For the use only of a Registered Medical Practitioner or a Hospital or Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

WARNING: To be sold by retail on the prescription of a specialist in Medicine only"

Xenpozyme ®

1.GENERIC NAME

Olipudase alfa Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg vial:

Each 20 mg vial contains 21.2 mg of olipudase alfa.

For the full list of excipients, see **Section 7. Description**

3. DOSAGE FORM AND STRENGTH

Powder for concentrate for solution for infusion.

Xenpozyme is a sterile, white to off-white lyophilized powder (20 mg in single-use vial).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Acid sphingomyelinase deficiency (ASMD)

Xenpozyme (Olipudase alfa) is indicated as enzyme replacement therapy for long-term treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

4.2.1 GENERAL

Xenpozyme administration should be supervised by a healthcare professional experienced in the administration of biological products and with access to appropriate medical support to manage potential severe reactions such as serious systemic hypersensitivity reactions. During the maintenance phase of treatment, Xenpozyme may be administered at home by a healthcare professional (See section 4.2.2 ADMINISTRATION).

Posology

Dose escalation phase

The rapid metabolism of accumulated sphingomyelin (SM) by Xenpozyme generates pro-inflammatory breakdown products, which may induce infusion-associated reactions and/or transient liver enzyme elevations. A dose escalation regimen can minimize the majority of these adverse events. (Refer section 6.1.2 REPEAT DOSE TOXICITY)

The recommended starting dose of Xenpozymeis 0.1 mg/kg for adults administered every 2 weeks (refer to missed doses subsection for additional guidance) and subsequently, the dose should be increased according to the dose escalation regimen presented in **Table 1**

Table 1: Dose escalation regimen in adults

Adult patients (≥18 years old)	
First dose (Day 1/Week 0)	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 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)	3 mg/kg (recommended maintenance dose)

Obtain baseline transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels within 1 month prior to treatment initiation. Obtain transaminase levels within 72 hours prior to the next dose during any dose escalation phases (Refer section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for additional monitoring and dose adjustment recommendations**)**

Maintenance phase
The recommended maintenance dosage of Xenpozymeis 3 mg/kg every 2 weeks.

Patients with BMI>30
In patients with a body mass index (BMI) >30, the body weight that is used to calculate the dose of Xenpozyme is estimated via the following method (for dose escalation and maintenance phases).
Body weight (kg) to be used for dose calculation = 30 × (actual height in m)^2

Example:
For a patient with: BMI of 38
body weight of 110 kg
height of 1.70 m.
The dose to be administered will be calculated using a body weight of 30 × 1.7^2 = 86.7 kg.

Missed doses
A dose is considered missed when not administered within 3 days of the scheduled date. When a dose of Xenpozyme is missed, administer the next dose as described below as soon as possible. Thereafter, administration should be scheduled every 2 weeks from the date of the last administration.
During the dose escalation phase:

- If 1 infusion is missed: administer the last tolerated dose, before resuming dose escalation, according to the dose escalation regimen in adults (**Table 1).**
- If 2 consecutive infusions are missed: administer 1 dose below the last tolerated dose (using a minimal dose of 0.3 mg/kg), before resuming dose escalation according to **Table 1.**
- If 3 or more consecutive infusions are missed: resume dose escalation at 0.3 mg/kg according to **Table 1**.

At the next scheduled infusion after a missed dose, if the dose administered is 0.3 or 0.6 mg/kg, that dose should be administered twice as per **Table 1**.

During the maintenance phase:

- If 1 maintenance infusion is missed: administer the maintenance dose and adjust the treatment schedule accordingly.
- If 2 consecutive maintenance infusions are missed: administer 1 dose below the maintenance dose (i.e., 2 mg/kg). Then for subsequent infusions, administer the maintenance dose (3 mg/kg) every 2 weeks.
- If 3 or more consecutive maintenance infusions are missed: resume dose escalation at 0.3 mg/kg according to **Table 1.**

SPECIAL POPULATIONS

Pediatric patients

The recommended starting dose of Xenpozyme is 0.03 mg/kg for pediatric patients, every 2 weeks and the dose should be subsequently increased according to the dose escalation regimen presented in **Table 2.**

Table 2: Dose escalation regimen in pediatric patients

Pediatric patients (0 to <18 years old)	
First dose (Day 1/Week 0)	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 mg/kg
Eighth dose (Week 14)	2 mg/kg
Ninth dose (Week 16)	3 mg/kg (recommended maintenance dose)

For monitoring of transaminase levels, see section on posology in adults.

Maintenance phase

The recommended maintenance dosage of Xenpozymeis 3 mg/kg every 2 weeks.

Patients with BMI>30

In patients with a body mass index (BMI) >30, the body weight that is used to calculate the dose of Xenpozyme is estimated via the following method (See section 4.2.1 GENERAL)

Body weight (kg) to be used for dose calculation = 30 × (actual height in m)^2

For missed doses, using the dose escalation regimen in pediatric patients (**Table 2**) as reference.

Elderly patients

Clinical studies with Xenpozyme included 2 patients between 65 and 75 years of age No dose adjustment is recommended for patients over the age of 65. (See section 5.3 Pharmacokinetic properties)

Hepatic and Renal impairment

No dose adjustment is recommended in patients with renal or hepatic impairment. (See section 5.3 Pharmacokinetic properties)

4.2.2 ADMINISTRATION

For instructions for the preparation of Xenpozyme before administration and volumes of administration. (See section 8.4.1 PREPARATION AND HANDLING)

Xenpozyme is for intravenous use only. Xenpozyme should be administered every 2 weeks by a healthcare professional. Infusions should be administered in a stepwise manner preferably using an infusion pump.

After reconstitution and dilution, the solution is administered as an intravenous infusion using infusion rates as described in **Table 3** and **Table 4**

Table 3: Infusion rates and duration of infusion in adult patients

Dose (mg/kg)	Infusion rate (mL/hr)	Duration of infusion (Approximate time in minutes)
0.1	Step 1: 20 mL/hr over 20 min (+/- 5 min) if no IAR Step 2: 60 mL/hr for 15 min (+/- 5 min) if no IAR	35
0.3 to 3	Step 1: 3.33 mL/hr over 20 min (+/- 5 min) if no IAR Step 2: 10 mL/hr over 20 min (+/- 5 min) if no IAR Step 3: 20 mL/hr over 20 min (+/- 5 min) if no IAR Step 4: 33.33 mL/hr for160 min (+/- 5 min) if no IAR	220

IAR: Infusion-associated reactions; min: minute

Table 4: Infusion rates and duration of infusion in pediatric patients

Dose (mg/kg)	Infusion rate (mg/kg/hr)	Duration of infusion (Approximate time in minutes)
0.03	0.1 mg/kg/hr for the length of the infusion if no IAR	18
0.1	Step 1: 0.1 mg/kg/hr over 20 min (+/- 5 min), if no IAR Step 2: 0.3 mg/kg/hr for the remainder of the infusion if no IAR	35
0.3	Step 1: 0.1 mg/kg/hr over 20 min	60

	(+/- 5 min), if no IAR Step 2: 0.3 mg/kg/hr over 20 min (+/- 5 min), if no IAR Step 3: 0.6 mg/kg/hr for the remainder of the infusion if no IAR	
0.6	Step 1: 0.1 mg/kg/hr over 20 min (+/- 5 min), if no IAR Step 2: 0.3 mg/kg/hr over 20 min (+/- 5 min), if no IAR Step 3: 0.6 mg/kg/hr over 20 min (+/- 5 min), if no IAR Step 4: 1 mg/kg/hr for the remainder of the infusion if no IAR	80
1		100
2		160
3		220

IAR: Infusion-associated reactions; min: minute

Monitor for signs and symptoms of IARs, such as headache, urticaria, pyrexia, nausea and vomiting, and other signs or symptoms of hypersensitivity, during the infusion. Slow, pause or discontinue the infusion, depending on the symptom severity, and initiate appropriate medical treatment, as needed.(See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

In case of severe hypersensitivity and/or anaphylactic reaction, immediately discontinue treatment with Xenpozyme. (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

At the end of infusion (once the syringe or infusion bag is empty), the infusion line should be flushed with 9 mg/mL (0.9%) of sodium chloride solution using the same infusion rate as the one used for the last part of the infusion.

Home infusion during maintenance phase:

Home infusion under the supervision of a healthcare professional may be considered for patients on maintenance dose (Refer section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION)) and who are tolerating their infusions well. The decision to have patients moved to home infusion should be made after evaluation and recommendation by the prescribing physician.

Appropriate medical support, including personnel trained in emergency measures, should be readily available when Xenpozyme is administered. If anaphylactic or other acute reactions occur, immediately discontinue the Xenpozyme infusion, initiate appropriate medical treatment and seek the attention of a physician. (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If severe hypersensitivity reactions occur, subsequent infusions should only occur in a setting where resuscitation measures are available. Dose and infusion rates should remain constant while at home and should not be changed without supervision of the prescribing physician. In case of missed doses or delayed infusion, the prescribing physician should be contacted.

4.3 CONTRAINDICATIONS

Xenpozyme is contraindicated:

- **In patients with life-threatening hypersensitivity (anaphylactic reaction) to olipudase alfa or to any of the excipients when tailored desensitization was unsuccessful**. (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1 Infusion associated reactions (IARs)

IARs occurred in approximately 58% of patients treated with Xenpozyme in clinical studies. These IARs included hypersensitivity reactions and acute phase reactions. (See section 4.8 Undesirable effects) **The most frequent IARs were headache, urticaria, pyrexia, nausea, and vomiting**. (See section 4.8 Undesirable effects) **IARs typically occurred between the time of infusion and up to 24 hours after infusion completion.**

Hypersensitivity/anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Xenpozyme treated patients. (Refer section 4.8 Undesirable effects)

In clinical studies, hypersensitivity reactions occurred in 7 (17.5%) adult and 9 (45%) pediatric patients including one pediatric patient who experienced anaphylaxis. **Independent of the clinical study program, a 16-month-old patient with ASMD type A treated with Xenpozyme experienced 2 anaphylactic reactions**. **In both pediatric patients with anaphylaxis, anti-olipudase alfa IgE antibodies were detected.** (See section 4.8.3 IMMUNOGENICITY)

Mild to moderate hypersensitivity reactions reported in more than one adult patient included urticaria, erythema, and pruritus (See section 4.8 Undesirable effects). In pediatric patients, mild to moderate hypersensitivity reactions reported in more than one patient included urticaria, erythema and rash (See section 4.8 Undesirable effects).

Management

Observe patients closely during and for an appropriate period after the infusion, based on clinical judgement. Inform patients of the potential symptoms of hypersensitivity/anaphylaxis and instruct them to seek immediate medical care should symptoms occur. IARs management should be based on the severity of signs and symptoms and may include temporarily interrupting the Xenpozyme infusion, lowering the infusion rate, and/or appropriate medical treatment.

If severe hypersensitivity or anaphylaxis occurs, Xenpozyme should be discontinued immediately, and appropriate medical treatment should be initiated. The patient who experienced anaphylaxis in the clinical study underwent a tailored desensitization regimen that enabled the patient to resume treatment with Xenpozyme. The risks and benefits of readministering Xenpozyme following anaphylaxis or severe hypersensitivity reaction should be considered. If considering readministration of Xenpozyme following anaphylaxis, the prescribing physician should contact Sanofi`s Medical Affairs for advice. In such patients, extreme caution should be exercised, with appropriate resuscitation measures available, when Xenpozyme is readministered.

Physicians may consider testing for anti-olipudase alfa IgE antibodies in patients who have experienced severe hypersensitivity reactions (See section 4.8.3 IMMUNOGENICITY).

If mild or moderate IARs occur, the infusion rate may be slowed or temporarily stopped, the duration of each step for an individual infusion increased, and/or the Xenpozyme dose reduced. If a patient requires a dose reduction, re-escalation should follow dose escalation

described in Table 1 and Table 2 for adult and pediatric patients, respectively. (Refer section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION)

Patients were not routinely premedicated prior to infusion of Xenpozyme in the clinical studies. Medications (e.g., antihistamines, antipyretics, glucocorticoids) were used prior to or after Xenpozyme infusions in some patients. However, the efficacy of these treatments in ameliorating mild to moderate recurrent hypersensitivity reactions has not been established.

4.4.2 Transient Transaminases elevation

Transient transaminase elevations (ALT or AST) within 24 to 48 hours after infusions were reported in 4 adult and 7 pediatric patients during the dose escalation phase with Xenpozyme in clinical studies. (See section 4.8 UNDESIRABLE EFFECTS). **At the time of the next scheduled infusion, these elevated transaminase levels generally returned to the levels observed prior to the Xenpozyme infusion.**

After 52 weeks of treatment, most patients with elevated transaminase levels at baseline had values within the normal range. (See section 4.8 UNDESIRABLE EFFECTS)

Transaminases (ALT and AST) levels should be obtained within 1 month prior to Xenpozyme treatment initiation (See section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION)). **During dose escalation or upon resuming treatment following missed doses, transaminases levels should be obtained within 72 hours prior to the next scheduled Xenpozyme infusion (If either the baseline or a pre-infusion transaminase level is >2 times the ULN during dose escalation, then additional transaminase levels should be obtained within 72 hours after the end of the infusion (**See section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION)). **If the transaminase levels are elevated above baseline and the ULN, the Xenpozyme dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld, based on clinical judgment.**

Upon reaching the recommended maintenance dose, transaminase testing can be performed as part of routine clinical management of ASMD.

4.5 DRUGS INTERACTIONS

No drug interaction studies have been performed. Because olipudase alfa is a recombinant human protein, no cytochrome P450 mediated drug-drug interactions are expected.

Functional inhibitors of acid sphingomyelinase: Based on published in silico and in vitro data, tricyclic antidepressants and some cationic amphiphilic drugs including antihistaminic drugs may decrease olipudase alfa activity. The clinical relevance of this functional inhibition is not known. This theoretical interaction should be considered when Xenpozymeis prescribed concomitantly with chronic systemic treatment with functional inhibitors of acid sphingomyelinase.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

4.6.1 PREGNANCY

Women of childbearing potential.
It is recommended to perform a pregnancy test prior to treatment initiation with Xenpozyme.

There are no available data on Xenpozyme use in pregnant women. Studies in animals have shown developmental toxicity (See section 6.1.5 REPRODUCTIVE AND DEVELOPMENTAL

TOXICITY**). Xenpozyme is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the fetus.**

4.6.2 LACTATION

There are no available data on the presence of Xenpozyme in human milk, effects on milk production or on the breastfed infant. Olipudase alfa was detected in the milk of lactating mice (See section 6.1.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY). When a drug is present in animal milk, it may be present in human milk. **No conclusions can be drawn regarding whether or not Xenpozyme is safe for use during breastfeeding. Xenpozyme should not be used during breastfeeding unless the potential benefits to the mother outweigh the potential risks, including those to the breastfed child.**

4.6.3 FERTILITY

No human data are available to determine potential effects of Xenpozyme on fertility in males and females. Animal data did not show any effect on male or female fertility in mice (Refer section 6.1.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Because dizziness and hypotension have been reported in clinical studies, Xenpozymemay have a minor influence on the ability to drive and use machines(See section 4.8 UNDESIRABLE EFFECTS).

4.8 UNDESIRABLE EFFECTS

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;

Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

4.8.1 CLINICAL TRIALS

Summary of the safety profile

The pooled safety analysis from 4 clinical studies (DFI13412, DFI12712/ASCEND, DFI13803/ASCEND-Peds, and LTS13632) included a total of 60 patients (40 adult and 20 pediatric patients) treated with Xenpozyme at doses up to 3 mg/kg every 2 weeks.

Serious adverse reactions were reported in 1 (2.5%) adult patient and 4 (20%) pediatric patients. The adult patient had an event of extrasystoles in the context of a history of cardiomyopathy. In pediatric patients, the serious adverse reactions were anaphylactic reaction, urticaria, rash, hypersensitivity, and alanine aminotransferase level increase. No adverse reactions led to permanent treatment discontinuation.

The most frequently reported adverse drug reactions (ADRs) (occurring in ≥10% of Xenpozyme patients) were headache, pyrexia, urticaria, nausea, vomiting, abdominal pain, myalgia, pruritus, and C-reactive protein increased. ADRs reported in at least 2 patients treated with Xenpozyme in the pooled safety analysis of clinical studies are listed in **Table 5.**

Table 5 Adverse drug reactions occurring in at least 2 patients treated with Xenpozyme in

pooled safety analysis of clinical studies

System Organ Class	Frequency	
	Very common	Common
Blood and lymphatic system disorders		Lymph node pain
Immune system disorders		Anaphylaxis and hypersensitivity*
Nervous system disorders	Headache	Dizziness, lethargy, migraine
Cardiac disorders		Palpitations
Vascular disorders		Flushing, hypotension
Respiratory, thoracic, and mediastinal disorders		Dyspnoea, cough
Gastrointestinal disorders	Nausea, vomiting, abdominal pain	Abdominal pain upper, diarrhoea, abdominal discomfort, abdominal pain lower, aphthous ulcer, dyspepsia, flatulence
Hepatobiliary disorders		Hepatic pain
Skin and subcutaneous tissue disorders	Urticaria, pruritus	Rash, erythema, rash macular, macule, papule
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia, musculoskeletal chest pain, back pain, joint swelling, neck pain, pain in extremity, bone pain, muscle spasm, musculoskeletal discomfort
Renal and urinary disorders		Renal pain
General disorders and administration site conditions	Pyrexia	Fatigue, chills, asthenia, non-cardiac chest pain, pain
Investigations	C-reactive protein increased	Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, serum ferritin increased, body temperature increased, prothrombin time prolonged, weight increased

*** Based on Standard MedDRA Query (instead of Preferred Terms)**

<u>Infusion-associated reactions (IARs), including hypersensitivity/anaphylactic reactions</u>

IARs were reported in 22 of 40 (55%) adult and 13 of 20 (65%) pediatric patients. IAR symptoms reported in at least 3 adult patients (≥7.5%) were headache (22.5%), nausea (15%), urticaria (12.5%), arthralgia (10%), myalgia (10%), pyrexia (10%), pruritus (7.5%), vomiting (7.5%), and abdominal pain (7.5%). IAR symptoms reported in at least two pediatric patients (≥10%) were pyrexia (40%), urticaria (35%), vomiting (30%), headache (20%), nausea (20%), and rash (15%). IARs typically occurred between the time of infusion and 24 hours after infusion end. The majority of IARs were assessed as mild or moderate.

Hypersensitivity-related IARs, including anaphylaxis, occurred in 16 (26.7%) patients, 7 (17.5%) adult and 9 (45%) pediatric patients in clinical studies. The most frequently reported hypersensitivity related IAR symptoms were urticaria (20%), pruritus (6.7%), erythema (6.7%), and rash (5%).

One pediatric patient in the clinical studies incurred a severe anaphylactic reaction Error! Bookmark not defined.**. Also, independent of the clinical study program, a 16-month-old patient with ASMD type A treated with Xenpozyme experienced 2 anaphylactic reactions. Anti-olipudase alfa IgE antibodies were detected in both pediatric patients.**

In 2 adult and 3 pediatric patients, IAR symptoms were associated with changes in laboratory parameters (e.g., C-reactive protein, ferritin value) indicative of acute phase reaction, as reported by the investigator.

Transaminase elevations

Transient transaminase (ALT or AST) elevations within 24 to 48 hours after infusion occurred in some patients treated with Xenpozyme during the dose escalation phase in the clinical studies. These elevations generally returned to the previous pre-infusion transaminase levels by the next scheduled infusion.

Overall, after 52 weeks of treatment with *TM*, mean ALT decreased by 45.9% and mean AST decreased by 40.2%, compared to baseline levels. In adult patients, all 16 patients with an elevated baseline ALT had an ALT within the normal range and 10 of 12 adult patients with an elevated baseline AST had an AST within the normal range.

ASCEND study in adult patients (Study 1)

In the DFI12712/ASCEND study, 36 adult patients were randomized in a 1:1 ratio to receive either Xenpozyme or placebo. Treatment was administered in both groups once every 2 weeks for 52 weeks (primary analysis period [PAP]). Patients received Xenpozyme at doses escalating from 0.1 mg/kg to a target dose of 3 mg/kg. (See section 5.2.1 clinical efficacy/ clinical study).

The most frequently reported adverse events in both treatment groups during the PAP were headache, nasopharyngitis, upper respiratory tract infection, cough, and arthralgia. Serious adverse events were reported in 3 patients treated with Xenpozyme and 4 patients receiving the placebo during the PAP; none was considered treatment related. No serious adverse event led to permanent treatment discontinuation.

Table 6 presents the adverse events that occurred in at least 2 (≥10%) adult patients treated with Xenpozyme during the PAP and at a higher incidence than in the placebo group.

Table 6 Adverse Events Reported in ≥10% of Xenpozyme Patients during PAP with a Higher Incidence in Xenpozyme Group Versus Placebo Group

System Organ Class	Preferred Term	Placebo (N=18)	Olipudase alfa (N=18)
Nervous system disorders	Headache	8 (44.4%)	12 (66.7%)
Infections and infestations disorders	Nasopharyngitis	6 (33.3%)	8 (44.4%)
	Upper respiratory tract infection	4 (22.2%)	6 (33.3%)
Respiratory, thoracic, and	Cough	2 (11.1%)	5 (27.8%)
	Oropharyngeal pain	1 (5.6%)	3 (16.7%)

mediastinal disorders	**Throat irritation**	**0**	**2 (11.1%)**
Musculoskeletal and connective tissue disorders	**Arthralgia**	**3 (16.7%)**	**4 (22.2%)**
	Myalgia	**0**	**3 (16.7%)**
Gastrointestinal disorders	**Diarrhea**	**2 (11.1%)**	**3 (16.7%)**
	Constipation	**0**	**2 (11.1%)**
	Dyspepsia	**0**	**2 (11.1%)**
Vascular disorders	**Epistaxis**	**1 (5.6%)**	**2 (11.1%)**
Eye disorders	**Ocular hyperemia**	**1 (5.6%)**	**2 (11.1%)**

Over the duration of the study, which includes an open-label extended treatment period of more than 4 years, the adverse events reported in at least 6 patients (≥15%) were headache, (60%), nasopharyngitis (37.1%), nausea (34.3%), upper respiratory tract infection (31.4%), arthralgia (25.7%%), pruritus (25.7%), abdominal pain (25.7%), abdominal pain upper (25.7%), back pain (25.7%), pyrexia (22.9%), myalgia (22.9%), cough (22.9%), diarrhea (17.1%), fatigue (17.1%), urinary tract infection (17.1%) and procedural pain (17.1%).No adverse event led to permanent treatment discontinuation.

ASCEND-Peds study (Study 2)

In the DFI13803/ASCEND-Peds study, 20 pediatric patients <18 years of age received Xenpozyme once every 2 weeks for 64 weeks (See section 5.2.1 clinical efficacy/clinical study section).

Adverse Events that occurred in at least 4 patients (≥20%) were pyrexia (75%), cough (70%), vomiting (60%), diarrhea (55%), nasopharyngitis (55%), upper respiratory tract infection (40%), headache (40%), contusion (30%), abdominal pain (30%), nasal congestion (30%), rash (30%), urticaria (20%), epistaxis (20%), and scratch (20%).Three patients experienced serious adverse events related to Xenpozyme treatment: anaphylactic reaction, alanine aminotransferase elevations, urticaria, and rash. No serious adverse event resulted in permanent treatment discontinuation.

Except for a higher incidence of hypersensitivity-related IARs in pediatric patients compared to adults, the safety profile of Xenpozyme in pediatric and adult patients was similar.

Long-term Use

Overall, the pattern of adverse events observed in adult and pediatric patients who participated in the respective clinical study extension phases was consistent with that observed during the predecessor studies.

4.8.2 POSTMARKETING

Not Applicable.

4.8.3 IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity to Xenpozyme.

Immunogenicity was evaluated in adult patients from 3 clinical studies (DFI13412, DFI12712/ASCEND, and LTS13632) and in pediatric patients from 2 clinical studies (DFI13803/ASCEND-Peds, and LTS13632).

In adult patients, 16 out of 40 (40%) patients treated with Xenpozyme developed treatment-emergent antidrug antibodies (ADA). The median time to seroconversion from first Xenpozyme infusion was approximately 33 weeks. All adult patients except two (intermediate response with ADA titer of 800 and 3200) had a low ADA response (≤400) with a median IgG peak titer of 75. Four out of these 16 adult patients had neutralizing antibodies (NAb) that inhibited the olipudase alfa activity, but only one patient had NAb at more than one time point. None of the patients developed NAb that inhibited the cellular uptake of olipudase alfa.

In pediatric patients, 13 out of 20 (65%) pediatric patients treated with Xenpozyme developed treatment-emergent ADA. The median time to seroconversion from first Xenpozyme infusion was 10 weeks. The majority (9 out of 12) of pediatric patients with a treatment-induced response had a low ADA response with a median ADA peak titer of 200 and 3 patients had an intermediate response with ADA peak titer ranging between 800 to 1600. One patient had a treatment boosted ADA response. Five out of the 13 pediatric patients developed NAb that inhibited olipudase alfa activity, but only two patients had NAb at more than one time point. None of the patients developed Nab that inhibited the cellular uptake of olipudase alfa. One pediatric patient experienced an anaphylactic reaction and developed IgE ADA, and IgG ADA with a peak titer of 1600.

IgE ADA testing may be considered for patients who experienced a severe hypersensitivity reaction to olipudase alfa (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No effect of ADA was observed on pharmacokinetics and efficacy of Xenpozyme in adult and pediatric populations. There was a higher percentage of patients with treatment-emergent IARs (including hypersensitivity reactions) in patients who developed treatment-emergent ADA versus those who did not (75.9% versus 41.9%). The IARs were manageable and did not result in discontinuation of treatment.

4.9 OVERDOSE

Signs and symptoms

There has been no overdose of olipudase alfa reported in clinical studies Using a dose escalation regimen, intravenous doses of Xenpozyme up to 3 mg/kg have been administered in clinical studies.

Management

There is no known specific antidote for Xenpozyme overdose. For the management of adverse reactions linked to Xenpozyme overdose. (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 UNDESIRABLE EFFECTS).

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST

None specified.

ABUSE AND DEPENDENCE

Xenpozyme does not cross the brain-blood barrier in animal models, therefore no abuse or dependence effects are anticipated.

5 PHARMACOLOGY

5.1 MECHANISM OF ACTION

Acid sphingomyelinase deficiency (ASMD) is a rare and potentially life-threatening lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene. The phenotype spectrum ranges from the severe infantile neurovisceral form (ASMD type A, historically known as Niemann-Pick disease type A) to the chronic visceral form (ASMD type B, Niemann-Pick disease type B), with an intermediate or chronic neurovisceral phenotypic presentation also being described (ASMD type A/B, Niemann-Pick disease Type A/B).

ASM catalyzes the hydrolysis of SM to ceramide and phosphocholine. The enzymatic deficiency causes an intracellular accumulation of SM (as well as cholesterol and other cell membrane lipids) in organs including the spleen, liver, bone marrow, lungs, lymph nodes and brain.

Olipudase alfa (recombinant human acid sphingomyelinase) provides an exogenous source of ASM reducing SM accumulation in organs of patients with ASMD.

Xenpozyme is not expected to cross the brain-blood barrier or modulate the CNS manifestations of the disease.

5.2 PHARMACODYNAMIC PROPERTIES

Ceramide and lyso-sphingomyelin (a deacylated form of SM) were used for the assessment of the pharmacodynamic activity of Xenpozyme patients with ASMD.

Following repeated administration of Xenpozyme in both adult and pediatric patients, plasma ceramide levels showed a transient increase after each dose (post-infusion), with a gradual decrease in the plasma levels over the treatment period. In the DFI12712/ASCEND study, the Least Squares (LS) mean percentage change from baseline to Week 52 (Standard Error, SE) in pre-infusion plasma ceramide level was -36.4% (5.3) in the Xenpozyme treatment group compared to -0.2% (5.6) in the placebo group. In pediatric patients, LS mean pre-infusion plasma ceramide level was reduced by 57% (SE: 5.1) compared to baseline following 52 weeks of treatment.

Lyso-sphingomyelin is substantially elevated in plasma of adult and pediatric ASMD patients. After repeated administration of *TM*, plasma lyso-sphingomyelin levels declined significantly, reflecting reduction of sphingomyelin content in tissue. In the DFI12712/ASCEND study, the LS mean percentage change from baseline to Week 52 (SE) in pre-infusion plasma lyso-sphingomyelin level was -77.7 % (3.9) in the Xenpozyme treatment group compared to -5% (4.2) in the placebo group. In pediatric patients, LS mean plasma pre-infusion lyso-sphingomyelin level was reduced by 87.2% (SE: 1.3) as compared to baseline following 52 weeks of treatment.

In adult patients, the liver sphingomyelin content, as assessed by histopathology, decreased by 92% (SE: 8.1) from baseline to Week 52 in the Xenpozyme treatment group (compared to +10.3% (SE: 7.8) in the placebo group).

5.2.1 CLINICAL EFFICACY/CLINICAL STUDIES

The efficacy of Xenpozyme has been evaluated in 3 clinical studies (DFI12712/ASCEND study in adult patients, DFI13803/ASCEND-Peds study in pediatric patients and LTS13632 extension study in adult and pediatric patients) involving a total of 61 patients with ASMD.

Clinical Study in adult patients:

The ASCEND study is a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III study in adult patients with ASMD (clinical diagnosis consistent with ASMD type B and

A/B). A total of 36 patients were randomized in a 1:1 ratio to receive either Xenpozyme or placebo. Treatment was administered in both groups as an IV infusion once every 2 weeks. Patients receiving Xenpozyme were up titrated from 0.1 mg/kg to a target dose of 3 mg/kg. The study was divided into 2 consecutive periods: a randomized placebo-controlled, double-blinded primary analysis period (PAP) which lasted to Week 52, followed by an extension treatment period (ETP) for up to 4 years. Patients randomized to the placebo arm in the PAP crossed over to active treatment in the ETP to reach the targeted dose of 3 mg/kg, while patients in the original Xenpozyme arm continued treatment. The longest study duration per patient was of up to 5 years and 3 months.

Patients enrolled in the study had a diffusion capacity of the lungs for carbon monoxide (DLco)≤70% of the predicted normal value, a spleen volume ≥6 multiples of normal (MN) measured by magnetic resonance imaging (MRI) and scores ≥5 in splenomegaly related score (SRS). Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 30 years (range: 18-66). Two patients (11.1%) with mild renal impairment (60 mL/min ≤ creatinine clearance < 90 mL/min) were included in each group. There were no patients with moderate or severe renal impairment.

EU and ROW

This study included 2 separate primary efficacy endpoints: the percentage change in DLco (in % predicted of normal) and spleen volume (in MN), as measured by MRI, from baseline to Week 52.

Secondary efficacy endpoints included the percentage change in liver volume (in MN) and platelet count from baseline to Week 52.

Improvements in mean percent change in % predicted DLco (p=0.0004) and spleen volume (p<.0001) as well as in mean liver volume (p<.0001) and platelet count (p=0.0185) were observed in the Xenpozyme group as compared to the placebo group during the 52-week primary analysis period (see Table 7, Figure 1and Figure 2). A significant improvement in mean percent change in % predicted DLco, spleen volume, liver volume and platelet count was noted at Week 26 of treatment, the first postdose endpoint assessment.

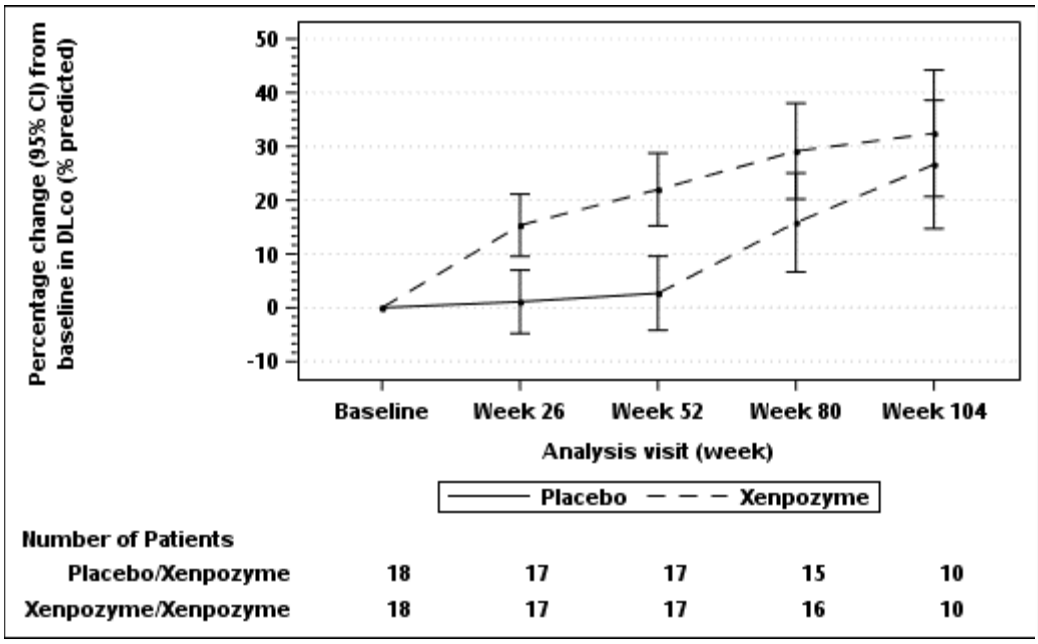
Table 7 - Mean (SD) values for efficacy endpoints at baseline and LS mean percentage change (SE) from baseline to Week 52.

	Placebo (n=18)	Xenpozyme(n=18)	Difference [95% CI]	p value*
Primary Endpoints				
Mean % predicted DLco at baseline	48.45 (10.77)	49.44 (10.99)	NA	NA
Percent change in % predicted DLco from baseline to Week 52	2.96 (3.38)	21.97 (3.34)	19.01 (4.76) [9.32, 28.70]	0.0004
Mean spleen volume (MN) at baseline	11.21 (3.84)	11.70 (4.92)	NA	NA
Percent change in Spleen volume from baseline to Week 52	0.48 (2.50)	-39.45 (2.43)	-39.93 (3.50) [-47.05, -	<0.0001

			32.80]	
Secondary endpoints				
Mean liver volume (MN) at baseline	1.62 (0.50)	1.44 (0.32)	NA	NA
Percent change in Liver volume from baseline to Week 52	-1.47 (2.54)	-28.06 (2.49)	-26.60 (3.59) [-33.91, -19.28]	<0.0001
Mean platelet count (10^9/L) at baseline	115.58 (36.27)	107.18 (26.93)	NA	NA
Percent change in Platelet Count from baseline to Week 52	2.49 (4.19)	16.82 (3.96)	+14.33 (5.78) [2.56, 26.10]	0.0185

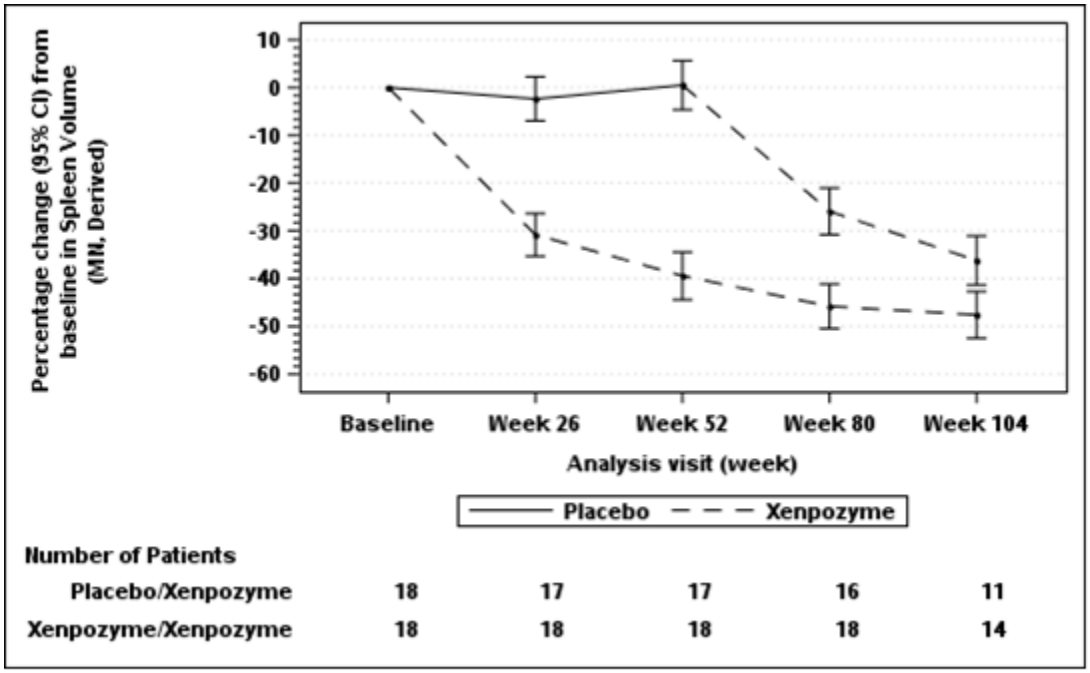
*Statistically significant after multiplicity adjustment

Figure 1: Plot of the LS means (95%CI) of the percentage change in DLco (% predicted) from baseline to Week 104 - mITT population



The vertical bars represent the 95% CIs for the LS means.
The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week104.
Patients in placebo/Xenpozyme group received placebo by Week 52 and switched to Xenpozyme thereafter.

Figure 2: Plot of the LS means (95%CI) of the percentage change in spleen volume (MN) from baseline to Week 104 - mITT population



The vertical bars represent the 95% CIs for the LS means.
The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week104
Patients in placebo/Xenpozyme group received placebo by Week 52 and switched to Xenpozyme thereafter.

US only

The study included 2 separate primary efficacy endpoints: the percentage change in DLco (in % predicted of normal) from baseline to Week 52, and the percentage change in spleen volume (in MN) measured by MRI, combined with the change in patient perception related to spleen volume measured by splenomegaly-related score (SRS) from baseline to Week 52 (referred to as the combination spleen endpoint).

Secondary efficacy endpoints included the percentage change in liver volume (in MN) and platelet count from baseline to Week 52.

An improvement in the mean percent change in % predicted DLco was observed in the Xenpozyme group as compared to the placebo group during the 52-week primary analysis period (p=0.0004). A reduction in spleen volume was observed in the Xenpozyme group as compared to the placebo group at Week 52 (p<0.0001). However, since the reduction in SRS score was not statistically different between both groups (p=0.636), the combination spleen endpoint was not met.

An improvement in mean percent change in % predicted DLco and spleen volume was already noted at Week 26 of treatment, the first postdose endpoint assessment.

The results are presented in Table 8, Figure 1 and Figure 2.

Table 8 -: LS Mean Percentage Change (SE) or Change (SE) from Baseline to Week 52 for Primary Endpoints

	Placebo (n=18)	TRADENAME (n=18)	Difference [95% CI]	p value

Mean % predicted DLco at baseline	48.45 (10.77)	49.44 (10.99)	NA	NA
Percent change in % predicted DLco	2.96 (3.38)	21.97 (3.34)	19.01 (4.76) [9.32, 28.70]	0.0004*
Components of the spleen combination endpoint:				
Mean spleen volume (MN) at baseline	11.21 (3.84)	11.70 (4.92)	NA	NA
Percent change in Spleen Volume (in MN)	0.48 (2.50)	-39.45 (2.43)	-39.93 (3.50) [-47.05, -32.80]	<0.0001*
Mean SRS score † (MN) at baseline	28.05(10.56)	24.55 (11.13)	NA	NA
Change in SRS score	-9.28 (2.42)	-7.66 (2.35)	+1.62 (3.39) [-5.30, 8.54]	0.636

* Statistically significant after multiplicity adjustment

The Splenomegaly-Related Score rates the 5 following patient-reported items: abdominal pain, abdominal discomfort, early satiety, abdominal body image, and ability to bend down.

Insert Figures 1 and 2 (same as for EU and ROW)

A decrease in mean liver volume and an increase in mean platelet count were noted in the Xenpozyme group as compared to the placebo group at Week 52 (see

Table **9**).

Table 9: LS Mean Percentage Change (SE) or Change (SE) from Baseline to Week 52 for Secondary Endpoints.

	Placebo (n=18)	**TRADENAME (n=18)**	**Difference [95% CI]**
Mean liver volume (MN) at baseline	1.62 (0.50)	1.44 (0.32)	NA
Percent change in Liver volume from baseline to Week 52	-1.47 (2.54)	-28.06 (2.49)	-26.60 (3.59) [-33.91, -19.28]
Mean platelet count (109/L) at baseline	115.58 (36.27)	107.18 (26.93)	NA
Percent change in Platelet Count from baseline to Week 52	2.49 (4.19)	16.82 (3.96)	+14.33 (5.78) [2.56, 26.10]

The study utilized a sequential testing procedure to control the Type-I error rate for the multiple secondary endpoints if both primary endpoints reach statistical significance. Since one of the

primary endpoints did not reach statistical significance, formal hypothesis testing was terminated for all secondary endpoints.

All regions

Seventeen of 18 patients previously receiving placebo and 18 of 18 patients previously treated with Xenpozyme for 52 weeks (PAP) started or continued treatment with Xenpozyme respectively, for up to 4 years. At Week 104, patients initially randomized to placebo had received Xenpozyme for 52 weeks and demonstrated the following changes in clinical parameters from baseline (before first administration of Xenpozyme): mean (SE) percent increase in % predicted DLco was 28.04% (6.16) (see Figure 1); mean (SE) percent reduction in spleen volume (MN) was 35.93% (2.99) i (see Figure 2); mean (SE) percent reduction in liver volume (MN) was 30.66 (2.45) mean (SE) percent increase in platelet count was 21.73 (6.43)

Patients in the previous Xenpozyme group demonstrated sustained improvement from baseline to Week 104 in the following parameters: mean (SE) percent increase in % predicted DLco was 28.49 (6.16) (see Figure 1); mean (SE) percent reduction in spleen volume (MN) was 46.95 (2.65) (see Figure 2); mean (SE) percent reduction in liver volume (MN) was 33.42 (2.16) mean (SE) percent increase in platelet count was 24.94 (6.91)

Clinical Study in pediatric patients:

The ASCEND-Peds study (Phase 1/2 clinical study) is a multi-center, open-label, repeated-dose study to evaluate the safety and tolerability of Xenpozyme administered for 64 Weeks in pediatric patients aged <18 years with ASMD (clinical diagnosis consistent with ASMD type B and A/B). In addition, exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at Week 52.

A total of 20 patients (4 adolescents from 12 to <18 years old, 9 children from 6 to <12 years old, and 7 infants/children < 6 years old) were up titrated with Xenpozyme via a dose escalation regimen from 0.03 mg/kg to a target dose of 3 mg/kg. Treatment was administered as an IV infusion once every 2 weeks for up to 64 weeks.

Patients enrolled in the study had a spleen volume ≥5 MN measured by MRI. Patients were distributed across all age cohorts from 1.5 to 17.5 years old, with both sexes equally represented.

Treatment with Xenpozyme resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and linear growth progression (as measured by Height Z-scores) at Week 52 as compared to baseline (see Table 10).

Table 10: LS Mean percentage change (SE) or change (SD) from baseline to Week 52 (all age cohort)

	Baseline value (n=20)	**Week 52 (n=20)**
Mean % predicted DLco (SD)	54.79 (14.23)	71.66 (14.80)
Percent change in % predicted DLco* 95% CI P value		32.94 (8.27) 13.37, 52.50 0.0053
Mean spleen volume (MN) (SD)	18.98 (8.77)	9.27 (3.89)
Percent change in Spleen Volume (in MN) 95% CI		-49.21 (1.99) -53.39, -45.04 <.0001

P value		
Mean liver volume (MN) (SD) Percent change in Liver Volume (in MN) 95% CI P value	2.65 (0.74)	1.53 (0.32) -40.56 (1.67) -44.07, -37.05 <.0001
Mean platelet count (109/L) (SD) Percent change in Platelet Count 95% CI P value	137.74 (62.32)	173.61 (60.46) 34.03 (7.63) 17.94, 50.13 0.0003
Mean Height Z-scores (SD) Change in Height Z-scores 95% CI P value	-2.14 (0.84)	-1.64 (0.78) 0.56 (0.385) (0.377,0.733) <0.0001

*DLco was evaluated in 9 pediatric patients aged ≥ 5 years who were able to perform the test
a: Nominal p value

The effects of Xenpozyme on spleen and liver volumes, and height z-scores were similar across all pediatric age cohorts included in the study.

Although different studies designs were employed, efficacy results in adult and pediatric populations were consistent.

Extension study in adult and pediatric patients:

Patients who participated in the DFI13412 (open label ascending dose study in adult ASMD patients) or DFI13803/ASCEND-Peds studies continued treatment in an open-label extension study (LTS13632). Five adult patients from the DFI13412 study and 20 pediatric patients from the DFI13803/ASCEND-Peds study received Xenpozyme at 3 mg/kg once every 2 weeks by IV infusion for up to >7 years and >5 years in adults and pediatric patients, respectively.

Sustained improvements in % predicted DLco, spleen and liver volume and platelet count, compared to baseline, were noted in adult and pediatric patients over the course of the study. In addition, pediatric patients (all age cohorts) showed a continued improvement in Height Z-score and an improvement in bone age (by hand X-ray) at Month 48, indicating that bone age was getting closer to chronological age.**Error! Bookmark not defined.**

5.3 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of olipudase alfa were assessed in 49 adult ASMD patients from all clinical studies, receiving single or multiple administrations.

Olipudase alfa exhibited linear pharmacokinetics over the dose range of 0.03 to 3 mg/kg. Following a dose escalation regimen from 0.1 mg/kg to the maintenance dose of 3 mg/kg administered once every 2 weeks, there was minimal accumulation in plasma levels of olipudase alfa. At the dose of 3 mg/kg administered once every 2 weeks, the mean (percent coefficient of variation, CV%) maximum concentration (C_{max}) and area under the concentration-time curve over a dosing interval ($AUC_{0-\tau}$) at steady state were 30.2 µg/mL (17%) and 607 µg.h/mL (20%), respectively.

Absorption

There is no absorption since Xenpozyme is administered intravenously.

Distribution

The estimated mean (CV%) volume of distribution of olipudase alfa is 13.1 L (18%)

Metabolism

Olipudase alfa is a recombinant human enzyme and is expected to be eliminated via proteolytic degradation into small peptides and amino acids.

Elimination

The mean (CV%) clearance of olipudase alfa is 0.331 L/h (22%). The mean terminal half-life ($t_{1/2}$) ranged from 31.9 to 37.6 hours.

Special populations

Gender

There were no clinically relevant differences in olipudase alfa pharmacokinetics based on gender.

Race

There is limited information of olipudase alfa pharmacokinetics in non-Caucasian ethnic groups.

Elderly (≥ 65 years old)

There is limited information on olipudase alfa pharmacokinetics in elderly patients (only 2 patients between 65 and 75 years of age included in clinical studies with Xenpozyme)

Pediatric

The PK of olipudase alfa were assessed in 20 pediatric patients including 4 adolescent patients, 9 child patients and 7 child/infant patients (Table 11). Olipudase alfa exposures were lower in pediatric patients compared to those in adult patients. These differences were not considered to be clinically relevant.

Table 11 - Mean (CV%) of olipudase alfa PK parameters following administration of 3 mg/kg every 2 weeks in adolescent, child, and child/infant patients with ASMD

Age Group	Age (year)	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg.h/mL)
Adolescent (n=4)	12, < 18	27.5 (8)	529 (7)
Child (n=9)	6, <12	24 (10)	450 (15)
Child/Infant (n=7)	< 6	22.8 (8)	403 (11)

Descriptive statistics represent the post hoc estimates of steady-state exposures using population PK analysis. AUC0-τ: area under the plasma concentration versus time curve over a dosing interval; Cmax: maximum plasma concentration; n: total number of patients.

Hepatic Impairment

Olipudase alfa is a recombinant protein and is expected to be eliminated by proteolytic degradation. Therefore, impaired liver function is not expected to affect the pharmacokinetics of olipudase alfa.

Renal Impairment

There were no clinically relevant differences in olipudase alfa pharmacokinetics in patients with mild renal impairment. The impact of moderate to severe renal impairment on the pharmacokinetics of olipudase alfa is not known. Olipudase alfa is not expected to be eliminated through renal

excretion. Therefore, renal impairment is not expected to affect the pharmacokinetics of olipudase alfa.

6 NONCLINICAL SAFETY DATA

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

6.1.1 SINGLE DOSE TOXICITY

In mice, rats, dogs, and monkeys, a single IV administration of olipudase alfa was well-tolerated up to 12, 30, 30, and 30 mg/kg (highest doses tested in each study), respectively.

In acid sphingomyelinase knockout (ASMKO) mice (a disease model for ASMD), single doses of olipudase alfa resulted in mortality at doses ≥ 10 mg/kg administered as an IV bolus injection[ii]. Observations (lethargy, coolness to touch, and unwillingness to move), combined with the adrenal hemorrhage, suggested that hypotensive shock may be the cause of death. These findings were accompanied by elevations of ceramide, sphingosine and sphingosine 1-phosphate in the serum, catabolites of accumulated sphingomyelin as well as elevations in the serum concentrations of inflammatory mediators, such as cytokines and acute phase proteins.
Dose-related microscopic findings consisting of focal areas of necrosis and apoptosis in the liver and adrenal glands, and hemorrhage in the adrenal glands were noted.

The lack of adverse findings in BALB/c, C57BL/6 mice, rats, dogs, and monkeys at comparable olipudase alfa doses suggested that the dose-related toxicity observed in ASMKO mice may be due to the rate and amount of substrate degradation.

6.1.2 REPEAT DOSE TOXICITY

Repeat dose toxicology studies were conducted in ASMKO mice, Sprague-Dawley rats and Cynomolgus monkeys.

Although mortality was observed in ASMKO mice after a single dose ≥ 10 mg/kg administered as an IV bolus injection, repeated dose studies in ASMKO mice show that administration of olipudase alfa via a dose escalation regimen, 3 mg/kg administered IV every other day, followed by a single IV dose of 20 mg/kg 3 days later, did not result in compound-related mortality and reduced the severity of other toxicity findings. When olipudase alfa was administered every 2 weeks, the no-observed-adverse-effect-level (NOAEL) in ASMKO mice was 3 mg/kg; however, when a dose escalation regimen of olipudase alfa was employed prior to every 2 weeks dosing, the NOAEL for olipudase alfa was ≥30 mg/kg.

The biweekly IV administration of olipudase alfa to Sprague Dawley rats (bolus injection) and Cynomolgus monkeys (30-minute infusion) for 26 weeks did not result in compound-related adverse effects at doses up to 30 mg/kg/administration[iii]. The NOAEL was considered to be 30 mg/kg/administration, corresponding to exposures 2.3 to 3.9-fold those in patients at therapeutic dose.

The assessment of local tolerability was incorporated into the repeat-dose toxicology study in Cynomolgus monkeys by macroscopic and microscopic evaluation of the IV infusion sites. No findings related to olipudase alfa administration were observed.

6.1.3 GENOTOXICITY

No studies were conducted to evaluate genotoxicity of olipudase alfa.

6.1.4 CARCINOGENICITY

No studies were conducted to evaluate carcinogenicity of olipudase alfa.

6.1.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

A combined male and female fertility study conducted in CD-1 mice at doses of 0, 3.16, 10, and 30 mg/kg via a bolus IV administration showed no effects on mating and fertility of the male or female mice or on early gestation parameters of female mice The mortality that occurred in all olipudase alfa groups was considered due to hypersensitivity from olipudase alfa administration. The male and female reproductive NOAELs were 30 mg/kg/dose.

The IV administration of olipudase alfa to pregnant CD-1 mice once daily from Gestation Days (GD) 6 through 15 at doses of 3, 10, or 30 mg/kg/day resulted in maternal effects limited to an increased incidence of decreased activity at ≥3 mg/kg/day. Exencephaly was observed in 1 litter in each of the 10 and 30 mg/kg dose groups (2 and 3 fetuses, respectively). The incidence was slightly higher than historical control data. The increased incidence of exencephaly was observed in pregnant mice at exposure levels less than the human exposure at the recommended maintenance therapeutic dose and frequency. On the basis of these data, the developmental NOAEL for olipudase alfa is 3 mg/kg/day ($AUC_{0\text{-}24}$ 83.1 µg.hr/mL) corresponding to 0.14-fold the exposure at therapeutic dose The relevance of this observation for humans is unknown.

The IV infusion (10 minutes) of olipudase alfa to pregnant NZW rabbits once daily from GD 6 through 19 at doses of 0, 3, 10, or 30 mg/kg/day did not result in olipudase alfa-related maternal effects at any dose. There were no olipudase alfa-related effects on embryo-fetal survival or fetal body weights, and there were no olipudase alfa-related fetal external, visceral, or skeletal abnormalities at any dose. Therefore, the developmental NOAEL was 30 mg/kg/day ($AUC_{0\text{-}24}$ of 6350·hr *mg /mL) corresponding to 10.5-fold the exposure at therapeutic dose.

In a pre- and postnatal developmental toxicity study, the IV administration of olipudase alfa to pregnant CD-1 mice at doses of 0, 3.16, 10 or 30 mg/kg once every other day from GD6 through postpartum Day 19 or 20 did not induce any effect on maternal (F1) reproductive function. There was no olipudase alfa-related mortality. Mortality noted was considered due to hypersensitivity from olipudase alfa administration based on the time of death following dose administration, and in conjunction with adverse clinical observations. There were no toxicologically significant differences in any developmental and reproductive parameters evaluated in the F1 generation male and female offspring. The maternal NOAEL and the NOAEL for reproduction in the dams and for viability and growth in the offspring were 30 mg/kg/dose.

In mice administered 3 mg/kg olipudase alfa on postpartum day 7, olipudase alfa was detected in milk 2 days after administration.

6.1.6 OTHER TOXICITY STUDIES

Safety Pharmacology

In Beagle dogs and Cynomolgus monkeys, the single IV administration of olipudase alfa at doses up to 30 mg/kg did not induce adverse effect on the cardiovascular and respiratory functions.

In ASMKO mice, a dose-dependent reduction in heart rate accompanied by a decrease in motor activity and followed by a slow decline in blood pressure was noted after a single IV administration at 3, 10, and 20 mg/kg. After 2 doses of olipudase alfa at 3 and 10 mg/kg to ASMKO mice, a slight decline in heart rate was noted following the second administration.

7. DESCRIPTION

Olipudase alfa is a recombinant human acid sphingomyelinase consisting of 570 amino acids. Olipudase alfa is produced in a Chinese Hamster Ovary cell line by recombinant DNA technology.

Sphingomyelinase C (synthetic human); recombinant DNA derived des-(1-13)-human sphingomyelin phosphodiesterase (acid sphingomyelinase, EC-3.1.4.12), glycoform alfa.

List of excipients (per 20 mg vial):

Sucrose (250 mg), L-methionine (74.6 mg), sodium phosphate dibasic heptahydrate (8.45 mg), sodium phosphate monobasic monohydrate (9.4 mg).

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

In the absence of compatibility studies, Xenpozyme must not be mixed with other medicinal products.

8.2 SHELF-LIFE

Unopened vial: Refer outer carton.

8.3 PACKAGING INFORMATION

Xenpozyme is supplied in single-use, 20 mL type I borosilicate glass vials. The closure system consists of a siliconized gray chlorobutyl-elastomer lyophilization stopper and an aluminum seal with a plastic flip-off cap.

8.4 STORAGE AND HANDING INSTRUCTIONS

Store in a refrigerator between 2°C and 8°C (36°F and 46°F)

AFTER RECONSTITUTION AND DILUTION

The reconstituted solution and diluted solutions of Xenpozyme should be used immediately. This product contains no preservatives. If immediate use is not possible, the reconstituted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F), or 12 hours at room temperature (up to 25°C/77°F). After dilution, the solution can be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F) followed by 12 hours (including infusion time) at room temperature (up to 25°C/77°F).

8.4.1 PREPARATION AND HANDLING

Xenpozyme should be reconstituted, diluted, and administered under the supervision of a healthcare professional. Infusions should be administered in a stepwise manner preferably using an infusion pump.

Preparation of the dosing solution

The powder for concentrate for solution for infusion must be reconstituted with sterile water for injection, diluted with 9 mg/mL (0.9%) of sodium chloride solution and then administered by intravenous infusion.

The reconstitution and dilution steps must be completed under aseptic conditions. Filtering devices should not be used at any time during the preparation of the infusion solution. Avoid foaming during reconstitution and dilution steps.

a) Determine the number of vials to be reconstituted based on the individual patient's weight and the prescribed dose.

   Patient weight (kg) × dose (mg/kg) = patient dose (in mg). Patient dose (in mg) divided by 20 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

b) Remove the required number of vials from refrigeration and set aside for approximately 20 to 30 minutes to allow them to reach room temperature.

c) Reconstitute each vial by injecting 5.1 mL of Sterile Water for Injection, USP into the vial using a slow drop-wise addition technique to the inside wall of the vial.

d) Tilt and roll each vial gently. Each vial will yield a 4 mg/mL clear, colorless solution.

e) Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. Xenpozyme solution should be clear and colorless. Any vials exhibiting opaque particles or discoloration should not be used.

f) For actual volumes of infusion based on body weight

- Prepare an infusion solution at 0.1 mg/mL by adding 0.25 mL (1 mg) of the reconstituted solution prepared in step c and 9.75 mL of 0.9% sodium chloride for injection in an empty 10 mL syringe.
- Calculate the volume (mL) required to obtain the patient dose (mg).

  Example: 0.3 mg ÷ 0.1 mg/mL = 3 mL
- Transfer the required volume of 0.1 mg/mL infusion solution to an empty sterile syringe of the closest size appropriate to contain the volume of infusion.

  For fixed volumes of infusion (see Table 12 for the recommended total infusion volume based on patients age and/or weight):
- Withdraw the volume of reconstituted solution, corresponding to the prescribed dose, from the appropriate number of vials and dilute with 9 mg/mL (0.9%) of sodium chloride solution.

Table 12: Volumes of Administration

	Body weight ≥3 kg to <10 kg	Body weight ≥10 kg to <20 kg	Body weight ≥20 kg (pediatric patients <18 years)	Adult patients (≥18 years)
Dose (mg/kg)	Total infusion volume (mL)	Total infusion volume (mL)	Total infusion volume (mL)	Total infusion volume (mL)
0.03	Actual Volume will vary based on body weight Container: syringe	Actual Volume will vary based on body weight Container: syringe	5 Container: syringe	NA
0.1	Actual Volume will vary based on body weight Container: syringe	5 Container: syringe	10 Container: syringe	20 Container: syringe
0.3	5 Container: syringe	10 Container: syringe	20 Container: syringe	100 Container: infusion bag
0.6	10 Container: syringe	20 Container: syringe	50 Container: infusion bag	100 Container: infusion bag
1	20 Container: syringe	50 Container: infusion bag	100 Container: infusion bag	100 Container: infusion bag
2	50 Container: infusion bag	75 Container: infusion bag	200 Container: infusion bag	100 Container: infusion bag
3	50 Container: infusion bag	100 Container: infusion bag	250 Container: infusion bag	100 Container: infusion bag

- Dilution instructions for 5 mL ≤ total volume ≤ 20 mL using a syringe:

- Pull back the empty 5 mL, 10 mL or 20 mL syringe to the marking for the required final volume as per table 10 so that it is full of air to the desired volume.
- Insert the needle of the syringe containing the reconstituted solution from step c) into the tip of the empty 5 mL, 10 mL, or 20 mL syringe and inject the volume slowly to the inside wall of the syringe.

- Add slowly the quantity sufficient of 9 mg/mL (0.9%) sodium chloride solution to obtain the required total infusion volume (avoid foaming within the syringe).

- Dilution instructions for a total volume ≥ 50 mL using an infusion bag:
  - Empty infusion bag:
    - In the appropriate size sterile infusion bag, inject slowly the reconstituted solution from step c)
    - Add slowly the quantity sufficient of 9 mg/mL (0.9%) sodium chloride solution to obtain the required total infusion volume (avoid foaming within the bag)
  - Prefilled infusion bag:
    - From the appropriate size infusion bag prefilled with 9 mg/mL (0.9%) sodium chloride solution, withdraw the volume of normal saline equivalent to the volume of reconstituted solution (volume in the syringe prepared in step f) to obtain a final volume as specified in Table x.
    - Add slowly the solution withdrawn in step f) into the infusion bag (avoid foaming within the bag).

g) Gently invert the syringe or the infusion bag to mix. Do not shake. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution must be filtered through an in-line low protein-binding 0.2 μm filter during administration.

h) After the infusion is complete, the infusion line should be flushed with 9 mg/mL (0.9%) of sodium chloride solution using the same infusion rate as the one used for the last part of the infusion

i) Vials are for single dose only. Discard any unused solution.

9. PATIENT COUNSELLING INFORMATION

Hypersensitivity Reactions including Anaphylaxis

Advise the patients and caregivers that reactions related to administration and infusion may occur during and after Xenpozyme treatment, including anaphylactic reactions, serious or severe hypersensitivity reactions, and IARs. Patients who have experienced anaphylactic or hypersensitivity reactions may require close observation during and after Xenpozyme administration. Inform patients of the signs and symptoms of anaphylactic and severe hypersensitivity reactions and have them seek medical care should signs and symptoms occur.

10. DETAILS OF MANUFACTURER

Manufactured by:

Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland. (Fill / Finish, Labelling, Secondary Packaging, Release and Quality Control Testing).

Importer:
Sanofi Healthcare India Private Limited, Gala No.4, Ground Floor, Building No Bl, City Link Warehousing Complex, S No. 121/ 10/A, 121/10/B And 69, NH3 Vadape Tal- Bhiwandi 16, Thane Z5, Bhiwandi, Maharashtra (India) – 421302.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

IL/BIO-000284-RC/BIO-000271 dated 22 Mar 2024

12. DATE OF REVISION

Date of Update: Mar 2024

Source: CCDS-v3.0 dated 23 Jun 2022.