NCT: NCT06949358

CLINICAL TRIAL PROTOCOL

A Long-Term follow-up Study to evaluate safety and tolerability of olipudase alfa in patients who completed the DFI12712 or the LTS13632 Study in France

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INN	**Olipudase alfa**
Study phase:	**2 open-label**
Sponsor name:	**Sanofi Winthrop Industrie**
Legal registered address:	**82 Avenue Raspail 94250 Gentilly, FRANCE**
Monitoring team's representative name and contact information:	

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Amended Clinical Trial Protocol No. 02 (01-June-2023)

This amended protocol (02) is considered to be nonsubstantial 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 does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Title	Changed: "Sanofi-Aventis France" to "Sanofi Winthrop Industrie"	The legal entity of Sanofi will change on 01-Jul-2023 from Sanofi-Aventis France to Sanofi Winthrop Industrie.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Long-Term follow-up Study to evaluate safety and tolerability of olipudase alfa in the patients who completed the DFI12712 or the LTS13632 Study in France.

Rationale:

No approved treatment is available for ASMD. Clinical studies have been performed to demonstrate the efficacy and safety of olipudase alfa in ASMD patients with non-neurologic manifestations. In France, one adult patient with ASMD participated in Study DFI12712 and two patients in Study LTS13632. The efficacy and safety of olipudase alfa ERT have been demonstrated, and the studies DFI12712 and LTS13632 will end once the European marketing authorization (EMA) has been granted by the European Commission. The present study intends to ensure safety follow-up and treatment continuation for patients who participated in the DFI12712 study or in the LTS13632 study in France while Sanofi is seeking to obtain reimbursement in France.

This study also intends to fulfill an unmet critical need while Sanofi is seeking reimbursement approval of olipudase alfa by providing treatment of the patient in France with ASMD who meets the criteria listed in Section 5 .

Objective and endpoints:

The objective of this study is to assess safety and tolerability of olipudase alfa in the patients with ASMD who completed the DFI12712 or the LTS13632 study in France until olipudase alfa reimbursement is granted in France or until 5 years whichever comes first.

Safety reporting is required. Submission of safety reports to Sanofi is mandatory for the patient to be eligible to continue in this study.

Overall design:

This bi-center study in France has an open label, repeated dose design.

This is an open-label study to provide ERT with olipudase alfa to the patients with ASMD who completed the DFI12712 or the LTS13632 Study in France until olipudase alfa reimbursement is granted in France.

- Study and treatment duration: the period between the patient's completion of StudyDFI12712 or LTS13632 and olipudase alfa reimbursement is available in France. In case reimbursement will not be obtained, this study will end 5 years after starting.

- Visit frequency: every 2 weeks.

Study phase:

- open-label extension

Observations:

- Safety assessments are required in this study.

Intervention name:

- Olipudase alfa.

Intervention form:

- Intravenous (IV) infusion.

Disease studied:

- Acid sphingomyelinase deficiency.

Study and treatment duration:

- Period between the patient's completion of Study DFI12712 or LTS13632 and olipudase alfa reimbursement becoming available in France. In case reimbursement will not be obtained, this study will end 5 years after starting.

Number of participants:

- Up to 3

Statistical considerations:

Safety analysis will be based on the review of individual values. All AEs reported and safety parameters in the study will be listed. Demographic data and concomitant medications will also be listed.

Data monitoring/other committee:

- No

1.2 SCHEMA

Not applicable

1.3 SCHEDULE OF ACTIVITIES

	Treatment period[a]			Post-treatment	
	Every 2 weeks (±3 days)	**Every 3 months (±14 days)**	**Every 12 months or end of treatment**	**End of study[b] (early discontinuation)**	**Safety follow-up phone call (15 days after last infusion visit)**
The informed consent form (ICF) must be signed, inclusion/exclusion criteria must be verified, and a participant number must be assigned before the participant's first study visit. Demographics and baseline characteristics (date of first ASMD diagnosis, alcohol and tobacco use history, prior medications for 30 days before enrollment, age, sex, height, weight, body mass index [BMI], medical history, and specific information on any relevant prior or current medical conditions/surgical procedures) should be confirmed and will be recorded on the case report form (CRF) at the baseline visit (the first olipudase alfa infusion visit). The participant number in this study and in Study DF12712 or in LTS13632 will also be recorded on the CRF.					
Assessment of AEs[c]	◄				►
Concomitant treatment	◄				►
Abbreviated physical examination[d]	X	X	X		
Weight[e], BMI		X	X		
Height (for pediatric patient)			X		
Vital sign measurements[f]	X	X	X	X	
Liver function [g]		X	X	X	
ADA (IgG) (and specific dosages for hypersensitivity)		X	X	X	
Pregnancy testing[h]	Every 4 weeks				

Abbreviations: AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; CRF = case report form; ICF = informed consent form; ADA = anti-drug antibodies

[a] Olipudase alfa will be infused once every 2 weeks (±3 days), in reference to the date of the first infusion. The first infusion visit is the baseline visit. Unless otherwise specified, study procedures should preferably take place before the infusion and at approximately the same time of day at each visit, in reference to the baseline visit.

[b] The end of study visit will take place within 2 weeks after the final infusion.

[c] Adverse events will be recorded from the time the participant provides signed informed consent through the safety follow-up period (15 days after the last olipudase alfa infusion).

[d] Only general appearance will be assessed before and after each olipudase alfa infusion.

[e] Weight at the previous visit may be used to calculate the dose of olipudase alfa at the current visit.

[f] Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. At all visits, vital signs will be measured prior to the infusion (within 30 ±10 minutes of infusion start), halfway through the infusion (ie, when half the expected infusion duration has elapsed), and at the end of the infusion ±10 minutes. At any visit, the Investigator may decide that a longer monitoring period is required.

[g] If a re-escalation is needed (in the case the patient missed 3 or more infusions), blood samples will be collected for liver function within 24 hours before the infusion and 24 ±3 hours after the end of the infusion at dose escalation visits. At any visit, the Investigator may decide that a longer monitoring period is required.

[h] Female participants of childbearing potential: Every 4 weeks a urine pregnancy test (β-HCG) will be performed up to 24 hours before the olipudase alfa infusion. If any urine pregnancy test is positive, a serum pregnancy test should be performed.

2 INTRODUCTION

Acid sphingomyelinase deficiency (ASMD) is a rare, potentially life-threatening lysosomal storage disease for which only symptomatic treatments currently exist. Patients with ASMD have variable impairment of sphingomyelin metabolism due to pathogenic variants in *SMPD1*, the gene encoding acid sphingomyelinase (ASM), that result in expression of defective ASM with reduced activity. Because ASM catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine, reduced ASM activity results in progressive lysosomal accumulation of sphingomyelin. This accumulation is mostly in cells of the monocyte/macrophage lineage residing in reticuloendothelial tissues, including the spleen, liver, lung, bone marrow, and lymph nodes. Neurons may also be affected in severe disease. ASMD is historically known as Niemann-Pick disease (NPD), although the nomenclature is evolving and the term ASMD, rather than NPD, is becoming more common.

ASMD is an autosomal recessive single-gene disease. It is known to generate a spectrum of phenotypes, which have been classified as Type A, Type B, and Type A/B. ASMD Type A is the early onset and acute neuropathic form of ASMD, and results in failure to thrive, hepatosplenomegaly, rapidly progressive neurologic degeneration, and death, usually before the age of 3 years (1). ASMD Type B is usually diagnosed after the age of 2 years, when hepatosplenomegaly (the most common disease manifestation in all patients with ASMD) is observed. It is characterized by slower progression with little or no neurologic involvement. Other, more variable, features include liver dysfunction, pulmonary disease, retinal stigmata, and growth retardation. Patients with ASMD Type B can survive into adulthood. ASMD Type A/B includes disease manifestations intermediate to those of Type A and Type B. Patients with ASMD Type A/B may develop neurologic symptoms in childhood and can have dominant neurodegenerative and/or visceral manifestations. Prolonged survival distinguishes Type A/B from Type A, though premature death can occur, often from liver and respiratory disease.

2.1 STUDY RATIONALE

No approved treatment is available for ASMD. Clinical studies have been performed to demonstrate the efficacy and safety of olipudase alfa. In France, one adult patient with ASMD participated in Study DFI12712 and two patients with ASMD in the LTS13632 Study. The efficacy and safety of olipudase alfa ERT have been demonstrated, and the DFI12712 and the LTS13632 studies will end once the European MA has been granted by the European Commission. The present study intends to ensure safety follow-up and treatment continuation for patients who participated in the DFI12712 or the LTS13632 study in France while Sanofi is seeking to obtain reimbursement in France (after the European MA and until reimbursement is granted in France).

This study also intends to fulfill an unmet critical need while Sanofi is seeking regulatory approval of olipudase alfa by providing treatment of the patient in France with ASMD who meets the criteria listed in Section 5 . In case reimbursement will not be obtained, this study will continue for 5 years.

2.2 BACKGROUND

Olipudase alfa is a recombinant human acid sphingomyelinase expressed in Chinese hamster ovary cells. The resulting gene product retains the enzymatic activity and lysosomal targeting of the native protein. Olipudase alfa is being developed for the treatment of non-central nervous system manifestations in patients with a confirmed diagnosis of ASMD.

A review of clinical experience with olipudase alfa is in the Investigator's Brochure (IB).

Olipudase alfa is administered by IV infusion every 2 weeks (±3 days). The dose should be based on the patient's weight. During the dose escalation period, patient should be monitored for 3 hours after the end of each infusion. Treatment begins with a dose escalation period. The maximum administered dose is 3 mg/kg.

Olipudase alfa has been evaluated in 72 patients. ASCEND trial (DFI12712, NCT02004691) is a Phase 2/3 double blind, placebo-controlled, randomized, multicenter study, with a primary analysis period of 52 weeks and an OLE of less than 4 years. A total of 36 adults with ASMD type B patients were included. After 52 weeks of follow-up, the study was declared positive as it met the first primary endpoint of DLco (Diffusion capacity of lung for carbon monoxide). The DLco was significantly improved versus placebo ($p<0.0004$). Spleen volume statistically decreased ($p<0.0001$ vs placebo), accompanied by increased platelet count, reflecting correction of hypersplenism. Liver volume also significantly decreased ($p<0.0001$ vs placebo) due to clearance of sphingomyelin (supported by histological evidence from serial liver biopsies). Olipudase alfa showed a favorable safety and tolerability profile. No patient died and there were no permanent discontinuations of olipudase alfa due to adverse events. All serious adverse events (SAEs) were considered unrelated to treatment (3 olipudase alfa patients had 5 SAEs and 4 placebo patients had 11 SAEs).
IARs, which are expected with ERT, were mild or moderate and easily managed. 8/18 olipudase alfa patients (44%) and 6/18 placebo patients (33%) had IARs. Treatment-induced anti-drug antibodies (ADAs) occurred in 4/18 olipudase alfa patients (22%) : 2 of these patients had transient antibodies and the remaining 2 patients had persistent but low antibody titers No patient developed neutralizing antibodies that interfered with cell uptake of enzymes.

ASCEND-Peds trial (DFI13803, NCT02292654) is a Phase 1/2 1-year open-label multi-center study to evaluate safety, tolerability, PK, and efficacy of olipudase alfa in pediatric patients with ASMD for 64 weeks. The study included 20 children and showed that olipudase alfa is generally well-tolerated with significant improvements in clinically relevant disease endpoints. Most AE were mild or moderate, including IARs (primarily urticaria, pyrexia, and/or vomiting) in 11 patients. Three patients had SAE considered related to treatment: one with transient asymptomatic alanine and aminotransferase increases, another with urticaria and rash, and a third with an anaphylactic ADA+ reaction (who successfully underwent desensitization and reached the 3 mg/kg maintenance dose). Mean splenomegaly and hepatomegaly significantly improved ($p < 0.0001$). Mean % predicted DLco significantly improved by 32.9% ($p=0.0053$) in patients able to perform the test. Mean height Z-scores improved by 0.56 ($p < 0.0001$).

Patients who have completed ASCEND-Peds trial can then be included in the long-term phase 2 study LTS13632 (NCT02004704).

2.3 BENEFIT/RISK ASSESSMENT

Information on the known and expected benefits and risks of, and reasonably expected adverse events associated with, treatment with olipudase alfa is in the IB and the written subject information and informed consent form (ICF).

Considering the measures taken to minimize risk to the patient participating in this study, the potential risks identified in association with treatment with olipudase alfa are justified by the anticipated benefits that may be afforded to this patient.

3 OBJECTIVE AND ENDPOINTS

The objective of this study is to assess safety and tolerability of olipudase alfa in patients in France with acid sphingomyelinase deficiency (ASMD) who have completed DFI12712 or LTS13632 study from market authorization until reimbursement of olipudase alfa in France or until 5 years, whichever comes first.

Safety reporting is required. Submission of safety reports to Sanofi is mandatory for the participant to be eligible to continue in this study.

4 STUDY DESIGN

This is an open-label extension, bi-center, French study of safety and tolerability in the patients who have previously participated in DFI12712 or LTS13632 study of olipudase alfa in France.

Safety assessments are required. Efficacy, pharmacodynamic, and pharmacokinetic assessments are not required.

This study is intended to assure safety follow-up and study treatment continuation for the patients who completed the DFI12712 or the LTS13632 study in France while Sanofi is seeking regulatory approval of olipudase alfa in France.

4.1.1 Determination of the end of the study

The participants may continue to receive olipudase alfa until the earliest of the participants' own voluntary withdrawal; this study ending; olipudase alfa reimbursement becoming available in France; or determination by the participant's physician that this treatment is no longer appropriate.

The duration of the study is expected to depend on local regulations and on the date when olipudase alfa reimbursement becomes available in France.

In case reimbursement will not be obtained, this study will end after 5 years.

5 STUDY POPULATION

Up to 3 participants are expected to be enrolled in this study.

5.1 INCLUSION CRITERIA

The patient is eligible to be included in the study only if the following criteria apply:

I 01. The patient has completed Study DFI12712 (ASCEND) in France, a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with ASMD and has benefited from the drug olipudase alfa or the patient has completed Study LTS13632 in France, a Long-Term Study to assess the ongoing safety and efficacy of olipudase alfa in patients with ASMD.

I 02. The patient must provide signed, informed consent prior to performing any study-related procedures. Consent of a legally authorized guardian(s) is (are) required for legally minor patients as defined by local regulation. If the patient is legally minor, signed written consent shall be obtained from parent(s)/legal guardian and assent obtained from patients, if applicable

I 03. The patient is willing to comply with the clinical protocol.

I 04. The patient, if female and of childbearing potential, must have a negative pregnancy test result [urine beta-human chorionic gonadotropin (β-HCG)] at enrollment. Sexually active female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or to use 2 acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device, or intrauterine system for the entire duration of the treatment period and for at least 28 days after receiving the last study drug dose. Sterilized or infertile patients (defined as having undergone surgical sterilization, ie, vasectomy/bilateral tubectomy, hysterectomy and bilateral ovariectomy or as being postmenopausal, defined as at least 12 months of amenorrhea prior to enrollment) will be exempted from the requirements to use contraception in this study.

5.2 EXCLUSION CRITERIA

A patient is excluded from the study if any of the following criteria apply:

E 01. Any patient who has not participated in the Study DFI12712 or the Study LTS13632

E 02. A patient who experienced any systemic hypersensitivity reactions to olipudase alfa in Study DFI12712 or Study LTS13632 which, in the opinion of the Investigator, could indicate that treatment continuation may present an unreasonable risk.

E 03. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

E 04. The patient is unwilling or unable to abstain from alcohol for 1 day prior to and 3 days after each olipudase alfa infusion for the duration of the treatment period.

E 05. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 06. The patient is concurrently participating in another clinical study of investigational treatment.

E 07. Any of the following medical conditions:

- 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's participating in or completing the study.
- Requirement for recurrent dose adjustment of anticoagulation treatment over the last 6 months.
- Pregnancy or breastfeeding.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Not applicable

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/ADMINISTRATION OF STUDY ADMINISTRATION

Not applicable

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION ADMINISTERED

Olipudase alfa is a sterile, nonpyrogenic white to off-white lyophilized cake supplied in single-use, 20 cc Type 1 glass vials. Each vial contains approximately 20 mg of extractable olipudase alfa.

The lyophilized powder should be reconstituted with 5.1 mL of sterile water for injection to yield a concentration of approximately 4.0 mg/mL olipudase alfa, which will be further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered. Detailed instructions for the preparation, storage, and administration of olipudase alfa will be given in the pharmacy manual and the IB, which will be provided to the Investigator. Physicians seeking additional treatment-related information during the course of olipudase alfa treatment should communicate with the Sanofi local medical representative.

Olipudase alfa is administered by IV infusion every 2 weeks (±3 days) in reference to the date of the first infusion. The dose should be based on the participant's weight. For an adult participant with a body mass index >30, the dose should be based on weight (mass) in kilograms corresponding to a BMI of 30, given the participant's height.

Infusions should be supervised by a health care provider with experience in ERT. The potential risk of severe infusion-associated reactions (IARs) requires appropriate resuscitation equipment to be readily available. During the dose escalation period, the participant should be monitored for 3 hours after the end of each infusion. There are no restrictions on infusion timing with respect to meals.

The participants will start this study at his/her last dose received in Study DFI12712 or Study LTS13632. If more than 1 dose is missed between studies, instructions on dose escalation are provided below in this section.

- The dose for an adult should be escalated as shown below.

Table 1 Dose Escalation for Adults

Week[a]	Olipudase alfa dose, mg/kg
0[b]	0.1
2	0.3
4[b]	0.3
6	0.6
8	0.6
10	1.0
12	2.0
14	3.0
≥16	3.0

[a] Weeks do not account for rechallenges.
[b] Rechallenges are allowed only once, at Week 0 and at Week 4.

The participant will receive intravenous olipudase alfa over approximately 20 minutes to 4.5 hours, depending on the dose. The length of the infusion time may be adjusted based on the participant's tolerance of the infusion.

The dose escalation regimen may be adjusted based on the participant's tolerance of the infusion and clinical judgement.

If a mild systemic hypersensitivity reaction occurs,1 rechallenge each is allowed for the doses administered at Week 0 (0.1 mg/kg olipudase alfa) and at Week 4 (0.3 mg/kg olipudase alfa).

If a moderate or severe systemic hypersensitivity reaction occurs with the rechallenge, the following should take place:

- The olipudase alfa infusion should immediately be terminated, and appropriate medical treatment should be initiated.
- The event should be clearly documented on the adverse event (AE) form.
- The Sanofi local medical representative should immediately be informed.

During dose escalation the following guidelines should be observed (refer to the IB):

Only AEs not related to the participant's underlying condition should affect dose escalation.

These guidelines apply to AEs considered related to olipudase alfa treatment.

- If the participant experiences no AE or a mild AE, escalate to the next dose.
- If the participant experiences a moderate AE, repeat the same dose at the next infusion.
- If the participant experiences a severe AE, decrease to the prior dose at the next infusion.

If the participant presents on the day of infusion with either an unresolved AE or an acute illness, neither of which meets the criteria for permanent discontinuation of treatment, the infusion may be withheld or administered at the Investigator's discretion.

- The dose for a pediatric patient should be escalated as shown below:

Table 2 Dose Escalation for Pediatric Patients

Week[a]	Olipudase alfa dose, mg/kg
0	0.03
2	0.1[b]
4	0.3[c]
6	0.3[c]
8	0.6[d]
10	0.6[d]
12	1.0[d]
14	2.0[d]
≥16	3.0[e]

a Weeks do not account for rechallenges.
b If the initial dose of 0.03 mg/kg is tolerated (1 rechallenge with 0.03 mg/kg is allowed)
c If 0.1 mg/kg is tolerated
d If 2 consecutive doses of 0.3 mg/kg are tolerated
e If 3.0 mg/kg is not tolerated, the patient should receive the highest tolerated dose for the rest of his/her time in the program.

Missed doses

A dose is considered missed when it is not administered within 3 days of the scheduled date. When a dose of olipudase alfa is missed, administer the next dose as described below as soon as possible. Thereafter, infusions should be scheduled every other week from the date of the last infusion.

Missed doses during the dose escalation period

- If 1 infusion is missed administer the last tolerated dose before resuming dose escalation according to Table 1.
- If 2 consecutive infusions are missed, administer 1 dose below the last tolerated dose (minimal dose 0.3 mg/kg), before resuming dose escalation according to Table 1.

- If 3 or more consecutive infusions are missed, resume dose escalation starting at 0.3 mg/kg, according to Table 1.
- At the next 2 scheduled infusions after a missed dose, if the dose administered is to be 0.3 or 0.6 mg/kg, that dose should be administered twice, according to Table 1.

Missed doses when dose escalation is complete

- If 1 maintenance infusion is missed, administer the same dose and adjust the treatment schedule accordingly.
- If 2 consecutive maintenance infusions are missed, administer 2 mg/kg. At subsequent infusions, administer 3 mg/kg.
- If 3 or more consecutive infusions are missed, resume dose escalation starting at 0.3 mg/kg, according to Table 1. If 3 or more consecutive infusions are missed, a baseline assessment of liver function (AST/ALT) will be required before treatment initiation. Please refer to the requirements for safety assessment during dose re-escalation (Section 8.1).

Dose interruption

If any of the following AEs occurs dosing should be temporarily stopped, taking into consideration the relationship of the AE to treatment with olipudase alfa):

- Any serious adverse event (SAE), not related to the participant's underlying condition and considered related to treatment with olipudase alfa.
- Any increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, or alkaline phosphatase (AP) to >3× the baseline value (prior to the start of olipudase alfa therapy) and above the upper limit of normal (ULN).
- Any increase in total bilirubin or AP to >1.5× the baseline value with AST or ALT >2× ULN.
- Any increase in ALT or AST to >3× ULN and >2× the baseline value with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (eosinophils >ULN).
- Any serious or severe AE that raises significant concern about the safety of olipudase alfa at the administered dose.

When dosing with olipudase alfa is interrupted, safety monitoring of the participant should continue. If the AE(s) is/are reversible and results of clinical laboratory tests (including liver function tests) approach or reach baseline values, the participant can resume dosing and receive the previously-tolerated lower dose (ie, the dose administered at a previous visit without incident).

Depending on the participant's response, either dose escalation should continue or the participant should go on receiving the previously tolerated dose (ie, the highest tolerated dose).

Management of hypersensitivity and infusion-related reactions

The information in this section is based on clinical trial experience with olipudase alfa and is in accordance with the IB. All IARs should be documented on the AE form.

In general, pretreatment is not recommended for prophylactic management of IARs. For a participant who experiences moderate to severe or recurrent IARs suggestive of hypersensitivity (Section 8.2.6), pretreatment (eg, antihistamines; antipyretics; glucocorticoids) may be considered by the Investigator according to his or her clinical judgment. The need for oral or IV cationic amphiphilic antihistamines should be carefully considered, given the potential risk of functional inhibition of olipudase alfa activity by these drugs.

Mild IARs may be mitigated by reducing the infusion rate (eg, by half) or temporarily interrupting the infusion.

A participant reporting signs or experiencing symptoms suggesting hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, during infusion of olipudase alfa should be treated according to the local SOC. If anaphylaxis or other severe allergic reactions occur, the infusion should immediately be terminated, appropriate medical treatment should be initiated, and a Sanofi local medical representative informed.

All infusions during dose escalation must take place in a monitored hospital setting. The potential risk of severe hypersensitivity IARs during dose escalation mandates the requirement for clinicians and appropriate resuscitation equipment to be readily available.

Home infusion

Infusion of olipudase alfa at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the investigator. A patient’s underlying co-morbidities and ability to adhere to the home infusion requirements need to be taken into account when evaluating the patient for eligibility to receive home infusion. The following criteria should be considered and documented in medical files by investigator:

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may affect patient’s ability to tolerate the infusion.
- The patient is considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.
- The patient must have received olipudase alfa infusions in a hospital or infusion center for a few months and finish dose escalation. Documentation of a pattern of well-tolerated

infusions with no IARs, or mild IARs that have been controlled with premedication, is a prerequisite for the initiation of home infusion.

- The participant must be willing and able to comply with home infusion procedures.
- Any identified risk of noncompliance with monitoring of study requirements, or potential for loss to follow -up, should result in a participant's not being eligible for home infusion
- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. The healthcare professional must be available at all times during the home infusion and a specific time after-infusion, depending on patient's tolerance prior to starting home infusion and determined at the discretion of the investigator.
- If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, and appropriate medical treatment should be initiated. Subsequent infusions may need to occur in a hospital or infusion center until no such adverse reaction is present.
- Dose and infusion rate must not be changed without consulting the investigator.
- Prior to beginning home infusions, the home infusion agency staff, including new staff members, must have been trained by the site or sponsor in proper procedures for administering infusions, monitoring participants, documenting procedures, and reporting to site on a timely basis. Any new staff member must be trained by the site or sponsor prior to resuming home infusions. The site must confirm that the home infusion agency staff has received training at least equivalent to that provided to new staff members.
- The home infusion agency staff should be readily available when olipudase alfa is administrated and through the post-infusion observation period determined at the discretion of the investigator..
- The home infusion agency staff must be trained in basic life support (cardiopulmonary resuscitation) and should have a process for requesting additional emergency services if needed.
- The home infusion agency must keep source documentation of each infusion, including documentation of any AEs. The home infusion agency must be amenable to providing specific source documentation to Sanofi and must agree to be monitored.

The Investigator (PI) is responsible for approving initiation of home infusions and is still responsible for all study procedures and the participant's safety, even when delegating infusion responsibilities to the home infusion agency during this clinical study.

It is the Investigator's responsibility to guide staff in clinical management of the participant in case of IARs or hypersensitivity or anaphylactic reactions. The Investigator will be the point of contact for home infusion agency staff in the event of questions or emergency situations.

Infusions given in the home setting versus in the clinic will be captured in the electronic case report forms (eCRFs) for AEs and exposure.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Sanofi will supply olipudase alfa vials and coordinate packaging and distribution services in accordance with the administration schedule. The clinical site should provide syringes and diluent bags.

Olipudase alfa will be provided as a sterile lyophilized powder to be reconstituted with sterile water for injection and further diluted with 0.9% sodium chloride in an infusion bag and/or syringe for administration.

The olipudase alfa label text will meet the national legislation requirements of France and will comply with Good Manufacturing Practice. The label text will minimally include the protocol number, description of the vial contents, packaging number, storage conditions, Sanofi's name and address, and any required caution statement as mandated by the participating country. Only the Investigator should prescribe olipudase alfa. Under no circumstance will olipudase alfa be used other than as directed by this protocol.

Olipudase alfa must be kept in a secure area with restricted access. Unreconstituted olipudase alfa should be stored under adequate refrigerated conditions at 2°C to 8°C (36°F to 46°F). Temperature excursions should be handled as described in the pharmacy manual.

Reconstituted olipudase alfa is stable at 20°C to 25°C for 24 hours plus the duration of the infusion, at 0.1 to 3.5 mg/mL. It is recommended that reconstituted olipudase alfa be used immediately after reconstitution.

The Investigator or other authorized persons (ie, pharmacists or designees) are responsible for storing olipudase alfa provided by Sanofi in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of storage conditions, especially control of temperature (eg, refrigerated storage) and of information on in-use stability and instructions for handling olipudase alfa should take place according to the rules provided by Sanofi.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received, and that any discrepancies are reported and resolved before use of the study intervention.

Only the participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Sanofi must be promptly informed of any quality issue noticed with the receipt or use of olipudase alfa, such as deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc. Some deficiencies may be recorded through a complaint procedure (Section).

A potential defect in the quality of olipudase alfa 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, to recall olipudase alfa and eliminate potential hazards.

Under no circumstances will the Investigator supply olipudase alfa to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow olipudase alfa to be used other than as directed by this clinical trial protocol, or dispose of olipudase alfa in any other manner.

6.3 STUDY INTERVENTION COMPLIANCE

The participants will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.4 DOSE MODIFICATION

Dose modification (dose escalation and procedures for missed doses and dose interruption) is described in Section 6.1).

6.5 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

The study will end when olipudase alfa reimbursement becomes available in France. In case reimbursement will not be obtained, this study will end 5 years after starting.

6.6 TREATMENT OF OVERDOSE

In the event of an overdose, of olipudase alfa, the Investigator should:

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for any AE/serious adverse event (SAE) and laboratory abnormalities.
- Document appropriately in the report form.

6.7 CONCOMITANT THERAPY

Based on published in silico and in vitro data, tricyclic antidepressants and some cationic amphiphilic drugs, including select antidepressants (eg, imipramine, desipramine, some selective serotonin reuptake inhibitors), select antipsychotics (eg, chlorpromazine), and some antihistamines (eg, loratadine, desloratadine, astemizole, ebastine, clemastine) may decrease olipudase alfa activity. The relevance of this functional inhibition in humans is not known. This theoretical interaction should be considered when olipudase alfa is prescribed concomitantly with chronic systemic treatment with functional inhibitors of acid sphingomyelinase.

The need for oral or intravenous administration of cationic amphiphilic antihistamines in the participant receiving olipudase alfa should be carefully considered. There is no restriction of topical antihistamines.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Treatment may be discontinued temporarily or permanently. Any treatment discontinuation should be documented. Permanent discontinuation should be a last resort. Sanofi should be immediately notified (within 5 business days) if the participant withdraws from the study. Any treatment discontinuation should be fully documented in the progress report.

7.1 TEMPORARY TREATMENT DISCONTINUATION

Treatment discontinuation is temporary when >1 olipudase alfa infusion is not administered, as decided by the Investigator. Administration of olipudase alfa should be reinitiated with close, appropriate clinical and/or laboratory monitoring, after the Investigator has considered, in his/her best medical judgment, that the relationship of olipudase alfa to the event of concern was unlikely, and if the participant still meets the enrollment criteria (Section 5).

7.2 PERMANENT TREATMENT DISCONTINUATION

Treatment discontinuation is permanent when there is a definite decision by the Investigator, Sanofi, or the participant to not re-expose the participant to olipudase alfa at any time, or if the reimbursement has not been obtained after 5 years.

7.3 CRITERIA FOR PERMANENT TREATMENT DISCONTINUATION

The participant may withdraw from treatment if he or she decides to do so, at any time and irrespective of the reason; withdrawal may also be the decision of the Investigator or of Sanofi, or if the reimbursement has not been obtained after 5 years. All efforts will be made to document the reasons for discontinuation in the progress report.

The participant should be withdrawn from this study for the following reasons:

- The participant or their parent(s) / guardian(s) wishes treatment to be withdrawn.
- The participant has become pregnant or is breastfeeding.
- The participant is noncompliant with treatment or the requirements of the program.

In addition, Sanofi may decide to discontinue this study early for any other reason.

Any clinically significant abnormal laboratory value will be immediately rechecked for confirmation before a decision to permanently discontinue treatment with olipudase alfa.

Sanofi must be notified of termination of patient participation as soon as possible. If the participant is to be discontinued from the study for any reason, safety data should continue to be collected for at least 30 days after the last administration of olipudase alfa.

Pregnancy

Pregnancy will always result in treatment discontinuation. There have been no studies of olipudase alfa in pregnant women. To ensure participant safety in this study, a female participant of childbearing potential must have a serum β-HCG pregnancy test at the time of enrollment and a urine β-HCG pregnancy test up to 24 hours before her first olipudase alfa infusion and then once every 4 weeks before infusion. The participant must be willing to practice true abstinence in line with their preferred and usual lifestyle or to use 2 acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device, or intrauterine system for the entire duration of the treatment period and for at least 28 days after receiving the last study drug dose.. Every effort will be made to prevent pregnancy during this study. Sterilized or infertile patients (defined as having undergone surgical sterilization, ie, vasectomy/bilateral tubectomy, hysterectomy and bilateral ovariectomy or as being postmenopausal, defined as at least 12 months of amenorrhea prior to enrollment) will be exempted from the requirements to use contraception in this study

Effective Contraceptive Methods for a Female Participant

- User-dependent
  - Combined (estrogen + progestogen) hormonal contraceptive (oral, intravaginal, or transdermal)
  - Progestogen-only hormonal contraceptive (oral or injectable).
- User-independent
  - Progestogen-only hormonal contraceptive implant
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Vasectomized partner, if the participant has no other partners and absence of sperm is confirmed.

Male Participant

A male participant whose partner is a woman of childbearing potential must agree to the following while receiving olipudase alfa and for 15 days after his last infusion:

- Refrain from donating sperm.

- Use a male condom while his partner uses 1 highly effective contraceptive method or abstain from heterosexual intercourse.

7.3.1 Handling of the participant after permanent treatment discontinuation

A participant who has received at least 1 olipudase alfa infusion and who is withdrawn from this study should receive a safety follow-up telephone call from the clinical site 30 days after the final infusion. Any instance of permanent treatment discontinuation must be recorded by the Investigator in the progress report when it is considered to be confirmed.

7.3.2 Procedure and consequence for participant withdrawal from the study

The participant may withdraw from this study if he or she decides to do so, at any time and for any reason. He or she should preferably withdraw consent in writing. If the participant refuses or is physically unavailable to do so, the Investigator should document and sign the reason for the participant's not withdrawing consent in writing.

The reason for withdrawal should be recorded. The participant or their parent(s)/guardian(s) should be explicitly asked about the contribution of possible AEs to his or her decision to withdraw, and any resulting AE information should be documented and reported to Sanofi.

When the fails to return to the site, the Investigator should make the best effort to recontact him or her (eg, contacting the participant's family or private physician, reviewing available registries or health care databases), and to determine his or her health status, including at least his or her vital status. Attempts to contact the participant (eg, dates and times of attempted telephone contact; receipt for a registered letter) should be documented in the participant's records.

7.4 LOSS TO FOLLOW-UP

The participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if the participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter sent to the participant's last known mailing address, or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Given the nature of this study, reporting of clinical efficacy endpoints is not mandatory, except where required by the applicable government health authorities.

8.1 ASSESSMENTS

Required assessments before enrollment

Not applicable

Assessments after enrollment in case 3 or more missed infusion

If the patient missed 3 or more infusion, a re-escalation is needed. In this case, liver function tests will be performed during dose escalation.

During dose escalation or upon resuming treatment following missed doses, transaminases (ALT and AST) levels should be obtained within 72 hours prior to the next scheduled infusion. If either the baseline or a pre-infusion transaminase level is >2 times the ULN during dose escalation, then additional transaminase levels should be obtained within 72 hours after the end of the infusion. If the transaminase levels are elevated above baseline and the ULN, the dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld, based on clinical judgment..

Baseline is defined as the following:

- For dose re-escalation: last value prior to the first re-escalation dose.

Antidrug antibody (ADA) testing if indicated for hypersensitivity

If the participant experiences a moderate/severe or recurrent IAR that is suggestive of a hypersensitivity reaction, additional blood samples are recommended to be collected and tested for anti-olipudase alfa antibody (immunoglobulin G [IgG] and immunoglobulin E [IgE]). For IgE anti-olipudase alfa antibody determination, a predose serum sample collected for anti-olipudase alfa IgG testing may be used if the IAR occurs at that study visit. If a predose sample was not collected on that day, the participant should return to the study site at least 3 days after the event for a serum sample to be collected. Investigator will contact Sanofi France Immunosurveillance program to receive support on ADA testing. Samples will be sent to LabCorp by the official transporter and report results will be made available to the investigator in the dedicated platform.

Laboratory safety variables

Safety laboratory tests will be performed at a local laboratory, depending on the site's laboratory and facilities. Serum or urine may be used for pregnancy testing for a female participant of childbearing potential.

Only clinically significant laboratory test results will be recorded as AEs in the case report form.

8.2 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs are in Appendix 3 (Section 10.3). The definition of an adverse event of special interest (AESI) is in Section 8.2.6.

AEs will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up all AEs or AEs that are serious, considered related to the study intervention, or caused the participant to discontinue treatment or withdraw from the study (Section 7).

Recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are discussed in Appendix 3 (Section 10.3).

8.2.1 Time period and frequency for collecting AE and SAE information

All SAEs and AESIs will be recorded and reported to the Sponsor within 24 hours of occurrence, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The Investigator is not obligated to actively seek information on AEs or SAEs after conclusion of the participant's study participation. However, if the Investigator learns of any SAE, including a

death, at any time after the participant has left the study and considers the event to be reasonably related to the study intervention or study participation, he or she must promptly notify the Sponsor.

8.2.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when identifying AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method of inquiring about AEs.

8.2.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator should proactively follow the participant at subsequent visits. Further information on follow-up procedures is in Appendix 3 (Section 10.3.3).

8.2.4 Regulatory reporting requirements for SAEs

Prompt notification of the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the participant's safety and the safety of the study intervention are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, the institutional review boards (IRB)/independent ethics committees (IEC), and Investigator.

- Serious adverse events that are considered expected will be specified in the reference safety information in the Investigator Brochure.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to the Investigator as necessary.
- When receiving an Investigator safety report from the Sponsor describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs), the Investigator will review and file it with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR and is expedited to regulatory authorities.

8.2.5 Collection of pregnancy information

Female participant who becomes pregnant

- The Investigator should collect pregnancy information for a female participant who becomes pregnant while receiving olipudase alfa in this study. Pregnancy in a female participant or the partner of a male participant during this study will be recorded as an

AESI with immediate notification of Sanofi local pharmacovigilance in all cases. It will be qualified as an SAE only if it fulfills seriousness criteria.

- Pregnancy information should be submitted to Sanofi within 24 hours of learning of the pregnancy.
- The pregnancy should be followed to determine its outcome. Information on the status of the mother and child should be submitted to Sanofi local pharmacovigilance.
- Generally, follow-up needs to be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or the indication for termination.
- While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy should be reported as an AE or SAE.
- A spontaneous abortion should always be reported as an SAE.

Any SAE occurring as a result of a pregnancy after the end of treatment with olipudase alfa which the Investigator considers reasonably related to the treatment should be reported to Sanofi. While the Investigator is not obligated to actively seek this information from a former participant in this study, he or she may learn of an SAE from spontaneous reporting.

Male participant with partner who becomes pregnant

- The Investigator will attempt to collect pregnancy information for any woman who becomes pregnant while her partner is receiving olipudase alfa in this study.
- After obtaining signed informed consent from the participant's partner, the Investigator should submit the pregnancy information to Sanofi local pharmacovigilance within 24 hours of learning of the partner's pregnancy.
- The pregnancy should be followed to determine its outcome. Information on the status of the mother and child should be submitted to the Sponsor.
- Generally, follow-up needs to be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported to Sanofi local pharmacovigilance regardless of fetal status (presence or absence of anomalies) or the indication for termination.

8.2.6 Adverse events of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to olipudase alfa or to this single-center, single-participant study, for which ongoing monitoring and rapid communication by the Investigator to Sanofi may be appropriate. Such events may require further investigation to characterize and understand them. AESIs may be added to or removed from this program with a protocol amendment.

AESIs include:

- **Pregnancy** in a female participant or in a female partner of a male participant.
- **Symptomatic overdose** (serious or non-serious) of olipudase alfa
  - An overdose (accidental or intentional) of olipudase alfa, defined as an increase of at least 30% in the dose administered for the specified duration, or administration of the dose for less than half the recommended duration,
  - An asymptomatic overdose should be reported as a standard AE.
- **Infusion-associated reactions**

  Some AEs may be manifestations of IARs, including hypersensitivity reaction, acute phase reaction (APR), and cytokine release syndrome (CRS); however, the original signs and symptoms may be reported as AEs.

  IARs are defined as AEs that occur during the infusion or within 24 hours after the start of the infusion and are considered as related or possibly related to the treatment by the Investigator or Sanofi. An event occurring ≥24 hours after the start of an infusion may be judged by the Investigator or Sanofi as an IAR. For this study, IARs may present as hypersensitivity reactions, APRs, and CRS.

  If the participant experiences a moderate or severe or recurrent IAR suggestive of a hypersensitivity reaction, collection of additional blood samples is recommended for determination of anti-olipudase alfa IgE.

- **Hypersensitivity reactions**

  Infusion-associated hypersensitivity reactions seen with other ERTs are typically IgG/IgE-mediated and occur after sensitization. After subsequent exposure to the antigen, typically early during the infusion or shortly afterward, a “sensitized” participant 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. Anaphylactoid or nonimmunologic anaphylaxis reactions may present with similar serious clinical manifestations to anaphylaxis but without prior exposure to the antigen, 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 ERTs include urticaria, rash, dyspnea, and, less frequently, orofacial angioedema. Other symptoms of hypersensitivity IARs include fever, hypotension, tachycardia, nausea, vomiting, pain, and headache.

- **Acute phase reactions**

  Symptoms consistent with acute phase reactions (APRs) were reported in 2 adult and 3 pediatric patients in clinical trials. The main symptoms included pyrexia, nausea, vomiting, fatigue, and pain and occurred within 12 to 72 hours after the end of infusion during the dose escalation phase. These symptoms were associated with increases in

serum/plasma high-sensitivity C-reactive protein and may have been associated with various changes in other acute phase reactants including, but not limited to, neutrophils, iron, ferritin, fibrinogen, D-dimer, transferrin, albumin, prothrombin time, and partial thromboplastin time. Accordingly, APRs will be determined based on combined significant laboratory findings and clinical symptoms.

- **Cytokine release syndrome**

  Cytokine release syndrome is another type of IAR, attributed to release of excessive amounts of cytokines shortly after 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. Increases were observed after a single dose of ≥0.3 mg/kg olipudase alfa in the Phase 1 single-dose study for interleukin 8 and interleukin 6, macrophage inflammatory protein 1 alpha component (MIP-1α) and beta component (MIP-1β), and other cytokines and biomarkers, based on the Myriad Rules-Based Medicine Human Multi-Analyte Profile® antigen panel. Unlike immunoglobulin-mediated hypersensitivity reactions, no prior antigen exposure is required for 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), typical symptoms include pyrexia, nausea, vomiting, fatigue, pain, myalgia, and, in severe cases, multi-organ system dysfunction or failure, severe headache, and pulmonary edema. CRS should be determined based on combined significant laboratory findings and clinical symptoms.

8.2.7 Guidelines for reporting product complaints

Any defect in olipudase alfa must be reported by the Investigator as soon as possible. The monitoring team will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents such as pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3 PHARMACOKINETICS

Not applicable

8.4 BIOMARKERS

Not applicable

8.5 IMMUNOGENICITY ASSESSMENTS

Antibody testing if indicated for hypersensitivity is described in Section 8.1.

8.6 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Not applicable

9 STATISTICAL CONSIDERATIONS

Safety analysis will be based on the review of individual values. All reported AEs and safety parameters in the study will be listed.

Demographic data and the concomitant medications will also be listed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to the participant.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation, except for changes necessary to eliminate an immediate hazard to the participant.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (according to Sanofi policy) should be returned to the participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his or her designated health care professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. If the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, the Investigator should seek independent ethical advice before determining next steps.
    - If the participant or the participant's parent(s)/guardian(s) has decided to opt out, the Investigator must record in the site medical files that he or she does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participant or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

The Investigator will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under his or her responsibility, should fully inform the participant of all pertinent aspects of this study, including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). The participant should be informed to the fullest extent possible about the study in language and terms he or she can understand. The patient must be informed that his or her participant is voluntary.

Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study, and the date written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form (ICF).

In case of ICF amendment while the participants are still included in the study, they must provide consent again, using the most current version of the ICF. Where participants are no longer in the study, those in charge of the amendment must define if those participants must or not reconsent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).

A copy of the ICF must be provided to the participant or legally authorized representative(s).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, IRB/IEC members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participant, the Sponsor takes all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- The participant will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; the participant's name or any information that would make the participant identifiable will not be transferred to the Sponsor.
- The participant or the participant's parent(s)/guardian(s) must be informed that his or her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant or the participant's parent(s)/guardian(s) as described in the informed consent.
- The participant or the participant's parent(s)/guardian(s) must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The participant or the participant's parent(s)/guardian(s) must be informed that his or her study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal of processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. If the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as these data are required to be processed by applicable regulations. The same rule applies if the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intragroup transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the Commission Nationale de l'Informatique et des Libertés (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 30 years, unless further retention is required by applicable regulations.

- To facilitate the maintenance of the Investigator's personal data, especially if he or she contribute to studies sponsored by several pharmaceutical companies, Sanofi participates in the Shared Investigator Platform and in the Transcelerate Investigator Registry project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once and for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request access to and rectification of their personal data, as well as their erasure (where applicable), by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact)

10.1.5 Committee structure

Not applicable

10.1.6 Dissemination of clinical study data

Study participant

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations.

While making information available, Sanofi continues to protect the privacy of participants in its clinical trials

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to health care organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation, or by a code of conduct such as the "FPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic forms unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The

Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the forms.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification of the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on report forms that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must also be available.
- The Investigator must maintain accurate documentation (source data) that support the information entered on report forms.
- Study monitors will perform ongoing source data verification to confirm that data entered on report forms by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of the participant are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason, at the sole discretion of the Sponsor. The sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigator, the IRB/IEC, and the regulatory authorities of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The following liver function tests will be performed during dose escalation only if re-escalation is needed:

- ALT
- AST
- AP
- Gamma glutamyl transferase
- Total and direct bilirubin.

Note: Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

10.3 APPENDIX 3: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of adverse event

- An AE is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the definition of an adverse event

- Any abnormal laboratory test result (hematology, clinical chemistry, or urinalysis) or other result (eg, vital sign measurement), including a result that worsens from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease):
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation and/or
  - Leading to discontinuation of olipudase alfa or dose modification of dosing and/or
  - Fulfilling a seriousness criterion and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Sign, symptom, or the clinical sequela of a suspected drug-drug interaction.
- Sign, symptom, or the clinical sequela of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Events NOT meeting the definition of an adverse event

- Any clinically significant abnormal laboratory findings or other abnormal assessments associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected from the participant's condition.
- Any medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study, that do not worsen.

10.3.2 Definition of serious adverse event

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) to the hospital or emergency department for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to perform normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
        - Allergic bronchospasm
        - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
        - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
    - Development of drug dependence or drug abuse
    - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
    - Suicide attempt or any event suggestive of suicidality
    - Syncope; loss of consciousness (except if documented as a consequence of blood sampling)
    - Bullous cutaneous eruption

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. “Severe” is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The Investigator will also consult the IB.
- For each AE/SAE, the Investigator **must** document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sanofi. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** Sanofi**.**
- The Investigator may change his/her opinion of causality in light of follow-up information, and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform, or arrange for the conduct of, supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.
- If the participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sanofi with a copy of any postmortem findings, including histopathology.]
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, the site can report this information on a paper SAE form or to the Sponsor's representative by telephone.
- Contacts for SAE reporting will be provided.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method of transmitting this information to the Sponsor.
- Contacts for SAE reporting will be provided.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Information on contraception is in Section 7.3.

10.5 APPENDIX 5: COUNTRY-SPECIFIC REQUIREMENTS

10.6 APPENDIX 6: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Not applicable

10.7 APPENDIX 7: ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASM	acid sphingomyelinase
ASMD	acid sphingomyelinase deficiency
AST	aspartate aminotransferase
CRS	cytokine release syndrome
ERT	enzyme replacement therapy
IAR	infusion-associated reaction
IB	Investigator's Brochure
ICF	informed consent form
IEC	independent ethics committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IRB	institutional review board

IV	intravenous
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

10.8 APPENDIX 8: PROTOCOL AMENDMENT HISTORY

Not applicable

11 REFERENCES

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2. XENPOZYME 20 mg, powder for concentrate for solution for infusion (Olipudase alfa) draft Summary of Product Characteristics - Marketing Authorization Application EMEA/H/C/004850 (Centralized Procedure) [EMA submission dossier 26/10/2021].