



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

Data Lock Point (DLP)	31-OCT-2022
RMP Version number	Version 2.3
Date of final sign-off	06-NOV-2023



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

Rationale for submitting an updated RMP	The RMP has been updated to revise phase 2/3 clinical trial (DFI12712 ASCEND) final study report submission milestone and LTS13632 study milestone.
Summary of significant changes in this RMP	The following modules and annexes have been updated: Cover page, Part I and Part III. Annexes 2 and 8.

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 2.2
Approved with procedure	EMA/H/C/004850/III/0001/G
Date of approval (opinion date)	16-Mar-2023

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

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
AESI:	Adverse Event of Special Interest
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
DALA:	Drug Abuse Liability Assessment
DDD:	Defined Daily Dose
DDI:	Drug-Drug Interaction
DLP:	Data Lock Point
DMC:	Data Monitoring Committee
DNA:	Deoxyribonucleic Acid
DPH:	Diphenhydramine
EAIR:	Exposure-Adjusted Incident Rate
ECG:	Electrocardiogram
ECHO:	Echocardiography
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
eIND:	Emergency Investigational New Drug
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
ETP:	Extension Treatment Period
EU:	European Union
FIASMA:	Functional Inhibitors of Acid Sphingomyelinase
G-CSF:	Granulocyte-Colony Stimulating Factor
GLP:	Good Laboratory Practice
HCP:	Healthcare Professional
HIV:	Human Immunodeficiency Virus
IAR:	Infusion Associated Reaction
ICH:	International Conference for Harmonization
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G

IL:	Interleukin
IND:	Investigational New Drug
INN:	International Nonproprietary Name
INR:	International Normalized Ratio
IP:	Intraperitoneal
IV:	Intravenous
MAA:	Marketing Authorization Application
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
Max:	Maximum
Min:	Minimum
MIP:	Macrophage Inflammatory Protein
MRI:	Magnetic Resonance Imaging
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
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
PY:	Patient Year
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
SMPD1:	Sphingomyelin Phosphodiesterase-1 Gene
SRS:	Splenomegaly Related Score
SSRI:	Selective Serotonin Reuptake Inhibitor
TEAE:	Treatment Emergent Adverse Event
URL:	Uniform Resource Locator
US:	United States
WHO:	World Health Organization
WOCBP:	Women of Child Bearing Potential

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Olipudase alfa
Pharmacotherapeutic group(s) (ATC Code)	A16AB25
Marketing Authorization Holder	Genzyme Europe B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	XENPOZYME
Marketing authorization procedure	Centralized procedure
Brief description of the product	<u>Chemical class:</u> Olipudase alfa is a rhASM developed as an ERT.
	<u>Summary of mode action:</u> Olipudase alfa catalyzes the hydrolysis of SM, reducing the amount of SM that accumulates in organs of patients with ASMD.
	<u>Important information about its composition:</u> Olipudase alfa is produced in a CHO cell line by recombinant 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 e-CTD sequence 0016 Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	<u>Current:</u> Olipudase alfa is an enzyme replacement therapy for the treatment of non-CNS manifestations of ASMD in pediatric and adult patients with type A/B or type B.
	<u>Proposed:</u> Not applicable
Dosage in the EEA	<u>Current:</u> Posology Initial treatment/dose escalation phase The rapid metabolism of accumulated SM by olipudase alfa generates proinflammatory breakdown products, which may induce IARs and/or transient liver enzyme elevations. A dose escalation regimen can minimize the majority of these AEs.

Olipudase alfa dose is based on the actual body weight for patient with a 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 20 mg of olipudase alfa.

Proposed:

Not applicable

Is/will the product (be) subject to additional monitoring in the 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; IAR: Infusion Associated Reaction; INN: International Nonproprietary Name; rhASM: Recombinant form of Human Acid Sphingomyelinase; RMP: Risk Management Plan; SM: Sphingomyelin.

RISK MANAGEMENT PLAN - 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-CNS manifestations of ASMD in pediatric 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
<p>Incidence (birth prevalence)</p>	<p>Acid sphingomyelinase deficiency is an autosomal recessive disease. The phenotype spectrum ranges from the severe infantile neurovisceral form (ASMD type A, historically known as NPD A) to the chronic visceral form (ASMD type B, NPD B), with an intermediate or chronic neurovisceral phenotypic presentation also being described (ASMD type A/B, NPD A/B).</p> <p>While ASMD type A is usually diagnosed before one year of age, the chronic forms are diagnosed during childhood or later, often after a patient presents with organomegaly. Misdiagnosis and delayed diagnosis are prevalent in this population due to the rarity of ASMD and the unfamiliarity of the specific signs and symptoms of the disease. (1)</p> <p>The rarity of the disease renders accurate estimations of incidence and prevalence difficult, and robust epidemiological data for ASMD in various regions are lacking. In particular, natural history studies are most often limited to small numbers of patients, and would not allow to derive incidence or prevalence data (no denominator). (2)(3) Disease frequency estimates have been based on clinically suspected cases referred for biochemical and genetic testing. Population-wide screening has not been performed, but genetic screening may be performed in patients from certain populations with common SMPD1 pathogenic variants, such as patients with Ashkenazi Jewish backgrounds.</p> <p>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 live-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; (4) placing the birth incidence of ASMD at about 0.4 to 0.6 per 100 000 births.</p> <p>Newborn screening studies have reported an incidence of about 4 to 5 per 100 000. (5)(6)</p> <p>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. (6)(7)(8)</p> <p>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. (5)(9) 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. (10)</p> <p>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. (4)(5)(7) 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). (8) The highest frequencies of chronic forms of ASMD have been reported in individuals of Turkish,</p>

Indication	Acid sphingomyelinase deficiency
	<p>Arabic, and North African descent, although the disorder affects many other distinct populations. (7) For example, estimates for the Chilean population based on the allele frequency of the p.(Ala359Asp) variant suggest a birth prevalence rate of about 2 cases per 100 000 births. (10)</p>
<p>Demographics of the population in the authorized indication</p>	<p>Acid Sphingomyelinase Deficiency is a multisystemic disorder with heterogeneous manifestations and represents a spectrum of disease, classified as:^a (6)</p> <ul style="list-style-type: none"> • Acid Sphingomyelinase Deficiency type A or Infantile neurovisceral ASMD, historically known as 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 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, 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. <p>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. (11)</p> <p>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. (12)</p>
<p>Main existing treatment options</p>	<p>To date, only symptomatic therapy is available. This includes 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.</p> <p>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. (13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)</p> <p>Early diagnosis and appropriate management are essential for reducing the risk of complications, improving quality of life, and addressing disease complications.</p>
<p>Natural history of the indicated condition in the untreated population including mortality and morbidity</p>	<p>Almost all patients with ASMD have massive hepatosplenomegaly and an atherogenic lipid profile (cholesterol abnormalities), (6)(12)(25)(26) 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. (27)(28) Other common clinical manifestations include liver dysfunction, and growth delays. (6)(11)(26)</p> <p>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.</p>

Indication	Acid sphingomyelinase deficiency
	<p>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. (6) Greater than 80% of patients with ASMD type B have radiographic evidence of infiltrative lung disease, although some patients may not have overt symptoms. (27)(28) 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.</p> <p>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. (6)</p> <p>Chronic forms of ASMD have a progressive course. (2) Clinically significant pulmonary, hepatic, bleeding and cardiac complications are common causes of mortality. (29) In patients with chronic forms of ASMD (type A/B and B), the prognosis is more variable than with ASMD type A. (6) 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. (6) 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. (30) 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. (25) 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. (2)(11) 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.</p>
Important co-morbidities	<p>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; (31) hence it is challenging to establish whether or not ASMD patients have a higher risk of depression and to quantify such a risk.</p>

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; NPD A: Niemann-Pick Disease Type A; NPD B: Niemann-Pick Disease Type B; SMPD1: Sphingomyelin Phosphodiesterase-1 Gene.

RISK MANAGEMENT PLAN - 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 (32) 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 (33) that lacks ASM activity. These ASMKO mice were used to evaluate the pharmacokinetic (PK), biodistribution (BD), and pharmacodynamic (PD) 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 cynomolgus 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 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-1 α , IL-1 β , and macrophage inflammatory protein [MIP]-1 α) 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 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 (FIASMs). Functional inhibitors of ASM are a large group of cationic amphiphilic molecules that may disrupt the interaction of ASM with the lysosomal membrane. (34) Most FIASMs 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. (35) 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
<p>Toxicity</p> <ul style="list-style-type: none"> • 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 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 	<p>Toxicity</p> <ul style="list-style-type: none"> • 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. • Transient elevations in transaminases during dose escalation have been observed in clinical trials, and do not raise a concern; no other findings indicating hepatotoxicity 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]).

Key Safety Findings	Relevance to human usage
<p>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.</p> <ul style="list-style-type: none"> 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 DPH; IP administration. 	<ul style="list-style-type: none"> No serious and/or severe APRs have been observed in clinical trials.
<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 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]).
<ul style="list-style-type: none"> Measurable levels of olipudase alfa were detected in the milk of lactating mice 2 days following administration of 3 mg/kg. 	<ul style="list-style-type: none"> The use of olipudase alfa in lactating women is considered missing information in the RMP (see [Part II SVII]).
<p>Safety pharmacology</p> <ul style="list-style-type: none"> A 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 ICH S7A and S7B guidelines. The results indicated that there were no test article-related changes in neurobehavioral or ECG 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 	<p>Safety pharmacology</p> <ul style="list-style-type: none"> There were no severe cardiac events reported in the clinical studies. There was one 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 has continued in the study. The potentially adverse effect of olipudase alfa on the cardiac function in humans has been mitigated by the dose escalation regimen.

Key Safety Findings	Relevance to human usage
<p>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.</p> <ul style="list-style-type: none"> No adverse effects on cardiac function have been observed in ASMKO mice when olipudase alfa was administered via a dose escalation regimen. 	
<p>Other toxicity-related information or data Not applicable</p>	Not applicable

APR: Acute Phase Reaction; ASMD: Acid Sphingomyelinase Deficiency; ASMKO: Acid Sphingomyelinase Knock-Out; CD: Cluster of Differentiation; CNS: Central Nervous System; DPH: Diphenhydramine; ECG: Electrocardiogram; G-CSF: Granulocyte-Colony Stimulating Factor; GLP: Good Laboratory Practice; ICH: International Conference for Harmonization; IL: Interleukin; IP: Intraperitoneal; 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.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

The clinical development program for olipudase alfa in ASMD includes 5 clinical trials with olipudase alfa treatment and 5 non-interventional natural history studies without olipudase alfa treatment (See [Table 8](#) and [Table 9](#)).

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	25 (5 adult + 20)	Single arm, Patients will receive an IV	Up to 9 years or marketing approval	Ongoing

Protocol Number	Phase	Age Category	Protocol Title	Number of Patients	Treatment	Duration of Treatment	Study Status
			and Efficacy of Olipudase alfa in Patients With ASMD	pediatric patients)	infusion of olipudase alfa every 2 weeks (\pm 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 Ongoing

^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.

Table 9 - Acid Sphingomyelinase Deficiency Natural History Studies (no treatment with olipudase alfa administered)

Protocol Number	Age Category	Study Design	Number of Patients	Study Status
SPHINGO-001-00	Pediatric/Adult	A Multicenter, multi-national prospective, cross sectional survey study of patients with NPD B	59 (30 Pediatric and 29 Adult)	Complete
SPHINGO-003-02	Adult	Multicenter, multi-national, Retrospective Natural History Study of Patients with ASM Deficiency	100	Complete
RHASHC09538	Pediatric	Natural History of ASMD During Childhood and Adolescence: A Retrospective Observational Study (US)	1	Complete
RHASHC09539	Pediatric	Natural History of ASMD Among European Patients During Childhood and Adolescence: A Retrospective Observational Study	approximately 20	Complete

Protocol Number	Age Category	Study Design	Number of Patients	Study Status
PIR16183	Pediatric/Adult	A prospective and retrospective cohort study to refine and expand the knowledge on patients with chronic forms of ASMD	87	Ongoing

ASM: Acid Sphingomyelinase; ASMD: Acid Sphingomyelinase Deficiency; NPD B: Niemann-Pick Disease Type B; US: United States.

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 to the ongoing long-term study LTS13632.

Ongoing 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 ongoing DFI12712 study.

Overall, 46 adult patients have been exposed to olipudase alfa in both completed and ongoing 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 are now enrolled in the ongoing long-term 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.

Table 10 shows duration of exposure. Overall, sixty patients had a median of 3.11 years (range 0.4 to 7.8) of exposure to olipudase alfa. Almost all patients (98.3%) received ≥ 1 year of olipudase alfa treatment, 88.3% received ≥ 2 years of treatment, and 51.7% received ≥ 3 years of treatment. The treatment exposure was larger in adult patients than pediatric patients.

Table 10 - Duration of exposure

Extent of Treatment Exposure	Pediatric (N = 20)	Adult (N = 40)	Overall (N = 60)
Cumulative duration of olipudase alfa exposure (patient-years)	80.29	135.78	216.08
Duration on olipudase alfa (years)			
Number of patients with value	20	40	60
Mean (SD)	4.01 (1.195)	3.39 (1.868)	3.60 (1.689)
Median	4.15	2.95	3.11
Min : Max	2.5 : 5.7	0.4 : 7.8	0.4 : 7.8
Distribution of duration on olipudase alfa, n (%)			
>0 to <1 year	0	1 (2.5%)	1 (1.7%)
≥ 1 to <2 years	0	6 (15.0%)	6 (10.0%)
≥ 2 to <3 years	7 (35.0%)	15 (37.5%)	22 (36.7%)
≥ 3 to <4 years	2 (10.0%)	9 (22.5%)	11 (18.3%)
≥ 4 to <5 years	7 (35.0%)	4 (10.0%)	11 (18.3%)
≥ 5 to <6 years	4 (20.0%)	0	4 (6.7%)
≥ 6 to <7 years	0	0	0
≥ 7 years	0	5 (12.5%)	5 (8.3%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)			
>0 year	20 (100.0%) (80.29)	40 (100.0%) (135.78)	60 (100.0%) (216.08)
≥ 1 year	20 (100.0%) (80.29)	39 (97.5%) (135.40)	59 (98.3%) (215.69)
≥ 2 years	20 (100.0%) (80.29)	33 (82.5%) (124.98)	53 (88.3%) (205.27)

Extent of Treatment Exposure	Pediatric (N = 20)	Adult (N = 40)	Overall (N = 60)
≥3 years	13 (65.0%) (61.70)	18 (45.0%) (86.84)	31 (51.7%) (148.54)
≥4 years	11 (55.0%) (54.63)	9 (22.5%) (56.04)	20 (33.3%) (110.66)
≥5 years	4 (20.0%) (22.49)	5 (12.5%) (38.63)	9 (15.0%) (61.12)
≥6 years	0 (0)	5 (12.5%) (38.63)	5 (8.3%) (38.63)
≥7 years	0 (0)	5 (12.5%) (38.63)	5 (8.3%) (38.63)
Duration on olipudase alfa in initial dose escalation period (years)			
Number of patients with value	20	40	60
Mean (SD)	0.38 (0.147)	0.32 (0.166)	0.34 (0.161)
Median	0.34	0.27	0.29
Min : Max	0.3 : 1.0	0.2 : 1.2	0.2 : 1.2

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_2021/REPORT/PGM/cdc_exposure_t.sas OUT=REPORT/OUTPUT/cdc_exposure_t_i.rtf (22JUN2021 - 6:47)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 11 shows exposure by age group and gender. Overall, sixty patients received 216.08 patient-years of olipudase alfa. The treatment exposure among the 40 adult patients, 135.78 patient-years was higher than in the 20 pediatric patients, 80.29 patient-years.

Table 11 - Exposure by age group and gender

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)
Cumulative duration of olipudase alfa exposure (patient-years)	13.43	9.50	19.82	15.06	5.73	16.76	71.78	62.52	1.48	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)
Duration on olipudase alfa (years)										
Number of patients with value	4	3	5	4	1	3	23	16	1	0
Mean (SD)	3.36 (0.802)	3.17 (0.858)	3.96 (1.167)	3.76 (1.121)	5.73 (NC)	5.59 (0.069)	3.12 (1.772)	3.91 (1.957)	1.48 (NC)	0
Median	3.35	2.85	4.74	3.86	5.73	5.58	2.69	3.06	1.48	0
Min : Max	2.6 : 4.2	2.5 : 4.1	2.6 : 4.9	2.5 : 4.8	5.7 : 5.7	5.5 : 5.7	0.4 : 7.8	2.1 : 7.7	1.5 : 1.5	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	5 (21.7%)	0	1 (100.0%)	0
≥2 to <3 years	2 (50.0%)	2 (66.7%)	2 (40.0%)	1 (25.0%)	0	0	7 (30.4%)	8 (50.0%)	0	0
≥3 to <4 years	1 (25.0%)	0	0	1 (25.0%)	0	0	5 (21.7%)	4 (25.0%)	0	0
≥4 to <5 years	1 (25.0%)	1 (33.3%)	3 (60.0%)	2 (50.0%)	0	0	3 (13.0%)	1 (6.3%)	0	0
≥5 to <6 years	0	0	0	0	1 (100.0%)	3 (100.0%)	0	0	0	0
≥6 to <7 years	0	0	0	0	0	0	0	0	0	0
≥7 years	0	0	0	0	0	0	2 (8.7%)	3 (18.8%)	0	0
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)										
>0 year	4 (100.0%) (13.43)	3 (100.0%) (9.50)	5 (100.0%) (19.82)	4 (100.0%) (15.06)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	23 (100.0%) (71.78)	16 (100.0%) (62.52)	1 (100.0%) (1.48)	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)
≥1 year	4 (100.0%) (13.43)	3 (100.0%) (9.50)	5 (100.0%) (19.82)	4 (100.0%) (15.06)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	22 (95.7%) (71.39)	16 (100.0%) (62.52)	1 (100.0%) (1.48)	0 (0)
≥2 years	4 (100.0%) (13.43)	3 (100.0%) (9.50)	5 (100.0%) (19.82)	4 (100.0%) (15.06)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	17 (73.9%) (62.46)	16 (100.0%) (62.52)	0 (0)	0 (0)
≥3 years	2 (50.0%) (8.09)	1 (33.3%) (4.14)	3 (60.0%) (14.43)	3 (75.0%) (12.55)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	10 (43.5%) (45.52)	8 (50.0%) (41.32)	0 (0)	0 (0)
≥4 years	1 (25.0%) (4.16)	1 (33.3%) (4.14)	3 (60.0%) (14.43)	2 (50.0%) (9.41)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	5 (21.7%) (28.68)	4 (25.0%) (27.35)	0 (0)	0 (0)
≥5 years	0 (0)	0 (0)	0 (0)	0 (0)	1 (100.0%) (5.73)	3 (100.0%) (16.76)	2 (8.7%) (15.57)	3 (18.8%) (23.06)	0 (0)	0 (0)
≥6 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7%) (15.57)	3 (18.8%) (23.06)	0 (0)	0 (0)
≥7 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7%) (15.57)	3 (18.8%) (23.06)	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)	0.36 (0.212)	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 : 1.2	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 3mg/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_2021/REPORT/PGM/cdc_expybysst_sas OUT=REPORT/OUTPUT/cdc_expybysst_age_i.rtf (22JUN2021 - 6:48)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Extent of Treatment Exposure	While at Infusion Dose (mg/kg)						
	0.03 (N = 20)	0.1 (N = 60)	0.3 (N = 60)	0.6 (N = 60)	1 (N = 60)	2 (N = 60)	3 (N = 59)
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%) (6.20)	60 (100.0%) (5.89)	60 (100.0%) (6.64)	60 (100.0%) (7.59)	59 (100.0%) (186.32)
≥1 year	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	2 (3.3%) (2.55)	58 (98.3%) (186.20)
≥2 years	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	0 (0)	45 (76.3%) (166.24)
≥3 years	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%) (3.14)	0 (0)	26 (44.1%) (119.97)
≥4 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (27.1%) (85.45)
≥5 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (13.6%) (51.07)
≥6 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.8%) (29.85)
≥7 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.8%) (29.85)

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_2021/REPORT/PGM/cdc_expbyss1_t.sas OUT=REPORT/OUTPUT/cdc_expbyss1_t_inf_overall_i.rtf (22JUN2021 - 6:48)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 13 - Exposure by ethnic origin

Extent of Treatment Exposure	Hispanic (N = 12)	Non-Hispanic (N = 46)
Cumulative duration of olipudase alfa exposure (patient-years)	32.59	172.85
Duration on olipudase alfa (years)		
Number of patients with value	12	46
Mean (SD)	2.72 (0.766)	3.76 (1.729)
Median	2.84	3.38
Min : Max	1.7 : 4.2	0.4 : 7.8
Distribution of duration on olipudase alfa, n (%)		
>0 to <1 year	0	1 (2.2%)
≥1 to <2 years	3 (25.0%)	3 (6.5%)
≥2 to <3 years	6 (50.0%)	15 (32.6%)
≥3 to <4 years	2 (16.7%)	9 (19.6%)
≥4 to <5 years	1 (8.3%)	10 (21.7%)
≥5 to <6 years	0	4 (8.7%)
≥6 to <7 years	0	0
≥7 years	0	4 (8.7%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)		
>0 year	12 (100.0%) (32.59)	46 (100.0%) (172.85)
≥1 year	12 (100.0%) (32.59)	45 (97.8%) (172.46)
≥2 years	9 (75.0%) (27.12)	42 (91.3%) (167.51)
≥3 years	3 (25.0%) (11.04)	27 (58.7%) (129.85)
≥4 years	1 (8.3%) (4.16)	18 (39.1%) (98.86)
≥5 years	0 (0)	8 (17.4%) (53.47)
≥6 years	0 (0)	4 (8.7%) (30.98)
≥7 years	0 (0)	4 (8.7%) (30.98)
Duration on olipudase alfa in initial dose escalation period (years)		
Number of patients with value	12	46
Mean (SD)	0.31 (0.091)	0.35 (0.177)

Extent of Treatment Exposure	Hispanic (N = 12)	Non-Hispanic (N = 46)
Median	0.27	0.31
Min : Max	0.3 : 0.5	0.2 : 1.2

Percentages are based on the number of safety set in each group.

Initial dose escalation period is the first time when patient reached the 3mg/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.

Two adults had ethnicity "not reported" or "unknown".

PGM=PRODOPS/GZ402665/OVERALL/ISS_2021/REPORT/PGM/cdc_expybysst_t.sas

OUT=REPORT/OUTPUT/cdc_expybysst_t_ethnicity_i.rtf (22JUN2021 - 6:48)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 14 shows exposure by race. Overall, most of the patients were white (n = 53, 88.3%).

Table 14 - 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)	189.53	10.51	6.07	9.97
Duration on olipudase alfa (years)				
Number of patients with value	53	2	2	3
Mean (SD)	3.58 (1.737)	5.25 (0.678)	3.03 (0.637)	3.32 (1.463)
Median	3.10	5.25	3.03	2.99
Min : Max	0.4 : 7.8	4.8 : 5.7	2.6 : 3.5	2.1 : 4.9
Distribution of duration on olipudase alfa, n (%)				
>0 to <1 year	1 (1.9%)	0	0	0
≥1 to <2 years	6 (11.3%)	0	0	0
≥2 to <3 years	19 (35.8%)	0	1 (50.0%)	2 (66.7%)
≥3 to <4 years	10 (18.9%)	0	1 (50.0%)	0
≥4 to <5 years	9 (17.0%)	1 (50.0%)	0	1 (33.3%)
≥5 to <6 years	3 (5.7%)	1 (50.0%)	0	0
≥6 to <7 years	0	0	0	0
≥7 years	5 (9.4%)	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%) (189.53)	2 (100.0%) (10.51)	2 (100.0%) (6.07)	3 (100.0%) (9.97)
≥1 year	52 (98.1%) (189.14)	2 (100.0%) (10.51)	2 (100.0%) (6.07)	3 (100.0%) (9.97)
≥2 years	46 (86.8%) (178.73)	2 (100.0%) (10.51)	2 (100.0%) (6.07)	3 (100.0%) (9.97)
≥3 years	27 (50.9%) (129.62)	2 (100.0%) (10.51)	1 (50.0%) (3.49)	1 (33.3%) (4.92)
≥4 years	17 (32.1%) (95.23)	2 (100.0%) (10.51)	0 (0)	1 (33.3%) (4.92)
≥5 years	8 (15.1%) (55.38)	1 (50.0%) (5.73)	0 (0)	0 (0)
≥6 years	5 (9.4%) (38.63)	0 (0)	0 (0)	0 (0)
≥7 years	5 (9.4%) (38.63)	0 (0)	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)	0.34 (0.170)	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 : 1.2	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_2021/REPORT/PGM/cdc_expybysst.t.sas

OUT=REPORT/OUTPUT/cdc_expybysst_race_i.rtf (22JUN2021 - 6:48)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

Table 15 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 15 - 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)	4.34	211.74
Duration on olipudase alfa (years)		
Number of patients with value	3	57
Mean (SD)	1.45 (1.044)	3.71 (1.645)
Median	1.48	3.14
Min : Max	0.4 : 2.5	1.7 : 7.8
Distribution of duration on olipudase alfa, n (%)		
>0 to < 1 year	1 (33.3%)	0
≥1 to <2 years	1 (33.3%)	5 (8.8%)
≥2 to <3 years	1 (33.3%)	21 (36.8%)
≥3 to <4 years	0	11 (19.3%)
≥4 to <5 years	0	11 (19.3%)
≥5 to <6 years	0	4 (7.0%)
≥6 to <7 years	0	0
≥7 years	0	5 (8.8%)
Cumulative distribution of duration on olipudase alfa, n (%) (patient-years)		
>0 year	3 (100.0%) (4.34)	57 (100.0%) (211.74)
≥1 year	2 (66.7%) (3.95)	57 (100.0%) (211.74)
≥2 years	1 (33.3%) (2.47)	52 (91.2%) (202.80)
≥3 years	0 (0)	31 (54.4%) (148.54)
≥4 years	0 (0)	20 (35.1%) (110.66)
≥5 years	0 (0)	9 (15.8%) (61.12)
≥6 years	0 (0)	5 (8.8%) (38.63)
≥7 years	0 (0)	5 (8.8%) (38.63)
Duration on olipudase alfa in initial dose escalation period (years)		
Number of patients with value	3	57

Extent of Treatment Exposure	Having Baseline Cirrhosis (N = 3)	Not having Baseline Cirrhosis (N = 57)
Mean (SD)	0.57 (0.531)	0.33 (0.118)
Median	0.27	0.30
Min : Max	0.3 : 1.2	0.2 : 1.0

Percentages are based on the number of safety set in each group.

Initial dose escalation period is the first time when patient reached the 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_2021/REPORT/PGM/cdc_expyss_t.sas OUT=REPORT/OUTPUT/cdc_expyss_t_cirr_i.rtf
(22JUN2021 - 6:48)

Max: Maximum; Min: Minimum; N: Number; SD: Standard Deviation.

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

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

Table 16 - 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 HIV infection, INR >1.5, platelet count <60.0x10 ³ /μL, significant cardiac disease (eg, pulmonary artery pressure >40 mm Hg, moderate or severe valvular dysfunction, or <40% left ventricular ejection fraction by ECHO), 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 of the safety profile of olipudase alfa.	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
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). (34) Efficacy assessments could be impaired by these medications.	No	The clinical relevance of this theoretical interaction with FIASMA is unknown. (Section SVII.1).

ASM: Acid Sphingomyelinase; ASMD: Acid Sphingomyelinase Deficiency; ECHO: Echocardiography; FIASMA: Functional Inhibitors of Acid Sphingomyelinase; HIV: Human Immunodeficiency Virus; INR: International Normalized Ratio; 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 17 - Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women Lactating women	Not included in the clinical development program. 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.

Type of special population	Exposure
Patients with ASMD type A	Not included in the clinical development program. One patient with ASMD type A, via an emergency 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; IND: Investigational New Drug.

Pregnant women

There are no data from the use of olipudase alfa in pregnant women. In study DFI12712, there was one pregnancy in a partner of a patient exposed to olipudase alfa. The partner gave birth to a child 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.

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

To date, 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. (34)(35) 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](#)).



RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

The marketing authorization holder (MAH) is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience and has been doing so since December 2019.


As World Health Organization (WHO) defined daily dose (DDD) for parenteral formulation is not available, the patient exposure in patient years (PYs) could not be estimated for infusion powder, injection liquid (solution)¹ and injection.

Sales from the cumulative experience is available from MARCO for the period from 01 May 2020 through 30 September 2022.

A total of 83 vials of infusion powder, 2914 vials of injection liquid (solution) and 2202 vials of injection powder were sold worldwide during the cumulative period.

Detailed usage data are not available therefore presentation of sales data by age, sex, and indication is not possible. Consequently, it is only presented by country and formulation:

Table 18 - Olipudase alfa worldwide sales - Sanofi (01 May 2020 to 30 September 2022^a) in units

COUNTRY	OLIPUDASE ALFA		
	INFUSION POWDER 20 mg/5 mL	INJECTION LIQUID (SOLUTION) 20 mg/1 mL	INJECTION POWDER 20 mg/5 mL
			
Grand Total	83	2914	2202

UNITS:

INFUSION, POWDER/INJECTION, LIQUID (SOLUTION)/INJECTION, POWDER: Total number of Vials.

SOURCE: MARCO database updated (13-OCT-2022).

^a Sales data is available from May-2020 in Marco database.

MARCO: Margin Consolidated; US: United States.

¹ Injection, liquid (solution) should be considered as infusion, powder (data entry error). This formulation concerns free goods for hospitals.

RISK MANAGEMENT PLAN - 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.

RISK MANAGEMENT PLAN - 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. (36) 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 19 - Important identified risk considered for inclusion in the list of safety concerns: Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions

Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions	
Scientific evidence that has led to the inclusion	<p><u>Clinical trial experience:</u></p> <ul style="list-style-type: none"> • 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 IgG and/or IgE ADA have been observed in the clinical program (phase 1/2 trial DF113803 in pediatric patients, repeat-dose 1b trial DF113412 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, both 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. <p><u>Other:</u></p> <p>One pediatric patient, [REDACTED] 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).</p> <p><u>Class effects:</u></p> <p>The potential of developing an IAR is reported in the product information of some marketed ERTs, including FABRAZYME®, MYOZYME®, CEREZYME®, NAGLAZYME®.</p> <p><u>Scientific literature:</u></p> <p>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%. (37)</p>

Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, 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.
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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 20 - 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. <u>Clinical trial experience:</u> No medication errors have been identified in home infusion setting by the time of data cutoff.
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 21 - Important potential risk considered for inclusion in the list of safety concerns: Foetal toxicity

Foetal toxicity	
Scientific evidence that has led to the inclusion	<u>Preclinical data:</u> 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 22 - 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.

Use in lactating women	
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 23 - 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 will be collected through the ongoing studies LTS13632 in adults and pediatric patients and DF112712 ASCEND ETP in adult patients. Patients currently 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

No new safety concerns or reclassification have been considered since the last RMP approved version.

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
 - Long-term safety (beyond 2 years)

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

Table 24 - Important identified risk: Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions

Important identified Risk	Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions
Potential mechanism	<ul style="list-style-type: none"> 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 (eIND).
Characterization of the risk	<p>Details of the events related to the sub-types and their impact on patient's treatment and outcome are presented below:</p> <p>Frequency:</p> <p>In the clinical studies</p> <ul style="list-style-type: none"> 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 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 antiolipudase alfa antibodies. There were two pediatric patients (10.0%) who were positive for IgG antiolipudase alfa antibodies and experienced serious hypersensitivity reactions (urticaria, rash, and hypersensitivity). All three patients' events occurred within 72 hours of infusion. One patient with type A ASMD experienced two severe allergic/anaphylactic-like reactions during infusion that responded well to therapy (eIND). There were no anaphylactic reactions reported in adult patients. <p>Severity and nature of risk:</p> <p><u>Infusion associated reactions:</u></p> <ul style="list-style-type: none"> Overall, 30 (50.0%) patients experienced a total of 302 mild events, 17 (28.3%) 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 55.0%, respectively). Among the most frequently reported IARs, the EAIR was higher in pediatric than adult patients for: urticaria (11.35 versus 4.21 patients per 100 PY); pyrexia (14.85 versus 3.37); and vomiting (10.38 versus 2.35). The EAIR was higher in adult patients than pediatric patients for headache (9.72 versus 6.00 patients per 100 PY) and was similar in adult and pediatric patients for nausea (5.61 and 6.02, respectively). <p><u>Systemic hypersensitivity:</u></p> <ul style="list-style-type: none"> 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 DF113803, one serious case of anaphylactic reaction [REDACTED] 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 have continued treatment and are enrolled in LTS13632. <p><u>Anti-drug antibody mediated hypersensitivity reactions:</u></p> <ul style="list-style-type: none"> Overall, 29 of 60 (48.3%) patients in the clinical studies developed treatment-emergent ADA; however, the ADA titers were predominantly ≤ 400 (median ADA titer was 100),

Important identified Risk	Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions
	<p>which are considered as low response. Only 5 patients, 3 pediatric and 2 adults, developed intermediate titers that ranged from 800 to 3200. Some of the TEAEs associated with ADA also resemble to IARs and were generally mild-to-moderate and clinically manageable. One pediatric patient, who experienced anaphylaxis (described above), developed IgE ADA and had a peak IgG ADA titer of 1600, the highest titer in the pediatric olipudase alfa safety set.</p> <ul style="list-style-type: none"> Overall, there was a higher percentage of patients with treatment emergent IARs in patients who developed treatment emergent ADA versus those who did not (75.9% versus 41.9%). The treatment emergent IARs with a higher incidence by PT in adult or pediatric patients who developed treatment emergent ADA versus those who did not, respectively, were: <ul style="list-style-type: none"> Adult patients: Urticaria (31.3% versus 0%), Pruritus (18.8% versus 0%) Pediatric patients: Urticaria (53.8% versus 0%), Pyrexia (46.2% versus 28.6%), Erythema (15.4% versus 0%), Abdominal pain (15.4% versus 0%). <p>Seriousness and outcome:</p> <p>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.</p> <p>All patients were found to be positive for IgG ADA, with 2 of 3 patients having peak ADA titers in the intermediate range (800-1600), which modestly decreased over time, and 1 patient was low titer (200). In addition, 1 patient was positive for IgE ADA.</p> <p>All three patients experiencing a serious IAR/systemic hypersensitivity event recovered; resumed olipudase alfa treatment; and are currently enrolled in LTS13632.</p> <p>Background incidence/prevalence:</p> <p>Immunogenicity is specific to the biologic product and does not occur in untreated patients with ASMD.</p>
Risk factors and risk groups	<p><u>Systemic hypersensitivity and IARs:</u></p> <ul style="list-style-type: none"> Patients with previous hypersensitivity/allergy to olipudase alfa and its excipients. Available clinical data suggest children may have greater predisposition, compared to adults. <p>Additional risk characterization has not been fully established.</p> <p><u>Anti-drug antibody mediated hypersensitivity reactions:</u></p> <p>The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. Adults had a median ADA peak titer of 50 (range 50-3200) compared to pediatric patients with a median ADA peak titer of 200 (range 50-1600).</p>
Preventability	<p>Labelling statements (See Section V.1) and educational materials (see Section V.2)</p> <ul style="list-style-type: none"> To remind the prescribing/treating physician with appropriate patient selection for home infusion, the 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	<p>Although systemic hypersensitivity reactions including anaphylaxis; ADA mediated hypersensitivity reactions; and IARs have been seen in the clinical program, the overall</p>

Important identified Risk	Immunogenicity: Infusion associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions
	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; eIND: Emergency Investigational New Drug; ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IV: Intravenous; PT: Preferred Term; PY: Patient Year; SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event.

Table 25 - Important potential risk: Medication errors in home infusion setting

Important potential risk	Medication errors in home infusion setting
Potential mechanism	There is 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. <u>Clinical trial experience:</u> No medication errors have been identified by the time of data cutoff (15-Mar-2021).
Characterization of the risk	The risk associated with administration of the product may result in lack of treatment efficacy or overdose.
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	While the possibility of medication errors cannot be excluded, patients receiving home infusion have an acceptable safety profile, 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.

ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; RMP: Risk Management Plan.

Table 26 - Important potential risk: Foetal toxicity

Important potential risk	Foetal toxicity
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Non-clinical data

Important potential risk	Foetal toxicity
Characterization of the risk	Potential embryo-foetal toxicity
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). 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; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

SVII.3.2 Presentation of the missing information

Table 27 - 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.

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

Table 28 - Missing information: Long-term safety (beyond 2 years)

Missing Information	Long-term safety (beyond 2 years)
Evidence source(s) and strength of evidence	Patients with ASMD are treated throughout their lifespan.
Anticipated risk/consequence of the missing information	The benefit-risk profile of olipudase alfa is expected to remain favorable in type A/B and type B ASMD patients already exposed to olipudase alfa for more than 2 years. Therapeutic proteins have the potential to induce immunogenicity and generate ADA. However, not all ADA have clinical consequences. The majority of patients developed a low ADA response (ADA titer ≤ 400). The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. In general, ADA titers tended to slowly decrease over time, but of note, did not increase with repeated exposure to drug. Overall, the median peak ADA titer since the first dose of olipudase alfa was 200 for pediatric patients and decreased to 100 by the end of the study. In adult patients, the median peak ADA titer was 75 and decreased to 50. In addition, 6.7% of patients tolerized or reverted to become ADA-negative by the end of the study. These data support that olipudase alfa has a low immunogenicity risk relative to ADA impact on clinical outcomes.



Missing Information	Long-term safety (beyond 2 years)
	Long-term use safety data beyond 2 years in ASMD patients will be collected through the ongoing studies LTS13632 in adults and pediatric patients and DF112712 ASCEND ETP in adult patients. Patients currently enrolled in the clinical studies are expected to continue treatment with commercial product and will be monitored through routine pharmacovigilance.

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period.



RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	Immunogenicity: <ul style="list-style-type: none">• 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)

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

RISK MANAGEMENT PLAN - 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)/periodic benefit-risk evaluation report (PBRER) for spontaneous reports related to identified and potential risks.
- Continued analysis of safety in clinical trials.

The ongoing clinical trial program (DFI12712 and LTS13632) includes safety assessment with collection of adverse events of special interest (AESIs) which are defined as AEs, serious or nonserious, that need to be monitored, documented and managed in a pre-specified manner. These AESIs include pregnancy, symptomatic overdose, laboratory values meeting pre-specified criteria (dose limiting toxicities based on transaminase and alkaline phosphatase levels and symptoms), Infusion-associated reactions including hypersensitivity reactions, APRs and cytokine release syndrome).

In addition to the Sponsor, an external independent data monitoring committee (DMC) was, and will continue to be responsible for monitoring the safety of patients enrolled in phase 2/3 trials (DFI12712 ASCEND and LTS13632) up to the approval for marketing authorization of olipudase alfa of the three major markets (EU, US or Japan).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance in the postmarketing setting includes:

- An ongoing multinational, multicenter, nonrandomized, open-label, long-term extension, maintenance trial LTS13632 (final report planned in 2024) which aims to assess the long-term safety (up to 9 years) of olipudase alfa in adult and pediatric patients with ASMD (see details below and protocol in [Part VII Annex 3]).
- An ongoing extension phase of phase 2/3 clinical trial (DFI12712 ASCEND), multicenter, randomized, double-blind, placebo-controlled, repeat-dose study to evaluate the efficacy, safety, PD and PK of olipudase alfa in adult patients with ASMD (see details below and protocol in [Part VII Annex 3]).

Table 29 - Additional pharmacovigilance activities (category 1 to 3) summary

LTS13632 - A long-term clinical trial - ongoing (Cat. 3)

Study short name and title

LTS13632 - A long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with ASMD

Rationale and study objectives

To obtain data regarding the safety and efficacy of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa.

Primary objective:

To assess the long-term safety of olipudase alfa in patients with ASMD.

Secondary objective:

To assess the maintenance of effect of olipudase alfa and to characterize the PDs and PKs following long-term administration.

Study design

Multinational, multicenter, non-randomized, open-label, long-term treatment study of patients who completed the treatment period of the DF113412 or DF113803 Peds, respectively, with an acceptable safety profile.

Patients are receiving olipudase alfa every 2 weeks for 9 years or marketing approval, whichever comes first. Patients started this study at the same dose they were receiving at the end of their primary study, provided that they have not missed more than 1 biweekly dose between studies.

Study populations

Pediatric and adult patients with ASMD: 25 (5 adults, 20 pediatrics)

The patient completed the treatment period of a previous study (DF113412 or DF113803 Peds) of olipudase alfa with an acceptable benefit-risk outcome (in the opinion of the investigator and sponsor).

The patient has no new condition or worsening of an existing condition which in the opinion of the investigator would preclude the patient from enrollment in the open label extension phase or could interfere with the patient participating in or completing the study.

Milestones

First patient First Visit: 04-Dec-2013

First Interim Report: Cut-off date 10-Dec-2019

Second Interim Report: Cut-off date 01-Mar-2021 included in the initial MAA

Last patient Last Visit: 06-Sep-2023

Final Study Report submission planned: Aug-2024

DF112712 ASCEND Adults Phase 2/3 clinical trial - ongoing (Cat. 3)

Study short name and title

DF112712 - 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

Rationale and study objectives

To evaluate the efficacy, safety, PDs and PKs of olipudase alfa in adult patients with ASMD.

Primary objective:

To evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in.

- Spleen volume as measured by abdominal MRI.
 - Infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide.
-

Secondary objectives:

- To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks.
 - To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration.
 - To characterize the effect of olipudase alfa on the following endpoints assessed sequentially:
 - The effect of olipudase alfa on liver volume after 52 weeks of study drug administration
 - The effect of olipudase alfa on platelet count after 52 weeks of study drug administration
 - The effect of olipudase alfa after 52 weeks of study drug administration on fatigue
 - The effect of olipudase alfa after 52 weeks of study drug administration on pain
 - The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea
-

Study design

A Phase 2/3 clinical trial, multicenter, randomized, double-blinded, placebo-controlled, repeat-dose study.

The trial was divided into 2 consecutive major periods:

- A randomized placebo-controlled double-blind PAP from day 60 to week 52 followed by
 - An ETP that resulted in a total study period of up to 5 years and 3 months in duration.
-

Study populations

Adults, 18 years or older, with a documented deficiency of ASM, as measured by ASM activity in peripheral leukocytes, cultured fibroblasts, or lymphocytes; and a clinical diagnosis consistent with ASMD.

Primary Analysis Period: 36 (18 placebo, 18 olipudase alfa)

Extension Treatment Period: 36 (18 placebo/olipudase alfa, 18 olipudase alfa/olipudase alfa)

Milestones

First patient first visit: 17-Dec-2015

Last patient last visit for PAP: 17-Oct-2019

First Interim Report: Cut-off date 17-Oct-2019

Second Interim Report: Cut-off date 15-Mar-2021 included in the initial MAA

Last patient last visit for ETP: anticipated Oct-2023

Final Study Report submission planned: Aug-2024

ASM: Acid Sphingomyelinase; ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period; MAA: Marketing Authorization Application; MRI: Magnetic Resonance Imaging; PAP: Primary Analysis Period; PD: Pharmacodynamic; PK: Pharmacokinetic; SRS: Splenomegaly Related Score.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 30 - 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				

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
LTS13632 - A long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with ASMD Ongoing	To obtain data regarding the safety and efficacy of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa. <u>Primary objective:</u> To assess the long-term safety of olipudase alfa in patients with ASMD. <u>Secondary objective:</u> To assess the maintenance of effect of olipudase alfa and to characterize the PDs and PKs following long-term administration.	<ul style="list-style-type: none"> Immunogenicity: Infusion Associated Reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. Medication errors in home infusion setting. Long-term safety (beyond 2 years). 	First patient First Visit: First Interim Report: Second Interim Report: Last patient Last Visit: Final study Report submission planned:	04-Dec-2013 Cut-off date 10-Dec-2019 Cut-off date 01-Mar-2021 included in the initial MAA 06-Sep-2023 Aug-2024
DFI12712 ASCEND 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 Ongoing	To evaluate the efficacy, safety, PDs and PKs of olipudase alfa in adult patients with ASMD. <u>Primary objectives:</u> To evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in: <ul style="list-style-type: none"> Spleen volume as measured by abdominal MRI. Infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide. <u>Secondary objectives:</u> <ul style="list-style-type: none"> To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks. To characterize the effect of olipudase alfa on the 	<ul style="list-style-type: none"> Immunogenicity: Infusion Associated Reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. Medication errors in home infusion setting. Long-term safety (beyond 2 years). 	First patient First visit: Last patient Last Visit for PAP: First Interim Report: Second Interim Report: Last patient last visit for ETP: Final study Report submission planned:	17-Dec-2015 17-Oct-2019 Cut-off date 17-Oct-2019 Cut-off date 15-Mar-2021 included in the initial MAA Anticipated Oct-2023 Aug-2024

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	<p>patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration.</p>	<ul style="list-style-type: none"> • To characterize the effect of olipudase alfa on the following endpoints assessed sequentially: <ul style="list-style-type: none"> - The effect of olipudase alfa on liver volume after 52 weeks of study drug administration - The effect of olipudase alfa on platelet count after 52 weeks of study drug administration - The effect of olipudase alfa after 52 weeks of study drug administration on fatigue - The effect of olipudase alfa after 52 weeks of study drug administration on pain - The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea 		

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period; IAR: Infusion Associated Reaction; MAA: Marketing Authorization Application; MRI: Magnetic Resonance Imaging; PAP: Primary Analysis Period; PD: Pharmacodynamic; PK: Pharmacokinetic; SRS: Splenomegaly Related Score.



RISK MANAGEMENT PLAN 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.



RISK MANAGEMENT PLAN - 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 31](#)) and additional risk minimization measures (ie, educational materials) (see [Table 32](#)).

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 31 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Immunogenicity: <ul style="list-style-type: none"> • Infusion Associated Reactions (IARs), • Systemic hypersensitivity including anaphylactic reactions, • Anti-drug antibody (ADA) mediated hypersensitivity reactions 	Routine risk communication: <ul style="list-style-type: none"> • Labeled in sections 4.4 and 4.8 of the SmPC. • Labeled in section 4 of the PL. Routine risk minimization activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> • 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: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.
Foetal toxicity	Routine risk communication: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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.

Safety concern	Routine risk minimization activities
Use in lactating women	<p>Routine risk communication:</p> <ul style="list-style-type: none"> • Labeled in sections 4.6 and 5.3 of the SmPC. • Labeled in section 2 of the PL. <p>Routine risk minimization activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. <p>Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.</p>
Long-term safety (beyond 2 years)	<p>Routine risk communication: Labeled in section 4.8 of the SmPC.</p> <p>Routine risk minimization activities recommending specific clinical measures to address the risk: None</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.</p>

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

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 32 - Additional risk minimization measures

A HCP guide for HCPs in home infusion setting including nurses	
Objectives	<p>This guide is designed to support home infusion HCPs and nurses in managing the following risks associated with the home use of olipudase alfa:</p> <ul style="list-style-type: none"> • Immunogenicity: Infusion-associated reactions (IARs), systemic hypersensitivity including anaphylactic reactions, ADA mediated hypersensitivity reactions. • Medication errors in home infusion setting.
Rationale for the additional risk minimization activity	<p>The guide is considered necessary and complementary to the product information, to re-inforce the key safety messages/instructions associated with olipudase alfa use.</p> <p>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.</p>
Target audience and planned distribution path	<p>Target audiences: Healthcare professionals and nurses responsible for the preparation and/or administration of olipudase alfa in home setting.</p>

	<p><u>Distribution paths:</u> To be adapted country by country depending on each local situation and public health system: mail, face to face distribution, electronic (email, web link, QR Code/URL).</p> <p><u>Periodicity of the distribution:</u> One single distribution at launch, then redistribution (eg, once a year, ad-hoc) can occur according to local regulatory requirements or national health systems.</p>
Plans to evaluate the effectiveness of the interventions and criteria for success	<p><u>Plans to evaluate the effectiveness of the interventions:</u> 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.</p> <p><u>Criteria for judging success:</u> Implementation status of the distribution plan, at each participating country level. Routine pharmacovigilance.</p>
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.
Rationale for the additional risk minimization activity	<p>The patient card is considered necessary and complementary to the PL.</p> <ul style="list-style-type: none"> • 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. • 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	<p><u>Target audiences:</u> Acid Sphingomyelinase Deficiency patients and/or caregivers through the prescribing/treating physicians and/or HCPs administering the treatment.</p> <p><u>Distribution paths:</u> 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.</p> <p><u>Periodicity of the distribution:</u> 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.</p>

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immunogenicity: <ul style="list-style-type: none"> • Infusion Associated Reactions (IAR), • Systemic hypersensitivity including anaphylactic reactions, • Anti-drug antibody (ADA) mediated hypersensitivity reactions 	Routine risk minimization measures: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: None Additional pharmacovigilance activities: <ul style="list-style-type: none"> • Study LTS13632 • Study DFI12712 (ASCEND)
Medication errors in home infusion setting	Routine risk minimization measures: 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: None Additional pharmacovigilance activities: <ul style="list-style-type: none"> • Study LTS13632 • Study DFI12712 (ASCEND)
Foetal toxicity	Routine risk minimization measures: <ul style="list-style-type: none"> • 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: None
Use in lactating women	Routine risk minimization measures: <ul style="list-style-type: none"> • 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: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term safety (beyond 2 years)	Routine risk minimization measures: <ul style="list-style-type: none"> • Section 4.8 of the SmPC. • Legal status: Restricted medical prescription. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: <ul style="list-style-type: none"> • Study LTS13632 • Study DFI12712 (ASCEND)

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

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for XENPOZYME (Olipudase alfa)

This is a summary of the risk management plan (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 summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (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 an enzyme replacement therapy for the treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric 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 Chinese hamster ovary (CHO) cell line by recombinant deoxyribonucleic acid (DNA) technology. XENPOZYME is given by intravenous (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 in the next sections.

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 advise 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, outlined in the next sections.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including periodic safety update report (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” outlined in the next section.

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 34 - List of important risks and missing information

Important identified risk	Immunogenicity: <ul style="list-style-type: none"> • 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)

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

II.B Summary of important risks

Table 35 - 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 (eIND).
Risk factors and risk groups	<p><u>Systemic hypersensitivity and IARs:</u></p> <ul style="list-style-type: none"> • Patients with previous hypersensitivity/allergy to olipudase alfa and its excipients. • Available clinical data suggest children may have greater predisposition, compared to adults. <p>Additional risk characterization has not been fully established.</p> <p><u>Anti-drug antibody mediated hypersensitivity reactions:</u></p> <p>The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. Adults had a median ADA peak titer of 50 (range 50-3200) compared to pediatric patients with a median ADA peak titer of 200 (range 50-1600).</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • 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. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • A HCP Guide for HCPs in home infusion setting including nurses. • A Patient Card for patients/caregivers.
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Study LTS13632 • Study DFI12712 (ASCEND) <p>See Section II.C of this summary for an overview of the post-authorization development plan.</p>

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

Table 36 - 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	<p>Potential medication error is listed as an important potential risk in the RMP of other marketed ERTs for which home infusion setting is possible.</p> <p><u>Clinical trial experience:</u></p> <p>No medication errors have been identified by the time of data cutoff (15-Mar-2021).</p>
Risk factors and risk groups	Patients receiving medication in home infusion setting.

Medication errors in home infusion setting

Risk minimization measures	Routine risk minimization measures: Legal Status: Restricted medical prescription. Additional risk minimization measures: A HCP guide for HCPs in home infusion setting including nurses.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">• Study LTS13632• Study DFI12712 (ASCEND) See Section II.C of this summary for an overview of the post-authorization development plan.

ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; RMP: Risk Management Plan.

Table 37 - Important potential risk with corresponding risk minimization 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: <ul style="list-style-type: none">• 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.

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

Table 38 - Missing information with corresponding risk minimization activities: Use in lactating women

Use in lactating women	
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none">• Sections 4.6 and 5.3 of the SmPC.• Section 2 of the PL.• Legal status: Restricted medical prescription. Additional risk minimization measures: None

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

Table 39 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety (beyond 2 years)

Long-term safety (beyond 2 years)	
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> • Section 4.8 of the SmPC. • Legal status: Restricted medical prescription. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none"> • Study LTS13632 • Study DF112712 (ASCEND)

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 40 - Other studies in post-authorization development plan

LTS13632 - A long-term clinical trial (Cat. 3)

Purpose of the study:

To obtain data regarding the safety and efficacy of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa.

Primary objective:

To assess the long-term safety of olipudase alfa in patients with ASMD.

Secondary objective:

To assess the maintenance of effect of olipudase alfa and to characterize the PDs and PKs following long-term administration.

DF112712 ASCEND Adults Phase 2/3 clinical trial (Cat. 3)

Purpose of the study:

To evaluate the efficacy, safety, PDs and PKs of olipudase alfa in adult patients with ASMD.

Primary objectives:

To evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in:

- Spleen volume as measured by abdominal MRI.
- Infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide.

Secondary objectives:

- To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks.
- To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration.

-
- To characterize the effect of olipudase alfa on the following endpoints assessed sequentially:
 - The effect of olipudase alfa on liver volume after 52 weeks of study drug administration
 - The effect of olipudase alfa on platelet count after 52 weeks of study drug administration
 - The effect of olipudase alfa after 52 weeks of study drugs administration on fatigue
 - The effect of olipudase alfa after 52 weeks of study drug administration on pain
 - The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea
-

ASMD: Acid Sphingomyelinase Deficiency; MRI: Magnetic Resonance Imaging; PD: Pharmacodynamic; PK: Pharmacokinetic; SRS: Splenomegaly Related Score.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES



**ANNEX 4 SPECIFIC ADVERSE DRUG REACTION
FOLLOW-UP FORMS**

NOT APPLICABLE

**ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK
MINIMISATION 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:

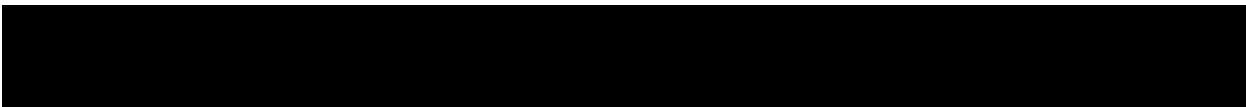
- HCP educational materials
- Patient/caregiver educational materials

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.

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- 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.

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.
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