CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761261Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	August 31, 2022
Reviewer(s):	Sally Peprah, PhD Division of Epidemiology I
Team Leader:	Benjamin Booth, PhD Division of Epidemiology I
Associate Division Director:	Wei Hua, MD, PhD, MHS, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name(s):	XENPOZYME (olipudase alfa-rpcp)
Application Type/Number:	BLA 761261
Applicant/sponsor:	Sanofi Genzyme
OSE RCM #:	2021-2148

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Olipudase alfa is a recombinant human acid sphingomyelinase (rhASM) expressed in Chinese hamster ovarian cells.[1] The resulting gene product retains enzymatic activity and lysosomal targeting of the native protein. In the current submission, the Sponsor is seeking approval of olipudase alfa 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.[2]

ASMD, historically referred to as Niemann-Pick disease (NPD) types A and B, is a serious, rare, and potentially life-threatening lysosomal storage disease for which there is currently no safe and effective direct treatment that can reverse the course of disease, only palliative and supportive care for managing symptomology exist.[3] The clinical manifestations of the disease are heterogeneous in both nature and severity, and patients have variable impairment in sphingomyelin metabolism due to pathogenic variants in SMPD1, the gene encoding acid sphingomyelinase (ASM) that results in the expression of defective ASM with reduced activity. ASMD type A results in failure to thrive, hepatosplenomegaly, rapidly progressive neurological degeneration, and death, usually before the age of three years. While ASMD type B is usually diagnosed after the age of two years, and after hepatosplenomegaly (the most common disease manifestation in all ASMD patients) is observed, it presents with a slower progression with little or no neurological involvement.

For adult patients, the recommended starting dose is 0.1 mg/kg administered as an intravenous infusion followed by a bi-weekly escalation regimen over 14 weeks to a maintenance dose of 3 mg/kg given every 2 weeks.[4] While for pediatric patients, the recommended starting dose is 0.03 mg/kg administered as an intravenous infusion followed by a bi-weekly escalation regimen over 16 weeks to a maintenance dose of 3 mg/kg every 2 weeks.[5] The escalation regimen is provided in order to minimize the risk of hypersensitivity and infusion-associated reactions and/or elevated transaminase levels.

[1] Sanofi Genzyme, Clinical study report (ASCEND trail, DFI12712) for olipudase alfa/GZ402665, submitted to BLA 761261 (eCTD 0002) on November 03, 2021.
[2] Ibid
[3] Ibid
[4] Sanofi Genzyme, Annotated Draft Labeling Proposed for olipudase alfa, submitted to BLA 761261 (eCTD 0056) on August 30, 2021. BLA761261 (761261 - 0056 - (56) - 2022-08-30 - TRIAGE-1 /Electronic Submission/Gateway) - Xenpozyme - Response to FDA Comments - AnnotatedPI (MS Word) - Aug-2022
[5] Ibid

1.2. Describe the Safety Concern

In their review of BLA 761261, the Division of Rare Diseases and Medical Genetics (DRDMG) noted that the safety information for pediatric patients less than two years of age with ASMD and for patients with ASMD Type A was limited.[6,7] This was informed by data from the clinical development program, where of the 38 ASMD type B or type A/B subjects who received the to-be-marketed formulation of the drug (process-C) and in whom safety was assessed, eight were pediatric subjects and only one was less than two years of age.[8] This included 30 adult subjects with a median (range) olipudase alfa exposure of 3.0 (1.4 – 4.7) years and eight pediatric subjects with a median age of 6.0 (range: 1 – 10) years and median exposure of 2.7 (2.5 – 3.1) years. Treatment emergent serious adverse events (SAEs) included anaphylactic reaction, rash, and urticaria, and were reported in 33.3% (10/30; Table 1) of adult subjects and in 50% (4/8) of pediatric subjects, for whom all the listed SAEs were reported. Hypersensitivity/infusion-associated reactions (IARs) are a class effect seen in ERTs and have been identified in patients receiving olipudase, including patients less than two years of age with ASMD type A. One severe anaphylactic reaction occurred in a 1.5-year-old subject and treatment was temporarily discontinued but restarted with a desensitization protocol and this patient reached the maintenance dosage. Additionally, another patient less than two years of age with ASMD Type A who received treatment through the expanded access program experienced anaphylaxis. Antidrug IgG and IgE antibodies were detected in both patients.

Table 1. Subjects With Any Serious Adverse Event Overall, and Adverse Events in FDA Medical Query (Broad) for Hypersensitivity, by Preferred Term, Safety Population, Pediatric Subjects (Trial Trials DFI13803, LTS13632 and Pooled (ISS)) and Adult Subjects (Trials DFI12712, DFI13412, LTS13632 and Pooled (ISS)) who Received only Process C

Group Query Preferred Term	Pooled Pediatric OA LTS13632/DFI13803 N=8, n (%)	Pooled Adult (DFI12712/DFI13412/LTS13632) N=30, n (%)
Any serious AE	4 (50.0)	10 (33.3)
Hypersensitivity FMQ Broad (GQ)	4 (50.0)	12 (40.0)
Urticaria	4 (50.0)	5 (16.7)
Pruritus	2 (25.0)	8 (26.7)
Rash	2 (25.0)	1 (3.3)
Anaphylactic reaction	1 (12.5)	-
Pharyngeal swelling	1 (12.5)	-
Skin exfoliation	1 (12.5)	-

Source: Division of Rare Diseases and Medical Genetics (DRDMG), Final Integrated Review of Xenpozyme (olipudase alfa-rpcp) BLA 761261. August 31, 2022. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5038752.

Note: Pediatric subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa period. Duration is up to the data cutoff dates.
Note: Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; FMQ, FDA medical query; GQ, group query; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa

[6] Division of Rare Diseases and Medical Genetics (DRDMG), Final Integrated Review of Xenpozyme (olipudase alfa-rpcp) BLA 761261. August 31, 2022. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5038752.
[7] Division of Rare Diseases and Medical Genetics (DRDMG), PMR/506B PMC Development Template for PMR 4291-1 for Xenpozyme (olipudase alfa-rpcp). August 30, 2022. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5038033.
[8] See footnote 6.

In 75% (6/8) of pediatric subjects and 50% (15/30) of adult subjects, IARs were reported. The IARs reported in ≥10% of pediatric subjects comprised urticaria, erythema, headache, pyrexia, vomiting, abdominal pain anaphylactic reaction, increase in blood alkaline phosphatase, total bilirubin, and C-reactive protein (CRP), muscle edema, rash, and skin mass. While for ≥10% of adult subjects IARs included headache, pruritus, urticaria, and vomiting. Ten events of acute phase reactions (APRs) were identified in 3.3% (1/30) of adult subjects and 12.5% (1/8) of pediatric subjects. Most of the APRs occurred at 48 hours post infusion during the dose escalation period. The clinical symptoms commonly associated with APRs were pyrexia and vomiting. All APRs resolved over time by repeating or reducing treatment dose at the subsequent infusion.

Based on this observation[9] and given that ASMD Type A is a rapidly progressing disease that is fatal by the second to third year of life, a postmarketing study is needed. This study will characterize the safety of olipudase alfa including hypersensitivity, infusion-associated reactions, and laboratory abnormalities in pediatric patients less than two years of age with ASMD and patients with ASMD Type A. This study will also obtain information to evaluate the tolerability of treatment as well as the relationship between antidrug antibodies and safety.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The Division of Epidemiology I (DEPI-I) assessed the feasibility of the desired postmarketing requirement (PMR) long-term safety evaluation of olipudase alfa in pediatric patients less than two years of age with ASMD and patients with ASMD Type A, using a five-year postmarketing observational study. Specifically, the PMR will require that the primary safety outcomes include severe hypersensitivity reactions, infusion associated reactions, and laboratory abnormalities. In the event of severe hypersensitivity reactions including anaphylaxis, the assessment of anti-olipudase antibody response (e.g., detection and titers of binding and neutralizing IgG antibodies and detection of IgE antibodies) to evaluate the relationship between antidrug antibodies and adverse events (safety) is of interest.

1.5. Effect Size of Interest or Estimated Sample Size Desired

To be negotiated and determined once draft protocol is submitted by the applicant.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired study must identify pediatric patients less than two years of age with ASMD and patients with ASMD Type A treated with olipudase alpha and having well characterized data on treatment administrations, gaps between administrations, dosing, infusion rates (i.e., slower infusions) and laboratory data.

[9] Limited pre-market safety information from pediatric patients <two years of age and from patients with ASMD Type A in this BLA (single patient each) and anaphylaxis experienced by these patients in the presence of anti-drug antibodies.

2.2 Is ARIA sufficient to assess the intended population?

No, identifying the study population is one of the major limiting factors for ARIA in this instance. ARIA might use co-occurrence of pharmacy claims for olipudase alpha and the following ICD-10-CM diagnosis codes[10] to reliably identify the intended population:

E75.24 NIEMANN-PICK DISEASE
E75.240 …… TYPE A
E75.241 …… TYPE B
E75.242 …… TYPE C
E75.243 …… TYPE D
E75.244 …… TYPE A/B
E75.248 …… OTHER NIEMANN-PICK DISEASE
E75.249 …… UNSPECIFIED

However, ASMD and specifically Type A ASMD is a very rare disease which often occurs before the age of three years. Therefore, an adequate sample of pediatric patients with disease under the age of two years may not adequately be captured by ARIA.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is treatment with olipudase alfa via intravenous infusion every 2 weeks at a recommended starting dose of 0.03 mg/kg followed by a 16-week bi-weekly escalation regimen (see Table 2) to the recommended maintenance dose of 3 mg/kg every 2 weeks in pediatric patients less than two years of age.

Table 2: XENPOZYME Dose Escalation Regimen for Pediatric Patients*

Pediatric Patients (0 to 17 years)	
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)

Source: Sanofi Genzyme, Annotated Draft Labeling Proposed for olipudase alfa, submitted to BLA 761261 (eCTD 0002) on November 03, 2021. \\CDSESUB1\evsprod\bla761261\0002\m1\us\annotatedpi.pdf
*Use actual body weight for patients with a BMI less than or equal to 30. For patients with a BMI greater than 30, calculate adjusted body weight (kg) = (actual height in m)^2 x 30.

In addition, the sequence of administrations, gaps between administrations, dosing, and infusion rates of olipudase alfa treatment are deemed desirable to help clarify whether they impact the tolerability of treatment.

3.2 Comparator Exposure(s)

Not applicable.

[10] https://icd.codes/icd10cm/E7524

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to capture procedure codes in outpatient administrative claims of physician-supervised administrations of intravenous therapeutics, such as olipudase alfa. However, the sequence of administrations, gaps between administrations, dosing, and infusion rates of olipudase alfa treatment are deemed desirable to help clarify whether or not they impact the tolerability of treatment are either not captured or not consistently captured in claims data.

4 OUTCOME(S)

4.1 Outcomes of Interest

The desired study must identify hypersensitivity reactions, infusion associated reactions, and laboratory abnormalities. For laboratory abnormalities, anti-olipudase antibody response including detection and titers of binding and neutralizing IgG antibodies and detection of IgE antibodies will be assessed.

4.2 Is ARIA sufficient to assess the outcome of interest?

Diagnostic codes in administrative claims data can capture with moderate accuracy the outcomes of anaphylaxis[11] and hypersensitivity reactions other than anaphylaxis[12]. Further, ARIA is deemed sufficient for identifying IARs for this study, which is defined as any treatment emergent adverse events occurring within 24 hours after the start of infusion. However, ARIA is not sufficient for non-routinely collected laboratory data as ARIA provides no practical means for retrieving results from laboratory tests, including tests for immunogenicity. Further, antidrug antibody titers are highly specialized and not collected during routine laboratory tests, this may require the prospective collection of blood samples during follow-up.

5 COVARIATES

5.1 Covariates of Interest

The occurrence of safety outcomes of interest may be further described by patient characteristics, including demographic (e.g., age, sex, calendar year, and geographic region), medical history and clinical characteristics (e.g., time since diagnosis, disease type/status, comorbidities and concomitant medications).

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes, ARIA is sufficient to assess these covariates which may be of interest. The SDD demographic table reliably and accurately captures patient age and sex, while covariates of patient medical history may be obtained through the SDD diagnosis table, which includes diagnosis codes, diagnosis code type, and principal diagnosis. Also, treatment covariates may be obtained from the SDD dispensing table, which captures relevant covariates including dispensing date and days supply, and the SDD procedure table, which captures pertinent covariates including procedure codes and procedure name.

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[11] Floyd JS, Carrell DS, Bann MA, et al., Improving Identification of Anaphylaxis, Presented at: The International Society for Pharmacoepidemiology All Access Meeting, 2020.

[12] Schneider, G, Kachroo S, Jones N, et al., 2012, A Systematic Review of Validated Methods for Identifying Hypersensitivity Reactions other than Anaphylaxis (Fever, Rash, and Lymphadenopathy), Using Administrative and Claims Data, Pharmacoepidemiology Drug Saf,21(S1), 248-255.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Observational five-year cohort study of pediatric patients less than two years of age with ASMD and patients with ASMD Type A who initiate treatment of olipudase alpha.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, analytic tools available in SDD enumerate exposures and outcomes, the information needed to assess the frequency and distribution of the outcomes of interest separately for patients with ASMD and ASMD Type A. Length of follow-up is not of concern as the five-year period pertains to enrollment and not the minimum period required for patient follow-up.

7 NEXT STEPS

DEPI-I has determined that ARIA is not sufficient and recommends that DRDMG proceed with their plan to issue PMR 4291-1 for the conduct of an observational study to characterize safety concerns for olipudase alfa including hypersensitivity, infusion-associated reactions, and laboratory abnormalities in pediatric patients less than two years of age with ASMD and patients with ASMD Type A and to obtain information to evaluate the relationship between antidrug antibodies and safety. Genzyme accepted the proposed PMR on August 26, 2022[13], and verbatim text[14] for PMR 4291-1 as stated in the final PMR template for PMR 4291-1 for Xenpozyme (olipudase alfa-rpcp) appears below.

> *PMR 4291-1: Conduct a five-year observational study to evaluate the long-term safety of olipudase alfa-rpcp including severe hypersensitivity reactions, infusion associated reactions, and laboratory abnormalities in pediatric patients younger than two years of age with ASMD and patients with ASMD Type A. Assess anti-olipudase antibody response and evaluate the relationship between antidrug antibodies and safety.*

[13] Sanofi Genzyme, PMR/PMC/General Correspondence-Response to FDA Information Request, submitted to BLA 761261 (eCTD 0054) on August 26, 2022.
[14] See footnote 7

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/s/

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GERALD J DALPAN on behalf of ROBERT BALL
08/31/2022 02:25:20 PM
for Robert Ball

MEMORANDUM

To: BLA 761261, Xenpozyme (olipudase alfa-rpcp)[1], Genzyme Corporation

From: Janice Weiner, J.D., M.P.H., Principal Regulatory Counsel, CDER/Office of Regulatory Policy/Division of Regulatory Policy I

Date: August 15, 2022

Subject: Applicability of 21 CFR 610.61(r)

This memorandum explains why the regulation at 21 CFR 610.61(r) does not apply to BLA 761261. As part of FDA's implementation of section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), there was renewed attention to the labeling requirement in § 610.61(r).[2] The regulation states, in pertinent part:

> The following items shall appear on the label affixed to each package containing a product: . . .
>
> (r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

Background

The text of the current regulation has not changed since this provision was promulgated in 1947 at 42 CFR 73.52(g).[3] The history of related regulations shows that the terms "official standard of potency" and "U.S. standard of potency" in § 610.61(r) have a specific historical meaning that no longer reflects how biological products are regulated. For example, 42 CFR 73.76 described that the government "made available" a physical sample that served as a standard for testing the

[1] Final acceptance of the proposed proprietary name and designation of the proper name for a biological product occur upon licensure of the biological product and may be subject to change prior to licensure.

[2] See, e.g., Q14 of the guidance for industry, *The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers* (March 2020).

[3] See General Notice of Proposed Rulemaking, 12 FR 6769 (Oct. 15, 1947) and 42 CFR part 73 (1947). In 1970, this provision was redesignated at 42 CFR 73.601(r) (see 35 FR 13929 (Sept. 2, 1970)). In 1972, after authority for biological products was transferred from the Division of Biologics Standards, National Institutes of Health (NIH) to the Bureau of Biologics, FDA, this provision was redesignated at 21 CFR 273.601(r) (see 37 FR 15993 (Aug. 9, 1972)). In 1973, this provision was redesignated at 21 CFR 610.61(r) (see 38 FR 32048 (Nov. 20, 1973)). We note that prior to the 1947 regulation, there were other regulations governing what potency-related information needed to appear in labeling, but these were subsequently repealed and superseded. See, e.g., 5 FR 4110 (Oct. 17, 1940) and 42 CFR 22.84 ("Official standard of potency; exceptions"); see also General Notice of Proposed Rulemaking, 11 FR 8374 (Aug. 2, 1946).

potency of a biological product.[4] The next regulation at 42 CFR 73.77[5] codified a minimum potency (e.g., units per volume) for certain products named in the preceding regulation.[6]

After 1947, the biological product regulations were expanded to include product-specific regulations. By 1973, these "additional standards" were described, for example, in part 620 ("Additional Standards for Bacterial Products") and then-part 630 ("Additional Standards for Viral Vaccines"). Such additional standards typically included two sequential regulations relevant to potency, like the regulations described in the preceding paragraph. The first regulation, usually titled "U.S. Standard preparations" or "U.S. Reference preparation,"[7] referred to the physical reference furnished by the government; the second regulation, usually titled "Potency test,"[8] set out the minimum potency of the product as established by that standard.

In 1996, part 620 and then-part 630 were removed from the CFR because they "duplicate standards that are also specified in product licenses required for biological products."[9] The preamble explained: "For many years, because of the potential for impeding scientific progress, FDA has not codified specific additional standards for licensed biological products, but instead has set the required standards in the product licenses. The deletion of these regulations will increase regulatory flexibility by allowing industry and the agency to more readily use and incorporate current scientific technology in the manufacture and regulation of licensed biological products."[10]

Similarly, in 2016, the regulations at §§ 610.20 and 610.21 were removed from the CFR. In the preamble, FDA reiterated what an official standard of potency is—"official standards of potency (*i.e.*, a specific test method described in regulation)"—and that "official potency tests no longer exist."[11] The preamble explained, "In addition to sometimes being duplicative of information provided in the BLA and unnecessarily restrictive regarding the source of standard preparations, the codification by regulation of many of the standard preparations and limits of potency for certain biological products sometimes does not keep abreast of technology advances in science related to manufacturing and testing. For many years, because of the potential for impeding

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[4] "Standard units or samples for comparison made available by the Institute shall be applied in testing for potency all forms of [list of biological products], and other products for which such units are available." 42 CFR 73.76 (1947).

[5] E.g., "Diphtheria antitoxin shall have a potency of not less than 500 units per milliliter." 42 CFR 73.77 (1947).

[6] These regulations were recodified and amended at 21 CFR 610.20 and 610.21. As amended, § 610.20 ("Standard preparations") continued to describe "Standard preparations made available by the Center for Biologics Evaluation and Research," and provided that such standards "shall be applied in testing, as follows: (a) Potency standards. . . ." As amended, § 610.21 ("Limits of potency") continued to describe the minimum potency of certain products in § 610.21: "The potency of the following products shall be not less than that set forth below . . . ."

[7] E.g., § 620.3 "U.S. Standard preparations" within Subpart A–Pertussis Vaccine (1995).

[8] E.g., § 620.4 "Potency test" within Subpart A–Pertussis Vaccine (1995).

[9] Revocation of Certain Regulations; Opportunity for Public Comment; Proposed Rule, 60 FR 53480, 53482 (Oct. 13, 1995); Revocation of Certain Regulations; Biological Products; Final Rule, 61 FR 40153 (Aug. 1, 1996).

[10] 60 FR at 53482.

[11] Standard Preparations, Limits of Potency, and Dating Period Limitations for Biological Products; Companion to Direct Final Rule; Proposed Rule, 81 FR 26753, 26756 (May 4, 2016).

scientific progress, FDA has not codified additional specific standard preparations and limits of potency for licensed biological products, but instead the standards are established in the BLA."[12]

Interpretation

21 CFR 610.61(r) can be divided into two clauses: [1] Minimum potency of product expressed in terms of official standard of potency or, [2] if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

The first clause applies to a particular biological product when an "official standard of potency" exists. As discussed above, "official standard of potency" is a historical term that means a specific test method described in regulation, which no longer exists because such standards are established in the BLA. Because there is no specific test method described in regulation for olipudase alfa products, it is impossible for the minimum potency of Xenpozyme to be expressed in terms of official standard of potency on the package label. Thus, the first clause does not apply to BLA 761261.

The second clause of § 610.61(r) applies when two conditions are met: (a) "if potency is a factor" and (b) if "no U.S. standard of potency has been prescribed." We interpret "no U.S. standard of potency has been prescribed" to mean there is no "official standard of potency," as described above. This is the case for olipudase alfa products, as no such specific standard preparations and potency tests or limits have been codified in FDA regulations.[13] Accordingly, to determine whether "No U.S. standard of potency" should appear on the package label of Xenpozyme, it is necessary to determine whether "potency is a factor."

CBER's Office of Vaccines Research and Review (OVRR) has historically interpreted "potency" in the phrase "potency is a factor" to be narrower than "potency" as used in section 351 of the PHS Act. This is reasonable because otherwise the phrase "if potency is a factor" would be redundant, as all biological products must be potent.[14] Specifically, "potency is a factor" only when FDA has determined that healthcare providers need to be aware of significant risk information related to product variability to use the product safely and effectively. For example, for non-standardized allergenic products, the products are formulated as weight/volume (w/v). There is no correlation of content to biological activity, and while w/v may be the same from lot-to-lot, the biological activity may not be the same from lot-to-lot. There is a boxed warning in the prescribing information for these products related to switching lots: "Patients with extreme sensitivity to these products, on an accelerated immunotherapy build-up, *switching to another*

[12] Id.

[13] Over the years, there have been questions about whether the existence of any USP monograph for a particular biological product would impact the applicability of § 610.61(r). There are relatively few USP monographs for biological products, and this memorandum does not take a position on whether USP monographs are applicable to biological products. As noted above, the regulatory history of § 610.61(r) and related provisions shows that the phrases "official standard of potency" and "U.S. standard of potency" refer to additional specific standard preparations and potency tests or limits as codified in regulation by FDA. The existence of any USP monograph for a particular biological product would not impact the interpretation or applicability of § 610.61(r).

[14] See, e.g., section 351(a)(2)(C)(i) of the PHS Act.

lot, receiving high doses of these products, and patients exposed to similar allergens may be at increased risk of a severe allergic reaction."[15] Inclusion of "No U.S. standard of potency" on the package label serves to reinforce this significant risk information to mitigate the risk of severe allergic reactions. However, for bacterial products and viral vaccines, "No U.S. standard of potency" does not appear on the package label—even though there are no longer official standards of potency for these products[16]—because the manufacturing process, including potency testing, ensures lot-to-lot consistency.[17] Accordingly, because potency is not a "factor" for these bacterial products and viral vaccines, the second clause of § 610.61(r) does not apply.

The above considerations for concluding that "potency is a factor" do not apply to Xenpozyme. Xenpozyme's prescribing information does not, for example, include a boxed warning containing significant risk information related to product variability. Lot variability is not a concern for Xenpozyme because Xenpozyme's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, potency is not "a factor" for Xenpozyme for purposes of § 610.61(r); and even though "no U.S. standard of potency has been prescribed" in regulation for this biological product, the phrase "No U.S. standard of potency" is not required to appear on Xenpozyme's package label for the reasons described above.

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[15] See, e.g., Non-Standardized Allergenic Extracts labeling, available at https://dailymed nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=7a04fcbd-969d-7acd-e053-2991aa0a7a84&type=display.

[16] See 60 FR 53480 (Oct. 13, 1995) and 61 FR 40153 (Aug. 1, 1996) (proposed and final rules removing the regulations that specified standards for these products, including the official standards of potency).

[17] FDA has recently become aware of potential inconsistent application of this regulation but intends to apply a consistent approach going forward.

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/s/

JENNY N DOAN
08/16/2022 09:36:54 AM
on behalf of Janice Weiner, J.D., M.P.H., Principal Regulatory Counsel, CDER/Office of Regulatory Policy/DRP I

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 28, 2022

To: Christine Y. Hon, Clinical Reviewer, M.D.
Division of Rare Diseases and Medical Genetics (DRDMG)

Jenny N. Doan, Regulatory Project Manager, DRDMG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorksy, Team Leader, OPDP

Subject: OPDP Labeling Comments for XENPOZYME (olipudase alfa-rpcp) for injection, for intravenous use

BLA: 761261

In response to DRDMG's consult request dated November 4, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for XENPOZYME (olipudase alfa-rpcp) for injection, for intravenous use (Xenpozyme).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG's (Jenny N. Doan) on July 20, 2022, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 29, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
07/28/2022 08:48:05 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Addendum to Division of Pediatric and Maternal Health Review

Date: 7/22/22 **Date consulted:** 11/4/21

From: Jane Liedtka, MD, Medical Officer (MO), Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health, DPMH

To: Jenny Doan, Regulatory Project Manager (RPM)
Division of Rare Diseases and Medical Genetics (DRDMG)

Drug: Olipudase alfa

BLA: 761261

Applicant: Genzyme Corporation

Subject: Pregnancy and Lactation Labeling/PMR recommendation

Indication: An enzyme replacement therapy for (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

Materials Reviewed:

- Applicant's submitted Integrated Summary of Safety, submitted 11/3/21
- DPMH review of (b) (4) NDA (b) (4)

[1] The (b) (4) consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

- DPMH review of Olipudase, BLA 761261, Jane Liedtka, M.D., 4/14/22. DARRTS Reference ID: 4971662

Consult Question: DRDMG would like DPMH input on the labeling and potential post-marketing study required for this new application.

INTRODUCTION AND BACKGROUND

- On 11/3/21, the applicant (Genzyme) submitted an original BLA for Olipudase alfa for the (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD-also known as Niemann-Pick disease) in pediatric and adult patients. DRDMG consulted DPMH on 11/4/21 to request assistance for the proposed prescribing information to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and potential post-marketing study required for this new application.
- On 4/14/22, DPMH archived their consult in DARRTS which recommended labeling language for a Warning and Precaution for embryofetal toxicity and for Section 8, including recommendations for VERIFYING STATUS PRIOR TO TREATMENT and for contraception. At that time, DPMH recommended a postmarketing study for a Descriptive Pregnancy Safety Study.

REVIEW

See previous DPMH review dated 4/14/22 for "Drug Characteristics", "Acid Sphingomyelinase Deficiency (ASMD) and Pregnancy, "Nonclinical Experience", "Review of Pharmacovigilance Database" and "Review of the Literature".

Reviewer's Comment
In 2021, DPMH reviewed (b) (4) *NDA* (b) (4) *At that time, DPMH decided not to ask for PMRs for either Pregnancy or Lactation Safety studies based on infeasibility due to the rare nature of ASMD/Niemann-Pick disease and the rarity of women patients reaching the age of reproductive potential and achieving pregnancy.*

In the "Discussion and Conclusions" section under "Pregnancy" in the 4/14/22 DPMH review, the reviewer states:

> There are no data in the published literature or in the applicant's pharmacovigilance database regarding olipudase alpha exposure in pregnant women. In a study of embryo-fetal development in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from gestation days (GD) 6 through 15. Exencephaly was observed in 5 fetuses of 2 pregnant mice treated with 10 and 30 mg/kg. The maternal No Observed Adverse Effect Level (NOAEL) is at a dose exposure ~1.6 the exposure associated with the MRHD. The developmental NOAEL is at a dose exposure approximately 1/7th the exposure associated with the MRHD. Based on these findings in animal studies, DPMH recommends the addition of an Embryo-Fetal Toxicity warning to the labeling for Olipudase to describe the potential risk to the developing fetus.

DPMH also recommends pregnancy testing prior to treatment and effective contraception in females of reproductive potential.

DPMH had a discussion with the DRDMG review team regarding the approach to labeling and whether a REMS would be appropriate. The conclusion of this discussion was to use labeling to mitigate the risk and that neither a REMS nor a contraindication was warranted at this time. This was based on the very low number of pregnancies expected in this population (based on very few being found in the literature) and concerns that a REMS would be likely to result in restricted access.

There are no human data available to inform the safety of olipudase alpha use during pregnancy, however, due to the low prevalence of pregnancy in women with ASMD and the fatality of this disease, DPMH does not believe that collection of data through the issuance of a post-marketing pregnancy registry safety study would be feasible. A previous application for a drug for ASMD set this as a precedent[1]. DPMH recommends a descriptive pregnancy safety study monitor for any reports of olipudase alpha exposures during pregnancy and follow up on maternal and infant outcomes.

Reviewer's Comment
Further discussion internally at DPMH and further discussion with the division led to the decision that, due to the rare nature of ASMD/Niemann-Pick disease and the rarity of women patients reaching the age of reproductive potential and achieving pregnancy, routine pharmacovigilance would be appropriate for follow up and monitoring of pregnancy exposures and outcomes.

CONCLUSION
Routine pharmacovigilance is appropriate for follow-up and monitoring of Olipudase-exposed pregnancies and maternal and infant outcomes for patients with ASMD.

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/s/

JANE E LIEDTKA
07/22/2022 08:59:15 AM

TAMARA N JOHNSON
07/22/2022 12:21:12 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 21, 2022
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761261
Product Name and Strength:	Xenpozyme (olipudase alfa-rpcp) for injection, 20 mg
Applicant/Sponsor Name:	Genzyme Corporation
OSE RCM #:	2021-2149-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised a container label and carton labeling received on June 29, 2022 for Xenpozyme. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Xenpozyme (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations.

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/s/

SALI MAHMOUD
07/21/2022 11:47:22 AM

ASHLEIGH V LOWERY
07/21/2022 04:29:04 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 27, 2022
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761261
Product Name, Dosage Form, and Strength:	Xenpozyme (olipudase alfa-rpcp) for injection, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genzyme Corporation
FDA Received Date:	November 3, 2021
OSE RCM #:	2021-2149
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

As part of the approval process for Xenpozyme (olipudase alfa-rpcp) for injection, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Xenpozyme prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G
Suggested edits to the Prescribing Information	H

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed prescribing information (PI), container labels, carton labeling, and determined that they may be improved to ensure safe product use. We note that the PI describes in complex detail the steps of calculating, measuring, and manipulating three types of containers (syringe, empty infusion bag, filled infusion bag) to obtain Xenpozyme infusion solution. The multiple dilutions, volumes, and rates of infusion present risk for medication errors. We also note under section 2.7 of missed doses that several pediatric scenarios are not accounted for and that following the listed instruction could lead to medication errors in those instances. Additionally, the instructions for dose escalation after missing 3 consecutive doses in the maintenance phase do not explicitly state if repeating the 0.3 mg/kg dose is recommended. The nature of this drug requires sequential dosing escalation and careful titration of the infusion rates to minimize anaphylaxis and infusion associated reactions. We consulted with Division of Rare Diseases and Medical Genetics (DRDMG) and Division of Risk Management (DRM) about the need for a Medication Guide or Instructions for Use to guide providers who

may be administering Xenpozyme. A decision was made to optimize labeling within the PI to stay consistent with other Enzyme Replacement Therapies. DMEPA agreed that optimizing the PI can decrease the vulnerability to error.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to ensure safe product use. We provide specific recommendations in sections 4.1 and 4.2 below. Appendix H contains portions of PI section 2 Dosage and Administration, section 3 Dosage Forms and Strengths, section 16 How supplied/Storage and handling and section 17 Patient Counseling Information to better capture our suggested edits.

4.1 RECOMMENDATIONS FOR DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

A. Highlights of Prescribing Information- Dosage and Administration

1. Dosage and Administration section does not contain required information. HPI lacks overview of dosage and administration information which makes HPI less effective. Recommend removing (b) (4) Add the following:

"Adults- The recommended starting dose of XENPOZYME is 0.1 mg/kg for adults administered every 2 weeks as an intravenous infusion.

Pediatrics- The recommended starting dose of XENPOZYME is 0.03 mg/kg for pediatric patients, administered every 2 weeks as an intravenous infusion."

B. Prescribing Information

1. Dosage and Administration Section (see Appendix H for edits in tracked changes)

a. Suggest changing the mathematical symbols of >, <, ≤, and ≥ to greater than, less than, less than or equal to, and greater than or equal to. Use of >, <, ≤, and ≥ is not recommended because it can be misunderstood and are listed on the Institute of Safe Medication Practices' list of Error-Prone Abbreviations[a].

[a] ISMP's List of Error-Prone Abbreviations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2021. Available from: https://www.ismp.org/recommendations/error-prone-abbreviations-list

b. Section 2.2- Change the adjusted body weight formula to be done in order of mathematical operations to minimize calculation errors: Body weight (kg) to be used for dose calculation = (actual height in m)^2 x 30

c. Section 2.4- Suggest streamlining preparation by assigning a final target concentration as in suggested table 3 (see appendix H). This will allow for consistent preparation regardless of container. It will allow for consistent infusion rates due to fixed concentrations.

d. Section 2.5- Tables 4 and 5- [redacted] (b) (4) column is redundant. Suggest deleting to reduce clutter.

e. Missed doses Section 2.7

   i. Consider displaying the regimen for missed doses in table format for clarity. Information on various missed dose scenarios is presented in list format. A table can display this information more effectively.

   ii. Clarify what the minimal dose during the escalation phase should be for pediatric patients who have missed doses. As proposed, the dose escalation instructions state that after missing two or three doses a pediatric patient is to re-start at 0.3 mg/kg . Clarify if a pediatric patient should restart at 0.03 mg/kg or at 0.3 mg/kg.

2. Section 16 How Supplied/Storage and Handling

   a. Delete the following to reduce redundancy: [redacted] (b) (4)

   This information is found in section 2.

4.2 RECOMMENDATIONS FOR GENZYME CORPORATION

A. General Comments (Container labels & Carton Labeling)

1. On March 18, 2022 the suffix "-rpcp" was granted for conditionally acceptable use with your product. Update the nonproprietary name to include the suffix on carton and container labels.
2. Consider supplying different vial strengths. As written preparing an adult size infusion will require the use of many vials while a pediatric dose will require an alternate dilution method to obtain the target concentration of 0.1 mg/mL. Creating vial strengths and sizes that better approximate likely dosing can minimize risk of medication errors.

B. Container Labels

1. Consider adding “Reconstitute with 5.1 mL of Sterile Water For Injection to yield concentration of 4 mg/mL solution.” Providing the information as space permits will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.
2. Move dosage statement to side panel; change to “Recommended Dosage: See Prescribing Information” to ensure consistency with the Prescribing Information
3. Add “single dose vial- discard unused portion” to principal display panel of container label.

C. Carton Labeling

1. Change to “Recommended Dosage: See Prescribing Information” to ensure consistency with the Prescribing Information.
2. GTIN number should appear with the other product identifiers (Lot, SN, Exp date) in the area reserved for serialization data on top flap.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xenpozyme received on November 3, 2021 from Genzyme Corporation.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Xenpozyme</th></tr>
<tr><td>Initial Approval Date</td><td>NA</td></tr>
<tr><td>Nonproprietary Name</td><td>olipudase alfa-rpcp</td></tr>
<tr><td>Indication</td><td>Enzyme replacement therapy for (b) (4) treatment of non–central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients</td></tr>
<tr><td>Route of Administration</td><td>Intravenous</td></tr>
<tr><td>Dosage Form</td><td>for injection</td></tr>
<tr><td>Strength</td><td>20 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Dose Escalation Phase
The recommended starting dose of XENPOZYME is 0.1 mg/kg (b) (4)
Table 1: (b) (4)
<table><tr><th colspan="2">Adult Patients (b) (4)</th></tr><tr><td>First dose (Day 1/Week 0)</td><td>0.1 mg/kg</td></tr><tr><td>Second dose (Week 2)</td><td>0.3 mg/kg</td></tr><tr><td>Third dose (Week 4)</td><td>0.3 mg/kg</td></tr><tr><td>Fourth dose (Week 6)</td><td>0.6 mg/kg</td></tr><tr><td>Fifth dose (Week 8)</td><td>0.6 mg/kg</td></tr><tr><td>Sixth dose (Week 10)</td><td>1 mg/kg</td></tr><tr><td>Seventh dose (Week 12)</td><td>2 mg/kg</td></tr><tr><td>Eighth dose (Week 14)</td><td>3 mg/kg (recommended maintenance dose)</td></tr></table>Maintenance Phase
(b) (4)</td></tr>
</table>

(b) (4)

Table 2: (b) (4)

Pediatric Patients (0 to (b) (4) 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)

Maintenance Phase

(b) (4)

How Supplied	A sterile white to off-white lyophilized powder for reconstitution in single-dose vials. (b) (4)
Storage	Store (b) (4) refrigerated at 2°C to 8°C (36°F to 46°F)
Container Closure	20 mm (b) (4) gray elastomeric stopper (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 19, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, olipudase. Our search identified no previous reviews.

APPEARS THIS WAY ON ORIGINAL

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Xenpozyme labels and labeling submitted by Genzyme Corporation.

- Container label received on November 3, 2021
- Carton labeling received on November 3, 2021
- Prescribing Information (Image not shown) received on November 3, 2021, available from \\CDSESUB1\evsprod\bla761261\0002\m1\us\annotatedpi.doc

G.2 Label and Labeling Images

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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ASHLEIGH V LOWERY
06/28/2022 09:14:57 AM

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From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Rare Diseases and Medical Genetics (DRDMG)

Subject: Review of linear growth progression to be included in pediatric labeling

Applicant: Genzyme Corporation[1]

Application number: BLA 761261

Drug: Olipudase alfa[2]

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[1] This review will refer to "Genzyme Corporation" as the "Applicant"

[2] This review will refer to the drug product as "Olipudase"

Drug Class: Enzyme Replacement Therapy

Proposed Indication: (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency in pediatric and adult patients

Proposed Dosage Form: Lyophilized powder for injection

Route of administration: Intravenous (IV)

Proposed Dosing Regimen: Pediatric Patients:
Initial dose of 0.03 mg/kg with dose escalation every 2 weeks for 16 weeks as per a dose escalation table up to a maintenance dose of 3 mg/kg every 2 weeks.

Adult Patients:
Initial dose of 0.1 mg/kg with dose escalation every 2 weeks for (b) (4) weeks as per a dose escalation table up to a maintenance dose of 3 mg/kg every 2 weeks.

For patients with a body mass index (BMI) greater than 30 kg/m^2, a body weight used for dosing is calculated as 30 times the actual height in meters squared for dose escalation and maintenance dosing.

Consult Request:
DRDMG requests that DPMH comment on the clinical relevance of the assessment in growth submitted from the pediatric trials for potential inclusion in labeling and/or the need for a post-marketing study.

Materials Reviewed/Referenced:

- The following documents entered into DARRTS under BLA 761261, November 3, 2021:
  - Clinical Overview, Module 2.5 (eCTD #2)
  - Summary of Clinical Efficacy, Module 2.7.3 (eCTD#2)
  - Summary of Clinical Safety, Module 2.7.4 (eCTD#2)
  - Clinical Study Report, Interim 2, Study DFI13803, Module 5.3.5.2, (eCTD #2)

- Efficacy Response Data Listing, Study DFI13803, Module 16.2.6 (eCTD #2)
- Clinical Study Report, Interim 2, Study LTS13632, Module 5.3.5.2, (eCTD #2)
- Efficacy Response Data Listing, Study LTS13632, Module 16.2.6 (eCTD #2)
- Other Safety Observations Data Listing, Part 1, Study DF113803, Module 16.2.7 (eCTD#2)

- The following documents entered into DARRTS under BLA 761261:
  - Clinical/Response to Information Request, Submitted May 13, 2022 Module 1.11.3, (eCTD#37)
  - Clinical/Response to Information Request, Submitted May 6, 2022 (eCTD#35)
  - Information Request, dated May 5, 2022
  - Mid-Cycle Communication, dated May 4, 2022
  - Information Request, dated April 28, 2022
  - Non-Clinical Overview, Submitted September 8, 2021, Module 2.4 (eCTD #1)
  - Clinical/Response to Information Request, Submitted March 18, 2022, Module 1.11.3, (eCTD #22)

- The following documents entered into DARRTS under IND 12757:
  - Amended Clinical Trial Protocol, V.6, Study LTS13632, Submitted February 11, 2021 (eCTD# 251)
  - Safety Report, Submitted October 20, 2020, Module 5.3.5.4 (eCTD#243)
  - Safety Report, Submitted March 20, 2020, Module 5.3.5.4 (eCTD#236)
  - Safety Report, Submitted January 16, 2020, Module 5.3.5.4 (eCTD#232)
  - Safety Report, Submitted February 27, 2018, Module 5.3.5.4 (eCTD#165)
  - DPMH Pediatrics Review Memorandum, dated November 4, 2015
  - Clinical Trial Protocol, Study DFI13803, Submitted October 3, 2014 (eCTD# 66)
  - Statistical Analysis Plan, Study DFI13803, Submitted October 3, 2014 (eCTD# 66)
  - Meeting Minutes from the October 4, 2011 Type C Meeting, dated November 4, 2011

- The following documents entered into DARRTS under IND (b) (4)
  - Acknowledge Withdrawal Letter, dated February 14, 2018
  - Advice/Information Request, dated December 1, 2017

- Primary Clinical Review, dated November 29, 2017

- The following documents entered into DARRTS under IND (b) (4)
  - Acknowledge Withdrawal Letter, dated April 29, 2022
  - Withdrawal Request – General Information/Application, dated April 27, 2022
  - Primary Clinical Review, dated September 14, 2020

I. Background

A. Acid Sphingomyelinase deficiency (ASMD):

Acid Sphingomyelinase Deficiency (ASMD), historically known as Niemann-Pick Disease (NPD), is a rare and potentially life-threatening lysosomal storage disease. Patients with ASMD have variable impairment in sphingomyelin metabolism due to pathogenic variants in sphingomyelin phosphodiesterase 1 (SMPD1), the gene encoding acid sphingomyelinase (ASM) that results in progressive lysosomal accumulation of sphingomyelin mostly within cells of the monocyte/macrophage lineage that reside in reticuloendothelial tissues, namely in the spleen, liver, lung, bone marrow, and lymph nodes. Severe disease is characterized by neurologic manifestations.

ASMD is inherited as an autosomal recessive disease. The spectrum of clinical presentations are classified into three categories, types A, B, and A/B depending on the onset of signs/symptoms and the degree of neurologic involvement. Visceral manifestations of ASMD include liver dysfunction, pulmonary disease, retinal stigmata, and growth retardation. ASMD Type A disease is the most severe; presenting within the first year of life and characterized by failure to thrive, progressive neurologic deterioration, hepatosplenomegaly, and death before 3 years of age. Type B disease is usually diagnosed after 2 years of age and presents primarily with visceral complications (e.g. hepatosplenomegaly) with mild or no neurologic manifestations and longer survival than type A disease. Type A/B disease represents and intermediary form of ASMD with patients developing neurologic symptoms during childhood with neurologic and/or visceral manifestations dominating. Survival beyond 3 years of age distinguishes type A/B from type A disease.

The natural history of ASMD is one that is characterized by growth delay in all types.[3,4] Mean height Z-scores reported in pediatric and adult patients older than 7 years of age with ASMD type B disease are -1.3 with larger deficiencies in adolescents 13 years of age and older (mean height Z-score of -2.7) versus younger patients (mean height Z-score of -1.4).[5] The majority of adolescents assessed have delayed bone age; the mean delay documented in children and adolescents with Type B disease is -2.5 years.[6] Short stature is also associated with large organ volumes and low IGF-1 levels.[7]

II. BLA 761261

A. Drug Product:

Olipudase is a recombinant human ASM expressed in Chinese hamster ovarian cells. The resulting gene product retains the enzymatic activity and lysosomal targeting of the native protein. In this NDA submission, the Applicant is seeking approval of olipudase alfa as a disease modifying enzyme replacement therapy for (b) (4) treatment of non-central nervous system (CNS) manifestations of ASMD in pediatric and adult patients. Olipudase does not cross the blood-brain barrier. As a result, it is not expected to provide amelioration or treatment of the neurologic manifestations of ASMD.

B. Non-Clinical Studies Supporting the Efficacy and Safety of Olipudase in Pediatric Patients:

Proof of concept for olipudase alfa therapy has been demonstrated in the complete acid sphingomyelinase knock out (ASMKO) mouse, which exhibits both systemic and neurological features of ASMD. Non-clinical studies focused on the assessment of sphingomyelin accumulation (e.g. reduction) in visceral organs and the lungs. Results of the non-clinical studies reveal that doses in the range of 0.1 to 3 mg/kg resulted in dose-dependent reductions in sphingomyelin in the liver, spleen, and lung. Chronic efficacy

[3] McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis. 2017 Feb 23;12(1):41

[4] McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008; 122(2): e341-9.

[5] Ibid

[6] Wasserstein MP, Larkin AE, Glass RB, Schuchman EH, Desnick RJ, McGovern MM. Growth restriction in children with type B Niemann-Pick disease. J Pediatr. 2003; 142(4): 424-8.

[7] Ibid

and safety data in ASMKO mice is limited due to the animals succumbing to the neurologic manifestations of disease in 6 to 8 months.

The Applicant conducted single- and repeat-dose toxicity studies of Olipudase in Sprague-Dawley rats, dogs, and cynomolgus macaques. Results of toxicity studies showed that doses of up to 30 mg/kg were well tolerated in normal rats, dogs, and macaques but not in ASMKO mice who developed lethargy, histopathologic changes consisting of focal areas of necrosis and apoptosis in the liver and adrenal glands, cardiovascular aberrations, and early death at doses of 10 mg/kg and greater. Much of this toxicity in ASMKO mice was mitigated by sequential administration of gradually increasing dose increments in repeat dose toxicity studies suggesting that the observed toxicity was related to the rate of degradation of the substrate. As a result, the no-observable-adverse-effect-level (NOAEL) for a single dose of Olipudase is 0.3 mg/kg and for repeated dosing is 3 mg/kg dosed once every 2 weeks. This NOAEL was based on the findings of only mild hepatocellular ballooning degeneration and inflammatory foci at the 3 mg/kg repeated dosing. The toxicity of Olipudase was mitigated, in part, by gradual increases of dose. The single- and multiple-dose NOAEL served as the basis for the starting dose and proposed dose escalation design in the pediatric clinical trials.

The Applicant conducted developmental and reproductive toxicity studies in CD-1 mice and New Zealand White Rabbits with no adverse effects noted at the highest 30 mg/kg dose tested.

C. Clinical Studies Supporting the Efficacy and Safety of Olipudase in Pediatric Patients:

The clinical drug development program for Olipudase included a total of 10 studies in patients with ASMD. Five of these were natural history studies, and 5 were interventional phase 1 to 3 trials. The non-interventional studies included 3 prospective, 1 retrospective and 1 prospective/retrospective multi-center, natural history study of pediatric and adult patients with ASMD. Two natural history studies were conducted in a pediatric study population, 2 in a combined adult and pediatric population, and 1 study in an adult-only patient population. The phase 1 to 3 studies using Olipudase include a total of 67 patients (47 adults and 20 pediatric patients with ASMD).

1. Study SPHINGO00605

SPHINGO00605 is a completed phase 1a single center, single-dose escalation trial of Olipudase administration in 11 adults with ASMD. The study was terminated after dosing

in 11 adults due to the occurrence of nausea, vomiting, fever, and hyperbilirubinemia in a a patient after receiving a 1 mg/kg dose.

2. Study DFI13412 (SPHINGO00812)

SPHINGO00812 is a completed phase 1b open-label, multicenter, ascending dose trial of the tolerability and safety of repeated bi-weekly doses of Olipudase administered in 5 pediatric and adult patients with ASMD through 26 weeks.

3. Study DFI13803 (ASCEND-Peds)

ASCEND-Peds is a completed phase 1/2 multicenter, open-label ascending dose trial to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, and exploratory efficacy of Olipudase in 20 pediatric patients with ASMD through 64 weeks of dosing. The study population consisted of patients with ASMD without acute or rapidly progressive neurologic abnormalities. This study was designed primarily to assess safety with secondary endpoints consisting of PK and exploratory efficacy assessments. The latter consisted of assessing spleen volumes by magnetic resonance imaging as well as pulmonary function tests. Patients were enrolled in three staggered cohorts beginning with adolescent patients aged 12 to less than 18 years, followed by patients 6 to less than 12 years of age, and finally patients from birth to less than 6 years of age. Enrollment in successive cohorts of patients began when at least 3 patients in the older cohort completed the dose escalation phase of treatment and the resulting safety data were reviewed by the Data Monitoring Committee (DMC). Inclusion criteria for participation in the trial included a height Z-score less than or equal to -1.

Patients initiated Olipudase at a dose of 0.03 mg/kg that was titrated to a maintenance dose of 3 mg/kg for the duration of the treatment period. The study included a 60-day screening period, 64-week treatment period, and a post-treatment period up to 37 days, unless the patients enrolled in study LTS12632 (long-term extension study). The study protocol stipulated assessment of height and weight at screening, baseline, and every two weeks prior to Olipudase infusions through the 64-week treatment period. Bone age assessed by x-ray of the left hand occurred at screening and at the 52-week visit. Sexual maturation, as assessed by Tanner staging, occurred at baseline, and weeks 12, 26, 38, and 52 during which a complete physical exam was conducted.

Measurement of height or length in Study DFI13803 (ASCEND-Peds) occurred at each study visit and prior to each Olipudase infusion. Height/length was measured at

screening, the baseline study visit, and every two weeks prior to Olipudase infusions thereafter through the 64-week treatment period and at study withdrawal if the patients did not continue in study LTS12632. Height Z-score was calculated for each measured height/ length. The study protocol does not specify how height was measured other than noting that shoes were removed for standing height assessment. The Statistical Analysis Plan does not specify which reference data were used to generate height Z-scores. Linear growth, as assessed by change in height Z-score, was an exploratory efficacy endpoint in ASCEND-Peds. Change in height/length Z-score is conducted on the modified intent-to-treat analysis set of patients which include all patients who tolerated 2 consecutive doses of Olipudase at doses of at least 0.3 mg/kg.

4. DFI12712 (ASCEND):

ASCEND is a phase 2/3 multicenter, randomized, double-blind, placebo-controlled, repeated dose trial designed to evaluate the efficacy, safety, PK, and PD of Olipudase in 36 adult patients with ASMD. The trial randomized patients 1:1 to Olipudase or placebo. The completed primary treatment analysis period lasted 52 weeks with an ongoing treatment extension period lasting up to 4 years. Patients initiated Olipudase at a dose of 0.1 mg/kg titrated to a maintenance dose of 3 mg/kg for the duration of the treatment period.

5. Study LTS13632:

Study LTS13632 is an ongoing multicenter, multinational, non-randomized, open-label, long-term treatment study assessing safety and efficacy of Olipudase in 20 pediatric and 5 adult patients with ASMD who completed studies SPHINGO00812 or ASCEND-Peds. The 20 pediatric patients had a mean age of 7.6 years at enrollment with a range of 1 to 17 years of age. There was an equal distribution (n=10, 50%) of males and females among the pediatric patients. At entry to this long-term extension trial, Olipudase was continued at the last weight-based dose patients were receiving at the end of their participation in studies SPHINGO00812 or ASCEND-Peds. Enrolled patients were to receive Olipudase infusions every 2 weeks for 9 years, or marketing approval, whichever occurs first. Over the 9 year treatment period, safety and efficacy assessment initially occurred at an interval of 3, 6, and 12 months with subsequent assessments occurring every 6 to 12 months thereafter. Patients completing or withdrawing from the study were to undergo a post-treatment visit 2 weeks after the last dose and a follow-up safety phone call 30 to 37 days after last dose administration. Height was measured at 3 months and 9 months during the first year and then every 6 months thereafter and at study completion/patient withdrawal. Bone age assessed by x-ray of the left hand occurred at 3

months and 9 months during the first year and every 6 months for the following 4 years and then yearly thereafter. Sexual maturation, as assessed by Tanner staging, was assessed at 3 months and 9 months during the first year and every 6 months for the following 4 years and then yearly thereafter.

The initial assessment of the change in height/length Z-score was conducted on the efficacy analysis set, which included all patients who received at least 1 infusion of Olipudase in Study LTS13632.

During the Mid-Cycle meeting held with the Applicant on April 21, 2022, the Division informed the Applicant that the analytic differences in Olipudase manufactured by Process B versus Process C (b) (4)/Process C (b) (4) will impact the efficacy and safety analyses in the ongoing BLA review because the submitted data consisted of patients who had received Olipudase manufactured via both processes. In a subsequent Information Request dated April 28, 2022, the Division asked the Applicant to provide baseline demographic and clinical characteristics of the safety population for the 12 pediatric patients who received Process B manufactured Olipudase and the 8 pediatric patients who received Process C manufactured Olipudase in ASCEND-Peds. The Division also requested in this Information Request as well as another Information Request dated May 5, 2022, that the Applicant provide separate analyses of changes in height, height Z-score, and bone age in ASCEND-Peds and LTS13632 for pediatric patients receiving Process B and Process C manufactured Olipudase.

The Division also informed the Applicant at the Mid-Cycle Meeting that the proposal to include patients with ASMD type A as well as ages down to birth in the indication is an ongoing review issue for the following reasons:

- Patients with ASMD type A were specifically excluded from enrollment in ASCEND-Peds and Study LTS13632. In a Type C meeting with the Applicant to discuss future clinical development plans for XENPOZYME, the Division recommended that the clinical development protocol should clearly identify the intended study population to include patients with “non-neuronopathic” ASMD as the drug product would likely not treat patients with “neuronopathic” ASMD. Although patients with ASMD type A develop non-neurologic manfiestations of disease, the neurologic manifestations of type A disease were thought to be too rapidly progressive and lethal to enable enrollment of this population for the trial duration.
- The youngest patient enrolled in the clinical program was 16 months old.

D. Assessment of Safety of Olipudase

Safety data from studies SPHINGO00812, ASCEND-Peds, ASCEND, and LTS13632 comprise the safety dataset for this NDA submission. The pediatric safety data set includes pediatric patients from studies ASCEND-Peds, and LTS13632. The overall and pediatric safety data sets include all patients that received at least one dose (partial or total) of Olipudase.

Twenty pediatric patients with ASMD enrolled in ASCEND-Peds and completed the study. All 20 pediatric patients are ongoing in their participation in study LTS13632.

As of the March 15, 2021 data cut-off date, the 20 pediatric patients received a median of 4 years (range 2.5 to 5.7 years) of Olipudase treatment. There were 7 patients less than 6 years of age, 9 patients 6 to less than 12 years of age, and 4 adolescents, 12 to less than 18 years of age enrolled in the trial. There were 10 male and 10 female pediatric patients enrolled. The median age of the pediatric patients at baseline was 8 years (range 1 to 17 years). The median age of symptom onset was 1 year with a median age of diagnosis of 1.9 years. Pediatric patients had a mean duration of disease from the time of diagnosis to study enrollment of 4.9 years. Forty percent of pediatric patients had neurologic manifestations of ASMD.

The dose escalation period lasted a mean of 139 days. The median duration of Olipudase treatment was longest at 5.7 years in the 4 adolescent patients compared to 4.3 years in patients 6 to less than 12 years of age and 3.1 years in patients less than 6 years of age.

All 20 patients received at least 1 concomitant medication, and the most frequently taken medications by therapeutic class were analgesics (100%), anti-inflammatory and antirheumatic products (70%), vaccines (70%), antibacterials for systemic use (70%), antihistamines for systemic use (55%), buccal mucosal preparations for topical use (70%), cough and cold preparations (45%), antibiotics and chemotherapeutics for dermatological use (55%), and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (55%). Lipid modifying agents were taken by 15% of patients.

There was a higher incidence of serious adverse events (SAEs) (45% versus 32.5%) as well as SAEs judged related to Olipudase treatment (20% vs. 2.5%) in pediatric patients compared with adults treated in ASCEND and ASCEND-Peds. The treatment-emergent adverse events (TEAE) that occurred in at least 10% of patients included pyrexia, vomiting, urticaria, and headache. The percentage of patients with treatment-related TEAEs was similar in adult and pediatric patients (70.0% versus 75.0%, respectively). Treatment-related TEAEs that were more frequently (greater than a 20% difference)

reported in pediatric patients compared with adult patients, were pyrexia (45.0% versus 15.0%), vomiting (35.0% versus 7.5%), and urticaria (35.0% versus 15.0%). The high percentages of SAEs and TEAEs observed in the pediatric population compared to adults may be misleading because of the small sample size (n=36 for adult and n=20 for pediatric patient enrollment) in the respective trials.

Four pediatric patients enrolled in ASCEND-Peds and continued in LTS13632 had 7 treatment-related SAEs. Three patients had infusion associated reactions with one of these patients developing an anaphylactic reaction. One patient had 3 treatment-related SAEs of Alanine Aminotransferase (ALT) elevations.

E. Assessment of Growth in Pediatric Studies

The same method was used to measure height/length during on-site visits in both the ASCEND-Peds and Study LTS13632. Recumbent length for patients 24 months of age and younger and a standing height in patients older than 24 months of age was measured in centimeters. Height/length were not assessed during home infusions. There were no specific provisions for patients older than 24 months of age who were not ambulatory. However, there were no patients older than 24 months of age who were unable to consistently have their height measured in the upright position. No specific equipment was required to measure height/length in the studies. The Applicant generated length/height Z-scores for supine length in study patients 24 months of age and younger and standing height in study patients older than 24 month of age using the World Health Organization (WHO) 2007 reference database.[8,9]

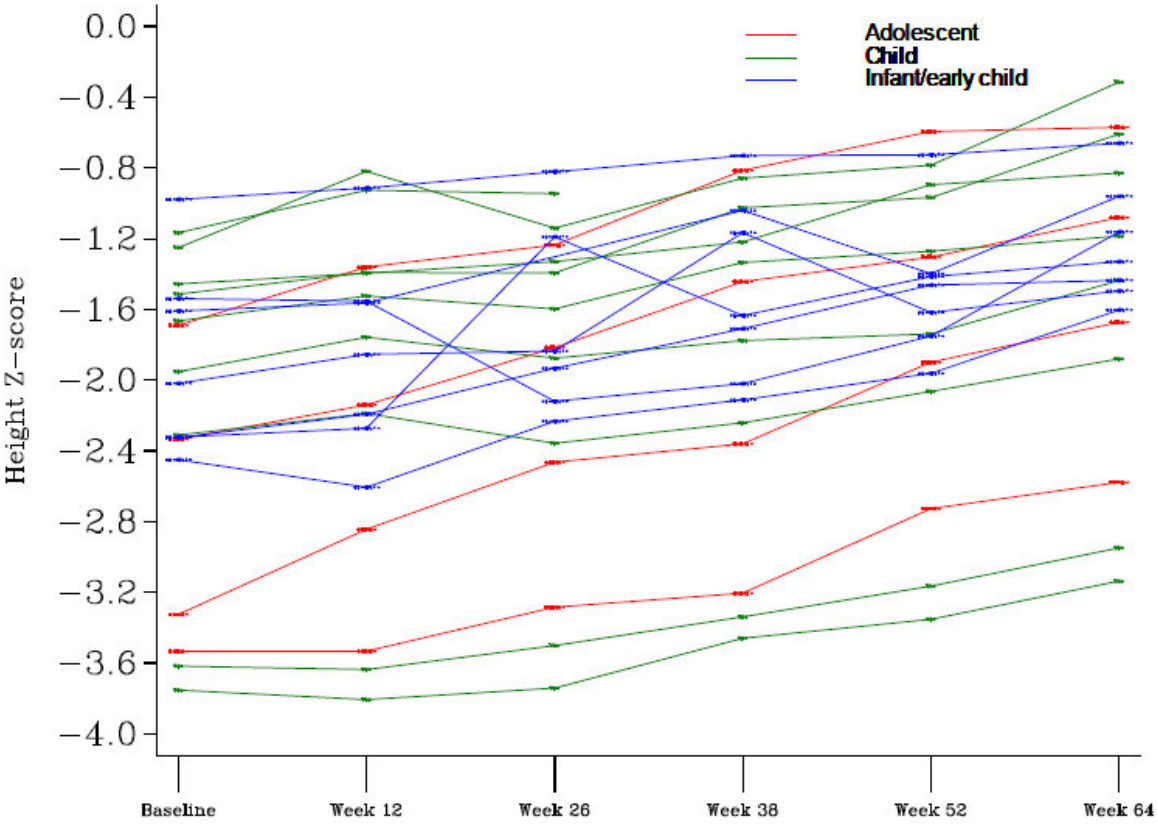
The baseline mean height Z-score in the overall study population in ASCEND-Peds was -2.1 (range -3.6 to -1). The mean height Z-score improved through the 64-week treatment period with a mean height Z-score in the remaining 19 patients in the study of -1.4 (range -3.1 to -0.3) for an overall mean improvement in height Z-score of +0.6 at 52-weeks and +0.8 at 64-weeks. One patient was excluded from evaluation of the change in height Z-score due to having surgery on both legs precluding follow-up height measurements. Through the 64-week treatment period the largest improvement in mean height Z-score occurred in the adolescent cohort (+1.0 [range +0.6 to +1.7]) followed by patients from birth to less than 6 years of age (e.g. infants/early childhood) (+0.8 [range +0.5 to +1.3]) and finally patients 6 to less than 12 years of age (e.g. children) (+0.6 [range +0.3 to +1]).

[8] Found at https://www.who.int/toolkits/child-growth-standards/standards/length-height-for-age

[9] Found at https://www.who.int/toolkits/growth-reference-data-for-5to19-years/indicators/height-for-age

The height Z-scores of patients receiving Olipudase through the 64-week treatment period in Study DFI13803 are shown in **Figure 1**.

Figure 1: Height Z-score by Study Visit in the mITT DFI13803 Study Population



Source: Figure 16 – By patient plot on height Z-score over time – mITT population from the Summary of Clinical Efficacy, Module 2.7.4 (eCTD#2).

The change in height-Z score from baseline in Studies ASCEND-Peds and LTS13632 is shown in **Table 1**.

Table 1: Changes in Height Z-scores by Age Cohort in Studies ASCEND-Peds and LTS13632

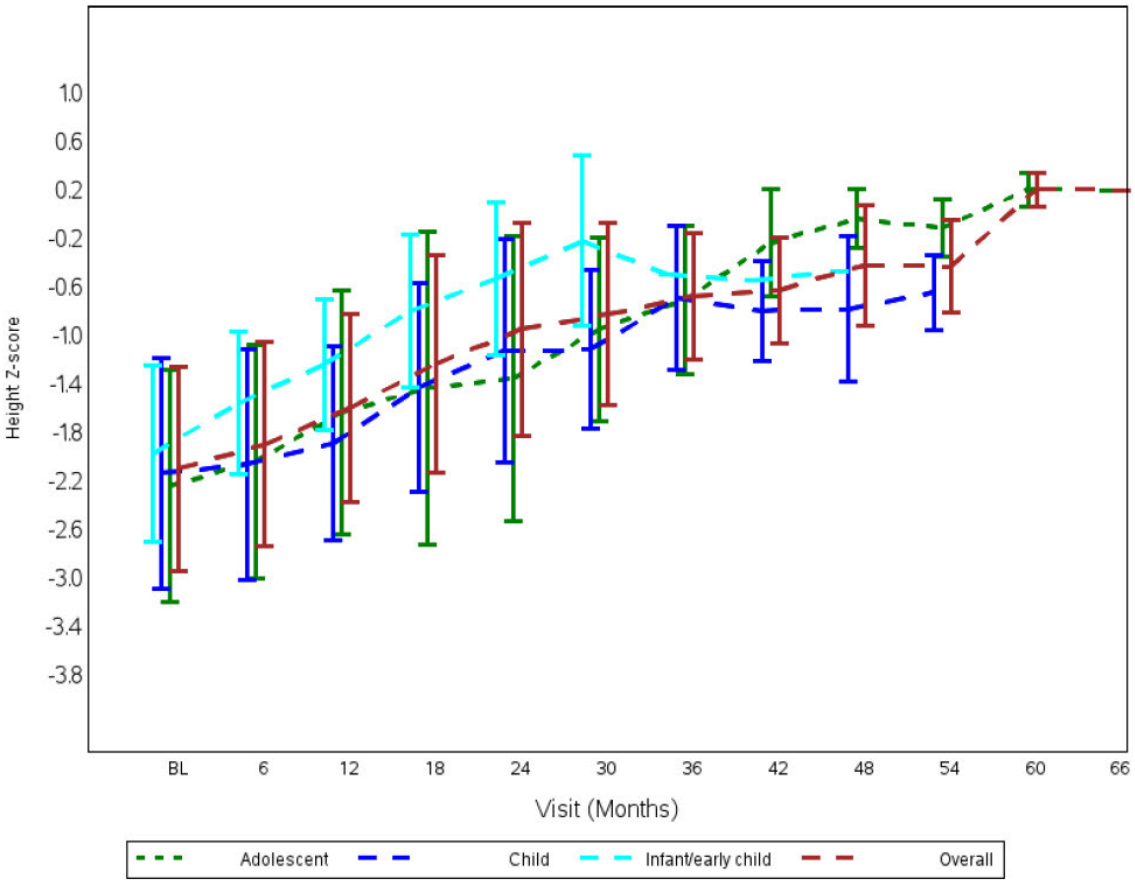
Study visit	Adolescent* (n)	Child* (n)	Infant/Early Childhood* (n)	Overall* (n)
Baseline	-2.3 (4)	-2.2 (9)	-2.0 (7)	-2.1 (20)
Month 3	+0.1 [-0.1, +0.3] (4)	+0.1 [0, +0.2] (9)	+ 0.2 [-0.1, +0.4] (7)	+0.1 [+0.1, +0.2] (20)
Month 6	+0.2 [-0.3, +0.8] (4)	+0.1 [-0.2, +0.3] (9)	+0.5 [+0.1, +0.9] (6)	+0.2 [+0.1, +0.4] (19)
Month 9	+0.5 [-0.2, +1.2] (4)	+0.3 [-0.1, +0.6] (8)	+0.6 [+0.3, +0.8] (7)	+0.4 [+0.3, +0.6] (19)
Month 12	+0.6 [-0.2, +1.4] (4)	+0.4 [+0.1, +0.6] (8)	+0.7 [+0.4, +0.7] (7)	+0.5 [+0.4, +0.7] (19)
Month 15	+0.8 [-0.1, +1.7] (4)	+0.6 [+0.4, +0.7] (8)	+0.9 [+0.7, +1.2] (7)	+0.8 [+0.6, +0.9] (19)
Month 18	+0.8 [-0.6, +2.3] (4)	+0.7 [+0.5, +0.9] (9)	+1.1 [+0.5, +1.7] (6)	+0.9 [+0.6, +1.1] (19)
Month 24	+0.9 [-2.8, +4.5] (3)	+1 [+0.7, +1.3] (7)	+1.5 [+1, +2.1] (6)	+1.2 [+0.9, +1.4] (16)
Month 30	+1.3 [-3.4, +6] (3)	+1.3 [+1, +1.4] (7)	+1.9 [+0.5, +3.3] (4)	+1.4 [+1.1, +1.7] (14)
Month 36	+1.5 [-4, +7.1] (3)	+1.4 [+0.8, +1.8] (5)	+2.8 [None] (1)	+1.6 [+1.2, +1.9] (9)
Month 42	+2.3 [None] (2)	+1.2 [+0.8, +1.7] (5)	+2.7 [None] (1)	+1.7 [+1.3, +2.1] (8)
Month 48	+2.5 [None] (2)	+1.9 [None], (2)	+2.8 [None] (1)	+2.3 [+1.7, +3] (5)
Month 54	+2.4 [None] (2)	+1.7 [-1.2, +4.6] (3)	- [None] (0)	+2 [+1.3, +2.6] (5)
Month 60	+2.7 [None] (2)	- [None] (0)	- [None] (0)	+2.7 [None] (2)
Month 66	+3.8 [None] (1)	- [None] (0)	- [None] (0)	+3.8 [None] (1)

*Height Z-score expressed as a mean for the baseline (e.g. screening study visit) and the difference in means [95% confidence interval for the difference in means] at each study visit. Patient sample size at each study visit noted is in parentheses. The difference in the mean height Z-score at each study visit reflects the difference in the height Z-score from the baseline value for those patients with measured height at the study visit.

Source: Adapted from Table 16.2.6.3.1: Summary of height Z-score (Pediatrics Only) over Time – Safety Population from the Efficacy Response Data Listing, Study LTS13632, Module 16.2.6 (eCTD #2)

Changes in height Z-scores in ASCEND-Peds and Study LTS13632 separated by age cohort are shown in **Figure 2**.

Figure 2: Height Z-scores by Age Cohort in Studies ASCEND-Peds and LTS13632



Source: Figure 33 – Summary plot of height Z-score by age cohort over time – Safety Population from Clinical Study Report, Interim 2, Study LTS13632, Module 5.3.5.2, (eCTD #2)

The baseline height Z-score, defined as the mean height Z-score during the screening visit for Study ASCEND-Peds, in the 20 pediatric patients enrolled in Study LTS13632 was -2.1 (range -3.8 to -1). The mean height Z-score improved through 48 months of follow-up when measured in each age cohort. However, the sample size in each age cohort progressively decreased with the length of follow-up in Study LTS13632 so that by 48 months, 5 of 20 pediatric patients had height measurements reported. With this limitation noted, the largest improvements in height Z-score occurred in the youngest patient cohort (e.g. birth to less than 6 years of age) through 24-months of follow-up at which time 6 of the 7 patients in this age cohort had a height measured. Overall 16 of 20 patients (80%) enrolled in Study LTS 13632 had height measured through 24-months.

Because of the analytical differences noted by the review team in Olipdase manufactured by Process B versus Process C, this reviewer separately analyzed the height data for the 20 patients in the safety dataset who had received Olipudase manufactured by both processes. These 20 patients consisted of the following:

- 8 patients who received Process C manufactured Olipudase across both trials and were all less than 12 years of age
- 12 patients who initiated treatment with Process B manufactured Olipudase in ASCEND-Peds
    - 2 patients transitioned to receive Process C Olipudase after the 12-month study visit
    - 10 patients continued on Process B Olipudase through the 64-week treatment period and then transitioned to receive Process C Olipudase between 18 and 30 months of treatment

As shown in **Table 2**, the baseline height Z-score, defined as the mean height Z-score during the screening visit for Study ASCEND-Peds, was similar in children aged 6 to less than 12 years of age between those that received Process B (height Z-score of -2.1) versus Process C (height Z-score of -2.3) manufactured Olipudase. For patients less than 6 years of age, the baseline height Z-score was lower in patients that received Process B (height Z-score of -2.3) versus Process C (height Z-score of -1.5) manufactured Olipudase. Changes in height Z-score through 15 months of Olipudase therapy were relatively consistent in patients 6 to less than 12 years of age receiving either Process B or Process C manufactured Olipudase. The trend was also similar for changes in height Z-score for patients less than 6 years of age although the larger improvements in height Z-score occurred in patients who received Process B manufactured Olipudase understanding that these patients had a lower baseline height Z-score. No adolescent patients received Process C manufactured Olipudase thus preventing these comparisons. Overall, the improvements in height Z-score were similar for patients receiving Process B versus Process C Olipudase in Ascend-Peds but with limited sample sizes in each age cohort.

Table 2: Changes in Height Z-scores by Age Cohort in ASCEND-Peds in Patients Receiving Process B and Process C Manufactured Olipudase

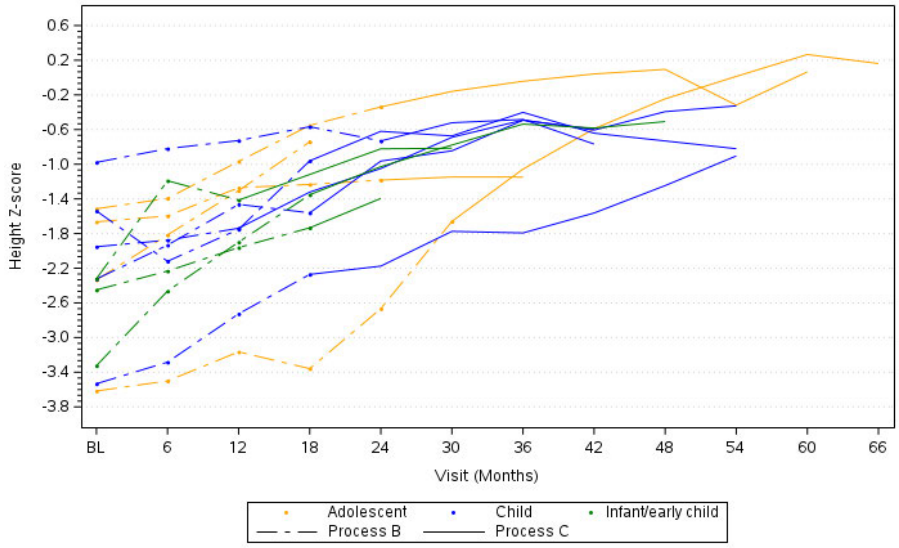
	Patients Receiving Process B Olipudase				Patients Receiving Process C Olipudase			
Study visit	**Adolescent* (n=4)**	**Child* (n=5)**	**Infant/ Early Child* (n=3)**	**Overall* (n=12)**	**Adolescent* (n=0)**	**Child* (n=4)**	**Infant/ Early Child* (n=4)**	**Overall* (n=8)**
Baseline	-2.3	-2.1	-2.7	-2.3	-	-2.3	-1.5	-1.9
Month 3	+0.1	+0.1	+0.1	+0.1	-	+0.1	+0.2	+0.2
Month 6	+0.2	+0.1	+0.7	+0.3	-	+0.1	+0.2	+0.2
Month 9	+0.5	+0.2	+0.7	+0.4	-	+0.4	+0.5	+0.5
Month 12	+0.6	+0.4	+1.0	+0.6	-	+0.3	+0.6	+0.5
Month 15	+0.8	+0.6	+1.2	+0.8	-	+0.5	+0.8	+0.7

*Height Z-score expressed as a mean for the baseline (e.g., screening study visit) and the difference in mean at each study visit. Patient sample size at each study visit noted is in parentheses. The difference in the mean height Z-score at each study visit reflects the difference in the height Z-score from the baseline value for those patients with measured height at the study visit.

Source: Adapted from the Summary Table of height Z-score by age cohort over time – Safety Population from the Clinical/Response to Information Request, Module 1.11.3, (eCTD#37)

Changes in height Z-scores that occurred in the 12 pediatric patients initiated on treatment with Olipudase manufactured by Process B in ASCEND-Peds and then switched to receive treatment with Olipudase manufactured by Process C in Study LTS13632 are shown in **Figure 3**.

Figure 3. Height Z-scores in Patients who Initiated Treatment with Process B Manufactured Olipudase and Transitioned to Process B Manufactured Olipudase



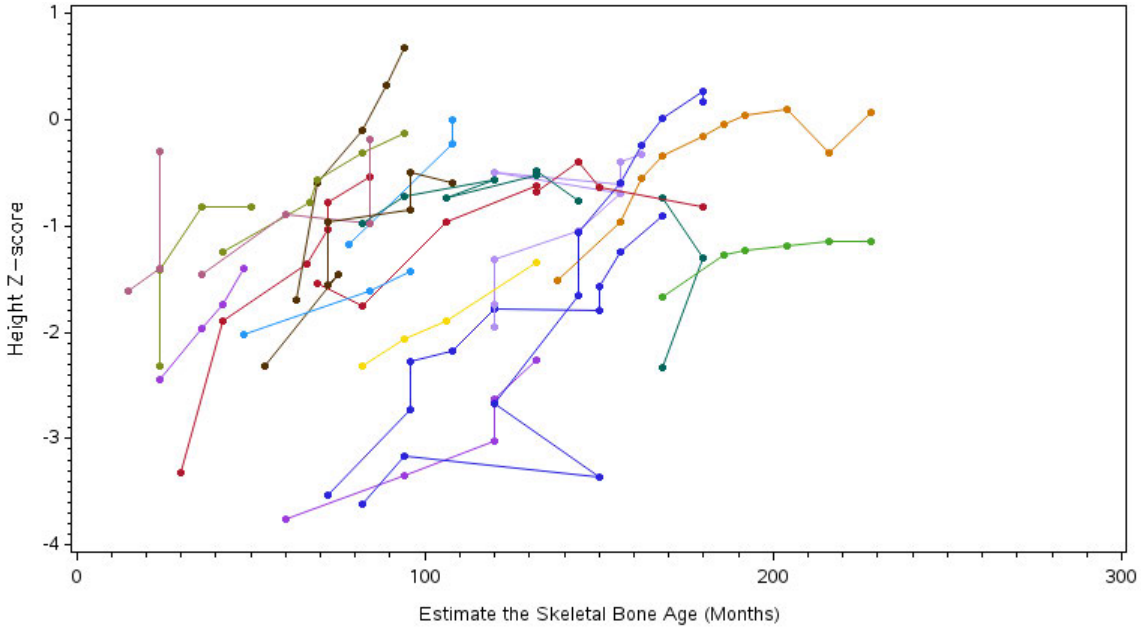
Source: Adapted from the By-patient plot of height Z-score over time for pediatric patients started on Process B – Safety Population from the Clinical/Response to Information Request, Module 1.11.3, (eCTD#37)

The slope of change in height Z-scores did not appreciably change in patients after transitioning to treatment with Process C manufactured Olipudase.

Assessment of bone age in patients enrolled in ASCEND-Peds revealed that, at baseline, patients had a mean delay in bone age compared with their chronological age of 24 months. The difference between the bone age and chronological age at baseline was largest in adolescent patients (n=4; 38 months delayed) followed by patients 6 to less than 12 years of age (n=9; 29 months delayed), and patients less than 6 years of age (n=7; 11 months delayed. At the 52-week assessment, the difference across the entire study population was unchanged (e.g., 23-month delay). At the 18-month assessment, the bone age matured towards the chronologic age of patients in all age cohorts with an overall mean improvement of 8 months for the entire pediatric study population. By the 30-month assessment in Study LTS13632, the bone age had improved to within 12 months of the chronologic age in the 16 pediatric study patients with a bone age assessment through that duration of treatment. Through the 30-month evaluation of bone age, the improvements in measured bone age relative to chronologic age were greatest in the cohort of patients aged 6 to < 12 years followed by adolescents and finally patients less than 6 years of age.

A plot of height/length Z-score by bone age for each of the 20 patients enrolled in Study LTS13632 is shown in **Figure 4.**

Figure 4: Height Z-scores by Bone Age in Study LTS13632



Source: Figure 2 – By patient plot of height Z-score by bone age – All pediatric patients in Study LTS13632, Module 1.11.3, (eCTD #22)

Changes in the difference between the measured bone age and chronological age of patients initially treated with Process B manufactured Olipudase in ASCEND-Peds and those initially started on Process C manufactured Olipudase in ASCEND-Peds and continued on this treatment in Study LTS13632 are shown in **Table 3**.

Table 3: Difference between Bone Age and Chronological Age (Months) by Age Cohort in Patients Initially Receiving Process B and Process C Manufactured Olipudase in ASCEND-Peds and Study LTS13632

	Patients Receiving Process B Olipudase				**Patients Receiving Process C Olipudase**			
Study visit	**Adolescent* (n)**	**Child* (n)**	**Infant/ Early Child* (n)**	**Overall* (n)**	**Adolescent (n)**	**Child* (n)**	**Infant/ Early Child* (n)**	**Overall* (n)**
Baseline	-38(4)	-24(5)	-11(3)	-25(12)	-	-36(4)	-10(4)	-23(8)
Month 12	+2(4)	+1(5)	-6(3)	-1(12)	-	+6(4)	+3(4)	+4(8)
Month 18	+9(4)	-	-	-	-	+21(4)	+6(4)	+13(8)
Month 24	+5(4)	-	-	-	-	+16(4)	+13(3)	+15(7)
Month 30	-	-	-	-	-	+30 (2)	+10(2)	+20(4)

*Difference between the measured bone age and chronological age expressed as the mean for the baseline (e.g., screening study visit) and the mean difference from baseline for each study visit for the patients with bone age measured at that study visit.

The baseline bone age was delayed by a mean of 25 months in the 12 patients who received initial treatment with Process B manufactured Olipudase in ASCEND-Peds and delayed by a mean of 23 months in the 8 patients who received initial treatment with Process C manufactured Olipudase. There were no adolescent patients who initially received Process C manufactured Olipudase in ASCEND-Peds precluding evaluation of changes in bone age that occurred in this age cohort. Improvements in bone age that provided a clinically meaningful narrowing of the difference between the bone age and chronological age manifested by 18 months of treatment in patients younger than 12 years of age receiving Process C Olipudase. These improvements continued at the 24-month measurement. The improvements were also noted at the 30-month evaluation, however, by this study visit, only 4 of the 8 patients who initiated Process C Olipudase in ASCEND-Peds had reached 30 months of treatment.

Evaluation of the Tanner staging in the 4 adolescent patients revealed that one 12-year-old female patient had Tanner stage I breast and pubic hair at screening which remained at Tanner stage I at the 52-week evaluation. This is consistent with pubertal delay. However, this patient progressed to Tanner stage V by the 60-month evaluation in Study LTS13632. The remainder of the 3 adolescents enrolled had pubertal development within the range of normal at screening with progression of puberty (e.g., advancing Tanner stage) to Tanner V within 3 to 30 months of screening in ASCEND-Peds.

F. Treatment of Patients with ASMD with Olipudase Outside of the Applicant Sponsored Trials:

Patients with ASMD type A disease were excluded from enrollment in ASCEND-Peds and Study LTS13632. Exclusion of patients with ASMD type A disease was based on the rationale that the neurologic manifestations of disease in this patient population were too rapidly progressive and lethal to enable enrollment. One patient with ASMD type A was treated with Olipudase within the context of an Expanded Access Investigational New Drug (IND) application.[10] The patient was a male with ASMD type A initiated on Olipudase treatment at 16 months of age due to the presence of clinically significant hepatosplenomegaly limiting food volume intake and growth. An immune tolerance protocol was initiated in this patient prior to Olipudase dosing in an attempt to decrease the immunogenicity of Olipudase treatment. The patient initiated every other week Olipudase treatment at a dose of 0.03 mg/kg. With his week 8 infusion of Olipudase at a dose of 0.3 mg/kg, the patient developed hives, facial swelling, cough, and wheezing consistent with anaphylaxis. The patient was treated with diphenhydramine, IV

[10] Treated under Expanded Access IND (b) (4)

solumedrol, and nebulized albuterol with completion of the infusion at 50% of the planned dose. A serum test taken on that date of this infusion for anti-Olipudase IgE antibodies was positive at a titer of 2.12 kUA/L. The patient's anti-Olipudase IgE antibody test was negative one month earlier at a level < 0.35kUA/L. The patient was dosed with Olipudase at the week 10 infusion and developed anaphylaxis which was treated in a similar fashion to that from the prior infusion with recovery without sequelae. The serum anti-Olipudase IgE antibodies was positive at a titer of 2.23 kUA/L at that infusion. Further dosing with Olipudase was suspended in this patient and the IND was withdrawn. The patient subsequently passed away for reasons determined to be likely secondary to sequelae of ASMD type A and probable pneumonia at 3 ½ years of age after presenting with decreased blood pressure and increased respiratory rate.

An additional patient with ASMD type A/B was treated within the context of an Expanded Access IND.[11] The patient was a 22-month-old male with ASMD type A/B with hepatosplenomegaly and lung disease requiring supplemental oxygen therapy during sleep and with respiratory infections. Olipudase treatment was initiated to potentially improve the patient's hepatosplenomegaly and lung disease facilitating improved tolerance of gastrostomy feedings and reductions in respiratory infections. The patient successfully completed dose escalation reaching the maximum dose of Olipudase of 3 mg/kg within 9 months of dose initiation. The patient had no drug-related serious adverse events (SAEs) during Olipudase treatment. The IND was withdrawn due to transitioning of the patient to another expanded access program.

G. Proposed Labeling by the Applicant for Changes in Height and Bone Age Observed in ASCEND-Peds and Study LTS13632

The Applicant is proposing to add the following information to subsections 14.2 and 14.3 of Olipudase labeling, regarding changes in linear growth and bone age observed in the pivotal pediatric trials:

- In subsection 14.2, the Applicant includes a statement that "Treatment with XENPOZYME resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes and platelet counts, and linear growth progression (as measured by height z-scores) at Week 52 as compared to baseline (see Table 10)."
- Table 10 in subsection 14.2, includes a row providing the mean height Z-scores and standard deviation at baseline and at Week 52 as well as the change in height Z-score and associated 95% confidence interval for this change.

[11] Treated under Expanded Access IND (b) (4)

- Language at the end of subsection 14.2 states that "The effects of XENPOZYME on liver and spleen volumes, and height z-scores were similar across all pediatric age cohorts included in the study."
- Subsection 14.3 described the long-term extension trial in Pediatric and Adult patients. The Applicant proposes to include "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."

III. Discussion

The natural history of ASMD is characterized by delays in linear growth, pubertal development, and bone maturation. The pediatric study population enrolled in the ASCEND-Peds and LTS13632 studies had delays in growth and bone maturation noted at baseline, consistent with the known natural history of this chronic, monogenetic disorder affecting multiple organ systems and the CNS. Pubertal maturation appeared largely within the normal range in 3 of the 4 adolescent patients enrolled.

The Applicant measured height and weight in ASCEND-Peds and Study LTS13632. Measurement of linear growth requires an accurate and standardized approach to measurement of height in patients who are ambulatory and length in those who are not. For ambulatory patients, a stadiometer is typically employed to measure standing height. For non-ambulatory patients, this is not possible and length in the supine position is usually measured. The Applicant specified in both study protocols that recumbent length was measured in patients 24 months and younger and that a standing height was measured in patients older than 24 months who were all able to stand for the measurement. The Applicant did state in both protocols height would be measured with shoes removed which is standard practice.

Assessment of linear growth is best done through the calculation of a height standard deviation score (e.g., height Z-score) relative to a reference population. The Applicant used the 2007 WHO reference growth data to calculate height Z-scores for study patients. Accurate assessment of growth requires the use of growth charts and/or tables developed from the reference population from which the patient is recruited for study participation. Ideally, when possible, use of growth charts developed from a population of patients with the same disease allows the practitioner to judge the growth based on the natural history of disease and not in reference to an otherwise healthy pediatric population. Growth charts specific for patients with ASMD have not been developed. As multinational, multi-center studies, the normal distribution of height and length across reference populations

from which the study patients were drawn may have differences that would affect the calculation of the height Z-score.

ASCEND-Peds evaluated changes in height Z-score over a 60-week treatment period with an assessment period in Study LTS13632 of up to 66 months. Linear growth is not a rapid process and requires an assessment timeline measured in months to years to understand if the process is proceeding normally or in an abnormal fashion. Study LTS13632 is ongoing, but the numbers of evaluable patients assessed for linear growth decreased significantly from the enrolled patient population after the 24 month assessment. This drop-off in enrolled patients over time limits the ability to assess changes in linear growth and bone age associated with continued Olipudase treatment beyond 24 months across all age cohorts.

Changes in linear growth limited to the 8 patients who received Olipudase treatment manufactured under process C were similar to the changes observed in the overall study population. The 8 patients were all less than 12 years of age because no adolescent patients initiated Process C Olipudase in ASCEND-Peds. Changes in height Z-score among these 8 patients who fell in the 6 to less than 12-year age group and the less than 6-year age group were consistent with those in the corresponding age cohorts from the entire treated population (e.g. Process B and C Olipudase treated patients) through 15 months of treatment in ASCEND-Peds. Furthermore, assessment of the slope of the change in height Z-score in patients after transitioning to Process C Olipudase treatment did not reveal a notable difference after transitioning from Process B Olipudase treatment in ASCEND-Peds and Study LTS13632.

Because linear growth is intimately tied to bone maturation and, in adolescents, hormonal changes leading to pubertal development, the pediatric program appropriately included provisions for assessing bone age. Measurement of bone age in ASCEND-Peds and Study LTS13632 occurred every 6 months which is an appropriate interval. Bone age was delayed at baseline by an average of 2 years in the pediatric study population. This is consistent with what has been documented for the natural history of ASMD in the published literature. The delays in bone age were largest for adolescent patients which is expected given the chronic nature of ASMD and the longer duration of time for bone age delays to manifest and progress relative to younger pediatric patients. Differences between the patient's bone age and chronologic age narrowed through the course of both studies. By the 30-month evaluation in Study LTS13632, the bone age had improved to within 12 months of the chronologic age in the pediatric study population. A correlation analysis conducted by the Applicant did not show a statistically significant correlation (correlation coefficient = 0.213, p-value = 0.367) for the change from baseline in the last observation carried forward (LOCF) height Z-score with the bone age. However,

examination of the individual longitudinal plots for patients in Study LTS13632 in Figure 3 reveals a trend for increasing height Z-score accompanied by an increase in bone age. Given the open-label study design and the exploratory nature of the bone age endpoint, definitively attributing the improvement in height Z-score and bone age to Olipudase treatment alone is difficult but is consistent with the improvement in linear growth observed in the trials.

Changes in bone age limited to the 8 patients who initiated Olipudase treatment manufactured under Process C were similar to the changes observed in the overall safety dataset. Changes in bone age with Process C manufactured Olipudase could not be assessed in the adolescent (12 to less than 17 years of age) cohort as all 4 adolescent patients were initiated on Process B manufactured Olipudase in ASCEND-Peds. For the remainder of the 8 patients initiated on Process C Olipudase in ASCEND-Peds and followed with additional bone age measurements in Study LTS13632, the delay in bone age relative to the patients' chronological age progressively improved over a 24-month follow-up period at which 7 of the 8 enrolled patients were evaluated. In patients between 6 and less than 12 years of age, bone age improved to within 20 months of the chronological age from a baseline delay of 36 months. In patients less than 6 years of age, the baseline delay of 10 months in bone age was completely resolved by the 24-month assessment. Overall, in the 8 patients initiated on treatment with process C manufactured Olipudase, the baseline delay in bone age of 23 months improved to a delay of 8 month by the 24-month assessment.

Unlike linear growth and bone age delays, pubertal maturation was largely within the normal range in the limited sample (n=4) of adolescent patients assessed. Pubertal delay was present at baseline in one 12-year-old female patient who subsequently initiated menarche and progressed to full pubertal maturation (e.g. tanner stage V) by the 60-month assessment in Study LTS13632. Attributing the largely normal pubertal development to Olipudase treatment in the two trials is not possible due to the small number of adolescent patients enrolled.

The lack of enrollment of patients with ASMD type A in the Applicant-sponsored trials may not necessarily preclude including patients with this phenotype in the approved indication if the non-CNS manifestations of ASMD targeted by Olipudase occur in patients with all 3 phenotypes (type A, A/B, and B) and, mechanistically, patients with type A disease would be expected to have the similar response to treatment for non-CNS manifestations as that observed in patients with type B and A/B disease. Patients with type A disease may be more likely to have low residual enzyme activity, placing them at a potentially increased risk for anaphylaxis with Olipudase treatment. Olipudase labeling will contain prominent language in Section 5 (Warnings and Precautions) cautioning

prescribers about the risk of anaphylaxis with use of this product. However, further consideration should be given as to how the Applicant could address this theoretical safety concern (e.g., post-marketing commitment for a registry, enhanced pharmacovigilance).

Similarly, the lack of enrollment of patients less than 1 year of age in the Applicant-sponsored trials or within Expanded Access INDs may not necessarily preclude approving this product down to birth if there are no age-related differences in drug disposition that are anticipated to impact the safety profile observed in older pediatric patients. The pathophysiologic alterations leading to the non-CNS manifestations of ASMD are initiated at the time of birth, especially in those with type A or type A/B disease.

IV. Conclusions:

Descriptive analyses of the height and bone age data collected in both ASCEND-Peds and Study LTS13632 support the conclusion that Olipudase treatment in both trials was associated with improvement in linear growth and maturation of bone age in the study population. The duration of the height assessment period in ASCEND-Peds was longer than 12 months and sufficient to assess linear growth in the entire enrolled pediatric population. The addition of height measurements in the long-term extension Study LTS13632 allows for a more robust evaluation of the changes in linear growth associated with Olipudase therapy although the assessment was limited due to the progressively decreasing sample of patients with height measurements with advancing time in the study. The assessment of changes in height were also further limited when restricting the analyses to patients who received Olipudase manufactured by process C. In this patient cohort, which includes patients younger than 12 years of age, measurement of height for which there is sufficient data to interpret changes with Olipudase C treatment is available through 15 months of treatment. Understanding this limitation, the overall trend showed an improvement in height Z-scores with Olipudase treatment through the course of ASCEND-Peds. A sufficient proportion (e.g. 80%) of the enrolled study population had a height measured to provide confidence in the ability to assess for improvement in linear growth with Olipudase treatment through this time period. However, definitively attributing the observed improvements in linear growth to Olipudase treatment is limited, in part, by the study designs which were not powered or controlled to assess for improvements in linear growth.

Overall, the measurement and assessment of changes in linear growth were conducted in a standardized fashion and measured over a sufficient time period to allow interpretable

results through 15 months of process C manufactured Olipudase treatment. A summary description of these changes in linear growth should be included in labeling. The Applicant used the 2007 WHO reference growth data to calculate height Z-scores, which is a reasonable approach given that the enrolled pediatric study population was multinational.

Assessment of changes in bone age were also conducted in a standardized fashion allowing valid interpretation through 24 months of process C manufactured Olipudase treatment. The improvements in bone age could not be assessed from baseline for adolescent patients as they were exclusively treated with process B manufactured Olipudase in ASCEND-Peds. With this understanding, improvements in bone age are noted in both younger age cohorts (< 6 years, 6 to < 12 years). These improvements were seen at the 6 month evaluation and became more pronounced through 24 months of evaluation. As a result, language in labeling should provide a summary of these improvements in bone age with process C manufactured Olipudase in the age cohorts for which an assessment provides interpretable results (e.g. patients less than 12 years of age).

ASMD patients with type A disease and/or low/minimal residual enzyme activity represent an important subgroup of patients that may benefit from Olipudase treatment but for which there is limited safety data informing the risk of immunogenicity and subsequent hypersensitivity/anaphylactic reactions as a critical safety finding. If the Division accepts the Applicant's proposal to include patients with type A disease in the approved indication, further discussion is needed to determine how to better characterize this potential safety concern in the post-market setting.

V. Recommendations:

- Revise language in the Section 14.2. to remove language (b) (4) (b) (4) Consider inclusion of language that the small sample size precludes comparisons across age cohorts.
- Include language in subsection 14.2 that improvements in height Z-scores were noted through 15 months of evaluation in patients less than 12 years of age.
- In addition, the point estimates for improvements in height Z-scores in Table 10 in subsection 14.2, which includes a row providing the mean height Z-scores with standard deviation at baseline and at Week 52 as well as the change in height Z-score and associated 95% confidence interval for this change, should be clearly noted to include only patients treated with process C manufactured Olipudase at ages less than 12 years.

- Revise language in subsection 14.3 to note that improvements in height Z-score and bone age continued to occur at Month 15 (b) (4)
- Include language in subsection 14.3 that summarizes the changes in bone age that occurred in patients less than 12 years of age with process C manufactured Olipudase.
- The proposed language in subsection 14.3 can be revised as follows:

  "In addition, pediatric patients less than12 years of age enrolled in Study 2 (b) (4) showed ~~a~~ improvement in height Z-score when evaluated through 15 months of XENPOZYME treatment."

  "Bone age, as assessed by hand x-ray, which was delayed by a mean of 23 months at baseline in pediatric patients enrolled in Study 2 improved to a mean delay of 8 months from the chronological age when assessed at Month 24 in Study 3"

- Consider a FDAAA 505(o) PMR with the potential approval of Olipudase in all three phenotypes to better elucidate the risk of immunogenicity, hypersensitivity, and the occurrence of anaphylactic reactions in patients with type A ASMD and/or low residual activity.
- Consider enhanced pharmacovigilance monitoring to identify the occurrence of anaphylaxis in ASMD type A patients and patients less than 1 year of age treated with Olipudase post-approval.

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/s/

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JOHN J ALEXANDER
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Clinical Inspection Summary

Date	May 20, 2022
From	Tina Chang, M.D., Reviewer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Christine Hon, PhD, Clinical Reviewer Anita Zaidi, MD, Clinical Team Leader Kathleen Donohue, M.D., Division Director Jenny Doan, Regulatory Project Manager Division of Rare Diseases and Medical Genetics (DRDMG)
BLA #	761261
Applicant	Genzyme Corporation, a Sanofi Company
Drug	Xenopozyme (olipudase alfa-rpcp)
NME (Yes/No)	Yes
Proposed Indication(s)	Treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients
Consultation Request Date	December 15, 2021
Summary Goal Date	May 1, 2022 (Original); May 31, 2022 (Extension)
Action Goal Date	June 30, 2022
PDUFA Date	July 3, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical investigators Drs. Melissa Wasserstein, Renata Gallagher, George Diaz, and Laila Arash-Kaps were inspected in support of BLA 761261, covering Protocols DFI12712 and DFI13803. Both studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication.

II. BACKGROUND

Olipudase alfa is a recombinant human acid sphingomyelinase. Genzyme submitted data from two studies (DFI 12712 and DFI 13803) to support the indication of olipudase alfa in the treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD), a rare and potentially life-threatening lysosomal storage disease that causes variable impairment in sphingomyelin metabolism in pediatric and adult patients. The

following briefly describes Protocols DFI12712 and DFI13803.

Protocol DFI12712 (ASCEND)

Study Title: "A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency"

Primary Objective: To evaluate the efficacy of olipudase alfa in adults with ASMD by assessing changes in (1) spleen volume measured by magnetic resonance imaging (MRI) (and for the United States [US] only, in association with patient perception related to spleen volume as measured by splenomegaly-related score [SRS]); (2) infiltrative lung disease as measured by the pulmonary function test (PFT) and diffusing capacity of the lung for carbon monoxide DLCO.

Primary Endpoints:

1. Percentage change in spleen volume (in MN) from baseline to Week 52
2. Percentage change in % predicted DLCO adjusted for hemoglobin and ambient barometric pressure from baseline to Week 52.

Spleen volume was calculated using the spleen volume assessed by abdominal MRI at the study sites and the subject's weight. Spleen volume was centrally assessed by (b) (4) a medical imaging core laboratory, and the final volume was provided electronically to Sanofi, who then converted the data to Multiples of Normal (MN). Certified copies of the centrally reviewed spleen volumes were sent to the sites before the time of inspection.

The percent predicted DLCO adjusted for hemoglobin (Hb) and ambient barometric pressure in mL/min/mm Hg was derived by Sanofi Biostatistics group using the ambient barometric pressure recorded in the PFT equipment, the hemoglobin (Hb) centrally assessed by (b) (4) (b) (4) as well as the subject's height, age, and sex. The closest Hb value in date/time to the DLCO value was used for derivation of the percent predicted DLCO adjusted for hemoglobin and barometric pressure. The raw DLCO values and barometric pressure data were measured by the pulmonary functions test machine and centrally reviewed by ERT. Certified copies of DLCO and barometric pressure were sent to the sites.

Male and female subjects aged 18 years of older with documented deficiency of acid sphingomylinase (ASM) were randomized 1:1 to olipudase alfa or placebo. This study was divided into two consecutive periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52 to be followed by 2) an open-label extension period (ETP) for at least 2 years and up to 4 years. The PAP served to demonstrate the difference between subjects treated with olipudase alfa or placebo primarily in change in baseline in spleen volume and infiltrative lung disease as measured by pulmonary function test diffusing capacity of the lung for carbon monoxide (DLCO). The ETP served to give the opportunity for subjects to be treated for four more years and to analyze the long-term safety and efficacy thru Week 260.

During the PAP, the study drug was administered intravenously every two weeks during the 52-week treatment period with a target dose of 3.0 mg/kg. During clinical development, changes were made to the olipudase alfa manufacturing process, and in this study, Process B, Process C (b) (4), and Process C (b) (4) were administered to subjects.

Number of Subjects: 36
First Subject First Visit: (b) (6)
Last Subject Last Visit: (b) (6)
Subjects were enrolled in 16 centers.

Protocol DFI13803

Study Title: "A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency"

Primary Objective: To evaluate the safety and tolerability of olipudase alfa in pediatric subjects with ASMD every 2 weeks for 52 weeks.

Exploratory Efficacy Endpoints:

1. Percent change in spleen volume (in MN units), as measured by abdominal MRI from baseline to Week 52
2. Percent change in liver volume (in MN units), as measured by abdominal MRI from baseline to Week 52
3. Percent change in diffusing capacity of the lung for carbon monoxide (DLCO) adjusted for hemoglobin from baseline to Week 52
4. Platelet count at baseline and at Week 52

Spleen and liver volumes were calculated in a similar process as described above for Protocol DFI12712. The raw DLCO values were collected by the sites and Sanofi calculated the DLCO adjusted for hemoglobin using the Hb that was centrally assessed (b) (4) For the platelet counts, blood was collected at the site and shipped to (b) (4) central laboratory services where results are then displayed to the investigators in the (b) (4) portal. A report is also generated and sent to the sites.

Male or female subjects aged from birth to <18 years of age received olipudase alfa intravenously once every 2 weeks for 64 weeks with a gradual dose-escalation to a target dose of 3.0 mg/kg (or their highest tolerated dose). Given that the primary purpose of the study was safety and tolerability in pediatric patients, there was no comparator group. Two IMP manufacturing processes (Process B and Process C) were used during the study. The first 12 subjects received olipudase alfa manufactured with Process B and were enrolled in a staggered fashion into three age cohorts:

- Adolescent cohort: 12 to <18 years, at least 3 subjects
- Child cohort: 6 to <12 years, at least 3 subjects
- Infant/Early child cohort: <6 years, at least 2 subjects

Following enrollment in the youngest age cohort and by protocol amendment, an additional/last 8 subjects <12 years of age were treated with Process C with at least 4 subjects in the child cohort and at least 2 subjects in the infant/early child cohort without staggering enrollment. Per the review division, Process C drug product is the drug product of interest for this pediatric study.

Number of Subjects: 20
First Subject First Visit: (b) (6)
Last Subject Last Visit: (b) (6)
Subjects were enrolled in 6 countries (Brazil, France, Germany, Italy, United Kingdom, and the United States).

Rationale for Site Selection

The clinical investigators Drs. Melissa Wasserstein, Renata Gallagher, George Diaz, and Laila Arash-Kaps were selected for GCP inspections using a risk-based approach that considered numbers of enrolled subjects, treatment effect, and prior inspectional history. Dr. Laila Arash-Kaps was selected for the pediatric study DFI13803 because all the pediatric subjects enrolled at this site received Process C, and Process C is the drug product of interest for the exploratory efficacy endpoints in the study DFI13803.

III. RESULTS (by site):

1. **Dr. Melissa Wasserstein**
   344 Wayne Avenue
   Floor 9
   Bronx, NY 10467-2552
   Study DFI12712, Site 840006
   Clinical Inspection Dates*:* January 20 – 26, 2022
   Dr. Melissa Wasserstein has not been previously inspected.

For study DFI12712, Dr. Wasserstein screened and randomized four subjects. All four subjects completed the primary analysis period of the study and went on to the extension period. One subject discontinued from the extension period due to travel conflicts. Records were reviewed for all four subjects.

The inspection reviewed study approval, informed consent, subject eligibility, study monitoring, adverse events, concomitant medications, protocol deviations, lab values, investigational products, vital signs, subject records, and regulatory binders. The efficacy data review included the certified copies of the centrally reviewed Baseline and Week 52 spleen volumes in MN units, the certified copies of the Baseline and Week 52 DLCO values, barometric pressure, and the subject's hemoglobin, height, age, sex, and weight at those

corresponding visits.

For the primary endpoint data verification, the raw data used to calculate the spleen volume and the DLCO adjusted for hemoglobin and ambient barometric pressure were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. **Dr. Renata Gallagher**
   505 Parnassus Avenue
   Floor 12
   San Francisco, CA, 94143
   Study DFI12712, Site 840005
   Clinical Inspection dates: January 24 - 26, 2022
   Dr. Gallagher has not been previously inspected.

For study DFI12712, Dr. Gallagher screened three subjects and randomized one subject. The one randomized subject completed the study. Records for all three subjects were reviewed during the inspection.

The inspection reviewed the study protocol and amendments, regulatory binders, IRB approvals, clinical investigator CV, financial disclosures, monitoring visits, staff training logs, delegation of authority log, site procedures, informed consent forms, eligibility criteria, concomitant medications, investigational drug accountability and safety reports. The efficacy data review included the certified copies of the centrally reviewed Baseline and Week 52 spleen volumes in MN units, the certified copies of the Baseline and Week 52 DLCO values and barometric pressure, and the subject's hemoglobin, height, age, sex, and weight at those corresponding visits.

For the primary endpoint data verification, the raw data used to calculate the spleen volume and the DLCO adjusted for hemoglobin and ambient barometric pressure were compared against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

3. **Dr. George Diaz**
   1 Gustave L Levy Pl
   New York, NY 10029-6504
   Study DFI13803, Site 84001
   Clinical Inspection Dates: January 11- 18, 2022
   Dr. George Diaz has been previously inspected on 5/9/12 and classified as NAI.

For study DFI13803, Dr. Diaz screened and randomized six subjects. All six randomized subjects completed the study and moved over to the long-term study. Records for all six subjects were reviewed during the inspection.

The inspection reviewed study approval, informed consent, subject eligibility, study monitoring, adverse events, concomitant medications, protocol deviations, lab values, investigational products, vital signs, subject records, and regulatory binders. The efficacy data review included the Baseline and Week 52 platelet counts, certified copies of the centrally reviewed Baseline and Week 52 spleen and liver volumes in MN units, the Baseline and Week 52 DLCO values and the subject's hemoglobin, height, age, sex, and weight at those corresponding visits.

For verification of the exploratory endpoints, the raw data used to calculate the exploratory endpoint data for Baseline and Week 52 spleen and liver volumes, DLCO adjusted for hemoglobin and platelet counts were compared against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

4. **Dr. Laila Arash-Kaps**
   University Medical Center-Mainz- Center For Pediatric And Adolescent Medicine,
   Langenbeckstr. 1
   Mainz, Rhineland-Palatinate, 55131
   Germany
   Study DFI13803, Site 276001
   Clinical Inspection Dates: April 4-7, 2022
   Dr. Arash-Kaps has been previously inspected on 11/6/20 and classified as NAI.

For study DFI13803, Dr. Arash-Kaps screened six subjects and randomized four subjects. All four randomized subjects completed the study. All records for the four subjects who completed the study were reviewed during the inspection.

The inspection reviewed the records of procedures related to the protocol and its amendments, subject selection criteria, consenting, test article controls, including accountability and blinding, source data evaluation, adverse event reporting, radiological and lab testing, and the data submitted to the agency. The efficacy data review included the Baseline and Week 52 platelet counts, certified copies of the centrally reviewed Baseline and Week 52 spleen and liver volumes in MN units, the Baseline and Week 52 DLCO values and the subject's hemoglobin, height, age, sex, and weight at those corresponding visits.

For verification of the exploratory endpoints, the raw data used to calculate the Baseline and Week 52 spleen and liver volumes, DLCO, and platelet counts were compared against the sponsor data line listings, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Review

Date: 4/14/22 **Date consulted:** 11/4/21

From: Jane Liedtka, MD, Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Division Director, DPMH

To: Jenny Doan, Regulatory Project Manager (RPM)
Division of Rare Diseases and Medical Genetics (DRDMG)

Drug: Olipudase alfa

BLA: 761261

Applicant: Genzyme Corporation

Subject: Pregnancy and Lactation Labeling

Indication: An enzyme replacement therapy for (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

Materials Reviewed:

- Applicant's submitted Integrated Summary of Safety, submitted 11/3/21

- DPMH review of [redacted] (b) (4) NDA [redacted] (b) (4)

Consult Question: DRDMG would like DPMH on the labeling and potential post-marketing study required for this new application.

INTRODUCTION AND BACKGROUND

On 11/3/21, the applicant (Genzyme) submitted an original BLA for Olipudase alfa for [redacted] (b) (4) [redacted] (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD-also known as Niemann-Pick disease) in pediatric and adult patients. DRDMG consulted DPMH on 11/4/21 to request assistance for the proposed prescribing information to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and potential post-marketing study required for this new application.

Olipudase Alfa Drug Characteristics[2]

Mechanism of Action	Olipudase alfa [recombinant human acid sphingomyelinase (ASM)] provides an exogenous source of ASM reducing sphingomyelin (SM) accumulation in organs of patients. Olipudase alfa is not expected to cross the brain-blood barrier or modulate the CNS manifestations of the disease.
Molecular Weight	63,648 Daltons
Mean Terminal Half-life	Ranged from 31.9 to 37.6 hours
Protein Binding	Protein binding was not measured
Bioavailability	Not relevant since given IV
Dosing Regimen	<u>For Adult Patients</u> • The proposed starting dose is 0.1 mg/kg every two weeks (Q2W) and subsequently, the dose should be escalated to a maintenance dose of 3 mg/kg. The proposed 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. <u>For Pediatric Patients (0 to <18 years old)</u> • The proposed starting dose is 0.03 mg/kg Q2W and subsequently, the dose should be escalated to a maintenance dose of 3 mg/kg. The proposed 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. • If BMI >30, the dose should be based on the mass (in kg) corresponding to a BMI of 30 given the specific patient's height.
Adverse Reactions	Headache, pyrexia, urticaria, nausea, vomiting, abdominal pain, myalgia, pruritus, and C-reactive protein increased.

[1] The [redacted] (b) (4) consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2]Proposed labeling verified by the division

REVIEW
PREGNANCY
ASMD Disease and Pregnancy
According to the applicant, 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 (SM) phosphodiesterase 1 (SMPD1) gene. The phenotypic spectrum ranges from the severe infantile neurovisceral form ASMD type A, (historically known as Niemann-Pick Disease (NPD) type A) to the chronic visceral form ASMD type B (historically known as NPD type B), with an intermediate form also described, ASMD type A/B (NPD Type A/B, also called NPD Type C in some references).

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 provides an exogenous source of ASM reducing SM accumulation in organs of patients with ASMD. Olipudase alfa is not expected to cross the brain-blood barrier or modulate the central nervous system (CNS) manifestations of the disease.

Neither the applicant nor this reviewer was able to locate any reports of pregnancy in patients with ASMD once the diagnosis had been made. There were reports of 2 pregnancies in a study of adult onset ASMD in women who had given birth prior to their diagnosis before they began to manifest symptoms of their disease.[3]

Nonclinical Experience
In a study of embryo-fetal development in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from gestation days (GD) 6 through 15. There was no maternal toxicity that was not attributed to hypersensitivity. Exencephaly was observed in the fetuses of pregnant mice treated with 10 and 30 mg/kg. The maternal No Observed Adverse Effect Level (NOAEL) is 30 mg/kg; the $AUC_{0\text{-}24}$ at this dose is ~1.6 the exposure associated with the MRHD. The developmental NOAEL is 3 mg/kg; the $AUC_{0\text{-}24}$ at this dose is approximately $1/7^{th}$ the exposure associated with the MRHD.

Reviewer's Comments
These findings were discussed with the division on 4/4/22. DPMH recommends an embryo fetotoxicity Warning be added to labeling for Olipudase based on these findings in animals. DPMH also recommends pregnancy testing before beginning treatment and contraception in females of reproductive potential. Other options such as a REMS and A Contraindication were also discussed. Based on the low number of pregnancies associated with the underlying condition of ASMD disease, DPMH does not recommend a REMS as this would be burdensome and might limit access to this potentially life-prolonging therapy. DPMH also does not recommend a Contraindication as it is unclear whether untreated ASMD disease might cause adverse pregnancy outcomes and there may be situations in which a patient might accept the

[3] Sévin, M et al. The Adult Form of Niemann-Pick Disease Type C. Brain. 2007; 130 (1): 120–33.

potential risk to the fetus and wish to maintain the pregnancy while continuing to undergo Olipudase treatment.

Review of Pharmacovigilance Database

There were no pregnancy exposures reported during the clinical development program. The product is not approved for any indications in any country at the time that this review was completed, therefore, there are no post-marketing pharmacovigilance data available.

Review of Literature

DPMH conducted a search of published literature in PubMed on 11/9/21 using the search terms "olipudase alpha AND pregnancy," "olipudase alpha and pregnancy and birth defects," "olipudase alpha and pregnancy and congenital malformations," "olipudase alpha and pregnancy and stillbirth," "olipudase alpha AND teratogenicity" and "olipudase alpha AND prematurity", "olipudase alpha AND low birth weight" and "olipudase alpha and pregnancy and miscarriage." No reports of adequate and well-controlled studies of olipudase alpha use in pregnant women were identified. One publication referenced above by Sevin[3] (2007) under "ASMD Disease and Pregnancy" describes two cases in which a pregnancy occurred in the setting of ASMD before the symptomatic onset of disease. This publication is not relevant since no exposure to olipudase was involved so it will not be discussed further. In addition, there were a few case reports of pregnancies in untreated ASMD, which are described below. DPMH also searched Micromedex[4] for olipudase alpha summary information; no information was found.

- Fried and Langer[5] (1982) describe a 27-year-old woman diagnosed with Niemann-Pick disease type B at age 17, who delivered a female infant (birthweight 2280 g, Apgar score 10) via Caesarian section at 36 weeks because of fetal distress and meconium-stained amniotic fluid. The pregnancy was uncomplicated except for slight anemia and leukopenia.
- Porter[6] KB et al (1996) described a 26-year-old white woman diagnosed with Niemann-Pick disease type B at age 4 who delivered via cesarean a 3100-g female neonate with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The patient's course was complicated by abnormal bleeding which, despite anticipation and prophylactic treatment with vasopressin, subsequently required platelet and blood replacement. The mother and infant were doing well 6 months postpartum.
- Tanacan[7] A et al. (2018) report the case of a 23-year-old nulliparous, splenectomized woman with NPD B who died because of severe postpartum hemorrhage (PPH). She was admitted to intensive care unit (ICU) after cardiopulmonary arrest during urgent hysterectomy. She subsequently died from hypoxic brain injury leading to brain death.

Reviewer's Comment

In 2021, DPMH reviewed (b) (4) *NDA* (b) (4)

[4] Truven Health Analytics information, http://www micromedexsolutions.com/.

[5] Fried K and Langer R. Childbirth in a woman with chronic Niemann-Pick (type B) disease. Clinical Genetics 1982: 22: 47.

[6] Porter KB et al. Neimann-Pick Disease Type B in pregnancy. Obstetrics and Gynecology. 1996. 859-860.

[7] Tanacan A et al. Fatal Postpartum Hemorrhage in a Patient with Niemann-Pick Disease Type B. Case Reports in Obstetrics and Gynecology. 2018; 2018.

(b) (4) *At that time, DPMH decided not to ask for PMRs for either Pregnancy or Lactation Safety studies based on infeasibility due to the rare nature of ASMD/Niemann-Pick disease and the rarity of women patients reaching the age of reproductive potential and achieving pregnancy.*

LACTATION

Nonclinical Experience
There are no animal lactation studies nor sampling of drug concentration in rat milk during the pre- and postnatal development study.

Review of Literature
DPMH conducted a search of Medications and Mother's Milk[8], the Drugs and Lactation Database (LactMed),[9] Micromedex[4], and of published literature in PubMed using the search terms "olipudase alpha and lactation" and "olipudase alpha and breastfeeding." No observational studies or case reports of olipudase alpha use in lactating women were found. Olipudase alpha is not referenced in Medications and Mother's Milk[5] or in LactMed[6].

Reviewer comment:
There are no available data on the presence of olipudase alpha in human or animal milk. However, we do not anticipate breastfeeding to be common (since pregnancy is very rare in this population) so DPMH does not consider a lactation study to be warranted.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
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 no observed adverse effect levels (NOAELs) were 30 mg/kg/dose.

Review of Literature
DPMH performed a search of PubMed using search terms "olipudase alpha and fertility or reproduction." There were no published studies that evaluated the effects of olipudase alpha on human reproductive potential.

DISCUSSION AND CONCLUSIONS
Pregnancy
There are no data in the published literature or in the applicant's pharmacovigilance database regarding olipudase alpha exposure in pregnant women. In a study of embryo-fetal development

[8] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[9] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from gestation days (GD) 6 through 15. Exencephaly was observed in 5 fetuses of 2 pregnant mice treated with 10 and 30 mg/kg. The maternal No Observed Adverse Effect Level (NOAEL) is at a dose exposure ~1.6 the exposure associated with the MRHD. The developmental NOAEL is at a dose exposure approximately 1/7th the exposure associated with the MRHD. Based on these findings in animal studies, DPMH recommends the addition of an Embryo-Fetal Toxicity warning to the labeling for Olipudase to describe the potential risk to the developing fetus. DPMH also recommends pregnancy testing prior to treatment and effective contraception in females of reproductive potential.

DPMH had a discussion with the DRDMG review team regarding the approach to labeling and whether a REMS would be appropriate. The conclusion of this discussion was to use labeling to mitigate the risk and that neither a contraindication nor a REMS was warranted at this time. This was based on the very low number of pregnancies expected in this population (based on very few being found in the literature) and concerns that a REMS would be likely to result in restricted access.

There are no human data available to inform the safety of olipudase alpha use during pregnancy, however, due to the low prevalence of pregnancy in women with ASMD and the fatality of this disease, DPMH does not believe that collection of data through the issuance of a post-marketing pregnancy registry safety study would be feasible. A previous application for a drug for ASMD set this as a precedent[1]. DPMH recommends a descriptive pregnancy safety studymonitor for any reports of olipudase alpha exposures during pregnancy and follow up on maternal and infant outcomes.

Lactation

There are no data regarding the presence of olipudase alpha in animal or human milk, its effects on a breastfed infant or on milk production. Due to the low incidence of pregnancy in women with ASMD, there would also be a low incidence of lactating women with ASMD. A lactation study would not warranted since we expect a very low rate of pregnancy in this population. DPMH recommends routine pharmacovigilance to follow up on any reports of olipudase alpha exposures during lactation.

Females and Males of Reproductive Potential

There is no available human fertility information with olipudase alpha. Animal data do indicate an adverse effect from olipudase alpha on pregnancy. Based on animal findings of increased risk of exencephaly in pups born to olipudase-exposed dams, there is a need for pregnancy testing prior to administering Olipudase and for contraception recommendations. DPMH refers to the final NDA action for final labeling.

LABELING RECOMMENDATIONS

DPMH revised the HPI, Section 5, subsections 8.1,8.2, 8.3 and Section 17 of the olipudase alpha labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 4/19/22. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------Dosage and Administration----------

- Prior to initiating treatment, verify pregnancy status in females of reproductive potential. (2.X)

----------Warnings and Precautions----------

- Embryo-Fetal Toxicity: Based on animal findings, TRADENAME may cause fetal harm. TRADENAME is not recommended for use in pregnant women. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception (5.X, 8.1, 8.3).

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.X Pregnancy Evaluation Prior to Initiating Treatment

Before initiating XENOPYZYME, verify pregnancy status in females of reproductive potential *[see Warnings and Precautions (5.X), and Use in Specific Populations (8.1, 8.3)].*

5 WARNINGS AND PRECAUTIONS

5.X Risk of Embryo-Fetal Toxicity

Based on findings from animal reproduction studies, TRADENAME may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, exencephaly was observed in offspring of mice that were treated with olipudase alfa at an exposure less than the exposure at the maximum recommended human dose (MRHD). TRADENAME is not recommended for use during pregnancy. Verify pregnancy status in females of reproductive potential prior to initiating treatment with TRADENAME. Advise females of reproductive potential to use effective contraception during treatment with TRADENAME *[see Use in Specific Populations (8.1, 8.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, TRADENAME may cause fetal harm when administered to a pregnant woman and is not recommended for use during pregnancy. Administration of olipudase alpha to pregnant mice produced a rare malformation (exencephaly) in offspring at an exposure less than the exposure at the maximum recommended human dose (MRHD) (*see data*). There are no available data on TRADENAME use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. If pregnancy occurs while taking TRADENAME, the patient should be apprised of the potential risk to the fetus [*see Warnings and Precautions (5.X)].*

The estimated background risk for major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
In a study of embryo-fetal development in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from gestation days (GD) 6 through 15. Exencephaly was observed in 1 litter at each of the 10 and 30 mg/kg dose groups (2 and 3 fetuses, respectively). These data are consistent with published literature reports that brief embryonic exposure to sphingomyelin metabolites or a sphingosine-1-phosphate agonist produced neural tube defects, including exencephaly, in chicks and mice.

The maternal No Observed Adverse Effect Level (NOAEL) is 30 mg/kg; the AUC0-24 at this dose is ~1.6 the exposure associated with the MRHD. The developmental LOAEL is 10 mg/kg; the AUC0-24 at this dose is approximately 0.25-fold the exposure associated with the MRHD.

In a study of embryo-fetal development in pregnant rabbits, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from GD 6 through GD 19. There was no maternal or developmental toxicity. Maternal and developmental NOAELs were 30 mg/kg. The AUC0-24 associated with this dose was ~ 10.9-fold the exposure associated with the MRHD.

In a study of pre-and postnatal development in mice, olipudase alfa was administered intravenously every other day from GD 6 through 18; then resumed every other day after parturition, from Lactation Day (LD) 1 through LD 19. The maternal and developmental NOAELs are 30 mg/kg. Exposures at this dose, based on the embryo-fetal development study, were estimated to be ~1.6-fold the MRHD of olipudase alfa.

8.2 Lactation
Risk Summary
There are no data on the presence of olipudase alfa-rpcp in either human or animal milk, effects on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status for females of reproductive potential prior to administering TRADENAME.

Contraception
Females
TRADENAME may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].* Advise female patients of reproductive potential to use effective contraception during treatment with TRADENAME.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- TRADENAME may cause fetal harm when administered to a pregnant woman. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.1)]*.
- Advise female patients of reproductive potential to use effective contraception during treatment with TRADENAME *[see Use in Specific Populations (8.3)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANE E LIEDTKA
04/20/2022 02:13:38 PM

TAMARA N JOHNSON
04/22/2022 10:50:12 AM

LYNNE P YAO
04/22/2022 10:54:21 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 16, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Jenny Doan
Division of Rare Diseases and Medical Genetics

Subject: QT Consult to BLA 761261 (SDN 002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/7/2022 regarding the Division's QT related question. We reviewed the following materials:

- Clinical study report for Study SPHINGO00605 (BLA761261 / SDN0002; link);
- Clinical study report for Study DFI12712 (BLA761261 / SDN0002; link);
- Clinical study report for Study DFI13412 (BLA761261 / SDN0002; link);
- Clinical study report for Study DFI13803 (BLA761261 / SDN0002; link);
- Clinical study report for Study LTS13632 (BLA761261 / SDN0002; link);
- Non-clinical (in vivo) study report 08002 (BLA761261 / SDN0001; link);
- Summary of clinical safety (BLA761261 / eCTD 0002; link);
- ISS appendix 5 (BLA761261 / eCTD 0002; link); and
- Proposed drug label (BLA761261 / SDN0002; link);

1 Responses for the Review Division

Question from the Review Division: DRDMG requests IRT to review the ECG safety data and labeling and comment whether the submitted information is adequate to support the indication.

IRT's response: Large targeted proteins, such as olipudase alfa, have a low likelihood of direct ion channel interactions, and a thorough QT/QTc study is therefore not necessary unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from nonclinical or clinical studies (ICH E14, Q&A 6.3).

The available nonclinical and clinical data for olipudase alfa do not indicate QTc prolongation. Our general practice is not to include QT language in the product labeling for these products and we therefore agree with the sponsors proposal of not including QT language in the label.

2 Internal Comments for the Division

- Email communication with the division clarified that the intent of the consult was to request review of the ECG safety data and labeling. The question in the consult was therefore revised accordingly.
- Few PR outliers (≥200 ms and Δ ≥ 20 ms) were observed (pediatrics: n=1; adults: n=5). Two of the six patients experienced an increase in PR >25% over baseline (IDs: (b) (6)). The observed increases were not dose related and were observed at isolated timepoints within each subject. These increases in the PR interval do not appear to be mediated by direct effects on cardiac ion channels. Furthermore, there was no PR interval prolongation in the in vivo monkey study at 50x the clinical exposure.

3 BACKGROUND

3.1 Product Information

Olipudase alfa (MW = 76,000 Daltons) is a recombinant human acid sphingomyelinase (rhASM) which hydrolyses sphingomyelin to phosphorylcholine and ceramide and therefore prevents accumulation of sphingomyelin, cholesterol, and other lipids in the visceral organs of the body. The sponsor (Genzyme Corporation) seeks US marketing approval (BLA) for the indication of enzyme replacement therapy (ERT) for (b) (4) treatment of non-central system manifestation of acid sphingomyelinase deficiency (ASMD). The recommended starting dose for olipudase alfa in adult patients is intravenous infusion (IV) of 0.1 mg/kg every 2 weeks (Q2W) and can be escalated to the recommended maintenance dose of 3 mg/kg IV Q2W. The recommended starting and maintenance doses in pediatric patients are 0.03 mg/kg IV Q2W and 3 mg/kg IV Q2W respectively. Dose escalation schedules are presented in the proposed olipudase alfa drug label.

The clinical pharmacokinetics of olipudase alfa was characterized in patients with ASMD. Olipudase alfa exhibits linear pharmacokinetics over the dose range of 0.03 to 3 mg/kg, and steady state mean C_{max} and AUC in adult patients of 30.2 µg/mL and 607 µg×h/mL, respectively. The sponsor reports that in pediatric patients mean C_{max} (22 – 27 µg/mL) and AUC (403 – 529 µg×h/mL) is lower than in adult patients. The mean (CV%) clearance of olipudase alfa is 0.331 L/h (22%) and the mean terminal half-life ($t_{1/2}$) range from 31.9 to 37.6 hours. Additional details on the pharmacokinetics of olipudase alpha are presented in the proposed olipudase alfa drug label. In brief, olipudase alfa has minimal accumulation after bi-weekly dosing, and age, sex, hepatic impairment, and renal impairment are not expected to have clinically relevant impact on its exposures (C_{max} and AUC).

3.2 Sponsor's position related to the question

The sponsor evaluated the proarrhythmic potential of olipudase alfa in 1 *in vivo* animal study and in 5 phase 1 and phase 2/ 3 studies (Section 3.5) and concluded that despite the observed few potentially clinically significant ECG abnormalities, olipudase alfa has no risk for QT prolongation (Section 3.5).

3.3 Nonclinical Cardiac Safety

The GLP in vivo study (08002) assessed pharmacological effects of intravenous (IV) doses of olipudase alfa on hemodynamic and electrocardiographic (ECG) activity in conscious, telemetered cynomolgus monkeys. Six monkeys (3 males and 3 female) received the vehicle ((b) (4) mM NaPO4, (b) (4) M (b) (4) Methionine (b) (4) % Sucrose, pH 6.5) or the test article, olipudase alfa, at a dose of 30 mg/kg, via a 30-minute intravenous infusion via a syringe pump at a volume of 7.7 mL/kg on Days 1 and 4/5, respectively. This study was conducted using a dose de-escalation design in which the animals that received the vehicle on Day 1 also received 30 mg/kg of olipudase alfa on Day 4/5. The electrocardiograms (ECGs) were recorded from the animals via telemetry for at least 2 hours before each dosing through 24 hours after each dosing. Blood samples were collected for toxicokinetic study from one time point before dosing, immediately after the end of infusion (± 30 seconds) and at 1, 3, 6, and 24 hours after the start of infusion. The mean (± SD) C_{max} at 30 mg/kg was 1521 ± 191 µg/mL. The exposure exceeded (50x) the anticipated clinical exposure in humans (30.2 µg/mL). There were no drug-related changes in the PR, QRS and QTcB intervals following the 30 mg/kg dose. No positive drugs were used in the study.

In summary, the results from the GLP in vivo study showed that olipudase alfa caused no changes in PR, QRS and QTcB intervals in monkeys at exposure 50-fold anticipated clinical exposure in humans.

3.4 Clinical Cardiac Safety

No clinically significant cardiac safety concerns were observed in the completed studies. Refer to the integrated summary of safety (ISS).

3.5 QTc assessments

3.5.1 ECG Assessments

The sponsor collected safety ECGs in 5 clinical studies, i.e., study SPHINGO00605, study DFI12712, study DFI13412, study DFI13803, and study LTS13632 (Table 2 for additional details). The sponsor's integrated summary of proportion of subjects with ECG abnormalities is presented in Table 1.

Table 1. Summary of PCSA in electrocardiogram - Olipudase alfa Safety Set

Parameter	Post-baseline PCSA criteria	Pediatric (N=20)	Adult (N=40)	Overall (N=60)
Heart Rate(beats/min)	Number of patients with at least one post-baseline non-missing value, N1	20	40	60
	High	3(15.0%)	0	3 (5.0%)
	Adult >=120 bpm and increase from baseline >=20 bpm	0	0	0
	12 to 16/18 years old (Adolescents): >=120 bpm and increase from baseline >=20 bpm	0	-	0
	6 to <12 years old (Children): >=120 bpm and increase from baseline >=20 bpm	2	-	2
	24 months/2 years to <6 years old (Early children): >=140 bpm and increase from baseline >=20 bpm	1	-	1
	28 days/1 month to 23 months old (Infants): >=175 bpm and increase from baseline >=20 bpm	0	-	0
	Low	1 (5.0%)	3 (7.5%)	4 (6.7%)
	Adult <=50 bpm and decrease from baseline >=20 bpm	1	3	4
	12 to 16/18 years old (Adolescents): <=50 bpm and decrease from baseline >=20 bpm	0	-	0
	6 to <12 years old (Children): <=50 bpm and decrease from baseline >=20 bpm	0	-	0
	24 months/2 years to <6 years old (Early children): <=75 bpm and decrease from baseline >=20 bpm	0	-	0
	28 days/1 month to 23 months old (Infants): <=80 bpm and decrease form baseline >=20 bpm	0	-	0
PR Interval(msec)	Number of patients with at least one post-baseline non-missing value, N1	20	40	60
	High	6(30.0%)	5(12.5%)	11(18.3%)
	Adult >=200 ms and increase from baseline >=20 ms	1	5	6
	12 to 16/18 years old (Adolescents): >=180 ms	2	-	2
	6 to <12 years old (Children): >=170 ms	3	-	3
	24 months/2 years to <6 years old (Early children): >=160 ms	1	-	1
	28 days/1 month to 23 months old (Infants): >=140 ms	1	-	1
QRS Duration(msec)	Number of patients with at least one post-baseline non-missing value, N1	20	40	60
	High	1 (5.0%)	0	1 (1.7%)
	Adult >=120 ms	0	0	0
	12 to 16/18 years old (Adolescents): >=110 ms	1	-	1
	6 to <12 years old (Children): >=100 ms	0	-	0
	24 months/2 years to <6 years old (Early children): >=95 ms	0	-	0
	28 days/1 month to 23 months old (Infants): >=85 ms	0	-	0
QTcB - Bazett's Correction Formula(msec)	Number of patients with at least one post-baseline non-missing value, N1	20	40	60
	Borderline - absolute	12(60.0%)	15(37.5%)	27(45.0%)
	Adult Males: 431-450ms, Females: 451-470 ms	1	15	16
	12 to 16/18 years old (Adolescents): 431–450 ms (Boys), 451-470 ms (Girls)	2	-	2

	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): 431–450 ms	11	-	11
	Borderline - increase	6(30.0%)	18(45.0%)	24(40.0%)
	Adult: Increase from baseline 30-60 ms	0	18	18
	12 to 16/18 years old (Adolescents): Increase from baseline 30-60 ms	2	-	2
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): Increase from baseline 30-60 ms	5	-	5
	Prolonged - absolute	6(30.0%)	5(12.5%)	11(18.3%)
	Adult Males: >450 ms, Females: >470 ms	0	5	5
	12 to 16/18 years old (Adolescents): >450 ms (Boys), >470 ms (Girls)	1	-	1
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): >450 ms	5	-	5
	Prolonged - increase	0	2 (5.0%)	2 (3.3%)
	Adult: Increase from baseline >60 ms	0	2	2
	12 to 16/18 years old (Adolescents): Increase from baseline >60 ms	0	-	0
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): Increase from baseline >60 ms	0	-	0
	Additional - absolute	0	0	0
	Adult Males: >=500 ms, Females: >=500 ms	0	0	0
	12 to 16/18 years old (Adolescents): >=500 ms	0	-	0
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): >=500 ms	0	-	0
QTcF - Fridericia's Correction Formula(msec)	Number of patients with at least one post-baseline non-missing value, N1	20	40	60
	Borderline - absolute	4(20.0%)	7(17.5%)	11(18.3%)
	Adult Males: 431-450ms, Females: 451-470 ms	0	7	7
	12 to 16/18 years old (Adolescents): 431–450 ms (Boys), 451-470 ms (Girls)	1	-	1
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): 431–450 ms	3	-	3
	Borderline - increase	5(25.0%)	11(27.5%)	16(26.7%)
	Adult: Increase from baseline 30-60 ms	0	11	11
	12 to 16/18 years old (Adolescents): Increase from baseline 30-60 ms	0	-	0
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): Increase from baseline 30-60 ms	5	-	5
	Prolonged - absolute	2(10.0%)	3 (7.5%)	5 (8.3%)
	Adult Males: >450 ms, Females: >470 ms	0	3	3
	12 to 16/18 years old (Adolescents): >450 ms (Boys), >470 ms (Girls)	1	-	1
	Birth/0 to <12 years old (Neonates, Infants, Early children, Children): >450 ms	1	-	1
	Prolonged - increase	0	0	0
	Adult: Increase from baseline >60 ms	0	0	0

12 to 16/18 years old (Adolescents): Increase from baseline >60 ms	0	-	0
Birth/0 to <12 years old (Neonates, Infants, Early children, Children): Increase from baseline >60 ms	0	-	0
Additional - absolute	0	0	0
Adult Males: >=500 ms, Females: >=500 ms	0	0	0
12 to 16/18 years old (Adolescents): >=500 ms	0	-	0
Birth/0 to <12 years old (Neonates, Infants, Early children, Children): >=500 ms	0	-	0

Source Sponsor's Integrated Summary of Safety Appendix 5.2.2. Page 98/619 - 104/619

Reviewer's comments: No significant QTcF outliers (i.e., >500 or > Δ60) were observed in the safety population. Outliers for QTcB were observed, however QT correction using Bazett's method has been shown to be inferior in adults and is therefore not recommended (ICH E14, Q&A 1.5). Emerging data in pediatrics is similarly suggesting that Bazett's correction methodology is inferior in pediatrics (Andrsova et al., BMC Pediatrics 2020).

Few PR outliers (≥200 ms and Δ ≥ 20 ms) were observed (pediatrics: n=1; adults: n=5). Of these patients, two patients experienced an increase in PR >25% over baseline (IDs: (b) (6) and (b) (6)). The observed increases were not dose related and were observed at isolated timepoints within each subject. These increases in the PR interval do not appear to be mediated by direct effect on cardiac ion channels. There was no PR interval prolongation in the in vivo monkey study at 50x the clinical exposure.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

4 Appendix

Table 2. Studies Used for ECG Assessments

Protocol	Age Category	Design	Number Patients	Treatment	ECG
SPHINGO00605	Adult	Phase 1, single-center, single-dose, dose escalation study of rhASM in adults with ASMD	11	Cohort 1, 0.03 mg/kg (n=3), cohort 2, 0.1 mg/kg (n=3), cohort 3, 0.3 mg/kg (n=2), cohort 4, 0.6 mg/kg (n=2), and cohort 5, 1.0 mg/kg (n=1).	Standard 12-lead ECGs were performed at screening, pre-infusion, at the end of infusion, and at the following time points post-infusion: 1, 2, 6, 12, and 24 hours; and on Day 14 (or final study visit).
DFI12712 ASCEND	Adult	Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat-dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with ASMD	36	1:1 Randomization to placebo or olipudase alfa, blinded within patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	Standard 12-lead ECG data were collected on week 0 day 1, weeks 14, 26, 38 and 52 at within 24 hours before infusion and at 4, 12, and 24 hours after the end of infusion.
DFI13412 (SPHINGO00812)	Adult	Open-label, multicenter, ascending dose study of the tolerability and safety of rhASM in patients with ASMD	5 (4 from SPHINGO00605)	Single arm, within patient dose escalation of 0.03 mg/kg (pediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	Standard 12-lead ECGs were collected on infusion days immediately pre-infusion and at halfway through infusion, at end of infusion, and post-infusion at 4, 12, 24, and 48 hours.

Protocol	Age Category	Design	Number Patients	Treatment	ECG
DFI13803 (ASCEND Peds)	Pediatric	Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with ASMD	20	Single arm, within patient dose escalation of 0.03 mg/kg (pediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg,b intravenous infusion of rhASM every 2 weeks	Standard 12-lead ECGs were collected during screening, during dose escalation visits (for doses ≥ 0.3 mg/kg, at 2nd infusion of the highest tolerated dose), and during quarterly visits (i.e., weeks 0, 12, 26, 38, and 52). During these ECG visits, the ECGs were collected pre-infusion, at the end of infusion and at 24- and 48-hours post-infusion.
LTS13632	Pediatric/Adult	Long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with ASMD	25 (5 adult +20 pediatric patients)	Single arm, within patient dose escalation of 0.03 mg/kg (pediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	

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CHRISTINE E GARNETT
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Consult to DRDMG from DPACC

Date of request:	11/10/21
BLA:	761261
Product:	Olipudase alfa (rhASM); GZ402665 [enzyme replacement therapy]
Sponsor:	Genzyme Corporation
Indication:	Acid sphingomyelinase deficiency (ASMD)
To:	Christine Hon, Clinical reviewer, DRDMG
From:	Khalid Puthawala, MD, Clinical Reviewer, DPACC
Through:	Robert Lim, MD, Clinical Team Leader, DPACC
Through:	Banu Karimi-Shah, MD, Deputy Division Director, DPACC

Introduction

DRDMG has requested a consult for olipudase alpha (rhASM). The Applicant, Genzyme, has submitted a BLA to DRDMG for olipudase alfa, an enzyme replacement therapy, for the proposed indication of the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency in pediatric and adult patients.

In the BLA, the primary support for efficacy was based on trial DFI12712 (ASCEND). In ASCEND, the mean percent change in percent predicted diffusion capacity (DLCOpp) was one of the primary endpoints to support approval.

DRDMG requests DPACC comment on the clinical meaningfulness of the improvement in DLCOpp observed, and discuss any confounders that may affect interpretation of DLCOpp.

Acid Sphingomyelinase Deficiency (ASMD)

ASMD, also known as Niemann-Pick disease (A and B), is a rare lysosomal storage disease (prevalence ~1 in 250,000 newborns) due to deficient acid sphingomyelinase (ASM) enzyme activity, resulting in the accumulation of sphingomyelin in various organs. In type A disease, there is a complete absence of ASM activity leading to death by 2 to 3 years of age, whereas in type B decreased ASM activity is present. As the ASCEND trial enrolled type B patients only, type A is not discussed further. In ASMD type B disease, patients present in adolescence or early adulthood, with hepatosplenomegaly, thrombocytopenia (due to hypersplenism), short stature, dyslipidemia, and interstitial lung disease (ILD). The ILD in ASMD type B is progressive due to the continued accumulation of sphingomyelin in alveolar macrophages, the alveolar septa, bronchial walls, and pleura. At presentation, there is generally preservation of spirometry (FEV1 and FVC) with a more severe impact on diffusion capacity (DLCO)[1]. As the disease progresses, there is a gradual worsening of restriction and diffusion. Radiographically, ASMD type B patients typically have ground glass opacities (GGOs) predominantly in lower lung zones, and mild smooth thickening of intralobular and interlobular septa (crazy-paving patterns), with a general preservation of

[1] Wasserstein MP, Desnick RJ, Schuchman EH, et al. The Natural History of Type B Niemann-Pick Disease: Results From a 10-Year Longitudinal Study. Pediatrics 2004;114;e672

lung architecture[2]. This correlates with the histopathology, showing intra-alveolar foamy macrophages, and elements of a lipoid pneumonia with Niemann-Pick cells, all without significant architectural distortion[3,4,5].

There is no approved treatment for ASMD. Olipudase alfa, recombinant human acid sphingomyelinase, is proposed as enzyme replacement therapy for the treatment of ASMD.

ASCEND Trial

To support the BLA, the sponsor submitted data from 5 trials (see Appendix: Clinical trials with Olipudase alfa). Of these, this review only discusses DFI1271 (ASCEND) in detail as the other trials have design and interpretability issues (e.g., lack of a comparator arm, lack of blinding, single dose treatment).

The ASCEND trial was a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose study to evaluate efficacy, safety, pharmacodynamics, and PK of intravenous olipudase alfa (given every 2 weeks) vs. matched placebo, in patients with ASMD. The primary analysis period (PAP) was 52 weeks, with an approximate 4-year extension treatment period (ETP). During the open-label ETP, PAP placebo patients crossed over to olipudase, while olipudase arm patients from the PAP continued olipudase treatment. PFTs and HRCT assessments were conducted at baseline and approximately every 6 months (Weeks 26, 52, 80, 104); PFTs were conducted per ATS/ERS standards. The primary endpoints were percent change in DLCOpp and percent change in spleen volume (both comparing baseline to Week 52). Secondary endpoints included change in platelets, liver volume, and various PROs (pain, fatigue, dyspnea). Additional relevant endpoints were changes in chest imaging (e.g., HRCT ground glass scores), and changes in FVC. The study enrolled adult patients with documented ASM deficiency, DLCO $\leq$ 70%, and splenomegaly (6x ULN). The primary analysis population (mITT) was all randomized patients who received at least 1 infusion.

Of the 62 screened patients, 36 were randomized (n=18 each arm), and one placebo patient did not complete 52 weeks of treatment. Patients in this study had a mean age of 35 years, were generally balanced for gender, were mostly white, and enrollment was regionally balanced. The study populations baseline lung function reflected significant diffusion limitation without significant restrictive physiology (mean DLCOpp 49%, mean FVCpp 82%), consistent with ASMD natural history studies[6,7].

Over the controlled 52 week treatment period (PAP), key pulmonary endpoints (DLCO, FVC, chest imaging) improved in olipudase treated patients (Table 1). The absolute change in DLCOpp in olipudase

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[2] von Ranke FM, Pereira Freitas HM, Mançano AD, et al. Pulmonary Involvement in Niemann-Pick Disease: A State-of-the-Art Review. Lung. 2016 Aug;194(4):511-8

[3] Capron T, Trigui Y, Gautier C, et al. Respiratory impairment in Niemann-Pick B disease: Two case reports and review for the pulmonologist. Respir. Med and Res 76 (2019) 13–18.

[4] Guillemot N, Troadec C, de Villemeur TB, et al. Lung disease in niemann–pick disease. Pediatr Pulmonol. 2007; 42:1207–1214.

[5] Nicholson AG, Florio R, Hansell DM, et al. Pulmonary involvement by Niemann–Pick disease. A report of six cases. Histopathology 2006, 48, 596–603

[6] Wasserstein MP, Desnick RJ, Schuchman EH, et al. The Natural History of Type B Niemann-Pick Disease: Results From a 10-Year Longitudinal Study. Pediatrics 2004;114;e672

[7] Von Ranke FM, Freitas HMP, Mancano AD, et al. Pulmonary Involvement in Niemann–Pick Disease: A State-of-the-Art Review. Lung (2016) 194:511–518.

treated patients was greater than placebo treated patients (as well as percentage change, the primary endpoint). The approximate 9% improvement over placebo in absolute DLCOpp was accompanied by nominally significant improvements in FVCpp, FVC in mL (approximately 4% FVCpp, 100mL FVC in mL), and imaging endpoints (HRCT ground glass and interstitial scores, and CXR interstitial scores). A DLCOpp responder analysis at week 52 (using a 15% threshold for response) was consistent with the primary endpoint results.

Table 1. Key Pulmonary Endpoints in ASCEND during 52-week PAP

Measure	Placebo (n=18)	Olipudase (n=18)	Difference
Change from baseline in LS means [95%CIs]			
DLCOpp, week 52	1.23 [-1.5, 4.0]	10.18 [7.5, 12.9]	8.950 [5.1, 12.8], p<0.0001
FVCpp, week 52	1.40 [-1.12, 3.9]	5.43 [2.7, 8.1]	4.0 [0.3, 7.7], p=0.0107
FVC (mL), week 52	61.5 [-4.91, 128]	163.5 [90.6, 236]	102 [SE 49.6], p=0.0433
HRCT ground glass scores, week 52	+0.18 [-0.15, 0.5]	-0.49 [-0.8, -0.2]	-0.67 [-1.1, -0.2], p=0.0056
HRCT interstitial scores, week 52	+0.09 [-0.2, 0.4]	-0.36 [-0.7, -0.05]	-0.45 [-0.9, -0.01], p=0.047
CXR interstitial scores, week 52	+0.28 [0.02, 0.5]	-0.91 [-1.2, -0.7]	-1.19 [-1.6, -0.8], p<0.0001
Abbreviations: DLCOpp – diffusion capacity of lung for carbon monoxide percent predicted; FVCpp – forced vital capacity percent predicted; HRCT – high resolution computed tomography; CXR – chest x-ray *Note: units for numerical data are the same as the measure (e.g., FVCpp difference is 8.950 percent predicted)			

Results from the ETP, while uncontrolled, were consistent with the PAP results: improvement in patients switched from placebo to olipudase was generally similar in magnitude to the PAP results for both DLCOpp and FVCpp. Similar improvements in DLCOpp were noted in DFI13803 Peds (n=9, 56% responders, DFI13412 (n=5 adults x 26 weeks treatment, mean increase 13%). Results for the ETP are summarized in Appendix Table *2*.

Because DLCO was one of the primary endpoints in the ASCEND trial, and because DPACC has been asked to discuss the clinical meaningfulness of this endpoint, this is discussed further in the next section.

Discussion

DLCO

Before discussing DLCO results from ASCEND, it is worthwhile to discuss the measure itself. DLCO is a standard part of pulmonary function testing (PFT). DLCO measures the ability of the respiratory system to transfer gas from the alveolar space (inhaled air) to the pulmonary vasculature across the alveolar capillary membranes. Clinically, DLCO is used in conjunction with spirometry to monitor disease progression (or improvement) in many pulmonary disorders (e.g., emphysema, IPF, sarcoidosis). Because carbon monoxide (CO) has a >200 fold affinity for hemoglobin than oxygen, CO is used to measure gas exchange at extremely low (0.3%) but measurable levels. Measurement of DLCO is done via a 10 second breath hold maneuver in which the subject inhales test gas (0.3% CO) rapidly (<4second) from a state of full exhalation (residual volume [RV]) to total lung capacity, exhaling back to RV. The maneuver is repeated at least twice. Results are adjusted for hemoglobin, carboxyhemoglobin levels, and altitude (as well as lung volumes), as these factors can influence the measured value. ATS/ERS standards for acceptability are based on repeatability, various timings related to the maneuver (e.g.,

sample collected within 4 seconds of start of exhalation, total breath hold within 8 to 12 seconds), and volumes measured (e.g., inhaled volume within 10% of vital capacity).

Despite following existing guidelines and standards, the accuracy and reproducibility of DLCO measurements is generally less than spirometric measures, FEV1 and FVC[8]. DLCO measurements can have considerable variability, which can be intra-individual, intra-laboratory, or inter-laboratory[9,10,11]. In ASCEND, several measures were in place to minimize variability (PFT procedures, equipment calibration, and test administration protocols standardized to ATS guidelines; PFTs collected, processed, coded, and evaluated by a central reader; PFT equipment provided by a central vendor). Beyond the variability in the measurements themselves, external factors can also influence DLCO measurements (e.g., volume of the breath hold, body mass, circulating pulmonary blood volume, alveolar hemorrhage)[12,13].

In addition to problems with variability, there is no established threshold (regulatory or literature-based) for a clinically meaningful DLCO change in response to an intervention. Although a threshold of 15% decline in DLCOpp has been proposed by some professional organizations to represent clinically significant disease progression for some ILDs (IPF[14,15,16],CTD-ILD[17]), it is not certain that this threshold could be used to determine a meaningful treatment response. In other words, the magnitude of decline in diffusion capacity indicating worsening disease may not be the same as the magnitude of improvement needed to determine a clinically meaningful response to a therapeutic intervention. As such, the threshold for a clinically meaningful DLCO treatment response for ILDs, and by extension the ILD component of ASMD, remains unclear. For these reasons, DPACC has not used DLCO as the primary basis to support any drug approvals.

However, despite the aforementioned limitations in assessing and analyzing DLCO, the demonstration of a highly statistically significant increase on DLCO (as observed in ASCEND) provides, at the very least, strong support that olipudase treatment results in a pharmacodynamic effect. Furthermore, the magnitude of treatment effect seen in DLCOpp in the ASCEND trial was larger than that seen in many of

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[8] Jensen RL, Teeter JG, England RD, et al. Instrument accuracy and reproducibility in measurements of pulmonary function. Chest. 2007 Aug;132(2):388-95. Epub 2007 Jun 15.

[9] Hegewald MJ, Markewitz BA, Wilson EL, et al. Single-breath diffusing capacity for carbon monoxide instrument accuracy across 3 health systems. Respir Care. 2015 Mar;60(3):430-6

[10] Hathaway EH, Tashkin DP, Simmons MS. Intraindividual variability in serial measurements of DLCO and alveolar volume over one year in eight healthy subjects using three independent measuring systems. Am Rev Respir Dis. 1989;140(6):1818

[11] Mushtaq M, Hayton R, Watts T, et al. An audit of pulmonary function laboratories in the West Midlands. Respir Med. 1995;89(4):263.

[12] Saydain G, Beck KC, Decker PA, et al. Clinical significance of elevated diffusing capacity. Chest. 2004;125(2):446.

[13] Johnson DC. Importance of adjusting carbon monoxide diffusing capacity (DLCO) and carbon monoxide transfer coefficient (KCO) for alveolar volume. Respir Med. 2000;94(1):28.

[14] Xaubet A, Molina-Molina M, Acosta O, et al. Guidelines for the medical treatment of idiopathic pulmonary fibrosis. Arch Bronconeumol 2017 May;53(5):263-9.

[15] Cottin V, Crestani B, Cadranel J, et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis – 2017 update. Full-length version. Rev Mal Respir. 2017 Oct;34(8):900-68

[16] Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

[17] Khanna D, Mittoo S, Aggarwal R, et al. Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) - Report from OMERACT CTD-ILD Working Group. J Rheumatol. 2015 Nov;42(11):2168-71.

the other pivotal trials for approved ILD therapies (~9% ASCEND vs. no significant difference[18,19,20]). This is noteworthy as the evaluation of DLCO for ILD programs in DPACC has focused on reduction in *decline* rather than *improvement*. DPACC has not evaluated any ILD program demonstrating an improvement in DLCO.

Other endpoints

Although DPACC was not asked to comment on the other pulmonary outcomes assessed in ASCEND, in light of the aforementioned challenges associated with interpreting DLCO changes, discussion of additional pulmonary outcome measures from ASCEND may provide further context for the observed DLCOpp changes in ASCEND. Given the regulatory use of FVC as the basis for approvals in ILD programs, the improvement in FVC in the ASCEND trial provides support for a possible olipudase treatment response for the ILD component of ASMD. The magnitude of the point estimate for the FVC treatment effect in ASCEND was similar to or larger than that observed in other ILD trials, and nominal p-values of <0.05 were observed. Furthermore, in contrast to a reduction in decline in FVC seen in the other ILD trials, the FVC treatment effect in ASCEND showed improvement. Thus, consistent with DLCOpp, FVC data are also supportive of an olipudase treatment effect.

For radiographic endpoints, there are similar challenges to the aforementioned challenges noted with DLCO (e.g., unclear thresholds for meaningful treatment response for changes in HRCT scores, concerns with HRCT techniques and variations in image acquisition)[21]. Notwithstanding these challenges, imaging endpoints can provide important supportive information, similar to the complementary role radiography plays in clinical practice. Rather than focusing on the quantitative results (as thresholds for meaningful change are unknown), the direction of change for the radiographic endpoints in ASCEND corroborates the FVC and DLCO results previously discussed. Specifically, mean HRCT interstitial and ground glass scores and CXR interstitial scores *increased* for placebo treated patients (indicating worsening), whereas olipudase treated patients had *decreased* mean values (indicating improvement), all nominally significant differences (Table 1).

Overall, across the pulmonary related endpoints, results were consistent in that improvements were observed across all parameters and strongly suggest that olipudase treatment may improve pulmonary status in patients with ASMD.

Summary and Conclusions

The sponsor, Genzyme, has submitted a BLA for the approval of olipudase alfa, recombinant human acid sphingomyelinase (enzyme replacement therapy), for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. In the pivotal trial (ASCEND), DLCO was used as one of the primary endpoints to support approval. Key pulmonary results from ASCEND were notable for improvements in DLCOpp and FVC, a spirometric endpoint used

[18] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022535Orig1s000MedR.pdf (p.120)
[19] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205832Orig1s000MedR.pdf (p.80)
[20] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/125276Orig1s131.pdf (p.269)
[21] Chen A, Karwoski RA, Gierada DS, et al. Quantitative CT Analysis of Diffuse Lung Disease. RadioGraphics 2020; 40:28–43

as the basis of approval for other ILDs. Improvements in these parameters in olipudase treated patients versus placebo had 95%CIs that excluded null and/or p-values<0.05.

In the context of the pathogenesis of this rare disease (enzyme deficiency) and the mechanism of action of olipudase (enzyme replacement), improvement in diffusion capacity as a result of increased clearance of alveolar sphingomyelin is biologically plausible. Similarly, sphingomyelin clearance more broadly in the entire respiratory circuit could explain decreasing restrictive physiology and likely accounts for the concurrent FVC and DLCO improvements observed in ASCEND, both supported by imaging endpoint results (improved HRCT and CXR interstitial scores).

While DPACC has not used DLCO as a primary endpoint in our interstitial lung disease programs for the reasons cited above, we have also not had any programs to date which have shown increases in DLCO to the extent seen in the ASCEND trial. The pathophysiology of the ILDs within our Division and underlying MOA of the drugs have only demonstrated a minimal (and often variable) slowing of the decline in DLCO in treated patients.

Therefore, considering the mechanism of action and the improvements observed in DLCOpp and the other key pulmonary endpoints, there appears to be relatively strong support that treatment of patients with ASMD with olipudase results in improvement in pulmonary status. However, given the uncertainties regarding the magnitude of change in DLCOpp that would be clinically meaningful in patients with ASMD, DPACC cannot definitively conclude the observed change in ASCEND constitutes a clinically meaningful change (i.e., a change in how a patient feels, functions, or survives). Be that as it may, in the context of a rare disease characterized by gradual worsening in pulmonary function and for which there are no approved therapies, such data may be sufficient to base efficacy conclusions. Given DRDMG's expertise in this drug development space, DPACC defers to DRDMG whether observed improvements are clinically meaningful in this rare disease.

Appendix

Clinical trials with Olipudase alfa

Protocol Number	Phase	Age Category	Protocol Title	Number of Patients	Treatment	Duration of Treatment	Study Status
SPHINGO00605	1a	Adult	A Phase 1, Single-center, Single-dose, Dose Escalation Study of Recombinant Human Acid Sphingomyelinase (rhASM) in Adults with Acid Sphingomyelinase Deficiency (ASMD)	11	Single arm, single dose of olipudase alfa (0.03, 0.1, 0.3, 0.6, 1.0 mg/kg), no dose escalation	Single dose	Complete
DFI13412 (SPHINGO00812)	1b		An Open-label, Multicenter, Ascending Dose Study of the Tolerability and Safety of Recombinant Human Acid Sphingomyelinase (rhASM) in Patients with Acid Sphingomyelinase Deficiency (ASMD)	5 (4 from SPHINGO00605)		26 weeks	Complete
DFI13803 (ASCEND-Peds)	1/2	Pediatric	A phase 1/2, Multi-center, Open-Label, Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Exploratory Efficacy of Olipudase Alfa in Pediatric Patients Aged <18 Years with Acid Sphingomyelinase Deficiency	20	Single arm, within patient dose escalation of 0.03 mg/kg (pediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	64 weeks	Complete
LTS13632[a]	2	Pediatric / Adult	A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency	25 (5 adult + 20 pediatric patients)		Up to 9 years or marketing approval	Ongoing
DFI12712 ASCEND	2/3	Adult	A Phase 2/3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Repeat-Dose Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency	36 (1 from SPHINGO00605)	1:1 Randomization to placebo or olipudase alfa, blinded within patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	52 weeks PAP & up to 4 years and 3 months extension	PAP Complete ETP Ongoing

a LTS13632 includes 5 adult patients from DFI13412 (SPHINGO00812) and 20 pediatric patients from DFI13803 (ASCEND-Peds)

ASMD = Acid Sphingomyelinase Deficiency, ETP = extension treatment period, PAP = primary analysis period, rhASM = recombinant human acid sphingomyelinase

Source: Clinical Overview from sponsor submission, p.15, Table 1

Table of Key Pulmonary Results

Table 2: Key Pulmonary Results from ASCEND trial

	Measure	Placebo (n=18)	Olipudase (n=18)	Difference[1]
Primary Analysis Period (PAP)				
DLCO	Change from baseline in DLCOpp, week 52	LS mean 1.23 [95%CI -1.5, 3.96]	LS mean 10.18 [95%CI 7.48, 12.88]	8.950 [95%CI 5.11,12.8], p<0.0001
	Change from baseline in DLCOpp, week 26	LS mean 0.541 [95%CI -1.89, 2.97]	LS mean 7.067 [95%CI 4.661,9.474]	6.526 [95%CI 3.1,9.95], p=0.0005
	Responders (Change in DLCOpp ≥ 15%), week 52	0	5 (28%)	OR 14.4 [95%CI 0.8, 271], p=0.075
FVC	Change from baseline in FVCpp, week 52	LS mean 1.399 [95%CI -1.12, 3.92]	LS mean 5.427 [95%CI 2.745,8.11]	4.028 [95%CI 0.346,7.709], p=0.0107[3]
	Average absolute change in FVC (mL), week 52	LS mean 61.5 [95%CI -4.91,128]	LS mean 163.5 [95%CI 90.63, 236]	102 [SE 49.6] p=0.0433[3]
Imaging	Change from baseline in HRCT ground glass scores, week 52	LS mean +0.181 [95%CI -0.15,0.51]	LS mean -0.491 [95%CI -0.81,-0.17]	-0.67 [95%CI -1.13, -0.21], p=0.0056
	Change from baseline in HRCT interstitial lung scores, week 52	LS mean +0.087 [95%CI -0.23, 0.40]	LS mean -0.360 [95%CI -0.67, -0.05]	-0.447 [95%CI -0.89, -0.01], p=0.0474
	Change from baseline in CXR interstitial scores at week 52	LS mean +0.280 [95%CI 0.02,0.54]	LS mean -0.911 [95%CI -1.16,-0.66]	-1.191 [95%CI -1.55, -0.83], p<0.0001
Extension Trial Period (ETP)[2]				
DLCO	Available data	n=10	n=10	
	Change from baseline DLCOpp, week 104	LS mean 13.3 [95%CI 7.16,19.46]	LS mean 14.5 [95%CI 8.35,20.65]	1.189 [95%CI -7.585, 9.963]
	Responders (ΔDLCOpp ≥ 15%), week 104	4 (40%)	5 (50%)	
FVC	Available data	n=10	n=9	
	Change from baseline FVCpp LS mean change, week 104:	LS mean 6.534 [95%CI 0.99,12.08]	LS mean 5.674 [95%CI -0.173,11.521]	-0.860 [95%CI -8.970,7.251]
Imaging	Available data	n=14	n=16	
	Change from baseline HRCT ground glass scores, week 104	LS mean -0.369 [-0.531,-0.206]	LS mean -0.482 [95%CI -0.634,-0.330]	-0.113 [95%CI -0.337,0.110]
	Change from baseline HRCT ground glass scores, week 104	LS mean 0.058 [95%CI -0.3,0.41]	LS mean -0.356 [95%CI -0.69,-0.02]	-0.414 [95%CI -0.903,0.075]

	Abbreviations: DLCOpp – diffusion capacity of lung for carbon monoxide percent predicted; FVCpp – forced vital capacity percent predicted; LS – least squares; HRCT – high resolution computed tomography; CXR – chest x-ray. [1] All differences are LS mean [2] Timepoints beyond 104 weeks not shown as limited available data [3] Analyses conducted by FDA Biostatistical team

Source: CSR 10.3.2 p.165; Efficacy response data supplement 16.2.6 (non-interim) pp. 23-24, 49, 60, 738, 740, 770-771, 793, 800

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