CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761261Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761261
PDUFA Goal Date	October 3, 2022
OSE RCM #	2021-2150,
Reviewer Name(s)	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Associated Director for REMS Evaluation and Design	Laura Zendel, PharmD, BCPS
Review Completion Date	August 5, 2022
Subject	Evaluation of Need for a REMS
Established Name	Olipudase alfa-rpcp
Name of Applicant	Genzyme Sanofi
Trade Name	Xenpozyme
Therapeutic Class	Recombinant human acid sphingomyelinase
Formulation(s)	20 mg single-dose vial lyophilized powder for reconstitution for intravenous (IV) infusion Genzyme Sanofi
Dosing Regimen	The dosing regimen are as follows: • For Adults: 0.1 mg/kg/ IV every 2 weeks (Q2W), with dose escalation to targeted maintenance dose of 3mg/kg. The dose escalation regimen includes 0.1, 0.3, 0.3, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W over 14 weeks. • For pediatrics: 0.03 mg/kg IV every 2 weeks, with dose escalation to targeted maintenance dose of 3mg/kg. The dose escalation regimen includes 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W over 16 weeks.

- For patients with BMI > 30: Calculate the adjusted body weight (BW) for dosing, use the following formular: Dosing BW = (actual height in meter)^2 X 30

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Xenpozyme (olipudase alfa) is necessary to ensure the benefits outweigh its risks. Genzyme Sanofi (Genzyme) submitted a Biologics Licensing Application (BLA) 761261 for olipudase alfa with the proposed indication as an enzyme replacement therapy (ERT) for the treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. The risks associated with olipudase alfa are hypersensitivity reactions including anaphylaxis and infusion-associated reactions (IARs), transient transaminase elevations, and potential for embryo-fetal toxicity, particularly, exencephaly. Genzyme did not submit a REMS with this application but proposed additional voluntary risk mitigation materials complementary to the prescribing information to support the safe and appropriate use of olipudase alfa. These voluntary risk mitigation materials include (b) (4)

(b) (4)

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of Xenpozyme outweigh its risks. Hypersensitivity reactions including anaphylaxis and IARs are known risks in the ERT drug-class and were mainly mild to moderate in severity. Transient elevations in transaminases mostly occur during initiation and dose escalations. Transaminase levels often return to pre-infusion levels prior to the next infusion dose. Monitoring of transaminase levels during initiation and dose escalations will help mitigate this risk. The risk of exencephaly was only observed in gestational mouse studies. There are no published reports of olipudase alfa use in pregnant women and it is not certain whether untreated ASMD might cause adverse pregnancy outcomes. In addition, due to the low prevalence of pregnancies in women with ASMD, a REMS may potentially hinder access to the only available therapy for ASMD, if approved. The review team concluded that labeling would be adequate to communicate these risks. Consistent with other approved enzyme replacement therapies, a boxed warning will be required to inform prescribers on the risk of hypersensitivity reactions including anaphylaxis. Labeling would include warnings for hypersensitivity reactions (including anaphylaxis and IARs), transient elevations in transaminases, and the risk of embryo-fetal toxicity. Further, Xenpozyme is intended to be administered by healthcare providers (HCPs) in either inpatient or outpatient settings using a dose-escalation regimen to further mitigate the risks of hypersensitivity and transient elevations in transaminases. We expect the prescribing community and those HCPs involved with administration of the product would be familiar with identifying and managing adverse events associated with the use of biological therapies such as Xenopozyme.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xenpozyme (olipudase alfa) is necessary to ensure the benefits outweigh its risks. Genzyme Sanofi (Genzyme) submitted a Biologic Licensing Application (BLA) 761261 for olipudase alfa with the proposed indication as an enzyme replacement therapy (ERT) for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. This application is under review in the Division of Rare Drug and Metabolism Genetics

(DRDMG). The Applicant did not submit a REMS with this application but proposed additional voluntary risk mitigation materials to support the safe and appropriate use of olipudase alfa along with labeling and routine pharmacovigilance. These voluntary materials include (b) (4) (b) (4) (b) (4) These additional educational materials are intended to be complementary to the product labeling.

2 Background

2.1 PRODUCT INFORMATION

Xenpozyme (olipudase alfa- rpcp) is a new molecular entity (NME)[a] proposed as an enzyme replacement therapy (ERT) for (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. Xenpozyme provides an exogenous source of acid sphingomyelinase (ASM) to catalyze the hydrolysis of sphingomyelin (an important fatty substance in the cell) to ceramide and phosphocholine, reducing sphingomyelin accumulation in organs of patients with ASMD. Xenpozyme does not cross the blood brain barrier and is not expected to treat the CNS manifestations of the disease.

Xenpozyme is formulated as a 20mg/vial lyophilized powder for reconstitution for intravenous (IV) infusion, preferably using an infusion pump. The recommended dosing is based on body weight beginning with the following proposed step-wise dosing and titration regimen to reduce the risks of hypersensitivity, infusion-associated reactions (IARs), and elevated transaminase levels[b].

Adults (≥ 18 years old)		**Pediatric Patients (0 to < 18 years old)**	
First dose (Day 1/Week 0)	0.1 mg/kg	First dose (Day 1/Week 0)	0.03 mg/kg
Second dose (Week 2)	0.3 mg/kg	Second dose (Week 2)	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg	Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg	Fourth dose (Week 6)	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg	Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg	Sixth dose (Week 10)	0.6 mg/kg
Seventh dose (Week 12)	2 mg/kg	Seventh dose (Week 12)	1 mg/kg
Eighth dose (Week 14)	3 mg/kg (recommended maintenance dose)	Eighth dose (Week 14)	2 mg/kg
		Ninth dose (Week 16)	3 mg/kg (recommended maintenance dose)

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Use actual body weight for patients with a BMI less than or equal to 30. For patients with BMI > 30: calculate the adjusted body weight (kg) = (actual height in meter)^2 X 30

The administration of Xenpozyme should be supervised by a healthcare provider (HCP) in a clinical setting such as in an infusion center. Home administration under the supervision of an HCP may be considered for patients on maintenance dosing who are tolerating their infusions well. Xenpozyme is currently not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761261 relevant to this review:

- 8/3/2000: Orphan Drug Status for olipudase alfa for the treatment of Niemann-Pick Disease (NPD) type B
- 4/23/2007: Fast-Track Designation granted to olipudase alfa for the treatment of ASMD
- 12/18/2007: Orphan Drug Status amended to include all types of NPD
- 5/26/2015: Breakthrough Therapy Designation for non-neurological manifestations of ASMD
- 10/17/2018: Rare Pediatric Disease Designation to treat pediatric patients with non-neurological manifestation of ASMD
- 3/24/2021: Rolling review submission granted in the Type B pre-BLA meeting
- 9/8/2021: Genzyme submitted Part 1 (Non-Clinical) of the rolling review for Xenpozyme (olipudase alfa) BLA 761261
- 11/3/2021: Genzyme submitted Part II (Clinical and CMC) of the rolling review for Xenpozyme (olipudase alfa) BLA 761261
- 4/19/2022: In the Mid-cycle meeting (MCM), the Agency informed the Applicant that there are currently no plans for a REMS, however, there are ongoing review issues related to manufacturing processes, scope of proposed indication, dosing concerns that may lead to medication errors, and the potential risk of embryo-fetal toxicity based on animal studies.
- 4/20/22: The Applicant submitted an amendment which included an update to the carton labeling and an updated integrated safety set.
- 4/22/2022: An Information Request (IR) was sent to the Applicant to inform them that the voluntary educational materials (b) (4) (b) (4) do not need to be submitted to the BLA for review. Advisory comments could be provided separately by the Office of Prescription Drug Promotion (OPDP).
- 5/6/2022: The Agency issued a major amendment for the April 20, 2022 amendment submission, and the PDUFA date is extended to October 3, 2022.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acid sphingomyelinase deficiency (ASMD), commonly known as Niemann-Pick disease (NPD), is a rare autosomal recessive lysosomal storage disorder resulting from deficiency of the lysosomal enzyme, acid sphingomyelinase (ASM), caused by pathogenic variants of the SMPD1 gene.[1,2] ASM catalyzes the hydrolysis of sphingomyelin (an important fatty substance for the cell) to ceramide and phosphocholine. In ASMD, the lysosomal enzymatic deficiency causes progressive intracellular accumulation of sphingomyelin and other lipids affecting major organs such as the spleen, liver, bone marrow, lungs, lymph nodes and brain and manifests as various multi-system disease.[c] The estimated incidence of ASMD is 0.4 to 0.6 per 100,000 births.[3d]

ASMD manifests as a spectrum of disease with varying severity and is classified by phenotypic subtypes. Infantile neurovisceral ASMD, also known as NPD A, is the most severe form, often with early onset during infancy and with rapidly progressive severe multiorgan and neurodegeneration manifestations including failure to thrive, neurodegenerative bleeding, and respiratory infections. Death occurs typically by 3 years of age. Chronic neurovisceral ASMD, also known as the intermediate form, NPD A/B or NPD B variant, has slower progression of neurological symptoms and prolonged survival. Chronic visceral ASMD also known as NPD B, has a later onset and variable progression rate and prognosis; patients may live into later adulthood but may develop significant pulmonary, liver, and cardiac diseases that commonly contribute to premature death in the patients, but does not manifest in the central nervous system (CNS).

3.2 Description of Current Treatment Options

There are no currently approved therapies for the treatment of ASMD. Only symptomatic therapy is available which includes lifestyle and diet modifications, statin therapy to lower cholesterol levels, supplemental oxygen, bronchodilators, appropriate vaccinations, and blood transfusions to treat patients with acute episodes of bleeding due to splenomegaly and low platelet counts. Hematopoietic stem cell transplantation has been evaluated with variable results. Due to the severity and lack of available treatments, there is an unmet medical need for available therapies to treat ASMD.

4 Benefit Assessment

The efficacy of olipudase alfa is primarily supported by the pivotal phase 2/3 study in adults, DFI12712 (ASCEND [NCT02004691]). Additional support is provided by the phase 1/2 study, DFI13803 (ASCEND-Peds [NCT01722526]) along with its long-term extension trial (LTE), study LTS13632 (NCT02004704]. Of

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

note, different manufacturing processes (A, B, and C) were employed during the clinical development program. Per the Chemistry, Manufacturing, and Controls (CMC) division, process A and B materials are not comparable to process C materials consisting of C (b)(4) and C (b)(4) with C (b)(4) being the proposed commercial product upon approval.[4] As the process materials are analytically not comparable, the primary analysis for efficacy and safety in this review will focus on subjects who received the process C products.

Study in adults with ASMD

DFI12712 (ASCEND) is a multicenter randomized, double-blinded, placebo-controlled, repeat dose study trial, consisting of both a one-year (52 week) primary analysis period (PAP) as well as an up-to 4 year open label extension treatment period (ETP). A total of thirty-six patients were randomized 1:1 (18 in each treatment group) to receive IV infusion of olipudase alfa or placebo every 2 weeks (Q2W) in the PAP with a protocol-specified dose escalation scheme for the first 14 weeks and then maintained on 3 mg/kg or maximum tolerated dose (MTD) thereafter into the ETP. Of note, 13 subjects in the active treatment group received process C product. Therefore, only data from the 13 treatment group subjects (modified intent-to-treat population) and the 18 placebo-treatment group subjects will be evaluated for efficacy and safety. In general, the baseline characteristics and disease characteristics were balanced between the treatment arms. The mean ages in the placebo and olipudase alfa treatment groups were 33.5 and 36.2 years, respectively. There was a slight gender imbalance between the treatment arms (28% males in placebo arm versus 50% males in the treatment arm). Race was well-balanced between treatment arms; 89% were White in both arms. Efficacy analyses were conducted for changes at baseline to week 52 for all endpoints. The two primary endpoints were: (1) the percentage change in diffusion capacity for carbon monoxide (DLco) and, (2) a combination endpoint of the percentage change in spleen volume in multiples of normal (MN), and the change in splenomegaly-related score (SRS), a patient-reported outcome (PRO). There were five secondary endpoints consisting of change in liver volume in multiples of normal (MN), percentage change in platelet counts, changes in fatigue severity as measured by the Brief Fatigue Inventory (BFI) scale, change in pain severity as measured by the Brief Pain Inventory (BPI) scale, and change in dyspnea severity as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea tool. Per the study protocol, testing of secondary endpoints proceeded only if both the DL_{CO} and combination endpoints were significant.

The clinical reviewer concluded the primary endpoint of the % change in DLco was statistically significant showing advantage for patients treated with olipudase alfa over placebo. By week 52, the % predicted DLco from baseline for the olipudase alfa group compared to placebo group was 24.2% versus 3.08%, respectively, with a least square mean (LSM) difference of 21.1% (p-value < 0.0001). The clinical reviewer concluded that the responder analysis[e] for DL_{CO} showed a clear advantage for the olipudase alfa arm (33% or 4 out of 12 subjects as responders) over placebo (none), despite relatively few total responders. Both males and females showed statistically significant improvement for patients treated with olipudase alfa over placebo (LSM difference of 21.1, p <0.0001); there was a slightly larger effect

[e] Subjects were considered responders if they exhibit a change in spleen volume ≤ -30%, an improvement in DL_{CO} ≥15%, or a change in SRS of ≤-12.5 points, in the three respective analyses.

size in men versus women though not statistically significant; this may be influenced by the small sample sizes within cohorts. The spleen volume component of the combination primary endpoint also showed a strong, statistically significant advantage for patients treated with olipudase alfa over placebo. By week 52 these proportional decreases from baseline had become -38.8%, and -0.4% respectively with LSM difference of -39.2% (p-value <0.0001). Responder analysis for spleen volume again showed improvement over placebo in patients treated with olipudase alfa (92% or 12/13 subjects as responders in the olipudase arm; none in placebo arm). The SRS component of the combination primary endpoint was the only primary endpoint that did not show an advantage for patients treated with olipudase alfa over placebo. By week 52 the decrease from baseline had become -5.32 and -9.81, respectively, with LSM of 3.77 (p-value = 0.15). Responder analysis for SRS showed little difference between the treatment arms. The clinical reviewer considered that several factors such as substantial variability within both treatment groups for SRS could have influenced the lack of significance for this endpoint. As the change in SRS component of the combination primary endpoint was not statistically significant, formal testing of all secondary endpoints could not proceed due to the multiplicity adjustment criteria. However, the clinical reviewer noted that key pulmonary endpoints such as the percent predicted FVC, FVC (mL), high-resolution computed tomography (HRCT) ground glass scores, HRCT interstitial scores, and chest x-ray interstitial showed positive results and provided confidence for the DLco primary endpoint. In addition, the clinical reviewer noted an array of other endpoints (i.e., liver volume, hemoglobin, platelets, lipid panel, and liver function tests) with nominally significant improvements provided favorable results toward benefits of olipudase alfa over placebo.

Study in pediatric patients with ASMD

DFI13803 (ASCEND-Peds) is a multi-center, open-label, ascending dose study for 64 weeks in patients aged less than 18 years with non-central system manifestations of ASMD. After completion of the 64-week treatment period, patients are eligible to enroll in the long-term study, LTS13632. A total of 20 subjects were enrolled, of which 8 received process C products and were evaluated. These patients received IV infusion of olipudase alfa Q2W for a total of 64 weeks. Patients underwent dose escalation within the first 16 weeks or longer and then maintained on 3mg/kg or MTD for the rest of the study. As this is an open-label study and mainly for the purpose of evaluating the safety and tolerability of olipudase alfa in the pediatric population, all efficacy endpoints were considered exploratory. The exploratory efficacy endpoints include changes from baseline and/or percentage change from baseline to Week 52 or 64 of DLco, spleen and liver volumes (in MN), pulmonary function tests and imaging, lipid profile, health outcomes questionnaires (PedsQL), cognitive function and adaptive behavior. The mean age was 6 years old; all of the subjects were White, and there was an even distribution of males to females. Improvements were observed for all age groups for the changes from baseline to Week 52 for the % predicted DLco, spleen volume and liver volume (in MN). DLco values are not available for any subjects below age 7 and there were only three subjects in the ASCEND-Peds trial that had DLco. The clinical reviewer noted that the mean increase in % predicted DLco from baseline to Week 52 was 50.6% in the ASCEND-Peds trial compared to 24.2% in the ASCEND trial. The mean reduction in spleen and liver volumes from baseline to Week 52 was -46.7% and -37.3% , compared to 38.8% and 26.5%, respectively, in the ASCEND-Peds and ASCEND trials. Improvement was also observed on % predicted FVC, FEV1, and total lung capacity. The clinical reviewer concluded that though this study did not have a

control comparison, it showed positive trends for olipudase alfa compared to placebo and provided further confidence in the results of trial DF112712 (ASCEND).

Overall, the clinical reviewer concluded that olipudase alfa demonstrated strong statistically significant advantage in improvement of DLco and spleen volume in adult patients compared to placebo. Although, there was no statistical significance for reduction in SRS in ASCEND, the clinical meaningfulness of this is unclear. Further confidence on the effectiveness of olipudase is supported from pulmonary and other endpoints, which also showed significant and positive results and from the ASCEND-Ped trial, which largely mirrors the significant changes in DLco, spleen, and liver volume results, though the efficacy data were exploratory. The main efficacy results were largely similar across age groups and the clinical reviewer concluded that taken as a whole, this provides substantial evidence of efficacy to allow for the indication to include pediatric patients. [f]

5 Risk Assessment & Safe-Use Conditions

The safety of olipudase is supported by data from the two main studies, DFI12712 (ASCEND) and DFI13803 (ASCEND-Ped). Additional support for safety in adults and pediatrics is provided in Study DFI13412 (NCT01722526), a phase 1b, open-label, repeat-dose study in 5 adults with ASMD and LTS 13632 (NCT02004704), an ongoing phase 2, multinational, multicenter, open-label long-term extension study in adults and pediatric subjects who have completed trials DF113412 or DF113803-Peds. Pooled safety data from a total of 38 patients (30 adult and 8 pediatric subjects) with ASMD type B or A/B were evaluated, with a median (range) of olipudase alfa exposure of 3.0 (1.4-4.7) years in adult subjects and 2.7 (2.5 – 3.1) years in pediatric subjects. This represents a safety database consisting of 2.2 to 3.3% of ASMD patients in US receiving at least 1.4 years of olipudase alfa treatment.

All subjects experienced at least one adverse event (AE). Most were mild-to-moderate (80% in adult and 62.5% in pediatric subjects). No AEs resulted in permanent discontinuation of study drug. Serious adverse events (SAEs) were reported in 33.3% (10/30) adult and in 50% (4/8) pediatric subjects; none of the SAEs were fatal or life-threatening. An SAE of anaphylactic reaction occurred in a single subject who was <2 years old in olipudase alfa clinical program (described further below in 5.1). No deaths were reported in both adult and pediatric populations in the clinical studies.

Adverse events of special interest (AESIs) are hypersensitivity reactions (including anaphylaxis and infusion associated reactions), transient transaminase elevations, and potential for embryo-fetal toxicity. These AESIs are described below.

5.1 HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS AND INFUSION ASSOCIATED REACTIONS (IARS)

ERT drugs are associated with a risk of hypersensitivity reactions including anaphylaxis and IARs. Hypersensitivity AEs were reported in 40% (12/30) of adult patients and in 50% (4/8) of pediatric

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

subjects.[g] All hypersensitivity AEs were of mild or moderate intensity and resolved with dose interruption or temporarily treatment discontinuation. An SAE of anaphylaxis occurred in a single subject who was 1.5 years old. Olipudsae alfa was temporarily discontinued. The patient restarted olipudase alfa with a desensitizing protocol and achieved targeted maintenance dose. No adult or pediatric patient permanently discontinued olipudase alfa treatment due to anaphylaxis.

Protocol-defined infusion-associated reactions (IARs)[h] were reported in 50% (15/30) of adult subjects and in 75% (6/8) of pediatric subjects. IARs that occurred in at least two adults subjects included headache, pruritis, urticaria, vomiting, erythema, nausea, and pyrexia. The IARs reported in at least 2 pediatric subjects include urticaria, erythema, headache, and nausea. The IARs were considered mild to moderate and did not required discontinuation of treatment.

Treatment with olipudase may result in IARs due to the rapid metabolism of accumulated sphingomyelin into ceramide and other pro-inflammatory breakdown products that may induce acute phase reaction (APR) and cytokine release syndrome (CRS) especially during the dose escalation phase (i.e., the first 14/16 weeks after initiation of olipudase alfa). Sixteen events of APRs were identified in 3 (7.5%) adult and 5 (25%) pediatric subjects. No CRS were identified for subjects who received process C products. Most of the APRs occurred at 48 hours post infusion during the dose escalation period. Subjects who had APC events were treated like other IARs by repeating or reducing olipudase dose at the subsequent infusion. All APRs resolved over time, and all subjects reached the maintenance dose of 3mg/kg.

Consistent with other ERTs, the risk of hypersensitivity reactions including anaphylaxis will be addressed in labeling as a boxed warning (BW) specifically for hypersensitivity including anaphylaxis. The labeling would also include warnings for hypersensitivity reactions including anaphylaxis and IARs. As the IARs were considered mild to moderate with no discontinuation, the clinical team determined a boxed warning for IARs is not required. The labeling will include a dose-escalation regimen when initiating treatment to provide a gradual debulking of sphingomyelin and gradual release of ceramide decreasing the inflammatory response such as hypersensitivity and IARs. Labeling will also include a modified dose escalation regimen for when olipudase doses are restarted due to missed doses or dose interruptions.

5.2 TRANSIENT TRANSAMINASE ELEVATIONS

Transient elevations in transaminases >2x ULN 24-48 hours post-infusion possibly associated with ceramide release during dose escalation were observed in the clinical trials. Mean baseline transaminase and total bilirubin levels were higher in pediatric subjects compared to adult subjects. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and total bilirubin levels pre-infusion decreased over 52 weeks in the active treatment group; no changes in these

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[h] Protocol defined infusion associated reactions is any related or possibly related TEAEs within 24 hours after infusion start and were considered related or possibly related to the study treatment by the investigator

parameters occurred in the placebo group. Transient increases in ALT, AST, and total bilirubin levels were observed within 72 hours after olipudase alfa infusion; most of these elevations returned close to pre-infusion values prior to the next infusion. Increases in liver transaminases and total bilirubin were also observed in subjects who received placebo infusion during ASCEND PAP. No transient transaminase elevation was deemed severe or prevented patients from reaching the maintenance dose of 3 mg/kg. Transient transaminase elevations will be included as a warning in labeling. In addition, labeling will include dose-escalation regimens for initiation of therapy and when olipudase doses are restarted due to missed doses or dose interruptions to reduce the inflammatory response such as elevations in transaminase levels.

5.3 POTENTIAL FOR EMBRYO-FETAL TOXICITY

There is no available information to inform on the safety of olipudase alfa use during pregnancy and no pregnancy exposures reported in the clinical development program. Published literature reports brief embryonic exposure to sphingomyelin metabolites or the sphingosine-1-phosphate (S1P) agonist, fingolimod, produces neural tube defects, including exencephaly, in chicks and mice.

Exencephaly was observed in five fetuses of two pregnant mice treated with 10 and 30 mg/kg daily from gestation day (GD) 6 to 15. The maternal No Observed Adverse Effect Level (NOAEL) is at a dose exposure ~1.6 times the exposure associated with the maximum recommended human dose (MRHD) and the developmental NOEAL is at a dose exposure approximately 1/7th the exposure associated with the MRHD. However, this malformation was not seen when olipudase (3, 10, or 30 mg/kg) was administered to rabbits daily (GD 6 to 19). The clinical reviewer noted that these data are consistent with literature reports that brief embryonic exposure to sphingomyelin metabolites or the S1P agonist fingolimod produces neural tube defects, including exencephaly, in chicks and mice. Women of childbearing potential will be advised to use contraception in the labeling. In addition, the risk of embryo-fetal toxicity (specifically, exencephaly) will be included as a warning in labeling. (See discussion section for further details).

6 Expected Postmarket Use

Medical management for patients with ASMD is typically provided by metabolic disease specialists. However, primary care providers and other specialists (e.g., pediatricians, cardiologists, pulmonologists, hepatologists, gastroenterologists, and hematologists) are likely to be part of a team's approach to patient care. As many of the rare disease conditions involve biological therapies (e.g., Pompe and Gaucher disease), specialists in rare diseases would be familiar with the risk of hypersensitivity reactions (including anaphylaxis) and IARs involved with ERT infusions. The administration of olipudase alpha should be supervised by HCPs in a clinical setting such as in an infusion center. Home administration under the supervision of a HCP, such as an infusion nurse, may be considered for patients stabilized on their maintenance dose who are tolerating their infusions well. These HCPs are trained to monitor and manage adverse events associated with infusions of biological therapies and have access to appropriate medical support to manage potential severe reactions such as systemic hypersensitivity reactions. Institutions and infusion agencies are required to meet credentialing criteria and have protocols in place

to administer biological therapies intravenously and manage patients for AEs in the inpatient, outpatient, and home settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed the following risk management activities:

> Along with routine pharmacovigilance activities consisting of standard AE reporting and labeling, the Applicant proposes voluntary risk mitigation materials to support the safe and appropriate use of olipudase alfa. The materials include (b) (4) (b) (4)

Reviewer's Comments: *We note that these voluntary risk mitigation materials proposed by the Applicant are outside of the scope of the REMS program. We defer to of the Office of Prescription Drug Promotion (OPDP) for their post-approval review and input.*

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Xenpozyme on the basis of the efficacy and safety information currently available.

ASMD is a rare and serious disease that can lead to deterioration in liver function, splenomegaly, and interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages that results in frequent respiratory infections and eventual respiratory failure. There are currently no approved treatment options for ASMD.

DFI12712 (ASCEND) provided the primary evidence to support the efficacy of olipudase alfa with statistically significant improvement of the primary endpoints of DL_{CO} and the change in spleen volume (MN), over placebo (p-value<0.0001) even though the SRS component of the combination primary endpoint did not show an advantage over placebo. However, the clinical reviewer cited several factors that may affect the results of SRS, a patient reported outcome, that may influence the sensitivity of the SRS component to the treatment effect of olipudase alfa. Secondary endpoints results were positive, though not tested for significance, and provided additional confidence on the efficacy of olipudase alfa in ASMD. The exploratory results from the pediatric study, DFI13803 (ASCEND-PEDS), which aligns with the results from ASCEND provided further support of the efficacy of olipudase alfa. In addition, pharmacodynamic data on reduction of plasma ceramide and lyso-SPM levels provides acceptable mechanistic evidence for the effectiveness of olipudase alfa and existing nonclinical data suggest olipudase treatment attenuates aspects of ASMD pathology.

The clinical reviewer finds the benefit-risk profile acceptable and concluded that the Applicant provided adequate efficacy evidence along with confirmatory evidence including the etiology of the disease and mechanism of action of the therapy to support approval of olipudase alfa for the treatment of ASMD. The clinical reviewer also noted that because the pathophysiology and progression of the disease are

sufficiently similar and the response to treatment is also expected to be similar in adult and pediatric patients, partial extrapolation of efficacy results from the ASCEND study is appropriate to support efficacy in the pediatric patents. Further, the clinical reviewer concluded that while the neurological manifestation differs among ASMD type A, B, and A/B, the disease pathophysiology is the same and similar somatic manifestations are observed in all disease phenotypes. Therefore, olipudase alfa may be helpful in survival and may provide substantial clinical benefit in patients with ASMD type A. The approved indication for Xenpozyme will be for treatment of non-central nervous system (CNS) manifestation of acid-sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

The safety profile of olipudase includes the risk of hypersensitivity including anaphylaxis and IARs, as expected for ERT. Other risks identified in the clinical development program include transient elevations in transaminase and potential embryo-fetal toxicity, observed as exencephaly in mouse fetus studies. These risks will be included in a boxed warning for hypersensitivity including anaphylaxis as well as warnings and precautions for elevations in transaminases and potential embryo-fetal toxicity. It is thought that rapid metabolism of accumulated sphingomyelin (SM) by olipudase alfa generates proinflammatory breakdown products, which may induce infusion-associated reactions and/or transient liver enzyme elevations. In the clinical trials, IARs were considered mild to moderate events and managed with temporary dose discontinuation, redosing, or slower escalation of dosages. In addition to the boxed warning and warnings and precautions, this risk as well as the transient elevations in ALT and AST can be mitigated by using the dose-escalation regimen when starting treatment to provide a gradual debulking of SPM and a gradual release of ceramide to decrease the inflammatory response. A modified-dose escalation regimen is also included in the label for restarting treatment after missed doses or therapy interruptions. Further, as olipudase alfa is intended to be administered by HCPs in either inpatient or outpatient settings, these HCPs and their agencies are trained in the monitoring and management of adverse events and have ready access to specialists should an adverse event occur.

The risk of embryo-fetal toxicity (exencephaly) was observed in mouse reproductive studies. DRDMG consulted the Division of Pediatrics and Maternal Health (findings, DPMH DPMH) for their input on labeling and potential postmarketing study requirements. Based on the animal study results, DRDMG recommended an embryo-fetal toxicity warning be added to labeling with recommendations for pregnancy testing before treatment and use of contraception in females of reproductive potential.[5] DPMH did not recommend a contraindication (CI) as it is unclear whether untreated ASMD disease causes adverse pregnancy outcomes and there may be situations in which a patient might accept the potential risk to the fetus and wish to maintain a pregnancy while continuing to undergo olipudase treatment. The review team concluded that a REMS to mitigate the risk of embryo-fetal toxicity and a registry study to study outcomes in pregnancy are not necessary as the prevalence of pregnancy in this population is low. In addition, a REMS may potentially limit access to the only available therapy for this disease state. This risk will be mitigated through labeling as a warning (section 5.4) that olipudase alfa is not recommended for use in pregnancy. Prescribers should verify pregnancy status in females of reproductive potential prior to initiating treatment and counsel the patient to use contraception during treatment with olipudase alfa (b) (4) In

addition, DPMH recommends routine pharmacovigilance to monitor for any reports of olipudase alpha exposures during pregnancy in this population.[6]

9 Conclusion & Recommendations

Based on the clinical review, a REMS is not necessary for Xenpozyme to ensure the benefits outweigh the risks. The review team concluded that there was substantial evidence of effectiveness. Given the patient perspective, significant unmet need, and adequate risk mitigation addressed in labeling including a dose-escalation regimens for initiating and for missed doses, boxed warning for hypersensitivity including anaphylaxis, and that the risks are reversible with treatment discontinuation, the benefits of olipudase alfa therapy outweigh the risks for adults and pediatric patients with ASMD. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

1. McGovern MM, Dionisi-Vici C, Giugliani R, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. *Genet Med.* 2017;19(9):967-974.
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4. DCN. Draft integrated review for BLA 761261, accessed June 15, 2022.
5. Liedtka J. DPMH. Reivew of Olipudas Alfa, BLA 761261, dated April 22, 2022.
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