the sentence: "If marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's approval in accordance with local regulations"	For consistency
Clinical Trial Summary- Dose regimen; Sections 1- Study Flow Charts; 8.1.1-Treatment administered,	Add "Quarterly visits will occur at the site. If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic) and home infusion is already approved for the eligible patient, quarterly visits will be done at home. Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments)".	To facilitate treatment continuation via home infusion in circumstances like COVID-19 pandemic when site visit is not available for eligible patients
Clinical Trial Summary--Dose regimen; Sections 1-Study Flow Charts; 8.1.1-Treatment administered, 8.1.5-Dosing delays or missed doses,	For patients who have missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa should occur at the hospital/study site. If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), reintroduction may be done via home infusion.	To facilitate treatment continuation via home infusion in circumstances like COVID-19 pandemic when site visit is not available for eligible patients
Clinical Trial Summary-Endpoints	Add Weight and Height (pediatric patients only) to the list of primary endpoints	For consistency with section 9.1.1 Primary Objectives
Clinical Trial Summary—Endpoints; Section 9.1.3-Other endpoints	Extend cognitive and adaptive assessments for patients who performed the assessments in DFI13803	To continue monitoring cognitive and adaptive functions beyond 6 years of age
Clinical Trial Summary—Endpoints; Section 9.1.3-Other endpoints; 9.3.10	Remove "Differential liver DNA methylation densities of peroxisome proliferator-activated receptor gamma (PPARγ) gene promoter in plasma circulating cell-free DNA (ccfDNA)"	This exploratory analysis uses left over samples from the time patients had a liver biopsy. The

Section # and Name	Description of Change	Brief Rationale
Differential liver DNA methylation densities of PPARγ gene promoter in plasma	from the list of other assessment endpoints.	samples have been challenging to obtain in this already small group of 5 adult patients. Therefore, the endpoint is being removed.
Clinical Trial Summary--Assessment schedule; Sections 1 - Study Flow Charts, 8.1.5, Dosing delays or missed doses	Remove ECG from the list of assessments to be done in case of dose reintroduction	Remove a redundant assessment that is done according to schedule
Sections 1- Study Flow Charts and 1.6 Pharmacokinetic sampling; 9.5-Sampled blood volume	Add "schedule of PK and IgG sample collection after introduction of drug product from updated manufacturing process. Also add "If a PK or IgG sample collection for the planned introduction of drug product from an updated manufacturing process was erroneously taken, the future sample collection will be adjusted to the blood volume per each age cohort in order to avoid excessive blood withdrawal"	For clarity and guidance in case of introduction of updated manufacturing process and in case of erroneously taken samples in relation to blood volume
Sections 1- Study Flow Charts: 1.1, 1.2, 1.3 ,1.4 1.5: footnote a	Add "Quarterly visit specific assessments that need a site visit will not be done at that time and will be done as unscheduled as soon as site visits become available. In such a case, some of the quarterly visit assessments may be done by home nurse (eg, lab sampling) and by the site through the phone (eg, Health-related quality of life instruments)"	Clarify details of assessments in case of site in availability and continuation of treatment via home infusion
Sections 1- Study Flow Charts: 1.1, 1.2, 1.3 ,1.4 1.5: footnote a	Provide option of Telehealth visit in accordance with local regulations	Facilitate treatment continuity if site visit is not available
Sections 1- Study Flow Charts	Footnote hierarchy changed due to addition	Formatting
Sections 1.3- Study Flow Charts	Add columns for "Study completion, patient discontinuation and withdrawal" visit schedule to Year 1 pediatric chart also add corresponding safety follow up visit schedule	Correct previous omission
Sections 1- Study Flow Charts: 1.1, 1.2, footnote d; 1.3 ,1.4, 1.5 footnote e	Add that weight is not required at home infusion visits unless quarterly visit occurs at home.	Clarify guidance regarding weight taking during home infusion
Section 8.1.1-treatment administration	Decrease dose reintroduction for patients who have missed 3 or more infusions to 0.3 instead of 0.6 mg/kg as follows: -"If the previous dose was ≧>0.6 mg/kg, the next dose must be ~~0.6~~ 0.3 mg/kg (0.3 mg/kg should be repeated at the subsequent infusion, similar to dose escalation schedule in the original study)"	Change reintroduction dose after missing multiple consecutive infusion to a lower dose
Section 9.1.10-Electrocardiograms	Spell out the word electrocardiograms	Clarity
Section 9.6- Future use of samples	Add the sentence "These samples will be stored for 15 years after end of the study in compliance with applicable country-specific regulations.	Add guidance for future sample use to match WSIs
Section 10.2.1-Home infusions	Modify IAR management guidance during home infusion " For patients experiencing an IAR while being infused at home, the	Clarify the guidance for IAR during home infusion regarding

Section # and Name	Description of Change	Brief Rationale
	investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion or return to the study site for their following infusion and when the patient would be ready to resume home infusion. In case home infusion continues, the investigator will guide the home infusion staff on the measures to be followed for subsequent infusion to manage the IAR (eg, infusion interruption, premedication, change the infusion rate, etc).	the need to site and home management
Section 10.2.1- Home infusions	Add language to detail management of severe hypersensitivity reaction and anaphylaxis: "If recurrent IARs or hypersensitivity reactions occur, the investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion. If a severe hypersensitivity reaction or an anaphylaxis reaction occurs, during an infusion given at home, treatment will be discontinued immediately, and appropriate medical treatment will be initiated. The patient will return to the study site for further management until the investigator agrees with the sponsor that it is safe for the patient to continue to be treated via home infusion.	Further safety details in case of home infusion
Section 14.2 Record retention in study sites	The investigator should retain the study documents at least ~~15~~ 25 years after the completion or discontinuation of the clinical trial.	Modify record retention at the study site to match SOPs and WSIs
Section 16 Bibliographic references	Modify the source of the article in reference number 1	Update reference data as the old URL was not valid
Section 17.2- appendix B: Protocol amendment history	insert amended protocol 4 summary of changes	Update appendices according to the amended protocol

17.2.3 Amended protocol 04 (31-Jul-2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is made to indicate the different assessments that will be done after manufacturing process update as per regulatory authorities' requirements. Previous omissions and errors were corrected.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Title was updated to reflect Amended Clinical Trial Protocol 04 and removed reference to recombinant human	Reflect the update of the amended clinical trial protocol.

Section # and Name	Description of Change	Brief Rationale
	acid sphingomyelinase from title.	
Title Page	The protocol date was changed to reflect 31-Jul-2019.	Reflect the updated date of approval of the document.
Names and Addresses Of	Sponsor information for Sanofi Genzyme was added.	The change was made to reflect the update of the amended clinical trial protocol.
Protocol Amendment Summary of Changes	Document History, Amended Clinical Trial Protocol, and Overall Rationale For The Amendment were added.	This change was made to adhere to Sanofi policy.
Protocol amendment summary of changes table	Summary of changes table was added to amended clinical trial protocol.	This change was made to adhere to Sanofi policy.
Clinical Trial Summary, Duration Of Study Period (per patient)	Addition of the following language was made to this section “and health authorities”.	Clarify that with sponsor’s and health authorities’ approval the study duration extension beyond 9 years would be considered.
1.1 Flow Chart For Adults: Year 1 Through Year 5	Footnote “j” was edited to describe PK testing upon the introduction of a drug product from a new or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.2 Flow Chart For Adults: Beyond Year 5	Information for testing Hematology, Hemoglobin level and platelet count if a drug product from an updated manufacturing process was administered was added to this section.	Assessment to be done after manufacturing process update.
1.2 Flow Chart For Adults: Beyond Year 5	Information for testing of anti olipudase alfa antibody (IgG) if introduction of a drug product from an updated manufacturing process or a manufacturing scale change occurs was added.	Assessment to be done after manufacturing process update.
1.2 Flow Chart For Adults: Beyond Year 5	Footnote “g” was added to this section that describes PK testing that will only occur upon the introduction of a drug product from a new manufacturing scale or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.3 Flow Chart For Pediatric (Former DFI13803) Patients: Year 1	Information for testing of anti olipudase alfa antibody (IgG) if introduction of a drug product from an updated manufacturing process or a manufacturing scale change occurs was added.	Assessment to be done after manufacturing process update.
1.3 Flow Chart For Pediatric (Former DFI13803) Patients: Year 1	Footnote “e” added information about collection of hemoglobin and platelet count if a drug product from an updated manufacturing process is administered.	Assessment to be done after manufacturing process update.
1.3 Flow Chart For Pediatric (Former DFI13803) Patients: Year 1	Footnote “j” added information to describe PK testing that will only occur upon the introduction of a drug product from a new manufacturing scale or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.4 Flow Chart For Pediatric (Former DFI13803) Patients: Year 2 Through Year 5	Information for testing of anti olipudase alfa antibody (IgG) if introduction of a drug product from an updated manufacturing process or a manufacturing scale change occurs was added.	Assessment to be done after manufacturing process update.
1.4 Flow Chart For Pediatric (Former DFI13803) Patients:	Footnote “g” added information about collection of hemoglobin and platelet count if a drug product from an	Assessment to be done after manufacturing process update.

Section # and Name	Description of Change	Brief Rationale
Year 2 Through Year 5	updated manufacturing process is administered.	
1.4 Flow Chart For Pediatric (Former DFI13803) Patients: Year 2 Through Year 5	Footnote “m” added information to describe PK testing that will only occur upon the introduction of a drug product from a new manufacturing scale or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.5 Flow Chart For Pediatric (Former DFI13803) Patients: Beyond Year 5	Information for testing Hematology, Hemoglobin level and platelet count if a drug product from an updated manufacturing process was administered was added to this section.	Assessment to be done after manufacturing process update.
1.5 Flow Chart For Pediatric (Former DFI13803) Patients: Beyond Year 5	Information for PK testing for visit/timing was added.	Assessment to be done after manufacturing process update.
1.5 Flow Chart For Pediatric (Former DFI13803) Patients: Beyond Year 5	Information for testing of anti olipudase alfa antibody (IgG) if introduction of a drug product from an updated manufacturing process or a manufacturing scale change occurs was added.	Assessment to be done after manufacturing process update.
1.5 Flow Chart For Pediatric (Former DFI13803) Patients: Beyond Year 5	Footnote “l” added information to describe PK testing that will only occur upon the introduction of a drug product from a new manufacturing scale or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.6 Study Flow Chart: Pharmacokinetic Sampling	Text is modified to describe the PK testing to be done as a result of the introduction of drug product from an updated manufacturing process, or an updated manufacturing process.	Assessment to be done after manufacturing process update.
1.6 Study Flow Chart: Pharmacokinetic Sampling Table 6: Pharmacokinetic sampling in adults	PK sampling in adults if an updated manufacturing process occurs was added to this table.	Assessment to be done after manufacturing process update.
1.6 Study Flow Chart: Pharmacokinetic Sampling Table 7: Pharmacokinetic sampling in pediatric patients	PK sampling in pediatric patients if introduction of a drug product an updated manufacturing process occurs was added to this table.	Assessment to be done after manufacturing process update.
4.2 Study Rationale	Addition of the following text was made to this section “and health authorities’ approval in accordance with local regulations’”.	Clarify that with sponsor’s and health authorities’ approval the study duration extension beyond 9 years would be considered.
6.1.1 Treatment period	Beyond 5 years, PK testing will only occur upon introduction of a drug from a new manufacturing scale or an updated manufacturing process. Description of the criteria to obtain PK sample collection was added.	Assessment to be done after manufacturing process update.
6.2 Interim Analysis	Interim CSR to support regulatory approvals and/or other submission/application requirement(s) was added to this section.	Clarify the plan for interim CSR.
8.1.8 Treatment discontinuation	Modify text for patient discontinuation due participating in another interventional investigational study.	Clarify language regarding the approvals needed in case of protocol

Section # and Name	Description of Change	Brief Rationale
		amendment to adhere to Sanofi policy.
9.1.15 Immune response assessments	Sample collection of anti-olipudase alfa IgG antibodies was edited to describe if introduction of drug product from an updated manufacturing process occurs.	Assessment to be done after manufacturing process update.
9.3.8.3.1 Sampling time in adults	For introduction of drug product from an updated manufacturing process, PK sample collection will only take place at the second infusion under the new manufacturing process update was added.	Assessment to be done after manufacturing process update.
9.3.8.3.2 Number of pharmacokinetic samples in adults, Table 9: Approximate number of plasma samples in adult patients	Table updated to add number of PK samples to be taken at the second infusion on updated manufacturing process.	Assessment to be done after manufacturing process update.
9.3.8.4.2 Number of pharmacokinetic samples in pediatric patients, Table 11: Approximate number of plasma samples by pediatric age cohort	Table updated to add number of PK samples to be taken at the second infusion on updated manufacturing process for adolescent, child, and infant/early child cohorts.	Assessment to be done after manufacturing process update.
9.5 Sampled Blood Volume	Text is modified to reference additional table and to clarify action in case of multiple samples from the same assessment in the 3 pediatric cohorts.	Explain blood samples needed and actions for assessments due to manufacturing process update.
9.5 Sampled Blood Volume, Table 14: Additional approximate sampled blood volume in patients ages 12 to <18 years with an olipudase alfa updated manufacturing process	Table added to show blood volume required in case of fracturing process update in patient aged 12 to <18.	Clarify of blood volume calculation for manufacturing process update.
9.5 Sampled Blood Volume, Table 18: Additional approximate sampled blood volume in the child cohort (6 to <12 years) and ages 3 to <6 years with an olipudase alfa manufacturing process update	Table added to show blood volume required in case of fracturing process update in the child cohort (6 to <12 years) and ages 3 to <6 years.	Clarify of blood volume calculation for manufacturing process update.
9.5 Sampled Blood Volume, Table 22: Additional approximate sampled blood volume in patients from birth to ≤2 years of age with an olipudase alfa manufacturing process update	Table added to show blood volume required in case of fracturing process update in patients from birth to ≤2 years of age.	Clarify of blood volume calculation for manufacturing process update.
10.2.1 Home infusions	"Updated manufacturing process" was added to criteria that must be met.	Assessment to be done after manufacturing process update.

Section # and Name	Description of Change	Brief Rationale
11.6.4 Analysis of pharmacokinetic and pharmacodynamic variables	Add manufacturing process update option to PK analysis.	Addition of manufacturing process update.
11.7 Interim Analysis	A formal summary of data or interim CSR may be produced to support regulatory approval(s) and/or other application submission requirement(s) was added to this section.	Clarify the plan for interim CSR.
15 Clinical Trial Protocol Amendments	Addition of required criteria for written approval/favorable opinion of any amendment to the clinical trial protocol "also by regulatory authorities if substantial" was added to this section.	This change was made to adhere to Sanofi policy.
17 Appendices	This entire section, including all subsections (17.1, 17.2, 17.2.1, 17.2.2, and 17.2.3) were added to the amended clinical trial protocol.	This change was made to adhere to Sanofi policy.

17.2.4 Amended protocol 03 based on Protocol Amendment 03 (25 April 2018)

REASON FOR AMENDMENT:

1. Extend the study treatment period from 5 years to 9 years

In section(s): Clinical Trial Summary: Study Design, Duration of Study Period; 1 Study Flow charts (1.1 through 1.6 [former protocol amendment 2 sections 1.1 through 1.4]); 4.2 Study Rational; 6 Study Design; 6.1.1 Treatment Period; 6.3 Duration of Study Participation

Rationale:

LTS13632 was set to follow patients rolling over from previous adult study (Phase 1b) and Pediatric study (Phase 1/2). The objective is to assess long term safety and efficacy for 5 years or until marketing approval whichever comes first. So far, there was no marketing approval and no other treatment option available in the study countries.

This change aim to extend safety and efficacy follow up of the enrolled patients if they wish, for 4 more years or until marketing approval whichever comes first. The treatment period will change from 5 years to 9 years to allow for better treatment options for patients at the end of treatment.

It is also included in this change that if marketing approval was not available, extension of follow up beyond 9 years would be considered with sponsor's approval.

Specific schedules of assessment for both adults and children populations in this extension period have been proposed.

2. Remove a redundant exclusion criterion

In section(s): Clinical Trail Summary: Study Population, Main Selection Criteria (Exclusion Criteria); 7.2.2 Exclusion criteria related to the current knowledge of the compound and condition

Rationale:

The exclusion criterion number E 06 states that “The patient has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >250 IU/L or total bilirubin >1.5 mg/dL”.

However, patients enter the study by rolling over from previous studies (adult Phase 1b and pediatric Phase 1/2) without any screening assessment before rolling over after end of treatment of the previous study.

Moreover, Liver Functions are strictly followed in previous studies and this extension study via Dose Limiting Toxicities (DLTs) and Dose Stopping Criteria which are also reviewed by Data Monitoring Committee (DMC).

Based on the above, EC 06 is redundant and this amendment proposes to remove.

3. Remove the option of another liver biopsy after 5 years treatment in adult patients

In section(s): 1.1 Flow Chart for Adults; 9.1.12 Liver biopsy for sphingomyelin in liver tissue (only patients who previously participated in the DFI13412 study)

Rationale:

In the current protocol (Protocol Amendment 2) it is indicated that an additional biopsy may take place at 5 years in the study, but only if necessary based on analysis of the 3 year biopsy for the group of adult patients.

The 3 year biopsy analysis of the adult patients did not show evidence suggestive of a progressive worsening of fibrosis to cirrhosis in patients treated with olipudase alfa. Hence it was decided that further biopsies after 5 years treatment is not needed.

4. Update the target number of patients to be approximately 25 instead of 17

In section(s): Clinical Trial Summary: Total Expected Number of Patients; Statistical Considerations, sample Size Determination; 6 Study Design; 11.2 Determination of the Sample Size

Rationale:

All adult patients were recruited. This change serves to update the target number of patients according to Phase 1/2 pediatric (DFI13803) study amendment 4 (dated 21-Aug-2017), which plans to enroll approximately 20 patients, instead of 12.

5. Remove selected assessments from the flow chart list

In section(s): 1.3 (former protocol amendment 2 Section 1.2) Flow Chart for Pediatric (Former DFI13803) Patients: Year 1; 1.4 (former protocol amendment 2 Section 1.2) Flow Chart for Pediatric (Former DFI13803) Patients: Year 2 Through Year 5; 9.3.3 Cycle ergometry;

Rationale:

Remove cycle ergometry in pediatric patients. The assessment has not provided any benefit to follow activities in children due to the difficult applicability and low compliance.

Remove Angiotensin Converting Enzyme measurement in both adult and pediatric populations. The assessment does not provide any benefit to follow efficacy or safety.

6. Add option to conduct a future additional questionnaire about home infusion experience to patients who received home infusion treatment

In section(s): 9.1.2 Secondary endpoints (efficacy); 9.2.6.3 Additional questionnaires; 10.2.1 Home infusions

Rationale:

This is a provision in the protocol of the option to conduct future additional short and one-time questionnaire about home infusion experience to patients who received home infusion treatment.

7. Add Differential liver DNA methylation densities of PPARɣ gene promoter in plasma ccfDNA

In section(s): Clinical Trial Summary (End Points), (Other endpoints); 9.1.3 Other endpoints; 9.3.10 Differential liver DNA methylation densities of PPARɣ gene promoter in plasma

Rationale:

Differential liver DNA methylation of peroxisome proliferator-activated receptor gamma (PPARɣ) gene promoter has recently been shown to stratify patients in terms of fibrosis severity. Plasma DNA methylation signatures reflect the molecular pathology associated with fibrosis liver disease. Remarkably, PPARɣ hypermethylation correlated with progression to cirrhosis in alcoholic liver disease (ALD) and with specific stages of liver fibrosis in non-alcoholic fatty liver disease (NAFLD). DNA methylation markers at the human PPARɣ promoter detectable in circulating cell-free DNA (ccfDNA) display differential methylation densities and could potentially be used to non-invasively stratify liver fibrosis severity in patients with NAFLD.

(Hardy T, et al. Gut 2016;0:1-8. doi:10.1136/gutjnl-2016-311526 [downloaded Apr 11, 2016] and Yi.it.B, et.al. Gut Epub ahead of print: doi:10.1136/ gutjnl-2017-315668 [downloaded Feb 26, 2018])

In order to assess this potential biomarker in ASMD patients, it would be clinically useful to compare the differential methylation densities of the adult patients participating in the LTS13632 study to base differential methylation densities while they were participating in the Phase 1b (DFI13412) study.

Whenever possible, and if enough volume of left-over plasma is available at all time points of interest, plasma samples that were obtained at the same time of the liver biopsy performed at Year 3 study visit will be used to assess ccfDNA differential methylation densities. These densities will

be compared with the samples taken from the same patients when they were participating in the Phase 1b (DFI13412) study, to detect change in fibrosis differentiation using this biomarker. In this way, there will be no additional blood draws or procedures added to the protocol.

8. Clarify language of collection of blood samples (beyond 5 years) and pharmacokinetics sample and analysis

In section(s): 1.6 (former protocol amendment 2 section 1.4) Study Flowchart: Pharmacokinetic sampling; 9.3.8 Pharmacokinetics; 9.3.8.3.1 Sampling time in adults; 9.3.8.4.1 Sampling time in pediatric patients; 9.5 Sampled Blood Volume

Rationale:

Clarify and update language to address study extension and clarify other procedures.

9. Clarify reporting guidelines of Adverse Events of Special Interest

In section(s): 10.5.2.5 Summary of adverse event reporting, table 22 (former protocol amendment 2 table 17)

Rationale:

Adding AESI lab values to the relevant table

17.2.5 Amended protocol 02 based on Protocol Amendment 02 (25 April 2017)

REASON FOR AMENDMENT:

1. Change in assessments that will not be repeated at end of study/early discontinuation visit

In section(s): 1.1, 1.3

Rationale:

Correction of error in previous section.

2. Dose calculation based on weight in site and home infusion visits

In section(s): 1.1, 1.2, 1.3

Rationale:

Weight change between visits is insignificant, therefore dose calculation using weight from previous site visit is allowed. In home infusion visit, the last weight taken on site will be used.

3. Clarification of time points at which vital signs should be taken

In section(s): 1.1, 1.2, 1.3

Rationale:

Time points added were missing from previous version.

4. Clarification of assessments needed upon manufacturing scale change

In section(s): 1.1, 1.2, 1.3, 1.4, 9.1.5, 9.2.1, 9.2.3, 9.3.8, 9.5, 10.2.1

Rationale:

Upon manufacturing scale change, certain assessments are requested by health authorities. Details were added in this amendment for clarification.

5. Clarification of neurological examination

In section(s): 1.2, 1.3, 9.1.6.2

Rationale:

Clarify that same neurologist to perform neurological examination from any of previous studies through this study and all throughout this study if possible

6. Change in dose stopping (and AESI) criteria

In section(s): 10.5.1.3.4

Rationale:

Correction of errors and clarify level of liver function criteria of dose stopping and AESI.

7. Addition of recommendation on usage of cationic amphiphilic antihistamines in rules on concomitant medications

In section(s): 8.6, 8.6.1

Rationale:

Addition of commonly used medications for clarification.

8. Clarification of IAR definition and treatment

In section(s): 8.6, 8.6.1

Rationale:

Clarify language of IAR description and caution of IAR suggestive of hypersensitivity treatment about medications that may affect study medication efficacy.

9. Clarification of liver biopsy evaluation

In section(s): 9.1.12

Rationale:

Clarification of liver biopsy assessment language

10. Addition of future use of samples section

In section(s): 9.6

Rationale:

Missing from previous version

17.2.6 Amended protocol 01 based on Protocol Amendment 01 (23 March 2016)

REASON FOR AMENDMENT:

Changes listed in this section are regarded as "substantial" because they have a significant impact on:

- The safety or physical or mental integrity of the patients,
- The scientific values of the trial; or,
- The conduct or management of the trial.

1. Change expected number of patients from "65-70 patients" to "up to 17 patients.

In sections: Clinical trial summary (Study population, Total expected number of patients), 6.

Rationale: This trial allows current patients to continue treatment. Based on the number of patients in this trial and the DFI13803 pediatric trial, the maximum number of patients is already known to be 17.

2. Provide option for home infusions.

In sections: Clinical trial summary (Dose regimen), 8.1.1, 10.2.

Rationale: Patients are on stable doses that they have been tolerating well. This provision eases the travel and hospitalization burden on patients without affecting patient safety.

3. **Provide specific guidelines on treatment "reintroduction" defined as management of patients who have missed 1 or more olipudase alfa doses.**

   In sections: Clinical trial summary (Dose regimen), 8.1.1, 8.1.5.

   Rationale: Issue was not addressed in previous version.

4. **Remove the requirement that the sponsor must be consulted to determine the appropriate dose of olipudase alfa for dose adjustments or if a patient misses 1 or more doses.**

   In section: Clinical trial summary (Dose regimen), 8.1.1, 8.1.4.

   Rationale: Guidance on how to restart treatment when patients have missed consecutive doses is provided in Section 8.1.1 of the protocol.

5. **Remove continuous heart rate monitoring as an endpoint.**

   In sections: Clinical trial summary (Endpoints, Primary endpoints, Data pertaining to the safety and tolerability of olipudase alfa), 1.1, 9.1.1, 9.2.

   Rationale: Patients in the LTS13632 trial have all completed the dose escalation regimen. As such, they are outside the period where fluctuations of ceramide could lead to more severe adverse events. The results of continuous ECG monitoring to date from studies DFI13412 and LTS13412 have not revealed any clinically significant changes. Moreover, enzyme therapies, as a class effect, are not known to detrimentally effect cardiac function. As such, continuous ECG monitoring was removed.

6. **Add these endpoints.**

   In sections: Clinical trial summary (Endpoints, Primary endpoints, Data pertaining to the safety and tolerability of olipudase alfa), 9.1, 9.2.2.1, 9.2.2.2, 9.2.7, 9.2.8, 9.2.9, 9.3, 9.3.7, 9.3.8, 9.3.9, 9.4.2, 9.4.7, 9.4.9.1.

   - **Primary:**
     - **Extended neurologic examinations in adults and pediatric patients,**
     - **Doppler echocardiography,**
     - **Liver biopsy (original adult patients),**
     - **Liver ultrasound with Doppler (pediatric patients).**
   - **Secondary:**
     - **Hand X-ray for bone age and bone maturation (pediatric patients),**
     - **Tanner staging (pediatric patients),**
     - **Linear patient growth by height Z--score (pediatric patients).**
   - **Other endpoints:**
     - **Cognitive and adaptive function (pediatric patients only, until age 6 years),**
     - **Bone biomarkers,**

- **Photographs (optional).**

Rationale: These are relevant clinical endpoints for pediatric patients entering the trial, which were part of the primary pediatric study, and for continued evaluation of adult patients (eg, liver biopsy).

7. **Specify that, "The term 'pediatric patients only' means patients coming from the original pediatric trial, DFI13803. Some of these patients will reach adult age [18 years old] while in this study. They will continue the assessments schedule they were on in the original trial. These patients will be adults by age, but they will remain part of the "pediatric patient" cohort." They will not follow the adult procedures in this study (eg, liver biopsy).**

   In sections: Clinical trial summary (Assessment schedule), 1.1, 9, 9.4.9.1.

   Rationale: Pediatric patients will not have some baseline assessments for comparison (eg, liver biopsy, DXA of femurs and spine). This statement is intended to clarify to site personnel which assessments pertain to adults and which to pediatric patients.

8. **Add that for patients who missed 3 infusions or more infusions between trials, some assessments may be repeated at study entry after discussion between the sponsor and the investigator.**

   In sections: Clinical trial summary (Assessment schedule), 1.1.

   Rationale: Since the rate at which sphingomyelin reaccumulates when olipudase alfa is interrupted, it may be necessary to repeat some efficacy assessments in case of prolonged investigational product suspension.

9. **Add: "If a patient has missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa for patients receiving infusions at home should occur at the hospital/study site. If a patient misses 2 or fewer doses, the investigator can decide whether reintroduction for patients receiving infusions at home should occur at the hospital/study site."**

   In sections: Clinical trial summary (Dose regimen), 1.1, 8.1.1, 8.1.5.

   Rationale: To ensure patient's safety.

10. **Add assessments for patients who require dose reintroduction.**

    - **Patients who require dose reintroduction will have these assessments at each infusion until reaching their usual dose of olipudase alfa:**
      - **Before infusion: vital signs, liver function tests, hematology, ECG, and safety biomarkers,**
      - **Immediately after infusion: vital signs and ECG,**
      - **24 hours: vital signs, liver function tests, and safety biomarkers,**

- **48 hours: vital signs, liver function tests, hematology, ECG, and safety biomarkers.**

In sections: Clinical trial summary (Assessment schedule), 1.1, 8.1.5.

Rationale: To monitor patient safety during reintroduction.

11. **Add that PK testing will only occur yearly and upon the introduction of a new manufacturing scale.**

    In sections: 1.2, 9.4.8.

    Rationale: Provide appropriate and continuous monitoring, in particular for manufacturing scale changes.

12. **Add that for a new manufacturing scale, if treatment is not interrupted, PK sample collection will take place at the patient's last infusion under the current manufacturing scale and at the first infusion under the new manufacturing scale.**

    In sections: 1.1, 1.2, 9.4.8.

    Rationale: To provide patients' data on drug comparability.

13. **Add that if a manufacturing scale change occurs, immune response assessments will be monthly for the first 6 months after starting the new scale, and quarterly after that.**

    In sections: 1.1, 1.2, 9.4.8.

    Rationale: Per FDA request.

14. **Add that in case reintroduction of olipudase alfa coincides with a manufacturing scale change, PK samples will be collected at the infusion at which patients receive their usual dose of olipudase alfa under the new manufacturing scale.**

    In sections: 1.2, 9.3.8.

    Rationale: To provide patients' data on drug comparability.

15. **Added PK sampling times, number of samples, and parameters in adults and pediatric patients.**

    In sections: 1.2, 9.3.8.3.

    Rationale: Clarify the number of samples for adults and pediatric patients and when they will be obtained.

16. **Added PK sampling time point at 96 hours for adults and pediatric patients.**

    In section: 1.2.

Rationale: Allow comparison of PK in adults and pediatric patients.

17. **Added PK total blood volumes for pediatric patients.**

    In sections: 1.2, 9.5.

    Rationale: Specify maximum blood volume for blood samples per health authority requirement.

18. **Add that the patients must be willing and able to avoid certain medications and herbal supplements for 10 days before and 3 days after liver biopsies.**

    In sections: 7.2.1, 8.6.

    Rationale: Decrease the risk of bleeding from liver biopsies and to avoid liver toxicity.

19. **Clarify patient stopping criteria.**

    In section: 8.1.7

    Rationale: The role of the DMC in an emergency is to review safety data and recommend stopping the study if necessary to ensure patient safety. However, this does not limit the ability of investigators to make an immediate decision to discontinue dosing in an individual patient due to any AE that raises significant concern regarding the safety of olipudase alfa, as described in Section 8.1.6 of the protocol.

20. **Remove O_2 saturation from vital signs.**

    In section: 9.2.4.

    Rationale: As part of this amendment to the protocol, dose escalation is not part of the trial. Patients are on stable doses, and therefore monitoring without measuring O2 saturation is appropriate.

21. **Change safety biomarker test from multiplex immunoassay to specific biomarkers including, but not limited to, hsCRP, iron, ferritin, cardiac troponin I, IL-6, IL-8, plasma ceramide and calcitonin.**

    In sections: 9.2.5, 9.2.10.

    Rationale: Given current knowledge about the study drug, broad immunoassay can be replaced by targeted testing.

22. **Change the definition of overdose from "at least twice the intended dose within the intended therapeutic interval" to "an increase of at least 30% of the dose to be administered in the specified duration, or if the dose is administered in less than half the recommended duration of administration."**

    In section: 10.5.2.3.1.

    Rationale: To align with the investigator brochure and the Sanofi template

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