EU-RISK MANAGEMENT PLAN FOR XENPOZYME® (OLIPUDASE ALFA)

Risk Management Plan (RMP) Version number	Version 3.3
Data Lock Point (DLP)	12-JAN-2024
Date of final sign-off	11-APR-2025

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	To address Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's responses on preliminary assessment report / Request for supplementary Information received on 24-Mar-2025 (third round of questions) during the Type II variation for the completion of the phase 2/3 clinical trial (DFI12712 ASCEND) and LTS13632 (procedure number EMEA/H/C/004850/II/0012/G).
Summary of significant changes in this RMP	Specific follow-up questionnaire and full protocol study (OBS17376) were added. Therefore, the following modules and annexes have been updated: Part III, Part V, Annex 3, Annex 4 and Annex 8.

EMEA: European Medicines Agency; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Version 2.3
Approved with procedure	EMEA/H/C/004850/IB/0007
Date of approval (opinion date)	18-Dec-2023

EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ADA:	Anti-Drug Antibody
AE:	Adverse Event
ANSM:	National Security Agency of Medicines and Health Products
APR:	Acute Phase Reaction
ASM:	Acid Sphingomyelinase
ASMD:	Acid Sphingomyelinase Deficiency
ASMKO:	Acid Sphingomyelinase Knock-Out
ATC:	Anatomical Therapeutic Chemical
BD:	Biodistribution
BMI:	Body Mass Index
CD:	Cluster of Differentiation
CHO:	Chinese Hamster Ovary
CMQ:	Company Medical Query
CNS:	Central Nervous System
CSF:	Consent Report Form
DALA:	Drug Abuse Liability Assessment
DDI:	Drug-Drug Interaction
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
EAIR:	Exposure-Adjusted Incident Rate
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMEA/EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
ETP:	Extension Treatment Period
EU:	European Union
FDA:	Food and Drug Administration
FIASMA:	Functional Inhibitors of Acid Sphingomyelinase
FPI:	First Patient In
G-CSF:	Granulocyte-Colony Stimulating Factor
GLP:	Good Laboratory Practice
HCP:	Healthcare Professional
IAR:	Infusion Associated Reaction
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IL:	Interleukin
IND:	Investigational New Drug
INN:	International Nonproprietary Name
IQR:	Interquartile Range
IV:	Intravenous

JPMDA:	Japan's Pharmaceuticals and Medical Devices Agency
LPLV:	Last Patient Last Visit
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
Max:	Maximum
Min:	Minimum
MIP:	Macrophage Inflammatory Protein
N:	Number
NAb:	Neutralizing Antibody
NOAEL:	No-Observed-Adverse-Effect-Level
NPD A:	Niemann-Pick Disease Type A
NPD B:	Niemann-Pick Disease Type B
NZW:	New Zealand White
PAP:	Primary Analysis Period
PBRER:	Periodic Benefit-Risk Evaluation Report
PD:	Pharmacodynamic
PK:	Pharmacokinetic
PL:	Package Leaflet
PMDA:	Pharmaceuticals and Medical Devices Agency
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
QR:	Quick Response
rhASM:	Recombinant form of Human Acid Sphingomyelinase
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SD:	Standard Deviation
SM:	Sphingomyelin
SmPC:	Summary of Product Characteristics
SSRI:	Selective Serotonin Reuptake Inhibitor
TEAE:	Treatment Emergent Adverse Event
URL:	Uniform Resource Locator
US:	United States
WOCBP:	Women of Child Bearing Potential
β-HCG:	Beta Human Chorionic Gonadotropin

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Olipudase alfa
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	A16AB25
Marketing Authorization Holder (MAH)	Sanofi B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xenpozyme
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Olipudase alfa is a recombinant form of Human Acid Sphingomyelinase; (rhASM) developed as an Enzyme Replacement Therapy (ERT).
	Summary of mode action: Olipudase alfa catalyzes the hydrolysis of sphingomyelin (SM), reducing the amount of SM that accumulates in organs of patients with Acid Sphingomyelinase Deficiency (ASMD).
	Important information about its composition: Olipudase alfa is produced in a Chinese Hamster Ovary (CHO) cell line by recombinant Deoxyribonucleic Acid (DNA) technology. Olipudase alfa is a sterile, lyophilized powder for concentrate for solution for infusion. Excipients: sucrose, L-methionine, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate.
Hyperlink to the product information	Refer to electronic Common Technical Document (e-CTD) sequence 0038 Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: *Olipudase alfa is an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.*
	Proposed: Not applicable

Dosage in the EEA

Current:

Posology

Initial treatment/dose escalation phase

The rapid metabolism of accumulated sphingomyelin (SM) by olipudase alfa generates pro-inflammatory breakdown products, which may induce infusion-associated reactions and/or transient liver enzyme elevations. A dose escalation regimen can minimize the majority of these adverse event (AEs).

Olipudase alfa dose is based on the actual body weight for patient with a body mass index (BMI) ≤30 or an optimal body weight for patient with a BMI > 30.

The recommended starting dose of olipudase alfa is 0.1 mg/kg for adults and the dose should be subsequently increased according to the dose escalation regimen presented in the table below:

Adult patients (≥18 years old)	
First dose (Day 1)	*0.1 mg/kg*
Second dose (Week 2)	*0.3 mg/kg*
Third dose (Week 4)	*0.3 mg/kg*
Fourth dose (Week 6)	*0.6 mg/kg*
Fifth dose (Week 8)	*0.6 mg/kg*
Sixth dose (Week 10)	*1.0 mg/kg*
Seventh dose (Week 12)	*2.0 mg/kg*
Eighth dose (Week 14)	*3.0 mg/kg (recommended maintenance dose)*

Maintenance phase

The recommended maintenance dose of olipudase alfa is 3 mg/kg every 2 weeks.

Pediatric population

The recommended starting dose of olipudase alfa is 0.03 mg/kg for pediatric patients and the dose should be subsequently increased according to the dose escalation regimen presented below:

Pediatric patients (0 to <18 years old)	
First dose (Day 1)	*0.03 mg/kg*
Second dose (Week 2)	*0.1 mg/kg*
Third dose (Week 4)	*0.3 mg/kg*
Fourth dose (Week 6)	*0.3 mg/kg*
Fifth dose (Week 8)	*0.6 mg/kg*
Sixth dose (Week 10)	*0.6 mg/kg*
Seventh dose (Week 12)	*1.0 mg/kg*
Eighth dose (Week 14)	*2.0 mg/kg*

	Ninth dose (Week 16) — *3.0 mg/kg (recommended maintenance dose)* *The recommended maintenance dose of olipudase alfa is 3 mg/kg every 2 weeks.*
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: *Powder for concentrate for solution for infusion.* *Each vial contains 4 mg or 20 mg of olipudase alfa.*
	Proposed: Not applicable
Is or will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

AE: Adverse Event; ASMD: Acid Sphingomyelinase Deficiency; ATC: Anatomical Therapeutic Chemical; BMI: Body Mass Index; CHO: Chinese Hamster Ovary; CNS: Central Nervous System; DNA: Deoxyribonucleic Acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; ERT: Enzyme Replacement Therapy; EU: European Union; INN: International Nonproprietary Name; MAH: Marketing Authorization Holder; rhASM: Recombinant form of Human Acid Sphingomyelinase; RMP: Risk Management Plan; SM: Sphingomyelin.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Olipudase alfa is an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of the acid sphingomyelinase deficiency

Indication	Acid sphingomyelinase deficiency
Incidence (birth prevalence)	The rarity of the disease renders accurate estimations of incidence and prevalence difficult, and robust epidemiological data for ASMD in various regions are lacking. (1)(2) In a systematic review of birth prevalence studies, based on data from ASMD type A and B patients referred to biochemical testing facilities, the birth prevalence per 100 000 life-births was reported as 0.4 in Australia, 0.53 in the Netherlands, 0.6 in Northern Portugal, 0.33 in Czech Republic, and 0.25 in United Arab Emirates. (3) Newborn screening studies have reported an incidence of about 4 to 5 per 100 000. (4)(5) Acid sphingomyelinase deficiency is a pan-ethnic disease; however, there is a higher birth prevalence of ASMD type A disease among persons with Ashkenazi Jewish ancestry. (5)(6)(7) In the Ashkenazi Jewish population, the only population that performs DNA-based screening, the carrier frequency of the 3 common pathogenic variants (L302P, R496L, fsP330) known to cause ASMD type A is 1 in 90 individuals, corresponding to a birth prevalence of about 3 per 100 000. (4)(8) In non-Jewish populations, the prevalence of ASMD type A is unknown, the sensitivity of carrier screening has not been established, and the pathogenic variants that account for the disease-causing changes may differ from those in Ashkenazi Jewish populations. (9) For chronic forms of ASMD, several factors contribute to the absence of accurate estimates of the prevalence, including under-diagnosis related to poor access to enzyme testing, misdiagnosis due to the high degree of variability in presenting symptoms, and/or lack of knowledge about chronic forms of ASMD in the clinical community. (3)(4)(6) The Orphanet survey estimated the prevalence of chronic forms of ASMD type B as 0.4 per 100 000 individuals (and a birth prevalence of 0.25 per 100 000 for type A). (7) The highest frequencies of chronic forms of ASMD have been reported in individuals of Turkish, Arabic, and North African descent, although the disorder affects many other distinct populations. (6)
Demographics of the population in the authorized indication	Acid Sphingomyelinase Deficiency is a multisystemic disorder with heterogeneous manifestations and represents a spectrum of disease, classified as:[a] (5) • Acid Sphingomyelinase Deficiency type A or Infantile neurovisceral ASMD, historically known as Niemann Pick Disease Type A (NPD A), has onset during infancy with severe multiorgan manifestations and neurodegeneration, rapid progression and death typically by 3 years of age. • Acid Sphingomyelinase Deficiency type B or Chronic visceral ASMD, historically known as Niemann Pick Disease Type B (NPD B), has a later onset and a variable progression rate and prognosis; patients may live into later adulthood but may be burdened with multiple morbidities, such as hepatosplenomegaly, progressive pulmonary dysfunction,

Indication	Acid sphingomyelinase deficiency
	thrombocytopenia, and dyslipidemia reflected in the clinically significant pulmonary, liver, and cardiac diseases that are common contributors to premature death in these patients. • Acid Sphingomyelinase Deficiency type A/B or Chronic neurovisceral ASMD, historically known as variant NPD B, intermediate type or NPD type A/B, in which patients survive early childhood but exhibit multiorgan manifestations and progressive neurological abnormalities. The intermediate phenotypic presentations support a position that ASMD represents rather a continuum of clinical subtypes, with the ASMD type A and ASMD type B being two ends of the spectrum. No publications have distinguished an occurrence ratio among the forms of ASMD or estimated the relative proportion of adult and pediatric patients with ASMD. Clinical experience has been that ASMD is often diagnosed during childhood. Of the patients who present symptomatically with ASMD, approximately 60% are diagnosed while in the pediatric age group. (10) There is limited information in the literature regarding pregnancy in ASMD. Personal observations from one physician note that women with chronic visceral ASMD type B having a wide range of disease manifestations including significant pulmonary disease and hepatosplenomegaly, appear to have normal pregnancies and healthy newborns. During pregnancy and the perinatal period, esophageal varices contribute to increased bleeding risks. (11)
Main existing treatment options	Until the first approval of Xenpozyme in Japan on 28-Mar-2022, only symptomatic therapy was available. This included lifestyle and diet modifications, statin therapy to lower cholesterol levels, supplemental oxygen, bronchodilators, vaccinations as appropriate for patients with underlying lung disease, vaccinations against viral hepatitis A and B, and blood transfusions to treat patients with acute episodes of bleeding due to splenomegaly and low platelet counts. Several attempts have been made to use cellular and solid organ transplantation as an indirect source of ASM replacement therapy. The experience to date with cell and organ transplantation has been limited. (12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23) Xenpozyme is an enzyme replacement therapy that reduces lysosomal sphingomyelin accumulation in patients with ASMD. It is the only disease-specific treatment for the disease currently available. (24)(25)(26)
Natural history of the indicated condition in the untreated population including mortality and morbidity	Almost all patients with ASMD have massive hepatosplenomegaly and an atherogenic lipid profile (cholesterol abnormalities), (5)(11)(27)(28) and most patients have interstitial lung disease with progressive impairment of pulmonary function and hematologic abnormalities including markedly reduced platelet counts from an early age. (29)(30) Other common clinical manifestations include liver dysfunction, and growth delays. (5)(10)(28) Patients with ASMD type A have severe neurologic manifestations. ASMD type A has a rapid and fatal neurodegenerative course and uniformly leads to death by 3 years of age. Patients with ASMD type B often survive into adulthood or can be diagnosed in the adulthood and have multi-systemic manifestations, including significant splenomegaly and hepatomegaly, progressive pulmonary dysfunction, musculoskeletal problems, thrombocytopenia, and dyslipidemia. (5) Greater than 80% of patients with ASMD type B have radiographic evidence of infiltrative lung disease, although some patients may not have overt symptoms. (29)(30) The most common symptoms include dyspnea, shortness of breath and bruising, fatigue, abdominal pain/discomfort, diarrhea, frequent bleedings, pulmonary infections, joint/limb pain, muscle weakness/cramps, as well as numbness and tingling in extremities. The disease interferes with functioning and activities of daily living, often leading to chronic fatigue, limited physical or social activity and difficulties in performing daily activities or work. Patients with ASMD type A/B have the disease manifestations mentioned above for ASMD type B, but also present with progressive neurologic manifestations resulting in a significantly shorter life span than those with ASMD type B. (5) Chronic forms of ASMD have a progressive course. (1) Clinically significant pulmonary, hepatic, bleeding and cardiac complications are common causes of mortality. (31) In patients

Indication	Acid sphingomyelinase deficiency
	with chronic forms of ASMD (type A/B and B), the prognosis is more variable than with ASMD type A. (5) In general, chronic forms of ASMD have a later onset and a variable prognosis; nevertheless pediatric patients with more severe manifestations of chronic ASMD are at particular risk for early mortality. (5) Patients with ASMD type A/B have a chronic, progressive disease that is considerably less severe than ASMD type A, but still carries a worse prognosis than ASMD type B. (32) Some patients with ASMD type B live into their 20s and possibly up to their 70s. A case series of 78 deceased patients with chronic forms of ASMD found a median age at death of 23.5 (range 0.58 to 72) years for ASMD type B and 8.5 (range 2 to 32) years for ASMD type A/B. (27) Many patients die before or in early adulthood, often from pneumonia/respiratory failure or liver failure. Mortality data for chronic forms of ASMD are limited. (1)(10) In an 11-year natural history study, which included patients with ASMD type B and A/B, 8 patients died of causes related to ASMD. Six deaths occurred before age 50 with three occurring before age 20. Individuals with either severe splenomegaly or prior splenectomy were ten times more likely to have died during the follow-up period than those with smaller or intact spleens. A recent German study including 33 chart records of patients with ASMD type B (n = 24) and type A/B (n = 9), with a median (interquartile range [IQR]) age of 8.0 [3.0-20.0] years and 1.0 [1.0-2.0] years, respectively, at diagnosis, reported nine deaths at a median (IQR) age of 17.0 [5.0-25.0] years, with 66.7% of overall patients deceased at less than 18 years of age. The median (IQR) age at death for patients with ASMD type B (n = 4) and type A/B (n = 5) was 31.0 [11.0-55.0] and 9.0 [4.0-18.0] years, respectively. The commonly reported manifestations were related to spleen (100.0%), liver (93.9%), and respiratory (77.4%) abnormalities. (33) A recent United States (US) study (N = 110) included 69 patients with ASMD type B, nine with type A/B, and 32 with ASMD “non-type A” (ASMD subtype was unknown, but patients were confirmed as not having ASMD type A). Most patients were male with a median age at diagnosis of 3.8 years. Thirty-eight patients died during the study observation period, at a median age of 6.8 years. The median (95% confidence interval) survival age from birth was 21.3 (10.2; 60.4) years. (34)
Important co-morbidities	Other than the genetic background, no other specificity or risk factor related to the target population has been identified. Therefore, it may be expected that any co-morbidities that are not related to the disease itself in the treated population, and not impacted by the disease itself, may be broadly similar to those in the general population. However, given the severity and variability of the disease spectrum, and the rarity of the disease itself, it is challenging to postulate or to establish whether or not a given comorbidity should be considered as independent from such a spectrum (ie, not influenced by ASMD disease itself). For example, antidepressant use has been reported in several patients with ASMD type B disease, but such data are limited due to the rarity of the disease; (35) hence it is challenging to establish whether or not ASMD patients have a higher risk of depression and to quantify such a risk.

a This document uses “chronic forms of ASMD” to refer to a combined category of patients with chronic visceral and chronic neurovisceral disease.

ASM: Acid Sphingomyelinase; ASMD: Acid Sphingomyelinase Deficiency; DNA: Deoxyribonucleic Acid; IQR: Interquartile Range; NPD A: Niemann-Pick Disease Type A; NPD B: Niemann-Pick Disease Type B; US: United States.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Preclinical development of olipudase alfa

A comprehensive non-clinical research program was conducted with olipudase alfa in a number of species and at a range of doses and dosing regimens. Animals in all studies were dosed intravenously, either as a bolus injection or infusion, as this is the route of administration used in patients (one exception was a study evaluating the subcutaneous route). These studies demonstrate that olipudase alfa safely and effectively metabolizes SM (36) in a mouse model of ASMD when a dose escalation regimen is used. The acid sphingomyelinase knock-out (ASMKO) mouse is a model of ASMD Type A (37) that lacks ASM activity. Acid sphingomyelinase knock-out mice were used to evaluate the pharmacokinetic (PK), biodistribution (BD), and pharmacodynamic (PD) properties of olipudase alfa following administration of clinically relevant doses. Since the ASMKO mice accumulate SM in target organs such as the liver, spleen and lungs, they can be used to evaluate the PD effects of olipudase alfa administration on SM reduction. These animals show a significant neurological phenotype that resembles neuropathic ASMD but this phenotype was not assessed in the non-clinical studies because olipudase alfa does not cross the blood brain barrier.

Toxicity studies were conducted in BALB/C mice, C57BL/6 mice, cluster of differentiation (CD-1) mice, ASMKO mice, Sprague-Dawley rats, beagle dogs, New Zealand White (NZW) rabbits, and cynomolgus monkeys. Study regimens varied from a single administration, dose escalation, to every other week administration for up to 6 months to support lifetime administration in ASMD patients. In studies conducted in BALB/c mice, C57Bl/6 mice, CD-1 mice, NZW rabbits, Sprague-Dawley rats, beagle dogs, and cynomolgous monkeys, olipudase alfa was well-tolerated.

Doses selected in the pivotal toxicity studies (3 to 30 mg/kg) were based on available data. The high dose was the maximum feasible dose based on olipudase alfa concentrations for the first batches, and for later batches represented a 10-fold dose margin over the high dose to be used clinically. The highest clinical dose was selected as the low dose in the pivotal toxicity studies.

The ASMKO mouse was considered to be the most sensitive toxicological species with acute toxicity findings at doses ≥10 mg/kg following a single dose in this species, whereas no toxicity was observed in all other species evaluated at doses up to 30 mg/kg. The lack of adverse findings at comparable olipudase alfa doses and exposures in the other non-clinical species evaluated suggested that the dose-related toxicity observed in ASMKO mice may be due to the rate and amount of substrate degradation.

Adverse effects, including mortality, were observed in ASMKO mice administered olipudase alfa at doses ≥10 mg/kg. Studies to evaluate these adverse effects were performed in ASMKO and C57BL/6 mice. There was a dose responsive increase in cytokines (interleukin [IL]-6, Granulocyte-Colony Stimulating Factor [G-CSF], IL-1α, IL-1β, and macrophage inflammatory protein [MIP]-1α) following a single administration of olipudase alfa at 3, 10, or 20 mg/kg, with no notable increases in cytokines observed at 0.3 mg/kg in the ASMKO mouse or at a single dose of 20 mg/kg of olipudase alfa in C57BL/6 mice. Concentrations of ceramide, sphingosine, and

sphingosine-1-phosphate (catabolites of the accumulated SM) were increased following high doses of olipudase alfa (≥10 mg/kg) in the ASMKO mouse, similar to that seen for cytokines.

These results suggested that a dose escalation regimen may be necessary to reduce the toxic response at higher olipudase alfa doses.

To test the hypothesis that the rapid accumulation of SM catabolites are responsible for the toxicity observed in the ASMKO mice, and upon request of Health Authorities to explore the mechanism of toxicity, repeat-dose studies were conducted to determine if a more gradual reduction in SM through dose escalation regimens could reduce the toxicity observed with a single high dose of olipudase alfa. When ASMKO mice received 4 intravenous (IV) doses of 3 mg/kg administered every other day, followed by a single IV dose of 20 mg/kg 72 hours later, no mortality was observed and other toxicity findings were reduced in severity. Additionally, increases in cytokine and ceramide concentrations in the serum were reduced with this dose escalation regimen. Results from this study suggested that increased plasma concentrations of both total and C16-ceramide correlated with increased lethality and poor clinical outcome. When olipudase alfa (3 mg/kg) was administered once a week to ASMKO mice in a dose escalation regimen, instead of every other day, prior to a bolus dose of 20 mg/kg, olipudase alfa was also well-tolerated. Furthermore, in a study where ASMKO mice were administered olipudase alfa at 3 mg/kg every other day for 4 doses followed by doses of 3, 10, or 30 mg/kg every other week for 13 weeks (7 total doses), olipudase alfa was well-tolerated with an no-observed-adverse-effect-level (NOAEL) of 30 mg/kg.

One study was performed to evaluate the potential PD drug interaction of two functional inhibitors of acid sphingomyelinase (FIASMAs). Functional inhibitors of ASM are a large group of cationic amphiphilic molecules that may disrupt the interaction of ASM with the lysosomal membrane. (38) Most FIASMAs have been identified by in silico analysis and substantial in vitro or in vivo data is lacking. Two common antidepressant drugs (citalopram and fluoxetine) with variable levels of predicted inhibitory activity against ASM were co-administered with olipudase alfa to evaluate their impact on PD response. Fluoxetine and citalopram were selected because they belong to the same class of drugs, selective serotonin reuptake inhibitors (SSRIs), and demonstrated different levels of inhibitory activity in vitro. Fluoxetine is predicted to be the more potent inhibitor with approximately 13% residual ASM activity remaining in an in vitro inhibitor assay whereas incubation with citalopram resulted in approximately 80% residual ASM activity. (39) The effect of fluoxetine and citalopram on SM reduction following a single administration of 1 mg/kg olipudase alfa was then evaluated in the spleen and liver of ASMKO mice. Fluoxetine did not impact olipudase alfa-mediated SM reduction in the liver and spleen despite previous in vitro data demonstrating robust ASM inhibition. Co-administration of citalopram did not impact olipudase alfa-mediated SM clearance in the liver. However, spleen SM levels were not significantly reduced compared to vehicle controls following co-administration of citalopram and olipudase alfa. These levels were not significantly different from the SM content in spleen from animals administered olipudase alfa alone, suggesting that this result may reflect the variability in PD effect at this dose rather than a true effect of citalopram inhibition. The inhibitor levels were in the lower end of the therapeutic range for both citalopram and fluoxetine, limiting the interpretation of these results. The data from this study suggest that fluoxetine is not a FIASMA in vivo, but a conclusion cannot be made regarding the inhibitory activity of citalopram.

Developmental and reproductive toxicity studies were conducted in CD-1 mice and NZW rabbits at doses up to 30 mg/kg. No olipudase alfa-related adverse effects were observed at the highest dose of olipudase alfa evaluated, 30 mg/kg, in a male and female fertility study in CD-1 mice, in an embryo-foetal toxicity study in NZW rabbits, or in a pre-/postnatal developmental toxicity study in CD-1 mice. An increased incidence of exencephaly was observed when pregnant mice were treated daily with olipudase alfa at exposure levels less than the human exposure at the recommended maintenance therapeutic dose and frequency. This incidence was slightly higher than historical control data. The relevance of this observation for humans is unknown. The daily IV administration of olipudase alfa to pregnant rabbits did not result in foetal malformations or variations at exposures significantly exceeding the human exposure at the recommended maintenance therapeutic dose and frequency. The developmental NOAELs in mice and rabbits are 3 and 30 mg/kg/day.

No juvenile toxicity studies were conducted. Juvenile toxicity studies in non-diseased animals would not provide information that is not already available in the described toxicity program. The ASMKO mouse is the most sensitive species, but unfortunately cannot be used for juvenile toxicity studies due to reproductive and neurological deficiencies in this mouse model. ASMKO mice have decreased litters, decreased numbers of pups, decreased sperm motility and sperm morphology issues, as well as decreased body size and increased cholesterol concentrations. ASMKO mice develop ataxia and neurological deficiencies by 2 to 4 months of age and die between 6 and 8 months of age. As olipudase alfa does not cross the blood-brain barrier, both treated and control groups would show similar background neurobehavioral abnormalities. These abnormalities, combined with resulting lethargy and ultimately death, renders distinguishing the ASMKO phenotype from potential toxicity difficult; neurobehavioral evaluations could not be adequately conducted.

Single dose BD studies were also conducted in CD-1 mice to evaluate the distribution of olipudase alfa to the milk of lactating mice and to the fetus of pregnant mice. Olipudase alfa was not detected in fetuses from pregnant CD-1 mice administered a single dose of 3 mg/kg on E15. However, significant levels of olipudase alfa were measured in the milk of lactating mice 2 days following administration of 3 mg/kg.

The key non-clinical findings are presented in the following table:

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Toxicity studies conducted in ASMKO mice, CD-1 mice, BALB/c mice, C57Bl/6 mice, Sprague-Dawley rats, NZW rabbits, beagle dogs, and cynomolgus monkeys, support the safety of olipudase alfa for clinical administration to ASMD patients at doses up to 3 mg/kg in conjunction with a dose escalation dose regimen. • Adverse effects, including mortality, were observed in ASMKO mice administered olipudase alfa doses ≥10 mg/kg. Studies to evaluate these adverse	**Toxicity** • Toxicity studies conducted in ASMKO mice, CD-1 mice, BALB/c mice, C57Bl/6 mice, Sprague-Dawley rats, NZW rabbits, beagle dogs, and cynomolgus monkeys, support the safety of olipudase alfa for clinical administration to ASMD patients at doses up to 3 mg/kg in conjunction with a dose escalation dose regimen. This dose escalation regimen has been implemented in all clinical studies starting with the Phase 1b trial (multiple ascending dose) and is part of the label.

Key Safety Findings	Relevance to human usage
effects were performed in ASMKO and C57BL/6 mice. Microscopic findings following a single dose included ballooning degeneration (≥1 mg/kg) and inflammatory foci noted in the liver (≥0.1 mg/kg) as well as adrenal gland congestion/hemorrhage (≥1 mg/kg). There was a dose-responsive increase in cytokines (IL6, G-CSF, IL-1α, IL-1β, and MIP-1α) following a single administration of olipudase alfa at 3, 10, or 20 mg/kg, with no notable increases in cytokines observed at 0.3 mg/kg in the ASMKO mouse or at a single dose of 20 mg/kg of olipudase alfa in C57BL/6 mice. Concentrations of ceramide, sphingosine, and sphingosine-1-phosphate (catabolites of the accumulated SM) were increased following high doses of olipudase alfa (≥10 mg/kg) in the ASMKO mouse, similar to that seen for cytokines. However, the toxicity can be ameliorated if a dose escalation dosing regimen is employed. Intravenous olipudase alfa at doses of 3 mg/kg administered to ASMKO mice every other day for four doses followed by doses of 3, 10, or 30 mg/kg every other week for 13 weeks (7 total doses) was well-tolerated. No increases in transaminases or adverse microscopic changes in the liver were observed. • Hypersensitivity reactions to olipudase alfa, a human protein, were sometimes observed, most notably in mice and rats with repeated administrations, which necessitated pre-treatment/post-treatment with Diphenhydramine; intraperitoneal administration.	• Transient elevations in transaminases during dose escalation have been observed in clinical trials, and do not raise a concern; no other findings indicating hepatoxicity were observed. • Infusion associated reactions of systemic hypersensitivity (a majority of which were mild/moderate in intensity) including anaphylactic reactions, antibody mediated hypersensitivity reactions were seen in clinical trials. Immunogenicity is considered as an important identified risk (see [Part II SVII]). • No serious and/or severe acute phase reactions (APRs) have been observed in clinical trials.
• An increased incidence of exencephaly was observed when pregnant mice were treated daily with olipudase alfa intravenously at exposure less than the human exposure at the recommended maintenance therapeutic dose and frequency. This incidence was slightly higher than historical control data. The daily IV administration of olipudase alfa to pregnant rabbits did not result in foetal malformations or variations at exposures significantly exceeding the human exposure at the recommended maintenance therapeutic dose and frequency. • Measurable levels of olipudase alfa were detected in the milk of lactating mice 2 days following administration of 3 mg/kg.	• Studies with olipudase alfa have not been performed in pregnant women. As with any investigational drug product, there may be a risk of congenital anomalies. The relevance of this observation in mice for humans is unknown. Results from animal studies are not always predictive with respect to effects on pregnancy, embryonic/foetal development, parturition, and postnatal development. Therefore, the potential reproductive toxicity and risks for humans are unknown. • As studies in animals have shown reproductive toxicity, "foetal toxicity" is considered an important potential risk in the RMP (see [Part II SVII]). • The use of olipudase alfa in lactating women is considered missing information in the RMP (see [Part II SVII]).
Safety pharmacology • A Good Laboratory Practice (GLP) safety pharmacology study was conducted in cynomolgus monkeys and cardiovascular, respiratory, and CNS evaluations performed as part of the GLP single dose study of olipudase alfa in beagle dogs. Endpoints encompassed the core battery as defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	**Safety pharmacology** • There was one serious adverse event (SAE) of extrasystoles moderate severity, which was considered by the investigator as treatment related, in a patient with a history of cardiomyopathy; The event occurred over 72-hours after infusion and resolved within 90 minutes; the patient completed the study. • There was one SAE of severe angina pectoris, which was considered by the investigator as not related to treatment,

Key Safety Findings	Relevance to human usage
(ICH) S7A and S7B guidelines. The results indicated that there were no test article-related changes in neurobehavioral or electrocardiogram parameters, heart rate, body temperature, activity or respiratory rate following administration at the highest dose of 30 mg/kg IV. • A dose-dependent reduction in heart rate following a single olipudase alfa administration at 3, 10, and 20 mg/kg in ASMKO mice occurred at approximately 60 minutes post-dose, which was accompanied by a decrease in motor activity and followed by a slow decline in blood pressure beginning approximately 130 to 140 minutes post-dose. In addition, cardiac function (hemodynamic response, heart rate, blood pressure, and activity) was measured following two doses of olipudase alfa at 3 and 10 mg/kg and, while a slight decline in heart rate was noted following the second olipudase alfa administration, the heart rate did not drop below 550 beats per minute. These data suggest that a controlled release of SM catabolites following repeated low dose administration of olipudase alfa would not negatively impact cardiac function. • No adverse effects on cardiac function have been observed in ASMKO mice when olipudase alfa was administered via a dose escalation regimen.	in an adult participant with history of hypercholesterolemia. • The potentially adverse effect of olipudase alfa on the cardiac function in humans has been mitigated by the dose escalation regimen.
Other toxicity-related information or data Not applicable	Not applicable

APR: Acute Phase Reaction; ASMD: Acid Sphingomyelinase Deficiency; ASMKO: Acid Sphingomyelinase Knock-Out; CD: Cluster of Differentiation; CNS: Central Nervous System; G-CSF: Granulocyte-Colony Stimulating Factor; GLP: Good Laboratory Practice; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IL: Interleukin; IV: Intravenous; MIP: Macrophage Inflammatory Protein; NZW: New Zealand White; RMP: Risk Management Plan; SAE: Serious Adverse Event; SM: Sphingomyelin.

No additional non-clinical data have been collected on the use of olipudase alfa in any special populations.

Olipudase alfa is an ERT not expected to be genotoxic or carcinogenic, and no studies have been conducted consistent with ICH Guideline S6 (R1) “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals” to examine its genotoxic, mutagenic, or carcinogenic potential.

In conclusion, toxicity studies conducted in ASMKO mice, CD-1 mice, BALB/c mice, C57Bl/6 mice, Sprague-Dawley rats, NZW rabbits, beagle dogs, and cynomolgus monkeys, support the safety of olipudase alfa for clinical administration to ASMD patients at doses up to 3 mg/kg in conjunction with a dose escalation dose regimen.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical development program for olipudase alfa in ASMD includes 5 clinical trials with olipudase alfa treatment (See Table 8).

Table 8 - Acid Sphingomyelinase Deficiency Clinical Trials of Olipudase Alfa Treatment

Protocol Number	Phase	Age Category	Protocol Title	Number of Patients	Treatment	Duration of Treatment	Study Status
SPHINGO-006-05	1a	Adult	A Phase 1, Single-center, Single-dose, Dose Escalation Study of rhASM in Adults with ASMD.	11	Single arm, single dose of olipudase alfa (0.03, 0.1, 0.3, 0.6, 1.0 mg/kg), no dose escalation.	Single dose	Complete
DFI13412 (SPHINGO-008-12)	1b	Adult	An Open-label, Multicenter, Ascending Dose Study of the Tolerability and Safety of rhASM in Patients with ASMD.	5 (4 from SPHINGO-006-05)	Single arm, within patient dose escalation of 0.03 mg/kg (pediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg, IV infusion of rhASM every 2 weeks.	26 weeks	Complete
DFI13803 (ASCEND-Peds)	1/2	Pediatric	A Phase 1/2, Multicenter, Open-Label, Ascending Dose Study to Evaluate the Safety, Tolerability, PKs, PDs and Exploratory Efficacy of Olipudase alfa in Pediatric Patients Aged <18 years with ASMD.	20	Single arm, Within patient dose escalation of 0.03 mg/kg up to 3.0 mg/kg IV infusion of rhASM every 2 weeks.	64 weeks	Complete
LTS13632[a]	2	Pediatric/ Adult	A Long-Term Study to Assess the Ongoing Safety and	25 (5 adult + 20	Single arm, Patients will receive an IV	Up to 9 years or marketing approval	Complete

Protocol Number	Phase	Age Category	Protocol Title	Number of Patients	Treatment	Duration of Treatment	Study Status
			Efficacy of Olipudase alfa in Patients With ASMD.	pediatric patients)	infusion of olipudase alfa every 2 weeks (± 3 days) at the same dose they were receiving at the end of the primary study.		
DFI12712 ASCEND	2/3	Adult	A Phase 2/3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Repeat-Dose Study to Evaluate the Efficacy, Safety, PDs, and PKs of Olipudase Alfa in Patients with ASMD.	36 (1 from SPHINGO-006-05)	1:1 Randomization to placebo or olipudase alfa, blinded, within patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg, IV infusion of rhASM every 2 weeks.	52 weeks PAP and up to 4 years and 3 months extension	PAP Complete ETP Complete

a LTS13632 includes 5 adult patients from DFI13412 (SPHINGO-008-12) and 20 pediatric patients from DFI13803 (ASCEND-Peds)
ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period; IV: Intravenous; PAP: Primary Analysis Period; PD: Pharmacodynamic; PK: Pharmacokinetic; rhASM; Recombinant form of Human Acid Sphingomyelinase.

Overall Clinical trial exposure for the 5 olipudase alfa studies

Eleven patients were treated in the single-dose Phase 1a trial (SPHINGO00605). The phase 1b trial DFI13412 enrolled 5 patients and 1 patient who had not been exposed to olipudase alfa (4 of whom had already participated in the phase 1a trial). Therefore, there were 12 adult patients who were exposed to olipudase alfa in completed trials. All 5 patients who completed DFI13412 were rolled over into the study LTS13632.

Study DFI12712 ASCEND enrolled 36 patients, including one who was previously exposed to olipudase alfa in SPHINGO00605. One patient who had not previously received olipudase alfa was randomized to placebo and discontinued from the study without ever receiving olipudase alfa. Therefore, 34 patients were newly exposed to olipudase alfa in the DFI12712 study.

Overall, 46 adult patients have been exposed to olipudase alfa in these studies.

There were 20 pediatric patients enrolled in the DFI13803 study, 4 adolescents (12 to <18 years of age), 9 children (6 to <12 years of age), and 7 infants/early children (birth to <6 years of age). All patients completed the trial and enrolled in the study LTS13632.

Therefore, a total of 66 patients (46 adult and 20 pediatric) have been exposed to olipudase alfa. Six (6) adults from phase 1a study (single dose study) did not enroll into phase 1b or DFI12712 study. Thus, following tables summarize the exposure for all olipudase alfa exposed patients in multiple dose studies (DFI13412, DFI12712, DFI13803 and LTS13632) including 40 adults (5 from phase 1b and 35 from DFI12721) and 20 pediatric patients.

All studies are now complete.

Table 9 shows duration of exposure. Overall, sixty patients had a median of 4.98 years (range 0.4 to 9.6) of exposure to olipudase alfa. Almost all patients (98.3%) received ≥1 year of olipudase alfa treatment, 96.7% received ≥2 years of treatment and 91.7% received ≥3 years of treatment.

Table 9 - Duration of exposure

Extent of Treatment Exposure	Pediatric (N = 20)	Adult (N = 40)	Overall (N = 60)
Cumulative duration of olipudase alfa exposure (patient-years)	121.04	193.31	314.35
Duration on olipudase alfa (years)			
Number of patients with value	20	40	60
Mean (SD)	6.05 (1.341)	4.83 (2.051)	5.24 (1.922)
Median	6.15	4.95	4.98
Min:Max	4.3:8.2	0.4:9.6	0.4:9.6
Distribution of duration on olipudase alfa, n (%)			
>0 to <1 year	0	1 (2.5%)	1 (1.7%)
≥1 to <2 years	0	1 (2.5%)	1 (1.7%)
≥2 to <3 years	0	3 (7.5%)	3 (5.0%)
≥3 to <4 years	0	14 (35.0%)	14 (23.3%)
≥4 to <5 years	7 (35.0%)	16 (40.0%)	23 (38.3%)
≥5 to <6 years	3 (15.0%)	0	3 (5.0%)
≥6 to <7 years	4 (20.0%)	0	4 (6.7%)
≥7 years	6 (30.0%)	5 (12.5%)	11 (18.3%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)			
>0 year	20 (100.0%) (121.04)	40 (100.0%) (193.31)	60 (100.0%) (314.35)
≥1 year	20 (100.0%) (121.04)	39 (97.5%) (192.92)	59 (98.3%) (313.97)
≥2 years	20 (100.0%) (121.04)	38 (95.0%) (191.27)	58 (96.7%) (312.31)
≥3 years	20 (100.0%) (121.04)	35 (87.5%) (182.41)	55 (91.7%) (303.45)

Extent of Treatment Exposure	Pediatric (N = 20)	Adult (N = 40)	Overall (N = 60)
≥4 years	20 (100.0%) (121.04)	21 (52.5%) (127.48)	41 (68.3%) (248.52)
≥5 years	13 (65.0%) (89.12)	5 (12.5%) (47.78)	18 (30.0%) (136.90)
≥6 years	10 (50.0%) (72.19)	5 (12.5%) (47.78)	15 (25.0%) (119.97)
≥7 years	6 (30.0%) (45.68)	5 (12.5%) (47.78)	11 (18.3%) (93.45)
Duration on olipudase alfa in initial dose escalation period (years)			
Number of patients with value	20	40	60
Mean (SD)	0.38 (0.147)	0.38 (0.484)	0.38 (0.403)
Median	0.34	0.27	0.29
Min:Max	0.3:1.0	0.2:3.2	0.2:3.2

Percentages are based on the number of safety set in each group.
Initial dose escalation period is the first time when patient reached the 3 mg/kg; or if a patient never reached 3 mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_exposure_t.sas OUT=REPORT/OUTPUT/cdc_exposure_t_i.rtf (22FEB2024 - 3:07).
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 10 shows exposure by age group and gender. Overall, sixty patients received 314.35 patient-years of olipudase alfa. The treatment exposure among the 40 adult patients, 193.31 patient-years, was higher than in the 20 pediatric patients, 121.04 patient-years.

Table 10 - Exposure by age group and gender

	Infant/early child (<6 years old)		Child (6 to <12 years old)		Adolescent (12 to <18 years old)		Adult (18 to <65 years old)		Elderly Adult (≥65 years old)	
Extent of Treatment Exposure	Female (N = 4)	Male (N = 3)	Female (N = 5)	Male (N = 4)	Female (N = 1)	Male (N = 3)	Female (N = 23)	Male (N = 16)	Female (N = 1)	Male (N = 0)
Cumulative duration of olipudase alfa exposure (patient-years)	21.28	15.03	30.75	22.74	8.16	23.09	103.48	86.14	3.68	0
Duration on olipudase alfa (years)										
Number of patients with value	4	3	5	4	1	3	23	16	1	0

Extent of Treatment Exposure	Infant/early child (<6 years old)		Child (6 to <12 years old)		Adolescent (12 to <18 years old)		Adult (18 to <65 years old)		Elderly Adult (≥65 years old)	
	Female (N = 4)	Male (N = 3)	Female (N = 5)	Male (N = 4)	Female (N = 1)	Male (N = 3)	Female (N = 23)	Male (N = 16)	Female (N = 1)	Male (N = 0)
Mean (SD)	5.32 (0.889)	5.01 (0.844)	6.15 (1.304)	5.69 (1.209)	8.16 (NC)	7.70 (0.553)	4.50 (1.958)	5.38 (2.174)	3.68 (NC)	0
Median	5.31	4.70	6.77	5.82	8.16	7.98	3.96	4.98	3.68	0
Min:Max	4.3:6.3	4.4:6.0	4.3:7.2	4.4:6.8	8.2:8.2	7.1:8.1	0.4:9.6	2.9:9.6	3.7:3.7	0
Distribution of duration on olipudase alfa, n (%)										
>0 to <1 year	0	0	0	0	0	0	1 (4.3%)	0	0	0
≥1 to <2 years	0	0	0	0	0	0	1 (4.3%)	0	0	0
≥2 to <3 years	0	0	0	0	0	0	1 (4.3%)	2 (12.5%)	0	0
≥3 to <4 years	0	0	0	0	0	0	10 (43.5%)	3 (18.8%)	1 (100.0%)	0
≥4 to <5 years	2 (50.0%)	2 (66.7%)	1 (20.0%)	2 (50.0%)	0	0	8 (34.8%)	8 (50.0%)	0	0
≥5 to <6 years	1 (25.0%)	1 (33.3%)	1 (20.0%)	0	0	0	0	0	0	0
≥6 to <7 years	1 (25.0%)	0	1 (20.0%)	2 (50.0%)	0	0	0	0	0	0
≥7 years	0	0	2 (40.0%)	0	1 (100.0%)	3 (100.0%)	2 (8.7%)	3 (18.8%)	0	0
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)										
>0 year	4 (100.0%) (21.28)	3 (100.0%) (15.03)	5 (100.0%) (30.75)	4 (100.0%) (22.74)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	23 (100.0%) (103.48)	16 (100.0%) (86.14)	1 (100.0%) (3.68)	0 (0)
≥1 year	4 (100.0%) (21.28)	3 (100.0%) (15.03)	5 (100.0%) (30.75)	4 (100.0%) (22.74)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	22 (95.7%) (103.10)	16 (100.0%) (86.14)	1 (100.0%) (3.68)	0 (0)

Extent of Treatment Exposure	Infant/early child (<6 years old)		Child (6 to <12 years old)		Adolescent (12 to <18 years old)		Adult (18 to <65 years old)		Elderly Adult (≥65 years old)	
	Female (N = 4)	Male (N = 3)	Female (N = 5)	Male (N = 4)	Female (N = 1)	Male (N = 3)	Female (N = 23)	Male (N = 16)	Female (N = 1)	Male (N = 0)
≥2 years	4 (100.0%) (21.28)	3 (100.0%) (15.03)	5 (100.0%) (30.75)	4 (100.0%) (22.74)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	21 (91.3%) (101.44)	16 (100.0%) (86.14)	1 (100.0%) (3.68)	0 (0)
≥3 years	4 (100.0%) (21.28)	3 (100.0%) (15.03)	5 (100.0%) (30.75)	4 (100.0%) (22.74)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	20 (87.0%) (98.45)	14 (87.5%) (80.28)	1 (100.0%) (3.68)	0 (0)
≥4 years	4 (100.0%) (21.28)	3 (100.0%) (15.03)	5 (100.0%) (30.75)	4 (100.0%) (22.74)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	10 (43.5%) (59.06)	11 (68.8%) (68.42)	0 (0)	0 (0)
≥5 years	2 (50.0%) (12.07)	1 (33.3%) (5.97)	4 (80.0%) (26.41)	2 (50.0%) (13.42)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	2 (8.7%) (19.21)	3 (18.8%) (28.57)	0 (0)	0 (0)
≥6 years	1 (25.0%) (6.33)	0 (0)	3 (60.0%) (21.19)	2 (50.0%) (13.42)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	2 (8.7%) (19.21)	3 (18.8%) (28.57)	0 (0)	0 (0)
≥7 years	0 (0)	0 (0)	2 (40.0%) (14.43)	0 (0)	1 (100.0%) (8.16)	3 (100.0%) (23.09)	2 (8.7%) (19.21)	3 (18.8%) (28.57)	0 (0)	0 (0)

Duration on olipudase alfa in initial dose escalation period (years)										
Number of patients with value	4	3	5	4	1	3	23	16	1	0
Mean (SD)	0.37 (0.111)	0.55 (0.355)	0.37 (0.032)	0.32 (0.039)	0.31 (NC)	0.32 (0.022)	0.46 (0.631)	0.27 (0.020)	0.27 (NC)	0
Median	0.32	0.38	0.38	0.31	0.31	0.31	0.27	0.27	0.27	0
Min:Max	0.3:0.5	0.3:1.0	0.3:0.4	0.3:0.4	0.3:0.3	0.3:0.3	0.2:3.2	0.2:0.3	0.3:0.3	0

Percentages are based on the number of safety set in each group.
Initial dose escalation period is the first time when patient reached the 3 mg/kg; or if a patient never reached 3 mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
Age is determined based on Day 1 of the first olipudase alfa study that a patient participated.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_expbyss_t.sas OUT=REPORT/OUTPUT/cdc_expbyss_t_age_i.rtf (05MAR2024 - 7:58).
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

For summary of exposure by dose in Table 11, since each study has a dose escalation phase, each patient was summarized into multiple dose groups.

Median duration of exposure to olipudase alfa was low across infusion doses between 0.03 to 2.0 mg/kg (range 0 to 3.1), the doses administered during dose escalation, compared to a median of 4.48 years (range 0.1 to 9.3) for the targeted maintenance dose of 3.0 mg/kg dose.

Table 11 - Exposure by dose

	While at Infusion Dose (mg/kg)						
Extent of Treatment Exposure	**0.03 (N = 20)**	**0.1 (N = 60)**	**0.3 (N = 60)**	**0.6 (N = 60)**	**1 (N = 60)**	**2 (N = 60)**	**3 (N = 60)**
Cumulative duration of olipudase alfa exposure (patient-years)	0.75	2.69	6.49	6.23	6.98	10.61	278.89
Duration on olipudase alfa (years)							
Number of patients with value	20	60	60	60	60	60	60
Mean (SD)	0.04 (0.002)	0.04 (0.033)	0.11 (0.078)	0.10 (0.081)	0.12 (0.403)	0.18 (0.397)	4.65 (1.941)
Median	0.04	0.04	0.08	0.08	0.04	0.04	4.48
Min:Max	0.0:0.0	0.0:0.3	0.1:0.6	0.0:0.6	0.0:3.1	0.0:2.5	0.1:9.3
Distribution of duration on olipudase alfa, n (%)							
>0 to <1 year	20 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)	59 (98.3%)	57 (95.0%)	2 (3.3%)
≥1 to <2 years	0	0	0	0	0	2 (3.3%)	1 (1.7%)
≥2 to <3 years	0	0	0	0	0	1 (1.7%)	5 (8.3%)
≥3 to <4 years	0	0	0	0	1 (1.7%)	0	18 (30.0%)
≥4 to <5 years	0	0	0	0	0	0	18 (30.0%)
≥5 to <6 years	0	0	0	0	0	0	3 (5.0%)
≥6 to <7 years	0	0	0	0	0	0	6 (10.0%)
≥7 years	0	0	0	0	0	0	7 (11.7%)

	While at Infusion Dose (mg/kg)						
Extent of Treatment Exposure	**0.03 (N = 20)**	**0.1 (N = 60)**	**0.3 (N = 60)**	**0.6 (N = 60)**	**1 (N = 60)**	**2 (N = 60)**	**3 (N = 60)**
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)							
>0 year	20 (100.0%) (0.75)	60 (100.0%) (2.69)	60 (100.0%) (6.49)	60 (100.0%) (6.23)	60 (100.0%) (6.98)	60 (100.0%) (10.61)	60 (100.0%) (278.89)
≥1 year	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	3 (5.0%) (5.03)	58 (96.7%) (278.04)
≥2 years	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	1 (1.7%) (2.53)	57 (95.0%) (276.66)
≥3 years	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	0 (0)	52 (86.7%) (263.37)
≥4 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	34 (56.7%) (198.70)
≥5 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (26.7%) (115.41)
≥6 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (21.7%) (99.06)
≥7 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (11.7%) (59.93)

Percentages are based on the number of safety set in each group.
The duration of exposure is the duration while patients are at that dose level.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_expbyss1_t.sas OUT=REPORT/OUTPUT/cdc_expbyss1_t_inf_overall_i.rtf (05MAR2024 - 7:57).
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 12 - Exposure by ethnic origin

Extent of Treatment Exposure	Hispanic (N = 12)	Non-Hispanic (N = 46)
Cumulative duration of olipudase alfa exposure (patient-years)	52.85	247.10
Duration on olipudase alfa (years)		
Number of patients with value	12	46
Mean (SD)	4.40 (0.881)	5.37 (2.014)
Median	3.96	4.99
Min:Max	2.9:6.3	0.4:9.6
Distribution of duration on olipudase alfa, n (%)		
>0 to <1 year	0	1 (2.2%)
≥1 to <2 years	0	1 (2.2%)
≥2 to <3 years	1 (8.3%)	2 (4.3%)
≥3 to <4 years	6 (50.0%)	8 (17.4%)
≥4 to <5 years	4 (33.3%)	18 (39.1%)
≥5 to <6 years	0	3 (6.5%)
≥6 to <7 years	1 (8.3%)	3 (6.5%)
≥7 years	0	10 (21.7%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)		
>0 year	12 (100.0%) (52.85)	46 (100.0%) (247.10)
≥1 year	12 (100.0%) (52.85)	45 (97.8%) (246.71)
≥2 years	12 (100.0%) (52.85)	44 (95.7%) (245.06)
≥3 years	11 (91.7%) (49.94)	42 (91.3%) (239.12)
≥4 years	5 (41.7%) (26.26)	34 (73.9%) (207.86)
≥5 years	1 (8.3%) (6.33)	16 (34.8%) (121.11)
≥6 years	1 (8.3%) (6.33)	13 (28.3%) (104.19)
≥7 years	0 (0)	10 (21.7%) (84.00)
Duration on olipudase alfa in initial dose escalation period (years)		
Number of patients with value	12	46

Extent of Treatment Exposure	Hispanic (N = 12)	Non-Hispanic (N = 46)
Mean (SD)	0.31 (0.091)	0.40 (0.456)
Median	0.27	0.31
Min:Max	0.3:0.5	0.2:3.2

Percentages are based on the number of safety set in each group.
Initial dose escalation period is the first time when patient reached the 3 mg/kg; or if a patient never reached 3 mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
All ethnicity groups considered include Hispanic or Latino (Hispanic), Not Hispanic or Latino (Not Hispanic), Not Reported, and Unknown.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_expbyss_t.sas
OUT=REPORT/OUTPUT/cdc_expbyss_t_ethnicity_i.rtf (05MAR2024 - 7:58)
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 13 shows exposure by race. Overall, most of the patients were white (n = 53, 88.3%).

Table 13 - Exposure by race

Extent of Treatment Exposure	White (N = 53)	Southeast Asian (N = 2)	Northeast Asian (N = 2)	Other (N = 3)
Cumulative duration of olipudase alfa exposure (patient-years)	274.38	15.36	8.94	15.67
Duration on olipudase alfa (years)				
Number of patients with value	53	2	2	3
Mean (SD)	5.18 (1.959)	7.68 (0.670)	4.47 (0.732)	5.22 (1.429)
Median	4.98	7.68	4.47	4.95
Min:Max	0.4:9.6	7.2:8.2	4.0:5.0	4.0:6.8
Distribution of duration on olipudase alfa, n (%)				
>0 to <1 year	1 (1.9%)	0	0	0
≥1 to <2 years	1 (1.9%)	0	0	0
≥2 to <3 years	3 (5.7%)	0	0	0
≥3 to <4 years	12 (22.6%)	0	1 (50.0%)	1 (33.3%)
≥4 to <5 years	21 (39.6%)	0	1 (50.0%)	1 (33.3%)
≥5 to <6 years	3 (5.7%)	0	0	0
≥6 to <7 years	3 (5.7%)	0	0	1 (33.3%)
≥7 years	9 (17.0%)	2 (100.0%)	0	0

Extent of Treatment Exposure	White (N = 53)	Southeast Asian (N = 2)	Northeast Asian (N = 2)	Other (N = 3)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)				
>0 year	53 (100.0%) (274.38)	2 (100.0%) (15.36)	2 (100.0%) (8.94)	3 (100.0%) (15.67)
≥1 year	52 (98.1%) (274.00)	2 (100.0%) (15.36)	2 (100.0%) (8.94)	3 (100.0%) (15.67)
≥2 years	51 (96.2%) (272.34)	2 (100.0%) (15.36)	2 (100.0%) (8.94)	3 (100.0%) (15.67)
≥3 years	48 (90.6%) (263.49)	2 (100.0%) (15.36)	2 (100.0%) (8.94)	3 (100.0%) (15.67)
≥4 years	36 (67.9%) (216.45)	2 (100.0%) (15.36)	1 (50.0%) (4.99)	2 (66.7%) (11.72)
≥5 years	15 (28.3%) (114.76)	2 (100.0%) (15.36)	0 (0)	1 (33.3%) (6.77)
≥6 years	12 (22.6%) (97.84)	2 (100.0%) (15.36)	0 (0)	1 (33.3%) (6.77)
≥7 years	9 (17.0%) (78.09)	2 (100.0%) (15.36)	0 (0)	0 (0)
Duration on olipudase alfa in initial dose escalation period (years)				
Number of patients with value	53	2	2	3
Mean (SD)	0.39 (0.427)	0.33 (0.027)	0.27 (0.002)	0.30 (0.063)
Median	0.30	0.33	0.27	0.27
Min:Max	0.2:3.2	0.3:0.3	0.3:0.3	0.3:0.4

Percentages are based on the number of safety set in each group.
Initial dose escalation period is the first time when patient reached the 3 mg/kg; or if a patient never reached 3 mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
Only race groups with patients are included in the table.
All race groups considered include American Indian or Alaska Native, Black, Native Hawaiian or Other Pacific Islander, White, South East Asian, North East Asian, Not Reported, Unknown and Other.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_expbyss_t.sas
OUT=REPORT/OUTPUT/cdc_expbyss_t_race_i.rtf (05MAR2024 - 7:58)
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 14 shows exposure by baseline cirrhosis. Because of the significant prevalence of cirrhosis in patients with ASMD, patients with baseline cirrhosis were chosen to be an intrinsic factor for analysis. There were 3 of 40 olipudase alfa-treated adult patients who had cirrhosis at baseline.

Table 14 - Exposure by baseline cirrhosis

Extent of Treatment Exposure	Having Baseline Cirrhosis (N = 3)	Not having Baseline Cirrhosis (N = 57)
Cumulative duration of olipudase alfa exposure (patient-years)	9.05	305.30

Extent of Treatment Exposure	Having Baseline Cirrhosis (N = 3)	Not having Baseline Cirrhosis (N = 57)
Duration on olipudase alfa (years)		
Number of patients with value	3	57
Mean (SD)	3.02 (2.371)	5.36 (1.848)
Median	3.68	4.98
Min:Max	0.4:5.0	1.7:9.6
Distribution of duration on olipudase alfa, n (%)		
>0 to <1 year	1 (33.3%)	0
≥1 to <2 years	0	1 (1.8%)
≥2 to <3 years	0	3 (5.3%)
≥3 to <4 years	1 (33.3%)	13 (22.8%)
≥4 to <5 years	1 (33.3%)	22 (38.6%)
≥5 to <6 years	0	3 (5.3%)
≥6 to <7 years	0	4 (7.0%)
≥7 years	0	11 (19.3%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)		
>0 year	3 (100.0%) (9.05)	57 (100.0%) (305.30)
≥1 year	2 (66.7%) (8.67)	57 (100.0%) (305.30)
≥2 years	2 (66.7%) (8.67)	56 (98.2%) (303.64)
≥3 years	2 (66.7%) (8.67)	53 (93.0%) (294.78)
≥4 years	1 (33.3%) (4.99)	40 (70.2%) (243.53)
≥5 years	0 (0)	18 (31.6%) (136.90)
≥6 years	0 (0)	15 (26.3%) (119.97)
≥7 years	0 (0)	11 (19.3%) (93.45)
Duration on olipudase alfa in initial dose escalation period (years)		
Number of patients with value	3	57
Mean (SD)	0.57 (0.531)	0.37 (0.398)
Median	0.27	0.30
Min:Max	0.3:1.2	0.2:3.2

Extent of Treatment Exposure	Having Baseline Cirrhosis (N = 3)	Not having Baseline Cirrhosis (N = 57)

Percentages are based on the number of safety set in each group.
Initial dose escalation period is the first time when patient reached the 3mg/kg; or if a patient never reached 3mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
PGM=PRODOPS/GZ402665/OVERALL/ISS_2023/REPORT/PGM/cdc_expbyss_t.sas
OUT=REPORT/OUTPUT/cdc_expbyss_t_cirr_i.rtf (05MAR2024 - 7:58)
Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 15 - Important exclusion criteria in pivotal studies in the development program

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnant women	To avoid potential harm to an unborn fetus through exposure of drug.	No	In animal studies, reproductive toxicity was observed. "Foetal toxicity" is considered as an important potential risk.
Lactating women	To avoid potential harm to a newborn through exposure of drug from breast milk.	Yes	Not applicable
Patient had major organ transplant (eg, bone marrow or liver)	Patients with organ transplants have maintenance medications and comorbidities that would confound the evaluation of the safety profile of olipudase alfa.	No	Olipudase alfa exposure in patients who have had a major organ transplant does not constitute an additional safety concern.
Patient has a medical condition, including serious inter-current illness, active hepatitis B or C or Human Immunodeficiency Virus infection, international normalized ratio >1.5, platelet count <60.0 x103/µL, significant cardiac disease (eg, pulmonary artery pressure >40 mm Hg, moderate or severe valvular dysfunction, or <40% left ventricular ejection fraction by Echocardiography), or any other extenuating circumstance that may significantly interfere with study compliance including all prescribed evaluations and follow-up activities.	Patients with serious inter-current illnesses were excluded from the study due to the possibility that it may significantly interfere with study compliance including all prescribed evaluations and follow-up activity, and measurement of safety (bleeding) and efficacy endpoints (improved platelet count).	No	Olipudase alfa exposure in patients having these medical conditions does not constitute an additional safety concern.
Clinical presentation or genetic defects in the pediatric population suggestive of ASMD type A disease.	The rapid neurologic progression and early death would confound the evaluation	No	Olipudase alfa will be not indicated in ASMD type A patients.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	of the safety profile of olipudase alfa.		
Patient with a total splenectomy.	Reduction in spleen size was a key efficacy endpoint in previous clinical studies, which could not be evaluated in splenectomized patients.	No	Olipudase alfa exposure in patients who have had a splenectomy does not constitute an additional safety concern.
The patient is scheduled during the study for in-patient hospitalization including elective surgery and excluding the liver biopsies required per protocol (Specific to DFI13803 and DFI12712).	Elective surgeries may interfere with the patient's compliance with study visit schedule.	No	Excluded for study operational and not for safety reasons.
Concomitant ingestion of several classes of medications (eg, fluoxetine, chlorpromazine, tricyclic antidepressants [eg, imipramine, or desipramine], cationic amphiphilic antihistamines [eg, loratadine, desloratadine, astemizole, ebastine and clemastine]).	Based on the available publications of in vitro and in silico data, ASM activity may be decreased in patients due to concomitant ingestion of certain selected cationic amphiphilic drugs (tricyclic antidepressants, SSRIs, and antihistamines). (38) Efficacy assessments could be impaired by these medications.	No	The clinical relevance of this theoretical interaction with FIASMAs is unknown. (Section SVII.1).

ASM: Acid Sphingomyelinase; ASMD: Acid Sphingomyelinase Deficiency; FIASMA: Functional Inhibitors of Acid Sphingomyelinase; SSRI: Selective Serotonin Reuptake Inhibitor.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect rare or very rare adverse reactions due to the small number of patients (n = 66).

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 16 - Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. One female participant in Study DFI12712 ASCEND became pregnant. Urine beta human chorionic gonadotropin (β-HCG) was done once every 4 weeks hence at 5 weeks of pregnancy, the fetus was

Type of special population	Exposure
	exposed to 1-2 infusions. Upon positive pregnancy test the patient withdrew from the olipudase alfa treatment.
Lactating women	Data available from animal studies only.
Patients with relevant comorbidities: • Patients identified with cirrhosis (ie, >stage 3 fibrosis on liver biopsy)	Although initially excluded, DFI12712 ASCEND was amended to allow including patients with cirrhosis. Three patients (5.12%) in adult safety population were cirrhotic at baseline in clinical studies.
• Patients with ASMD type A	Not included in the clinical development program. One patient with ASMD type A, via an emergency Investigational New Drug (IND), outside of the clinical development program, has been treated with olipudase alfa.
Populations with relevant different ethnic origin and different races	Clinical development program not enriched for specific populations.
Patients using the following classes of medications (eg, fluoxetine, chlorpromazine, tricyclic antidepressants [eg, imipramine, or desipramine], cationic amphiphilic antihistamines [eg, loratadine, desloratadine, astemizole, ebastine and clemastine]).	No drug interaction studies have been performed. Patients using these medications were not included in the clinical development program.

ASMD: Acid Sphingomyelinase Deficiency; β-HCG: Beta Human Chorionic Gonadotropin; IND: Investigational New Drug.

Pregnant women

There is limited data from the use of olipudase alfa in one pregnant woman. In study DFI12712, there was one pregnancy in a partner of a patient exposed to olipudase alfa. The partner gave birth to a male child (birthweight 4 kg) at week 38 of gestation by c-section and no congenital anomaly was reported. The child was breastfeeding soon after birth with no neonatal illness, need for resuscitation or corrective or intensive care treatment. Additionally, one female participant in Study DFI12712 ASCEND became pregnant. During the study, urine β-HCG was done once every 4 weeks hence at 5 weeks of pregnancy, the fetus was exposed to 1-2 infusions. Upon positive pregnancy test the patient withdrew from the olipudase alfa treatment. The pregnancy was uneventful, and the participant gave birth to a healthy baby.

Studies in animals have shown reproductive toxicity. An increased incidence of exencephaly was observed in a single species (mice) at exposure less than the human exposure at the recommended maintenance therapeutic dose and frequency; the relevance of this observation for humans is unknown. It is not recommended during pregnancy and in women of child bearing potential (WOCBP) not using effective contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the foetus (see [Module part II SII] Table 7).

Pregnant women are part of the target population. Therefore, “foetal toxicity” is considered as important potential risk (see Section SVII.1.1).

Lactating women

There are no data available concerning the use of olipudase alfa in lactating women.

Lactating women are part of the target population. Therefore, the use of olipudase alfa in lactating women is considered as missing information (see Section SVII.1.1).

Patients with relevant comorbidities

Hepatic cirrhosis is a known complication of ASMD. Cirrhosis was initially an exclusion criterion in DFI1712 ASCEND. The protocol was subsequently amended to allow the inclusion of ASMD patients with cirrhosis. There have been 3 patients with stage 3 cirrhosis enrolled in the clinical development program. Although data are limited, the tolerability of olipudase alfa in patient with cirrhosis is consistent with the entire ASMD adult population.

Populations with relevant different ethnic origin and different race

There is no information to suggest that patients with any specific racial or ethnic origins are differentially affected by olipudase alfa.

Patient with ASMD Type A

Olipudase alfa does not cross the blood brain barrier and is not expected to treat the CNS manifestations of the disease.

Patient taking several classes of medications

Based on the available publications of in vitro and in silico data, ASM activity may be decreased in patients due to concomitant ingestion of certain classes of medications with cationic amphiphilic structures including antihistamines and antidepressants. (38) (39) The clinical relevance of this theoretical interaction is unknown.

Drug-drug interactions (DDI) are routinely monitored as part of routine pharmacovigilance activity. It is not considered relevant for the RMP (see Section SVII.1.1).

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

Olipudase alfa was first approved in Japan on 28 March 2022 and is approved in 51 countries worldwide as of 31 March 2024.

SV.1.1. Method used to calculate exposure

Internal sales data have been used as the source for olipudase alfa exposure data retrieval. Sales figures for cumulative exposure can be retrieved from the period from 01 May 2020 through 31 March 2024 (as per Periodic Benefit Risk Evaluation Report [PBRER] olipudase alfa DLP: 31 March 2024).

The MAH has used the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience to calculate the patient-year exposure to estimate average dosage per patient among those treated with olipudase alfa.

As olipudase alfa exposure depends on a patient's body weight, it is necessary to make assumptions about the distribution of these factors within the patient population to estimate average per patient drug exposure. The MAH has applied the body weight assumptions described in Table 17 to calculate patient exposure.

Methodology:

The patient-year exposure is estimated according to the following calculations:

- Total number of vials of olipudase alfa x mg per vial = Total mg of olipudase alfa
- Total mg of olipudase alfa/Weighted average of mg per patient = Number of patients
- Number of patients/Number of weeks/52 weeks per year = Patient-year exposure

SV.1.2. Exposure

Table 17 - Assumptions applied to calculate the weighted average of mg of administration

Patient subgroup	% of population within age group	Median weight in each age group (kg)	Average dose (mg/kg)	Dose frequency (every x weeks)
Pediatric patients	40%	24.5	3	2.0
Adult patients	60%	63.8	3	2.0

A total of 3514 vials of infusion powder and 48 719 vials of injection powder were sold worldwide during the cumulative period.

Cumulative exposure to olipudase alfa in the postmarketing experience are estimated to be 274 patient-years.

Detailed usage data are not available therefore presentation of patient exposure by age, sex and indication is not possible. The usage data is only presented by country and formulation in the PBRER.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The properties of olipudase alfa do not indicate a potential for misuse for illegal purposes.

A drug abuse liability assessment (DALA) study was not performed with olipudase alfa as the protein has no ability to cross the blood-brain barrier with negligible exposure in the brain, and has shown no propensity for eliciting any neurological effects in toxicology studies.

The company medical query (CMQ) related to drug abuse and associated liabilities was used to identify relevant treatment emergent adverse event (TEAEs). During the double-blind PAP of DFI12712, preferred terms (PT) related to drug abuse and associated liabilities were reported more frequently in the placebo group, compared to the olipudase alfa treatment group and included anxiety (16.7% and 0%, respectively) and dizziness (11.1% and 0%). The PT of feeling abnormal was reported by 1 (5.6%) patient in the olipudase alfa group.

The most frequently observed PTs in the overall population (>20% of patients) were headache, pyrexia, nausea, abdominal pain, diarrhea, vomiting, myalgia, fatigue, dizziness and rhinorrhoea.

The potential for misuse of olipudase alfa for illegal purposes is considered low as this product has not been shown to have known pharmacological addictive effects, such as intentional overdose, abuse, or illegal use.

Routine pharmacovigilance activities thus, are considered sufficient to monitor a potential for misuse for illegal purposes related to olipudase alfa.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics were assessed as either not relevant to olipudase alfa RMP based on the currently available clinical evidence or not benefiting from additional pharmacovigilance or additional risk minimization activities.

The safety topics, evaluated in Section SVII.1.1 as not important for inclusion in the list of safety concerns in the RMP, are the following:

- Lack of efficacy due to neutralizing antidrug antibody (ADA)
- Reduced efficacy of olipudase alfa due to ASM inhibition in context of PD DDI
- Potential harm from overdose
- Potential for transmission of infectious agents
- Potential for off-label use
- Effect on fertility
- Use in pediatric patients

The following safety topics were considered important for inclusion in the list of safety concerns in the initial RMP. They are discussed in Section SVII.1.2:

Important identified risk:

- Immunogenicity:
  - Infusion associated reactions (IARs),
  - Systemic hypersensitivity including anaphylactic reactions,
  - Anti-Drug Antibody (ADA) mediated hypersensitivity reactions,

Important potential risks:

- Medication errors in home infusion setting
- Foetal toxicity

Missing information:

- Use in lactating women
- Long-term safety (beyond 2 years)

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

Risks known to be associated with other therapeutic ERTs, but assessed as not relevant to olipudase alfa and its benefit-risk balance, based on the currently available evidence or which would not benefit from additional risk minimization activities or from further evaluation:

- **Lack of efficacy due to Neutralizing antibodies:**

There has been no evidence throughout the clinical development program for olipudase alfa that detection of in vitro neutralizing antibodies (NAb) is associated with lack of efficacy.

Neutralizing antibodies are a subset of binding ADAs that bind to the drug and inhibit its pharmacological function by preventing target binding and biologic activity of the drug.

Patients were initially screened for development of ADA and confirmed ADA positive samples were further evaluated for the presence of NAb that could inhibit enzymatic activity or uptake into cells. (40) Overall, 9 of 60 patients (15%) developed NAb that inhibited olipudase alfa catalytic activity. Three (3) patients had a persistent response that was intermittent, and 6 patients had a transient response which was NAb-positive at only one timepoint that reverted to NAb-negative. There were no patients who developed NAb that inhibited cellular uptake. Overall, the development of NAb, did not have a meaningful effect on PK, PD (plasma lyso-sphingomyelin), safety and efficacy parameters in these patients including the 3 patients with persistent NAb.

Given the totality of the data, “Lack of efficacy due to NAb” is not considered as an important potential risk in the RMP. Routine pharmacovigilance should suffice to address and monitor potential lack of efficacy.

Other reasons for considering the risks not important for inclusion in the RMP:

- **Lack of efficacy due to acid sphingomyelinase inhibition in context of pharmacodynamic drug-drug interaction**

Based on the available publications of in vitro and in silico data, ASM activity may be decreased in patients due to concomitant use of FIASMAs. Functional inhibitors of acid sphingomyelinase are a large group of cationic amphiphilic molecules that may disrupt ASM interaction with the lysosomal membrane and are found in certain classes of medications, including tricyclic antidepressants and some anti-histamines. The clinical relevance of this theoretical functional inhibition is not known.

A non-clinical PD drug interaction study (Study 19-01094) was conducted in ASMKO mice that suggested that fluoxetine and citalopram may not affect SM clearance following a single administration of 1 mg/kg olipudase alfa. Co-administration of olipudase alfa with fluoxetine (300 µg/day) or citalopram (192 µg/day) had no effect on olipudase alfa-mediated SM reduction in the liver and spleen, but the circulating levels of fluoxetine and citalopram were in

the lower end of the therapeutic window for each drug. The possibility of reduced efficacy of olipudase alfa due to ASM inhibition in the context of PD DDI cannot be excluded.
These concomitant medications were prohibited during the clinical development program.; thus, there are no data to confirm the findings from the study in ASKMO mice, nor have any DDIs been reported. The clinical relevance of this DDI risk with FIASMAs remains unclear but is likely low. Therefore, if patients need to use these concomitant medications, the benefit-risk profile would remain favorable considering the severity of the disease and the limited treatments available.

The risk is not considered as an important risk for the RMP.

- **Potential harm from overdose:**

No instance of asymptomatic or symptomatic overdose has been observed in clinical studies during the dose escalation or the maintenance periods. Highest dose tested in preclinical studies was a NOAEL. Dose escalation regimen are described in the summary of product characteristics (SmPC) for adult and pediatric patients.

- **Potential for transmission of infectious agents:**

The potential for transmission of an infectious agent by olipudase alfa is considered very low based upon the following:

- No human-derived material is used during the manufacturing process;
- Animal derived material used during the manufacturing process complies with the current Committee for Human Medicinal Products, Note for Guidance, entitled "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathic Agents via Human and Veterinary Medicinal Products";
- Animal serum used during the manufacturing process is irradiated to mitigate the risk of adventitious virus contamination;
- There is robust virus reducing capacity during the product purification process; total reduction factors vary from ≥5.7 log to ≥15.9 log for the four-model virus tested. The process includes a 20 nm filter which is robust and completely removed all model viruses tested, including demonstrated clearance of ≥5.8 log of mouse minute virus (the smaller virus tested);
- Characterization testing has confirmed the absence of infectious adventitious and endogenous agents in the Master Cell Bank, Working Cell Bank, and End of Production cells;
- In the event of suspected or confirmed transmission of infectious agents or other contamination, pharmacovigilance will perform an assessment of the risk to patient safety.

Other concerns not considered important for inclusion in the RMP:

- **Effect on fertility:**

Administration of olipudase alfa had no effects on mating and fertility of the male or female mice or litter parameters of female mice and rabbits evaluated at mid-gestation (NOAELs were 30 mg/kg, highest dose evaluated).

- **Potential for off-label use:**

According to current knowledge, it is unlikely that this drug will be prescribed for any other indication than ASMD.

- **Use in pediatric patients:**

The safety and efficacy of olipudase alfa was studied in pediatric population (patients were eligible from birth to <18 years) as part of the target population. With the exception of the higher frequency of treatment emergent infusion associated reactions in pediatric patients, which were manageable and did not preclude continuation of treatment, the safety and efficacy profile of treatment with olipudase alfa in pediatric patients was found to be consistent with that seen in adults.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 18 - Important identified risk considered for inclusion in the list of safety concerns: Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions

Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions	
Scientific evidence that has led to the inclusion	Clinical trial experience: • Infusion associated reactions have been observed in all studies in the olipudase alfa clinical development program; 58.3% of patients in the overall safety population had at least one protocol defined infusion associated reaction. • Systemic hypersensitivity including anaphylactic reactions; antibody-mediated hypersensitivity reactions with positive immunoglobulin G (IgG) and/or immunoglobulin E (IgE) ADA have been observed in the clinical program. (phase 1/2 trial DFI13803 in pediatric patients, repeat-dose 1b trial DFI13412 in adult patients). • One pediatric patient had one event of anaphylaxis, and another pediatric patient had three events of hypersensitivity. Both pediatric patients were ADA positive, however, patients recovered and continued in the study including the long-term extension. • The clinical findings support that olipudase alfa has a low immunogenicity risk relative to ADA impact on clinical outcomes. A higher incidence of treatment emergent IARs and hypersensitivity was seen in patients who developed treatment emergent ADA versus those who did not; however, the IARs were manageable and did not preclude continuation of treatment. Other: One pediatric patient, age 16 months with ASMD type A, was treated under an emergency IND, extrinsic to the clinical development program. This patient experienced two anaphylactic reactions (see 5.3.5.4 Investigator initiated emergency IND report). Class effects: The potential of developing an IAR is reported in the product information of some marketed ERTs, including Fabrazyme®, Myozyme®, Cerezyme®, Naglazyme®. Scientific literature: Olipudase alfa contains trace amounts of polysorbate 80 (<0.02% by weight). Hypersensitivity reactions (generalized pruritus, erythema, and orofacial angioedema) to polysorbate have been reported rarely in the literature with polysorbate 80 concentrations as low as 0.0015%. (41)

Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions	
Risk-benefit impact	Although IARs, severe hypersensitivity reactions and ADA mediated hypersensitivity reactions may occur with olipudase alfa, the benefit-risk profile of olipudase alfa remains favorable. The clinical findings support that olipudase alfa has a low immunogenicity risk relative to ADA impact on clinical outcomes.

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; ERT: Enzyme Replacement Therapy; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IND: Investigational New Drug.

Table 19 - Important potential risk considered for inclusion in the list of safety concerns: Medication errors in home infusion setting

Medication errors in home infusion setting	
Scientific evidence that has led to the inclusion	There is potential for human error with respect to administration of the product (eg, dose calculation, reconstitution, underdose/overdose, etc.) in the home infusion setting. Potential medication error is listed as an important potential risk in the RMP of other marketed ERTs for which home infusion setting is possible. Clinical trial experience: No medication errors have been identified in home infusion setting.
Risk-benefit impact	Although the possibility of medication errors cannot be excluded, home infusion is considered safe and feasible for patients once selected by the prescribing/treating physician and the benefit-risk profile of olipudase alfa is expected to remain favorable in this setting.

ERT: Enzyme Replacement Therapy; RMP: Risk Management Plan.

Table 20 - Important potential risk considered for inclusion in the list of safety concerns: Foetal toxicity

Foetal toxicity	
Scientific evidence that has led to the inclusion	Preclinical data: In studies in animals, reproductive toxicity was observed. An increased incidence of exencephaly was observed when pregnant mice were treated daily with olipudase alfa intravenously at exposures levels comparable to the human exposure at the recommended maintenance therapeutic dose and frequency. This incidence was slightly higher than historical control data. The relevance of this observation for humans is unknown. The daily IV administration of olipudase alfa to pregnant rabbits did not result in foetal malformations or variations at exposures significantly exceeding the human exposure at the recommended maintenance therapeutic dose and frequency.
Risk-benefit impact	Patients with ASMD are treated throughout their lifespan and, therefore, may include WOCBP. Additional data are needed to characterize the safety profile in this population.

ASMD: Acid Sphingomyelinase Deficiency; IV: Intravenous; WOCBP: Women of Childbearing Potential.

Table 21 - Missing information considered for inclusion in the list of safety concerns: Use in lactating women

Use in lactating women	
Scientific rationale for anticipating a different safety profile in the particular subpopulation	Acid sphingomyelinase deficiency patients are treated throughout their lifespan and, therefore, may include lactating women. Non-clinical data do not suggest adverse effects on growth and development of nursing pups.
Risk-benefit impact	Olipudase alfa should be used during lactation only if the potential benefits to the mother outweigh the potential risks for the newborn. The benefit-risk profile of olipudase alfa is expected to remain favorable in this population.

Table 22 - Missing information considered for inclusion in the list of safety concerns: Long-term safety (beyond 2 years)

Long-term safety (beyond 2 years)	
Scientific rationale for anticipating a different safety profile in the particular subpopulation	Acid sphingomyelinase deficiency patients are treated throughout their lifespan.
Risk-benefit impact	The benefit-risk profile of olipudase alfa is expected to remain favorable in ASMD patients exposed to olipudase alfa for more than 2 years. Long-term use safety data beyond 2 years in ASMD patients have been collected through the studies LTS13632 in adults and pediatric patients and DFI12712 ASCEND ETP in adult patients. Patients enrolled in the clinical studies are expected to continue treatment with commercial product and will be monitored through routine pharmacovigilance.

ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

"Long-term safety (beyond 2 years)" in ASMD patients has been collected through the completed studies LTS13632 (in adults and pediatric patients) and DFI12712 ASCEND ETP (in adult patients). Patients enrolled in the clinical studies are expected to continue treatment with commercial product and will be monitored through routine pharmacovigilance as well as new prescribed patients never enrolled before in clinical trials.

Long-term safety data (for a maximum observation period of 5 years in DFI12712; >9 years for adult and >7 years for the pediatric population in LTS13632) demonstrated that treatment with olipudase alfa was well-tolerated. No new safety concerns emerged. Therefore, the missing information "Long-term safety (beyond 2 years)" is proposed to be removed from the RMP list of safety concerns.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified as relevant for inclusion in olipudase alfa RMP:

- Important identified risk:
  - Immunogenicity:
    - Infusion associated reactions (IARs),
    - Systemic hypersensitivity including anaphylactic reactions,
    - Anti-Drug Antibody (ADA) mediated hypersensitivity reactions,
- Important potential risks:
  - Medication errors in home infusion setting
  - Foetal toxicity
- Missing Information:
  - Use in lactating women

SVII.3.1. Presentation of important identified risks and important potential risks

Table 23 - Important identified risk: Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions

Important identified risk	**Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions**
Potential mechanism	• As with other ERTs, IARs are expected. • Hypersensitivity reactions are possible and expected with most subcutaneous or IV administered protein products. • Immunoglobulin G and/or IgE ADA mediated immune response is possible.
Evidence source(s) and strength of evidence	Clinical trial experience, class effects, scientific literature, other (emergency IND), postmarketing experience.
Characterization of the risk	Details of the events related to the sub-types and their impact on patient's treatment and outcome are presented below: **Clinical trial experience** **Frequency:** • Infusion associated reactions have been observed in all studies in the olipudase alfa clinical development program; 60% of patients in the overall (adults and pediatrics) safety population had at least one protocol defined IAR. • One pediatric patient (5.0%, 1/20 patients) experienced a serious anaphylactic reaction in the clinical trial program and was determined to have IgG and IgE anti-olipudase alfa antibodies. Two additional pediatric patients (10.0%, 2/20 patients) had 4 serious hypersensitivity related IARs: one patient experienced urticaria (1 event) and rash (1 event) on separate occasions; one patient experienced hypersensitivity on 2 occasions. Both patients were positive for IgG anti-olipudase alfa antibodies. All three patients' events occurred within 72 hours of infusion. • There were no anaphylactic reactions reported in adult patients.

Important identified risk	Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions
	Severity and nature of risk: Infusion associated reactions: • Overall, 31 (51.7%) patients experienced a total of 346 mild events, 18 (30%) patients experienced a moderate event and 1 (1.7%) patient experienced a severe event of IAR. • Similar percentages of pediatric patients and adult patients had IARs (65.0% and 57.5%, respectively). Among the most frequently reported IARs, the exposure adjusted incident rate (EAIR) was higher in pediatric than adult patients for: urticaria (9.22 versus 4.15 patients per 100 patient-years); pyrexia (10.21 versus 2.35); and vomiting (6.94 versus 1.66). The EAIR was higher in adult patients than pediatric patients for headache (7.35 versus 4.08 patients per 100 patient-years) and was similar in adult and pediatric patients for nausea (4.60 and 4.08, respectively). Systemic hypersensitivity: • In one patient of the 3 pediatric patients who experienced systemic hypersensitivity, the events were severe ie, anaphylactic reaction (1 patient 1 event). Specifically, in study DFI13803, one serious case of anaphylactic reaction in a 1 year-old boy occurred at week 12 (16-Jul-2019) during infusion (scheduled dose 0.6 mg/kg). This patient was successfully desensitized using a tailored regimen. All three pediatric patients continued treatment, enrolled and completed LTS13632. Anti-drug antibody mediated hypersensitivity reactions: • Overall, 34 of 60 (56.7%) patients in the clinical studies developed treatment emergent ADA; however, the ADA titers were predominantly $\leq$400 (median ADA titer was 200), which are considered as low response. Only 7 patients, 4 pediatric and 3 adults, developed intermediate titers that ranged from 800 to 6400. Some of the TEAEs associated with ADA also resemble IARs and were generally mild-to-moderate and clinically manageable. One pediatric patient, who experienced anaphylactic reaction (described above), developed IgE ADA and had a peak IgG ADA titer of 1600, the highest titer in the pediatric olipudase alfa safety set. • Overall, there was a higher percentage of patients with treatment emergent IARs in patients who developed treatment emergent ADA versus those who did not (70.6% versus 46.2%). **Seriousness and outcome:** • Three pediatric patients (2 in Study DFI13803 Peds and 1 in Study LTS13632) experienced protocol-defined IARs/systemic hypersensitivity that were SAEs. No event resulted in permanent treatment discontinuation. No serious IARs were reported in study DFI12712. • All patients were found to be positive for IgG ADA, all 3 of the patients having peak ADA titers in the intermediate range (800-1600), which modestly generally decreased over time. In addition, 1 of the 3 patients was positive for IgE ADA. • All three patients experiencing a serious IAR/systemic hypersensitivity event recovered; resumed olipudase alfa treatment; enrolled in and completed LTS13632. **Other:** Outside of the olipudase alfa clinical development program, one patient with type A ASMD experienced two severe allergic/anaphylactic like reactions during infusion that responded well to therapy (emergency IND). **Postmarketing experience including Managed Access Program and post-trial access:** Four cases of overdose with associated clinical events have been reported in pediatric patients during dose escalation from study HUM01 ICAP (an individual patient use study

Important identified risk	Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions
	from a Sanofi sponsored humanitarian program with olipudase alfa). All the 4 patients experienced serious adverse reactions within 24 hours of treatment initiation, including death. The main clinical findings included respiratory failure, hypotension, marked elevations in liver function tests, and gastrointestinal bleeding. **Background incidence/prevalence:** Immunogenicity is specific to the biologic product and does not occur in untreated patients with ASMD.
Risk factors and risk groups	Systemic hypersensitivity and IARs: • Patients with previous hypersensitivity/allergy to olipudase alfa and its excipients. • Available clinical data suggest children may have greater predisposition, compared to adults. Additional risk characterization has not been fully established. Anti-drug antibody mediated hypersensitivity reactions: The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. Adults had a median ADA peak titer of 200 (range 50-6400) compared to pediatric patients with a median ADA peak titer of 200 (range 50-1600).
Preventability	Labelling statements (See Section V.1) and educational materials (see Section V.2) • To remind the prescribing/treating physician with appropriate patient selection for home infusion, the healthcare professionals (HCPs) with monitoring of IARs and hypersensitivity/anaphylaxis during and post infusion, importance of dose escalation, management of IARs and hypersensitivity/anaphylaxis and missed doses. • To remind patients/caregivers with signs and symptoms of IARs and hypersensitivity/anaphylaxis, and to report missed dose to the prescribing/treating physician.
Impact on the benefit-risk balance of the product	Although systemic hypersensitivity reactions including anaphylaxis; ADA mediated hypersensitivity reactions; and IARs have been seen in the clinical program and the postmarketing setting, the overall benefit-risk profile remains favorable. The clinical findings support that olipudase alfa has a low immunogenicity risk relative to ADA impact on clinical outcomes.
Public health impact	The public health impact has not been evaluated. The intended indication is a very rare disease. The public health impact of this risk is expected to be low.

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; EAIR: Exposure Adjusted Incident Rate; ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IND: Investigational New Drug; IV: Intravenous; SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event.

Table 24 - Important potential risk: Medication errors in home infusion setting

Important potential risk	Medication errors in home infusion setting
Potential mechanism	There is a potential for human error with respect to preparation and administration of the product (eg, dose calculation, reconstitution, etc.) in a home infusion setting.
Evidence source(s) and strength of evidence	Potential medication error is listed as an important potential risk in the RMP of other marketed ERTs for which home infusion setting is possible.
Characterization of the risk	The risk associated with administration of the product may result in lack of treatment efficacy or overdose.

Important potential risk	Medication errors in home infusion setting
	Clinical trial experience: No medication errors have been identified in home infusion setting by the time of the RMP DLP (12-Jan-2024). **Postmarketing experience including Managed Access Program, and post-trial access:** No pattern of medication errors or safety concerns have been identified in home infusion setting as of the RMP DLP (12-Jan-2024). However, in postmarketing reports, information on the infusion setting is sparse.
Risk factors and risk groups	Patients receiving medication in home infusion setting.
Preventability	Home infusion supervised by HCPs only (see Section V.1). Educational materials for HCPs in home setting including a detailed preparation/infusion description (see Section V.2).
Impact on the benefit-risk balance of the product	The safety profile in patients receiving home infusion is acceptable, with appropriate education of HCPs administering olipudase alfa in the home setting and for selected patients. The product is expected to be safely administered at home like other similar ERTs. The benefit-risk profile of olipudase alfa is expected to be favorable in home infusion setting.
Public health impact	Public health impact has not been evaluated. The benefit of home infusions on public health (reducing hospital burden) is expected to outweigh the risks in the treatment of this rare disease population requiring chronic and frequent ERT.

DLP: Data Lock Point; ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; RMP: Risk Management Plan.

Table 25 - Important potential risk: Foetal toxicity

Important potential risk	Foetal toxicity
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Non-clinical data.
Characterization of the risk	Potential embryo-foetal toxicity **Based on final clinical data:** There was 1 case of pregnancy and 1 case of pregnancy of partner (study DFI12712). For the 1 case of pregnancy, urine β-HCG was done once every 4 weeks hence at 5 weeks of pregnancy, the fetus was exposed to 1-2 infusions. Upon positive pregnancy test the patient withdrew from the olipudase alfa treatment. Both the pregnancies were uneventful, and babies were healthy. **Postmarketing experience:** There was no pregnancy reported in the postmarketing setting.
Risk factors and risk groups	Pregnant women and WOCBP.
Preventability	Pregnant women and WOCBP not using effective contraception should be cautioned. Advise to use effective contraception during treatment and for 14 days after the last dose, if olipudase alfa is discontinued as defined in the labeling section 4.6 of the SmPC. (see Section V.1).

Important potential risk	Foetal toxicity
	Educational materials for patients (see Section V.2).
Impact on the benefit-risk balance of the product	Patients with ASMD are treated throughout their lifespan and therefore may include women of childbearing potential. Additional data are needed to characterize the safety profile in this population.
Public health impact	Public health impact has not been evaluated.

ASMD: Acid Sphingomyelinase Deficiency; β-HCG: Beta Human Chorionic Gonadotropin; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

SVII.3.2. Presentation of the missing information

Table 26 - Missing information: Use in lactating women

Missing Information	Use in lactating women
Evidence source(s) and strength of evidence	Patients with ASMD are treated throughout their lifespan and therefore may include lactating women. Olipudase alfa has been detected in the milk of lactating mice. Non-clinical data do not suggest adverse effects on growth and development of nursing pups.
Anticipated risk/consequence of the missing information	Potential adverse effects in breastfed babies. Caution in exposing this population as defined in the labeling section 4.6 of the SmPC. Educational materials for patients (see Section V.2).

ASMD: Acid Sphingomyelinase Deficiency; SmPC: Summary of Product Characteristics.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 27 - Summary of the safety concerns

Important identified risk	Immunogenicity: • Infusion associated reactions (IARs), • Systemic hypersensitivity including anaphylactic reactions, • Anti-Drug Antibody (ADA) mediated hypersensitivity reactions.
Important potential risks	Medication errors in home infusion setting Foetal toxicity
Missing information	Use in lactating women

ADA: Anti-Drug Antibody; IAR: Infusion Associated Reaction.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of olipudase alfa will be continuously monitored from product launch, using following routine pharmacovigilance activities:

- Routine pharmacovigilance practices allowing a comprehensive, continuous and global overview of postmarketing safety profile of olipudase alfa and signal detection.
- Periodic assessment in periodic safety update reports (PSURs)/PBRER for spontaneous reports related to identified and potential risks.
- Continued safety monitoring of on-going studies with olipudase alfa.

In addition, the following routine pharmacovigilance activity beyond adverse reactions reporting and signal detection is in place:

- Follow-up Questionnaire for HCPs. (see [Annex 4]).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Following the completion of LTS13632 and DFI12712 ASCEND studies, the ongoing post-authorization studies have been included as additional pharmacovigilance activities to further characterize the RMP safety concerns - see Table 28.

Table 28 - Additional pharmacovigilance activities (category 1 to 3) summary

OBS17376 - post-marketing safety surveillance study in Japan to collect safety data in patients receiving olipudase alfa - (Cat. 3)
Study short name and title This is the observational prospective cohort surveillance need to be conducted at postmarketing during the re-examination period. This surveillance is required by local health authority, PMDA (Pharmaceuticals and Medical Devices Agency).
Rationale and study objectives Primary Objectives: To collect the safety information of olipudase alfa for ASMD in actual medical practice, especially, incidence of IAR, Transient transaminase elevation and other AEs. Secondary Objectives: To collect the effectiveness of olipudase alfa in actual medical practice.
Study design This is an active surveillance program where all patients receiving Xenpozyme will be surveyed according to the central registry. This survey collects information using paper consent report form (CRF). The physician-in-charge fills out the CRF appropriately. Study duration and follow up: From the launch to one year after the last case registration.

The duration per patient is 5 years at the maximum and is 1 year at the minimum.

Registration period: 4 years.

Study populations

All patients (in Japan only) treated with olipudase alfa for ASMD.

Milestones

First Patient In (FPI): 10-Nov-2022

Last Patient Last Visit (LPLV): expected Jun-2028

Final study report submission date: expected End 2028 to Japan's Pharmaceuticals and Medical Devices Agency (JPMDA)

OBS18020 - observational study in US to assess the Long term Safety and immunogenicity of olipudase alfa therapy during routine clinical care in pediatric patients less than two years of age with ASMD and in patients with ASMD type A (without age restriction), in real-world clinical practice - (Cat. 3)

Study short name and title

A prospective observational study to assess the long-term safety and immunogenicity of olipudase alfa therapy during routine clinical care in pediatric patients less than 2 years of age with acid sphingomyelinase deficiency.

Rationale and study objectives

To collect data to characterize the long-term safety and immunogenicity of olipudase alfa rpcp (Xenpozyme) (referred to as olipudase alfa in this document) in pediatric patients with ASMD <2 years of age at time of treatment initiation, and in patients with ASMD type A (without age restriction), in real-world clinical practice**.**

To evaluate the relationship of anti-olipudase alfa antibodies and safety.

Study design

US, multicenter, cohort, open label observational study with primary data collection. Ancillary protocol-specified procedures to address the study objectives (eg, assessment of ADA) may be considered outside the standard.
The total overall study duration will be 5 years.
The follow-up period will be a minimum of 1 year to a maximum of 3 years.
The enrollment period will be up to 4 years, to allow a minimum of 1 year of follow-up for the last participant enrolled.

Study populations

The US participant must have ASMD type A/B or B and must be <2 years of age at the time of treatment initiation, OR ASMD type A (without age restriction). of care for ASMD, but the study methodology remains non-interventional, as the additional collection of data from participants will not dictate treatment.

Milestones

FPI: 16-Apr-2024

LPLV: 15-Jan-2029

Final study report submission date: expected Apr-2030 to US Food and Drug Administration (FDA)

OBS17422 (OPERA) - ASMD Type B and A/B: French data analysis in early access of patients treated with olipudase alfa - (Cat 3)

Study short name and title

Acid Sphingomyelinase Deficiency (ASMD): Data Analysis of adult and pediatric patients on Early Access to olipudase alpha in France.

Rationale and study objectives

Primary objective: to describe the lung, spleen and liver outcomes of olipudase alfa (effectiveness outcomes).

Secondary: to describe patients's characteristic, use of olipudase alfa, safety data related to the use of olipudase alfa and complementary effectiveness outcomes parameters.

Study design This is a national, multicenter observational retrospective and prospective cohort data collection study. Retrospective is defined as collection of data from all patients, including deceased patients, who were already on early access olipudase alfa in France before the start of this study.
Study populations Male and female patients of all ages (in France only).
Milestones FPI: 10-Jun-2022 LPLV: expected Quarter (Q)1-2025 Final study report submission date: expected Q3-2025 to National Security Agency of Medicines and Health Products (ANSM)

ADA: Anti-Drug Antibody; AE: Adverse Event; ANSM: National Security Agency of Medicines and Health Products; ASMD: Acid Sphingomyelinase Deficiency; CRF: Consent Report Form; FDA: Food and Drug Administration; FPI: First Patient In; IAR: Infusion Associated Reaction; JPMDA: Japan's Pharmaceuticals and Medical Devices Agency; LPLV: Last Patient Last Visit; PMDA: Pharmaceuticals and Medical Devices Agency; Q: Quarter US: United States.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 29 - Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
OBS17376 – post-marketing safety surveillance study in Japan to collect safety data in patients receiving olipudase alfa. **Ongoing**	To collect the safety information of olipudase alfa for ASMD in actual medical practice, especially, incidence of IAR, Transient transaminase elevation and other AEs. To collect the effectiveness of olipudase alfa in actual medical practice.	• Immunogenicity – Infusion associated reactions (IARs), – Systemic hypersensitivity including anaphylactic reactions, – Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. • Medication errors in home infusion setting. • Foetal toxicity. • Use in lactating women.	FPI LPLV Final Report	10-Nov-2022 Expected Jun-2028 Expected End-2028

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
OBS18020 - observational study in US to assess the Long Term Safety and immunogenicity of olipudase alfa therapy during routine clinical care in pediatric patients less than two years of age with ASMD and in patients with ASMD type A (without age restriction), in real-world clinical practice. **Ongoing**	To collect data to characterize the long-term safety and immunogenicity of olipudase alfa rpcp (Xenpozyme) (referred to as olipudase alfa in this document) in pediatric patients with ASMD <2 years of age at time of treatment initiation, and in patients with ASMD type A (without age restriction), in real-world clinical practice. To evaluate the relationship of anti-olipudase alfa antibodies and safety.	• Immunogenicity - Infusion associated reactions (IARs), - Systemic hypersensitivity including anaphylactic reactions, - Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. • Medication errors in home infusion setting.	FPI LPLV Final Report	16-Apr-2024 15-Jan-2029 Expected Apr-2030
OBS17422 (OPERA) – ASMD Type B and A/B: French data analysis in early access of patients treated with olipudase alfa. **Ongoing**	To describe the lung, spleen and liver outcomes of olipudase alfa (effectiveness outcomes). To describe patients' characteristic, use of olipudase alfa, safety data related to the use of olipudase alfa and complementary effectiveness outcomes parameters.	• Immunogenicity - Infusion associated reactions (IARs), - Systemic hypersensitivity including anaphylactic reactions, - Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. • Medication errors in home infusion setting. • Foetal toxicity • Use in lactating women	FPI LPLV Final Report	10-Jun-2022 Expected Q1 2025 Expected Q3-2025

ADA: Anti -Drug Antibody; AE: Adverse Event; ASMD: Acid Sphingomyelinase Deficiency; FPI: First Patient In; IAR: Infusion Associated Reaction; LPLV: Last Patient Last Visit; Q: Quarter; US: United States.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for olipudase alfa.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

The risk management strategy for olipudase alfa consists in routine risk minimization measures (such as communication on the risks, specific clinical measures and legal status reported in the product information aimed to patients and HCPs) (see Table 30) and additional risk minimization measures (ie, educational materials) (see Table 31).

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 30 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Immunogenicity: • **Infusion Associated Reactions (IARs),** • **Systemic hypersensitivity including anaphylactic reactions,** • **Anti-Drug Antibody (ADA) mediated hypersensitivity reactions**	**Routine risk communication:** • Labeled in sections 4.4 and 4.8 of the SmPC. • Labeled in section 4 of the Package Leaflet (PL). **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in sections 4.2, 4.3 and 4.4 of the SmPC. • Labeled in sections 2, 3 and 4 of the PL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Medication errors in home infusion setting	**Routine risk communication:** • Labeled in sections 4.2 and 4.9 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in sections 4.2 and 4.9 of the SmPC. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Foetal toxicity	**Routine risk communication:** • Labeled in sections 4.6 and 5.3 of the SmPC. • Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Use in lactating women	**Routine risk communication:** • Labeled in sections 4.6 and 5.3 of the SmPC.

Safety concern	Routine risk minimization activities
	• Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

ADA: Anti-Drug Antibody; IAR: Infusion Associated Reaction; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 31 - Additional risk minimization measures

A HCP guide for HCPs in home infusion setting including nurses	
Objectives	This guide is designed to support home infusion HCPs and nurses in managing the following risks associated with the home use of olipudase alfa: • Immunogenicity: Infusion-associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. • Medication errors in home infusion setting. • This Guide is also aimed to reinforce reporting of ADRs and events of medication errors, pregnancy and breastfeeding.
Rationale for the additional risk minimization activity	The guide is considered necessary and complementary to the product information, to re-inforce the key safety messages/instructions associated with olipudase alfa use. In addition, the guide includes contact information of the prescribing/ treating physician/centre that can be reached at any time, information on signs and symptoms related to IARs, hypersensitivity/anaphylaxis and recommended actions for the management of ADRs when symptoms occur, medical evaluation of the patients prior to administration of the infusion at home, requirements and organization of the home infusion, details and instructions on the preparation, reconstitution, dilution and administration, a calculation template as a basis for recording infusion details in the patient's medical record. This Guide reminds the HCPs involved in patients care to report ADRs and the events of medication errors, pregnancy and breastfeeding.
Target audience and planned distribution path	**Target audiences**: Healthcare professionals and nurses responsible for the preparation and/or administration of olipudase alfa in home setting. **Distribution paths**: To be adapted country by country depending on each local situation and public health system: mail, face to face distribution, electronic (email, web link, Quick Response [QR] Code/Uniform Resource Locator [URL]). **Periodicity of the distribution**: One single distribution at launch, then redistribution (eg, once a year, ad-hoc) can occur according to local regulatory requirements or national health systems.

Plans to evaluate the effectiveness of the interventions and criteria for success	**Plans to evaluate the effectiveness of the interventions:** Distribution Process outcome. Spontaneous reports of IARs, systemic hypersensitivity including anaphylactic reactions, and ADA mediated hypersensitivity reactions in home infusion setting. Spontaneous reports of medication errors. **Criteria for judging success:** Implementation status of the distribution plan, at each participating country level. Routine pharmacovigilance.
A Patient Card for patients/caregivers	
Objectives	This card is aimed to mitigate the risk of IARs of systemic hypersensitivity and their negative clinical consequences and provide instruction to WOCBP including in case of pregnancy and lactation.
Rationale for the additional risk minimization activity	The patient card is considered necessary and complementary to the PL. • To remind through a synthetic tool the signs and symptoms of IARs, so that patients/caregivers can react quickly, allowing early intervention and medical care. • To remind the WOCBP to discuss with the prescribing/treating physician the need for effective contraceptive measures during treatment and for 14 days after the last dose if Xenpozyme is discontinued. • To remind the WOCBP to contact their prescribing/treating physician if they suspect they might be pregnant or plan pregnancy and breastfeeding. • To document the prescribing/treating physician's emergency contact information for easy agreed reference. • To provide patients with electronic access to patient card and PL in countries where applicable. The wallet size format enables the information to be easily available and shown to any HCP easily.
Target audience and planned distribution path	**Target audiences**: Acid Sphingomyelinase Deficiency patients and/or caregivers through the prescribing/treating physicians and/or HCPs administering the treatment. **Distribution paths**: Educational materials for patients will be distributed as hard copies (and in digital format where possible via QR Code/URL) via prescribing/treating physicians or HCPs administering the treatment, depending on the local country options and requirements. **Periodicity of the distribution:** One single distribution at launch, then redistribution (eg, once a year, ad-hoc.) could be envisaged according to local regulatory requirements and national healthcare systems.
Plans to evaluate the effectiveness of the interventions and criteria for success	**Plans to evaluate the effectiveness of the interventions:** Distribution Process outcome. **Criteria for judging success:** Implementation of the distribution plan, within each country. Routine pharmacovigilance.

ADA: Anti-Drug Antibody; ADR: Adverse Drug Reaction; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; PL: Package Leaflet; QR: Quick Response; URL: Uniform Resource Locator; WOCBP: Women of Childbearing Potential.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 32 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immunogenicity: • **Infusion Associated Reactions (IAR),** • **Systemic hypersensitivity including anaphylactic reactions,** • **Anti-Drug Antibody (ADA) mediated hypersensitivity reactions**	**Routine risk minimization measures:** • Sections 4.2, 4.3, 4.4 and 4.8 of the SmPC. • Sections 2, 3 and 4 of the PL. • Legal Status: Restricted medical prescription. **Additional risk minimization measures:** • A HCP Guide for HCPs in home infusion setting including nurses. • A Patient Card for patients/caregivers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up Questionnaire for HCPs. **Additional pharmacovigilance activities:** • OBS17376 – surveillance program in Japan • OBS18020 **-** observational study in US in pediatric patients • OBS17422 – early access program in France
Medication errors in home infusion setting	**Routine risk minimization measures:** • Sections 4.2 and 4.9 of the SmPC. • Legal Status: Restricted medical prescription. **Additional risk minimization measures:** A HCP Guide for HCPs in home infusion setting including nurses.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up Questionnaire for HCPs. **Additional pharmacovigilance activities:** • OBS17376 - surveillance program in Japan • OBS18020 **-** observational study in US in pediatric patients • OBS17422 - early access program in France
Foetal toxicity	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** A Patient Card for patients/caregivers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • OBS17376 - surveillance program in Japan • OBS17422 - early access program in France
Use in lactating women	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • OBS17376 - surveillance program in Japan • OBS17422 – early access program in France

Safety concern	Risk minimization measures	Pharmacovigilance activities

ADA: Anti-Drug Antibody; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Xenpozyme (Olipudase alfa)

This is a summary of the RMP for Xenpozyme. The RMP details important risks of Xenpozyme how these risks can be minimized, and how more information will be obtained about Xenpozyme's risks and uncertainties (missing information).

Xenpozyme's SmPC and its PL give essential information to HCPs and patients on how Xenpozyme should be used.

This summary of the RMP for Xenpozyme should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xenpozyme's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B. It contains olipudase alfa as the active substance, a recombinant human acid sphingomyelinase produced in a CHO cell line by recombinant DNA technology. Xenpozyme is given by IV infusion.

Further information about the evaluation of Xenpozyme's benefits can be found in Xenpozyme's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/xenpozyme

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Xenpozyme, together with measures to minimize such risks and the studies for learning more about Xenpozyme's risks are outlined below

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advise on correct use, in the PL and SmPC addressed to patients and HCPs respectively;
- Important advice on the medicine's packaging;

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Xenpozyme, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Xenpozyme is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Xenpozyme are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xenpozyme. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 33 - List of important risks and missing information

Important identified risk	Immunogenicity: • Infusion associated reactions (IARs), • Systemic hypersensitivity including anaphylactic reactions, • Anti-Drug Antibody (ADA) mediated hypersensitivity reactions
Important potential risks	Medication errors in home infusion setting Foetal toxicity
Missing information	Use in lactating women

ADA: Anti-Drug Antibody; IAR: Infusion Associated Reaction.

II.B Summary of important risks

Table 34 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Immunogenicity: Infusion associated reactions (IAR), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions

Immunogenicity: Infusion associated reactions (IAR), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trial experience, class effects, scientific literature, other (emergency IND), postmarketing experience.
Risk factors and risk groups	Systemic hypersensitivity and IARs: • Patients with previous hypersensitivity/allergy to olipudase alfa and its excipients. • Available clinical data suggest children may have greater predisposition, compared to adults. Additional risk characterization has not been fully established. Anti-drug antibody mediated hypersensitivity reactions: The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. Adults had a median ADA peak titer of 200 (range 50-6400) compared to pediatric patients with a median ADA peak titer of 200 (range 50-1600).
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.2, 4.3, 4.4 and 4.8 of the SmPC. • Sections 2, 3 and 4 of the PL. • Legal Status: Restricted medical prescription. **Additional risk minimization measures:** • A HCP Guide for HCPs in home infusion setting including nurses. • A Patient Card for patients/caregivers.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • OBS17376 – surveillance program in Japan • OBS18020 - observational study in US in pediatric patients • OBS17422 – early access program in France See Section III.2 of this summary for an overview of the post-authorization development plan.

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IND: Investigational New Drug; PL: Package Leaflet; SmPC: Summary of Product Characteristics; US: United States.

Table 35 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Medication errors in home infusion setting

Medication errors in home infusion setting	
Evidence for linking the risk to the medicine	Potential medication error is listed as an important potential risk in the RMP of other marketed ERTs for which home infusion setting is possible.
Risk factors and risk groups	Patients receiving medication in home infusion setting.
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.2 and 4.9 of the SmPC. • Legal Status: Restricted medical prescription.

Medication errors in home infusion setting	
	Additional risk minimization measures: A HCP guide for HCPs in home infusion setting including nurses.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • OBS17376 – surveillance program in Japan • OBS18020 - observational study in US in pediatric patients • OBS17422 – early access program in France See Section III.2 of this summary for an overview of the post-authorization development plan.

ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; US: United States.

Table 36 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Foetal toxicity

Foetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical data.
Risk factors and risk groups	Pregnant women and WOCBP.
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** A Patient Card for patients/caregivers.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • OBS17376 – surveillance program in Japan • OBS17422 – early access program in France See Section III.2 of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

Table 37 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in lactating women

Use in lactating women	
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • OBS17376 – surveillance program in Japan • OBS17422 – early access program in France

Use in lactating women	
	See Section III.2 of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Xenpozyme.

II.C.2 Other studies in post-authorization development plan

Table 38 - Other studies in post-authorization development plan

OBS17376 - post-marketing safety surveillance study in Japan to collect safety data in patients receiving olipudase alfa - (Cat. 3)
Purpose of the study: To collect the safety information of olipudase alfa for ASMD in actual medical practice, especially, incidence of IAR, Transient transaminase elevation and other AEs. To collect the effectiveness of olipudase alfa in actual medical practice.
OBS18020 - observational study in US to assess the Long term Safety and immunogenicity of olipudase alfa therapy during routine clinical care in pediatric patients less than two years of age with ASMD and in patients with ASMD type A (without age restriction), in real-world clinical practice - (**Cat. 3)**
Purpose of the study: To collect data to characterize the long-term safety and immunogenicity of olipudase alfa rpcp (Xenpozyme) (referred to as olipudase alfa in this document) in pediatric patients with ASMD <2 years of age at time of treatment initiation, and in patients with ASMD type A (without age restriction), in real-world clinical practice**.** To evaluate the relationship of anti-olipudase alfa antibodies and safety.
OBS17422 (OPERA) – ASMD Type B and A/B: French data analysis in early access of patients treated with olipudase alfa - (Cat 3)
Purpose of the study: To describe the lung, spleen and liver outcomes of olipudase alfa (effectiveness outcomes). To describe patients's characteristic, use of olipudase alfa, safety data related to the use of olipudase alfa and complementary effectiveness outcomes parameters.

AE: Adverse Event; ASMD: Acid Sphingomyelinase Deficiency; IAR: Infusion Associated Reaction; US: United States.

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PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

sanofi

Olipudase alfa (Xenpozyme®)
Follow-up Questionnaire (FUQ) for Health Care Professionals (HCP)

The goal of this questionnaire is to collect the very essential information on reported event(s) **with olipudase alfa**. For any other additional adverse event(s), please complete the corresponding "other experienced adverse event(s)" section at the end of this form.
By providing this information, you will make a useful contribution to the safety of this product for the benefit of patients.

Sanofi Case ID:	**Program ID:**
Reporter Information *(person who provides the information reported on this form)*: Name or Initials: Qualification: ☐Health Care Professional (HCP) ☐Non-HCP Email address:	Phone Number:
Patient Information: Name or Initials or ID: Date of Birth: Height: _____ ☐ inches ☐ cm	Gender: ☐Male ☐Female ☐Unknown Age or Age Group: Weight: _____ ☐ lbs ☐ kg

SPECIFIC INFORMATION

Please use DD/MM/YYYY for dates.

Sanofi Suspect Product

Infusion setting: ☐ At home ☐ At hospital

If at home:

- Date of first home infusion: _____
- How many home infusions did the patient receive up to the time of adverse event: _____
- Who administered the home infusion associated with this event:
  ☐ Infusion therapist ☐ Nurse ☐ Other: _____
- Was a 0.2-micron in-line filter used for the infusion: ☐ Yes ☐ No
- Did a similar adverse event occur during a hospital-based infusion? ☐ Yes ☐ No

Administration schedule: please provide **date(s) of infusion and dose(s) (mg/kg).** Indicate each individual dose during the dose escalation phase.

☐ Initial dose escalation: _____
☐ Maintenance phase: _____
☐ Re-escalation: _____

Date of last dose prior to this event: _____
Batch Number: _____

Adverse Event Information

Diagnosis: _____
Was the event an Infusion-Associated Reaction (i.e., side effects related to the infusion occurring during or within 24 hours)? ☐ Yes ☐ No

If yes:

- How long after the infusion started did the reaction begin: _____
- Severity: ☐ Mild ☐ Moderate ☐ Severe
- Corrective treatment administered: ☐ Yes (specify): _____ ☐ No

Specify if any **additional actions were taken during the infusion:**

☐ Rate slowed down ☐ Interrupted then eventually restarted ☐ Halted and not restarted

Medication error that may explain the event: ☐ Yes (specify): _____ ☐ No

Laboratory testing ordered: ☐ Yes ☐ No

If yes (specify):

Test	Date	Result	Normal Range

Immunology testing ordered: ☐ Yes ☐ No

If yes (specify):

Test	Date	Result	Normal Range

Event onset date: _____

Seriousness: ☐ Non-Serious ☐ Serious (select at least one criteria below):
☐Death | *Date of Death*: _____ | *Autopsy Performed*: ☐ No ☐ Yes ☐ Unknown
☐Life-threatening ☐Hospitalization or prolongation of hospitalization
☐Persistent or significant disability or incapacity ☐Medically significant (as per HCP)
☐Suspected transmission of infectious agent ☐Congenital anomaly, birth defect

Outcome:
☐ Recovered/Resolved ☐ Recovered/Resolved with Sequelae ☐ Not Recovered/Not Resolved
☐ Recovering/Resolving ☐ Fatal ☐ Unknown
Specify date of resolution, if applicable: _____
If patient recovered with sequelae, describe sequelae: _____

Action taken due to adverse event:
☐ Dose increased ☐ Dose reduced (e.g., patient received less than the target dose at infusion)
☐ Dose not changed (e.g., patient received the complete dose) ☐ Dose withdrawn (only if permanent withdrawal)
☐ Not applicable

Did the patient receive the next Xenpozyme® infusion? ☐ Yes ☐ No

Event Relationship to Sanofi product: ☐Related ☐Not Related ☐Unknown
Specify the reason for considering related/not related: _____

Could the event have been due to: ☐ Worsening of the underlying condition ☐ Decreased drug effect ☐ None

If the event was a medication error (unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient), please provide the following:

- **Type of error:**

☐ Potential (Recognition of circumstances that could lead to a medication error, and may or may not involve a patient)
☐ Intercepted (An error occurred, but was recognized and intercepted before the patient received/used the product)
☐ Actual, specify date of occurrence, date recognized, if error led to AE: _____

- **Stage of the process:**

☐ Prescribing: indicate prescribed dose, dosing rate, frequency: _____
☐ Storage ☐ Dispensing ☐ Preparation for administration ☐ Administration ☐ Medication monitoring

- In what **location** did the error first occur?

☐ Inpatient (hospital, nursing home, care home) ☐ Outpatient (specialist practice, ambulatory)
☐ Pharmacy (e.g., Hospital, Drug store) ☐ Private (e.g., home) ☐ Other, please provide details

- **What contributing factor(s) may have led to the error, if any?** Examples include:

☐ Patient or healthcare staff related factors: behavior (e.g., distraction, fatigue), performance (e.g., breach of standard of care), communication (e.g., illegible handwriting on prescriptions, discharge recordings), misunderstanding, unawareness of posology, method of administration.
☐ Work-related factors: work environment, staffing issues, workload shift work, healthcare policy, transition of patient care
☐ Factors beyond the control of the HCP or patient: medication unavailability, IT software issues
☐ Other, specify: _____

- What **covariates defining the treated population** may have led to the error, if any? Examples include:

☐ Dose adjustment based on age, weight, body mass index
☐ Normal age-related weight increase over time in a growing pediatric patient
☐ Transitions of care such as admission and discharge ☐ Co-morbidities and polypharmacy

- If the same error has occurred **in the past**, specify how often it occurred: _____

Please provide any other relevant additional information **regarding the reported event** (e.g., other suspect product(s), other additional information on reported adverse event, patient's medical history, concomitant medications, etc.):

Medical history, including **previous adverse drug reaction(s)** attributed to this present enzyme replacement therapy:

☐ Yes (specify): _____
☐ No

Other suspect product(s):

☐ Yes (specify): _____
☐ No

Pre-infusion medication(s): ☐ Yes (please complete table below) ☐ No

Product Name	Dose	Start Date	Last Administration Date (or ongoing)

Concomitant medication(s): ☐ Yes (please complete table below) ☐ No

Product Name	Indication	Dose	Start Date	Last Administration Date (or ongoing)

ADDITIONAL INFORMATION

Please provide relevant information regarding **any other experienced adverse event(s)** (e.g., event onset date(s), outcome(s), if it led to hospitalization, relationship(s) with Sanofi product, etc.):

Additional requests for the reporter (if any):

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Key messages of the additional risk minimization measures

Prior to the launch of Xenpozyme in each member state the marketing authorization holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at minimizing specific safety concerns.

The MAH shall ensure that in each Member State where Xenpozyme is marketed, all healthcare professionals (HCP) and patients/caregivers who are expected to prescribe, dispense, use Xenpozyme have access to/are provided with the following educational message to be disseminated through professional bodies:

- HCP educational materials
- Patient/caregiver educational materials

1. HCP educational materials:

1.1 HCP Guide for HCPs in home infusion setting including nurses:

The HCP guide includes the following key elements:

- On the front page, contact information of the prescribing/treating physician/centre that can be reached at any time.
- Reminder to read the summary of product characteristics (SmPC) prior to initiating treatment.
- To ensure awareness about the risk of immunogenicity, its monitoring and management, the guide includes the following:
  - Requirements that the home infusion HCPs/nurses should be trained for emergency measures and should have resuscitative equipment ready prior to initiating care.
  - Information on signs and symptoms of Infusion associated reactions (IARs), severe hypersensitivity or anaphylaxis and recommended actions for the management of adverse drug reactions (ADRs) if they occur.
  - Reminder to apply only maintenance dose (mg/kg) as prescribed by the treating/prescribing physician.
- Instruction to contact the prescribing/treating physician if the patient experienced signs/ symptoms of IARs, hypersensitivity, anaphylaxis or if one or more infusions are missed or delayed.
- Medical evaluation of the patient prior to administration of the infusion at home.
- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.

- Details and instructions on the preparation, reconstitution, dilution and administration of the product to prevent the risk of medication errors. A calculation template to prepare the infusion solution based on prescribed maintenance dose and patient's body weight with instructions to record the calculation and infusion date.
- The calculation template can be used as a basis for recording infusion details in the patient's medical record.
- Reminder to check if additional supplies are required.
- Reminder for reporting ADR and events of medication errors, pregnancy and breastfeeding.

2. Patient educational materials:

2.1 Patient Card for patients/caregivers

The patient card includes the following elements:

- Instruction to the patients/caregivers to seek urgent medical attention if any signs and symptoms of IARs, severe hypersensitivity or anaphylaxis listed in the card appear or worsen during and after infusion and to report the event to the treating/prescribing physician.
- Contact information of the prescribing/treating physician/centre that can be reached at any time.
- Reminder to the women of childbearing potential (WOCBP) to discuss with the prescribing/treating physician the need for effective contraceptive measures during treatment and for 14 days after the last dose if Xenpozyme is discontinued.
- Reminder to the WOCBP to contact their prescribing/treating physician if they suspect they might be pregnant or plan pregnancy and breastfeeding.