Report on the Deliberation Results

March 2, 2022

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Xenpozyme for I.V. Infusion 20 mg
Non-proprietary Name	Olipudase Alfa (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	September 30, 2021

Results of Deliberation

In its meeting held on February 25, 2022, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients have been collected to keep track of information on patient characteristics, and collect safety and efficacy data as soon as possible. The applicant is required to take whatever measures are necessary to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

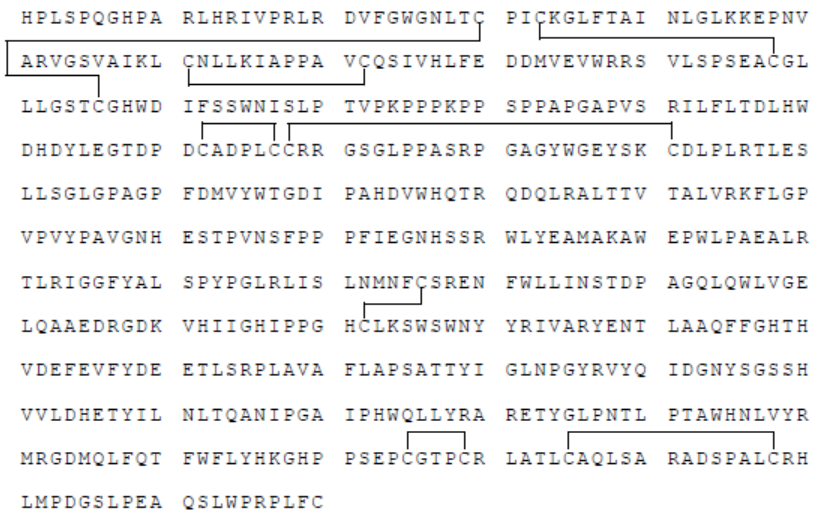
February 7, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Xenpozyme for I.V. Infusion 20 mg
Non-proprietary Name	Olipudase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	September 30, 2021
Dosage Form/Strength	Lyophilized powder for injection, each vial containing 21.2 mg of olipudase alfa (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Olipudase Alfa is a recombinant human sphingomyelin phosphodiesterase analog corresponding to amino acids 14 – 583 of human sphingomyelin phosphodiesterase. Olipudase Alfa is produced in Chinese hamster ovary cells, which is a glycoprotein (molecular weight: ca. 76,000) consisting of 570 amino acid residues.

Structure

Amino acid sequence:



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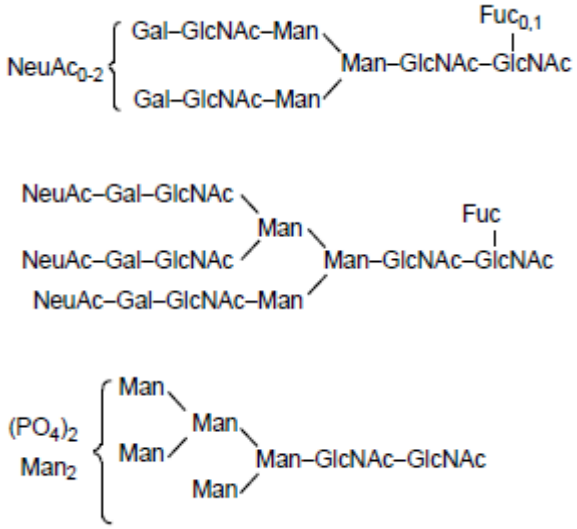
The solid line indicates a disulfide bond.

Partial processing: H1
Glycosylation: N27, N116, N276, N336, N444, and N461

Deduced major glycan structure



Man, mannose; GlcNAc, *N*-acetylglucosamine; NeuAc, *N*-acetylneuraminic acid;
Gal, galactose; Fuc, fucose; PO_4, phosphoric acid

Molecular formula: $C_{2900}H_{4373}N_{783}O_{791}S_{24}$ (protein moiety)
Molecular weight: approximately 76,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 487 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0918-6 dated September 18, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 1 of 2017 [*29 yaku*]; PSEHB/PED Notification No. 0421-1 dated April 21, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
SAKIGAKE comprehensive assessment consultation conducted

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of acid sphingomyelinase deficiency, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Acid sphingomyelinase deficiency

Dosage and Administration

Usually, olipudase alfa (genetical recombination) is administered as an intravenous infusion every other week. The starting dose and subsequent doses should be determined in accordance with the dose escalation regimen shown below. The usual maintenance dose is 3 mg per kg of body weight.

Dose escalation regimen for adult patients	
Initial dose (first day of treatment)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth and subsequent doses (Week 14 and thereafter)	3 mg/kg

Dose escalation regimen for pediatric patients	
Initial dose (first day of treatment)	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 and subsequent doses (Week 16 and thereafter)	3 mg/kg

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients have been collected to keep track of information on patient characteristics, and collect safety and efficacy data as soon as possible. The applicant is required to take whatever measures are necessary to ensure proper use of the product.

Attachment

Review Report (1)

December 24, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Xenpozyme for I.V. Infusion 20 mg
Non-proprietary Name	Olipudase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	September 30, 2021
Dosage Form/Strength	Lyophilized powder for injection, each vial containing 21.2 mg of olipudase alfa (genetical recombination)

Proposed Indication

Acid sphingomyelinase deficiency (ASMD)

Proposed Dosage and Administration

Usually, olipudase alfa (genetical recombination) is administered as an intravenous infusion every other week. The starting dose and subsequent doses should be determined in accordance with the dose escalation regimen shown below. Usually, the maintenance dose is 3 mg per kg of body weight.

Dose escalation regimen for adult patients	
Initial dose (first day of treatment)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)	3 mg/kg (maintenance dose)

Dose escalation regimen for pediatric patients	
Initial dose (first day of treatment)	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 (maintenance dose)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Xenpozyme is a powder for injection containing the active ingredient of olipudase alfa (genetical recombination) (hereinafter referred to as "olipudase alfa"), a recombinant human acid sphingomyelinase (rhASM) developed by a US-based company, Genzyme (currently Sanofi, France).

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease, which is an autosomal recessive disorder resulting from mutation in the *SMPD1* gene encoding acid sphingomyelinase (ASM), a lysosomal hydrolase. It has the effect of decreasing ASM activity and results in accumulation of sphingomyelin in lysosomes in multiple organs including the spleen, liver, and lungs. Sphingomyelin accumulation may lead to a variety of manifestations including infiltrative lung disease, hepatosplenomegaly, atheroma formation due to lipid accumulation, osteoporosis/bone density decreased, pancytopenia, hepatic impairment, heart disease, retinopathy, and growth retardation (*Genet Med.* 2013;15:618-23, *Pediatrics.* 2004;114:e672-7). Acid sphingomyelinase deficiency, which is also called Niemann-Pick disease (types A and B), can be classified into 3 categories: infantile neurovisceral type ASMD, characterized by neurologic manifestations from birth with acute neuropathic disorder; chronic visceral type ASMD, characterized by absence of neurologic manifestations; and chronic neurovisceral type ASMD, characterized by onset of neurologic disorders developed over the clinical course.

The estimated incidence of ASMD is 0.4 to 0.6 in 100,000 newborns (*Pediatrics.* 2008;122:e341-9). In a nationwide epidemiological survey conducted in Japan in fiscal year 2018, 3 patients were reported to have ASMD based on the secondary survey (funded by Health and Labour Sciences Research Grants [Practical Research Project for Rare/Intractable Disease] "Nationwide epidemiological survey on lysosomal storage diseases and peroxisomal disorders" [Fiscal Year 2018 General Partial Research Report]).

There are currently no approved therapies for ASMD in Japan. Olipudase alfa is a rhASM, which, after intravenous infusion, is taken up by lysosomes in cells in various tissues via mannose-6-phosphate (M6P) receptors, promoting metabolism of sphingomyelin, thereby suppressing its accumulation. Enzyme replacement therapy (ERT) with olipudase alfa is therefore expected to be effective in improving a range of symptoms in patients with ASMD.

Recently, the applicant filed an application for marketing approval based on clinical study results and other data that demonstrated the efficacy and safety of olipudase alfa in the treatment of ASMD.

Outside Japan, applications for approval of olipudase alfa were filed in Europe in [redacted] 20[redacted] and in the US in [redacted] of the same year, and these applications are under review. As of December 2021, olipudase alfa has not been approved in any country or region.

Olipudase alfa was granted SAKIGAKE designation for the intended indication of "acid sphingomyelinase deficiency" on April 21, 2017 (SAKIGAKE Drug Designation No. 1 of 2017 [*29 yaku*]), and also orphan drug

designation for the intended indication of “acid sphingomyelinase deficiency” (Orphan Drug Designation No. 487 of 2020 [*R2 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Gene fragments coding human acid sphingomyelinase cloned from cDNA library derived from [redacted] cells were inserted into the expression vector to create an expression construct for olipudase alfa. The expression construct was introduced into Chinese hamster ovary (CHO) cells. The master cell bank (MCB) and working cell bank (WCB) were prepared based on a clone optimal for the production of olipudase alfa.

Characterization and purity testing were conducted for the MCB, WCB, and end of production cells (EOPC) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), ICH Q5B, and ICH Q5D Guidelines. The results of the characterization and purity testing demonstrated genetic stability during production. Within the range tested, no viral or non-viral adventitious agents were detected other than general endogenous retrovirus-like particles from rodent-derived cell lines.

Both the MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for creating a new MCB for the life of the product, but a new WCB will be created as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: expansion culture, production culture, preparation/clarification of harvest solution, [redacted] chromatography, [redacted] chromatography, virus inactivation ([redacted] treatment), [redacted] chromatography, [redacted] chromatography, virus removal filtration, [redacted], dilution, and formulation/filtration/filling/storage/testing.

Expansion culture, production culture, [redacted] chromatography, virus inactivation ([redacted] treatment), [redacted] chromatography, virus removal filtration, and formulation/filtration/filling/storage/testing have been defined as critical process steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug substance.

2.1.3 Safety evaluation of adventitious agents

Raw materials of biological origin used in the manufacturing process of the drug substance are CHO cell lines, which are the host cells, and bovine serum (New Zealand) in the culture step. Fetal bovine/bovine sera (New

Zealand), and trypsin from porcine pancreas are used during preparation of the MCB and WCB. All of these materials conform to the Standard for Biological Ingredients.

Purity was tested on the MCB, WCB, and EOPC [see Section 2.1.1 "Generation and control of cell substrate"]. The mycoplasma testing, *in vitro* adventitious virus testing, vesicular stomatitis virus testing, testing for minute virus of mice, bovine viral diarrhea virus testing, and bioburden testing were performed on unprocessed/unpurified bulk on a commercial scale. Within the range tested, no contamination with viral or non-viral adventitious agents were detected. All testing of unprocessed/unpurified bulk, except for vesicular stomatitis virus testing and bovine viral diarrhea virus testing, are designated as in-process controls.

A viral clearance study was performed with model viruses for the purification process. The results showed that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Viral reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Feline calicivirus	Minute virus of mice
[redacted] chromatography	≥[redacted]	≥[redacted]	[redacted]	≥[redacted]
Virus inactivation ([redacted] treatment)	≥[redacted]	≥[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration[a)]	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
Overall reduction factor	≥15.92	≥11.90	≥5.68	≥12.00

a) [redacted]

2.1.4 Manufacturing process development

The major changes made to the manufacturing process during the development of the drug substance are shown below (the manufacturing processes are referred to as Process A, Process B, and the proposed commercial process). The formulation produced with the drug substance manufactured by Process A or B was used in the phase I/II study (Study DFI13803), while the formulation produced with the drug substance manufactured by Process A, B, or the proposed commercial process was used in the phase II/III study (Study DFI12712).

- Change from Process A to Process B involved [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], formulation, and other changes
- Change from Process B to the proposed commercial process involved [redacted] and other changes

When these changes were made to the manufacturing process, comparability was evaluated with respect to the quality attributes. The evaluation for the change from Process B to the proposed commercial process demonstrated that pre- and post-change drug substances are comparable. On the other hand, the evaluation for the change from Process A to Process B indicated a difference in enzyme activity, while confirming that pre- and post-change drug substances were similar for the rest of evaluation items [see Section "2.R.1 Evaluation of comparability between the drug substance manufactured by Process A and that by Process B"].

The manufacturing process was developed using a quality by design (QbD) approach [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed.

Table 2. Evaluation items for characterization

Primary/higher-order structure	Amino acid sequence, N- and C-terminal amino acid sequence, post-translational modification (deamidation variants, oxidants, and C-terminal modification), free thiol groups, disulfide bonds, secondary structure, tertiary structure
Physicochemical properties	Molecular weight, size variants (low molecular weight variants, dimers), charge variants
Carbohydrate structure	M6P content, sialic acid content, oligosaccharide profile, [redacted], monosaccharide composition
Biological properties	Enzyme activity, cellular uptake activity, binding affinity for M6P receptor

Characterization of the biological properties is summarized as follows:

- Enzyme activity was measured based on the rate of hydrolysis of [redacted] and [redacted]. The Michaelis constant (K_m) was [redacted] to [redacted] µmol/L and the turnover number (k_{cat}) was [redacted] to [redacted] S^{-1} for [redacted], while K_m was [redacted] to [redacted] µmol/L and k_{cat} was [redacted] to [redacted] S^{-1} for [redacted].
- The binding affinity for the cation-independent M6P receptor was evaluated by surface plasmon resonance (SPR) and [redacted] high performance liquid chromatography (HPLC) with [redacted] column.
- The cellular uptake activity was evaluated by measuring hydrolysis of cellular sphingomyelin using HepG2 cells overexpressing the cation-independent M6P receptor.

2.1.5.2 Product-related substances/Product-related impurities

On the basis of the results of characterization in Section "2.1.5.1 Structure and characterization," aggregates, dimers, low molecular weight variants, truncating variants, Impurity A, and Impurity B/Impurity C were identified as product-related impurities. No molecular species have been identified as product-related substances.

Of product-related impurities, aggregates, dimers, low molecular weight variants, and truncating variants are controlled by the specifications for the drug substance and drug product. Impurity A is controlled in the manufacturing process for the drug substance. It has been confirmed that Impurity B/Impurity C are adequately removed during the manufacturing process.

2.1.5.3 Process-related impurities

Host cell proteins (HCPs), host cell DNA, hamster ASM, Impurity D, bovine serum proteins (bovine serum albumin, bovine IgG), Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, pyrogenic substances, and microorganisms were defined as process-related impurities. It has been confirmed that all process-related impurities are adequately removed during the manufacturing process. HCPs, host cell DNA, and microorganisms are controlled by the specifications for the drug substance. Pyrogenic substances are controlled by the specifications for the drug substance and drug product.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping), osmolality, pH, charge inhomogeneity (image capillary isoelectric focusing [icIEF]), glycan profiles (HPLC), free thiol content, purity (size exclusion liquid chromatography [SEC], reverse phase-ultra high performance liquid chromatography [RP-UHPLC], HCPs, host cell DNA), pyrogenic substances, bioburden, [redacted] (enzyme activity), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 summarizes main stability studies for the drug substance.

Table 3. Summary of main stability studies for drug substance

	Number of batches[a)]	Storage condition	Test period	Storage package
Long-term	5	[redacted] ± [redacted]°C	[redacted] weeks	Polyethylene bag
Accelerated	5	25 ± 2°C/60 ± 5%RH	[redacted] weeks	
Photostability	1	Cumulative illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m^2		Tightly capped glass vial

a) Drug substance manufactured by [redacted]

The long-term test showed no clear change in quality attributes throughout the testing period.

The accelerated testing showed an increase in [redacted] (SEC), decrease in [redacted] (RP-UHPLC), and an increase in Impurity B (RP-UHPLC).

The photostability testing showed that the drug substance is photolabile.

On the basis of the above, a shelf life of [redacted] weeks has been proposed for the drug substance when stored at 5 ± 3°C in a polyethylene bag, protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a glass vial (20 mL) containing 21.2 mg of olipudase alfa. Excipients contained in the drug product are sodium dihydrogen phosphate monohydrate, sodium phosphate dibasic heptahydrate, sucrose, and L-methionine. Each vial contains more than the labeled amount, so that the labeled amount (20 mg) of olipudase alfa can be withdrawn after reconstitution with 5.1 mL of water for injection (Japanese Pharmacopoeia [JP]).

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of aseptic filtration/filling, lyophilization, capping, inspection, and labeling/packaging/storage/testing.

[redacted] and [redacted] have been defined as critical process steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

2.2.3 Manufacturing process development

Major changes made to the drug product manufacturing process during development are [redacted], [redacted], [redacted] of [redacted] process, and formulation (the manufacturing process after the change is defined as the proposed commercial process).

When these manufacturing changes are made to the process, comparability has been evaluated with respect to the quality attributes. The results has demonstrated the comparability between the pre- and post-change formulations.

The manufacturing process was developed using a QbD approach [see Section "2.3 QbD"].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmolality, pH, free thiol content, purity (SEC, RP-UHPLC), water content, pyrogenic substances, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], [redacted] (enzyme activity), potency (cellular uptake testing), M6P receptor affinity (SPR), and assay (ultraviolet-visible spectrophotometry). The M6P receptor affinity (SPR) was specified during the review process.

2.2.5 Stability of drug product

Table 4 shows main stability studies for the drug product. The formulation manufactured by the proposed commercial process was used in the stability studies.

Table 4. Summary of main stability studies for drug product

	Manufacturing process of drug substance	Number of batches	Storage condition	Test period	Storage package
Long-term[a)]	[redacted]	4	5 ± 3°C	60 months[b)]	Chlorobutyl rubber stopper and glass vial
	Proposed commercial process	4		[redacted] months[c)]	
Accelerated	[redacted]	3	25 ± 2°C/60 ± 5%RH	[redacted] months	
Photostability	Proposed commercial process	1	Cumulative illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m^2		

a) Testing for potency (cellular uptake testing) has not been established.
b) The stability testing of [redacted] batches has been performed for [redacted] months.
c) The stability testing of [redacted] batches has been performed for [redacted] or [redacted] months. The testing is ongoing for up to 60 months.

The long-term and accelerated tests showed no clear change in quality attributes throughout the testing period.

The results of the photostability testing demonstrated that the drug product is photostable.

The applicant explained it would submit additional potency data (cellular uptake testing) subsequent to 60 months for the 3 formulation batches manufactured with Process B drug substance.

2.3 QbD

The drug substance was developed using a QbD approach. A quality control strategy was established based on the analyses including the following:

- Identification of critical quality attributes (CQAs):

  Concerning product-related impurities [see Section "2.1.5.2 Product-related substances/Product-related impurities"], process-related impurities [see Section "2.1.5.3 Process-related impurities"], and other quality attributes, the following CQAs were identified based on the information obtained during the development of olipudase alfa and relevant findings:

  - CQA: pH, description, osmolality, [redacted], insoluble particulate matter, water content, protein content, identification, enzyme activity, cellular uptake, low molecular weight variants, truncating variants, aggregates, dimer variants, charge variants, glycan profiles ([redacted], [redacted], [redacted], [redacted], [redacted]), free thiol/[redacted] ([redacted]), [redacted], Impurity A, [redacted], host cell DNA, HCPs, Residual impurity F, Residual impurity E, Residual impurity J, adventitious agents, viruses, pyrogenic substances, mycoplasma, sterility, and [redacted].

- Process characterization

  In the process characterization risk assessment, risks for each process parameter were rated to identify critical process parameters and performance attributes that have a significant impact on CQAs and process performance.

- Development of control method

  On the basis of process knowledge including the process characterization above, results of batch analysis and stability studies, and other data, the method for controlling the quality attributes of olipudase alfa through the combination of control of process parameters and performance attributes, in-process controls, and the specifications was developed [for the controls of product-related impurities and process-related impurities, see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities," respectively].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and review in the following sections, PMDA concluded that the quality of the drug substance is adequately controlled. The results of the stability studies for the drug product need to be verified; therefore, the final conclusion on the quality of the drug product will be reported in Review Report (2).

2.R.1 Evaluation of comparability between the drug substance manufactured by Process A and that by Process B

When the changes were made to the manufacturing process of the drug substance from Process A to Process B, comparability was evaluated. The enzyme activity, as measured by hydrolysis of the synthetic substrate, was lower in Process B drug substance than in Process A drug substance.

The applicant's explanation:

The analysis of enzyme activity using a synthetic substrate has confirmed that modification of C-terminal cysteine increased enzyme activity of olipudase alfa. Therefore, it is considered that the above results are associated with the high proportion of molecular species with unmodified C-terminal cysteine residue in Process B drug substance. The cellular uptake study, which is assumed to represent the *in vivo* mechanism of action of olipudase alfa more accurately, demonstrated that decomposition of cellular sphingomyelin by Process A drug substance was similar to that by Process B drug substance. In addition, a study in which Process A drug substance or Process B drug substance was administered to acid sphingomyelinase knockout (ASMKO) mice demonstrated no difference in reduction of sphingomyelin between the drug substances [see Section "3.1.1.2 Comparison of pharmacodynamics of olipudase alfa manufactured by Process A with that by Process B"]. The above results indicate that the difference in enzyme activity measured with the synthetic substrate does not affect the *in vivo* biological activity of olipudase alfa, suggesting that the pre- and post-change drug substances are comparable.

PMDA's view:

In addition to the applicant's explanation, data from the clinical studies indicated no significant differences between the formulations in enzyme activity that may suggest pharmacodynamic, efficacy, or safety issues in clinical settings [see Section "6.R.1 Effects of difference in the manufacturing process of drug substance"]; therefore, it was concluded that the applicant's explanation about Process A drug substance and Process B drug substance being comparable is acceptable.

2.R.2 Novel excipients

The drug product contains a new excipient L-methionine in an amount exceeding that of the previous uses for intravenous administration.

2.R.2.1 Specifications and stability

PMDA concluded that there are no particular problems with L-methionine, which conforms to the requirements specified in the JP, in terms of L-methionine's specifications and stability.

2.R.2.2 Safety

On the basis of the submitted data, PMDA concluded that L-methionine has no safety-related problems at the intended dosage.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In vivo studies of primary pharmacodynamics were conducted to investigate the effects of olipudase alfa on tissue sphingomyelin content and other parameters in ASMKO mice. Studies of secondary pharmacodynamics include investigation of the effects of olipudase alfa on sphingomyelin catabolites and cytokines. Safety pharmacology studies include investigation of effects on the cardiovascular system and respiratory system. Effects on the central nervous system were evaluated in a single-dose toxicity study in dogs. A pharmacodynamic drug interaction study was conducted to investigate pharmacodynamic drug interactions with functional inhibitors of acid sphingomyelinase. The following sections outline the results of main studies.

3.1 Primary pharmacodynamics

3.1.1 Single-dose studies in ASMKO mice

3.1.1.1 The substrate reduction effect of olipudase alfa (CTD 4.2.1.1-3)

A single dose of olipudase alfa 5 mg/kg was intravenously administered to male and female ASMKO mice (8-10 weeks old, n = 3/time point). Sphingomyelin content in the tissues (liver, spleen, lung, and kidney) and plasma sphingomyelin concentrations were measured before administration and on Days 1, 3, 7, 21, and 28. In all the tissues, sphingomyelin content decreased from pre-treatment levels, and thereafter showed a trend towards accumulation (Table 5).

Table 5. Tissue sphingomyelin content and plasma sphingomyelin concentrations after single-dose administration of olipudase alfa 5 mg/kg

Measurement time point	Liver	Spleen	Lung	Kidney	Plasma
Pre-treatment	11.12 ± 4.18	19.95 ± 13.78	7.51 ± 4.42	11.26 ± 4.12	0.028, 0.055
Day 1	2.88 ± 0.78	7.00 ± 0.97	4.78 ± 3.36	7.86 ± 2.79	0.073, 0.078
Day 3	2.21 ± 2.11	6.49 ± 3.91	5.55 ± 2.71	8.63 ± 0.22	0.026, 0.066
Day 7	0.53 ± 0.16	4.04 ± 3.16	4.25 ± 2.00	3.29 ± 0.33	0.019, 0.053
Day 21	2.36 ± 0.28	10.69 ± 6.11	7.34 ± 3.09	18.46 ± 12.86	0.015, 0.070
Day 28	5.00 ± 3.09	8.96 ± 10.04	5.83 ± 3.52	10.00 ± 11.36	0.031, 0.061

Mean ± standard deviation; individual values for n = 2
Units: mg/g tissue for liver, spleen, lung, and kidney; mg/mL for plasma

3.1.1.2 Comparison of pharmacodynamics of olipudase alfa manufactured by Process A with that by Process B (CTD 4.2.1.1-5)

A single dose of olipudase alfa (1 or 3 mg/kg) manufactured by Process A or Process B, or vehicle[1)] was intravenously administered to male and female ASMKO mice (8-14 weeks old, n = 12/group), and tissue sphingomyelin content (liver, spleen, and kidney) was measured at Day 3. Sphingomyelin content decreased in the groups receiving 3 mg/kg of olipudase alfa manufactured by Process A or Process B compared with those in the vehicle group. Blood ceramide concentrations were measured at 10, 45, 120, and 540 minutes, and 3 days after administration of 3 mg/kg of olipudase alfa manufactured by Process A or Process B. In groups receiving olipudase alfa manufactured by Process A and those manufactured by Process B, blood ceramide concentrations at 10, 45, and 120 minutes after administration were similar to the concentrations in the vehicle group. The blood ceramide concentrations increased at 540 minutes after administration, but on Day 3, decreased to below the level at 540 minutes. The tissue sphingomyelin content and blood ceramide

[1)] Vehicle for Process A drug substance: 20 mmol/L sodium phosphate, 100 mmol/L methionine, 0.1 mmol/L EDTA, 5% sucrose (pH 6.5); vehicle for Process B drug substance: 20 mmol/L sodium phosphate, 100 mmol/L methionine, 5% sucrose (pH 6.5)

concentrations after administration of olipudase alfa manufactured by Process A did not differ markedly from those manufactured by Process B.

3.1.2 Repeated-dose studies in ASMKO mice (CTD 4.2.1.1-8, 4.2.1.1-9)

Olipudase alfa (0.1, 0.3, or 1 mg/kg) or vehicle was intravenously administered to male and female ASMKO mice (10 weeks old, n = 8/group) once every 2 weeks for 12 weeks, and tissue sphingomyelin content (liver, spleen, lung, and kidney) was measured at 1 and 2 weeks post-final dose. As shown in Table 6, the sphingomyelin content decreased in a dose-dependent manner in the liver and spleen after the final dose of olipudase alfa. The sphingomyelin content similar to or higher than that of the vehicle was observed at 2 weeks post-final dose (olipudase alfa 0.1 mg/kg group) and at 1 and 2 weeks post-final dose (olipudase alfa 0.3 mg/kg group) in the lung; and at 1 week post-final dose (olipudase alfa 0.1 mg/kg group) in the kidney. The sphingomyelin content in the lung and kidney was lower in the olipudase alfa group than in the vehicle group at all time points except for the above-mentioned time points.

Table 6. Tissue sphingomyelin content after repeated-dose administration of olipudase alfa

Treatment	Time point	Liver	Spleen	Lung	Kidney
Vehicle	1 week post-final dose	52.25 ± 8.18	73.98 ± 12.68	38.33 ± 10.21	54.93 ± 10.55
	2 weeks post-final dose	50.76 ± 10.62	52.62 ± 7.44	41.77 ± 10.86	62.91 ± 32.10
Olipudase alfa 0.1 mg/kg	1 week post-final dose	27.28 ± 9.09	36.18 ± 12.62	30.40 ± 14.64	60.92 ± 9.97
	2 weeks post-final dose	29.19 ± 7.78	43.98 ± 3.99	43.58 ± 10.13	56.03 ± 8.90
Olipudase alfa 0.3 mg/kg	1 week post-final dose	6.86 ± 2.63	17.93 ± 4.61	45.45 ± 5.89	37.86 ± 9.94
	2 weeks post-final dose[a)]	12.21 ± 0.40	21.68 ± 7.69	44.24 ± 2.63	42.83 ± 9.79
Olipudase alfa 1 mg/kg	1 week post-final dose	2.33 ± 0.75	6.49 ± 1.09	36.43 ± 9.66	27.70 ± 2.29
	2 weeks post-final dose[a)]	9.53 ± 2.82	12.45 ± 0.65	32.60 ± 14.12	34.47 ± 2.88

Mean ± standard deviation; unit, mg/g tissue
a) n = 3

Olipudase alfa (0.3, 1, or 3 mg/kg) or vehicle was intravenously administered to male and female ASMKO mice (8-10 weeks old, n = 6/group) once every 2 weeks for 12 weeks, and tissue sphingomyelin content (liver, spleen, and lung) was measured at 24 hours post-final dose in all groups as well as at 4 weeks post-final dose in the vehicle group and the olipudase alfa 3 mg/kg group. As shown in Table 7, in all olipudase alfa groups, the sphingomyelin content decreased in all the tissues at 24 hours post-final dose. In the liver and spleen, the sphingomyelin content in the olipudase alfa group was higher at 4 weeks post-final dose than that at 24 hours post-final dose, but was lower than that in the vehicle group. In the lung, the sphingomyelin content in the olipudase alfa group at 4 weeks post-final dose was similar to that in the vehicle group.

Table 7. Tissue sphingomyelin content after repeated-dose administration of olipudase alfa

Treatment	Time point	Liver	Spleen	Lung
Vehicle	24 hours post-final dose	91.48 ± 13.76	67.35 ± 14.94	33.96 ± 6.48
	4 weeks post-final dose	108.43 ± 13.79	76.54 ± 13.38	27.09 ± 7.10
Olipudase alfa 0.3 mg/kg	24 hours post-final dose	2.33 ± 4.04	11.58 ± 3.03	23.00 ± 3.13
Olipudase alfa 1 mg/kg	24 hours post-final dose[a)]	5.57 ± 8.01	0.83 ± 1.66	13.41 ± 2.82
Olipudase alfa 3 mg/kg	24 hours post-final dose[a)]	6.25 ± 7.74	0.00 ± 0.00[b)]	14.34 ± 7.11
	4 weeks post-final dose	31.76 ± 9.70	13.68 ± 3.44	29.19 ± 3.87

Mean ± standard deviation; unit, mg/g tissue
a) n = 5; b) below the limit of detection in all animals

3.2 Secondary pharmacodynamics

3.2.1 Single-dose studies

3.2.1.1 Investigation of total ceramide and C16-ceramide concentrations (CTD 4.2.1.2-10)

A single dose of olipudase alfa 10 or 20 mg/kg was intravenously administered to male and female ASMKO mice (8-10 weeks old, n = 7-8/group) to investigate the correlation between plasma concentrations of sphingomyelin catabolites (total ceramides and C16-ceramide) and mortality. The results showed that 5 of 7 animals in the olipudase alfa 10 mg/kg group died within 72 hours of administration, while 4 of 8 animals in the olipudase alfa 20 mg/kg group were sacrificed moribund at 9 hours after administration due to worsened clinical signs. Total ceramide concentrations in plasma of survived animals did not differ from those of died or sacrificed animals at either dose level. On the other hand, while plasma C16-ceramide concentrations in died or sacrificed animals did not differ markedly from those in survived animals in the olipudase alfa 10 mg/kg group, plasma C16-ceramide concentrations were higher in died or sacrificed animals than in survived animals at 10, 45, 120, and 240 minutes post-dose in the olipudase alfa 20 mg/kg group.

3.2.1.2 Investigation of total ceramides, SPH, and S1P concentrations (CTD 4.2.1.2-4)

A single dose of olipudase alfa 20 mg/kg was intravenously administered to male and female ASMKO mice (8-10 weeks old, n = 7/group), and plasma concentrations of sphingomyelin catabolites, namely total ceramides, sphingosine (SPH), and sphingosine-1-phosphate (S1P), were measured before administration and at 5, 30, 60, 240, and 540 minutes after administration of olipudase alfa. Total ceramide concentrations in plasma increased at 5 and 30 minutes post-treatment compared with pre-treatment and then showed a trend towards a decrease at 60 minutes post-treatment, but increased again at 240 minutes post-treatment and thereafter. The plasma concentrations of SPH, a decomposition product of ceramide, increased at 240 minutes post-treatment and thereafter compared with pre-treatment. The plasma concentrations of S1P, a decomposition product of SPH, increased at 240 minutes post-treatment compared with pre-treatment but remained at similar levels as pre-treatment at 540 minutes post-treatment.

3.2.1.3 Investigation of proinflammatory cytokines (CTD 4.2.1.2-2, 4.2.1.2-3)

A single dose of olipudase alfa (0.3, 3, or 10 mg/kg) or vehicle was intravenously administered to female ASMKO mice (8-10 weeks old, n = 3/time point/group), and proinflammatory cytokine concentrations in serum were measured at 2, 3, 4, 6, and 9 hours after administration of olipudase alfa. At 3 hours post-treatment and subsequent time points, interleukin (IL)-6 and granulocyte-colony stimulating factor (G-CSF) concentrations increased at ≥3 mg/kg of olipudase alfa compared with the vehicle group. The concentrations of IL-1α, IL-1β, macrophage inflammatory protein-1α (MIP-1α), and keratinocyte chemoattractant/growth-regulated oncogene (KC/GRO) showed trends towards an increase. Cytokine concentrations did not increase in animals treated with a single dose of olipudase alfa 0.3 mg/kg at any time point. No increase in the concentration of tumor necrosis factor alpha (TNFα) was detected at any time point and dose level of olipudase alfa.

A single dose of vehicle or olipudase alfa 20 mg/kg was intravenously administered to male and female ASMKO mice (8-10 weeks old, n = 3-4/group), and proinflammatory cytokine concentrations in serum were measured at 1, 2, 3, 4, and 6 hours after administration of olipudase alfa. At 2 hours post-treatment and subsequent time points, IL-6, G-CSF, MIP-1α, and KC/GRO concentrations increased in the olipudase alfa group compared with the vehicle group. Furthermore, nitrite and nitrate concentrations after single dose administration of olipudase alfa 20 mg/kg were measured to evaluate the serum concentration of nitric oxide. The serum nitric oxide concentrations were higher in the olipudase alfa group than in the vehicle group at 6 hours post-treatment. No increase in the concentration of TNFα was detected at any time point.

3.2.2 Repeated-dose studies

3.2.2.1 Investigation of total ceramide, SPH, and S1P concentrations (CTD 4.2.1.2-13)

A single dose of olipudase alfa 3 mg/kg or repeated doses of olipudase alfa (3 mg/kg on Days 1, 3, 5, and 8 and 20 mg/kg on Day 10) were intravenously administered to male and female ASMKO mice (8-12 weeks old, n = 8/group), and plasma concentration of the sphingomyelin catabolites (total ceramides, SPH, and S1P) were measured. The plasma concentrations of total ceramides, SPH, and S1P were lower in the olipudase alfa repeated-dose group than in the 3 mg/kg single-dose group and were also lower than the concentration data from a study in which a single dose of olipudase alfa 20 mg/kg was administered (CTD 4.2.1.2-4).

3.2.2.2 Investigation of proinflammatory cytokines (CTD 4.2.1.2-8, 4.2.1.2-9)

Male and female ASMKO mice (8-10 weeks old, n = 3/time point/group) were intravenously given either a single dose of olipudase alfa 3 mg/kg, 2 to 4 repeated-doses of olipudase alfa 3 mg/kg (2 or 3-day interval), or 4 repeated-doses of olipudase alfa 3 mg/kg (Days 1, 4, 6, and 8) plus 1 dose of 20 mg/kg (Day 11), and proinflammatory cytokine concentrations in serum were measured. In all the olipudase alfa 3 mg/kg repeated-dose groups, IL-6, IL-1α, IL-1β, G-CSF, MIP-1α, KC/GRO, and TNFα concentrations at 4 and 9 hours post-dose were lower than those in the 3 mg/kg single-dose group. In animals receiving a dose of 20 mg/kg after 4 doses of olipudase alfa 3 mg/kg, serum concentrations of these cytokines did not increase after 3 to 12 hours post-final dose.

Male and female ASMKO mice (8-10 weeks old, n = 6/group) were intravenously given olipudase alfa 3 mg/kg on Day 1 and olipudase alfa 20 mg/kg on Day 6, and serum concentrations of proinflammatory cytokines, including IL-6, IL-1α, G-CSF, MIP-1α, and KC/GRO were measured. The serum proinflammatory cytokine concentrations at 4 hours after administration of olipudase alfa 20 mg/kg were generally lower than those at 4 hours after administration of a single dose of olipudase alfa 20 mg/kg (CTD 4.2.1.2-2).

3.3 Safety pharmacology

As summarized in Table 8, the effects of olipudase alfa on the cardiovascular system and respiratory system were evaluated in the safety pharmacology studies, and the effects on the central nervous system were evaluated in a single-dose toxicity study in dogs.

Table 8. Summary of results of safety pharmacology studies

Organ system	Test system	Evaluation parameter/method	Dosage regimen	Route of administration	Findings	CTD
Cardiovascular system	ASMKO mouse (males and females, n = 4/group)	Blood pressure, heart rate, etc. Telemetry method	(1) Olipudase alfa 0,[a] 3, and 3 mg/kg on Days 1, 5, and 9, respectively (2) Olipudase alfa 10 and 10 mg/kg on Days 1 and 9, respectively (3) Olipudase alfa 20 mg/kg on Day 1	IV	In the treatment groups (2) and (3), dose-dependent decreases in heart rate, blood pressure, and activity occurred following a single dose of 20 mg/kg or 10 mg/kg. All animals receiving 20 mg/kg in (3), and 3 of 4 animals receiving the first dose of 10 mg/kg resulted in death or moribund sacrifice. One animal in (2), which received repeated doses of 10 mg/kg, had severe and acute drops in blood pressure and heart rate, but recovered.	4.2.1.3-1
	ASMKO mouse (males and females, N = 20)	ECG, etc.	Olipudase alfa 0, 20 mg/kg	IV	At ≥3 hours after administration of 20mg/kg, worsened clinical signs (lack of motivation, hunchback position, piloerection, cold sensation) were observed, and all animals were sacrificed moribund at 8 hours post-dose. A drop in heart rate, compared with the vehicle group, was observed 45 minutes after administration of 20 mg/kg and further decreased at 3 hours post-dose and thereafter. QT interval lengthened to 80 minutes after administration of olipudase alfa 20 mg/kg and shortened at 2 hours post-dose, followed by QT interval prolongation again.	4.2.1.3-2
	C57BL/6 mouse (males and females, N = 20)	ECG, etc.	Olipudase alfa 20 mg/kg	IV	No effect	4.2.1.3-3
Cardiovascular system Respiratory system	Cynomolgus monkey (n = 5/sex)	Blood pressure, heart rate, body temperature, ECG, respiratory rate, tidal volume, blood gas parameters, etc.	Olipudase alfa 0[a] or 30 mg/kg Morphine sulfate 0.5 mg/kg	IV[b]	While increased respiratory rate was observed in the positive control group at ≥30 minutes post-dose, there were no effects in the olipudase alfa group.	4.2.1.3-4
Cardiovascular system Respiratory system Central nervous system	Beagle dog (males and females, n = 8/group)	Clinical signs, vital signs, ECG, oxygen saturation, etc.	Olipudase alfa 0,[a] 3, 10, or 30 mg/kg	IV	Olipudase alfa: changes in clinical symptoms were observed (hypersalivation at ≥3 mg/kg; unformed stool and scratching face at all dose levels; hyperactivity at ≥10 mg/kg; cold to touch at 3 and 30 mg/kg. There were no changes in body temperature, respiratory rate, ECG, oxygen saturation or blood pressure.	4.2.3.1-19

a) 20 mmol/L sodium phosphate, 5% sucrose, 0.1 mol/L methionine, 0.1 mmol/L EDTA
b) Morphine sulfate was subcutaneously administered.

3.4 Pharmacodynamic drug interactions

3.4.1 Pharmacodynamic drug interactions with functional inhibitors of acid sphingomyelinase

Citalopram 192 μg/day or fluoxetine 300 μg/day was administered to male and female ASMKO mice (12-14 weeks old, n = 12/group) by continuous subcutaneous injection. Three days later, a single dose of olipudase alfa 1 mg/kg or vehicle was intravenously administered, and another 3 days later, sphingomyelin content in the liver and spleen was measured. Treatment groups were also established for olipudase alfa 1 mg/kg alone and vehicle alone. The sphingomyelin content in the liver and spleen in the citalopram/vehicle group was similar to that in the vehicle alone group. The liver sphingomyelin content in the citalopram/olipudase alfa group was

lower than that in the citalopram/vehicle group while the spleen sphingomyelin content in the citalopram/olipudase alfa group tended to be lower than that in the citalopram/vehicle group. The sphingomyelin content in the liver and spleen in the citalopram/olipudase alfa group was similar to that in the olipudase alfa alone group. The liver sphingomyelin content in the fluoxetine/vehicle group was similar to that in the vehicle alone group, while the spleen sphingomyelin content in the fluoxetine/vehicle group was lower than that in the vehicle alone group. The sphingomyelin content in the liver and spleen was lower in the fluoxetine/olipudase alfa group than in the fluoxetine/vehicle group. The sphingomyelin content in the liver and spleen in the fluoxetine/olipudase alfa group was similar to that in the olipudase alfa alone group.

3.R Outline of the review conducted by PMDA

3.R.1 The substrate reduction effect of olipudase alfa

The applicant's explanation:

Olipudase alfa is a rhASM, which is taken up into various tissues and cells by endocytosis via soluble cation-independent M6P receptors and delivered to lysosomes where it increases the enzyme activity. Primary pharmacodynamic studies investigated the ability of olipudase alfa to reduce sphingomyelin, the substrate of ASM. The single-dose studies (CTD 4.2.1.1-1, 4.2.1.1-2, and 4.2.1.1-3), in which olipudase alfa 1, 3, or 5 mg/kg was intravenously administered to ASMKO mice, showed a trend towards a dose-dependent decrease in the sphingomyelin content in the target tissues (liver, spleen, lung, and kidney) compared with pre-treatment up to 7 days post-dose. In the repeated-dose study (CTD 4.2.1.1.8), in which low dose levels of olipudase alfa (0.1, 0.3, or 1.0 mg/kg) were intravenously administered to ASMKO mice once every 2 weeks for 12 weeks, the mean sphingomyelin content following administration of olipudase alfa tended to be similar to that of the vehicle group especially in the lung. On the other hand, in the repeated-dose study (CTD 4.2.1.1.9), in which the regimens of olipudase alfa included a high dose level (0.3, 1.0, or 3.0 mg/kg) administered intravenously once every 2 weeks for 12 weeks, the lung sphingomyelin content decreased compared with the vehicle group at 24 hours post-dose at all dose levels. In all studies, the sphingomyelin content in the liver, spleen, and kidney decreased following administration of olipudase alfa. Therefore, the above findings demonstrated the substrate reduction effect of olipudase alfa in the target tissues, thus indicating the effectiveness of olipudase alfa in the treatment of ASMD.

PMDA's view:

Within the range of dose levels studied, the results from the primary pharmacodynamics studies have demonstrated decreased sphingomyelin content in the liver, spleen, lung, and kidney compared with that of the pre-treatment with olipudase alfa. Thus, olipudase alfa may reduce the sphingomyelin content in the target tissues in humans. The efficacy of olipudase alfa in humans will be discussed in Section "7.R.1 Efficacy."

3.R.2 Effects of sphingomyelin catabolites on cytokines

The applicant's explanation:

Deaths of mice treated with a high intravenous dose regimen (10 mg/kg) of olipudase alfa were reported in a single-dose toxicity study in ASMKO mice [see Section "5.1 Single-dose toxicity"]. On the mechanism of

toxicity in ASMKO mice receiving a high dose of olipudase alfa, it has been reported that ceramide, which is a sphingomyelin catabolite, increases the expression of nuclear factor kappa B (NFκB) and CCAAT/enhancer binding proteins (c/EBP), transcription factor families that induce the expression of cytokines; and that S1P, which is also a sphingomyelin catabolite, is involved in production of cytokines via NFκB activation and prostaglandin production (*Br J Pharmacol.* 2009;158:982-93, *Prog Lipid Res.* 2016;61:51-62). Taking account of these reports, secondary pharmacodynamic studies were conducted to evaluate the profiles of proinflammatory cytokines and sphingomyelin catabolites following administration of olipudase alfa. Following administration of a single intravenous dose of olipudase alfa ≥10 mg/kg to ASMKO mice (CTD 4.2.1.2-2 through 4.2.1.2-4, 4.2.1.2-10), concentrations of sphingomyelin catabolites (e.g., ceramides, SPH, and S1P) and proinflammatory cytokines increased, and some animals died. Plasma C16-ceramid concentrations tended to be higher in non-surviving animals than in surviving animals.

In view of the known correlation between activation of the S1P receptor and bradycardia (*Am Heart J.* 2014;168:632-44), olipudase alfa may cause high concentrations of sphingomyelin catabolites including S1P to be formed, leading to toxicity resulting in cardiotoxic death. Accordingly, the following investigations were performed. The effects of olipudase alfa on the cardiovascular system were investigated in a safety pharmacology study in ASMKO mice (CTD 4.2.1.3-2). Following administration of olipudase alfa, QT intervals increased in a biphasic manner, which closely mirrored the time-course increase in ceramide and S1P following single dose administration of olipudase alfa to ASMKO mice (CTD 4.2.1.2-11), suggesting that the prolonged QT intervals were caused by sphingomyelin catabolites. The results of the safety pharmacology study in ASMKO mice referred to above also suggested that the prolonged QT intervals observed were accompanied by decreases in heart rate. The mechanism underlying the effects above has been reported in the following investigations. The inhibition of the human ether-a-go-go related gene (hERG) in cells incubated with ceramide or sphingomyelinase has been reported in an *in vitro* study (*Cell Physiol Biochem.* 2007;20:429-40). In the secondary pharmacodynamics study in ASMKO mice (CTD 4.2.1.2-2), a single intravenous dose of olipudase alfa 20 mg/kg increased serum concentrations of nitric oxide, IL-6, and other biomarkers. Studies have suggested that nitric oxide is associated with QT prolongation and sudden cardiac death (*Acta Cardiol Sin.* 2013;29:217-25, *Cardiovascular Research.* 2010;87:593-600), and nitrites/nitrates may inhibit the activity of hERG (*Mol Pharmacol.* 1999;56:1298-308). There is a report on the correlation between an increase in the expression of IL-6 and QT interval prolongation in patients with inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus (*In Vivo.* 2015;29:619-36). The above studies suggest that increases in the concentrations of these cytokines may have some effect on the regulation of hERG activity.

On the basis of these findings, ceramide and other sphingomyelin catabolites produced after administration of olipudase alfa ≥10 mg/kg to ASMKO mice may be associated with increased toxicity including lethality. However, when olipudase alfa 3 mg/kg was administered to ASMKO mice on Days 1, 4, 6, and 8 to prevent rapid accumulation of sphingomyelin catabolites, followed by olipudase alfa 20 mg/kg on Day 11, elevation of proinflammatory cytokine concentrations was mitigated, and no lethality was reported following 20 mg/kg (CTD 4.2.1.2-9). Furthermore, in a repeated-dose safety pharmacology study in ASMKO mice (CTD 4.2.1.3-

1), the reduction in heart rate after 2 doses of olipudase alfa 3 mg/kg was of lesser extent compared with that after 1 dose of olipudase alfa. Therefore, the release of proinflammatory cytokines in ASMKO mice is associated with the rate and amount of substrate decomposition, suggesting that the release of proinflammatory cytokines can be reduced by controlling the decomposition rate of the substrate.

PMDA's view:

The results of the secondary pharmacodynamics studies indicated that the concentrations of sphingomyelin catabolites and proinflammatory cytokines increased following administration of olipudase alfa, suggesting that safety may be affected by sphingomyelin catabolites formed after administration of olipudase alfa. However, rapid elevation of sphingomyelin catabolites and proinflammatory cytokines may be prevented by adopting a dose-escalation regimen of olipudase alfa based on the following findings in the secondary pharmacodynamics studies: the concentrations of sphingomyelin catabolites in mice on the dose-escalation regimen of olipudase alfa (CTD 4.2.1.2-13) were lower than those in mice that received a single dose of olipudase alfa (CTD 4.2.1.2-4); the concentrations of proinflammatory cytokines in mice receiving olipudase alfa 3 mg/kg on Day 1 and 20 mg/kg on Day 6 (CTD 4.2.1.2-8) were generally lower than those in mice receiving a single dose of olipudase alfa (CTD 4.2.1.2-2); there were no increases in the concentrations of proinflammatory cytokines in mice that received 4 doses of olipudase alfa 3 mg/kg before 1 dose of 20 mg/kg (CTD 4.2.1.2-9). The concentrations of sphingomyelin catabolites and proinflammatory cytokines in blood following administration of olipudase alfa to humans as well as effects on safety will be discussed further in Section "7.R.2 Safety."

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics was evaluated in mice, rats, dogs, and monkeys following a single intravenous dose of olipudase alfa or ^{125}I-labeled olipudase alfa. The pharmacokinetics of repeated intravenous doses of olipudase alfa was evaluated based on the toxicokinetics in mouse, rabbit, rat, and monkey toxicity studies. The concentrations of olipudase alfa in serum were measured by enzyme-linked immunosorbent assay (ELISA). The lower limit of quantitation of olipudase alfa concentrations was 0.078 or 0.635 µg/mL in mice, 6.25 µg/mL in rats and dogs, 0.078 µg/mL in rabbits, and 0.05 µg/mL in monkeys. Radioactivity in biological samples was measured by gamma counter. Anti-olipudase alfa antibody (ADA) levels in serum were measured by ELISA. Results of the main studies are presented in the sections below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.1.3-4, 4.2.2.2-6, 4.2.3.1-18, 4.2.3.1-20)

Table 9 shows pharmacokinetic parameters of olipudase alfa after single dose administration of olipudase alfa as an intravenous bolus dose in male and female ASMKO mice, rats, and dogs, and as an intravenous infusion over 30 minutes in male and female monkeys.

Table 9. Pharmacokinetic parameters of olipudase alfa following a single intravenous dose of olipudase alfa

Animal species	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)
ASMKO mouse	3	M	3	41.87 ± 3.88	141.83 ± 7.94	5.83 ± 0.66	21.00 ± 1.20	177.60 ± 11.63
		F	4	42.26 ± 6.26	144.47 ± 28.92	4.29 ± 1.19	27.6 ± 7.2	161.70 ± 18.68
Rat	3	M	10	78.80 ± 10.66	161.98 ± 27.91	1.54 ± 0.80	19.20 ± 3.60	41.71 ± 8.90
		F	10	70.47 ± 7.76	123.05 ± 7.05	1.13 ± 0.60	24.60 ± 1.20	43.07 ± 10.20
	10	M	10	260.53 ± 72.23	530.03 ± 80.93	1.53 ± 0.71	19.2 ± 3.00	43.43 ± 15.19
		F	10	278.40 ± 42.99	473.12 ± 84.56	1.31 ± 0.56	21.6 ± 4.20	38.59 ± 3.19
	30	M	10	562.73 ± 51.21	1711.32 ± 1096.05	2.69 ± 2.95	21.60 ± 8.40	59.69 ± 19.87
		F	10	536.73 ± 45.12	967.78 ± 147.70	1.125 ± 0.44	31.80 ± 4.80	52.02 ± 3.45
Dog	3	M	4	55.42 ± 4.77	228.98 ± 42.60	5.61 ± 2.14	13.2 ± 3.00	97.97 ± 24.09
		F	4	60.75 ± 8.66	310.70 ± 99.86	10.04 ± 3.79	10.20 ± 3.6	128.39 ± 25.97
	10	M	4	140.42 ± 28.07	845.20 ± 323.45	6.01 ± 2.96	13.20 ± 5.40	96.99 ± 25.80
		F	4	176.83 ± 55.94	772.85 ± 106.08	6.04 ± 1.81	13.20 ± 1.80	107.65 ± 37.20
	30	M	4	427.75 ± 86.27	2495.79 ± 806.04	9.58 ± 4.11	13.20 ± 4.20	149.24 ± 40.49
		F	4	479.92 ± 53.32	1664.59 ± 414.02	4.52 ± 1.86	18.60 ± 4.20	105.25 ± 21.04
Monkey	30	M	2	1312.29, 1710.76	3226.02, 3878.04	7.50, 7.54	30.71, 27.15[a)]	262.24, 220.83[b)]
		F	3	1527 ± 183	3262 ± 434	7.17 ± 0.55	28.4 ± 4.31[a)]	228 ± 46.3[b)]

Mean ± standard deviation; individual values for n ≤ 2; "—," not calculated;
C_{max}, maximum serum concentration; $AUC_{0\text{-}inf}$, area under the serum concentration versus time curve from time 0 to infinity; $t_{1/2}$, elimination half-life; CL, total clearance; V_d, volume of distribution
a) Unit, mL/h; b) Unit, mL

4.1.2 Repeated-dose studies (CTD 4.2.3.2-11, 4.2.3.2-12, 4.2.3.5.2-1, 4.2.3.5.2-2)

Table 10 shows pharmacokinetic parameters of olipudase alfa after repeated doses of olipudase alfa as an intravenous bolus dose once every 2 weeks in male and female rats, or as an intravenous infusion over 30 minutes once every 2 weeks in male and female monkeys. In male and female rats, on Day 183, ADAs were detected in 3 of 10 animals (3 mg/kg), 5 of 10 animals (10 mg/kg), and 2 of 9 animals (30 mg/kg). In male and female monkeys, on Day 169, ADAs were detected in 14 of 14 animals (3 mg/kg), 13 of 14 animals (10 mg/kg), and 14 of 14 animals (30 mg/kg).

Table 10. Pharmacokinetic parameters of olipudase alfa following repeated intravenous doses of olipudase alfa

Animal species	Dose (mg/kg)	Sex	n	Time point	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)
Rat	3	M	5	Day 1	70.18 ± 21.21	123.30 ± 6.12	0.72 ± 0.24	24.60 ± 1.20	42.43 ± 9.14
			5	Day 85	91.81 ± 8.12	160.29 ± 24.81	0.60 ± 0.11	19.20 ± 3.60	29.01 ± 3.65
			5	Day 183	134.91 ± 11.17	230.94 ± 24.50	1.78 ± 0.25	13.20 ± 1.20	28.31 ± 2.93
		F	5	Day 1	75.15 ± 15.25	130.39 ± 7.77	0.63 ± 0.13	22.80 ± 1.20	39.52 ± 5.82
			4	Day 85	64.99 ± 6.34	101.64 ± 10.27	0.51 ± 0.12	30.00 ± 3.00	42.81 ± 3.52
			4	Day 183	96.29 ± 15.98	143.84 ± 19.07	1.45 ± 0.08	21.00 ± 2.40	37.33 ± 4.37
	10	M	5	Day 1	123.56 ± 36.80	235.26 ± 66.78	0.86 ± 0.27	45.60 ± 13.20	74.13 ± 26.63
			5	Day 85	226.83 ± 48.13	541.47 ± 269.99	1.43 ± 1.33	21.60 ± 8.40	41.55 ± 11.50
			5	Day 183	253.48 ± 54.56	449.14 ± 151.65	0.71 ± 0.31	24.60 ± 8.40	37.41 ± 9.19
		F	5	Day 1	122.74 ± 19.62	184.88 ± 47.66	0.63 ± 0.17	56.40 ± 11.40	74.11 ± 15.66
			5	Day 85	215.75 ± 27.73	398.99 ± 119.87	0.91 ± 0.56	27.00 ± 7.80	40.84 ± 7.32
			5	Day 183	191.75 ± 36.98	386.93 ± 114.04	1.50 ± 0.76	27.60 ± 7.20	52.09 ± 6.84
	30	M	4	Day 1	568.17 ± 110.49	679.32 ± 147.88	0.75 ± 0.67	45.60 ± 9.60	59.56 ± 15.51
			4	Day 85	880.90 ± 87.25	1871.77 ± 188.44	1.49 ± 0.47	16.20 ± 1.80	33.57 ± 6.51
			4	Day 183	810.04 ± 99.62	1689.73 ± 285.73	1.30 ± 0.12	18.00 ± 3.00	28.58 ± 2.97
		F	5	Day 1	540.63 ± 141.30	643.35 ± 91.29	0.76 ± 0.47	47.40 ± 6.60	52.99 ± 7.90
			5	Day 85	701.29 ± 33.91	1255.71 ± 267.42	1.22 ± 0.63	24.60 ± 4.80	42.37 ± 7.54
			5	Day 183	521.89 ± 137.58	1121.97 ± 175.06	1.48 ± 0.53	27.00 ± 4.20	52.40 ± 24.62
Monkey	3	M	7	Day 1	46.21 ± 7.10	217.99 ± 45.34	8.65 ± 2.19	46.31 ± 10.26[a)]	459.07 ± 103.05[b)]
			7	Day 71	38.94 ± 5.45	122.20 ± 64.05	4.90 ± 3.29	119.45 ± 75.52[a)]	481.64 ± 144.62[b)]
			7	Day 169	33.29 ± 9.36	98.81 ± 71.38	3.68 ± 3.88	168.20 ± 91.83[a)]	439.71 ± 149.98[b)]
		F	7	Day 1	41.84 ± 5.63	186.84 ± 21.59	8.16 ± 2.19	42.02 ± 7.70[a)]	386.82 ± 80.31[b)]
			7	Day 71	32.78 ± 8.62	113.93 ± 64.75	6.76 ± 5.52	102.25 ± 65.1[a)]	475.93 ± 211.03[b)]
			7	Day 169	26.80 ± 11.69	97.59 ± 81.36	2.75 ± 2.40	171.17 ± 124.16[a)]	347.75 ± 51.57[b)]
	10	M	6	Day 1	252.57 ± 26.47	1039.15 ± 187.73	12.44 ± 2.80	30.64 ± 5.90[a)]	372.76 ± 72.13[b)]
			7	Day 71	194.54 ± 32.53	726.31 ± 248.77	7.86 ± 3.28	56.54 ± 34.89[a)]	400.47 ± 110.02[b)]
			7	Day 169	200.63 ± 44.93	741.21 ± 317.13	10.09 ± 7.12	58.71 ± 33.37[a)]	434.25 ± 191.58[b)]
		F	6	Day 1	254.66 ± 25.00	936.15 ± 110.62	11.20 ± 3.04	27.66 ± 3.57[a)]	311.77 ± 60.94[b)]
			7	Day 71	199.68 ± 62.87	701.29 ± 153.44	8.06 ± 1.88	39.29 ± 8.39[a)]	367.60 ± 137.08[b)]
			7	Day 169	216.81 ± 70.73	601.84 ± 283.70	6.34 ± 4.99	53.65 ± 24.90[a)]	272.44 ± 122.17[b)]
	30	M	7	Day 1	721.89 ± 114.39	3834.81 ± 513.45	12.59 ± 2.15	24.06 ± 6.45[a)]	304.91 ± 72.89[b)]
			7	Day 71	625.54 ± 97.59	2724.63 ± 394.36	5.85 ± 1.28	37.43 ± 9.61[a)]	249.25 ± 64.22[b)]
			7	Day 169	707.09 ± 153.05	2434.22 ± 837.04	7.86 ± 4.00	48.36 ± 13.92[a)]	281.81 ± 80.49[b)]
		F	7	Day 1	690.64 ± 70.08	3589.51 ± 255.27	14.19 ± 3.46	21.67 ± 2.50[a)]	289.15 ± 59.93[b)]
			7	Day 71	1214.74 ± 791.93	2703.09 ± 308.02	4.93 ± 2.05	31.84 ± 4.70[a)]	184.49 ± 78.53[b)]
			6	Day 169	728.83 ± 148.04	2344.14 ± 837.70	4.77 ± 1.64	41.77 ± 11.02[a)]	199.78 ± 52.71[b)]

Mean ± standard deviation;
C_{max}, maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the serum concentration versus time curve from time 0 to infinity; $t_{1/2}$, elimination half-life; CL, total clearance; V_d, volume of distribution
a) Unit, mL/h; b) Unit, mL

Repeated doses of olipudase alfa 3, 10, or 30 mg/kg were administered to pregnant mice (gestation day 6, n = 2-7/time point) as an intravenous bolus dose once daily between gestation days 6 and 15. On gestation day 12, the mean C_{max} was 35.2 μg/mL (3 mg/kg), 176 μg/mL (10 mg/kg), and 409 μg/mL (30 mg/kg), and the mean $AUC_{0\text{-}24h}$ was 83.1 μg·h/mL (3 mg/kg), 278 μg·h/mL (10 mg/kg), and 916 μg·h/mL (30 mg/kg). On gestation day 13, ADAs were detected in 9 of 19 animals (3 mg/kg), 4 of 20 animals (10 mg/kg), and 3 of 20 animals (30 mg/kg).

Repeated doses of olipudase alfa 3, 10, or 30 mg/kg were administered intravenously over 10 minutes to pregnant rabbits (gestation day 6, n = 2-3/group) once daily between gestation days 6 and 19. On gestation day 12, the mean C_{max} was 114 μg/mL (3 mg/kg), 370 μg/mL (10 mg/kg), and 1180 μg/mL (30 mg/kg), and the mean $AUC_{0\text{-}24h}$ was 598 μg·h/mL (3 mg/kg), 2000 μg·h/mL (10 mg/kg), and 6350 μg·h/mL (30 mg/kg). On gestation day 12, ADAs were detected in 3 of 3 animals (3 mg/kg), 1 of 2 animals (10 mg/kg), and 2 of 2 animals (30 mg/kg).

4.2 Distribution (CTD 4.2.2.2-2, 4.2.2.3-1, 4.2.2.3-2, 4.2.2.3-8, 4.2.2.3-11)

A single dose of ^{125}I-labeled olipudase alfa 5 mg/kg was intravenously administered to male and female ASMKO mice (n = 3/time point). Virtually no radioactivity was detected in the brain.

A single dose of olipudase alfa 5 mg/kg was intravenously administered to male and female ASMKO mice (n = 3/time point). The mean amount of olipudase alfa per unit weight of tissue was 24.33 µg/g (liver), 5.61 µg/g (spleen), 3.00 µg/g (kidney), and 0.64 µg/g (lung) at 2 hours post-dose. At 96 hours post-dose, the mean amount of olipudase alfa per unit weight of tissue was 0.44 µg/g (liver), 1.11 µg/g (kidney), and 0.09 µg/g (lung), but it was below the limit of quantitation in the spleen in all individual animals.

Repeated doses of olipudase alfa 0.3, 1, or 3 mg/kg were intravenously administered to male and female ASMKO mice (n = 6) once every 2 weeks. At 24 hours post-final dose, in the liver, olipudase alfa was detected in 0 animals in the 0.3 mg/kg group, 4 of 5 animals in the 1 mg/kg group, and 1 of 5 animals in the 3 mg/kg group. The amount of olipudase alfa per unit weight of liver tissue was 5.84 µg/g (mean of 5 animals) in the 1 mg/kg group and 11.89 µg/g (from the 1 animal with detectable level of olipudase alfa) in the 3 mg/kg group. In the liver, olipudase alfa was not detected in the 3 mg/kg group at 28 days post-final dose.

Repeated-doses of vehicle, olipudase alfa 3, 10, or 30 mg/kg were intravenously administered to male and female rats (n = 3-5/time point) once every 2 weeks. The mean amount of olipudase alfa per unit weight of liver tissue at 24 hours post-final dose was 0.21 µg/g (vehicle), 0.57 µg/g (3 mg/kg), 0.83 µg/g (10 mg/kg), and 2.31 µg/g (30 mg/kg) in males, and 0.15 µg/g (vehicle), 0.57 µg/g (3 mg/kg), 0.89 µg/g (10 mg/kg), and 2.03 µg/g (30 mg/kg) in females. The mean amount of olipudase alfa per unit weight of liver tissue at 28 days post-final dose was 0.26 µg/g (3 mg/kg), 0.40 µg/g (10 mg/kg), and 0.38 µg/g (30 mg/kg) in males, and 0.31 µg/g (3 mg/kg), 0.44 µg/g (10 mg/kg), and 0.32 µg/g (30 mg/kg) in females.

4.3 Metabolism

No studies on metabolism have been conducted.

4.4 Excretion

No studies on excretion have been conducted.

4.R Outline of the review conducted by PMDA

4.R.1 Distribution of olipudase alfa

The applicant's explanation:

Olipudase alfa is a rhASM, which is taken up into various tissues and cells by endocytosis via soluble cation-independent M6P receptors. The results of tissue distribution studies in ASMKO mice showed that following intravenous administration of a single dose, a substantial part of olipudase alfa was found in the liver (45% the amount administered at 2 hours post-dose; CTD 4.2.2.3-2), in contrast to much smaller amounts distributed in the kidney, spleen, and lung (<1% of the amount administered at 2 hours post-dose in these tissues; CTD

4.2.2.3-2). Olipudase alfa was not detected in the brain at 8 hours post-dose, the final evaluation time point (CTD 4.2.2.3-1), indicating that olipudase alfa, following intravenous administration, is unlikely to cross the blood-brain barrier. The accumulation of olipudase alfa in the liver, presumably the major organ of its distribution, was evaluated based on the results of the tissue distribution studies in which repeated doses of olipudase alfa were intravenously administered to ASMKO mice and rats (CTD 4.2.3.2-8, 4.2.3.2-11). At 24 hours post-final dose, there was a trend towards increases in the concentration of olipudase alfa with increase in the dose level in rats treated with olipudase alfa 3, 10, or 30 mg/kg, and at 28 days post-final dose, the concentrations of all the dosage groups decreased to approximately the same level as that of the vehicle group at 24 hours post-final dose. A similar trend was observed in the ASMKO mouse study (olipudase alfa 0.3, 1, or 3 mg/kg).

In the tissue distribution studies, organs in which sphingomyelin accumulates in patients with ASMD were taken into consideration; therefore, distribution of olipudase alfa was studied only in the liver, kidney, spleen, and lung, and distribution was not investigated in other tissues. Thus, data from the histopathological examination of ASMKO mice following repeated-dose intravenous administration of olipudase alfa for 13 weeks were used to evaluate the possibility of distribution of olipudase alfa in other tissues (CTD 4.2.3.2-9). In the vehicle group, cytoplasmic vacuolation and foamy macrophages were observed in various tissues including the central nervous system and multiple visceral organs, indicating sphingomyelin accumulation. Following intravenous administration of olipudase alfa, there were no effects on the central nervous system; however, the incidence and severity of cytoplasmic vacuolation as well as the number and size of foamy macrophages decreased in the liver, kidney, bone marrow (sternum and femur), thymus, lymph nodes (submandibular and mesenteric), adrenal gland, small intestine (duodenum, jejunum, and ileum), spleen, stomach, trachea, pancreas, uterine cervix, ovary, uterus, and epididymis. The above findings suggest that although olipudase alfa may be distributed in the tissues mentioned above after intravenous administration of olipudase alfa, given that no toxicities associated with olipudase alfa have been reported in these tissues [see Section “5.2 Repeated-dose toxicity”], it is unlikely that safety-related problems will emerge as a result of distribution of olipudase alfa in these tissues.

PMDA accepted the applicant’s explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted single-dose toxicity studies, repeated-dose toxicity studies, reproductive and development toxicity studies, and other toxicity studies (*in vitro* hemocompatibility studies). Unless otherwise specified, a solution containing 20 mmol/L sodium phosphate, 5% sucrose, 100 mmol/L methionine, and 0.1 mmol/L EDTA (pH 6.5) was used as a vehicle. The following sections outline the results of main studies.

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in mice (wild-type mice and ASMKO mice), rats, and dogs (Table 11). Reported deaths in ASMKO mice were attributed to rapid accumulation of catabolites of sphingomyelin,

the substrate of olipudase alfa. The approximate lethal dose of olipudase alfa was determined to be >75 mg/kg for wild-type mice, 10 mg/kg for ASMKO mice, and >30 mg/kg for rats and dogs.

Table 11. Single-dose toxicity studies

Test system	Route of adminis-tration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Female mice (C57BL/6)	IV	75	No changes in toxicity	>75	Reference 4.2.3.1-9
Male/female mice (ASMKO heterozygous)	IV	0, 10, 20, 30	No changes in toxicity	>30	Reference 4.2.3.1-10
Male/female mice (C57BL/6)	IV	0, 3, 10, 20[a)]	No changes in toxicity	>10	Reference 4.2.3.1-5
Male/female mice (ASMKO)		0, 3, 10, 20[a)]	Died/sacrificed moribund: at 10 (3 of 6 males, 2 of 6 females), lethargy At ≥3, low body weight, high ALT, high AST, high bile acid, high cholesterol, high serum amyloid A, high serum amyloid P, hepatocyte apoptosis, hepatocyte ballooning degeneration/inflammatory foci, adrenal cortex apoptosis/degeneration/necrosis At 10, hemorrhage in the adrenal gland	10	
Male/female mice (ASMKO)	IV	0, 0.1, 0.3, 1	At ≥0.1, hepatic inflammatory foci At ≥0.3, adrenal cortex apoptosis At ≥1, high AST, high cholesterol, high creatine kinase, hepatocyte apoptosis, hepatocyte ballooning degeneration, adrenal cortex degeneration/necrosis	>1	Reference 4.2.3.1-6
Male/female mice (ASMKO)	IV	0, 0.03, 0.1, 0.3	At 0.3, hepatic inflammatory foci	>0.3	Reference 4.2.3.1-12
Male/female rats (SD)	IV	0,[b)] 3, 10, 30	No changes in toxicity	>30	4.2.3.1-17 Reference 4.2.3.1-18
Male/female dogs (beagle)	IV	0,[b)] 3, 10, 30	No changes in toxicity[c)]	>30	4.2.3.1-19 Reference 4.2.3.1-20

a) The dose was changed to 10 mg/kg due to early deaths or early sacrifices of moribund animals among ASMKO mice in the 20 mg/kg group.
b) A solution containing 20 mmol/L sodium phosphate, 5% sucrose, 100 mmol/L methionine, 0.1 mmol/L EDTA, 0.06% polysorbate 80 (pH 6.5)
c) Hypersensitivity reactions occurred in control animals immediately after dosing, which was determined to have been caused by polysorbate 80. All animals except for 1 male in the 10 mg/kg group were treated with diphenhydramine.

5.2 Repeated-dose toxicity

Thirteen-week repeated-dose toxicity studies in ASMKO mice and 26-week repeated-dose toxicity studies in rats and cynomolgus monkeys were conducted (Table 12). Except for hypersensitivity reactions, no toxicities were reported in association with olipudase alfa treatment.

In the 26-week repeated-dose toxicity studies in rats and cynomolgus monkeys, at the no-observed-adverse-effect level (NOAEL) (30 mg/kg for both studies), the C_{max} was 650 µg/mL (rats) and 717 µg/mL (cynomolgus monkeys) while the AUC was 1374 µg·h/mL (rats) and 2393 µg·h/mL (cynomolgus monkeys). The C_{max} values correspond to 21.5-fold (rats) and 23.7-fold (cynomolgus monkeys), and AUC values 2.3-fold (rats) and 3.9-fold (cynomolgus monkeys) compared with the exposure[2)] at the maximum clinical dose (3 mg/kg, every 2 weeks).

2) Estimated exposure values (C_{max}, 30.2 µg/mL and $AUC_{0\text{-}24h}$, 607 µg·h/mL) at steady state following administration of olipudase alfa 3 mg/kg every 2 weeks, the maximum clinical dose, calculated by the population pharmacokinetic analysis, which used plasma olipudase alfa concentration data from adult patients with ASMD.

Table 12. Repeated-dose toxicity studies

Test system	Route of adminis-tration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Male/female mice (ASMKO)	IV	12 weeks (every 2 weeks) + recovery period of 4 weeks	0, 0.3, 1, 3	At ≥0.3, low ALP in blood, low liver-to-body weight ratio, adrenal cortex degeneration/apoptosis[d)] At ≥1, inflammatory foci within the hepatic parenchyma[e)] At 3, hypersensitivity reaction,[f)] high cholesterol in blood	3	Reference 4.2.3.2-8
Male/female mice (ASMKO)	IV	13 weeks (every 2 weeks) + recovery period of 4 weeks	0, 0.3, 1, 3	Died or sacrificed moribund: at 3 (3 of 20 males), hypersensitivity reaction No changes in toxicity	3	Reference 4.2.3.2-9
Male/female rats (SD)	IV	26 weeks (every 2 weeks) + recovery period of 4 weeks	0,[a)] 0,[b)c)] 3,[d)] 10,[c)] 30[c)]	Died or sacrificed moribund: at 30 (3 of 15 males) At 10: high body weight gain, increased food consumption (males) At 30: high weights of the liver/prostate/thyroid gland/parathyroid (males)	30	4.2.3.2-10 Reference 4.2.3.2-11
Male/female cynomolgus monkeys	IV	26 weeks (every 2 weeks) + recovery period of 4 weeks	0, 3, 10, 30	No changes in toxicity	30	4.2.3.2-12

a) Physiological saline solution; b) A solution containing 20 mmol/L sodium phosphate, 5% sucrose, 100 mmol/L methionine, 0.1 mmol/L EDTA, and 0.06% polysorbate 80 (pH 6.5); c) Animals were given prophylactic diphenhydramine from the second dose to eighth dose; d) The finding was considered to be less toxicologically significant because it was mild in extent; e) The finding was considered to be less toxicologically significant because there were no changes in blood ALT, AST, and bilirubin levels; f) Occurred following the second or subsequent doses, and thereafter, all animals were given prophylactic diphenhydramine.

5.3 Genotoxicity

Olipudase alfa, which is a rhASM, is unlikely to interact directly with DNA or other chromosome components based on its chemical structure and mechanism of action; therefore, no genotoxicity studies were conducted.

5.4 Carcinogenicity

No carcinogenicity studies were conducted. The applicant's explanation about the carcinogenicity of olipudase alfa:

Olipudase alfa, which is a rhASM, is unlikely to react with DNA. No proliferative or preneoplastic lesions were found in any of the toxicity studies of olipudase alfa including 26-week repeated-dose toxicity studies in rats and monkeys or 13-week repeated toxicity studies in ASMKO mice. Furthermore, a published literature search was conducted to find relationship of ASM and tumor, and no reports suggestive of carcinogenicity of olipudase alfa were found. The above results indicated no carcinogenic potential of olipudase alfa.

5.5 Reproductive and developmental toxicity

Studies on fertility and early embryonic development to implantation in mice, embryo-fetal development studies in mice and rabbits, and a study for effects on pre-and post-natal development including maternal function in mice were conducted (Table 13). The results showed no effects on maternal fertility, embryos, fetuses, or live offspring.

In the embryo-fetal development studies in mice and rabbits, at the NOAEL (30 mg/kg/day for all studies), the C_{max} was 409 µg/mL (mice) and 1180 µg/mL (rabbits), while the AUC was 916 µg·h/mL (mice) and

6350 μg·h/mL (rabbits). The C_{max} values correspond to 14-fold (mice) and 39-fold (rabbits), and AUC values 1.5-fold (mice) and 10-fold (rabbits) compared with the exposure[2)] at the maximum clinical dose (3 mg/kg, every 2 weeks).

Table 13. Reproductive and developmental toxicity studies

Study type	Test system	Route of adminis-tration	Treatment period	Dose (mg/kg)[a)]	Major findings	NOAEL (mg/kg)	CTD
Fertility and early embryonic development to implantation	Male mice (CD-1)	IV	Males: 28 days before mating throughout the mating period up to Days 49-53 (every other day)	0, 0, 3.16, 10, 30	Parent animals: Died or sacrificed moribund: at 3.16 (7 of 25 males), at 10 (4 of 25 males),[b)] tremor, convulsion/muscle twitching, cold to touch At 30: increase in activity, ataxia, decrease in locomotor activity, tremor, labored breathing, abnormal phonation No effects on sperm parameters or fertility	Parent animals (general toxicity): 30 Parent animals (fertility): 30	4.2.3.5.1-1
	Female mice (CD-1)	IV	Females: 15 days before mating until gestation day 7 (every other day)	0, 0, 3.16, 10, 30	Parent animals: Died or sacrificed moribund: at 3.16 (6 of 25 females); at 10 (4 of 25 females); at 30 (1 of 25 females)[b)]; decrease/increase in locomotor activity, muscle twitching, ataxia, cold to touch, labored breathing No effects on implantation, embryos, or fetuses	Parent animals (general toxicity): 30 Parent animals (fertility): 30	
Embryo-fetal development	Female mice (CD-1)	IV	Gestation days 6-15 (once daily) Cesarean section on gestation day 18	0, 0, 3, 10, 30	Dams: At ≥3: decrease in activity No effects on embryos/fetuses	Dams (general toxicity): 30 Embryo-fetal development: 30	4.2.3.5.2-1
	Female rabbits (NZW)	IV	Gestation days 6-19 (once daily) Cesarean section on gestation day 29	0, 0, 3, 10, 30	Dams: no changes in toxicity No effects on embryos/fetuses	Dams (general toxicity): 30 Embryo-fetal development: 30	4.2.3.5.2-2
Effects on pre- and postnatal development, including maternal function	Female mice (CD-1)	IV	Dams: from gestation days 6 to lactation day 19 or 20 (every other day)	0, 0, 3.16, 10, 30	Dams: Died or sacrificed moribund: at 3.16 (5 of 25 animals); at 30 (2 of 25 animals)[b)] increase or decrease in locomotor activity, cold to touch, hunchback position, dehydration, paleness in the limbs, body swelling At 3.16 and 30: low live offspring survival rate At 30: high number of dams with stillbirths[c)] No effects on live F1 offspring	Dams (general toxicity): 30 Development of live F1 offspring: 30	4.2.3.5.3-1

a) In the reproductive and developmental toxicity studies in mice and rabbits, another group for vehicle plus physiological saline (administered intraperitoneally) was established in addition to the vehicle alone group. Animals in the rest of the treatment groups were treated with diphenhydramine administered intraperitoneally in addition to vehicle or olipudase alfa; b) The finding was attributed to hypersensitivity reaction against administration of olipudase alfa; c) It was considered that hypersensitivity reaction worsened clinical signs in dams, which had an impact on birth and nursing.

5.6 Other toxicity studies

5.6.1 *In vitro* hemocompatibility

An *in vitro* hemocompatibility study was conducted using human whole blood (Table 14). The results showed that olipudase alfa is not hemolytic.

Table 14. *In vitro* hemocompatibility study

Test system	Test method	Major findings	CTD
Human whole blood	After addition of olipudase alfa at a final concentration of 1.1 mg/mL, blood was incubated at 37°C for 60 minutes and the absorbance of the supernatant was measured at 545 nm	No hemolysis response	4.2.3.7.7-1

5.R Outline of the review conducted by PMDA

5.R.1 Toxicity found in ASMKO mice

The applicant's explanation about toxicities reported in the single-dose and repeated-dose toxicity studies in ASMKO mice:

Toxicological findings in single-dose studies of olipudase alfa in ASMKO mice include death, decreased heart rate, decreased blood pressure [see Section "3.3 Safety pharmacology"], high proinflammatory cytokine levels, necrosis and ballooning degeneration in the liver, and adrenal gland degeneration/apoptosis. It was considered that these effects were caused by rapid increases in blood concentrations of sphingomyelin catabolites, i.e., ceramides, SPH, and S1P, based on the following: the above findings were not reported in the toxicity studies in normal animals; sphingomyelin catabolites are known to have effects on the cardiovascular system and proinflammatory effects; and similar toxicological findings have been reported for approved drugs targeting S1P receptors. In exploratory toxicity studies, 4 doses of olipudase alfa 3 mg/kg were intravenously administered to ASMKO mice every other day followed by a single dose of olipudase alfa 20 mg/kg or 7 doses of 3, 10, or 30 mg/kg every 2 weeks for 13 weeks to prevent rapid accumulation of sphingomyelin catabolites. All dosing regimens were well-tolerated. Patients with ASMD develop hepatomegaly and chronic liver disorder resulting from sphingomyelin accumulation in hepatocytes. In the clinical studies of olipudase alfa, the liver volume decreased, and liver function test results became normal. On the other hand, ceramides may contribute to hepatic inflammation, and transient increases in transaminases were seen in the beginning phase of treatment in some patients in the clinical studies of olipudase alfa. In addition, while low blood pressure-related events occurred in the clinical studies, none of them were considered clinically significant. Although the risk of humans developing toxicities observed in the ASMKO mice studies cannot be entirely ruled out, the above results indicate that such risk in clinical use can be mitigated by a dose escalation regimen at the start of treatment and close monitoring of patients.

PMDA accepted the applicant's explanation. The effects of sphingomyelin catabolites on the safety in humans will further be discussed in Section "7.R.2 Safety."

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

During the development of olipudase alfa, formulations with different manufacturing processes (Process A, Process B, and the proposed commercial process) were used. The formulations used in the clinical studies are presented in Table 15.

Table 15. Formulations used in clinical studies

Manufacturing process of drug substance	Development phase (study ID)	
	Global study	Foreign study
Process A	Phase II/III (DFI12712)	Phase I (SPHINGO00605) Phase I (DFI13412) Phase I/II (DFI13803) Phase II (LTS13632)
Process B	Phase II/III (DFI12712)	Phase I/II (DFI13803) Phase II (LTS13632)
Proposed commercial process	Phase II/III (DFI12712)	Phase II (LTS13632)

Plasma concentrations of olipudase alfa were measured by ELISA. The lower limits of quantitation ranged from 0.04 to 0.156 μg/mL. ADAs in serum were measured by ELISA. Two neutralizing antibody (NAb) assay methods were used: the enzyme activity assay and cell-based assay.

6.2 Clinical pharmacology

The evaluation data submitted were the results from 2 studies (Studies DFI12712 and DFI13803). The reference data submitted were the results from 3 foreign studies (Studies SPHINGO00605, DFI13412, and LTS13632) and results of population pharmacokinetic analyses.

6.2.1 Investigation in patients

6.2.1.1 Foreign phase I study (CTD 5.3.3.2-1, Study SPHINGO00605 [December 2006 to March 2009], reference data)

An open-label study was conducted in non-Japanese patients with ASMD aged ≥18 years (target sample size, 12-30 subjects; 3 subjects [0.03 mg/kg], 3 subjects [0.1 mg/kg], 2 subjects [0.3 mg/kg], 2 subjects [0.6 mg/kg], and 2 subjects[3)] [1.0 mg/kg]) to evaluate safety and pharmacokinetics following administration of a single intravenous dose of olipudase alfa.

A single dose of 0.03, 0.1, 0.3, 0.6, or 1.0 mg/kg of olipudase alfa was intravenously administered over 20 to 100 minutes.

A total of 11 subjects received olipudase alfa (3 subjects [0.03 mg/kg], 3 subjects [0.1 mg/kg], 2 subjects [0.3 mg/kg], 2 subjects [0.6 mg/kg], and 1 subject [1.0 mg/kg]) and were included in the safety analysis set and pharmacokinetic analysis set.

Table 16 shows the pharmacokinetic parameters in individual subjects after a single intravenous dose of olipudase alfa 0.03, 0.1, 0.3, 0.6, or 1.0 mg/kg.

3) Although it was planned to assign 2 subjects, the first patient who received 1.0 mg/kg experienced severe blood bilirubin increased accompanied by nausea, vomiting, pyrexia, and fatigue, and the study was terminated.

Table 16. Pharmacokinetic parameters in individual subjects after a single intravenous dose of olipudase alfa

Dose (mg/kg)	n	Total dose (mg)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
0.03	3	2.3, 1.9, 1.8	401, 316, 294	857, 544, 535	0.45, 0.45, 0.25	3.54, 2.87, 2.76
0.1	3	6.2, 5.5, 5.4	1652, 1216, 1102	9224, 7629, 7357	0.683, 0.683, 0.617	11.23, 10.18, 8.86
0.3	2	31.9, 20.9	4509, 2592	40211, 16849	1, 0.967	15.96, 12.66
0.6	2	41.6, 33.1	7051, 4621	56826, 43398	1.3, 1.267	14.85, 12.77
1.0	1	71.7	11614	95811	1.65	15.34

C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration versus time curve to the last measurable time point; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal-phase elimination half-life

ADAs were evaluated before the start of olipudase alfa treatment and on Day 28. No subjects tested positive for ADAs at either time point.

Adverse events and adverse drug reactions occurred in 2 of 3 subjects and 0 of 3 subjects, respectively, in the 0.03 mg/kg group; 2 of 3 subjects and 0 of 3 subjects, respectively, in the 0.1 mg/kg group; 2 of 2 subjects and 1 of 2 subjects, respectively, in the 0.3 mg/kg group; 2 of 2 subjects and 2 of 2 subjects, respectively, in the 0.6 mg/kg group; 1 of 1 subject and 1 of 1 subject, respectively, in the 1.0 mg/kg group. There were no deaths. Serious adverse events occurred in 1 subject (procedural pain) in the 0.1 mg/kg group, and a causal relationship to the study drug was denied. No adverse events led to treatment discontinuation.

6.2.1.2 Foreign phase I study (CTD 5.3.5.2-1, Study DFI13412 [March 2013 to January 2014], reference data)

An open-label study was conducted in non-Japanese patients with ASMD aged ≥18 years (target sample size, 6 subjects) to evaluate safety, pharmacokinetics, and pharmacodynamics following administration of multiple intravenous doses of olipudase alfa.

Key inclusion criteria were patients who were diagnosed as having ASMD based on documented deficiency of ASM as measured by ASM activity of peripheral blood leukocytes, cultured fibroblasts, or lymphocytes, and had a percent predicted diffusing capacity of the lung for carbon monoxide (DLco) of >20% and ≤80% and a splenic volume of ≥6 multiples of normal[4)] (MN).

Each subject was to receive escalating intravenous doses of olipudase alfa once every 2 weeks for 26 weeks, in the order of 0.1, 0.3, 0.3, 0.6, 1.0, and 2.0 mg/kg up to 3.0 mg/kg.

A total of 5 subjects received treatment and were included in the safety, pharmacokinetic, and pharmacodynamic analysis sets.

Table 17 shows pharmacokinetic parameters following multiple intravenous doses of olipudase alfa once every 2 weeks.

4) Calculated based on the volume measured by magnetic resonance imaging (MRI) using the following equations: splenic volume (MN) = splenic volume (cm^3) / (body weight [kg] × 2); liver volume (MN) = liver volume (cm^3) / (body weight [kg] × 25).

Table 17. Pharmacokinetic parameters after multiple intravenous doses of olipudase alfa once every 2 weeks

Dose (mg/kg)	n	C_{max} (μg/mL)	$AUC_{0\text{-}t}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
0.3[a)]	5	3.27 ± 0.46	38.9 ± 6.2	23.6 ± 4.49	6.90 ± 1.29	196 ± 7.69
0.6	5	6.93 ± 2.07	81.9 ± 10.2	22.1 ± 2.53	6.75 ± 0.85	175 ± 36.7
1.0	5	11.80 ± 1.58	144.0 ± 16.2	21.3 ± 2.45	6.30 ± 0.69	163 ± 36.2
2.0	5	22.80 ± 2.18	304.0 ± 42.1	22.3 ± 1.92	6.11 ± 0.98	150 ± 14.4
3.0[b)]	5	39.70 ± 8.10	512.0 ± 50.7	22.2 ± 2.23	5.49 ± 0.43	134 ± 17.1
3.0[c)]	5	23.10 ± 2.23	395.0 ± 50.8	23.8 ± 3.24	6.66 ± 0.82	201 ± 20.5

Mean ± standard deviation;
C_{max}, maximum plasma concentration; $AUC_{0\text{-}t}$, area under the plasma concentration versus time curve to the last measurable time point; $t_{1/2}$, terminal-phase elimination half-life; CL, total clearance; V_{ss}, volume of distribution at steady state
a) at administration of the first dose of 0.3 mg/kg; b) at administration of the first dose of 3.0 mg/kg; c) at Week 26

Table 18 shows the results of pharmacodynamic analysis,[5)] the percent change from baseline in plasma lyso-sphingomyelin (lyso-SPM) concentration and ceramide concentration.

Table 18. Percent change from baseline in plasma lyso-SPM concentration and ceramide concentration

Indicator for evaluation		lyso-SPM[a)]	Ceramide[a)]
Dose (mg/kg)	Baseline	398.60 ± 226.76 (5)	8.64 ± 1.35 (5)
0.3	Week 2	−15.07 ± 12.59 (5)	−2.56 ± 20.45 (5)
	Week 4	−33.51 ± 15.87 (5)	−10.98 ± 18.02 (5)
0.6	Week 6	−48.88 ± 7.76 (5)	−23.63 ± 21.39 (5)
1.0	Week 8	−53.38 ± 10.31 (5)	−36.56 ± 23.13 (5)
2.0	Week 10[b)]	−66.02 ± 6.89 (5)	−41.40 ± 22.40 (5)
3.0	Week 12[c)]	−69.85 ± 4.03 (5)	−52.26 ± 8.46 (5)
	Week 14[d)]	−70.08 ± 6.84 (5)	−56.85 ± 18.53 (5)
	Week 16	−78.81, −75.14 (2)	−49.70 ± 17.20 (5)
	Week 26	−78.20 ± 7.94 (5)	−57.74 ± 8.40 (5)

Mean ± standard deviation (n); individual values for n ≤ 2;
Unit at baseline: μg/L for lyso-SPM and mg/L for ceramide; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa; b) 1 subject received 0.6 mg/kg; c) 1 subject received 1.0 mg/kg and another subject received 2.0 mg/kg; d) 1 subject received 2.0 mg/kg

The mean ± standard deviation of liver sphingomyelin content[6)] in biopsy samples was 33.3 ± 17.8% (n = 5) at baseline, and the mean percent change ± standard deviation from baseline to Week 26 was −86.6 ± 4.29% (n = 4).

ADAs were evaluated from before the start of treatment with olipudase alfa up to Week 26, and no subjects tested positive at any time point.

Adverse events and adverse drug reactions occurred in 5 of 5 subjects and 4 of 5 subjects, respectively. There were no deaths or serious adverse events. No adverse events led to treatment discontinuation.

5) Lyso-SPM, the deacetylated form of sphingomyelin, is formed by sphingomyelin deacylase. It has been reported that sphingomyelin within the lysosome is not readily transported to plasma (*J Cell Biol.* 1985;100:27-34, *J Cell Biol.* 1990;111:429-42). However, markedly elevated lyso-SPM levels in plasma have been reported in patients with ASMD (*Mol Genet Metab.* 2014;111:209-11). It was thought that lyso-SPM could be readily released to plasma from tissues, and therefore, it was decided to analyze the change in plasma lyso-SPM concentration over time as a pharmacodynamic indicator for olipudase alfa treatment. Also, the change in plasma concentration of ceramide, the direct catabolite of sphingomyelin, was evaluated over time as a pharmacodynamic indicator for olipudase alfa treatment.

6) The liver sphingomyelin content was measured by histomorphometric analysis, and the value was calculated as the percentage of the tissue area occupied by sphingomyelin relative to the total tissue area in the field of view of the microscope. Samples were collected before the administration of olipudase alfa.

6.2.1.3 Global phase II/III study (CTD 5.3.5.1-1, Study DFI12712 [ongoing since December 2015, data cut-off in October 2019])

A double-blind, placebo-controlled, parallel-group study was conducted in Japanese and non-Japanese patients with ASMD aged ≥18 years (target sample size, 36 subjects) to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics following administration of multiple intravenous doses of olipudase alfa [see Section "7.1 Global phase II/III study" for details of the study design and efficacy and safety results].

Table 19 shows pharmacokinetic parameters of olipudase alfa in plasma following multiple intravenous doses of olipudase alfa once every 2 weeks.

Table 19. Pharmacokinetic parameters in plasma after multiple intravenous doses of olipudase alfa once every 2 weeks

Treatment	Dose (time point)	Manufacturing process of drug substance	n	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg·h/mL)	t_{max} (h)	$t_{1/2z}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Olipudase alfa continuous treatment	0.3 mg/kg (Week 2)	A	5	2.44 ± 0.68	48.8 ± 10.7	4.33 [4.07, 5.08]	23.4 ± 1.67	6.41 ± 1.48	166 ± 34.5
		B	13	3.04 ± 0.68	60.6 ± 11.3	4.33 [3.67, 5.33]	25.2 ± 2.36	5.10 ± 0.93	148 ± 23.5
	1.0 mg/kg (Week 10)	A	4	10.4 ± 5.51	183 ± 47.1	4.34 [4.13, 4.75]	32.5 ± 4.25	5.70 ± 1.22	176 ± 44.9
		B	12	11.0 ± 2.58	232 ± 50.6[b)]	4.11 [3.03, 6.42]	34.1 ± 2.57[b)]	4.48 ± 0.88[b)]	147 ± 29.4[b)]
	2.0 mg/kg (Week 12)	B	2	26.7, 26.9	494, 623	2.08, 3.92	27.0, 32.4	3.21, 4.05	65.2, 147
	3.0 mg/kg (Week 14)	A	4	32.4 ± 10.0	544 ± 102	4.15 [3.88, 5.37]	34.8 ± 2.95	5.67 ± 1.13	183 ± 43.0
		B	10	28.5 ± 6.41[c)]	597 ± 103[c)]	3.88 [3.27, 4.43][c)]	35.2 ± 2.01	5.16 ± 0.94[c)]	184 ± 34.5[c)]
	3.0 mg/kg (Week 26)	A	4	24.7 ± 4.76	497 ± 113	4.52 [3.92, 5.17]	37.6 ± 3.99	6.24 ± 1.18	205 ± 41.7
		B	12	31.9 ± 8.54	609 ± 73.2	4.05 [3.75, 5.33]	38.6 ± 8.27	5.00 ± 0.67	180 ± 25.7
	3.0 mg/kg (Week 52)	B	17	37.2 ± 17.2	674 ± 136	4.00 [3.45, 5.48]	37.5 ± 6.14	4.64 ± 0.99	169 ± 39.1
	3.0 mg/kg (Week 80)	B	12	39.1 ± 11.9	732 ± 119	3.99 [3.55, 4.97]	39.1 ± 4.03	4.20 ± 0.67	155 ± 35.7
	3.0 mg/kg (Week 132)	B	4	36.5 ± 5.60	713 ± 152	4.28 [3.83, 4.58]	37.8 ± 5.02	4.33 ± 0.78	157 ± 19.6
Placebo/ olipudase alfa[a)]	0.1 mg/kg (First dose administration)	B	15	0.92 ± 0.33	17.7 ± 4.88[d)]	2.18 [1.83, 5.50]	19.6 ± 3.63[d)]	6.13 ± 1.96[d)]	154 ± 30.6[d)]
	2.0 mg/kg (Week 12)	B	2	17.3, 18.3	272, 315	4.33, 4.67	24.1, 27.9	6.34, 7.34	161, 209
	3.0 mg/kg (Week 14)	B	9	30.0 ± 6.99	575 ± 145[e)]	3.88 [3.72, 4.75]	28.2 ± 10.3[e)]	5.50 ± 1.33[e)]	154 ± 38.5[e)]
	3.0 mg/kg (Week 26)	B	10	28.6 ± 6.26	592 ± 139	3.77 [3.67, 4.78]	33.6 ± 7.61	5.31 ± 1.17	175 ± 40.5
	3.0 mg/kg (Week 78)	B	4	24.0 ± 5.51	557 ± 160	3.77 [3.63, 4.67]	34.2 ± 4.38	5.75 ± 1.69	191 ± 48.9

Mean ± standard deviation; t_{max} is median [range]; individual values for n ≤ 2;
C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the plasma concentration versus time curve over the dosing interval; t_{max}, time to maximum plasma concentration; $t_{1/2z}$, terminal-phase elimination half-life; CL, total clearance; V_{ss}, volume of distribution at steady state
a) In the placebo/olipudase alfa group, a time point is the duration from the start of treatment with olipudase alfa during the extension treatment period
b) 11 subjects; c) 9 subjects; d) 14 subjects; e) 8 subjects

Tables 20 and 21 show results of pharmacodynamic analysis, the percent change from baseline in plasma lyso-SPM concentration and ceramide concentration, in the primary analysis period and extension treatment period.

Table 20. Percent change from baseline in plasma lyso-SPM concentration and ceramide concentration (primary analysis period)

Indicator for evaluation		Lyso-SPM[a)]		Ceramide[a)]	
Treatment		Placebo	Olipudase alfa	Placebo	Olipudase alfa
Dose (mg/kg)	Baseline	473.6 ± 199.3 (17)	383.8 ± 194.2 (18)	4.14 ± 0.95 (18)	3.71 ± 1.19 (18)
0.3	Week 2	−0.31 ± 12.64 (17)	−8.69 ± 15.21 (18)	0.62 ± 13.73 (18)	−1.93 ± 13.09 (18)
	Week 4	2.94 ± 18.37 (16)	−32.33 ± 17.20 (17)	−1.83 ± 18.03 (17)	−2.43 ± 18.87 (17)
0.6	Week 6	0.44 ± 20.93 (16)	−40.34 ± 19.66 (17)	2.15 ± 11.48 (17)	−12.33 ± 11.17 (17)
	Week 8	6.82 ± 19.15 (17)	−51.38 ± 13.03 (17)	−0.10 ± 19.22 (18)	−19.72 ± 16.87 (17)
1.0	Week 10	−3.82 ± 23.49 (18)	−57.09 ± 9.77 (18)	−5.99 ± 22.42 (17)	−18.31 ± 12.89 (17)
2.0	Week 12	1.08 ± 18.12 (17)	−60.65 ± 9.53 (17)	−4.96 ± 24.65 (18)	−27.17 ± 9.66 (17)
3.0	Week 14	−4.51 ± 21.14 (15)	−70.45 ± 7.11 (16)	−4.41 ± 27.73 (16)	−25.15 ± 11.89 (17)
	Week 26	−3.50 ± 16.35 (16)	−73.95 ± 16.23 (18)	−5.60 ± 21.60 (17)	−25.93 ± 21.54 (18)
	Week 52	−6.12 ± 21.71 (15)	−77.97 ± 11.09 (18)	−3.52 ± 27.22 (16)	−34.82 ± 18.09 (18)

Mean ± standard deviation (n)
Unit at baseline: μg/L for lyso-SPM and mg/L for ceramide; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa;

Table 21. Percent change from baseline in plasma lyso-SPM concentration and ceramide concentration (extension treatment period)

Indicator for evaluation		lyso-SPM[a)]		Ceramide[a)]	
Treatment		Placebo/olipudase alfa	Olipudase alfa continuous	Placebo/olipudase alfa	Olipudase alfa continuous
Dose (mg/kg)[b)]	Baseline	473.6 ± 199.3 (17)	383.8 ± 194.2 (18)	4.14 ± 0.95 (18)	3.71 ± 1.19 (18)
0.1/3.0	Week 54	5.41 ± 16.99 (14)	−76.09 ± 13.09 (16)	−8.10 ± 17.17 (14)	−33.81 ± 23.70 (15)
0.3/3.0	Week 56	−16.35 ± 14.14 (14)	−77.86 ± 9.33 (17)	−10.16 ± 23.77 (15)	−36.29 ± 15.36 (16)
	Week 58	−31.96 ± 15.28 (13)	−78.47 ± 7.80 (16)	−18.49 ± 22.28 (13)	−34.73 ± 19.21 (16)
0.6/3.0	Week 60	−37.66 ± 12.50 (14)	−78.77 ± 7.89 (16)	−20.46 ± 21.37 (15)	−39.39 ± 18.10 (16)
	Week 62	−47.06 ± 12.63 (14)	−79.02 ± 7.71 (15)	−23.84 ± 27.34 (14)	−33.05 ± 13.61 (15)
1.0/3.0	Week 64	−53.83 ± 10.52 (14)	−76.21 ± 8.34 (14)	−28.85 ± 20.97 (15)	−31.51 ± 17.59 (13)
2.0/3.0	Week 66	−60.37 ± 9.16 (14)	−76.44 ± 5.78 (15)	−32.02 ± 15.99 (15)	−32.98 ± 12.51 (13)
3.0/3.0	Week 80	−79.01 ± 5.77 (12)	−79.90 ± 6.46 (12)	−46.48 ± 17.26 (11)	−39.24 ± 12.67 (12)
	Week 104	−82.30 ± 10.14 (6)	−75.87 ± 8.79 (7)	−50.00 ± 12.18 (6)	−36.06 ± 15.97 (7)
	Week 144	−86.62 ± 1.29 (3)	−80.81 ± 7.27 (4)	−35.3, −34.9 (2)	−41.39 ± 16.16 (4)
	Week 156	−82.13, −58.60 (2)	—	−71.8, −29.4 (2)	—
	Week 170	−57.80 (1)	—	—	—

Mean ± standard deviation (n); individual values for n ≤ 2; "—," not calculated;
Unit at baseline: μg/L for lyso-SPM and mg/L for ceramide; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa;
b) Dose levels for "placebo/olipudase alfa group"/"continuous olipudase alfa group"

The sphingomyelin content[6)] in liver biopsy samples at baseline (mean ± standard deviation) was 30.53 ± 9.69% (n = 17) in the placebo/olipudase alfa group and 28.52 ± 11.73% (n = 18) in the olipudase alfa continuous treatment group; the percent change from baseline was 10.89 ± 42.22% (n = 14) at Week 52 and −89.67 ± 11.39% (n = 2) at Week 104 in the placebo/olipudase alfa group and −92.71 ± 5.78% (n = 13) at Week 52 and −99.09 ± 0.72% (n = 6) at Week 104 in the olipudase alfa continuous treatment group. The plasma sphingomyelin concentration at baseline was 323.4 ± 51.9 mg/L (n = 17) in the placebo group and 276.6 ± 63.2 mg/L (n = 18) in the olipudase alfa group; the percent change from baseline at Week 52 was −6.0 ± 19.0% (n = 15) in the placebo group and −3.3 ± 35.5% (n = 18) in the olipudase alfa group.

The ADA assay results showed that 4 of 18 subjects (22.2%) in the placebo group and 2 of 18 subjects (11.1%) in the olipudase alfa group tested positive before the start of study drug treatment, while 1 of 18 subjects (5.6%) in the placebo group and 4 of 18 subjects (22.2%) in the olipudase alfa group tested positive after the start of treatment up to Week 52.[7)] Among subjects who tested positive for ADAs, NAbs that inhibit enzyme activity were detected in 2 of 4 subjects (50.0%) in the placebo group and 2 of 6 subjects (33.3%) in the olipudase alfa group, while NAbs that inhibit cellular uptake were not detected in either group. During the period of treatment with olipudase alfa including the extension treatment period, 2 of 16 subjects (12.5%) in the placebo/olipudase

7) Subjects who had tested negative for ADAs before olipudase alfa treatment and tested positive after treatment, or those who had tested positive for ADAs and had ≥4-fold rise in antibody titer after treatment with olipudase alfa compared with that before the treatment.

alfa group and 2 of 18 subjects (11.1%) in the olipudase alfa continuous treatment group tested positive before the start of treatment with olipudase alfa, while 4 of 16 subjects (25.0%) in the placebo/olipudase alfa group and 6 of 18 subjects (33.3%) in the olipudase alfa continuous treatment group tested positive after the start of treatment.[7)] Of the subjects who tested positive for ADAs, NAbs that inhibit enzyme activity were detected in 0 of 6 subjects (0%) in the placebo/olipudase alfa group and 2 of 8 subjects (25.0%) in the olipudase alfa continuous treatment group, while NAbs that inhibit cellular uptake were not detected in either group.

6.2.1.4 Foreign phase I/II study (CTD 5.3.5.2-2, Study DFI13803 [May 2015 to December 2019])

An open-label study was conducted in patients with ASMD aged <18 years (target sample size, ≥20 subjects; ≥3 subjects in the adolescent cohort [≥12 years and <18 years], ≥7 subjects in the child cohort [≥6 years and <12 years], and ≥4 subjects in the infant/early child cohort [<6 years]) to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics following multiple intravenous doses of olipudase alfa [see Section "7.2 Foreign phase I/II study" for details of the study design and efficacy and safety results].

Table 22 shows pharmacokinetic parameters of olipudase alfa in plasma following multiple intravenous doses of olipudase alfa once every 2 weeks.

Table 22. Pharmacokinetic parameters of olipudase alfa in plasma following multiple intravenous doses of olipudase alfa once every 2 weeks

Group	Dose (mg/kg)	Time point	Manufacturing process of drug substance	n	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg·h/mL)	t_{max} (h)	$t_{1/2z}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Adolescent cohort (≥12 years and <18 years)	0.3	Week 4	A	4	1.82 ± 0.28	29.0 ± 6.14	1.23 [1.15, 1.43]	18.6 ± 0.98	10.7 ± 2.32	247 ± 39.5
	1.0	Week 12		4	12.8 ± 2.66	149 ± 44.9	1.80 [1.80, 1.88]	22.8 ± 1.19	7.32 ± 2.80	162 ± 91.3
	3.0	Week 16		4	28.0 ± 4.88	478 ± 55.4	3.94 [3.87, 4.08]	17.1 ± 1.15	6.34 ± 0.74	133 ± 13.5
	3.0	Week 52		4	22.4 ± 1.02	489 ± 32.7	3.81 [3.67, 4.03]	24.3 ± 2.88	6.16 ± 0.41	172 ± 11.6
Child cohort (≥6 years and <12 years)	0.3	Week 4	A	5	2.13 ± 0.52	39.0 ± 12.0	1.35 [1.18, 1.60]	19.2 ± 4.10	8.44 ± 3.13	171 ± 39.7
			B	4	3.10 ± 0.60	49.5 ± 10.2	1.30 [1.25, 1.42]	21.1 ± 2.76	6.29 ± 1.50	135 ± 36.7
	1.0	Week 12	A	5	7.69 ± 2.09	125 ± 19.6	1.90 [1.83, 2.42]	19.2 ± 4.89	8.16 ± 1.30	171 ± 40.6
			B	4	10.6 ± 1.06	170 ± 30.1	2.03 [1.92, 2.12]	21.4 ± 2.04	6.04 ± 1.25	131 ± 24.1
	3.0	Week 16	A	5	20.9 ± 3.05	435 ± 117	4.08 [3.93, 4.70]	23.5 ± 2.50	7.28 ± 1.82	183 ± 44.4
			B	4	25.7 ± 3.40	503 ± 77.0	3.96 [3.83, 7.07]	22.5 ± 1.67	6.08 ± 1.06	144 ± 17.5
	3.0	Week 52	A	5	21.0 ± 2.50	492 ± 93.4	4.30 [3.92, 5.13]	23.3 ± 1.95	6.28 ± 1.23	157 ± 25.0
			B	4	28.6 ± 9.96	527 ± 136	4.08 [3.75, 9.78]	23.3 ± 0.53	6.02 ± 1.73	147 ± 44.1
Infant/early child cohort (<6 years)	0.3	Week 4	A	3	2.06 ± 0.09	—	1.52 [1.22, 1.60]	—	—	—
			B	4	5.25 ± 3.18	64.1, 73.5[a)]	1.60 [1.43, 1.73]	21.0, 21.8[a)]	4.08, 4.68[a)]	62.8, 99.2[a)]
	1.0	Week 12	A	3	7.87 ± 2.83	91.2, 139[a)]	1.88 [1.77, 8.18]	19.6, 22.8[a)]	7.19, 11.0[a)]	115, 240[a)]
			B	4	10.7 ± 1.91[b)]	172 ± 38.0[b)]	2.08 [2.08, 2.12][b)]	22.4 ± 1.82[b)]	6.02 ± 1.50[b)]	131 ± 21.0[b)]
	3.0	Week 16	A	3	20.3 ± 4.69	398 ± 40.9	4.03 [3.75, 4.50]	22.4 ± 0.48	7.58 ± 0.74	172 ± 20.1
			B	4	23.5 ± 9.12	457 ± 119	4.28 [4.00, 8.70]	22.7 ± 1.71	6.91 ± 1.82	159 ± 39.4
	3.0	Week 52	A	3	24.8 ± 4.35	447 ± 32.5	4.08 [4.08, 4.27]	23.7 ± 1.42	6.74 ± 0.50	155 ± 12.6
			B	4	20.6 ± 3.44	454 ± 92.6	5.29 [4.42, 5.87]	23.5 ± 1.52	6.83 ± 1.47	166 ± 26.4

Mean ± standard deviation; t_{max} is median [range]; individual values for n ≤ 2; "—," not calculated;
C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the concentration versus time curve over the dosing interval; t_{max}, time to maximum plasma concentration; $t_{1/2z}$, terminal-phase elimination half-life;
CL, total clearance; V_{ss}, volume of distribution at steady state
a) 2 subjects; b) 3 subjects

Table 23 shows the results of pharmacodynamic analysis, the percent change from baseline in plasma lyso-SPM concentration and ceramide concentration.

Table 23. Percent change from baseline in plasma lyso-SPM concentration and ceramide concentration

Indicator for evaluation	Dose (mg/kg)	Time point	Adolescent cohort (≥12 years and <18 years)	Child cohort (≥6 years and <12 years)	Infant/early child cohort (<6 years)
Lyso-SPM[a)]	0.03	Baseline	488.25 ± 153.49 (4)	653.67 ± 226.30 (9)	670.00 ± 382.14 (7)
	0.1	Week 2	−5.00 ± 7.36 (4)	0.06 ± 22.01 (9)	1.00 ± 12.27 (7)
	0.3	Week 4	−18.05 ± 4.66 (4)	−11.08 ± 19.37 (9)	−20.47 ± 16.02 (7)
	0.3	Week 6	−32.74 ± 14.72 (3)	−31.36 ± 12.99 (9)	−25.46 ± 15.14 (7)
	0.6	Week 8	−29.83 ± 16.42 (4)	−44.46 ± 16.13 (9)	−42.58 ± 5.67 (7)
	0.6	Week 10	−42.05 ± 8.34 (4)	−52.52 ± 12.29 (9)	−52.47 ± 16.15 (7)
	1.0	Week 12	−53.88 ± 12.85 (4)	−63.72 ± 11.10 (9)	−65.31 ± 9.37 (7)
	2.0	Week 14	−56.59 ± 17.49 (4)	−67.95 ± 8.43 (9)	−64.82 ± 9.77 (7)
	3.0	Week 16	−69.54 ± 10.97 (4)	−76.66 ± 5.81 (6)	−67.42 ± 10.20 (6)
		Week 26	−82.44 ± 6.55 (4)	−86.87 ± 3.31 (9)	−79.71 ± 14.34 (7)
		Week 52	−84.05 ± 5.25 (4)	−88.03 ± 8.16 (9)	−87.95 ± 1.78 (7)
		Week 64	−84.05 ± 11.49 (4)	−86.96 ± 7.42 (9)	−85.54 ± 4.58 (7)
Ceramide[a)]	0.03	Baseline	7.13 ± 2.14 (4)	5.57 ± 1.87 (9)	8.01 ± 5.30 (7)
	0.1	Week 2	−6.68 ± 18.35 (4)	−8.37 ± 17.72 (9)	−18.28 ± 13.13 (7)
	0.3	Week 4	−14.49 ± 18.40 (4)	−17.71 ± 31.01 (9)	−24.04 ± 10.09 (7)
	0.3	Week 6	−28.53 ± 35.31 (3)	−17.55 ± 22.91 (9)	−24.36 ± 35.88 (7)
	0.6	Week 8	−31.81 ± 17.12 (4)	−15.59 ± 31.58 (9)	−29.97 ± 23.33 (7)
	0.6	Week 10	−29.35 ± 31.44 (4)	−9.46 ± 39.29 (9)	−33.42 ± 17.60 (7)
	1.0	Week 12	−42.68 ± 12.98 (4)	−16.24 ± 28.12 (9)	−41.50 ± 20.57 (7)
	2.0	Week 14	−49.90 ± 10.18 (4)	−30.80 ± 16.29 (9)	−43.45 ± 25.24 (7)
	3.0	Week 16	−44.56 ± 10.18 (4)	−33.47 ± 22.37 (6)	−43.06 ± 22.53 (6)
		Week 26	−44.13 ± 39.87 (4)	−44.14 ± 21.73 (9)	−52.01 ± 37.75 (7)
		Week 52	−48.99 ± 19.31 (4)	−52.04 ± 31.55 (9)	−67.84 ± 9.75 (7)
		Week 64	−49.09 ± 28.15 (4)	−54.91 ± 22.84 (9)	−68.29 ± 13.48 (7)

Mean ± standard deviation (n); individual values for n ≤ 2; "—," not calculated;
Unit at baseline: μg/L for lyso-SPM and mg/L for ceramide; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa

The ADA assay results showed that 2 of 9 subjects in the child cohort (≥6 years and <12 years) tested positive before the start of treatment with olipudase alfa, and no subjects tested positive in the adolescent cohort (≥12 years and <18 years) or infant/early child cohort (<6 years old). Up to Week 64, 2 of 4 subjects in the adolescent cohort (≥12 years and <18 years), 7 of 9 subjects in the child cohort (≥6 years and <12 years), and 3 of 7 subjects in the infant/early child cohort (<6 years old) tested positive for ADAs.[7)] Among subjects who tested positive for ADAs, 1 of 7 subjects in the child cohort (≥6 years and <12 years) tested positive for NAbs that inhibit enzyme activity, while NAbs that inhibit cellular uptake were not detected in any cohort.

6.2.1.5 Foreign phase II extension study (CTD 5.3.5.2-3, Study LTS13632 [ongoing since December 2013, data cut-off in December 2019], reference data)

An open-label study was conducted in patients with ASMD (target sample size, 25 subjects) who had completed Study DFI13412 or DFI13803 to evaluate the long-term efficacy, safety, pharmacokinetics, and pharmacodynamics of olipudase alfa.

Olipudase alfa was administered intravenously once every 2 weeks at the starting dose, which was determined for each patient based on the number of interrupted doses of olipudase alfa between the previous study (Study DFI13412 or DFI13803) and Study LTS13632.[8)] The maintenance dose was 3.0 mg/kg.

8) Depending on the number of interrupted doses between the previous study and the extension study, treatment was resumed at a dose reduced from the dose immediately before interruption. If the dose after resuming treatment was <3.0 mg/kg, the dose was increased according to the specified dose escalation regimen. Patients were allowed to receive treatment at home.

A total of 24 subjects received olipudase alfa and were included in the safety, pharmacokinetic, and pharmacodynamic analysis sets.

Table 24 shows pharmacokinetic parameters of olipudase alfa in plasma following multiple intravenous doses of olipudase alfa 3.0 mg/kg once every 2 weeks.

Table 24. Pharmacokinetic parameters of olipudase alfa in plasma following multiple intravenous doses of olipudase alfa 3.0 mg/kg once every 2 weeks

Treatment group	Time point	Manufacturing process of drug substance	n	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg·h/mL)	t_{max} (h)	$t_{1/2z}$ (h)
Adult cohort (≥18 years)	Month 18	Process A	4	34.7 ± 6.48	600 ± 66.4	3.87 [3.52, 4.87]	18.0 ± 2.52
	Month 30	Process A	4	27.9 ± 1.54	509 ± 83.5	3.83 [3.75, 3.92]	18.5 ± 1.98
	Month 42	Process A	4	27.4 ± 7.46	521 ± 63.3	3.98 [3.70, 4.38]	27.0 ± 2.82
	Month 54	Process B or proposed commercial process	4	34.4 ± 9.34	796 ± 37.6	4.01 [3.77, 4.87]	23.1 ± 2.28
	Month 66	Process B or proposed commercial process	5	35.6 ± 9.49	763 ± 119	4.12 [3.82, 4.97]	26.2 ± 2.59
Adolescent cohort (≥12 years and <18 years)	Week 104	Process A	2	25.3, 28.0	491, 558	3.75, 4.07	17.8, 23.1
	Week 158	Process B or proposed commercial process	4	29.7 ± 3.95	677 ± 95.3	4.17 [3.83, 5.67]	22.4 ± 3.10
	Week 210	Process B or proposed commercial process	4	33.5 ± 3.82	721 ± 78.3	3.88 [3.67, 4.02]	25.6 ± 4.10
Child cohort (≥6 years and <12 years)	Week 104	Process B or proposed commercial process	3	25.5 ± 1.81	456, 518[a)]	4.00 [3.92, 4.42]	12.9, 29.0[a)]
	Week 158	Process B or proposed commercial process	5	31.7 ± 5.48	716 ± 41.8	4.17 [3.75, 7.63]	25.3 ± 1.17
Infant/early child cohort (<6 years)	Week 104	Process B or proposed commercial process	3	28.1 ± 6.76	623 ± 93.2	4.02 [3.80, 4.75]	26.9 ± 3.96

Mean ± standard deviation; t_{max} is median [range]; individual values for n ≤ 2;
C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the concentration versus time curve over the dosing interval; t_{max}, time to maximum plasma concentration; $t_{1/2z}$, terminal-phase elimination half-life
a) 2 subjects

Table 25 shows the results of pharmacodynamic analysis, the percent change from baseline in plasma lyso-SPM concentration and ceramide concentration.

Table 25. Percent change from baseline in plasma lyso-SPM concentration and ceramide concentration

Indicator for evaluation	Time point	Adult (≥18 years)	Adolescent cohort (≥12 years and <18 years)	Child cohort (≥6 years and <12 years)	Infant/early child cohort (<6 years)
lyso-SPM[a)]	Baseline	398.60 ± 226.76 (5)	488.25 ± 153.49 (4)	653.67 ± 226.30 (9)	706.33 ± 405.15 (6)
	Month 3	−69.85 ± 4.03 (5)	−52.88 ± 12.85 (4)	−63.72 ± 11.10 (9)	−66.35 ± 9.81 (6)
	Month 6	−78.20 ± 7.94 (5)	−82.44 ± 6.55 (4)	−86.87 ± 3.31 (9)	−78.81 ± 15.49 (6)
	Month 9	−78.20 ± 8.44 (5)	−84.26 ± 4.67 (4)	−89.59 ± 2.83 (7)	−86.35 ± 8.92 (4)
	Month 12	−80.61 ± 4.55 (5)	−84.05 ± 5.25 (4)	−88.03 ± 8.16 (9)	−88.21 ± 1.80 (6)
	Month 15	−78.39 ± 6.40 (5)	−84.05 ± 11.49 (4)	−86.96 ± 7.42 (9)	−85.57 ± 5.02 (6)
	Month 18	−78.70 ± 7.53 (5)	−75.96 ± 15.71 (3)	−89.65 ± 4.25 (4)	−88.54 ± 5.04 (3)
	Month 24	−75.29 ± 4.96 (5)	−85.37 ± 3.95 (4)	−88.92 ± 3.74 (3)	−90.16 ± 5.99 (3)
	Month 33	−74.55 ± 8.26 (5)	−81.33 ± 8.67 (3)	−89.17 ± 5.42 (3)	−86.90, −83.82 (2)
	Month 36	−61.53 ± 21.82 (5)	−85.67 ± 3.21 (4)	−91.04 ± 3.56 (5)	—
	Month 42	−80.40 ± 8.18 (5)	−80.45 ± 9.70 (4)	−90.40 ± 2.35 (3)	—
	Month 48	−82.11 ± 6.38 (5)	−85.33 ± 6.45 (4)	—	—
	Month 78	−85.85, −62.77	—	—	—
Ceramide[a)]	Baseline	8.64 ± 1.35 (5)	7.13 ± 2.14 (4)	5.57 ± 1.87 (9)	8.60 ± 5.55 (6)
	Month 3	−52.26 ± 8.46 (5)	−42.68 ± 12.98 (4)	−16.24 ± 28.12 (9)	−42.87 ± 22.19 (6)
	Month 6	−57.74 ± 8.40 (5)	−44.13 ± 39.87 (4)	−44.14 ± 21.73 (9)	−54.01 ± 40.94 (6)
	Month 9	−46.56 ± 9.60 (4)	−32.25 ± 11.87 (4)	−62.68 ± 8.81 (8)	−43.23 ± 41.81 (4)
	Month 12	−46.18 ± 15.46 (5)	−48.99 ± 19.31 (4)	−52.04 ± 31.55 (9)	−68.40 ± 10.55 (6)
	Month 15	−58.21 ± 8.57 (5)	−49.09 ± 28.15 (4)	−54.91 ± 22.84 (9)	−71.89 ± 10.44 (6)
	Month 18	−50.19 ± 13.05 (5)	−37.81 ± 35.08 (3)	−26.58 ± 37.06 (4)	−90.8, −64.5 (2)
	Month 24	−39.56 ± 18.75 (5)	−57.65 ± 19.28 (4)	−55.13 ± 17.04 (3)	−84.21 ± 5.72 (3)
	Month 36	−51.97 ± 13.30 (5)	−73.14 ± 13.20 (4)	−68.16 ± 11.22 (5)	—
	Month 48	−53.87 ± 21.63 (5)	−76.61 ± 10.59 (4)	—	—

Mean ± standard deviation (n); individual values for n ≤ 2; "—," not calculated;
Unit at baseline: μg/L for lyso-SPM and mg/L for ceramide; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa

The ADA assay results showed that 0 of 5 subjects aged ≥18 years and 2 of 19 subjects aged <18 years tested positive before the start of treatment with olipudase alfa, while 3 of 5 subjects aged ≥18 years and 11 of 19 subjects aged <18 years tested positive after the start of treatment with olipudase alfa.[7)] Among subjects who tested positive for ADAs, NAbs that inhibit enzyme activity were detected in 2 of 3 subjects aged ≥18 years and 4 of 11 subjects aged <18 years, while NAbs that inhibit cellular uptake were not detected in either age group.

Adverse events and adverse drug reactions occurred in 5 of 5 subjects and 4 of 5 subjects, respectively, among those aged ≥18 years, and 19 of 19 subjects and 13 of 19 subjects, respectively, among those aged <18 years. There were no deaths in either group. Serious adverse events occurred in 1 of 5 subjects aged ≥18 years and 8 of 19 subjects aged <18 years. Hypersensitivity, alanine aminotransferase [ALT] increased, and anaphylactic reaction that occurred in 3 of the subjects aged <18 years were identified as adverse drug reactions. No adverse events led to treatment discontinuation in either age group.

6.2.2 Population pharmacokinetic analyses (CTD 5.3.3.5.1)

Population pharmacokinetic analyses were performed using plasma olipudase alfa concentration data from 5 studies conducted in and outside Japan in patients with ASMD (Studies SPHINGO00605, DFI13412, DFI13803, LTS13632, and DFI12712). Data from 69 subjects (32 males and 37 females; race, 4 Asians including 1 Japanese and 65 non-Asians) measured at 3100 time points were analyzed (software, NONMEM ver.7.4.1).

The subjects in the population pharmacokinetic analyses had the following characteristics: a median age [range] of 23.0 years [1.48, 67.0], median body weight of 58.0 kg [9.9, 107], and median creatinine clearance of 137 mL/min/1.73 m^2 [52.7, 378].

A 3-compartment model comprising the transfer between the central compartment and peripheral compartment C2 (Q2), and transfer between the central compartment and peripheral compartment C3 (Q3), with zero-order absorption and first-order elimination processes was developed as the base model. Sex, age,[9)] race, body weight,[9)] creatinine clearance, liver function parameters, disease characteristics (splenic volume, hepatic volume, plasma sphingomyelin concentration), presence of ADAs, manufacturing process of the drug substance (Process A or B), and lipid parameters were evaluated by stepwise covariate modeling as covariates for the clearance (CL) from the central compartment of olipudase alfa, volume of distribution (V1) in the central compartment, and volume of distribution (V2 and V3) in the peripheral compartment. As a result, body weight and manufacturing process were chosen as covariates for CL, V1, and V2, body weight as a covariate for V3. These covariates were incorporated into the final model.

9) Because body weight and age change during the study period, value at each time point was used.

On the basis of the evaluation of covariates obtained from the final model, the following estimation was obtained. Compared with the C_{max} and $AUC_{0-\tau}$ of olipudase alfa in plasma at steady state following administration of Process B formulation 3.0 mg/kg to a subject weighing 58.0 kg, the C_{max} and $AUC_{0-\tau}$ following administration of Process B formulation 3.0 mg/kg to a subject weighing 77.6 kg are 1.08-fold and 1.16-fold, respectively, while those to a subject weighing 19.0 kg are 0.70-fold and 0.60-fold, respectively. The C_{max} and $AUC_{0-\tau}$ following administration of Process A formulation to a subject weighing 58.0 kg are 0.86-fold and 0.81-fold, respectively, higher than the C_{max} and $AUC_{0-\tau}$ of Process B formulation.

6.R Outline of the review conducted by PMDA

6.R.1 Effects of difference in the manufacturing process of drug substance

The applicant's explanation:

In the studies that used both Process A formulation and Process B formulation, olipudase alfa exposure was higher in subjects treated with Process B formulation than in those treated with Process A formulation (Tables 19, 22, and 24). On the basis of the population pharmacokinetic analyses, which used data from 5 studies conducted in patients with ASMD [see Section "6.2.2 Population pharmacokinetic analyses"], the C_{max} and $AUC_{0-\tau}$ at steady state were inferred to be higher in subjects treated with Process B formulation 3.0 mg/kg than in subjects treated with Process A formulation 3.0 mg/kg by 16% and 24%, respectively. The difference in exposure seems to result from the lower clearance and smaller distribution volume in subjects receiving Process B formulation 3.0 mg/kg than in those receiving Process A formulation 3.0 mg/kg, by 25% and 18% to 21%, respectively. However, the main factor that caused the difference is not known. To evaluate the clinical significance of the difference in exposure, data were analyzed by manufacturing process from the viewpoints of pharmacodynamics, efficacy, and safety.

Pooled data from Studies DFI12712, DFI13412, DFI13803, and LTS13632 were analyzed in terms of pharmacodynamics. Table 26 shows the percent change from baseline in plasma lyso-SPM concentration in subjects receiving either Process A formulation or Process B formulation. In both age groups (≥18 years group and <18 years group), there are no marked differences between the formulations.

Table 26. Percent change from baseline in plasma lyso-SPM concentration[a)]

Group	Time point	Process A formulation only[b)]	Process B formulation only	Switching from Process A formulation to Process B formulation[b)]
≥18 years	Baseline	397.10 ± 196.42 (10)	433.45 ± 200.17 (29)	397.10 ± 196.42 (10)
	Week 26	−79.04 ± 8.13 (9)	−72.28 ± 18.29 (13)	−78.25 ± 8.06 (10)
	Week 52	−80.61 ± 4.55 (5)	−78.18 ± 11.75 (19)	−81.72 ± 5.00 (10)
	Week 104	−75.29 ± 4.96 (5)	−79.79 ± 7.20 (4)	−73.77 ± 6.28 (10)
<18 years	Baseline	627.4 ± 242.98 (12)	624.63 ± 338.78 (8)	627.4 ± 242.98 (12)
	Week 26	−84.94 ± 5.79 (12)	−81.28 ± 13.22 (8)	−84.94 ± 5.79 (12)
	Week 52	−87.84 ± 4.57 (12)	−86.25 ± 7.95 (8)	−87.84 ± 4.57 (12)
	Week 64	−86.43 ± 7.32 (12)	−85.06 ± 7.45 (8)	−86.43 ± 7.32 (12)

Mean ± standard deviation (n); unit at baseline, μg/L; unit for percent change from baseline, %

a) Samples were collected before administration of olipudase alfa;

b) All subjects who received Process A formulation at the beginning of treatment were switched to Process B formulation in the middle of the study. Values in "Process A formulation only" represent data from the period only when Process A formulation was used, while values in "Switching from Process A formulation to Process B formulation" represent data including those from the period after switching formulation.

Pooled data from Studies DFI12712, DFI13412, DFI13803, and LTS13632 were analyzed in terms of efficacy. Table 27 shows the percent change (mean ± standard deviation) from baseline in splenic volume (MN[4)]) in subjects receiving either Process A formulation or Process B formulation. In both age groups (≥18 years group and <18 years group), the results of percent change from baseline in splenic volume were generally similar across the formulation groups.

Table 27. Percent change from baseline in splenic volume

Group	Time point	Process A formulation only[a)]	Process B formulation only	Switching from Process A formulation to Process B formulation[a)]
≥18 years	Baseline	12.5 ± 5.1 (10)	11.2 ± 4.3 (29)	12.5 ± 5.1 (10)
	Week 26	−31.3 ± 5.8 (9)	−28.0 ± 7.5 (24)	−31.9 ± 5.7 (10)
	Week 52	−34.5 ± 4.7 (5)	−37.8 ± 8.1 (19)	−37.7 ± 5.8 (10)
	Week 104	−43.9 ± 4.0 (5)	−49.1 ± 9.1 (3)	−45.0 ± 7.3 (10)
<18 years	Baseline	19.4 ± 10.6 (12)	18.3 ± 5.6 (8)	19.4 ± 10.6 (12)
	Week 26	−41.2 ± 7.7 (12)	−37.8 ± 6.7 (7)	−41.2 ± 7.7 (12)
	Week 52	−50.9 ± 9.1 (12)	−46.7 ± 10.7 (8)	−50.9 ± 9.1 (12)
	Week 78	−53.0 ± 6.2 (8)	−50.8 ± 6.9 (4)	−54.7 ± 8.5 (12)

Mean ± standard deviation (n); unit at baseline, MN; unit for percent change from baseline, %
a) The same as the Note b) to Table 26

Pooled data from Studies DFI12712, DFI13412, DFI13803, and LTS13632 were analyzed in terms of safety. Table 28 shows the incidence of adverse events in subjects receiving either Process A formulation or Process B formulation.

Table 28. Incidence of adverse events by manufacturing process

Events	Group	Process A formulation only[a)]	Process B formulation only	Switching from Process A formulation to Process B formulation[a)]
All adverse events	≥18 years	100 (10/10)	96.6 (28/29)	100 (10/10)
	<18 years	100 (12/12)	100 (8/8)	100 (12/12)
Serious adverse events	≥18 years	20.0 (2/10)	20.7 (6/29)	30.0 (3/10)
	<18 years	25.0 (3/12)	50.0 (4/8)	41.7 (5/12)
IAR[b)]	≥18 years	70.0 (7/10)	48.3 (14/29)	70.0 (7/10)
	<18 years	58.3 (7/12)	62.5 (5/8)	58.3 (7/12)
Hypersensitivity-related adverse events[c)]	≥18 years	20.0 (2/10)	17.2 (5/29)	20.0 (2/10)
	<18 years	41.7 (5/12)	37.5 (3/8)	41.7 (5/12)

Incidence, % (number of subjects with event/number of patients assessed)
a) The same as Notes b) to Table 26
b) Adverse events occurring within 24 hours of the start of infusion, and are considered by the investigator to be related or possibly related to the study treatment
c) Events classified under the Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) “hypersensitivity” (broad and narrow)

In both age groups (≥18 years group and <18 years group), the incidence of adverse events was similar across the formulation groups regardless of the manufacturing process. In subjects aged ≥18 years, although the incidence of serious adverse events and the incidence of hypersensitivity-related adverse events did not differ significantly among formulation groups, the incidence of infusion associated reactions (IARs) tended to be higher in subjects receiving Process A formulation only than in subjects receiving Process B formulation only. In subjects aged <18 years, the incidence of serious adverse events tended to be higher in subjects receiving Process B formulation only than in subjects receiving Process A formulation only. Among subjects aged <18 years who received only Process B formulation, serious adverse events occurred in 2 of 4 subjects (urticaria/rash, anaphylactic reaction) were classified as adverse drug reactions. The outcome of these events was reported as resolved. Switching of formulations from Process A formulation to Process B formulation showed no trends towards an induction of adverse events. The above findings revealed no particular trends in safety profiles associated with the difference in the manufacturing process.

The above results suggest the difference in olipudase alfa exposure in subjects receiving Process A formulation and in subjects receiving Process B formulation does not have a clinically significant impact on pharmacodynamics, efficacy, or safety.

PMDA's view:

Although the mechanism in which different drug substance manufacturing processes (Process A and Process B) led to the pharmacokinetic differences of olipudase alfa has not been clearly elucidated, PMDA confirmed that submitted data indicate no marked difference that may cause clinically relevant changes in terms of the pharmacodynamics, efficacy, or safety of olipudase alfa due to different manufacturing processes.

6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations

The applicant's explanation:

In Study DFI12712, 1 Japanese patient was enrolled. This patient was assigned to placebo in the primary analysis period and olipudase alfa in the extension treatment period. Table 29 shows C_{max} and $AUC_{0-\tau}$ at each time point after administration of olipudase alfa 0.1 or 3.0 mg/kg to the Japanese patient and non-Japanese patients. The results indicated no marked difference in the parameters between Japanese and non-Japanese patients.

Table 29. Pharmacokinetic parameters following administration of olipudase alfa 0.1 or 3.0 mg/kg to Japanese and non-Japanese patients

Dose	C_{max} (ng/mL)		$AUC_{0-\tau}$ (ng·h/mL)	
	Japanese	Non-Japanese	Japanese	Non-Japanese
0.1 mg/kg[a)]	0.78 (1)	0.926 ± 0.341 (14)	15.7 (1)	17.9 ± 5.04 (14)
3.0 mg/kg[b)]	22.9 (1)	29.6 ± 6.55 (16)	482 (1)	593 ± 122 (17)
3.0 mg/kg[c)]	21.4 (1)	30.8 ± 7.51 (21)	529 (1)	605 ± 107 (21)
3.0 mg/kg[d)]	32.1 (1)	35.5 ± 12.9 (15)	682 (1)	688 ± 152 (15)

Mean ± standard deviation (n); individual values for n ≤ 2;
C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the concentration versus time curve over the dosing interval;
a) at Week 0; b) at Week 14; c) at Week 26; d) at Week 78 (placebo/olipudase alfa group) or at Week 80 (olipudase alfa continuous treatment group)

Table 30 shows percent change from baseline in plasma lyso-SPM concentration. The results indicated no marked difference in the parameters between Japanese and non-Japanese patients.

Table 30. Percent change from baseline in plasma lyso-SPM concentration[a)] in Japanese and non-Japanese patients

Treatment	Placebo/olipudase alfa		Olipudase alfa continuous treatment
Race	Japanese	Non-Japanese	Non-Japanese
Baseline	705.00 (1)	459.19 ± 196.40 (16)	383.78 ± 194.16 (18)
Week 26[b)]	−81.13 (1)	−78.82 ± 6.01 (11)	−73.95 ± 16.23 (18)
Week 52[c)]	−88.37 (1)	−81.09 ± 10.84 (5)	−77.97 ± 11.09 (18)
Week 104[d)]	−82.13 (1)	−58.60 (1)	−75.87 ± 8.79 (7)

Mean ± standard deviation (n); individual values for n ≤ 2; unit at baseline, μg/L; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa
b) At Week 80 for the placebo/olipudase alfa group; c) At Week 104 for the placebo/olipudase alfa group; d) at Week 156 for the placebo/olipudase alfa group

The above results suggest that pharmacokinetics and pharmacodynamics after administration of olipudase alfa are similar between Japanese and non-Japanese patients.

PMDA's view:

Since there was only 1 Japanese patient who received olipudase alfa in Study DFI12712, it is difficult to draw any conclusions on the similarity of the pharmacokinetics and pharmacodynamics of olipudase alfa between Japanese and non-Japanese populations. However, PMDA confirmed that submitted data indicate no marked difference in the pharmacokinetics and pharmacodynamics of olipudase alfa between Japanese and non-Japanese patients.

6.R.3 Effects of age on pharmacokinetics of olipudase alfa

The applicant's explanation of proposing the same maintenance dose for pediatric patients and adult patients:

Table 31 shows the C_{max} and $AUC_{0\text{-}\tau}$ by age group after intravenous administration of Process B formulation 3.0 mg/kg once every 2 weeks estimated based on the population pharmacokinetic analysis using pooled data in patients with ASMD. Plasma olipudase alfa concentrations tended to be lower in patients in the <18 years groups than those in the ≥18 years groups. In the population pharmacokinetic analysis, body weight was identified as a covariate that has an impact on the pharmacokinetic parameters of olipudase alfa and was incorporated into the final model. When body weight was taken into consideration, age was not incorporated into the final model as a covariate that has an impact on the pharmacokinetic parameters. Body weight was considered as one of the causes for a trend towards lower exposure among patients aged <18 years than those aged ≥18 years based on several factors including the following: the exposure at olipudase alfa 3.0 mg/kg is estimated to be lower in low-weight patients than in high-weight patients [see Section "6.2.2 Population pharmacokinetic analyses"]; in contrast to patients aged ≥18 years, body weight tends to decrease with decrease in age in patients aged <18 years (Table 31). While olipudase alfa exposure tends to be lower in the <18 years groups than in the ≥18 years groups, the analysis of the correlation between clinical response (e.g., decrease in splenic volume) and olipudase alfa exposure (AUC) following olipudase alfa treatment showed no trends suggestive of a correlation (CTD 5.3.4.2-1), indicating that the efficacy of olipudase alfa in these groups do not differ from that in adult patient groups. Therefore, the same maintenance dose of olipudase alfa can be used for patients aged <18 years and for patients aged ≥18 years.

Table 31. Body weight and pharmacokinetic parameters following multiple intravenous doses of olipudase alfa 3.0 mg/kg once every 2 weeks

Age group	n	Body weight (kg)	C_{max} (μg/mL)	$AUC_{0\text{-}\tau}$ (μg·h/mL)
≥65 years	2	47.4, 105.4	30.5, 34.5	606, 754
≥18 years and <65 years	47	62.8 [44.3, 106.9]	30.1 ± 5.15	604 ± 121
≥12 years and <18 years	4	41.45 [28.0, 51.5]	27.5 ± 2.21	529 ± 35.2
≥6 years and <12 years	9	21.6 [19.2, 31.9]	24.0 ± 2.43	450 ± 67.9
<6 years	7	14.5 [9.9, 18.4]	22.8 ± 1.75	403 ± 42.6

Mean ± standard deviation; body weight is median [range]; individual values for n ≤ 2;
C_{max}, maximum plasma concentration; $AUC_{0\text{-}\tau}$, area under the plasma concentration versus time curve over the dosing interval

PMDA's view:

In light of the difference in olipudase alfa exposure across age groups, the efficacy and dosage regimen of olipudase alfa for pediatric patients will be discussed further in Section 7, taking into account the results from the efficacy and safety studies on olipudase alfa.

6.R.4 Effects of antibody production on pharmacokinetics and pharmacodynamics

The applicant's explanation:

The effects of production of ADAs on the pharmacokinetics and pharmacodynamics of olipudase alfa were investigated in 59 patients with ASMD. Table 32 shows pharmacokinetic parameters in plasma following administration of olipudase alfa by ADA status,[7)] and Table 33 shows percent change from baseline in plasma lyso-SPM concentration, one of the pharmacodynamic indicators, by ADA status. Both pharmacokinetic and pharmacodynamic parameters after administration of olipudase alfa were similar between ADA-positive and negative patients.

Table 32. Pharmacokinetic parameters of olipudase alfa by ADA status

ADA		C_{max} (ng/mL)		$AUC_{0-\tau}$ (ng·h/mL)	
		Negative	Positive	Negative	Positive
≥18years	Week 14	29.0 ± 6.3 (17)	34.4 ± 7.8 (10)	576 ± 117 (16)	569 ± 94 (10)
	Week 26	29.7 ± 8.0 (21)	26.0 ± 5.0 (10)	586 ± 121 (21)	518 ± 87 (10)
	Week 52	40.0 ± 20.2 (11)	32.1 ± 9.2 (6)	678 ± 144 (11)	665 ± 132 (6)
	Month 18	37.1 ± 12.3 (10)	33.3 ± 10.8 (10)	672 ± 116 (10)	699 ± 164 (10)
	Month 30	29.4 ± 2.7 (3)	35.4 ± 7.1 (4)	578 ± 77 (3)	661 ± 209 (4)
<18 years	Week 16	24.4 ± 5.4 (8)	24.0 ± 5.6 (11)	464 ± 110 (8)	463 ± 69 (11)
	Week 52	22.9 ± 3.2 (8)	23.5 ± 6.8 (12)	470 ± 63 (8)	494 ± 98 (12)
	Week 104	27.9 ± 4.4 (5)	23.5 ± 3.0 (5)	567 ± 102 (5)	499 ± 38 (5)
	Week 156	30.9 ± 3.1 (4)	30.8 ± 6.1 (5)	711 ± 38 (5)	688 ± 90 (5)

Mean ± standard deviation (n)

C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the concentration versus time curve over the dosing interval;

Table 33. Percent change from baseline in plasma lyso-SPM concentration[a)] by ADA status

ADA		Negative	Positive
≥18 years	Baseline	439.7 ± 202.6 (26)	392.9 ± 190.0 (13)
	Week 12	−56.49 ± 12.10 (24)	−59.48 ± 22.81 (13)
	Week 26	−75.97 ± 16.82 (14)	−73.18 ± 11.60 (9)
	Week 52	−78.07 ± 12.24 (18)	−81.58 ± 3.99 (11)
	Week 80	−82.11 ± 6.58 (8)	−81.29 ± 7.31 (8)
	Week 104	−79.36 ± 4.70 (7)	−71.62 ± 6.73 (7)
	Week 130	−82.88, −79.58 (2)	−77.13 ± 9.99 (3)
	Week 182	−88.10, −87.86 (2)	−75.35 ± 6.17 (3)
	Week 208	−89.59, −86.28 (2)	−78.22 ± 4.69 (3)
	Week 234	−86.76, −86.67 (2)	−76.59 ± 10.81 (3)
	Week 286	−90.07, −89.70 (2)	−77.71 ± 11.38 (3)
<18 years	Baseline	604.9 ± 213.7 (8)	640.6 ± 320.1 (12)
	Week 12	−59.92 ± 9.85 (8)	−63.90 ± 12.12 (12)
	Week 24	−84.22 ± 6.28 (8)	−82.98 ± 11.17 (12)
	Week 52	−87.20 ± 3.26 (8)	−87.21 ± 7.44 (12)
	Week 64	−83.92 ± 7.75 (8)	−87.19 ± 6.85 (12)
	Week 90	−84.89 ± 2.52 (5)	−86.09 ± 5.17 (6)
	Week 130	−81.40 ± 8.62 (6)	−89.91 ± 3.62 (4)
	Week 156	−86.48 ± 2.85 (4)	−90.39 ± 4.68 (5)
	Week 182	−83.96, −66.05 (2)	−88.54 ± 3.11 (5)
	Week 220	−90.52, −86.98 (2)	−86.92, −82.61 (2)

Mean ± standard deviation (n); individual values for n ≤ 2; unit at baseline, μg/L; unit for percent change from baseline, %

a) Samples were collected before administration of olipudase alfa

Table 34 shows the pharmacokinetic parameters of olipudase alfa by NAbs that inhibit enzyme activity, and Table 35 shows percent change from baseline in plasma lyso-SPM concentration by NAbs status. Both pharmacokinetic and pharmacodynamic parameters after administration of olipudase alfa were similar between NAb-positive and negative patients.

Table 34. Pharmacokinetic parameters by NAb status

NAb		C_{max} (ng/mL)		$AUC_{0-\tau}$ (ng·h/mL)	
		Negative	Positive	Negative	Positive
≥18years	Week 14	30.6 ± 6.94 (24)	34.0 ± 10.7 (3)	571 ± 113 (23)	591 ± 50.7 (3)
	Week 26	28.1 ± 6.69 (28)	31.7 ± 13.0 (3)	565 ± 116 (28)	556 ± 121.8 (3)
	Week 52	36.6 ± 17.6 (16)	47.3 (1)	667 ± 137 (16)	779 (1)
	Month 18	33.3 ± 8.51 (17)	45.9 ± 21.4 (3)	669 ± 148 (17)	675 ± 73.7 (3)
	Month 30	33.7 ± 6.21 (6)	27.5 (1)	657 ± 150 (6)	434 (1)
<18 years	Week 16	24.7 ± 4.99 (15)	22.0 ± 7.1 (4)	479 ± 88.6 (15)	402 ± 35.9 (4)
	Week 52	23.6 ± 6.10 (16)	21.9 ± 2.0 (4)	486 ± 87.7 (16)	478 ± 85.0 (4)
	Week 104	27.2 ± 4.01 (7)	22.1 ± 2.3 (3)	541 ± 94.6 (7)	514 ± 43.2 (3)
	Week 156	31.6 ± 2.69 (6)	29.4 ± 8.1 (3)	722 ± 36.3 (6)	649 ± 101.1 (3)

Mean ± standard deviation (n); individual values for n ≤ 2;
C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the concentration versus time curve over the dosing interval

Tale 35. Percent change from baseline in plasma lyso-SPM concentration[a)] by NAb status

NAb		Negative	Positive
≥18years	Baseline	441.9 ± 193.4 (36)	210.7 ± 104.2 (3)
	Week 12	−57.0 ± 17.0 (34)	−63.7 ± 4.5 (3)
	Week 26	−75.3 ± 15.8 (20)	−71.8 ± 4.2 (3)
	Week 52	−79.8 ± 10.5 (26)	−75.8 ± 1.6 (3)
	Week 104	−75.4 ± 6.9 (11)	−75.6 ± 8.5 (3)
	Week 130	−79.7 ± 3.1 (3)	−87, −67 (2)
	Week 182	−85.4 ± 4.5 (3)	−77, −68 (2)
	Week 286	−90.0 ± 0.2 (3)	−75, −68 (2)
<18 years	Baseline	618.4 ± 270.5 (16)	658.0 ± 341.7 (4)
	Week 12	−62.7 ± 9.8 (16)	−60.7 ± 17.6 (4)
	Week 26	−82.9 ± 10.2 (16)	−86.0 ± 4.9 (4)
	Week 52	−86.9 ± 5.9 (16)	−88.6 ± 7.2 (4)
	Week 130	−82.3 ± 8.2 (7)	−90.7 ± 4.0 (3)
	Week 182	−81.5 ± 10.5 (4)	−88.9 ± 4.3 (3)
	Week 220	−86.7 ± 4.0 (3)	−86.9 (1)

Mean ± standard deviation (n); individual values for n ≤ 2; unit at baseline, μg/L; unit for percent change from baseline, %
a) Samples were collected before administration of olipudase alfa

The above results suggest that ADAs and NAbs are unlikely to have a significant impact on pharmacokinetics or pharmacodynamics of olipudase alfa.

PMDA's view:

The submitted data indicated that neither the ADA status nor NAb status resulted in significant differences in pharmacokinetics or pharmacodynamics. The effects of ADA production on the safety and efficacy of olipudase alfa will be discussed further in Section "7.R.2.3 Effects of antibody production."

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 2 studies summarized in Table 36. The applicant also submitted the results of foreign clinical studies (Studies DFI13412 and LTS13632) as reference data.

Table 36. List of clinical studies on efficacy and safety

Data	Location	Study ID	Phase	Study population	Number of enrollment	Summary of dosage regimen	Main endpoint
Evaluation	Global	DFI12712	II/III	Adult patients with ASMD	36	Each subject received escalating intravenous doses of placebo or olipudase alfa in the order of 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, and 2.0 mg/kg once every 2 weeks, as an IV infusion up to the target dose of 3.0 mg/kg.	Efficacy Safety
	Foreign	DFI13803	I/II	Pediatric patients with ASMD	20	Each subject received escalating intravenous doses of olipudase alfa in the order of 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, and 2.0 mg/kg once every 2 weeks, as an IV infusion up to the target dose of 3.0 mg/kg or maximum tolerated dose.	Pharmacokinetics Pharmacodynamics Efficacy Safety

The following sections provide an outline of the clinical studies.

7.1 Global phase II/III study (CTD 5.3.5.1-1, Study DFI12712 [ongoing since December 2015, data cut-off in October 2019])

A double-blind, placebo-controlled, parallel-group study was conducted in patients with ASMD[10)] including 1 Japanese patient (target sample size, 36 subjects,[11)] n = 18/group) to evaluate the efficacy and safety of intravenous olipudase alfa [see Section "6.2.1.3 Global phase II/III study" for pharmacokinetics and pharmacodynamics].

Key eligibility criteria are as follows: patients aged ≥18 years with documented ASM deficiency as measured by ASM activity in peripheral leukocytes, cultured fibroblasts, or lymphocytes and a clinical diagnosis of ASMD. Eligible patients have a % predicted DLco of ≤70%, a splenic volume of ≥6 MN[4)] as measured by MRI, and a splenomegaly-related score (SRS) of ≥5.

The study consisted of a screening period (up to 60 days), a primary analysis period (52 weeks), and an extension treatment period.

In the primary analysis period, subjects received escalating doses of placebo or olipudase alfa in the order of 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, and 2.0 mg/kg once every 2 weeks, as an intravenous infusion up to the target dose of 3.0 mg/kg. In the extension treatment period, subjects who had been receiving olipudase alfa in the primary analysis period were to remain at the same dose level (olipudase alfa continuous treatment group), while those who had been receiving placebo in the primary analysis period were to receive olipudase alfa according to the dose escalation regimen that had been used in the olipudase alfa group in the primary analysis period (placebo/olipudase alfa group).

Thirty-six subjects were randomly assigned to the study drugs (18 subjects [including 1 Japanese subject] to placebo and 18 subjects to olipudase alfa). All subjects who received the study drug were included in the safety

10) Patients from Japan, the US, Argentina, Australia, Brazil, Chile, France, Germany, Italy, the Netherlands, Spain, Turkey, and the UK.

11) The number of patients necessary to demonstrate the superiority of olipudase alfa over placebo was 36 based on the calculation using the following assumptions: 30% between-group difference in the percent change in splenic volume (MN) from baseline to Week 52, common standard deviation of 11.8%, and a dropout rate of 11% from the mITT population, with a two-sided significance level of 5% and a statistical power of 99%; and 25% between-group difference in the percent change in % predicted DLco from baseline to Week 52, common standard deviation of 20%, and a dropout rate of 11% from the mITT population, with a two-sided significance level of 5% and a statistical power of 93%.

analysis set and the modified intent-to-treat (mITT) population, and the primary efficacy analysis set was the mITT population. In the primary analysis period, 1 subject in the placebo group was withdrawn from the study (protocol noncompliance). Of the 35 subjects who completed the primary analysis period, 34 subjects entered the extension treatment period (16 subjects, including 1 Japanese subject, in the placebo/olipudase alfa group and 18 subjects in the olipudase alfa continuous treatment group). No subjects were withdrawn from the study during the extension treatment period (up to the data cut-off date in October 2019).

Table 37 shows the primary endpoints, percent change from baseline in % predicted DLco and splenic volume at Week 52. The results demonstrate the superiority of olipudase alfa over placebo.

Table 37. Percent change from baseline in % predicted DLco and splenic volume at Week 52 (Study DFI12712, primary analysis period; mITT population)

Endpoint	Treatment	Baseline	Week 52	Change from baseline (%)	Difference from placebo[a)]	*P*-value[b)]
% Predicted DLco (%)	Placebo (n = 18)	48.45 ± 10.77	49.86 ± 11.08	2.96 ± 3.38	19.01 [9.32, 28.70]	0.0004
	Olipudase alfa (n = 18)	49.44 ± 10.99	59.35 ± 12.51	21.97 ± 3.34		
Splenic volume (MN)	Placebo (n = 18)	11.21 ± 3.84	11.20 ± 4.18	0.48 ± 2.50	−39.93 [−47.05, −32.80]	<0.0001
	Olipudase alfa (n = 18)	11.70 ± 4.92	7.16 ± 3.57	−39.45 ± 2.43		

Mean ± standard deviation; change from baseline (%), least squares mean ± standard error; difference from placebo, least squares mean [95% confidence interval (CI)]

a) Difference from placebo is based on the analysis of mixed model for repeated measures (MMRM) with unstructured covariance structure using baseline value, age at baseline, treatment, time point (Week 26 vs. Week 52), and time point-treatment interaction as covariates.

b) Hochberg test was used to adjust for multiplicity, two-sided significance level of 5%

Table 38 shows percent change from baseline in % predicted DLco and splenic volume in the primary analysis period and extension treatment period.

Table 38. Percent change from baseline in % predicted DLco and splenic volume (Study DFI12712, primary analysis period and extension treatment period; mITT population)

Endpoint	% Predicted DLco (%)		Splenic volume (MN)	
Treatment	Placebo/olipudase alfa	Olipudase alfa continuous treatment	Placebo/olipudase alfa	Olipudase alfa continuous treatment
Baseline	48.45 ± 10.77 (18)	49.44 ± 10.99 (18)	11.21 ± 3.84 (18)	11.70 ± 4.92 (18)
Week 52	3.08 ± 11.24 (17)	22.06 ± 17.01 (17)	0.42 ± 11.99 (17)	−39.39 ± 8.12 (18)
Week 80	17.01 ± 15.72 (12)	27.42 ± 18.22 (12)	−26.38 ± 10.06 (11)	−46.46 ± 9.17 (12)
Week 104	27.23 ± 28.29 (6)	26.83 ± 13.55 (6)	−38.36 ± 12.55 (6)	−48.31 ± 10.41 (6)
Week 132	43.14 ± 29.32 (3)	43.26 ± 23.29 (3)	−38.69 ± 8.42 (4)	−53.57 ± 6.96 (3)
Week 156	23.54, 28.65 (2)	—	−42.40, −39.87 (2)	—

Mean ± standard deviation (n); "—," not applicable

Table 39 shows the results for key secondary endpoints (percent change from baseline).

Table 39. Results for key secondary endpoints (percent change from baseline) (Study DFI12712, primary analysis period and extension treatment period; mITT population)

Endpoint	Hepatic volume (MN)		Platelet count (10^9/L)	
Treatment	Placebo/olipudase alfa	Olipudase alfa continuous treatment	Placebo/olipudase alfa	Olipudase alfa continuous treatment
Baseline	1.62 ± 0.50 (18)	1.44 ± 0.32 (18)	115.58 ± 36.27 (18)	107.18 ± 26.93 (18)
Week 26	−1.53 ± 6.43 (17)	−21.00 ± 10.33 (18)	−5.93 ± 10.11 (15)	11.12 ± 15.73 (18)
Week 52	−1.70 ± 4.79 (17)	−27.38 ± 13.70 (17)	1.93 ± 16.30 (16)	17.14 ± 17.96 (18)
Week 80	−24.47 ± 8.27 (11)	−26.27 ± 11.65 (12)	19.21 ± 19.82 (12)	22.09 ± 22.52 (12)
Week 104	−32.18 ± 7.47 (6)	−37.76 ± 8.15 (6)	16.71 ± 23.43 (6)	20.32 ± 19.10 (6)
Week 132	−32.06 ± 8.45 (4)	−33.84 ± 5.43 (3)	14.47 ± 8.42 (4)	15.16 ± 11.11 (4)
Week 156	−41.23, −34.71 (2)	—	−22.04, 13.84 (2)	—

Mean ± standard deviation (n); "—," not applicable

Table 40 shows the results for key efficacy endpoints (percent change from baseline) in 1 Japanese subject (placebo/olipudase alfa group, female aged [redacted] years).

Table 40. Results for key efficacy endpoints (percent change from baseline) (Study DFI12712, primary analysis period and extension treatment period; Japanese patient)

Endpoint	% Predicted DLco (%)	Splenic volume (MN)	Hepatic volume (MN)	Platelet count (10^9/L)
Baseline	57.59	10.68	1.84	85.3
Week 26	−17.42	−3.38	−0.38	−8.56
Week 52	−8.98	−1.39	−2.17	3.17 [a)]
Week 80	−2.94	−23.34	−27.09	−3.87
Week 104	17.94	−26.61	−37.71	21.92
Week 132	18.23	−37.13	−34.15	9.03
Week 156	28.65	−42.40	−41.23	−17.94

a) Value at Week 54

Table 41 shows the incidence of adverse events occurring in ≥3 subjects in both groups and those classified as adverse drug reactions in the primary analysis period. The Japanese patient (placebo group) experienced 8 adverse events (haemorrhage subcutaneous/abdominal pain/periodontitis/hepatic haemorrhage/shock haemorrhagic/nausea/vomiting/neck pain). A causal relationship to the study drug was denied for all these events.

Table 41. The incidence of adverse events occurring in ≥3 subjects in both groups and those classified as adverse drug reactions (Study DFI12712, primary analysis period; safety analysis set)

	Placebo (n = 18)		Olipudase alfa (n = 18)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	100 (18)	33.3 (6)	100 (18)	66.7 (12)
Headache	44.4 (8)	16.7 (3)	66.7 (12)	44.4 (8)
Nasopharyngitis	33.3 (6)	0 (0)	44.4 (8)	0 (0)
Upper respiratory tract infection	22.2 (4)	0 (0)	33.3 (6)	0 (0)
Cough	11.1 (2)	0 (0)	27.8 (5)	0 (0)
Pyrexia	22.2 (4)	0 (0)	22.2 (4)	11.1 (2)
Arthralgia	5.6 (1)	0 (0)	22.2 (4)	5.6 (1)
Nausea	44.4 (8)	16.7 (3)	16.7 (3)	11.1 (2)
Abdominal pain	16.7 (3)	0 (0)	16.7 (3)	11.1 (2)
Musculoskeletal chest pain	16.7 (3)	0 (0)	16.7 (3)	11.1 (2)
Myalgia	0 (0)	0 (0)	16.7 (3)	11.1 (2)
Abdominal pain upper	16.7 (3)	0 (0)	16.7 (3)	5.6 (1)
Oropharyngeal pain	5.6 (1)	0 (0)	16.7 (3)	0 (0)
Diarrhoea	11.1 (2)	5.6 (1)	16.7 (3)	0 (0)
Insomnia	16.7 (3)	0 (0)	11.1 (2)	0 (0)
Back pain	22.2 (4)	0 (0)	11.1 (2)	0 (0)
Pain in extremity	22.2 (4)	0 (0)	11.1 (2)	0 (0)
Vomiting	38.9 (7)	11.1 (2)	5.6 (1)	5.6 (1)
Fatigue	16.7 (3)	11.1 (2)	5.6 (1)	5.6 (1)
Blood bilirubin increased	16.7 (3)	11.1 (2)	5.6 (1)	5.6 (1)
Anaemia	16.7 (3)	0 (0)	0 (0)	0 (0)
Anxiety	16.7 (3)	5.6 (1)	0 (0)	0 (0)
Pruritus	16.7 (3)	5.6 (1)	0 (0)	0 (0)
Fall	16.7 (3)	0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with events); MedDRA/J ver.22.0

Table 42 shows the incidence of adverse events occurring in ≥3 subjects in both groups and those classified as adverse drug reactions in the primary analysis period and extension treatment period. In the extension treatment period, the Japanese subject (placebo/olipudase alfa group) experienced a total of 16 adverse events (headache and rhinitis [3 events each]; deafness unilateral, rash, haemorrhage subcutaneous, dental caries [2 events each]; urinary tract infection and pruritus [1 event each]). A causal relationship to the study drug was denied for all these events.

Table 42. The incidence of adverse events occurring in ≥3 subjects in both groups and those classified as adverse drug reactions (Study DFI12712, primary analysis period + extension treatment period; safety analysis set)

	Placebo/olipudase alfa (n = 16)		Olipudase alfa continuous treatment (n = 18)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	93.8 (15)	62.5 (10)	100 (18)	72.2 (13)
Headache	43.8 (7)	12.5 (2)	66.7 (12)	44.4 (8)
Nasopharyngitis	18.8 (3)	0 (0)	50.0 (9)	0 (0)
Upper respiratory tract infection	6.3 (1)	0 (0)	33.3 (6)	0 (0)
Nausea	43.8 (7)	6.3 (1)	27.8 (5)	11.1 (2)
Myalgia	6.3 (1)	0 (0)	27.8 (5)	11.1 (2)
Abdominal pain upper	12.5 (2)	0 (0)	27.8 (5)	5.6 (1)
Cough	12.5 (2)	6.3 (1)	27.8 (5)	0 (0)
Pyrexia	25.0 (4)	6.3 (1)	22.2 (4)	11.1 (2)
Abdominal pain	25.0 (4)	6.3 (1)	22.2 (4)	11.1 (2)
Arthralgia	12.5 (2)	0 (0)	22.2 (4)	5.6 (1)
Musculoskeletal chest pain	0 (0)	0 (0)	16.7 (3)	11.1 (2)
Eczema	0 (0)	0 (0)	16.7 (3)	5.6 (1)
Gastroenteritis	6.3 (1)	0 (0)	16.7 (3)	0 (0)
Oropharyngeal pain	12.5 (2)	0 (0)	16.7 (3)	0 (0)
Diarrhoea	12.5 (2)	6.3 (1)	16.7 (3)	0 (0)
Back pain	18.8 (3)	0 (0)	16.7 (3)	0 (0)
Procedural pain	18.8 (3)	0 (0)	11.1 (2)	0 (0)
Vomiting	25.0 (4)	12.5 (2)	5.6 (1)	5.6 (1)
ALT increased	18.8 (3)	18.8 (3)	5.6 (1)	5.6 (1)
AST increased	18.8 (3)	18.8 (3)	5.6 (1)	5.6 (1)
Pruritus	25.0 (4)	18.8 (3)	0 (0)	0 (0)

Incidence % (number of subjects with events); MedDRA/J ver.22.0

There were no deaths. In the primary analysis period, serious adverse events occurred in 4 subjects in the placebo group (liver abscess; hepatic haemorrhage/shock haemorrhagic [Japanese subject]; appendicitis/peritonitis/anaemia/syncope/epistaxis; pleural effusion) and 3 subjects in the olipudase alfa group (cellulitis/gastritis viral/lower limb fracture; transient ischaemic attack; hepatic haemorrhage). A causal relationship to the study drug was denied for all these events. In the extension treatment period, serious adverse events occurred in 4 subjects in the placebo/olipudase alfa group (urinary tract infection [Japanese subject]; loss of consciousness/phlebitis superficial; extrasystoles; pneumothorax) and 1 subject in the olipudase alfa continuous treatment group (aortic dilatation). Extrasystoles in 1 subject (placebo/olipudase alfa group) were classified as an adverse drug reaction. No adverse events led to treatment discontinuation.

7.2 Foreign phase I/II study (CTD 5.3.5.2-2, Study DFI13803 [May 2015 to December 2019])

An open-label, uncontrolled study was conducted in pediatric patients with ASMD (target sample size, ≥20 subjects: ≥3 subjects in the adolescent cohort [≥12 years and <18 years], ≥7 subjects in the child cohort [≥6 years and <12 years], and ≥4 subjects in the infant/early child cohort [<6 years]) to evaluate the pharmacokinetics, pharmacodynamics, efficacy, and safety of intravenous olipudase alfa [see Section "6.2.1.4 Foreign phase I/II study" for pharmacokinetics and pharmacodynamics].

Key eligibility criteria are as follows: pediatric patients aged <18 years with documented ASM deficiency as measured by ASM activity in peripheral leukocytes, cultured fibroblasts, or lymphocytes and a clinical diagnosis of ASMD. Eligible patients have a splenic volume of ≥5 MN[4)] as measured by MRI, and a height of ≤−1 Z-score relative to the normal growth curve.

The study consisted of a screening period (up to 60 days), a study drug treatment period (64 weeks), and a post-treatment period (up to 37 days).[12)]

In this study, subjects received escalating doses of olipudase alfa in the order of 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, and 2.0 mg/kg once every 2 weeks, as an intravenous infusions up to the target dose of 3.0 mg/kg or maximum tolerated dose.

A total of 20 subjects received olipudase alfa (4 subjects in the adolescent cohort, 9 subjects in the child cohort, and 7 subjects in the infant/early child cohort) and were included in the safety analysis set and mITT population, and the primary efficacy analysis set was the mITT population.

Table 43 shows the results for key efficacy endpoints.

Table 43. Results for key efficacy endpoints (percent change from baseline) (Study DFI13803, mITT population)

Endpoint	Time point	Age cohort			Total
		Adolescent cohort	Child cohort	Infant/early child cohort	
Splenic volume (MN)	Baseline	16.56 ± 9.08 (4)	19.34 ± 11.40 (9)	19.90 ± 4.88 (7)	18.98 ± 8.77 (20)
	Week 26	−37.01 ± 6.87 (4)	−39.86 ± 7.28 (9)	−42.15 ± 8.25 (6)	−39.98 ± 7.34 (19)
	Week 52	−46.94 ± 3.04 (4)	−46.04 ± 11.77 (9)	−54.59 ± 7.56 (7)	−49.21 ± 9.71 (20)
Hepatic volume (MN)	Baseline	2.28 ± 0.60 (4)	2.73 ± 0.79 (9)	2.76 ± 0.78 (7)	2.65 ± 0.74 (20)
	Week 26	−29.78 ± 8.09 (4)	−32.48 ± 7.46 (9)	−34.93 ± 9.14 (6)	−32.69 ± 7.90 (19)
	Week 52	−41.28 ± 6.13 (4)	−36.74 ± 10.47 (9)	−45.06 ± 8.20 (7)	−40.56 ± 9.37 (20)
Platelet count ($\times 10^9$/L)	Baseline	98.93 ± 9.28 (4)	148.82 ± 87.50 (9)	145.66 ± 28.01 (7)	137.74 ± 62.32 (20)
	Week 26	37.18 ± 61.01 (3)	47.33 ± 41.83 (8)	47.54 ± 43.14 (7)	45.72 ± 42.79 (18)
	Week 52	45.01 ± 42.95 (4)	30.67 ± 43.60 (9)	31.76 ± 22.45 (6)	34.03 ± 36.42 (19)
% Predicted DLco (%)	Baseline	53.43 ± 23.43 (3)	55.48 ± 10.13 (6)	—	54.79 ± 14.23 (9)
	Week 26	14.90 ± 10.12 (3)	22.08 ± 9.41 (5)	—	19.39 ± 9.68 (8)
	Week 52	28.01 ± 16.22 (3)	35.41 ± 35.08 (6)	—	32.94 ± 29.13 (9)
Height Z-score[a)]	Baseline	−2.28 ± 0.96 (4)	−2.18 ± 0.96 (9)	−2.02 ± 0.73 (7)	−2.14 ± 0.84 (20)
	Week 26	0.21 ± 0.21 (4)	0.07 ± 0.28 (9)	0.48 ± 0.42 (6)	0.23 ± 0.35 (19)
	Week 52	0.61 ± 0.29 (4)	0.37 ± 0.34 (8)	0.74 ± 0.42 (7)	0.56 ± 0.39 (19)

Mean ± standard deviation (n); "—," not applicable
a) The change from baseline

Table 44 shows the incidence of adverse events occurring in ≥4 subjects in the overall study population and those classified as adverse drug reactions.

12) The end of the study was defined as the date when the last patient entered the extension study LTS13632.

Table 44. Incidence of adverse events occurring in ≥4 subjects in the overall study population and those classified as adverse drug reactions (Study DFI13803, safety analysis set)

	Adolescent cohort (n = 4)		Child cohort (n = 9)		Infant/early child cohort (n = 7)		Total (N = 20)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	100 (4)	50.0 (2)	100 (9)	66.7 (6)	100 (7)	71.4 (5)	100 (20)	65.0 (13)
Pyrexia	25.0 (1)	25.0 (1)	77.8 (7)	44.4 (4)	100 (7)	42.9 (3)	75.0 (15)	40.0 (8)
Cough	50.0 (2)	0 (0)	77.8 (8)	0 (0)	71.4 (5)	0 (0)	70.0 (14)	0 (0)
Vomiting	50.0 (2)	0 (0)	66.7 (6)	44.4 (4)	57.1 (4)	42.9 (3)	60.0 (12)	35.0 (7)
Nasopharyngitis	50.0 (2)	0 (0)	55.6 (5)	0 (0)	57.1 (4)	0 (0)	55.0 (11)	0 (0)
Diarrhoea	50.0 (2)	0 (0)	55.6 (5)	0 (0)	57.1 (4)	0 (0)	55.0 (11)	0 (0)
Headache	50.0 (2)	25.0 (1)	55.6 (5)	33.3 (3)	14.3 (1)	14.3 (1)	40.0 (8)	25.0 (5)
Nausea	25.0 (1)	0 (0)	66.7 (6)	33.3 (3)	14.3 (1)	14.3 (1)	40.0 (8)	20.0 (4)
Gastroenteritis	0 (0)	0 (0)	44.4 (4)	0 (0)	57.1 (4)	0 (0)	40.0 (8)	0 (0)
Upper respiratory tract infection	0 (0)	0 (0)	33.3 (3)	0 (0)	71.4 (5)	0 (0)	40.0 (8)	0 (0)
Rhinitis	50.0 (2)	0 (0)	22.2 (2)	0 (0)	42.9 (3)	0 (0)	35.0 (7)	0 (0)
Rash	0 (0)	0 (0)	33.3 (3)	11.1 (1)	42.9 (3)	28.6 (2)	30.0 (6)	15.0 (3)
Abdominal pain	0 (0)	0 (0)	55.6 (5)	22.2 (2)	14.3 (1)	0 (0)	30.0 (6)	10.0 (2)
Nasal congestion	0 (0)	0 (0)	33.3 (3)	0 (0)	42.9 (3)	0 (0)	30.0 (6)	0 (0)
Oropharyngeal pain	25.0 (1)	0 (0)	33.3 (3)	0 (0)	28.6 (2)	0 (0)	30.0 (6)	0 (0)
Contusion	0 (0)	0 (0)	33.3 (3)	0 (0)	42.9 (3)	0 (0)	30.0 (6)	0 (0)
Fall	0 (0)	0 (0)	44.4 (4)	0 (0)	28.6 (2)	0 (0)	30.0 (6)	0 (0)
Abdominal pain upper	25.0 (1)	0 (0)	44.4 (4)	11.1 (1)	0 (0)	0 (0)	25.0 (5)	5.0 (1)
Ear pain	25.0 (1)	0 (0)	11.1 (1)	0 (0)	42.9 (3)	0 (0)	25.0 (5)	0 (0)
Urticaria	0 (0)	0 (0)	22.2 (2)	2 (22.2)	28.6 (2)	28.6 (2)	20.0 (4)	20.0 (4)
C-reactive protein increased	0 (0)	0 (0)	22.2 (2)	22.2 (2)	28.6 (2)	28.6 (2)	20.0 (4)	20.0 (4)
Macule	0 (0)	0 (0)	22.2 (2)	22.2 (2)	28.6 (2)	0 (0)	20.0 (4)	10.0 (2)
Pain in extremity	0 (0)	0 (0)	33.3 (3)	11.1 (1)	14.3 (1)	0 (0)	20.0 (4)	5.0 (1)
Epistaxis	0 (0)	0 (0)	33.3 (3)	0 (0)	14.3 (1)	0 (0)	20.0 (4)	0 (0)
Rhinorrhoea	25.0 (1)	0 (0)	11.1 (1)	0 (0)	28.6 (2)	0 (0)	20.0 (4)	0 (0)
Dermatitis contact	0 (0)	0 (0)	33.3 (3)	0 (0)	14.3 (1)	0 (0)	20.0 (4)	0 (0)
Pruritus	25.0 (1)	0 (0)	33.3 (3)	0 (0)	0 (0)	0 (0)	20.0 (4)	0 (0)
Scratch	0 (0)	0 (0)	22.2 (2)	0 (0)	28.6 (2)	0 (0)	20.0 (4)	0 (0)

Incidence % (number of subjects with events); MedDRA/J ver.22.0

There were no deaths. Serious adverse events occurred in 1 subject in the child cohort (pneumonia mycoplasmal/respiratory failure/talipes /femur fracture) and 4 subjects in the infant/early child cohort (ALT increased, gastroenteritis, gastroenteritis/anaphylactic reaction, urticaria/rash). Among these events, ALT increased, urticaria/rash, and anaphylactic reaction that occurred in 3 subjects in the infant/early child cohort were classified as adverse drug reactions. No adverse events led to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation:

Acid sphingomyelinase deficiency is a disease caused by decreased ASM activity resulting from a mutation of the *SMPD1* gene encoding ASM. Inactivity of ASM leads to progressive lysosomal accumulation of sphingomyelin in monocyte-macrophage cells in reticuloendothelial tissues, mainly, the spleen, liver, lung, bone marrow, and lymph node. Manifestations of the infantile neurovisceral type of ASMD include failure to thrive, hepatosplenomegaly, and rapidly progressive neurological degeneration, while manifestations of the chronic visceral type of ASMD include hepatosplenomegaly, hepatic impairment, lung disease, cherry red spot, and growth retardation. The chronic neurovisceral type is the intermediate type between the infantile neurovisceral type and chronic visceral type.

Olipudase alfa, a rhASM, was developed as an ERT in pediatric and adult patients with ASMD specifically for symptoms other than those involving the central nervous system.

In Study DFI12712, which was conducted in adult patients with ASMD, foamy macrophages were observed in the alveolar space, alveolar walls, subpleural space, and lymphatic vessels of patients with ASMD; therefore, the percentage of DLco relative to the predicted normal values, which is assumed to reflect the improvement in the pathophysiological condition of form cell infiltration in lung tissues, was selected as a primary endpoint. Splenic volume was also selected as a primary endpoint. Table 37 shows percent change from baseline up to Week 52 in % predicted DLco and splenic volume (MN[4)]). The percent change from baseline in % predicted DLco (least squares mean ± standard error) at Week 52 was 21.97 ± 3.34% in the olipudase alfa group and 2.96 ± 3.38% in the placebo group, demonstrating the superiority of olipudase alfa over placebo. The percent change from baseline in splenic volume (least squares mean ± standard error) at Week 52 was −39.45 ± 2.43% in the olipudase alfa group and 0.48 ± 2.50% in the placebo group, similarly demonstrating the superiority of olipudase alfa over placebo. Table 39 shows the results for key secondary endpoints, namely, hepatic volume (MN[4)]) and platelet count, both of which improved compared with placebo. The long-term efficacy of olipudase alfa was evaluated using pooled data[13)] from Study DFI12712, Study DFI13412 (foreign phase I study in adult patients with ASMD) and its extension study, Study LTS13632 (Table 45). The efficacy of olipudase alfa tended to be maintained at all endpoints.

Table 45. Changes over time in the endpoints of Studies DFI12712, DFI13412, and LTS13632 (percent change from baseline; pooled analysis set)

Endpoints	% Predicted DLco (%)	Splenic volume (MN)	Hepatic volume (MN)	Platelet count (10^9/L)
Baseline	50.4 ± 11.6 (39)	11.5 ± 4.5 (39)	1.5 ± 0.4 (39)	117.3 ± 39.7 (39)
Week 26	14.7 ± 14.4 (34)	−29.2 ± 7.2 (34)	−21.7 ± 10.3 (34)	—
Week 52	22.7 ± 19.1 (28)	−37.8 ± 7.3 (29)	−28.4 ± 13.1 (28)	15.7 ± 16.2 (29)
Week 80	30.7 ± 19.2 (15)	−44.7 ± 8.6 (16)	−27.5 ± 11.3 (16)	—
Week 104	32.8 ± 24.3 (13)	−45.9 ± 7.5 (13)	−34.5 ± 11.7 (13)	12.2 ± 22.1 (13)
Week 130	35.1 ± 40.5 (5)	−47.2 ± 4.4 (5)	−36.2 ± 15.1 (5)	20.6 ± 12.9 (5)
Week 182	33.3 ± 33.4 (5)	−51.0 ± 7.2 (5)	−37.0 ± 16.5 (5)	—
Week 208	—	−47.2 ± 7.8 (5)	−34.6 ± 22.0 (5)	—
Week 234	49.4 ± 48.0 (5)	−53.1 ± 5.3 (5)	−40.3 ± 14.1 (5)	26.8 ± 22.6 (5)
Week 286	50.0 ± 45.8 (5)	−58.8 ± 1.9 (4)	−44.6 ± 18.9 (4)	29.3 ± 22.0 (5)
Week 338	8, 64 (2)	—	—	22, 53 (2)

Mean ± standard deviation (n); individual values for n = 2; "—," not applicable

Table 43 shows the efficacy results from Study DFI13803, which was conducted in pediatric patients with ASMD. All endpoints, namely, % Predicted DLco, splenic volume, hepatic volume, platelet count, and height Z-score, improved from baseline, and this trend was consistent for all age cohorts. Table 46 shows the long-term efficacy results for the analysis of pooled data from Study DFI13803 and its extension study of Study LTS13632.[13)] The efficacy of olipudase alfa tended to be maintained in all endpoints, and this trend was consistent for all age cohorts.

13) A pooled data analysis in subjects receiving olipudase alfa. Adult data were obtained from Study DFI12712 (data cut-off date in October 2019), Study DFI13412 (foreign phase I study), and its extension study of Study LTS13632 (data cut-off date in December 2019) while pediatric data were obtained from Study DFI13803 and its extension study of Study LTS13632 (data cut-off date in December 2019).

Table 46. Changes over time in the endpoints of Studies DFI13803 and LTS13632 (percent change from baseline; pooled analysis set)

Endpoints	% Predicted DLco (%)	Splenic volume (MN)	Hepatic volume (MN)	Platelet count (10^9/L)	Height Z-score[a)]
Baseline	54.8 ± 14.2 (9)	19.0 ± 8.8 (20)	2.6 ± 0.7 (20)	137.7 ± 62.3 (20)	−2.18 ± 0.85 (19)
Week 26	19.4 ± 9.7 (8)	−40.0 ± 7.3 (19)	−32.7 ± 7.9 (19)	45.7 ± 42.8 (18)	0.24 ± 0.36 (18)
Week 52	32.9 ± 29.1 (9)	−49.2 ± 9.7 (20)	−40.6 ± 9.4 (20)	34.0 ± 36.4 (19)	0.55 ± 0.40 (18)
Week 78	35.2 ± 31.0 (6)	−53.7 ± 8.1 (16)	−47.1 ± 8.7 (16)	—	0.90 ± 0.52 (15)
Week 104	37.4 ± 25.1 (6)	−60.6 ± 8.7 (12)	−49.6 ± 10.0 (12)	—	1.11 ± 0.54 (11)
Week 130	43.3 ± 31.6 (5)	−61.0 ± 7.9 (12)	−52.4 ± 10.8 (12)	42.9 ± 55.0 (10)	1.37 ± 0.64 (10)
Week 156	41.4 ± 40.7 (6)	−65.7 ± 6.1 (9)	−54.1 ± 9.0 (9)	—	1.40 ± 0.69 (8)
Week 208	63.6 ± 81.1 (3)	−68.3 ± 3.2 (4)	−54.8 ± 9.2 (4)	42.4 ± 22.1[b)] (4)	1.61, 3.37 (2)

Mean ± standard deviation (n); individual values for n = 2; "—," not applicable
a) Values at Week 26 and subsequent weeks indicate the change from baseline
b) Values at Week 220 were used

The Study DFI13803 results were compared with the data on pediatric patients with ASMD from a natural history study (MSC12840), which is a multicenter, multinational study aiming to collect prospective natural history data from patients with ASMD. Eligible patients were patients aged ≥6 years who were diagnosed as having ASMD on the basis of demonstrably deficient ASM activity in peripheral leukocytes, cultured fibroblasts or lymphocytes, and at least 2 of the following: thrombocytopenia, anaemia, neutropenia, hepatomegaly, splenomegaly, and lung disease. Splenic volume, hepatic volume, pulmonary function testing, platelet count, and other parameters were measured at baseline, year 1 visit, and final visit (which took place approximately 5-11 years after the year 1 visit). In the comparative analysis of Study DFI13803 versus the natural history study, data from patients aged <18 years who had been enrolled in the natural history study and met the applicable criteria among those specified for Study DFI13803, such as splenic volume and height Z-score, were used. Data of patients aged <5 years from Study DFI13803 were not included in the analysis. The comparison of patient characteristics at baseline in Study DFI13803 and those in the natural history study showed that while there were differences in age (12.9 ± 3.1 years [mean ± standard deviation] in the natural history study and 9.9 ± 3.7 years in Study DFI13803) and plasma sphingomyelin concentration (551.3 ± 72.7 mg/L in the natural history study and 394.6 ± 153.9 mg/L in Study DFI13803), there were no significant differences in other patient characteristics. Table 47 shows the results for key efficacy endpoints in Study DFI13803 and the natural history study.

Table 47. Key efficacy endpoints for comparative analysis of Study DFI13803 and natural history study

Endpoints	Time point	Natural history study (n = 14)	Study DFI13803 (n = 15)
Splenic volume (MN)	Baseline	15.8 ± 5.8 (13)	18.7 ± 9.8 (15)
	52 weeks after start[a)]	−1.45 [−6.64, 3.74] (9)	−47.71 [−53.31, −42.12] (15)
Hepatic volume (MN)	Baseline	2.5 ± 0.6 (13)	2.6 ± 0.7 (15)
	52 weeks after start[a)]	8.70 [−6.94, 24.33] (8)	−39.52 [−44.28, −34.76] (15)
Platelet count (10^9/L)	Baseline	168.2 ± 59.0 (13)	138.2 ± 71.6 (15)
	52 weeks after start[a)]	−10.96 [−29.81, 7.89] (13)	34.82 [18.43, 51.22] (15)
% Predicted DLco (%)	Baseline	48.8 ± 25.6 (9)	54.8 ± 14.2 (9)
	52 weeks after start[a)]	27.87 [−8.75, 64.49] (8)	27.82 [7.84, 47.79] (9)
Height Z-score	Baseline	−2.8 ± 1.0 (14)	−2.1 ± 0.9 (15)
	52 weeks after start[a)]	−0.03 [−0.22, 0.17] (13)	0.61 [0.21, 1.01] (14)

Baseline, mean ± standard deviation (n); at 52 weeks after start, least squares mean [95% CI] (n)
a) Percent change from baseline (the change from baseline is shown for the parameter of height Z-score)

The results for % predicted DLco in Study DFI13803 were similar to those in the natural history study. On the other hand, splenic volume, hepatic volume, platelet count, and height Z-score tended to be improved in Study DFI13803 compared with those in the natural history study.

Efficacy in Japanese patients is as follows: 1 Japanese patient was assigned to placebo in the primary analysis period of Study DFI12712 and started receiving olipudase alfa during the extension treatment period. The dose

of olipudase alfa was escalated according to the escalation regimen specified in the protocol up to the maintenance dose of 3.0 mg/kg. Table 40 shows the results for % predicted DLco, splenic volume, hepatic volume, and platelet count after the start of treatment with olipudase alfa. The table shows a trend towards improvement similar to the results for the olipudase alfa group in the primary analysis period.

The above findings indicate that olipudase alfa continues to demonstrate clinically significant benefits both in adult and pediatric patients with ASMD.

PMDA's view:

In Study DFI12712, which was conducted in adult patients with ASMD, decreases in plasma lyso-SPM concentrations have been reported after treatment with olipudase alfa [see Section "6.2.1.3 Global phase II/III study"]. It is understandable that the applicant selected pulmonary function-related indicators, namely, % predicted DLco and splenic volume as primary endpoints given that manifestations of ASMD include decreased pulmonary function and an increase in splenic volume. The results demonstrated the superiority of olipudase alfa over placebo in % predicted DLco and splenic volume. On the basis of the results for secondary endpoints, i.e., hepatic volume and platelet count, together with the long-term data, which suggest that improvements tend to be maintained for all these endpoints, the efficacy of olipudase alfa in the treatment of ASMD in adult patients has been demonstrated. Study DFI13803 was an open-label study in pediatric patients with ASMD. In Study DFI13803, although the sample size is small, plasma lyso-SPM concentration decreased after treatment with olipudase alfa [see Section "6.2.1.4 Foreign phase I/II study"]; in addition, the efficacy endpoints, namely, splenic volume, hepatic volume, platelet count, % predicted DLco, and height Z-score tended to improve from baseline, and the improvements tended to be maintained during the long-term treatment. On the basis of data including the results for splenic volume and other endpoints in pediatric patients, which were comparable to those in adult patients, olipudase alfa is expected to be efficacious also in the treatment of pediatric patients with ASMD.

7.R.2 Safety

The applicant's explanation:

Table 48 shows the incidence of adverse events in the analysis of pooled data[14)] from Studies DFI12712, DFI13412, DFI13803, and LTS13632.

14) The analysis used pooled data from patients with ASMD who had received olipudase alfa in the following studies: for adult data, Study DFI12712 (data cut-off date in October 2019), Study DFI13412 (foreign phase I study), and its extension study of Study LTS13632 (data cut-off date in December 2019); for pediatric data, Study DFI13803 and its extension study of Study LTS13632 (data cut-off date in December 2019).

Table 48. Incidence of adverse events in subjects receiving olipudase alfa (pooled analysis set)

		Pediatric (n = 20)	Adults (n = 39)	Total (N = 59)
All adverse events		100 (20)	97.4 (38)	98.3 (58)
All adverse drug reactions		70.0 (14)	69.2 (27)	69.5 (41)
Serious adverse events		45.0 (9)	23.1 (9)	30.5 (18)
Deaths		0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation		0 (0)	0 (0)	0 (0)
Adverse events leading to dose reduction[a)]		35.0 (7)	10.3 (4)	18.6 (11)
Severity	Mild	5.0 (1)	23.1 (9)	16.9 (10)
	Moderate	65.0 (13)	61.5 (24)	62.7 (37)
	Severe	30.0 (6)	12.8 (5)	18.6 (11)

Incidence % (number of subjects with events);
a) Including data from subjects who had not undergone dose escalation as scheduled and received the same dose level as before

In all clinical studies, adverse events occurred in all patients except for 1 adult patient. The majority of the adverse events were mild or moderate in severity. There were no deaths. Among adult patients, serious adverse events occurred in 9 subjects (23.1%), and extrasystoles that occurred in 1 of the subjects were classified as an adverse drug reaction. Among pediatric patients, serious adverse events occurred in 9 subjects (45.0%), and events that occurred in 4 of the subjects (anaphylactic reaction, urticaria/rash, hypersensitivity, and ALT increased) were classified as adverse drug reactions. The outcome of these events was reported as resolved. Adverse events leading to dose reduction reported in ≥2 adult subjects or ≥2 pediatric subjects were as follows: among adult patients, ALT increased (3 subjects) and AST increased (2 subjects); among pediatric patients, pyrexia (3 subjects), C-reactive protein increased (3 subjects), serum ferritin increased (3 subjects), vomiting (2 subjects), blood alkaline phosphatase increased (2 subjects), and blood bilirubin increased (2 subjects). Ten adult subjects and 6 pediatric subjects experienced dose reduction due to adverse events, treatment interruption, or other reasons. Among these subjects, 3 adult subjects and 0 pediatric subjects did not achieve the maintenance dose; 2 adult subjects and 0 pediatric subjects had achieved the maintenance dose before dose reduction but did not after dose reduction.

In the pooled analysis of adult patients[13)] (n = 39), commonly reported adverse events[15)] were headache (61.5%), nausea (43.6%), nasopharyngitis (41.0%), abdominal pain (33.3%), pyrexia (30.8%), upper respiratory tract infection (30.8%), back pain (28.2%), cough (28.2%), arthralgia (25.6%), diarrhoea (25.6%), and myalgia (25.6%). Severe adverse events occurred in 5 subjects (12.8%); however, no severe events occurred in ≥2 subjects. A causal relationship was denied for all the severe adverse events except for ALT increased in 1 subject. The outcome of these events was reported as resolved. In the pooled analysis of pediatric patients[13)] (n = 20), commonly reported adverse events[15)] were pyrexia (85.0%), cough (80.0%), nasopharyngitis (65.0%), diarrhoea (65.0%), vomiting (65.0%), headache (55.0%), abdominal pain (55.0%), upper respiratory tract infection (50.0%), nausea (45.0%), epistaxis (35.0%), urticaria (35.0%), contusion (35.0%), nasal congestion (30.0%), pain in extremity (30.0%), scratch (25.0%), arthralgia (25.0%), and myalgia (20.0%). Severe adverse events occurred in 6 subjects (30.0%); however, no severe events occurred in ≥2 subjects. A causal relationship was denied for all the severe adverse events except for anaphylactic reaction in 1 subject. The outcome of these events was reported as resolved. The incidence of commonly reported adverse events tend to be higher in

15)Commonly reported adverse events are defined as follows: the number of the adverse event accounts for ≥2% of the total number of all adverse events in either the overall study population, adult patient group, or pediatric patient group and the event occurred in ≥2 subjects, and furthermore, those occurring with an incidence of ≥20%.

pediatric patients than in adult patients, while the types of adverse events in pediatric patients were generally similar to those of adult patients. Similarly, the incidence of serious adverse events was higher in pediatric patients (45.0%) than in adult patients (23.1%). The outcome of these events was reported as resolved.

The analysis of the incidence of adverse events in the olipudase alfa group compared with the placebo group showed that in the primary analysis period of Study DFI12712, adverse events occurred in all subjects in both groups, and the number of adverse events was similar in both groups (242 adverse events in the olipudase alfa group and 267 adverse events in the placebo group). Adverse drug reactions occurred in 6 subjects (33.3%) in the placebo group and 12 subjects (66.7%) in the olipudase alfa group, with the incidence in the olipudase alfa group being higher than that in the placebo group. No serious adverse drug reactions were reported in either group. The incidence of serious adverse events was 16.7% (3 subjects) in the olipudase alfa group and 22.2% (4 subjects) in the placebo group, indicating no significant difference. No adverse events led to treatment discontinuation. An adverse event led to dose reduction in 1 subject (5.6%; ALT increased) in the olipudase alfa group.

Table 49 shows the incidence of adverse events based on the analysis of pooled data[14)] from Studies DFI12712, DFI13412, DFI13803, and LTS13632 by time of onset. There were no trends towards an increase in the incidence of specific events with increase in the duration of treatment with olipudase alfa. The incidence of commonly reported adverse events tended to be roughly the same or higher after the dose escalation period than during the dose escalation period. When the duration of exposure to olipudase alfa (median; 0.28 years during the dose escalation period and 1.78 years after the dose escalation period) is taken into account, the results suggest that adverse events tend to occur at a higher frequency during the dose escalation period than after the dose escalation period.

Table 49. Incidence of adverse events by time of onset (pooled analysis set)

Onset	Months 0-12 (n = 59)	Months 12-24 (n = 49)	Months 24-36 (n = 26)	Months 36-48 (n = 14)
All adverse events	98.3 (58)	93.9 (46)	88.5 (23)	100 (14)
IAR[a)]	52.5 (31)	28.6 (14)	15.4 (4)	7.1 (1)

Incidence % (number of subjects with events)

a) Adverse events occurring within 24 hours of the start of infusion, and are considered by the investigator to be related or possibly related to the study treatment.

As shown above, in all clinical studies in which olipudase alfa was administered, there were no deaths and no adverse events that led to treatment discontinuation. The outcome of all serious adverse events was reported as resolved. The incidence of adverse events tended to be higher in pediatric patients than in adult patients. However, the types of adverse events occurring in pediatric patients were generally similar to those seen in adult patients, indicating that olipudase alfa has an acceptable safety profile for both age groups.

PMDA's view:

The incidence of adverse events in the clinical studies indicated that olipudase alfa has an acceptable safety profile as long as appropriate cautionary statements are provided for the events that are discussed later. However, due to the limited number of patients evaluated in the clinical studies, the applicant should continue

to collect post-marketing information including safety-related data from patients who will be receiving olipudase alfa. Sections 7.R.2.1 through 7.R.2.3 discuss specific adverse events in greater detail.

7.R.2.1 Hypersensitivity-related adverse events and IARs

The applicant's explanation:

In the analysis of pooled data[14)] from Studies DFI12712, DFI13412, DFI13803, and LTS13632, the incidence of hypersensitivity-related adverse events[16)] was 55.9% (33 of 59 subjects) in the overall study population, 46.2% (18 of 39 subjects) in the adult patient group, and 75.0% (15 of 20 subjects) in the pediatric patient group. Commonly reported hypersensitivity-related adverse events occurring in >10% of adult patients were urticaria (15.4%), pruritus (15.4%), rash (12.8%), eczema (10.3%), and erythema (10.3%). Commonly reported hypersensitivity-related adverse events occurring in >10% of pediatric patients were urticaria (35.0%), rash (35.0%), pruritus (25.0%), dermatitis contact (20.0%), eczema (15.0%), skin exfoliation (15.0%), and conjunctivitis (15.0%). In both adult and pediatric patients, all the commonly reported hypersensitivity-related adverse events were mild or moderate in severity. No adverse events led to treatment discontinuation.

In the analysis of pooled data[14)] from Studies DFI12712, DFI13412, DFI13803, and LTS13632, the incidence of IAR[17)] was 55.9% (33 of 59 subjects) in the overall study population, 53.8% (21 of 39 subjects) in the adult patient group, and 60.0% (12 of 20 subjects) in the pediatric patient group. Commonly reported IARs occurring in >10% of adult patients were headache (23.1%), nausea (15.4%), urticaria (12.8%), pyrexia (10.3%), and arthralgia (10.3%). All IARs were mild or moderate in severity. To investigate the time to onset of IARs, the incidence of IARs during the dose escalation period was compared with that after the dose escalation period. Despite the short duration (median) of olipudase alfa exposure during the dose escalation period, the incidence of IARs was lower after the dose escalation period (46.2% during the dose escalation period and 33.3% after the dose escalation period). Commonly reported IARs occurring in >10% of pediatric patients were pyrexia (35.0%), vomiting (30.0%), urticaria (30.0%), headache (20.0%), nausea (20.0%), C-reactive protein increased (20.0%), serum ferritin increased (15.0%), and rash (15.0%). All these events were mild or moderate in severity except for anaphylactic reaction occurring in 1 subject. Serious IARs occurred in 3 pediatric subjects (anaphylactic reaction, hypersensitivity, urticaria/rash). The time to onset of IARs was investigated. Despite the short duration (median) of olipudase alfa exposure during the dose escalation period, the incidence of IARs during the dose escalation period was similar to that after the dose escalation period (50.0% during the dose escalation period and 45.0% after the dose escalation period).

The incidence of IARs in the primary analysis period in Study DFI12712 was higher in the olipudase alfa group (44.4%, 8 subjects) than in the placebo group (33.3%, 6 subjects).

16) Events classified under the SMQ "hypersensitivity" (broad and narrow)

17) Adverse events occurring within 24 hours of the start of infusion, and are considered by the investigator to be related or possibly related to the study treatment

The above results indicated that hypersensitivity and IARs as well as anaphylactic reaction are risks associated with olipudase alfa, and the applicant plans to include a precautionary statement in the package insert.

PMDA's view:

In the primary analysis period in Study DFI12712, the incidence of IARs was higher in the olipudase alfa group than in the placebo group, and serious IARs including anaphylactic reaction were reported; therefore, hypersensitivity including IARs are risks associated with olipudase alfa. Given that no hypersensitivity-related adverse events led to treatment discontinuation, and that many of the events were mild or moderate in severity, the risks are acceptable. However, when olipudase alfa is administered, attention should be paid to the possible onset of IARs and anaphylactic reaction; therefore, the applicant should provide an appropriate cautionary statement regarding the events in the package insert.

7.R.2.2 Effects of sphingomyelin catabolites

The applicant's explanation:

When sphingomyelin accumulated in the body is rapidly metabolized, ceramide, a proinflammatory degradation product, increases. Ceramide is a physiologically active sphingolipid involved in the formation of lipid rafts, promoting dimerization of toll-like receptors and other receptors involved in inflammation and protein-protein interaction, thereby enhancing proinflammatory signaling to liposaccharides (*FEBS Lett.* 2010;584:1895-900). It has been suggested that *de novo* synthesized ceramide is involved in proinflammatory adipokine secretion, and interaction between adipocytes and macrophages (*J Nutr Biochem.* 2014;25:1309-16). Ceramide 1-phosphate (C1P), a phosphorylation product of ceramide, is known to have proinflammatory properties (*Biochim Biophys Acta.* 2016;1861:402-9). In the nonclinical study in ASMKO mice, olipudase alfa led to increases in the levels of proinflammatory cytokines such as IL-6, IL-1α, IL-1β, G-CSF, and MIP-1α, and resulted in death as well as decreases in heart rate and blood pressure [see Section "3.2 Secondary pharmacodynamics"]; accordingly, the effects of sphingomyelin catabolites on safety in the clinical studies were evaluated.

Table 50 shows plasma ceramide concentrations in Study DFI12712 (primary analysis period). Plasma ceramide concentrations increased at 24 hours and 48 hours post-initial dose of olipudase alfa. While plasma ceramide concentrations slightly increased following administration at Week 52 but to a lesser degree compared with the increase at initial dosing. Throughout the treatment period, pre-dosing plasma ceramide concentrations decreased at each time point in the olipudase alfa group.

Table 50. Change in plasma ceramide concentrations over time in Study DFI12712 (primary analysis period)

Time point		Placebo	Olipudase alfa
Initial dose	Pre-dosing	4.14 ± 0.95 (18)	3.71 ± 1.19 (18)
	24 hours post-dose	4.56 ± 0.84 (18)	8.30 ± 2.50 (18)
	48 hours post-dose	4.57 ± 1.67 (18)	8.17 ± 2.58 (18)
Week 26	Pre-dosing	3.89 ± 0.78 (17)	2.70 ± 1.00 (18)
	24 hours post-dose	4.01 ± 0.82 (17)	5.13 ± 2.16 (18)
	48 hours post-dose	4.18 ± 0.84 (17)	4.77 ± 2.31 (18)
Week 52	Pre-dosing	4.06 ± 1.22 (16)	2.36 ± 0.76 (18)
	24 hours post-dose	4.25 ± 0.98 (15)	4.65 ± 2.00 (18)
	48 hours post-dose	4.04 ± 0.90 (16)	3.87 ± 1.83 (18)

Unit, mg/L; mean ± standard deviation (n)

Table 51 shows change in IL-8 in Study DFI12712 (primary analysis period). The median IL-8 decreased over time throughout the study period and was lower in the olipudase alfa group than in the placebo group at pre-dosing, 24 hours post-dose, and 48 hours post-dose in Week 52.

Table 51. Change in IL-8 over time in Study DFI12712 (primary analysis period)

Time point		Placebo	Olipudase alfa
Initial dose	Pre-dosing	24.05 [10.4, 2928.0] (18)	18.25 [4.8, 2928.0] (18)
	24 hours post-dose	25.70 [11.5, 2928.0] (18)	23.60 [6.5, 2928.0] (18)
	48 hours post-dose	27.00 [8.5, 2928.0] (18)	26.15 [7.1, 2928.0] (18)
Week 26	Pre-dosing	23.60 [6.7, 2928.0] (15)	15.40 [5.0, 2928.0] (18)
	24 hours post-dose	28.40 [12.7, 2928.0] (15)	18.45 [9.7, 2928.0] (18)
	48 hours post-dose	28.90 [11.3, 2928.0] (15)	19.30 [8.0, 2928.0] (18)
Week 52	Pre-dosing	20.50 [10.2, 2928.0] (15)	9.70 [5.7, 29.0] (18)
	24 hours post-dose	24.10 [10.9, 2928.0] (14)	10.90 [4.9, 25.4] (18)
	48 hours post-dose	21.10 [8.8, 2928.0] (15)	12.20 [6.6, 30.4] (18)

Unit, ng/L; median [range] (n)

Effects on heart rate and blood pressure were analyzed based on the vital sign data from Study DFI12712 (primary analysis period). Table 52 shows subjects whose heart rate and blood pressure were considered to be affected.

Table 52. Change in heart rate and blood pressure in Study DFI12712 (primary analysis period)

		Placebo (n = 18)	Olipudase alfa (n = 18)
Heart rate[a)]	Increased	5.6 (1)	0 (0)
	Decreased	11.1 (2)	5.6 (1)
Systolic blood pressure[b)]	Increased	11.1 (2)	22.2 (4)
	Decreased	50.0 (9)	44.4 (8)
Diastolic blood pressure[c)]	Increased	5.6 (1)	11.1 (2)
	Decreased	16.7 (3)	22.2 (4)

Incidence % (number of subjects with events)

a) Increased, ≥120 bpm and an increase from baseline by ≥20 bpm; decreased, ≤50 bpm and a decrease from baseline by ≥20 bpm

b) Increased, ≥160 mmHg and an increase from baseline by ≥20 mmHg; decreased, ≤95 mmHg and a decrease from baseline by ≥20 mmHg

c) Increased, ≥110 mmHg and an increase from baseline by ≥10 mmHg; decreased, ≤45 mmHg and a decrease from baseline by ≥10 mmHg

In addition to IARs discussed in Section 7.R.2.1, other events that may occur due to elevation of sphingomyelin catabolites, such as ceramide, specifically, the incidence of transaminases increased and cytokine release syndrome was investigated.

In the clinical studies, >2-fold elevation above the upper limit of normal range of transaminases (ALT or AST) occurred in 4 of 18 adult subjects in the olipudase alfa group in the primary analysis period and 3 of 16 adult subjects in the placebo/olipudase alfa group in the extension treatment period in Study DFI12712, and 7 of 20 pediatric subjects in Study DFI13803. In all cases, the elevation occurred 24 to 48 hours post-infusion during the dose escalation period. The transaminase levels tended to decrease at the next dosing time and decreased

to the pre-dosing levels or were within the normal range during the treatment period in all subjects. To prevent elevation of transaminase levels, the dose escalation regimen was to be used to slowly decrease the level of sphingomyelin accumulated in the body, thereby suppressing the peak level of ceramide formed after administration of olipudase alfa. The applicant plans to include cautionary statements in the package insert to the effect that prior to administration of olipudase alfa and during the dose escalation period, transaminase levels (ALT and AST) should be monitored to assess whether dose adjustment is needed or the dose can be appropriately administered.

In the clinical studies, no cytokine release syndrome has been reported. Taking also the change in IL-8 levels in Study DFI12712 (Table 51) into account, it is not necessary to provide a cautionary statement on cytokine release syndrome at present.

PMDA's view:
In the nonclinical studies, elevated ceramide and other sphingomyelin catabolite concentrations were reported, and proinflammatory cytokine levels increased in some animals, supposedly due to rapid elevation of sphingomyelin catabolites, and resulted in lethality in some cases. Therefore, events that may occur as a result of elevation of sphingomyelin catabolites are considered potential risks of treatment with olipudase alfa. To prevent rapid elevation, clinical studies were conducted in which initial treatment with low-dose infusions of olipudase alfa was followed by gradual escalation to the maintenance dose. While transaminase levels increased transiently in some patients after infusion during dose escalation, treatment with olipudase alfa continued. A transient increase in plasma ceramide concentrations occurred at every dosing, which seems to be caused by the pharmacological effects of olipudase alfa; however, no elevation in IL-8 levels or cytokine release syndrome were reported. In addition, the percentage of patients who presented with decreases in blood pressure or heart rate in the olipudase alfa group is similar to that in the placebo group. On the basis of the incidence of cardiovascular adverse events in the clinical studies, as well as the above findings, the data from the clinical studies so far have not raised significant concerns in terms of the effects on the cardiovascular system. Taken together, data do not indicate that the above events will cause clinical problems at present. However, given that ceramide and other sphingomyelin catabolites may affect the safety of treatment with olipudase alfa, it is important to clearly specify dose escalation as the regimen of olipudase alfa. Furthermore, as explained by the applicant, it is appropriate to provide cautionary statements to the effect that prior to administration of olipudase alfa and during the dose escalation period, transaminase levels should be monitored to assess whether dose adjustment is needed or the dose can be appropriately administered. Furthermore, the applicant should collect post-marketing data on the events assumed to be associated with the elevation of sphingomyelin catabolite levels.

7.R.2.3 Effects of antibody production

The applicant's explanation:
In the primary analysis period in Study DFI12712, 4 of 18 subjects (22.2%) in the olipudase alfa group tested positive for ADAs after administration of olipudase alfa, while 2 subjects tested positive for ADAs at baseline.

In the placebo group, 4 subjects tested positive for ADAs at baseline. Two subjects each in the olipudase alfa group and placebo group tested positive for NAbs that inhibit enzyme activity.

Table 53 shows the incidence of adverse events by ADA status in the analysis of pooled data[14)] from Studies DFI12712, DFI13412, DFI13803, and LTS13632.

Table 53. Incidence of adverse events by ADA status (pooled analysis set)

	Pediatric patients (n = 20)		Adult patients (n = 39)		Overall (N = 59)	
ADA	Positive (n = 12)	Negative (n = 8)	Positive (n = 13)	Negative (n = 26)	Positive (n = 25)	Negative (n = 34)
All adverse events	100 (12)	100 (8)	100 (13)	96.2 (25)	100 (25)	97.1 (33)
Serious adverse events	50.0 (6)	37.5 (3)	30.8 (4)	19.2 (5)	40.0 (10)	23.5 (8)
IAR[a)]	83.3 (10)	25.0 (2)	69.2 (9)	46.2 (12)	76.0 (19)	41.2 (14)
Anaphylactic reaction	8.3 (1)	0 (0)	0 (0)	0 (0)	4.0 (1)	0 (0)

Incidence % (number of subjects with events)

a) Adverse events occurring within 24 hours of the start of infusion, and are considered to be related or possibly related to the study treatment by the investigator.

Both in adult and pediatric patients, the incidence of serious adverse events was higher in ADA-positive subjects than in ADA-negative subjects. There were no adverse events occurring in ≥2 subjects in either group, and data indicated no particular trends. The incidence of IARs was higher among subjects who tested positive for ADAs, while all IAR events that occurred in the clinical studies were manageable and led to treatment discontinuation. However, the applicant plans to include a precautionary statement in the package insert regarding hypersensitivity and IARs regardless of the ADA status of patients.

Table 54 shows key efficacy results by ADA status in the analysis of pooled data from Studies DFI12712, DFI13412, DFI13803, and LTS13632. Both in adult and pediatric patients, the results were similar regardless of the ADA status.

Table 54. Key efficacy results by ADA status (percent change from baseline, pooled analysis set)

Endpoint	Time point	Adult patients (n = 39)		Pediatric patients (n = 20)	
		Positive (n = 13)	Negative (n = 26)	Positive (n = 12)	Negative (n = 8)
Splenic volume (MN)	Baseline	10.4 ± 4.3	12.0 ± 4.6	18.7 ± 8.7	19.4 ± 9.5
	Week 52	−38.9 ± 6.3	−37.0 ± 8.0	−49.9 ± 10.2	−48.1 ± 9.5
Platelet count (10^9/L)	Baseline	128.6 ± 34.7	111.7 ± 41.5	144.8 ± 72.6	127.1 ± 45.2
	Week 52	16.3 ± 7.7	15.4 ± 20.0	35.7 ± 43.0	31.8 ± 27.5

Mean ± standard deviation

PMDA's view:

No clear effect of ADA status on efficacy is observed. In contrast, the incidence of serious adverse events and IARs tended to be higher in patients who tested positive for ADAs than in those who tested negative for ADAs. Although some events led to treatment discontinuation in patients who tested positive for ADAs, given that treatment was resumed and that reported IARs and other events were mostly mild or moderate in severity, the safety profile in patients who tested positive for ADAs is acceptable. The applicant should collect data when ADA measurements are taken in the post-marketing setting, and continue to investigate safety in patients who tested positive for ADAs.

7.R.3 Clinical positioning and indication

The applicant's explanation:

Currently, there are no therapies that improve ASMD or slow down the progression of the disease, and no approved drugs are available. Olipudase alfa, a rhASM, was developed as an ERT in pediatric and adult patients with ASMD. In Study DFI12712, which was conducted in adult patients with ASMD, the results for the primary endpoints, namely, % predicted DLco and splenic volume, demonstrated the superiority of olipudase alfa over placebo, and the safety profile of olipudase alfa is also acceptable. In Study DFI13803, which was conducted in pediatric patients with ASMD, % predicted DLco, splenic volume, and other parameters tended to improve, and the results indicated favorable tolerability in all age cohorts.

On the basis of the above, olipudase alfa is expected to be efficacious in the treatment of adult and pediatric patients with ASMD and become a new treatment option. The appropriate indication will be "acid sphingomyelinase deficiency (ASMD)."

In Studies DFI12712 and DFI13803, patients with chronic visceral type or chronic neurovisceral type of ASMD were enrolled. There has been no experience in the treatment of the infantile neurovisceral type with olipudase alfa. Although olipudase alfa, which does not cross the blood-brain barrier, is not expected to be efficacious in preventing progressive neurological degeneration, which is seen in patients with the infantile neurovisceral type of ASMD, olipudase alfa may be effective in patients with this type of ASMD for controlling clinical symptoms other than those involving the central nervous system. The applicant plans to include precautionary statements in the package insert to the effect that there is no experience with the use of olipudase alfa in patients with the infantile neurovisceral type in clinical studies, and that the efficacy of olipudase alfa has not been established for symptoms involving the central nervous system.

PMDA's view:
In the clinical studies, olipudase alfa is expected to be efficacious in the treatment of patients with ASMD and its safety is acceptable [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"]. Since there are no currently available drugs approved for the treatment of ASMD in Japan, olipudase alfa can be positioned as a new treatment option for ASMD, and it is meaningful to make the option available to clinical practice. The indication for olipudase alfa should be "acid sphingomyelinase deficiency."

Among patients with different types of ASMD, those with the infantile neurovisceral type were not enrolled in any of the clinical studies. Because of its inability to cross the blood-brain barrier, the efficacy of olipudase alfa is not expected in the treatment of central nervous system symptoms. However, on the basis of results from the clinical studies, there is no need to limit the use of olipudase alfa for the purpose of treatment of clinical symptoms other than those involving the central nervous system in patients with the infantile neurovisceral type; therefore, the applicant's plan to provide information that there is no experience with the use of olipudase alfa in patients with the infantile neurovisceral type in clinical studies is appropriate. Since olipudase alfa does not cross the blood-brain barrier, a cautionary statement to the effect that the efficacy in controlling symptoms involving the central nervous system is not established.

7.R.4 Dosage and administration

The applicant's explanation:

In the nonclinical studies in ASMKO mice, a dose-dependent increase in proinflammatory cytokine concentration was observed following a single dose of olipudase alfa. When repeated doses of olipudase alfa were administered in a dose-escalating manner, proinflammatory cytokine concentrations did not increase [see Section "3.R.2 Effects of sphingomyelin catabolites on cytokines"]. Accordingly, dose escalation regimens were used in the clinical studies.

In a phase I study (Study SPHINGO00605), a single dose of olipudase alfa 0.03, 0.1, 0.3, 0.6, or 1.0 mg/kg was administered to adult patients with ASMD. Olipudase alfa was well tolerated up to 0.1 mg/kg. As the dose level increased, the incidence of blood bilirubin increased also tended to increase (0 of 3 subjects in the 0.03 mg/kg group, 1 of 3 subjects in the 0.1 mg/kg group, 0 of 2 subjects in the 0.3 mg/kg group, 1 of 2 subjects in the 0.6 mg/kg group, and 1 of 1 subject in the 1.0 mg/kg group). Because of this and other results that raised safety concerns at high dose levels, it was decided to select a dose escalation regimen, in which escalating doses of olipudase alfa were to be administered in the order of 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg once every 2 weeks up to the target maintenance dose of 3.0 mg/kg, in Study DFI12712, which was conducted in adult patients with ASMD to evaluate the efficacy of olipudase alfa. A maintenance dose of 3.0 mg/kg was selected for the clinical studies because when olipudase alfa 0.1, 0.3, 1, or 3.0 mg/kg was administered to ASMKO mice once every 2 weeks in the nonclinical study, it was determined that olipudase alfa 3.0 mg/kg was required to treat pulmonary function-related symptoms.

In Study DFI12712, which was conducted in adult patients with ASMD, of the 36 subjects who had received the study drug, 1 subject in the placebo group who was withdrawn from the study due to protocol noncompliance was excluded. The remaining 35 subjects completed the primary analysis period, and no significant safety issues were found. In Study DFI13803, which was conducted in pediatric patients with ASMD, olipudase alfa treatment was started at 0.03 mg/kg due to safety considerations, and a dose escalation regimen, similar to that used in Study DFI12712 in adult patients with ASM, was employed for subsequent doses. All 20 subjects who had received olipudase alfa completed the study. In Study DFI12712 (primary analysis period) and Study DFI13803, all subjects except for 1 subject received the target dose of 3.0 mg/kg, and showed improvements in the endpoints including % predicted DLco, splenic volume, hepatic volume, and platelet count. Taking account of the above results, treatment should be started at 0.1 mg/kg in adult patients and 0.03 mg/kg in pediatric patients, and thereafter, doses should be increased according to the dose escalation regimen specified for each clinical study. The maintenance dose should be olipudase alfa 3.0 mg/kg.

In Studies DFI12712 and DFI13803, olipudase alfa was diluted with physiological saline to make the prespecified infusion volume based on the dose level and, for pediatric patients, body weight as well. The infusion rate was increased in a stepwise fashion at each dosing. When doses are interrupted, depending on the number of doses that were not administered according to the specified schedule, treatment was to be resumed at the reduced dose level immediately before the interruption. If the dose level after resumption is less than the

maintenance dose (3.0 mg/kg), the dose was to be increased according to the specified dose escalation regimen. The applicant also plans to include detailed information on the infusion rate as well as the rules for dose interruption and treatment resumption specified for the clinical studies in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the package insert.

PMDA's view:

On the basis of the efficacy and safety results for olipudase alfa in the clinical study data submitted [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"], there is no problem with the maintenance dose of olipudase alfa 3.0 mg/kg administered as intravenous infusion once every 2 weeks, which is the same as that specified in Studies DFI12712 and DFI13803. In addition, to prevent rapid elevation of the concentrations of ceramide and other sphingomyelin catabolites, which may induce proinflammatory cytokine release and other effects, dose escalation is important for olipudase alfa. Taking account of the specified regimen used in Studies DFI12712 and DFI13803, treatment with olipudase alfa should be started at 0.1 mg/kg in adult patients and 0.03 mg/kg in pediatric patients, and the dose escalation regimens selected in the studies should be specified as the dosage and administration. Furthermore, in Studies DFI12712 and DFI13803, treatment with olipudase alfa resumed in some patients after interruption of multiple doses, and all the patients continued receiving olipudase alfa after resumption. Given that all the patients who had received olipudase alfa in Study DFI12712 (primary analysis period) and Study DFI13803 completed the study, the applicant's plan to include the information regarding the infusion rate and specific rules for dose interruption and treatment resumption used in the clinical studies in the package insert is appropriate.

7.R.5 Post-marketing investigations

The applicant's explanation:

Due to the limited number of patients with ASMD treated with olipudase alfa, the applicant has planned to conduct a specified use-results survey to evaluate safety and efficacy covering all patients treated with olipudase alfa. On the basis of the observation period in Study DFI12712 (up to 5 years and 3 months), the observation period is from the enrollment to the end of the survey period (at least 1 year and up to 5 years maximum is expected) for each patient. In addition, ASMD, for which olipudase alfa is indicated, is an extremely rare disorder and only 3 patients are expected to be enrolled in Japan at present, and therefore, extension of the registration period is not likely to result in further enrollment of patients. Accordingly, the registration period will be 4 years. Safety data to be collected include incidence of IARs and other adverse drug reactions, AST, and ALT, while efficacy data to be collected include pulmonary function test data such as DLco, splenic volume, and hepatic volume.

PMDA's view:

Due to the limited number of patients with ASMD treated with olipudase alfa, the applicant should conduct post-marketing surveillance covering all patients who will be receiving olipudase alfa to keep track of the safety and efficacy of olipudase alfa. Although the applicant's plan for the post-marketing surveillance is

generally appropriate, the details of the surveillance will be finalized taking into account the comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that olipudase alfa has efficacy in the treatment of ASMD, and that olipudase alfa has acceptable safety in view of its benefits. Olipudase alfa, an enzyme replacement therapy for ASMD, is clinically meaningful because it offers a treatment option for patients with ASMD.

PMDA has concluded that olipudase alfa may be approved if olipudase alfa is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 7, 2022

Product Submitted for Approval

Brand Name	Xenpozyme for I.V. Infusion 20 mg
Non-proprietary Name	Olipudase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	September 30, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's view:

Study DFI12712, which was conducted in adult patients with ASMD, demonstrated the superiority of olipudase alfa over placebo in the primary endpoints, i.e., % predicted DLco and splenic volume. Taking account of the results for secondary endpoints, i.e., hepatic volume and platelet count, and the long-term data, which suggest that improvements tend to be maintained for all these endpoints, it is considered that the efficacy of olipudase alfa in the treatment of ASMD in adult patients has been demonstrated. Study DFI13803, which was conducted in pediatric patients with ASMD, the efficacy endpoints, i.e., splenic volume, hepatic volume, platelet count, % predicted DLco, and height Z-score, tended to improve from baseline, and the improvements tended to be maintained during the long-term treatment. On the basis of data including the results for splenic volume and other endpoints in pediatric patients, which were comparable to those in adult patients, olipudase alfa is expected to be efficacious also in the treatment of pediatric patients with ASMD.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

PMDA's view:

On the basis of the incidence of adverse events in the clinical studies, the safety of olipudase alfa is acceptable provided that appropriate cautionary advice is given regarding hypersensitivity-related adverse events and IARs, both of which are adverse events of special interest when administering olipudase alfa, as well as effects of sphingomyelin catabolites and antibody production. However, due to the limited number of patients evaluated in the clinical studies, safety and other data associated with treatment with olipudase alfa should continue to be collected in the post-marketing setting.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indication

PMDA's view:

As demonstrated in the clinical studies, the efficacy of olipudase alfa is expected in the treatment of patients with ASMD, and its safety is acceptable. Since there are no currently available drugs approved for the treatment of ASMD in Japan, olipudase alfa can be positioned as a new treatment option for ASMD, and it is meaningful to make the option available to clinical practice. The indication for olipudase alfa should be "acid sphingomyelinase deficiency."

Because of its inability to cross the blood-brain barrier, the efficacy of olipudase alfa is not expected in the treatment of central nervous system symptoms, and therefore patients with the infantile neurovisceral type of ASMD were not enrolled in the clinical studies. It was concluded that nevertheless, there is no need to limit the use of olipudase alfa for the purpose of treatment of clinical symptoms other than those involving the central nervous system in patients with the infantile neurovisceral type of ASMD. The applicant should provide information that there is no experience with the use of olipudase alfa in patients with the infantile neurovisceral type in clinical studies. Also, because olipudase alfa does not cross the blood-brain barrier, the applicant should provide a cautionary statement to the effect that the efficacy in controlling symptoms involving the central nervous system is not established.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above, and also made the following comments:

- Acid sphingomyelinase deficiency has been historically known as Niemann-Pick disease types A and B. In recent years, the term acid sphingomyelinase deficiency has been increasingly used; however, in Japan, it is expected that Niemann-Pick disease types A and B are still being used by healthcare professionals. Therefore, it is important to provide information that they refer to the same disease.

PMDA asked the applicant to provide information materials for healthcare professionals to advise them that Niemann-Pick disease types A and B and ASMD refer to the same disease. PMDA confirmed that the applicant took appropriate action.

1.4 Dosage and administration

PMDA's view:

On the basis of the efficacy and safety results for olipudase alfa in the clinical study data submitted, there is no problem with the maintenance dose of olipudase alfa 3.0 mg/kg administered as intravenous infusion once every 2 weeks, which is the same as that specified in Studies DFI12712 and DFI13803. In addition, to prevent rapid elevation of the concentrations of sphingomyelin catabolites, which may induce proinflammatory cytokine release and other effects, dose escalation is important for olipudase alfa. Treatment should be started at 0.1 mg/kg in adult patients and 0.03 mg/kg in pediatric patients based on the specified regimen used in Studies DFI12712 and DFI13803, and the dose escalation regimens selected in the studies should be specified as the dosage and administration. Furthermore, in Studies DFI12712 and DFI13803, treatment with olipudase alfa resumed in some patients after interruption of multiple doses, and all the patients continued receiving olipudase alfa after resumption. Given that all the patients who had received olipudase alfa in Study DFI12712 (primary analysis period) and Study DFI13803 completed the study, the information regarding the infusion rate and specific rules for dose interruption and treatment resumption used in the clinical studies should be included in the package insert.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion as set out in Section "7.R.5 Post-marketing investigations" in Review Report (1) and also made the following additional comments:

- The applicant currently plans to set the end date of survey period for feasibility reasons based on the limited number of patients in Japan. While it is understandable, given that there is limited experience in the treatment with olipudase alfa in Japan, as much information as possible on patients who will be receiving olipudase alfa should be gathered in the post-marketing setting.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for olipudase alfa should include the safety and efficacy specifications presented in Table 55, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Tables 56 and 57. PMDA requested the applicant to reinforce the safety data gathering system to ensure that data can be collected from any patient who starts treatment after the end of the specified use-results survey and confirmed that the applicant took appropriate action.

Table 55. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction, hypersensitivity reactions including anaphylaxis • Effects of sphingomyelin catabolites (e.g., elevated transaminase levels)	None	• Long-term safety
Efficacy specification		
• Long-term efficacy		

Table 56. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study[a)]	• Specified use-results survey (all-case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance

a) The ongoing Study DFI12712 (study in 1 Japanese patient) will be reclassified as a post-marketing clinical study after approval.

Table 57. Outline of specified use-results survey (draft)

Objective	To assess the safety and efficacy of olipudase alfa in clinical use
Survey method	Central registration
Population	Patients with ASMD
Observation period	From the start of treatment to the end of the survey period (up to 6 years)
Planned sample size	All patients treated with olipudase alfa
Main survey items	Patient characteristics, safety evaluation (e.g., adverse events), efficacy evaluation (e.g., splenic volume, hepatic volume, DLco)

1.6 Specification of the shelf life and quality of the drug product

The applicant submitted additional long-term test results for the potency (cellular uptake testing) for the 3 formulation batches manufactured with process B drug substance, each measured at [redacted], [redacted], and [redacted] months. From the results, none of the batches indicated clear changes in potency (cellular uptake testing).

PMDA concluded that a shelf life of 60 months is acceptable for the formulation manufactured by the proposed commercial process when stored at 2°C to 8°C in a glass vial with a chlorobutyl rubber stopper.

PMDA also concluded that the quality of the drug product has been adequately controlled based on the submitted data.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval conditions. Since the product is designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Acid sphingomyelinase deficiency

Dosage and Administration

Usually, olipudase alfa (genetical recombination) is administered as an intravenous infusion every other week. The starting dose and subsequent doses should be determined in accordance with the dose escalation regimen shown below. The usual maintenance dose is 3 mg per kg of body weight.

Dose escalation regimen for adult patients	
Initial dose (first day of treatment)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth and subsequent doses (Week 14 and thereafter)	3 mg/kg

Dose escalation regimen for pediatric patients	
Initial dose (first day of treatment)	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 and subsequent doses (Week 16 and thereafter)	3 mg/kg

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients have been collected to keep track of information on patient characteristics, and collect safety and efficacy data as soon as possible. The applicant is required to take whatever measures are necessary to ensure proper use of the product.

Appendix

List of Abbreviations

Adverse drug reaction	Adverse event for which a causal relationship to the study drug cannot be ruled out
ALT	Alanine aminotransferase
ASM	Acid sphingomyelinase
ASMD	Acid sphingomyelinase deficiency
ASMKO	Acid sphingomyelinase knockout
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
C_{max}	Maximum concentration
CQA	Critical quality attribute
DLco	Diffusing capacity of the lung for carbon monoxide
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EOPC	End of production cell
ERT	Enzyme replacement therapy
G-CSF	Granulocyte-colony stimulating factor
HCP	Host cell protein
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
IAR	Infusion associated reaction
ICH Q5A (R1) Guidelines	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D Guidelines	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
icIEF	Image capillary Isoelectric Focusing
JP	Japanese Pharmacopoeia
k_{cat}	Turnover number
KC/GRO	Keratinocyte chemoattractant/growth-regulated oncogene
K_m	Michaelis constant
lyso-SPM	Lyso-sphingomyelin
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MIP-1α	Macrophage inflammatory protein-1α
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MN	Multiples of normal
MRI	Magnetic resonance imaging
M6P	Mannose-6-phosphate
NZW	New Zealand White
Olipudase alfa	Olipudase alfa (genetical recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
Process A drug substance	Drug substance manufactured by Process A
Process A formulation	Drug product manufactured using Process A drug substance
Process B drug substance	Drug substance manufactured by Process B

Process B formulation	Drug product manufactured using Process B drug substance
QbD	Quality by design
rhASM	Recombinant human acid sphingomyelinase
RP-UHPLC	Reverse Phase-Ultra High Performance Liquid Chromatography
SD	Sprague-Dawley
[redacted]	[redacted]
SEC	Size exclusion liquid chromatography
SMQ	Standardized MedDRA query
SPH	Sphingosine
SPR	Surface plasmon resonance
SRS	Splenomegaly-related score
S1P	Sphingosine-1-phosphate
TNFα	Tumor necrosis factor alpha
WCB	Working cell bank
Xenpozyme	Xenpozyme for I.V. Infusion 20 mg