Report on the Deliberation Results

March 3, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Kanuma Intravenous Infusion 20 mg
[Non-proprietary name]	Sebelipase Alfa (Genetical Recombination) (JAN*)
[Applicant]	Synageva BioPharma Japan K.K. (a predecessor of Alexion Pharma Godo Kaisha)
[Date of application]	May 22, 2015

[Results of deliberation]
In the meeting held on February 24, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

[Conditions for approval]
- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients studied in Japan, the applicant is required to conduct a post-marketing drug use-results survey, covering all patients treated with the product during the re-examination period, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 4, 2016
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

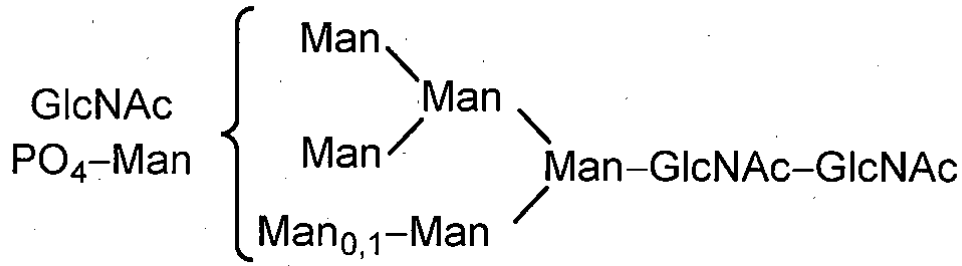
[Brand name]	Kanuma Intravenous Infusion 20 mg
[Non-proprietary name]	Sebelipase Alfa (Genetical Recombination)
[Applicant]	Synageva BioPharma Japan K.K. (a predecessor of Alexion Pharma Godo Kaisha)
[Date of application]	May 22, 2015
[Dosage form/Strength]	Injection: Each vial contains 20 mg of Sebelipase Alfa (Genetical Recombination).
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Definition]	Sebelipase Alfa is a recombinant human lysosomal acid lipase produced in egg white from transgenic Gallus, which is a glycoprotein (molecular weight, ca. 55,000) consisting of 378 amino acid residues.
[Structure]	See attachment.
[Items warranting special mention]	Orphan drug (Drug Designation No. 281 of 2015 [*24 yaku*], Notification No. 1029-1, dated October 29, 2015, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
[Reviewing office]	Office of New Drug I

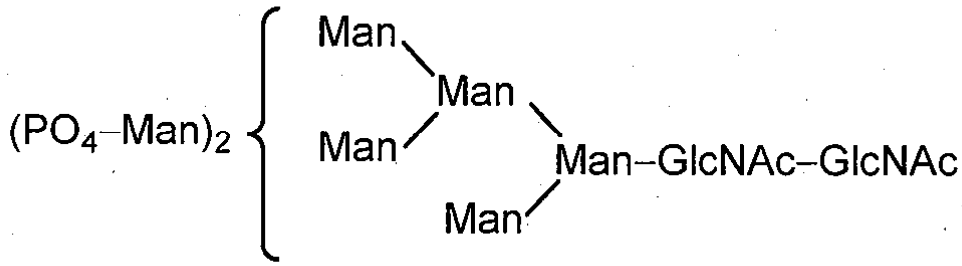
Amino acid sequence:

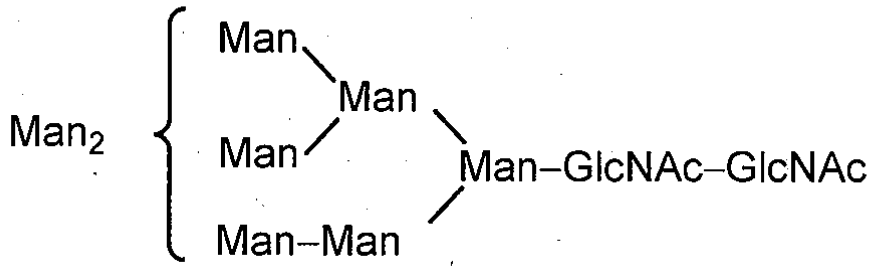
SGGKLTAVDP ETNMNVSEII SYWGFPSEEY LVETEDGYIL CLNRIPHGRK
NHSDKGPKPV VFLQHGLLAD SSNWVTNLAN SSLGFILADA GFDVWMGNSR
GNTWSRKHKT LSVSQDEFWA FSYDEMAKYD LPASINFILN KTGQEQVYYV
GHSQGTTIGF IAFSQIPELA KRIKMFFALG PVASVAFCTS PMAKLGRLPD
HLIKDLFGDK EFLPQSAFLK WLGTHVCTHV ILKELCGNLC FLLCGFNERN
LNMSRVDVYT THSPAGTSVQ NMLHWSQAVK FQKFQAFDWG SSAKNYFHYN
QSYPPTYNVK DMLVPTAVWS GGHDWLADVY DVNILLTQIT NLVFHESIPE
WEHLDFIWGL DAPWRLYNKI INLMRKYQ

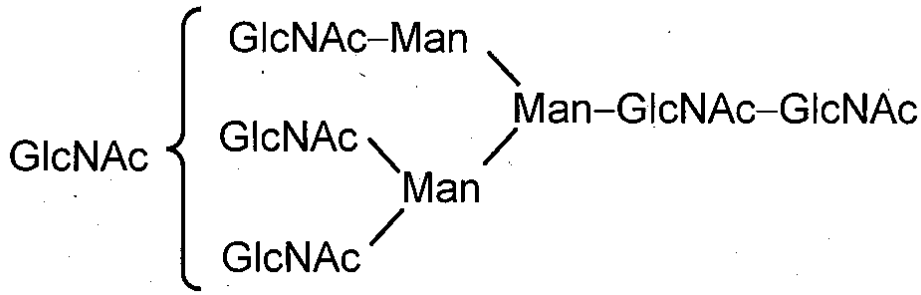
Putative major glycan structures:

N15, N51, N80, N140, N252, N300: glycosylation sites









Molecular formula: $C_{1968}H_{2945}N_{507}O_{551}S_{15}$ (Protein portion)

Review Results

February 4, 2016

[Brand name]	Kanuma Intravenous Infusion 20 mg
[Non-proprietary name]	Sebelipase Alfa (Genetical Recombination)
[Applicant]	Synageva BioPharma Japan K.K. (a predecessor of Alexion Pharma Godo Kaisha)
[Date of application]	May 22, 2015

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with lysosomal acid lipase deficiency (cholesteryl ester storage disease, Wolman disease) has been demonstrated and its safety is acceptable in view of its observed benefits. Safety issues such as hypersensitivity including anaphylaxis, the impact of antibody formation, and long-term safety need to be further investigated via post-marketing surveillance.

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

[Indication] Lysosomal acid lipase deficiency (cholesteryl ester storage disease, Wolman disease)

[Dosage and administration] The usual dosage is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once every other week as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once every other week or once weekly as an intravenous infusion.

The dosage in patients with infantile-onset, rapidly progressive lysosomal acid lipase deficiency is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once weekly as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once weekly as an intravenous infusion.

The dosage should be adjusted according to the patient's condition.

[Conditions for approval]

- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients studied in Japan, the applicant is required to conduct a post-marketing drug use-results survey, covering all patients treated with the product during the re-examination period, in order to obtain information on the characteristics of patients

treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

Review Report (1)

December 25, 2015

I. Product Submitted for Registration

[Brand name]	Kanuma Intravenous Infusion 20 mg
[Non-proprietary name]	Sebelipase Alfa (Genetical Recombination)
[Applicant]	Synageva BioPharma Japan K.K. (Alexion Pharma Godo Kaisha is the current applicant)
[Date of application]	May 22, 2015
[Dosage form/Strength]	Injection: Each vial contains 20 mg of Sebelipase Alfa (Genetical Recombination).
[Proposed indication]	Lysosomal acid lipase deficiency
[Proposed dosage and administration]	The usual dosage is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once every other week as an intravenous infusion. The usual dosage in infants with progressive lysosomal acid lipase deficiency is 1 mg/kg administered once weekly as an intravenous infusion.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Kanuma Intravenous Infusion 20 mg is a concentrated solution for injection containing Sebelipase Alfa (Genetical Recombination) (hereinafter referred to as "sebelipase alfa") as the active substance. Sebelipase alfa was developed by Synageva BioPharma Corp. (the US) which is a predecessor of Alexion Pharmaceuticals, Inc.

Lysosomal acid lipase deficiency (LAL deficiency) is an autosomal recessive disorder caused by mutations in the gene encoding lysosomal acid lipase (a lysosomal enzyme), which result in accumulation of cholesteryl esters and triglycerides in the lysosomes of various tissues and cells throughout the body. LAL deficiency is a progressive multisystem disease. Infantile-onset, rapidly progressive LAL deficiency is historically called Wolman disease. The complications of Wolman disease include failure to thrive with progressive liver dysfunction and rapid development of liver fibrosis, and Wolman disease is usually fatal within the first 6

months of life.[1] Most of patients with late-onset LAL deficiency (cholesteryl ester storage disease [CESD]) are also diagnosed with LAL deficiency before the age of 20, complicated by marked hepatomegaly, elevation of transaminases signalling chronic liver dysfunction, increased hepatic tissue levels of cholesteryl esters, liver disease such as liver fibrosis and cirrhosis manifesting early in life, or marked disturbances of lipid metabolism leading to dyslipidaemia, but the age of diagnosis and the rate of disease progression are highly variable.[2]

The estimated incidence of infantile-onset, rapidly progressive LAL deficiency (Wolman disease) is approximately 1.89 per million.[3] The prevalence of CESD among German newborns is estimated at 25 per million[4] and the predicted prevalence of CESD in the Caucasian and Hispanic populations is 7.7 per million.[5]

The accurate prevalence estimates of LAL deficiency are not available in Japan. The first case of infantile-onset, rapidly progressive LAL deficiency (Wolman disease) was reported in 1966,[6] and the patient's death was confirmed. According to the national survey conducted in 2001 by the Research Committee for Lysosomal Storage Disease (including Fabry's disease) of the Rare/Intractable Disease Research Project supported by the Ministry of Health, Labour and Welfare, the number of patients with Wolman disease was 0.[7] A survey on late-onset LAL deficiency (CESD) has not been conducted. A review of the literature, etc. published between 1989 and 2014 revealed 17 case reports of LAL deficiency. Based on the above, sebelipase alfa was designated as an orphan drug with the intended indication of "lysosomal acid lipase deficiency" (Drug Designation No. 281 of 2015 [*24 yaku*]).

In Japan, there are no effective drug therapies approved for patients with LAL deficiency, and supportive therapies have been used to lower serum cholesterol levels or to mitigate gastrointestinal symptoms such as diarrhoea.

Sebelipase alfa is a glycoprotein with N-linked glycosylation sites, which has an amino acid sequence identical to that of human lysosomal acid lipase. This glycoprotein contains high-mannose-type and phosphorylated high-mannose-type glycans. Sebelipase alfa is taken up by target cells via macrophage mannose receptors or mannose-6-phosphate receptors in various tissues to reduce accumulated cholesteryl esters and triglycerides in tissues and cells throughout the body.

Claiming that a multiregional phase III study (Study LAL-CL02) and other studies have demonstrated the efficacy and safety of the product in patients with LAL deficiency, the applicant has filed a marketing application for the product.

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[1] Grabowski GA, *et al*. Lysosomal acid lipase deficiencies: the Wolman disease/cholesteryl ester storage disease spectrum. In Scriver Valle D, *et al*. eds. *The Online Metabolic & Molecular Basis of Inherited Diseases*.2012, 8th ed. McGraw-Hill, New York.
[2] Bernstein DL, *et al*. *J Hepatol*. 2013; 58: 1230-43.
[3] Meikle PJ, *et al*. *JAMA*. 1999; 281: 249-54.
[4] Muntoni S, *et al*. *Arterioscler Thromb Vasc Biol*. 2007; 27: 1866-8.
[5] Scott SA, *et al*. *Hepatology*. 2013; 58: 958-65.
[6] Konno T, *et al*. *Tohoku J Exp Med*. 1966; 90: 375-89.
[7] Research Committee for Lysosomal Storage Disease (including Fabry's disease) of the Rare/Intractable Disease Research Project as one of research projects supported by MHLW

The product was approved in August 2015 in the EU and in December 2015 in the US. As of December 2015, the product has been approved in at least 30 countries worldwide.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Transgenic (Tg) chickens lay eggs that include a recombinant human lysosomal acid lipase (rhLAL) in the egg white. The sebelipase alfa drug substance is purified from these egg whites.

2.A.(1).1) Creation and control of Tg chickens

(a) Creation of Tg chickens

Based on the gene sequence for human lysosomal acid lipase (hLAL), DNA fragment [redacted] was [redacted]. The expression construct containing this DNA fragment within [redacted] with [redacted] was generated. The expression construct, the expression vector with [redacted] and [redacted], and the expression vector with [redacted] were transfected into [redacted] to generate a replication-defective recombinant retroviral vector for gene transfer into chicken early embryos. This viral vector was injected in [redacted] for [redacted], and generation zero (G0) Tg chickens were obtained. [redacted] Tg rooster carrying the transgene in semen as determined by genetic screening was chosen as the G0 founder.

The G0 founder was mated with [redacted] hen to generate G1 Tg hens (G1 hens), and [redacted] in their eggs was confirmed. Genetic analysis ([redacted]) of [redacted] was performed. As a result, integration of a single copy of the target gene into [redacted] was confirmed for all the analyzed chickens (G1 hemizygous chickens).

(b) Establishment and maintenance of production line

[redacted] to generate G2 [redacted], and the egg whites of eggs collected from Tg hens of G2 and subsequent generations (the production line) are used for the production of sebelipase alfa. Interbreeding between [redacted] homozygous and hemizygous animals or between homozygous animals is performed for [redacted] Tg chickens of [redacted] and subsequent generations which serve as the production line. In this way, a line of [redacted] Tg chickens that all carry the transgene is maintained.

The genetic stability of the transgene in [redacted] Tg chickens that constitute the production line up to [redacted] generation has been demonstrated by [redacted] ([redacted]), [redacted]

[redacted] ([redacted]), hLAL sequence ([redacted]), or rhLAL enzyme activity.

[redacted]

(c) Preservation of Tg chicken lineage

A line of Tg chickens is maintained by [redacted], and semen from Tg sires is stored in the vapor phase of liquid nitrogen regularly.

2.A.(1).2) Manufacturing process

The manufacturing process for the drug substance consists of [redacted], [redacted], [redacted] ("[redacted]"), [redacted], [redacted] ("[redacted]"), nanofiltration, [redacted], [redacted] ("[redacted]"), [redacted]/[redacted], and [redacted]. The obtained drug substance is filled in [redacted] and stored at 2°C to 8°C, protected from light.

A quality risk management approach was employed for the development of the manufacturing process. After the critical quality attributes (CQAs) listed below were identified, process characterization was performed, critical process parameters were identified, and the range for each critical process parameter was determined. Then a quality control strategy was developed.

- Identified CQAs of the drug substance and the drug product: appearance, pH, [redacted], [redacted], [redacted], [redacted], [redacted], aggregates, [redacted], egg white proteins ([redacted], [redacted], [redacted], and [redacted]), host-derived DNA, Impurity A, [redacted], [redacted], viral safety, bioburden, endotoxin, and mycoplasma

All process steps other than [redacted] have been defined as critical steps. [redacted] ("[redacted]") has been defined as a critical intermediate.

Validation of the commercial-scale manufacturing process for the drug substance has been performed.

2.A.(1).3) Adventitious agents safety evaluation

Raw materials of biological origin which are used in the manufacture of the drug substance are eggs collected from Tg chickens and human serum albumin added as an excipient during preparation of the drug substance. Both materials conform to the Standard for Biological Ingredients. The control of human serum albumin is equivalent to that of [redacted] approved for marketing in Japan.

Serological testing (*Salmonella Gallinarum, Salmonella Pullorum, Mycoplasma gallisepticum, Mycoplasma synoviae*, avian influenza A virus, and avian leukemia virus A, B, C, D, and J) of Tg hens and roosters used for production and lineage maintenance produced negative results. The egg white was tested for bioburden and endotoxin, tested *in vitro*[8] and *in vivo*[9] for viruses, tested by transmission electron microscopy, and tested via PCR for vertically transmissible viruses.[10] The clarified egg white was tested for bioburden, endotoxin, and mycoplasma and tested *in vitro* for viruses[8] and via PCR.[11] All test results were below limits or negative.

For monitoring of Tg chickens to be used for future production for infectious agents, the same serological tests as the above are performed in some Tg hens [redacted] times a month. As in-process controls, the egg white is tested for bioburden and endotoxin and tested by PCR for vertically transmissible viruses,[10] and the clarified egg white is tested for bioburden, endotoxin, and mycoplasma and tested *in vitro* for viruses[8] and by PCR.[11] Tg chickens are housed in a closed facility and controlled to prevent contamination with adventitious infectious agents by, for example, requiring [redacted].

Viral clearance studies of the purification process were performed with model viruses, and a certain robustness of the purification process was demonstrated (Table 1).

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})				
	Porcine parvovirus	Reovirus type 3	Encephalomyocarditis virus	Human influenza A virus	Xenotropic murine leukemia virus
[redacted]	[redacted]	[redacted] a)	[redacted] b)	[redacted] a)	[redacted] b)
Viral Inactivation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] a)	[redacted] a)
Nanofiltration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] a)	[redacted] a)	[redacted] a)	[redacted] a)	[redacted]
[redacted]	[redacted] b)	[redacted] b)	[redacted]	[redacted] b)	[redacted]
Overall reduction factor	≥8.40	≥7.54	≥9.84	≥14.37	≥13.66

a) Not used for calculation of overall reduction factor.
b) As [redacted] and [redacted] have the same separation mechanism, the higher value was used.

[8] Indicator cells: African green monkey kidney cells (Vero cells), human fibroblast cells (MRC-5 cells), and chicken embryo fibroblast cells (CEF cells)
[9] Chicken fetus
[10] Avian adenovirus group I, avian encephalomyelitis virus, avian orthoreovirus, avian reticuloendotheliosis virus, and chicken anemia virus
[11] West Nile virus and influenza A virus

2.A.(1).4) Manufacturing process development (Comparability)

Major changes made to the drug substance manufacturing process during development are shown below (Processes A, B, C, and D [the proposed commercial process]). The drug products produced from the drug substances manufactured by Process A, Process B, and Process C were used in clinical studies.

- Process A → Process B: Manufacturing site and scale changes, addition of [redacted], [redacted], and [redacted] in the chromatography steps, changes to [redacted] and [redacted], etc.
- Process B → Process C: Manufacturing site and scale changes, etc.
- Process C → Process D: Manufacturing scale change, changes to the setting of [redacted], etc.

When changes were made to the manufacturing process, comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug substances.

2.A.(1).5) Characterization

(a) Structure

- The primary structure of the drug substance was elucidated by amino acid compositional analysis, [redacted], liquid chromatography-tandem mass spectrometry (LC-MS/MS), peptide mapping, and N-terminal sequencing by Edman degradation.
- The higher-order structure was determined by [redacted], sedimentation velocity analytical ultracentrifugation, far-ultraviolet and near-ultraviolet circular dichroism (CD) spectra, differential scanning calorimetry (DSC), dynamic light scattering (DLS), and crystal structure analysis.
- The glycosylation sites and glycan structures were determined by monosaccharide compositional analysis, [redacted], capillary electrophoresis following [redacted] (“[redacted]”) treatment/[redacted] ([redacted]), [redacted]/[redacted] (“[redacted]”), [redacted] ([redacted])/[redacted], and [redacted] and [redacted]/[redacted] ([redacted]).

(b) Physicochemical properties

- The molecular weight was determined by [redacted].
- Size variants, charge variants, etc. were identified by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Coomassie staining and silver staining) (non-reduced and reduced) and Western blot (non-reduced and reduced), [redacted] (“[redacted]”), [redacted] (“[redacted]”), and [redacted] (“[redacted]”).
- The extinction coefficient was determined.

(c) Biological properties

- Michaelis constant (K_m) and catalytic rate constant (k_{cat}) were determined by measuring enzymatic activity using [redacted] as the substrate. Enzymatic activity was determined using [redacted] as the substrate.
- The ability of sebelipase alfa to bind to the [redacted] receptor and the mannose receptor was confirmed by [redacted].
- After incubation of [redacted] with sebelipase alfa, dose-dependent increases in LAL activity were observed. The cellular uptake of sebelipase alfa was competitively inhibited by addition of [redacted].
- The uptake of sebelipase alfa into rat alveolar macrophage cells (NR8383)[12] was inhibited by mannan in a concentration-dependent manner.
- [redacted] sebelipase alfa was localized to the lysosome in rat alveolar macrophage cells (NR8383).

(d) Product-related substances/product-related impurities

Based on the results of analyses presented in the above (a) to (c), low molecular weight species, aggregates, and denatured forms were considered product-related impurities. Product-related impurities are controlled by [redacted] specification (SDS-PAGE [redacted] [redacted], [redacted]) and the drug product specification (Western blot [redacted] and [redacted]). No product-related substances exist.

(e) Process-related impurities

Egg white proteins ([redacted], [redacted], [redacted], and [redacted]), host-derived DNA, and Impurity A were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed in the manufacturing process. Egg white proteins and Impurity A are controlled by the drug substance specification.

2.A.(1).6) Control of drug substance

The proposed specifications for the drug substance consist of concentration (sebelipase alfa and human serum albumin), appearance, identification (Western blot [redacted] and [redacted], peptide mapping [redacted], and [redacted] [redacted]), glycan analysis ([redacted] [redacted], [redacted] [redacted], and [redacted] [redacted]), pH, isoelectric point ([redacted]), molecular weight (SDS-PAGE [redacted] [redacted] and [redacted]), purity (Western blot [redacted] and [redacted], SDS-PAGE [redacted] [redacted] and [redacted], [redacted], [redacted], and Impurity A [redacted]), egg white proteins ([redacted], [redacted], [redacted], and [redacted] [redacted]), endotoxin, microbial limits, specific activity ([redacted]), and assay ([redacted]). Purity (Western blot [redacted] and [redacted]) was included in the specification in the course of regulatory review.

[12] Lane KB, *et al. J Leukoc Biol.* 1998; 64: 345-50.

In consideration of the influence of [redacted] added in the drug substance, tests other than appearance, identification (Western blot [redacted] and [redacted]), pH, purity (Western blot [redacted] and [redacted], [redacted], and Impurity A), microbial limits, specific activity, and assay are performed on [redacted].

2.A.(1).7) Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2.

Table 2. Overview of primary stability studies on drug substance

	Manufacturing process	No. of batches	Storage conditions	Testing period	Storage package
Long-term testing	C	3 batches	5 ± 3°C	24 months[a)]	[redacted]
	D			12 months[b)]	
Accelerated testing	C		25 ± 2°C/ 60 ± 5%RH	6 months	
	D				

a) Two batches were tested for 18 months. The stability study is ongoing and will be continued for up to 24 months.
b) The stability study is ongoing and will be continued for up to 24 months.

There were no significant changes observed under the long-term storage condition throughout the study period.

Decreases in [redacted] by [redacted] ([redacted] and [redacted]) and [redacted] were observed under the accelerated condition.

Photostability testing showed that the drug substance is photosensitive.

Based on the above, a shelf life of 12 months has been proposed for the drug substance when stored in [redacted] at 2°C to 8°C, protected from light. The long-term testing will be continued for 24 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a concentrated solution for injection containing 20 mg of sebelipase alfa in a 10 mL vial. It contains trisodium citrate dihydrate, citric acid monohydrate, human serum albumin, and water for injection as excipients. The primary container is a glass vial with [redacted], and the secondary container is a carton.

2.A.(2).2) Manufacturing process

The manufacturing process for the drug product consists of [redacted], sterile filtration, aseptic filling and capping, [redacted], and packaging/labeling/storage/testing. All process steps other than packaging/labeling/storage/testing have been defined as critical steps.

Validation of the commercial-scale manufacturing process for the drug product has been performed.

2.A.(2).3) Manufacturing process development (Comparability)

Manufacturing site and scale changes occurred during the drug product development. Comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug products.

2.A.(2).4) Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (Western blot [and]), pH, purity (Western blot [and],), pyrogen, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, specific activity (enzyme activity assay), and assay ( ). Pyrogen test and foreign insoluble matter test were included in the specification in the course of regulatory review [see "2.B.(3) Pyrogen test"].

2.A.(2).5) Stability of drug product

The primary stability studies on the drug product are shown in Table 3.

Table 3. Overview of primary stability studies on drug product

	Drug substance manufacturing process	No. of batches	Storage conditions	Testing period	Storage package
Long-term testing	B	5	5 ± 3°C	24 months[a)]	Glass vial with
	C	2		18 months[b)]	
	D	1		12 months[c)]	
Accelerated testing	B	5	25 ± 2°C/ 60 ± 5%RH	6 months	
	C	2			
	D	1			

a) Two batches were tested for 12 months. The stability study is ongoing and will be continued for up to 36 months.
b) One batch was tested for 12 months. The stability study is ongoing and will be continued for up to 36 months.
c) The stability study is ongoing and will be continued for up to 36 months.

There were no significant changes in quality attributes under the long-term storage condition throughout the study period.

Decreases in by (and) and were observed at the accelerated condition.

In-use stability study results demonstrated that the drug product is stable for 24 hours after dilution with saline when stored in an infusion bag and a syringe at 2°C to 8°C.

Based on the above results and the results of photostability testing of the drug substance, a shelf life of 24 months has been proposed for the drug product when stored in a glass vial at 2°C to 8°C (avoid freezing), protected from light.

2.A.(3) Reference materials

A reference material is prepared from and stored at ≤ °C. The stability of the reference material has been demonstrated for up to 24 months, and stability is tested every months during storage. The proposed

specifications for the in-house primary reference material and the in-house working reference material consist of strength, identification ([redacted], [redacted], Western blot [[redacted] and [redacted]]), molecular weight (SDS-PAGE [[redacted]] [[redacted] and [redacted]]), pH, purity (Western blot [[redacted] and [redacted]], SDS-PAGE [[redacted] and [redacted]] [[redacted] and [redacted]], [redacted] and [redacted]), egg white proteins, host-derived DNA, charge variant analysis ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), specific activity ([redacted]), assay ([redacted]) [redacted] ([redacted]), [redacted], [redacted], and ultracentrifugal analysis by [redacted].

2.B Outline of the review by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.B.(1) Control of adventitious infectious agents in Tg chickens

The applicant's explanation on the control of adventitious infectious agents in Tg chickens:
Chickens that lay eggs to be used for the production of sebelipase alfa have been demonstrated to be derived from a flock of Tg chickens free of specified infectious agents.

For agents which have been confirmed to infect chickens in the US among vertically transmissible agents listed in both Chapter 5.2.2 of the European Pharmacopoeia and VSM 800.65 issued by the US Department of Agriculture, serological, PCR, and *in vitro* tests and other tests are conducted on Tg chickens, [redacted], and [redacted]. Tg chickens are housed in a closed facility and controlled to prevent contamination with adventitious infectious agents by, for example, requiring [redacted], and periodic environmental monitoring is also conducted. No Tg chickens have so far been vaccinated to prevent infections. The effects of vaccination are currently being evaluated and whether vaccination is necessary will be determined in future.

Although [redacted] assessment, [redacted] assessment, and [redacted] assessment performed to date revealed infection with Marek's disease virus (MDV) serotype 2 in some Tg hens, there should be no safety concern about the finished product for the following reasons: (1) MDV serotype 2 is not pathogenic for chickens; (2) since MDV serotype 2 is not vertically transmissible, the virus is not shed into egg whites; (3) even if the virus is shed into egg whites, the virus is inactivated and removed in the purification process; and (4) the virus is not infectious or pathogenic for humans. In future, the use of MDV vaccines will be considered to be appropriate, in order to ensure production consistency.

Among vertically transmissible agents listed in both Chapter 5.2.2 of the European Pharmacopoeia and VSM 800.65 issued by the US Department of Agriculture, Newcastle disease virus, a human pathogen, is detectable by *in vitro* virus testing of [redacted], because (1) the risk is low in the US and (2) the virus is known to infect [redacted] and [redacted] efficiently, though the sensitivity of the test has not formally been assessed. In future, the applicant will undertake the development of a viral PCR test used in [redacted] for enhanced control of Newcastle disease virus.

PMDA concluded that the control of adventitious infectious agents in Tg chickens and eggs is acceptable at present, taking account of the following points: (1) In addition to the control of adventitious infectious agents in Tg chickens for egg production and in the drug substance manufacturing process, the drug substance purification process has a certain level of capacity to clear viruses and even if a virus is present, the virus will be inactivated/removed; and (2) PCR testing, vaccination, and other measures for enhanced control of adventitious infectious agents will continue to be considered.

2.B.(2) Cellular uptake activity

Cellular uptake activity was not included in the drug substance or drug product specification at the time of filing. PMDA instructed the applicant to take measures to control cellular uptake activity which is a critical quality attribute, considering the mechanism of action by which sebelipase alfa is taken up by cells to exert its therapeutic effect.

The applicant's response:

An assay for cellular uptake will be included in [redacted] and currently [redacted]. Also in Japan, cellular uptake activity will be controlled initially by including an assay for cellular uptake in the specification as [redacted]. Then an assay for cellular uptake will be included in [redacted] specification as soon as possible.

Taking into account the facts that [redacted] is known to affect cellular uptake and that [redacted] is currently controlled by [redacted] in the drug substance specification, PMDA accepted the applicant's response.

2.B.(3) Pyrogen test

The applicant's explanation:

Endotoxin testing was included in the drug product specification at the time of filing. However, an investigation of [redacted] showed [redacted] considered attributable to [redacted], and a more suitable [redacted] test method is currently under development. Until the new test method will be established, a test method developed in accordance with pyrogen test (the Japanese Pharmacopoeia [JP]) will be included in the drug product specification instead of endotoxin testing.

PMDA accepted the change of the test method.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

Primary pharmacodynamic studies conducted were *in vitro* studies and *in vivo* studies using rats lacking the gene encoding lysosomal acid lipase (LAL) (LAL-deficient rats). The effects of sebelipase alfa on the respiratory and cardiovascular systems were assessed in safety pharmacology studies, and the effects of sebelipase alfa on the central nervous system were assessed in a rat 4-week intravenous infusion toxicity study. No secondary pharmacodynamic or pharmacodynamic drug interaction studies have been conducted.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

(a) Studies in rat macrophage cells (4.2.1.1.1)

Sebelipase Alfa (Genetical Recombination) (hereinafter referred to as "sebelipase alfa") was fluorescently-labeled. Using fluorescently-labeled sebelipase alfa and a lysosomal marker, sebelipase alfa localization into lysosomes was examined by confocal fluorescence microscopy. Sebelipase alfa (5 μg/mL) and the lysosomal marker were incubated with macrophage mannose receptor-expressing rat alveolar macrophage cells (NR8383)[12] for 2 hours. The co-localization of sebelipase alfa and lysosomal marker staining indicated the uptake of sebelipase alfa by cells and subsequent transportation to lysosomes.

Fluorescently-labeled sebelipase alfa (5 μg/mL) and mannan (0-10 mg/mL), a mannose-containing oligosaccharide, were incubated with rat alveolar macrophage cells for 2 hours and the cellular uptake was determined by flow cytometry. Mannan was shown to inhibit the cellular uptake of sebelipase alfa in a concentration-dependent manner, indicating the cellular uptake of sebelipase alfa via the macrophage mannose receptor.

(b) Study in human fibroblast cells (4.2.1.1.1)

Normal human fibroblasts expressing the mannose-6-phosphate receptor and fibroblasts isolated from a patient with LAL deficiency were incubated with or without sebelipase alfa (0.16, 0.5, 1.6, 5 μg/mL) for 4 hours, and the resultant cell lysates were assayed for LAL activity (the amount of active enzyme (nU) per cell).[13] LAL activity in sebelipase alfa-untreated LAL-deficient human fibroblasts was 0.19 nU/cell, which was lower than that in normal human fibroblasts (4.39 nU/cell). Sebelipase alfa increased LAL activity in a concentration-dependent manner in LAL-deficient human fibroblasts (0.76, 2.10, 3.55, and 5.48 nU/cell at 0.16, 0.5, 1.6, and 5 μg/mL of sebelipase alfa, respectively).

[13] One unit was defined as the amount of enzyme activity that catalyzes the hydrolysis of 1 μmol of the substrate 4-methylumbelliferyl oleate (4-MUO) per minute at 37°C.

3.(i).A.(1).2) *In vivo* studies

As an animal model of LAL deficiency, rats homozygous for a deletion at the 3' end of the LIPA gene encoding LAL were used.[14] The heterozygous rats do not display an LAL deficiency phenotype.

(a) Phenotypic characteristics of LAL-deficient rats (4.2.1.1.2 to 4.2.1.1.4)

The survival profiles of LAL-deficient rats (n = 10/sex) and wild-type rats[15] (n = 10/sex) were determined from 14 to 200 days of age. Ten of 20 LAL-deficient rats survived to 12 weeks of age and all 20 died by 14 weeks of age, whereas wild-type rats all survived to at least 200 days of age.

Clinical observations, etc. of LAL-deficient rats (n = 2/sex) and wild-type rats (n = 2/sex) were performed from 28 to 91 days of age. One of the 4 LAL-deficient rats (female) died at 87 days of age before necropsy. LAL-deficient rats exhibited several symptoms such as coarse fur, skin pallor, abnormal gait, and progressive abdominal swelling accompanied by decreased activity, resulting in moribundity at approximately 91 days of age. Observed changes in serum clinical chemistry parameters were elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, triglyceride, and low-density lipoprotein cholesterol (LDL-C) and a reduction in high-density lipoprotein cholesterol (HDL-C).

The body weights, organ weights, and histopathology of LAL-deficient rats (17 males, 20 females) and wild-type rats (41 males, 38 females) were evaluated from 3 to 12 weeks of age. The body weights of the wild-type rats continued to increase throughout the observation period, whereas the LAL-deficient rats were at their maximum weight at 7 weeks of age. By 12 weeks of age, the body weights of the wild-type rats were 2.76 to 3.04 times those of the LAL-deficient rats. Some of the animals were necropsied at 4, 8, or 10 weeks of age. Examination of organ weights (a percentage of total body weight) revealed increased weights of all tissues (liver, spleen, mesenteric lymph node, duodenum, jejunum, and ileum) in the LAL-deficient rats relative to the wild-type rats by 4 weeks of age. The increases in organ weights became more prominent at 8 and 10 weeks of age. Likewise, histopathological findings at 4 and 8 weeks of age included hepatomegaly with a distinct yellowish-orange color, splenomegaly, enlargement of the mesenteric and gastric lymph nodes, thickening of the small intestinal walls, and multifocal collections of foamy macrophages/Kupffer cells in the liver and foamy macrophages in the spleen. These findings were more severe at 8 weeks of age than at 4 weeks of age. Foamy histiocytes, vacuolation of hepatocytes, and cholesterol crystals in some histiocytes were noted.

(b) Effects on body weight, organ weight, tissue cholesterol and triglyceride, etc. (4.2.1.1.2, 4.2.1.1.5)

LAL-deficient rats (n = 3/group[16]) at 4 weeks of age were injected intraperitoneally with diphenhydramine[17] 5 mg/kg and then vehicle[18] or sebelipase alfa 5 mg/kg was administered by bolus intravenous injection once weekly for 4 weeks. Age-matched wild-type rats (n = 6) were used as controls. The results showed that LAL-deficient rats treated with sebelipase alfa exhibited a significant increase in body weight compared with

[14] Yoshida H, *et al. Lab Anim Sci.* 1990;40: 486-9.
[15] Age-matched, non-LAL-deficient animals
[16] 1 male and 2 females in the sebelipase alfa group, 3 females in the vehicle control group
[17] Rats were pretreated with diphenhydramine to alleviate immediate hypersensitivity-like reactions (e.g., hyperemia, pruritus, edema of limbs) to a glycoprotein.
[18] Saline

vehicle-treated LAL-deficient rats at ≥39 days of age. The body weights of LAL-deficient rats at 8 weeks of age were 170.8 ± 8.9 g in the sebelipase alfa group and 94.8 ± 7.4 g in the vehicle control group. The body weight of wild-type rats at 8 weeks of age was 208.8 ± 32.0 g. LAL-deficient rats treated with sebelipase alfa demonstrated a significant reduction in organ weight (a percentage of total body weight) in all tissues (liver, spleen, mesenteric lymph node, duodenum, jejunum, and ileum), compared with vehicle-treated LAL-deficient rats. The total cholesterol, cholesteryl ester, and triglyceride contents in the liver were significantly reduced in LAL-deficient rats treated with sebelipase alfa compared with vehicle-treated LAL-deficient rats. The liver color turned normal in LAL-deficient rats treated with sebelipase alfa.

LAL-deficient rats (n = 3/sex/group) at 8 weeks of age were injected intraperitoneally with diphenhydramine 5 mg/kg and then vehicle[18] or sebelipase alfa 3 mg/kg was administered by bolus intravenous injection once weekly for 19 weeks. LAL-deficient rats treated with sebelipase alfa survived to the last time point (27 weeks of age), whereas vehicle-treated LAL-deficient rats all became moribund at 9 to 12 weeks of age.[19] Body weight increased in the sebelipase alfa group compared with the vehicle control group. At the time of necropsy (at 9-12 weeks of age for the vehicle control group, at 27 weeks of age for the sebelipase alfa group), a reduction in organ weight (a percentage of total body weight) was noted in all tissues (liver, spleen, mesenteric lymph node, duodenum, jejunum, ileum, and brain) in the sebelipase alfa group compared with the vehicle control group, and there was a marked reduction in liver weight. The total cholesterol, free cholesterol, and cholesteryl ester contents in the liver and jejunum and the triglyceride content in the liver tended to be reduced in the sebelipase alfa group compared with the vehicle control group. While serum AST and serum LDL-C levels tended to be reduced in the sebelipase alfa group compared with the vehicle control group, serum HDL-C levels tended to be increased. Histopathological findings in the vehicle control group included vacuolar degeneration of hepatocytes and macrophages and marked hepatocyte necrosis, and findings in the sebelipase alfa group were small foci of necrotic macrophages and hepatocytes surrounded by inflammatory cells in the liver. Improvements were observed with sebelipase alfa compared with the vehicle control. Although all animals treated with sebelipase alfa were positive for anti-sebelipase alfa antibodies at the end of the study, no such antibodies were detected in any of the vehicle-treated animals.

(c) Dose response (4.2.1.1.2)

LAL-deficient rats (n = 2-11/group[20]) at 4 weeks of age were injected intraperitoneally with diphenhydramine 5 mg/kg and then vehicle[18] or sebelipase alfa was administered by bolus intravenous injection at dosages of 0.35, 1, and 5 mg/kg once weekly (qw), or 0.2, 1, 3, and 5 mg/kg once every other week (qow) for 4 weeks. Age-matched wild-type rats (15 males, 20 females) were used as controls. The result revealed a dose-dependent increase in body weight in LAL-deficient rats treated with sebelipase alfa. At 8 weeks of age, rats treated with sebelipase alfa at 5 mg/kg once weekly exhibited a 1.74-fold increase in body weight over the vehicle control animals. At 8 weeks of age, a dose-dependent reduction in organ weight (a percentage of total body weight)

[19] Samples from sebelipase alfa-treated animals at 27 weeks of age and those from vehicle control animals at the time of euthanasia (at 9 to 12 weeks of age) were used for analyses of tissues and serum.

[20] Vehicle control group (5 males, 6 females), sebelipase alfa 0.2 mg/kg qow group (3 males, 4 females), 0.35 mg/kg qw group (3 males, 2 females), 1 mg/kg qow group (4 males, 3 females), 1 mg/kg qw group (2 males, 3 females), 3 mg/kg qow group (4 males, 3 females), 5 mg/kg qow group (1 male, 1 female), 5 mg/kg qw group (2 males, 2 females)

was observed in all tissues (liver, spleen, mesenteric lymph node, duodenum, jejunum, ileum) in LAL-deficient rats treated with sebelipase alfa at a dose of 5 mg/kg qw, with the measured organ weights coming close to those of wild-type rats. The lipid (total cholesterol, cholesteryl ester, triglyceride) contents in the liver and spleen were increased markedly in vehicle-treated LAL-deficient rats compared with wild-type rats and reduced dose-dependently in LAL-deficient rats treated with sebelipase alfa. Serum ALT and AST levels were elevated in vehicle-treated LAL-deficient rats compared with wild-type rats. The serum AST levels in rats treated with sebelipase alfa 5 mg/kg qw or qow were reduced to similar levels measured in wild-type rats, whereas no such effects were observed clearly with lower doses of ≤3 mg/kg. No anti-sebelipase alfa antibodies were detected. The level of hepatic LAL activity was measured in LAL-deficient rats at 34 days of age (n = 1/time point) at 1, 24, and 72 hours following a single 5 mg/kg dose of sebelipase alfa. The level of hepatic LAL activity was also measured in an untreated LAL-deficient rat at 34 days of age (n = 1) and a wild-type rat (n = 1). At 72 hours post-dose, the hepatic LAL activity in the LAL-deficient rat was comparable to that measured in the wild-type rat.

(d) Re-accumulation of cholesterol and triglyceride in the liver following cessation of treatment (4.2.1.1.6)

LAL-deficient rats at 4 weeks of age (n = 3/sex/group/time point) were injected intraperitoneally with diphenhydramine 5 mg/kg and then sebelipase alfa 3 mg/kg was administered by bolus intravenous injection once weekly for 4 weeks. Necropsies were performed at different time points up to 20 weeks of age. All animals survived to the days of scheduled necropsies. Body weight increased until 4 weeks following cessation of treatment (11 weeks of age) and then decreased slowly. Organ weights (a percentage of total body weight) progressively increased in all tissues (liver, spleen, mesenteric lymph node, duodenum, jejunum, and ileum) beginning 3 weeks following cessation of treatment. The lipid (total cholesterol, free cholesterol, cholesteryl ester, triglyceride) content in the liver also increased beginning 3 weeks following cessation of treatment. Serum clinical chemistry parameters were evaluated. Serum ALT and AST levels were elevated beginning 3 weeks following cessation of treatment, serum triglyceride and LDL-C levels were increased beginning 5 weeks after cessation of treatment, serum cholesterol increased beginning 9 weeks following cessation of treatment, and serum HDL-C decreased beginning 3 weeks following cessation of treatment. Histopathological findings following cessation of treatment included accumulations of foamy macrophages and microvesicular hepatic lipidosis in the liver, showing progression of disease over time.

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Central nervous system (4.2.3.2.1)

Vehicle[21] (control group 1, control group 2) or sebelipase alfa (5, 20, 50 mg/kg) was administered by intravenous infusion once weekly for 4 weeks to rats (n = 10/sex/group). The animals in the control group 2 and the sebelipase alfa dose groups received intramuscular or subcutaneous injection of diphenhydramine 5 mg/kg before dosing of vehicle or sebelipase alfa. Findings included limited use of the right hind limb after dosing on Day 1 in the control group 2 and the sebelipase alfa dose groups, greater body temperature after dosing on Day 1 in the sebelipase alfa 5 mg/kg group, and greater mean nociceptive reflex after dosing on Day 1 in the 50 mg/kg group. The applicant explained that none of these changes were considered related to the administration of sebelipase alfa. There were no sebelipase alfa-related findings at Week 4.

The serum exposure to sebelipase alfa (maximum serum concentration [C_{max}]) at 50 mg/kg in rats was 93.7 μg/mL, which was approximately 129 times the human exposure (in patients with LAL deficiency) at the recommended clinical dose.[22]

3.(i).A.(2).2) Cardiovascular system (4.2.1.3.1)

Conscious male monkeys received a single intravenous infusion of vehicle[21] and sebelipase alfa 50 mg/kg in a crossover design, with a washout period of ≥6 days between doses. The animals received intramuscular injection of diphenhydramine 5 mg/kg before dosing of vehicle or sebelipase alfa. There were no effects on body temperature, heart rate, blood pressure (systolic blood pressure, diastolic blood pressure, mean blood pressure, pulse pressure), or ECG (PR interval, QT interval, QTc[23] interval, QRS duration) before dosing and at 0 to 19 hours after the start of infusion.

The serum exposure to sebelipase alfa (C_{max}) at 50 mg/kg in monkeys was 156 μg/mL,[24] which was approximately 215 times the human exposure (in patients with LAL deficiency) at the recommended clinical dose.[22]

3.(i).A.(2).3) Respiratory system (4.2.1.3.2)

Male rats (n = 8/group) received a single intravenous infusion of vehicle[21] (control group 1, control group 2) or sebelipase alfa (5, 20, 50 mg/kg). The control group 2 and the sebelipase alfa dose groups received intramuscular injection of diphenhydramine 5 mg/kg before dosing of vehicle or sebelipase alfa. Respiratory parameters (tidal volume, respiratory rate) measured by plethysmography were evaluated. No significant changes in tidal volume were observed in the sebelipase alfa dose groups compared with the control group 2 at any time point (the day before dosing, every 30 minutes from the start of infusion until 7 hours, 24 hours after the start of infusion). Although a trend toward higher respiration rates was observed in animals dosed at

[21] A solution prepared by diluting the same vehicle as that used in clinical studies (13.7 mg/mL of trisodium citrate dihydrate, 1.57 mg/mL of citric acid monohydrate, 10 mg/mL of human serum albumin) 1:1 with saline. The animals in the control and sebelipase alfa groups received the same dose of human serum albumin.

[22] Calculated based on the mean C_{max} of 724 ng/mL in patients receiving sebelipase alfa 1 mg/kg qow for 22 weeks in a phase III study (LAL-CL02).

[23] Bazett's correction formula

[24] C_{max} after the first dose in a 4-week repeat-dose toxicity study in monkeys (4.2.3.2.2)

20 or 50 mg/kg compared with the control group 2, no significant differences were found at any time point. Swelling of the feet and/or head was observed in all animals of the 50 mg/kg group.

The serum exposure to sebelipase alfa (C_{max}) at 50 mg/kg in rats was 93.7 μg/mL,[25] which was approximately 129 times the human exposure (in patients with LAL deficiency) at the recommended clinical dose. [22]

3.(i).B Outline of the review by PMDA

Mechanism of action of sebelipase alfa

PMDA asked the applicant to explain the mechanism of action of sebelipase alfa, taking account of the structure of sebelipase alfa, differences between sebelipase alfa and human LAL, and species differences between rat and human LAL.

The applicant's response:

LAL is a lysosomal enzyme that catalyzes the hydrolysis of cholesteryl esters, triglycerides, etc. LAL deficiency results in the absence or low levels of LAL enzyme activity, leading to accumulation of cholesteryl esters, triglycerides, etc. in macrophage-monocytic cells throughout the body, especially in hepatocytes and Kupffer cells.

Sebelipase alfa is an enzyme replacement therapy for absent or reduced LAL activity in patients with LAL deficiency. It is a recombinant human LAL consisting of 378 amino acids and its amino acid sequence is identical to that of human LAL.[26] Sebelipase alfa contains 6 N-linked glycosylation sites (Asn15, Asn51, Asn80, Asn140, Asn252, Asn300) and is modified with glycans containing N-acetylglucosamine, mannose, and mannose-6-phosphate, whereas the glycosylation profile of human LAL has not been determined. When the enzymatic activity of sebelipase alfa was measured using the natural substrate cholesteryl oleate, the Michaelis constant (K_m) of sebelipase alfa was 0.145 mM, which was almost comparable to the reported value of human LAL (0.142 mM[27]).

In vitro studies using rat macrophage cells and human fibroblast cells demonstrated that sebelipase alfa is taken up by cells via the macrophage mannose receptor and the mannose-6-phosphate receptor and subsequently transported to lysosomes and that sebelipase alfa causes an increase in LAL activity in LAL-deficient human fibroblast cells (4.2.1.1.1). LAL-deficient rats treated with sebelipase alfa demonstrated reductions in tissue content of cholesteryl ester and triglyceride in the liver and other organs, decrease in organomegaly, improvement of growth, normalization of serum lipid parameters, etc. (4.2.1.1.2, 4.2.1.1.5).

According to the published literature, the amino acid sequence of rat LAL (rats were used in primary pharmacodynamic studies) shows 79% homology with human LAL,[28] and as with human LAL, rat LAL is active at low pH.[29] While sebelipase alfa binds via terminal sugars of N-linked glycans to the receptors, the

[25] C_{max} after the first dose in a 4-week repeat-dose toxicity study in rats (4.2.3.2.1)
[26] Genbank Refseq, NM_000235.2 (Sebelipase alfa does not contain a leader sequence.)
[27] Ameis D, *et al. Eur J Biochem*. 1994; 219 : 905-14.
[28] Nakagawa, *et al. J Lipid Res*. 1995; 36 : 2212-8.
[29] Kuriyama M, *et al. J Lipid Res*. 1990; 31 : 1605-12, Sando GN, *et al. J Biol Chem*. 1985; 260: 15186-93, Ameis D, *et al. Eur J Biochem*. 1994; 219: 905-14.

glycosylation profiles of human and rat LAL have not been determined. The macrophage mannose receptor and the mannose-6-phosphate receptor contribute to the cellular uptake of LAL and the amino acid sequences of these receptors of the rat show 83% and 81% homology with the human receptors, respectively.[30]

As described above, sebelipase alfa is taken up by cells via the macrophage mannose receptor and the mannose-6-phosphate receptor and subsequently transported to lysosomes for restoration of LAL activity in the lysosomes, which results in LAL-catalyzed hydrolysis of accumulated substrates. Because of this mechanism, sebelipase alfa is expected to cause improvements in liver dysfunction, dyslipidemia, etc.

PMDA accepted the applicant's response.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics of sebelipase alfa were studied after a single dose in rats. Based on toxicokinetics assessed in rat, rabbit, and monkey repeat-dose toxicity studies, the repeat-dose pharmacokinetics of sebelipase alfa were evaluated. Serum concentrations of sebelipase alfa were determined by an enzyme-linked immunosorbent assay (ELISA) or an enzyme activity assay. The lower limit of quantitation of the enzyme activity assay in each study was 0.008 μg/mL (4.2.3.2.1) or 0.125 μg/mL (4.2.3.5.2.2) in rat serum, 0.0156 μg/mL (4.2.3.5.2.3) or 0.125 μg/mL (4.2.3.5.2.4) in rabbit serum, and 0.00156 μg/mL (4.2.3.2.3) or 0.008 μg/mL (4.2.3.2.2) in monkey serum.[31] The ELISA was used for the detection of anti-sebelipase alfa antibodies in serum, and the enzyme activity assay was used for the detection of neutralizing antibodies. The results from the main studies are described below.

3.(ii).A.(1) Absorption (4.2.1.1.2, 4.2.3.2.1 to 4.2.3.2.3, 4.2.3.5.2.2, 4.2.3.5.2.4)

Sebelipase alfa[32] 1 or 5 mg/kg was administered by single intravenous bolus injection to male rats (N = 1/group). The C_{max}, the area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration observed ($AUC_{0\text{-last}}$), and the elimination half-life ($t_{1/2}$) were 12.6 μg/mL, 1.7 μg·h/mL, and 6 minutes, respectively, for the 1 mg/kg dose and 68.1 μg/mL, 17.3 μg·h/mL, and 20 minutes, respectively, for the 5 mg/kg dose.

Table 4 shows the pharmacokinetic parameters in male and female rats and male and female monkeys following once-weekly administration of sebelipase alfa[33] by intravenous infusion in repeat-dose toxicity studies. All of the male and female rats assessed for antibodies (N = 3/sex) were positive for anti-sebelipase alfa and neutralizing antibodies. In a 4-week repeat-dose toxicity study in male and female monkeys, 2 of 10 monkeys in the 20 mg/kg group and 1 of 10 monkeys in the 50 mg/kg group were positive for anti-sebelipase alfa antibodies, but no monkey was found to be positive for neutralizing antibodies. In a 6-month repeat-dose

[30] Using the protein database of the National Center for Biotechnology Information (NCBI), the amino acid sequence homology was analyzed.
[31] The ELISA was used to determine serum concentrations in a single intravenous dose study in rats (4.2.1.1.2) only, and the lower limit of quantitation for the ELISA has not been established.
[32] Sebelipase alfa was prepared with saline prior to administration.
[33] Sebelipase alfa was prepared with the same vehicle as that used in clinical studies (13.7 mg/mL of trisodium citrate dihydrate, 1.57 mg/mL of citric acid monohydrate, 10 mg/mL of human serum albumin) and diluted 1:1 with saline prior to administration.

toxicity study in male and female monkeys, 9 of 10 monkeys in the 3 mg/kg group, 7 of 10 monkeys in the 10 mg/kg group, and 7 of 10 monkeys in the 30 mg/kg group were positive for anti-sebelipase alfa antibodies, and 4 of 10 monkeys in the 10 mg/kg group and 2 of 10 monkeys in the 30 mg/kg group were positive for neutralizing antibodies.

Table 4. Pharmacokinetic parameters following once-weekly administration of sebelipase alfa by intravenous infusion

Species (duration of dosing)	Dose (mg/kg)	Gender	Number of animals[a)]	C_{max} (μg/mL)		$AUC_{0\text{-last}}$ (μg·h/mL)		$t_{1/2}$ (min)	
				Day 1	Day 22 or Day 176[b)]	Day 1	Day 22 or Day 176[b)]	Day 1	Day 22 or Day 176[b)]
Rat (4 weeks)	5	M	3	0.880	0.997	4.04	3.28	—	—
		F	3	0.973	0.387	2.55	1.42	—	—
	20	M	3	9.47	16.1	42.2	63.3	—	—
		F	3	5.82	5.19	23.0	19.7	—	—
	50	M	3	127	106	413	450	—	—
		F	3	60.4	74.9	150	289	—	—
Monkey (4 weeks)	5	M	5	0.966 ± 0.216	1.16 ± 0.13	3.76 ± 0.50	4.86 ± 0.63	—	—
		F	5	0.978 ± 0.217	1.16 ± 0.20	3.90 ± 0.90	4.67 ± 1.15	—	—
	20	M	5	20.9 ± 4.6	24.5 ± 6.2	91.5 ± 29.9	84.7 ± 25.4	10.4[c)]	19.1[c)]
		F	5	16.0 ± 8.6	16.7 ± 8.9	65.1 ± 36.8	70.9 ± 41.6	11.2[c)]	—
	50	M	5	179 ± 65	120 ± 27	493 ± 138	443 ± 30	37.3 ± 5.70[d)]	26.8 ± 7.2[d)]
		F	5	133 ± 30	108 ± 26	443 ± 45	419 ± 46	35.3 ± 5.70[d)]	20.6, 22.0[e)]
Monkey (6 months)	3	M	5	1.43 ± 0.573	3.56 ± 1.93	3.37 ± 1.28	5.84 ± 3.22[d)]	—	19.6[c)]
		F	5	1.16 ± 0.209	3.62 ± 2.29	2.94 ± 0.697	6.36 ± 3.88	—	33.1[c)]
	10	M	5	17.6 ± 8.13[d)]	43.8 ± 7.63	41.2 ± 16.1[d)]	103 ± 19.4	15.3[c)]	61.8 ± 90.6
		F	5	17.7 ± 14.3	47.8 ± 15.8	40.4 ± 34.1	107 ± 40.6	11.4[c)]	23.2 ± 14.5
	30	M	5	216 ± 45.2	351 ± 80.7	597 ± 171	1086 ± 273	69.0 ± 68.4[d)]	39.5 ± 8.82
		F	5	207 ± 46.1	320 ± 114	598 ± 103	1040 ± 426	31.2 ± 7.56[d)]	40.6 ± 9.90

Mean, Mean ± SD, —: not determined

C_{max}: maximum serum concentration, $AUC_{0\text{-last}}$: area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration observed, $t_{1/2}$: elimination half-life

a) Rat (4 weeks), N = 3/sex/time point (N = 9/sex); Monkey (4 weeks, 6 months), N = 5/sex

b) Rat (4 weeks) and Monkey (4 weeks), Day 22; Monkey (6 months), Day 176

c) N = 1, d) N = 4, e) N = 2 (individual values)

Pregnant rats (N = 4/time point) were treated with sebelipase alfa[33] by intravenous infusion at 6, 20, and 60 mg/kg on gestation days 6, 9, 12, 15, and 17. The C_{max} and $AUC_{0\text{-last}}$ values on gestation day 17 were 0.560 μg/mL and 2.16 μg·h/mL, respectively, in the 6 mg/kg group, 2.85 μg/mL and 12.1 μg·h/mL, respectively, in the 20 mg/kg group, and 57.9 μg/mL and 227 μg·h/mL, respectively, in the 60 mg/kg group.

Pregnant rabbits (N = 4/group) were treated with sebelipase alfa[33] by intravenous infusion at 10, 25, and 50 mg/kg on gestation days 7, 10, 13, 16, and 19. The C_{max} values on gestation days 7 and 19 were 3.68 and 2.62 μg/mL, respectively, in the 10 mg/kg group,[34] 48.7 and 69.5 μg/mL,[35] respectively, in the 25 mg/kg group, and 147 and 132 μg/mL, respectively, in the 50 mg/kg group. The $AUC_{0\text{-last}}$ values on gestation days 7 and 19 were 12.2 and 12.2 μg·h/mL, respectively, in the 10 mg/kg group,[34] 250 and 379 μg·h/mL,[35] respectively, in the 25 mg/kg group, and 863 and 730 μg·h/mL, respectively, in the 50 mg/kg group.

3.(ii).A.(2) Distribution (4.2.1.1.2)

Following a single intravenous bolus dose of 5 mg/kg of sebelipase alfa[32] to LAL-deficient rats (N = 1/time point), the levels of hepatic LAL enzymatic activity were measured. The enzymatic activity levels at pre-dose

[34] N = 3
[35] N = 2

and 1, 24, and 72 hours post-dose were 0.43, 51.5, 7.79, and 2.70 mU/mg liver protein, respectively. At 72 hours post-dose, the enzymatic activity was comparable to that demonstrated in the wild-type rat (2.47 mU/mg liver protein).

3.(ii).A.(3) Metabolism

No metabolism studies have been performed.

3.(ii).A.(4) Excretion

No excretion studies have been performed.

3.(ii).B Outline of the review by PMDA

Non-linear pharmacokinetics of sebelipase alfa

The applicant's explanation:

Glycans containing N-acetylglucosamine, mannose, and mannose-6-phosphate are attached to the N-linked glycosylation sites on sebelipase alfa. Sebelipase alfa binds to the macrophage mannose receptor or the mannose-6-phosphate receptor and is subsequently internalized and localized to the lysosome (4.2.1.1.1). Once localized to the lysosome, as with other glycoproteins, sebelipase alfa is expected to be degraded through hydrolysis into smaller peptides and amino acids. Non-clinical studies showed that sebelipase alfa exposure tended to increase in a greater than dose-proportional manner (Table 4). Clinical studies (e.g., a phase I/II study in non-Japanese patients with LAL deficiency) also showed a similar trend and the pharmacokinetics of sebelipase alfa were non-linear. The non-linear pharmacokinetics of sebelipase alfa are considered attributable to the saturation of cellular uptake of sebelipase alfa via binding to the macrophage mannose receptor and the mannose-6-phosphate receptor at high doses. Such non-linear pharmacokinetics have been reported also for other enzyme replacement therapies for lysosomal storage diseases.[36]

PMDA accepted the applicant's explanation.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The results from single-dose, repeat-dose, and reproductive and developmental toxicity studies were submitted.[37] The results from non-GLP studies were submitted as the reference data.

3.(iii).A.(1) Single-dose toxicity

Single intravenous dose toxicity study in monkeys (4.2.3.1.1, reference data)

A single dose of 5 or 40 mg/kg of sebelipase alfa was administered as an intravenous infusion to male cynomolgus monkeys. The animals were injected intramuscularly with 5 mg/kg diphenhydramine 30 minutes

[36] Agalsidase beta: Keating GM & Simpson D. *Drugs*. 2007; 67: 435-55, Eng CM, *et al*. *Am J Hum Genet*. 2001; 68: 711-22.
Idursulfase, Elaprase (Idursulfase); FDA Clinical Pharmacology Review
Galsulfase, Naglazyme (Galsulfase); FDA Clinical Pharmacology Review

[37] In line with the ICH S6 (R1) guideline, no genotoxicity or carcinogenicity studies have been conducted.

prior to the infusion of sebelipase alfa. There were no deaths up to the highest dose tested (40 mg/kg) in this study.

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Rat 4-week intravenous infusion toxicity study (4.2.3.2.1)

Sebelipase alfa 0 (Control 1[21]), 0 (Control 2[21]), 5, 20, or 50 mg/kg was administered by intravenous infusion once weekly for 4 weeks to male and female SD rats. Animals in the sebelipase alfa 0 (Control 2), 5, 20, and 50 mg/kg groups were used for a recovery study consisting of a 4-week dosing period and a 2-week recovery period. The sebelipase alfa dose groups and the Control 2 group received intramuscular or subcutaneous injection of diphenhydramine 5 mg/kg before each dose.

On the day of dosing, swelling of the nose and swelling and redness of the paws occurred in a transient and dose-dependent manner in the sebelipase alfa dose groups. Albino rats have been shown to react to intraperitoneal or intravenous injection of polysaccharides and glycoproteins with a resulting acute inflammatory response characterized by an anaphylactoid type reaction (e.g., hyperemia, itching, edema of the extremities).[38] The findings observed following the administration of sebelipase alfa were similar to the published reports. No sebelipase alfa-related findings were noted at the end of the recovery period.

Based on the above, the no-observed-adverse-effect level (NOAEL) was determined to be 50 mg/kg.

3.(iii).A.(2).2) Monkey 4-week intravenous infusion toxicity study (4.2.3.2.2)

Sebelipase alfa 0 (control[21]), 5, 20, or 50 mg/kg was administered by intravenous infusion once weekly for 4 weeks to male and female cynomolgus monkeys. All animals received intramuscular injection of diphenhydramine 5 mg/kg before each dose. Groups of animals were used for a recovery study consisting of a 4-week dosing period and a 2-week recovery period.

At the end of the dosing period, vascular or perivascular inflammation was observed in some organs/tissues in the sebelipase alfa dose groups. At the end of the recovery period, vascular or perivascular inflammation was observed in all groups including the control group. The observed findings were infrequent, not dose-related, and also present in the control group. Therefore these changes were not due to an effect of sebelipase alfa and were considered associated with the administration of vehicle or human protein.

Based on the above, the NOAEL was determined to be 50 mg/kg.

3.(iii).A.(2).3) Monkey 6-month intravenous infusion toxicity study (4.2.3.2.3)

Sebelipase alfa 0 (control[21]), 3, 10, or 30 mg/kg was administered by intravenous infusion once weekly for 6 months to male and female cynomolgus monkeys. Groups of animals were used for a recovery study consisting

[38] Parratt JR, *et al. Br J Pharmacol Chemother*. 1958; 13: 65-70, Harris JM, *et al. Br J Pharmacol Chemother*. 1967; 29: 16-24, Ankier SI, *et al. Br J Pharmacol Chemother*. 1968; 33: 304-11, West GB. *Agents Actions*. 1981; 11: 75-6, Moodley I, *et al. Eur J Pharmacol*. 1982; 83: 69-81.

of a 6-month dosing period and a 2-week recovery period. Animals were not routinely pretreated with diphenhydramine except for 1 animal described below.

Sebelipase alfa-related findings were infusion-associated reactions (decreased activity, reddened face, frothing of the mouth) occurring in 1 of 5 males dosed with 10 mg/kg sebelipase alfa on dosing day 1 only. The animal was given intramuscular injection of diphenhydramine 5 mg/kg prior to subsequent doses of sebelipase alfa, and no new infusion-associated reactions were observed. Scattered multifocal myocardial degeneration and fibrosis of minimal severity were observed in 1 of 5 females dosed with 30 mg/kg sebelipase alfa. Since the incidence of this finding was within the range of the reported[39] incidences of spontaneous myocardial degeneration/necrosis and fibrosis, the finding was considered incidental. No sebelipase alfa-related findings were seen at the end of the recovery period.

Based on the above, the NOAEL was determined to be 30 mg/kg. The serum exposure to sebelipase alfa at the NOAEL on Day 176 ($AUC_{0\text{-last}}$) was 1086 μg·h/mL in males and 1040 μg·h/mL in females, which were approximately 783 and 750 times the human exposure at the recommended clinical dose, respectively.[40]

3.(iii).A.(3) Reproductive and developmental toxicity

3.(iii).A.(3).1) Rat study of fertility and early embryonic development to implantation

(a) Study in male rats (4.2.3.5.1.1)

Male SD rats were treated with sebelipase alfa at 0 (control[21]), 6, 20, and 60 mg/kg by intravenous infusion, twice weekly during the period beginning 28 days before cohabitation and ending on the day of necropsy (at Week 9), including the cohabitation period. Treated males were cohabited with naïve females. Males were necropsied at Week 9 and mated naïve females were necropsied on gestation day 13.

Clinical signs indicative of a hypersensitivity reaction (excessive scratching, swelling of the cranium or muzzle, etc.) were observed in a dose-dependent manner in all groups including the control group. Since a severe hypersensitivity reaction (hunched posture, respiratory distress, etc.) was observed during the 4th infusion in some of the animals treated with sebelipase alfa, diphenhydramine 5 mg/kg was administered by subcutaneous injection during the 4th infusion and before each subsequent dosing to all groups. As 4 of 22 animals in the 60 mg/kg group could not complete the 4th infusion due to a hypersensitivity reaction, this finding was considered due to a toxic effect of sebelipase alfa. There were no sebelipase alfa-related effects on mean number of days to mating, mating index, fertility index, conception rate of female animals, or sperm parameters.

Based on the above, the NOAEL in male animals was determined to be 20 mg/kg for general toxicity and 60 mg/kg for fertility and early embryonic development.

[39] Chamanza R, *et al*. *Toxicol Pathol*. 2006; 34: 357-63, Chamanza R, *et al*. *Toxicol Pathol*. 2010; 38: 642-57, Vidal JD, *et al*. *Toxicol Pathol*. 2010; 38: 297-302.

[40] Calculated based on the mean exposure (AUC_{ss}) of 1387 ng·h/mL in patients receiving sebelipase alfa 1 mg/kg qow for 22 weeks in a phase III study (Study LAL-CL02).

(b) Study in female rats (4.2.3.5.1.2)

Female SD rats were treated with sebelipase alfa at 0 (control[21]), 6, 20, and 60 mg/kg by intravenous infusion, twice weekly beginning 14 days before cohabitation, during cohabitation and continuing through gestation day 7. Treated females were cohabited with naïve males, and mated females were necropsied on gestation day 13.

Clinical signs indicative of a hypersensitivity reaction (e.g., decreased activity, red skin, swollen head or muzzle, excessive scratching) were observed in all groups including the control group. These findings were seen at a similar incidence in all groups. In addition, following the 4th dose, a severe hypersensitivity reaction (e.g., uncoordinated, respiratory distress) was observed at 6 and 20 mg/kg during the infusion. Thus, diphenhydramine 5 mg/kg was administered by subcutaneous injection during the 4th infusion and before each subsequent dosing to all groups. There were no sebelipase alfa-related effects on estrous cycle, mean number of days to mating, mating index, fertility index, conception rate, numbers of corpora lutea, implantation sites, live embryos, dead embryos, or preimplantation loss. One of 22 females in each of the sebelipase alfa-treated groups (≥6 mg/kg) had total resorption, which was not considered sebelipase alfa-related because this incidence was within the historical control range of data from the laboratory.

Based on the above, the NOAEL for general toxicity, fertility and early embryonic development in female animals was determined to be 60 mg/kg.

3.(iii).A.(3).2) Rat embryo-fetal development study (4.2.3.5.2.1, 4.2.3.5.2.2)

In a pilot study, pregnant SD rats were treated with sebelipase alfa at 0 (control[21]), 5, 15, 30, and 60 mg/kg by intravenous infusion on gestation days 6, 9, 12, 15, and 17. Animals were not routinely pretreated with diphenhydramine.

Clinical signs indicative of a hypersensitivity reaction (e.g., reddening of the skin and scabs, swelling of the head and limbs etc., excessive scratching) were observed in a dose-dependent manner in all groups including the control group. A reduction in food consumption was seen at ≥30 mg/kg, whereas there were no sebelipase alfa-related effects on the numbers of corpora lutea, implantation sites, live and dead fetuses, and resorptions, the sex ratio, pre- and post-implantation losses, fetal weights, or external fetal examination.

In the main study, pregnant SD rats were treated with sebelipase alfa at 0 (control[21]), 6, 20, and 60 mg/kg by intravenous infusion on gestation days 6, 9, 12, 15, and 17.

Reddening of the skin and scabs were observed in all groups including the control group. Clinical signs indicative of a hypersensitivity reaction (e.g., swelling of the muzzle and paws) were observed in a dose-dependent manner in the sebelipase alfa-treated groups, and severe hypersensitivity reactions (e.g., decreased activity, labored breathing) were also observed. Thus, diphenhydramine 5 mg/kg was administered by subcutaneous injection during the 4th infusion and before each subsequent dosing to all groups to alleviate hypersensitivity reaction. There were no sebelipase alfa-related effects on maternal body weight, food consumption, necropsy findings, ovarian and uterine findings, or fetal examinations.

Based on the above, the NOAEL for maternal general toxicity and embryo-fetal development was determined to be 60 mg/kg. The serum exposure to sebelipase alfa ($AUC_{0\text{-last}}$) at the NOAEL on gestation day 17 was 227 μg·h/mL, which was approximately 164 times the human exposure at the recommended clinical dose.[40]

3.(iii).A.(3).3) Rabbit embryo-fetal development study (4.2.3.5.2.3, 4.2.3.5.2.4)

In a pilot study, pregnant NZW rabbits were treated with sebelipase alfa at 0 (control[21]), 3, 10, 25, and 50 mg/kg by intravenous infusion on gestation days 7, 10, 13, 16, and 19. Animals were not routinely pretreated with diphenhydramine.

Maternal general toxicity was assessed. There were no sebelipase alfa-related effects observed. At 50 mg/kg, the number of late resorptions was increased, and lower number of live fetuses and an increased post-implantation loss were observed compared with controls and with the historical control data from the laboratory. The number of corpora lutea, implantation sites, preimplantation loss, and fetal weights were unaffected by sebelipase alfa. There were no sebelipase alfa-related fetal external abnormalities and variations. Since no increase in the number of late resorptions was observed in the main study, the finding was considered of little toxicological significance.

In the main study, pregnant NZW rabbits were treated with sebelipase alfa at 0 (control[21]), 10, 25, and 50 mg/kg by intravenous infusion on gestation days 7, 10, 13, 16, and 19. Animals were not routinely pretreated with diphenhydramine.

There were no sebelipase alfa-related effects on maternal general toxicity, maternal reproductive performance, fetal weights, or fetal morphology (fetal external, visceral, and skeletal examinations).

Based on the above, the NOAEL for maternal general toxicity and embryo-fetal development was determined to be 50 mg/kg. The serum exposure to sebelipase alfa ($AUC_{0\text{-last}}$) at the NOAEL on gestation day 19 was 730 μg·h/mL, which was approximately 526 times the human exposure at the recommended clinical dose (1 mg/kg).[40]

3.(iii).A.(3).4) Rat study on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant SD rats were treated with sebelipase alfa at 0 (control[21]), 6, 20, and 60 mg/kg by intravenous infusion on gestation days 6, 9, 12, 15, 18, and 20 and lactation days 4, 7, 10, 14, and 17. Dams delivered naturally and the development of the pups was assessed. Animals were not routinely pretreated with diphenhydramine.

Clinical signs indicative of a hypersensitivity reaction (swelling, excessive scratching) were observed in a dose-dependent manner during the gestation and lactation periods in all groups including the control group, whereas there were no sebelipase alfa-related effects on the length of gestation, pregnancy rate, or gestation index. There were no sebelipase alfa-related effects on the sex ratio of the F_1 pups, the number of live pups, or the number of malformed pups. A higher number of dead pups were seen in the 20 mg/kg group due to maternal

cannibalism of pups occurring in 2 of 22 dams in the same group. Maternal cannibalism of pups was noted also in 1 of 23 dams in the control group and 1 of 21 dams in the 60 mg/kg group and the number of dams with dead pups did not increase in the sebelipase alfa-treated groups. For this reason, the increase in the number of dead pups was not considered related to sebelipase alfa administration. There were no sebelipase alfa-related effects on clinical signs, survival, development, and reproductive performance in the F1 generation.

Based on the above, the NOAEL for maternal general toxicity and reproductive performance and F_1 offspring was determined to be 60 mg/kg.

3.(iii).B Outline of the review by PMDA

The applicant's explanation:

Hypersensitivity reactions observed in rats (hypersensitivity reaction tended to be exacerbated by the administration of sebelipase alfa in some studies) and vascular or perivascular inflammation observed in monkeys are of little toxicological significance because these findings are considered to be an immune response to human serum albumin present in the sebelipase alfa or vehicle formulation that was administered to rats or monkeys; human serum albumin is a foreign protein for the animals.

PMDA's view:

The applicant's explanation about hypersensitivity reactions observed in rats and vascular or perivascular inflammation observed in monkeys is acceptable from a toxicological point of view. PMDA will, however, continue to assess the effects in humans in the clinical section [see "4.(iii).B.(3).1) Hypersensitivity (including anaphylaxis)"]. Since no toxicologically significant findings were noted in toxicity studies of sebelipase alfa, there are no particular problems with the submitted data from a toxicological perspective.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

Sebelipase Alfa (Genetical Recombination) (hereinafter referred to as "sebelipase alfa") concentrations in human serum were determined using an enzyme activity assay, and the LLOQ was 9.375 ng/mL. An ELISA was used for the detection of anti-sebelipase alfa antibodies in serum, and an enzyme activity assay or a cell-based assay was used for the detection of neutralizing antibodies.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The applicant submitted evaluation data on Kanuma Intravenous Infusion 20 mg. The evaluation data consisted of the results from a multiregional phase III study in non-Japanese and Japanese patients with lysosomal acid lipase deficiency (LAL deficiency) (LAL-CL02) and a phase II/III study in non-Japanese patients with LAL deficiency (LAL-CL03). The applicant also submitted reference data, which consisted of the results from a phase I/II study in non-Japanese patients with LAL deficiency (LAL-CL01) and its extension study (LAL-CL04). The results of a population pharmacokinetic analysis using the data obtained from clinical studies

(LAL-CL01, LAL-CL02, LAL-CL03, and LAL-CL04) (5.3.3.5.1) were also submitted. The results from the main studies are described below.

4.(ii).A.(1) Phase I/II study in non-Japanese patients with LAL deficiency (5.3.3.2.1, Study LAL-CL01 [2011 to January 2012]; reference data)

An open-label, uncontrolled study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of sebelipase alfa in non-Japanese[41] adult patients with LAL deficiency[42] (target sample size, 9 subjects).

Sebelipase alfa 0.35, 1, or 3 mg/kg was administered as an intravenous infusion over approximately 2 hours once weekly for 4 weeks.

A total of 9 subjects received study treatment and all the treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

The pharmacokinetic parameters of sebelipase alfa at different time points are shown in Table 5. No anti-sebelipase alfa antibodies were detected.

Table 5. Pharmacokinetic parameters of sebelipase alfa at different time points

Dose	Time point	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·h/mL)	T_{max} (min)	$t_{1/2}$ (min)	V_Z (mL/kg)	CL (mL/h/kg)
0.35 mg/kg	Day 0 (n = 3)	0.370 (0.262, 0.718)	0.449 (0.441, 0.663)	40.2 (19.8, 94.8)	82.2 (36.0, 211)	1489 (455, 3653)	722 (524, 755)
	Day 21 (n = 3)	0.379 (0.330, 0.655)	0.510 (0.494, 0.757)	40.2 (40.2, 40.2)	46.8 (4.20, 123)	788 (48.0, 1964)	665 (462, 700)
1.0 mg/kg	Day 0 (n = 3)	0.836 (0.561, 5.484)	1.091 (0.846, 8.254)	60.0 (60.0, 90.0)	6.60 (6.60, 16.8)	151.9 (48.1, 183)	916 (121, 1180)
	Day 21 (n = 3)	1.212 (0.814, 5.991)	1.687 (1.026, 9.198)	75.0 (60.0, 90.0)	6.60 (4.80, 8.40)	70.0 (21.7, 118)	541 (109, 974)
3.0 mg/kg	Day 0 (n = 3)	15.03 (9.080, 19.90)	22.03 (12.80, 27.03)	90.0 (90.0, 90.0)	7.80 (6.00, 14.4)	25.8 (16.1, 78.1)	136 (111, 229)
	Day 21 (n = 3)	16.08 (9.616, 29.61)	22.14 (16.66, 31.44)	108 (105, 125)	7.80 (5.40, 9.60)	22.1 (18.3, 35.0)	136 (95.4, 180)

Median (Min., Max.)

C_{max}: maximum serum concentration, $AUC_{0\text{-last}}$: area under the serum concentration-time curve from the start of the infusion to the time of the last quantifiable concentration, T_{max}: time of maximum serum concentration, $t_{1/2}$: elimination half-life, Vz: the apparent volume of distribution during the terminal phase, CL: clearance

For pharmacodynamic assessments, clinical laboratory test results at different time points are shown in Table 6.

[41] The US, the UK, France, and the Czech Republic

[42] Key eligibility criteria: Documented decreased LAL activity relative to the normal range or documented result of molecular genetic testing confirming a diagnosis of LAL deficiency; evidence of liver involvement based on clinical presentation (hepatomegaly) and/or laboratory test results (ALT or AST ≥1.5×ULN); ≥18 and ≤65 years of age; and no history of hematopoietic stem cell or liver transplant. Patients receiving lipid-lowering medications had to be on a stable dose for at least 4 weeks prior to screening.

Table 6. Clinical laboratory test results at different time points

Dose	Time point	AST (U/L)	ALT (U/L)	LDL-C[a)] (mg/dL)	HDL-C (mg/dL)	Triglyceride (mg/dL)
0.35 mg/kg	Day 0 (n = 3)	56 (48, 69)	76 (60, 85)	208 (74, 300)	39 (28, 41)	108 (106, 218)
	Day 28 (n = 3)	27 (23, 55)	26 (23, 45)	287 (93, 300)	38 (29, 48)	174 (127, 303)
1.0 mg/kg	Day 0 (n = 3)	67 (52, 69)	70 (22, 119)	118 (70, 137)	23 (22, 45)	102 (92, 115)
	Day 28 (n = 3)	47 (31, 67)	38 (26, 48)	158 (84, 289)	23 (16, 46)	135 (78, 194)
3.0 mg/kg	Day 0 (n = 3)	41 (37, 65)	86 (57, 110)	135 (112, 143)	43 (26, 49)	266 (80, 277)
	Day 28 (n = 3)	29 (29, 32)	43 (29, 59)	283 (150, 674)	35 (28, 45)	351 (279, 462)

Median (Min., Max.)
AST: aspartate aminotransferase
ALT: alanine aminotransferase
LDL-C: low-density lipoprotein cholesterol
HDL-C: high-density lipoprotein cholesterol
a) Direct method

Adverse events occurred in 7 of 9 subjects (1 subject receiving the 0.35 mg/kg dose, 3 subjects receiving the 1 mg/kg dose, and 3 subjects receiving the 3 mg/kg dose). Of these, 6 events reported by 2 of the 9 subjects were assessed as adverse drug reactions, i.e., adverse events for which a causal relationship to study drug could not be ruled out.[43] Four events occurred in 1 subject receiving the 0.35 mg/kg dose (nausea [3] and diarrhoea [1]), and 2 events occurred in 1 subject receiving the 3 mg/kg dose (hypercholesterolaemia and hypertriglyceridaemia). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2) Multiregional phase III study in non-Japanese and Japanese patients with LAL deficiency (5.3.5.1.1, Study LAL-CL02 [ongoing since January 2013 (data cutoff in [redacted])])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of sebelipase alfa in Japanese and non-Japanese patients with LAL deficiency (target sample size, 50 subjects) [see "4.(iii).A.(1) Multiregional phase III study in non-Japanese and Japanese patients with late-onset LAL deficiency" for the details of the study design and efficacy and safety results].

The pharmacokinetic parameters after administration of sebelipase alfa 1 mg/kg once every other week are shown in Table 7. Of 35 subjects in the sebelipase alfa group, 5 (including 1 Japanese subject) were positive for anti-sebelipase alfa antibodies during the double-blind period, and none of these 5 subjects developed neutralizing antibodies. None of the subjects in the placebo group had positive anti-sebelipase alfa antibody titers.

[43] Adverse events considered related or probably related to study drug.

Table 7. Pharmacokinetic parameters after administration of sebelipase alfa 1mg/kg once every other week (Study LAL-CL02)

Subjects	Time point	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·h/mL)	T_{max} (min)	V_Z (mL/kg)	CL (mL/h/kg)
≥18 years	Week 0 (n = 17)	1.196 ± 0.520	1.732 ± 0.641	81.6 ± 40.8	361.4 ± 399.8[a)]	607.7 ± 198.2[a)]
	Week 22 (n = 11)	1.352 ± 0.553	1.914 ± 0.879	102 ± 37.8	337.7 ± 409.7	649.7 ± 357.9
<18 years	Week 0 (n = 46)	0.790 ± 0.854	1.029 ± 1.065	67.2 ± 41.4	—	—
	Week 22 (n = 21)	0.568 ± 0.433	0.732 ± 0.739	73.8 ± 52.2	—	—

Mean ± SD; —, not calculated
C_{max}: maximum serum concentration
$AUC_{0\text{-last}}$: area under the serum concentration-time curve from the start of the infusion to the time of the last quantifiable concentration
T_{max}: time of maximum serum concentration
Vz: the apparent volume of distribution during the terminal phase
CL: clearance
a) n = 13

4.(ii).A.(3) Population pharmacokinetic analysis (5.3.3.5.1)

A population pharmacokinetic (PPK) analysis was performed (software, NONMEM [ver.7.2.0]) using sebelipase alfa serum concentrations obtained from 79 subjects at 987 points in clinical studies in patients with LAL deficiency conducted in and outside Japan (Studies LAL-CL01, LAL-CL02, LAL-CL03, and LAL-CL04).

The PPK dataset was comprised of 79 subjects (42 male subjects, 37 female subjects). The baseline patient characteristics [mean (min., max.)] were as follows: the age was 16.5 (0.09, 58) years, body weight was 48.9 (3.36, 125) kg, body surface area was 1.4 (0.21, 2.33) m^2, aspartate aminotransferase (AST) was 86.8 (37, 547) U/L, alanine aminotransferase (ALT) was 101 (22, 297) U/L, albumin was 41.7 (18, 47) g/L, alkaline phosphatase was 251 (59, 977) U/L, total bilirubin was 18.3 (3, 80) μmol/L, serum creatinine was 53.1 (12, 96.4) μmol/L, and creatinine clearance was 152 (64.1, 238) mL/min.

A 1-compartment model with zero-order absorption with body surface area as a covariate on CL for doses <3 mg/kg was developed as the base model, and potential covariates on individual parameter estimates including age, body weight, height, body surface area, sex, race (Caucasian, Black, Asian, Hispanic, Japanese, others), hepatic function (albumin, AST, ALT, alkaline phosphatase, total bilirubin), renal function (serum creatinine, creatinine clearance), anti-sebelipase alfa antibody, and antibody titer were tested using the stepwise method. As a result, body surface area, the previously included covariate on CL for doses <3 mg/kg, was incorporated in the final model.

Using the final model, the pharmacokinetic parameters were estimated for patients weighing 10 to 25 kg, 25 to 50 kg, 50 to 75 kg, and >75 kg who received 1 mg/kg of sebelipase alfa. The steady-state AUC_{ss} (median) was 813, 1200, 1700, and 2180 ng·h/mL, respectively, and the CL was 24.4, 31.1, 37.0, and 38.8 L/h, respectively.

4.(ii).B Outline of the review by PMDA

Pharmacokinetics in Japanese and non-Japanese patients

PMDA asked the applicant to discuss the pharmacokinetics of sebelipase alfa and to explain whether there is a trend towards substantial pharmacokinetic differences between Japanese and non-Japanese patients.

The applicant's response:

The exposure to sebelipase alfa increased in a dose-proportional manner between the 0.35 mg/kg and 1 mg/kg doses and increased in a greater than dose-proportional manner between the 1 mg/kg and 3 mg/kg doses (a 3-fold increase in dose resulted in approximately 10- to 15-fold increases in exposure). Sebelipase alfa was rapidly eliminated at all dose levels and no accumulation was observed following multiple dosing of 1 or 3 mg/kg. The apparent clearance (CL) of sebelipase alfa at 3 mg/kg may change over time.

The pharmacokinetic parameters in Japanese and non-Japanese subjects receiving sebelipase alfa 1 mg/kg once every other week in Study LAL-CL02 are shown in Table 8.

Table 8. Pharmacokinetic parameters in Japanese and foreign subjects receiving sebelipase alfa 1 mg/kg once every other week (Study LAL-CL02)

Time point		Week 0		Week 22	
PK parameter		C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·h/mL)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·h/mL)
≥18 years	Japanese subject	1.114 (n = 1)	2.204 (n = 1)	1.993 (n = 1)	3.439 (n = 1)
	Non-Japanese subjects	1.201 ± 0.536 [0.672, 2.555] (n = 16)	1.703 ± 0.650 [0.690, 3.363] (n = 16)	1.288 ± 0.538 [0.501, 2.167] (n = 10)	1.761 ± 0.758 [0.639, 3.143] (n = 10)
<18 years	Japanese subject	0.487 (n = 1)	0.621 (n = 1)	0.450 (n = 1)	0.548 (n = 1)
	Non-Japanese subjects	0.797 ± 0.862 [0.023, 5.864] (n = 45)	1.038 ± 1.076 [0.035, 6.415] (n = 45)	0.574 ± 0.444 [0.025, 2.018] (n = 20)	0.741 ± 0.757 [0.050, 3.505] (n = 20)

Japanese subject, values in 1 subject; Non-Japanese subjects, Mean ± SD [Min., Max.]
C_{max}: maximum serum concentration
$AUC_{0\text{-last}}$: area under the serum concentration-time curve from the start of the infusion to the time of the last quantifiable concentration

The number of Japanese patients in Study LAL-CL02 was very limited, i.e., 1 patient each in the age groups of ≥18 and of <18 years. This leads to limitations to the comparison of data between Japanese and non-Japanese patients, but the pharmacokinetic parameters in the Japanese patients were largely within the range of the pharmacokinetic parameters in the non-Japanese patient population. The PPK model-derived pharmacokinetic parameters for the 2 Japanese subjects at Weeks 0 and 22 in Study LAL-CL02 were within the range of the pharmacokinetic parameters in the overall study population.

PMDA's view:

It is difficult to reach a definitive conclusion on pharmacokinetic similarities between Japanese and non-Japanese patients due to insufficient pharmacokinetic data from the very limited number of Japanese patients participating in Study LAL-CL02 (1 patient each in the age groups of ≥18 and of <18 years), but there is no trend towards substantial pharmacokinetic differences between Japanese and non-Japanese patients. Therefore, PMDA accepted the applicant's response.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted evaluation data, which consisted of the results from a multiregional phase III study in non-Japanese and Japanese patients with late-onset LAL deficiency (cholesteryl ester storage disease [CESD]) (Study LAL-CL02) and a foreign phase II/III study in non-Japanese patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) (Study LAL-CL03). The applicant also submitted reference data,

which consisted of the results from an extension study (Study LAL-CL04) of a foreign phase I/II study in non-Japanese adult patients with LAL deficiency (Study LAL-CL01) and an observational natural history study of non-Japanese patients with infantile-onset, LAL deficiency (Study LAL-1-NH01), etc. The results from the main studies are described below.

4.(iii).A.(1) Multiregional phase III study in non-Japanese and Japanese patients with late-onset LAL deficiency (5.3.5.1.1, Study LAL-CL02 [ongoing since January 2013 (data cutoff in [redacted])])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of sebelipase alfa in Japanese and non-Japanese[44] patients with LAL deficiency[45] (target sample size, 50 subjects) [see "4.(ii).A.(2) Multiregional phase III study in non-Japanese and Japanese patients with LAL deficiency" for pharmacokinetic data].

The study consisted of a screening period (up to 6 weeks), a double-blind treatment period (20 weeks), an open-label extension period (up to 130 weeks), and a follow-up period (4 weeks).

Subjects received sebelipase alfa 1 mg/kg or placebo[46] as an intravenous infusion once every other week during the 20-week double-blind period (randomized in a 1:1 ratio). Then all subjects could begin the open-label treatment with sebelipase alfa at a dose of 1 mg/kg intravenous infusion once every other week during the extension period. During the double-blind period, subjects who exhibited evidence of significant clinical progression were allowed to discontinue from the double-blind period and transition into the open-label extension period. During the open-label period, dose escalation to 3 mg/kg once every other week was permitted if the patient continued to meet the criteria for significant clinical progression after at least 4 consecutive open-label infusions at a dose of 1 mg/kg once every other week. Dose reduction to 0.35 mg/kg once every other week was permitted in the event of poor tolerability.

A total of 66 subjects received study treatment and all the treated subjects (36 [including 2 Japanese] in the sebelipase alfa group, 30 in the placebo group) were included in the Safety Analysis Set and in the Full Analysis Set (FAS), and the FAS was used for efficacy analysis. One subject in the sebelipase alfa group discontinued the double-blind period (due to adverse event). This subject who discontinued the double-blind period and 65 subjects who completed the double-blind period (35 [including 2 Japanese] in the sebelipase alfa group, 30 in the placebo group) entered the open-label period. As of the data cutoff date for the ongoing open-label period, 16 subjects (including 1 Japanese) in the sebelipase alfa group completed 32 weeks of treatment with sebelipase alfa and 9 subjects in the placebo/sebelipase alfa group completed 14 weeks of treatment with sebelipase alfa.

The proportion of subjects who achieved ALT normalization at the end of the double-blind period (Week 20)

[44] The US, Canada, Australia, Croatia, the Czech Republic, Greece, France, Germany, Italy, Poland, Spain, the UK, Turkey, the Russian Federation, Mexico, and Argentina

[45] Key eligibility criteria: LAL enzyme deficiency confirmed by dried blood spot (DBS) testing at screening; ALT ≥1.5×ULN (based on age- and sex-specific normal ranges of the central lab) on 2 consecutive screening ALT measurements obtained at least 1 week apart; ≥4 years of age; and no history of hematopoietic stem cell or liver transplant. Patients receiving lipid lowering medications had to be on a stable dose for at least 6 weeks prior to randomization.

[46] Prepared with the same vehicle and excipients as those used for the sebelipase alfa drug product.

as the primary efficacy endpoint was 6.7% (2 of 30 subjects) in the placebo group and 30.6% (11 of 36 subjects) in the sebelipase alfa group, demonstrating the superiority of sebelipase alfa over placebo (P = 0.0271, two-sided significance level of 5%, Fisher's exact test).

The results of the primary and secondary endpoints in the double-blind period are shown in Table 9.

Table 9. Results of the primary and secondary endpoints (Study LAL-CL02, double-blind period, FAS)

Endpoint		Placebo (n = 30)	Sebelipase alfa (n = 36)
Proportion of subjects who achieved ALT normalization (%)	Baseline	0.0 (0/30)	0.0 (0/36)
	End of double-blind period (Week 20)	6.7 (2/30)	30.6 (11/36)
Proportion of subjects who achieved AST normalization (%)	Baseline	3.3 (1/30)	0.0 (0/36)
	End of double-blind period (Week 20)	3.4 (1/29)	41.7 (15/36)
LDL-C[a)] (mg/dL)	Baseline [a)]	229.5 ± 69.95	189.9 ± 57.16
	End of double-blind period (Week 20)	213.3 ± 65.88	138.8 ± 66.38
	Percent change from baseline (%)	-6.35 ± 12.98	-28.47 ± 22.30
Non-HDL-C (mg/dL)	Baseline [a)]	263.8 ± 75.48	220.5 ± 61.48
	End of double-blind period (Week 20)	242.8 ± 66.87	161.6 ± 69.37
	Percent change from baseline (%)	-6.94 ± 10.92	-27.97 ± 18.61
HDL-C (mg/dL)	Baseline	33.4 ± 7.46	32.4 ± 7.09
	End of double-blind period (Week 20)	33.1 ± 8.52	38.3 ± 9.53
	Percent change from baseline (%)	-0.29 ± 12.36	19.57 ± 16.83
Triglyceride (mg/dL)	Baseline [a)]	174.4 ± 65.90	152.8 ± 54.43
	End of double-blind period (Week 20)	148.4 ± 58.62	113.7 ± 55.60
	Percent change from baseline (%)	-11.10 ± 28.88	-25.45 ± 29.50

Mean ± SD; Proportion of subjects, % (Number of subjects/Number of evaluable subjects)
a) Calculated using the Friedewald formula.

Table 9. Results of the primary and secondary endpoints (Study LAL-CL02, double-blind period, FAS) (continued)

Endpoint		Placebo (n = 30)	Sebelipase alfa (n = 36)
Liver fat content [b)] (%)	Baseline	8.16 ± 2.80 (n = 26)	8.75 ± 3.95 (n = 35)
	End of double-blind period (Week 20)	8.08 ± 3.20 (n = 26)	5.16 ± 1.70 (n = 32)
	Percent change from baseline (%)	-4.21 ± 15.56 (n = 25)	-31.98 ± 26.76 (n = 32)
Liver volume [b)] (MN[c)])	Baseline	1.50 ± 0.31 (n = 28)	1.44 ± 0.41 (n = 36)
	End of double-blind period (Week 20)	1.45 ± 0.29 (n = 28)	1.28 ± 0.32 (n = 33)
	Percent change from baseline (%)	-2.66 ± 10.11 (n = 27)	-10.28 ± 10.51 (n = 33)
Spleen volume [b)] (MN[c)])	Baseline	3.26 ± 1.32 (n = 28)	3.37 ± 2.70 (n = 36)
	End of double-blind period (Week 20)	3.74 ± 2.00 (n = 28)	3.00 ± 2.04 (n = 33)
	Percent change from baseline (%)	5.79 ± 12.21 (n = 27)	-6.75 ± 13.59 (n = 33)
Hepatic steatosis score [d)]	Baseline	34.30 ± 24.84 (n = 13)	29.67 ± 20.00 (n = 19)
	End of double-blind period (Week 20)	28.41 ± 12.35 (n = 10)	16.86 ± 9.82 (n = 16)
	Proportion of subjects who showed improvement (%)	40.0 (4/10)	62.5 (10/16)

Mean ± SD; Proportion of subjects, % (Number of subjects/Number of evaluable subjects)
b) Assessed by multi-echo gradient-echo MRI (MEGE-MRI) (abdominal MRI).
c) MN (multiples of normal), liver or spleen volume measured by abdominal MRI was adjusted for body weight to take into account differences in liver or spleen volume between the age groups (liver or spleen volume adjusted for body weight = volume [cc]/body weight [kg]×100) and reported as multiples of normal (normal liver volume was set as 2.5% of the body weight [kg] and normal spleen volume was set as 0.2% of the body weight [kg]).
d) Assessed by liver biopsy.

The results of the main endpoints in the open-label period are shown in Table 10.

Table 10. Results of main endpoints (Study LAL-CL02, open-label period)

Endpoint		Placebo/Sebelipase alfa (n = 30)	Sebelipase alfa (n = 36)	Total (n = 66)
Proportion of subjects who achieved ALT normalization (%)	Baseline	0.0 (0/30)	0.0 (0/36)	0.0 (0/66)
	Last time point	33.3 (9/27)	33.3 (11/33)	33.3 (20/60)
Proportion of subjects who achieved AST normalization (%)	Baseline	0.0 (0/30)	0.0 (0/36)	0.0 (0/66)
	Last time point	33.3 (9/27)	54.5 (18/33)	45.0 (27/60)
LDL-C[a] (mg/dL)	Baseline	210.2 ± 60.5 (n = 30)	189.9 ± 57.2 (n = 36)	199.1 ± 59.1 (n = 66)
	Last time point	204.4 ± 72.5 (n = 28)	124.5 ± 53.3 (n = 33)	161.2 ± 74.1 (n = 61)
	Percent change (%)	-2.4 ± 23.7 (n = 28)	-34.4 ± 16.3 (n = 33)	-19.7 ± 25.5 (n = 61)
Non-HDL-C (mg/dL)	Baseline	241.9 ± 63.6 (n = 30)	220.5 ± 61.5 (n = 36)	230.2 ± 62.9 (n = 66)
	Last time point	230.5 ± 75.3 (n = 28)	148.2 ± 59.0 (n = 33)	186.0 ± 78.2 (n = 61)
	Percent change (%)	-4.6 ± 21.3 (n = 28)	-32.9 ± 14.3 (n = 33)	-19.9 ± 22.7 (n = 61)
HDL-C (mg/dL)	Baseline	32.7 ± 7.9 (n = 30)	32.4 ± 7.1 (n = 36)	32.5 ± 7.4 (n = 66)
	Last time point	36.3 ± 9.9 (n = 28)	40.1 ± 10.9 (n = 33)	38.4 ± 10.5 (n = 61)
	Percent change (%)	11.6 ± 20.2 (n = 28)	24.5 ± 20.7 (n = 33)	18.6 ± 21.3 (n = 61)
Triglyceride (mg/dL)	Baseline	158.2 ± 57.8 (n = 30)	152.8 ± 54.4 (n = 36)	155.3 ± 55.6 (n = 66)
	Last time point	130.1 ± 38.2 (n = 28)	119.4 ± 58.9 (n = 33)	124.3 ± 50.4 (n = 61)
	Percent change (%)	-12.5 ± 25.0 (n = 28)	-22.9 ± 26.1 (n = 33)	-18.2 ± 25.9 (n = 61)
Liver fat content[b] (%)	Baseline	8.1 ± 3.2 (n = 26)	8.7 ± 4.0 (n = 35)	8.5 ± 3.6 (n = 61)
	Last time point	1.9 ± 0.7 (n = 2)	6.0 ± 1.7 (n = 3)	4.4 ± 2.5 (n = 5)
	Percent change (%)	-24.8 ± 82.3 (n = 2)	-30.9 ± 11.0 (n = 3)	-28.5 ± 42.0 (n = 5)
Liver volume[b] (MN[c])	Baseline	1.45 ± 0.29 (n = 28)	1.44 ± 0.41 (n = 36)	1.44 ± 0.36 (n = 64)
	Last time point	1.44 ± 0.20 (n = 2)	1.21 ± 0.25 (n = 4)	1.29 ± 0.24 (n = 6)
	Percent change (%)	-11.58 ± 7.96 (n = 2)	-23.23 ± 14.19 (n = 4)	-19.35 ± 13.03 (n = 6)
Spleen volume[b] (MN[c])	Baseline	3.74 ± 2.00 (n = 28)	3.37 ± 2.70 (n = 36)	3.53 ± 2.40 (n = 64)
	Last time point	5.05 ± 3.46 (n = 2)	2.25 ± 0.78 (n = 4)	3.18 ± 2.21 (n = 6)
	Percent change (%)	5.33 ± 4.25 (n = 2)	-21.75 ± 14.80 (n = 4)	-12.72 ± 18.18 (n = 6)

Mean ± SD; Proportion of subjects, % (number of subjects/number of evaluable subjects)
a) Calculated using the Friedewald formula.
b) Assessed by multi-echo gradient-echo MRI (MEGE-MRI) (abdominal MRI).
c) MN, multiples of normal

Table 11 and Table 12 show the results of the primary and main secondary endpoints (the endpoints of serum chemistry parameters and other endpoints) in the double-blind period and in the open-label period for individual Japanese subjects (Subject 1, [redacted]-year-old [redacted]; Subject 2, [redacted]-year-old [redacted]). Liver histology was assessed by liver biopsy for Subject 1 only and the subject had an improvement (a reduction in the percentage of steatosis) at the end of the double-blind period.

Table 11. The results of the endpoints of serum chemistry parameters in individual Japanese subjects (Study LAL-CL02, Japanese subgroup)

Endpoint	Subject number	Baseline	Week 4	Week 10	Week 20	Open-label period Week 24	Open-label period Week 32
ALT (U/L)	Subject 1	116	25	34	51	63	53
	Subject 2	91	59	45	48	58	—
AST (U/L)	Subject 1	96	35	39	43	78	55
	Subject 2	69	45	40	39	42	—
LDL-C[a)] (mg/dL)	Subject 1	222	135	81	114	75	107
	Subject 2	239	286	193	348	179	—
Non-HDL-C (mg/dL)	Subject 1	244	150	101	138	87	133
	Subject 2	280	324	224	378	213	—
HDL-C (mg/dL)	Subject 1	48	34	53	72	48	51
	Subject 2	27	27	26	32	36	—
Triglyceride (mg/dL)	Subject 1	109	74	98	119	59	128
	Subject 2	207	193	151	149	167	—

—, not applicable
a) Calculated using the Friedewald formula.

Table 12. Results of other endpoints in individual Japanese subjects (Study LAL-CL02, Japanese subgroup)

Endpoint	Subject number	Baseline	End of double-blind period	Percent change (%)	Open-label period
Liver fat content [a)] (%)	Subject 1	10.76	7.44	-30.86	—
	Subject 2	7.69	5.18	-32.64	—
Liver volume[a)] (MN[b)])	Subject 1	1.04	1.14	9.62	—
	Subject 2	2.91	2.36	-18.90	—
Spleen volume[a)] (MN[b)])	Subject 1	1.64	1.40	-14.63	—
	Subject 2	8.17	7.00	-14.32	—

—, not applicable
a) Assessed by multi-echo gradient-echo MRI (MEGE-MRI) (abdominal MRI)
b) MN, multiples of normal

Safety data were summarized. During the double-blind period, the incidences of adverse events were 93.3% (28 of 30 subjects) in the placebo group and 86.1% (31 of 36 subjects) in the sebelipase alfa group and the incidences of adverse drug reactions were 20.0% (6 of 30 subjects) in the placebo group and 13.9% (5 of 36 subjects) in the sebelipase alfa group. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in either treatment group are shown in Table 13. Two Japanese subjects (both in the sebelipase alfa group) experienced adverse events (nasopharyngitis in 1 and herpes zoster, allergic rhinitis, and constipation in 1), which were non-serious, and their causal relationship to study drug was ruled out.

Table 13. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in either treatment group (Study LAL-CL02, double-blind period)

	Placebo (N = 30)		Sebelipase alfa (N = 36)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	28 (93.3)	6 (20.0)	31 (86.1)	5 (13.9)
Headache	6 (20.0)	0 (0.0)	10 (27.8)	0 (0.0)
Pyrexia	6 (20.0)	2 (6.7)	7 (19.4)	0 (0.0)
Upper respiratory tract infection	6 (20.0)	0 (0.0)	6 (16.7)	0 (0.0)
Diarrhoea	5 (16.7)	1 (3.3)	6 (16.7)	0 (0.0)
Oropharyngeal pain	1 (3.3)	0 (0.0)	6 (16.7)	0 (0.0)
Epistaxis	6 (20.0)	0 (0.0)	4 (11.1)	0 (0.0)
Nasopharyngitis	3 (10.0)	0 (0.0)	4 (11.1)	0 (0.0)
Vomiting	3 (10.0)	0 (0.0)	3 (8.3)	0 (0.0)
Cough	3 (10.0)	0 (0.0)	3 (8.3)	0 (0.0)
Tonsillitis	4 (13.3)	0 (0.0)	2 (5.6)	0 (0.0)
Rhinitis	3 (10.0)	0 (0.0)	2 (5.6)	0 (0.0)
Rash	3 (10.0)	0 (0.0)	1 (2.8)	1 (2.8)
Procedural pain	3 (10.0)	0 (0.0)	1 (2.8)	0 (0.0)
Pharyngitis	5 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %); MedDRA ver.15.1

During the open-label period, the incidences of adverse events were 53.3% (16 of 30 subjects) in the placebo/sebelipase alfa group[47] and 91.7% (33 of 36 subjects) in the sebelipase alfa group and the incidences of adverse drug reactions were 6.7% (2 of 30 subjects) in the placebo/sebelipase alfa group and 19.4% (7 of 36 subjects) in the sebelipase alfa group. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in either treatment group are shown in Table 14. One of the 2 Japanese subjects (both in the sebelipase alfa group) experienced an adverse event (nasopharyngitis), which was non-serious, and its causal relationship to study drug was ruled out.

Table 14. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in either treatment group (Study LAL-CL02, open-label period)

	Placebo/Sebelipase alfa[a)] (N = 30)		Sebelipase alfa (N = 36)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	16 (53.3)	2 (6.7)	33 (91.7)	7 (19.4)
Headache	2 (6.7)	0 (0.0)	13 (36.1)	0 (0.0)
Diarrhoea	3 (10.0)	0 (0.0)	9 (25.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	7 (19.4)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	6 (16.7)	0 (0.0)
Upper respiratory tract infection	2 (6.7)	0 (0.0)	6 (16.7)	0 (0.0)
Oropharyngeal pain	1 (3.3)	0 (0.0)	6 (16.7)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	6 (16.7)	0 (0.0)
Nausea	1 (3.3)	0 (0.0)	4 (11.1)	1 (2.8)
Vomiting	1 (3.3)	0 (0.0)	4 (11.1)	0 (0.0)
Cough	4 (13.3)	0 (0.0)	5 (13.9)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	5 (13.9)	0 (0.0)

n (Incidence, %); MedDRA ver.15.1
a) Events occurring after initiation of treatment with sebelipase alfa

No deaths were reported throughout the study period. Serious adverse events occurred in 1 subject in the placebo group (road traffic accident) and 2 subjects in the sebelipase alfa group (gastritis and infusion related reaction) during the double-blind period and 1 subject in the placebo/sebelipase alfa group (gastroenteritis) during the open-label period. The infusion related reaction occurring in the sebelipase alfa group during the double-blind period was classified as an adverse drug reaction, which led to treatment discontinuation.

Although 5 subjects in the sebelipase alfa group tested positive for anti-sebelipase alfa antibodies at some time point, titers decreased to below the LLOQ by the last time point. No subject was found to have neutralizing antibodies.

There were no clinically meaningful differences in vital signs or 12-lead ECG between the sebelipase alfa and placebo groups.

[47] Events occurring after the initiation of treatment with sebelipase alfa

4.(iii).A.(2) Phase II/III study in non-Japanese patients with infantile-onset, rapidly progressive LAL deficiency (5.3.5.2.2, Study LAL-CL03 [ongoing since May 2011 (data cutoff in [redacted])])

An open-label, uncontrolled, dose escalation study was conducted to evaluate the efficacy and safety of sebelipase alfa in non-Japanese[48] patients with infantile-onset, rapidly progressive LAL deficiency[49] (target sample size, 10 subjects).

The study consisted of a screening period (up to 3 weeks), a treatment period (up to 4 years), and a follow-up period (30 days).

All subjects received a starting dose of 0.35 mg/kg of sebelipase alfa once weekly by intravenous infusion and the dose was escalated to 1 mg/kg once weekly if acceptable tolerability was demonstrated with at least 2 infusions at the dose of 0.35 mg/kg. Further dose increase to 3 mg/kg once weekly was permitted in subjects exhibiting a suboptimal treatment response after at least 4 infusions at a dose of 1 mg/kg, contingent upon acceptable safety of preceding infusions. An option for dose escalation to 5 mg/kg once weekly was given to subjects who had evidence for a continued suboptimal response or loss of efficacy in association with the presence of anti-drug antibodies. A reduction in dosing frequency (change from once-weekly dosing to every-other-week dosing at the same dose per infusion) was permitted in subjects who had been on a stable dose for ≥24 weeks. Any subject receiving every-other-week dosing who subsequently had a suboptimal clinical response was to either revert to once-weekly dosing schedule or, escalate their dose to 3 mg/kg every other week. The duration of treatment ranged from ≥18 months up to 4 years.

All of 9 treated subjects were included in the Safety Analysis Set and in the FAS, and the FAS was used for efficacy analysis. Excluded were 2 subjects who died during the screening period.[50] Three subjects discontinued the study treatment. All of these subjects had a history suggestive of multi-system organ failure syndrome and died 1 to 4 weeks after the initiation of treatment with sebelipase alfa.

As of the data cutoff, the median treatment duration was 60.29 weeks (range, 0.1-164.7 weeks). During the study period, 14 intravenous infusions of sebelipase alfa were administered at a dose of 0.35 mg/kg, 141 infusions at a dose of 1 mg/kg, 295 infusions at a dose of 3 mg/kg, 8 infusions at a dose of 5 mg/kg, and 4 infusions at other doses. Except for 1 subject who received 17 infusions at a dose of 3 mg/kg once every other week, all subjects received infusions once weekly. The median number of administered infusions was 61 (range, 1-146) and the majority of infusions were given at doses of 1 mg/kg (median, 10; range, 2-86) and 3 mg/kg (median, 54; range, 18-64).

[48] The US, the UK, France, Italy, Ireland, Turkey, Saudi Arabia, Egypt, and Taiwan

[49] Principal eligibility criteria: diagnosis of LAL deficiency confirmed by decreased LAL activity relative to the normal range or molecular genetic testing with 2 mutations; growth failure with onset before 6 months of age: and no history of hematopoietic stem cell or liver transplant.
Growth failure was defined by at least 1 of the following: (1) Weight decreasing across at least 2 of the 11 major centiles (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, and 99th) on a standard World Health Organization (WHO) weight-for-age (WFA) chart. (2) Body weight in kg below the 10th centile on a standard WHO WFA chart and no weight gain for the 2 weeks prior to screening. (3) Loss of >5% of birth weight in a child who is >2 weeks of age. The protocol amendment dated February 5, 2013 permitted enrollment of patients who do not meet the growth failure criteria as defined if patients have evidence of a rapidly progressive course of LAL deficiency for which the investigator has judged that urgent medical intervention is required.

[50] One subject had severe liver failure and the other subject had severe liver failure leading to massive bleeding.

The primary efficacy endpoint, the proportion of subjects surviving to 12 months of age (95% CI), was 66.7% (6 of 9 subjects) [29.93%, 92.51%].

The proportions of subjects surviving to 18 and 24 months of age (the main secondary endpoints) were 33.3% (3 of 9 subjects) and 22.2% (2 of 9 subjects), respectively. Table 15 shows the results of growth parameters and liver enzyme levels, indicating increases in height-for-age and weight-for-age and decreases in liver enzyme parameters were observed.

Table 15. Results of main secondary endpoints (Study LAL-CL03)

Endpoint	Baseline (n = 9)	Week 4 (n = 6)	Week 12 (n = 6)	Week 24 (n = 5)	Week 48 (n = 4)	Week 60 (n = 4)
Height-for-age [a)]	1.798 (0.00, 80.78) (n = 8)	3.157 (0.00, 83.15) (n = 6)	6.932 (0.06, 94.06) (n = 6)	10.75 (0.03, 91.62) (n = 5)	12.57 (0.29, 75.49) (n = 4)	14.98 (0.43, 61.41) (n = 4)
Weight-for-age [a)]	3.076 (0.00, 77.04) (n = 8)	3.057 (0.00, 60.26) (n = 6)	3.471 (0.14, 53.59) (n = 6)	1.044 (0.10, 64.06) (n = 5)	14.93 (7.08, 82.38) (n = 4)	21.44 (4.95, 88.88) (n = 4)
ALT (U/L)	145.0 (16.0, 297.0) (n = 9)	31.0 (14.0, 71.0) (n = 5)	27.0 (15.0, 44.0) (n = 5)	39.0 (15.0, 90.0) (n = 5)	28.5 (28.0, 29.0) (n = 4)	33.0 (29.0, 42.0) (n = 4)
AST (U/L)	125.0 (71.0, 716.0) (n = 9)	62.0 (35.0, 120.0) (n = 4)	44.0 (33.0, 75.0) (n = 5)	56.0 (28.0, 106.0) (n = 5)	39.5 (32.0, 45.0) (n = 4)	43.0 (37.0, 58.0) (n = 4)

Median (Min., Max.)
a) WHO percentile

Adverse events occurred in all of the 9 subjects (100.0%) and adverse drug reactions occurred in 5 subjects (55.6%). Adverse events and/or adverse drug reactions reported by ≥3 subjects are shown in Table 16.

Table 16. Adverse events and/or adverse drug reactions reported by ≥3 subjects (Study LAL-CL03)

	Adverse events	Adverse drug reactions
Any adverse event	9 (100.0)	5 (55.6)
Vomiting	6 (66.7)	3 (33.3)
Diarrhoea	6 (66.7)	1 (11.1)
Pyrexia	5 (55.6)	3 (33.3)
Rhinitis	5 (55.6)	0 (0.0)
Anaemia	4 (44.4)	0 (0.0)
Cough	3 (33.3)	1 (11.1)
Catheter site infection	3 (33.3)	0 (0.0)
Device related infection	3 (33.3)	0 (0.0)
Nasopharyngitis	3 (33.3)	0 (0.0)
Urticaria	3 (33.3)	2 (22.2)
Dermatitis diaper	3 (33.3)	0 (0.0)

n (Incidence, %); MedDRA ver.13.1

Three deaths (hepatic failure, peritoneal haemorrhage, cardiac arrest) were reported, but a causal relationship to study drug was ruled out for all cases. Serious adverse events occurred in 8 subjects (89%) (31 events) (hepatic failure; peritoneal haemorrhage; cardiac arrest; catheter site infection, device related infection, food intolerance, viral infection, respiratory tract infection, and pyrexia; catheter site infection [3 events], poor venous access, and upper respiratory tract infection; lymphadenopathy; hyperthermia, weight decreased, staphylococcal sepsis, diarrhoea, metabolic acidosis, dehydration, and roseola; failure to thrive, device related sepsis, tachycardia, pallor, chills, pyrexia, staphylococcal bacteraemia, escherichia pyelonephritis, and device related infection). Of these events, 4 infusion associated reactions (IARs) (tachycardia, pallor, chills, pyrexia) occurring in 1 subject were classified as adverse drug reactions. There were no adverse events leading to

treatment discontinuation.

Four of 7 subjects[51] (57%) tested positive for anti-sebelipase alfa antibodies at some time point, and 1 subject was antibody-positive at the last time point. Two subjects developed neutralizing antibodies.

Among findings on vital signs, elevated blood pressure was consistent across all subjects, but there was no association with administration of sebelipase alfa or its dose level. Changes in body temperature were reported as adverse events (pyrexia, hyperthermia, body temperature increased) for 6 of the 9 subjects. Many of these events were categorized as IARs, and a causal relationship to study drug was ruled out for the events other than IARs. Two subjects had transient increases in heart rate, which were reported as IARs (tachycardia).

There were no clinically meaningful changes in 12-lead ECGs.

4.(iii).A.(3) Long-term extension study in non-Japanese adult patients with LAL deficiency (5.3.5.2.1, Study LAL-CL04 [ongoing since [redacted] 2011 (data cutoff in [redacted] [redacted])]; reference data)

An open-label, uncontrolled study was conducted to evaluate the long-term safety of sebelipase alfa in non-Japanese adult patients with LAL deficiency who completed Study LAL-CL01[52] (target sample size, 9 subjects) [see "4.(ii).A.(1) Phase I/II study in non-Japanese patients with LAL deficiency" for the results from Study LAL-CL01].

In the extension study, each subject initiated treatment at the dosage of sebelipase alfa that he/she received at the end of Study LAL-CL01 (0.35 mg/kg, 1 mg/kg, or 3 mg/kg once weekly [qw]). After 4 initial doses, subjects who initiated dosing at 0.35 or 1 mg/kg qw were transitioned to dosing at 1 mg/kg once every other week (qow) (Cohort 1) and those who initiated dosing at 3 mg/kg qw were transitioned to dosing at 3 mg/kg qow (Cohort 2).

Eight subjects enrolled in the study (5 subjects in Cohort 1, 3 subjects in Cohort 2) were included in the Safety Analysis Set and in the FAS, and the FAS was used for efficacy analysis.

The results of efficacy endpoints are shown in Table 17. Liver histology was assessed by biopsy for 2 subjects and both subjects showed improvement in liver histology (a reduction in the percentage of steatosis).

[51] Since 2 subjects died before undergoing anti-drug antibody assessment, immunogenicity was assessed in 7 subjects.
[52] Key eligibility criteria: acceptable tolerability was demonstrated; and patients who received all of 4 scheduled doses of sebelipase alfa in Study LAL-CL01.

Table 17. Results of efficacy endpoints (Study LAL-CL04, FAS)

Endpoint	Baseline[a]		Change from baseline[b] (Week 24[c])		Change from baseline[b] (Week 52[c])		Change from baseline[b] (Week 104[c])	
	Cohort 1 (n = 5)	Cohort 2 (n = 3)	Cohort 1 (n = 5)	Cohort 2 (n = 3)	Cohort 1 (n = 5)	Cohort 2 (n = 3)	Cohort 1 (n = 5)	Cohort 2 (n = 3)
ALT (U/L)	82.0 ± 22.6 (n = 5)	84.3 ± 26.5 (n = 3)	-49.3 ± 9.5 (n = 5)	-62.8 ± 9.4 (n = 3)	-55.6 ± 8.4 (n = 4)	-58.1 ± 16.1 (n = 3)	-51.1 ± 20.2 (n = 4)	-71.0 ± 5.0 (n = 2)
AST (U/L)	58.8 ± 9.7 (n = 5)	47.7 ± 15.1 (n = 3)	-31.4 ± 12.3 (n = 5)	-32.1 ± 48.6 (n = 3)	-42.5 ± 15.9 (n = 4)	-43.4 ± 6.6 (n = 3)	-14.6 ± 49.2 (n = 4)	-53.9 ± 10.8 (n = 2)
LDL-C[d] (mg/dL)	154.0 ± 98.7 (n = 5)	130.0 ± 16.1 (n = 3)	-39.4 ± 8.4 (n = 5)	-55.4 ± 12.5 (n = 3)	-64.6 ± 11.0 (n = 4)	-54.9 ± 14.9 (n = 3)	-47.5 ± 6.2 (n = 4)	-66.0 ± 7.5 (n = 2)
HDL-C (mg/dL)	35.0 ± 9.6 (n = 5)	39.3 ± 11.9 (n = 3)	12.0 ± 15.0 (n = 5)	22.6 ± 15.8 (n = 3)	22.2 ± 17.9 (n = 4)	38.5 ± 30.8 (n = 3)	15.3 ± 13.1 (n = 4)	24.6 ± 41.4 (n = 2)
Triglyceride (mg/dL)	125.2 ± 52.2 (n = 5)	207.7 ± 110.7 (n = 3)	-16.8 ± 26.0 (n = 5)	-31.7 ± 28.9 (n = 3)	-47.1 ± 24.5 (n = 4)	-21.1 ± 42.4 (n = 3)	-21.0 ± 16.7 (n = 4)	-51.2 ± 13.4 (n = 2)
Liver fat content[e]	10.2 ± 2.1 (n = 3)	7.5 ± 5.0 (n = 2)	-37.5 ± 11.1 (n = 2)	7.4 ± 68.4 (n = 2)	-48.8 ± 4.5 (n = 2)	-24.5 ± 38.5 (n = 2)	-48.70 (n = 1)	-28.50 (n = 1)
Liver volume[e] (MN[f])	1.090 ± 0.15 (n = 5)	0.970 ± 0.02 (n = 3)	-0.058 ± 0.22 (n = 4)	-0.138 ± 0.04 (n = 3)	-0.072 ± 0.08 (n = 4)	-0.128 ± 0.02 (n = 3)	-0.181 ± 0.11 (n = 3)	-0.172 ± 0.07 (n = 2)
Spleen volume[e] (MN[f])	2.4 ± 0.67 (n = 5)	1.86 ± 0.35 (n = 3)	0.03 ± 0.50 (n = 4)	-0.09 ± 0.32 (n = 3)	0.19 ± 0.41 (n = 4)	-0.07 ± 0.34 (n = 3)	-0.25 ± 0.56 (n = 3)	0.10 ± 0.22 (n = 2)

Mean ± SD
Cohort 1, 0.35 or 1 mg/kg qw followed by 1 mg/kg qow; Cohort 2, 3 mg/kg qw followed by 3 mg/kg qow
a) Baseline was defined as the start of Study LAL-CL04 for liver fat content, liver volume, and spleen volume and as the start of Study LAL-CL01 for blood parameters.
b) Based on changes in liver volume and spleen volume and percent change (%) of other parameters.
c) The number of weeks was counted from treatment initiation in Study LAL-CL01.
d) Direct method
e) Assessed by multi-echo gradient-echo MRI (MEGE-MRI) (abdominal MRI).
f) MN, multiples of normal

Safety data were summarized. Adverse events occurred in all of the 8 subjects (100.0%) and adverse drug reactions occurred in 4 subjects (50.0%). Adverse events reported by ≥3 subjects in the study are shown in Table 18.

Table 18. Adverse events and/or adverse drug reactions reported by ≥3 subjects in the study (Study LAL-CL04)

	Cohort 1 (n = 5)		Cohort 2 (n = 3)		Total (n = 8)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	5 (100.0)	3 (60.0)	3 (100.0)	1 (33.3)	8 (100.0)	4 (50.0)
Nasopharyngitis	4 (80.0)	0 (0.0)	1 (33.3)	0 (0.0)	5 (62.5)	0 (0.0)
Abdominal pain	4 (80.0)	3 (60.0)	0 (0.0)	0 (0.0)	4 (50.0)	3 (37.5)
Abdominal pain upper	1 (20.0)	0 (0.0)	2 (66.7)	1 (33.3)	3 (37.5)	1 (12.5)
Diarrhoea	2 (40.0)	2 (40.0)	1 (33.3)	0 (0.0)	3 (37.5)	2 (25.0)
Back pain	2 (40.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (37.5)	0 (0.0)
Musculoskeletal pain	2 (40.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (37.5)	0 (0.0)

n (Incidence, %), MedDRA ver.13.1
Cohort 1, 0.35 or 1 mg/kg qw followed by 1 mg/kg qow
Cohort 2, 3 mg/kg qw followed by 3 mg/kg qow

No deaths were reported throughout the study period. Serious adverse events occurred in 1 subject (cholecystitis and cholelithiasis), but a causal relationship to study drug was ruled out for both events. There were no adverse events leading to treatment discontinuation.

One subject tested positive for anti-sebelipase alfa antibodies at 1 time point only and all subsequent results from this subject were negative. None of the subjects developed neutralizing antibodies.

There were no clinically meaningful changes in vital signs or 12-lead ECG.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of sebelipase alfa

The applicant's explanation:

LAL deficiency is an ultra-rare, autosomal recessive disorder and the deficiency of lysosomal acid lipase (LAL) results in accumulation of cholesteryl esters and triglycerides in the lysosomes of various tissues and cells throughout the body. LAL deficiency is a progressive multisystem disease, which frequently manifests early in life leading to serious complications. The complications of infantile-onset, rapidly progressive LAL deficiency (Wolman disease) include failure to thrive with progressive liver dysfunction and rapid development of liver fibrosis, and Wolman disease is usually fatal within the first 6 months of life. Late-onset LAL deficiency (CESD) is also complicated by marked hepatomegaly, elevation of transaminases signalling chronic liver dysfunction, and liver disease such as liver fibrosis and cirrhosis manifesting early in life. Patients with LAL deficiency exhibit dyslipidemia due to marked disturbances of lipid metabolism and are at risk for atherosclerosis.[53]

There are no treatments approved for patients with LAL deficiency in Japan, and statins and other medications to treat dyslipidemia, and supportive therapies have been used to mitigate gastrointestinal symptoms such as diarrhoea. Many of the patients have persistent dyslipidemia, leading to the progression of liver disease. Hematopoietic stem cell and liver transplantation has also been attempted, but these are highly invasive and exhibit limited efficacy.

Sebelipase alfa is a glycoprotein with N-linked glycosylation sites, which has an amino acid sequence identical to that of human LAL. This glycoprotein contains high-mannose-type and phosphorylated high-mannose-type glycans. Sebelipase alfa is an enzyme replacement therapy that replaces the missing enzyme (LAL) to reduce cholesteryl esters and triglycerides accumulated in the lysosomes, thus improving the symptoms of LAL deficiency.

As described above, since there are no effective therapies approved for patients with LAL deficiency, offering sebelipase alfa to healthcare professionals is of great significance.

PMDA's view:

LAL deficiency is a serious disease, and there is no drug approved for the indication of LAL deficiency in Japan. Sebelipase alfa replaces the missing enzyme, and offering sebelipase alfa as a therapeutic option to healthcare professionals who will use it to improve the symptoms in patients with LAL deficiency is of great significance.

[53] Ouimet M, *et al*. *Arterioscler Thromb Vasc Biol*. 2012;32: 575-81, Ouimet M, *et al*. *Cell Metab*. 2011;13: 655-67.

4.(iii).B.(2) Efficacy

Taking account of the rarity and seriousness of LAL deficiency, PMDA reviewed not only Japanese clinical studies but also foreign studies to assess the efficacy of sebelipase alfa. Since only 2 Japanese subjects participated in a multiregional phase III study (Study LAL-CL02) in which none of them were randomized to receive placebo,[54] PMDA evaluated the efficacy of sebelipase alfa in the overall study population and also assessed the efficacy in individual Japanese subjects.

4.(iii).B.(2).1) Efficacy in patients with late-onset LAL deficiency (CESD)

The applicant's explanation:

In a phase III study in non-Japanese and Japanese patients with late-onset LAL deficiency (Study LAL-CL02), the primary endpoint was the proportion of subjects who achieved ALT normalization at the end of the double-blind period (Week 20). The results were 6.7% (2 of 30 subjects) in the placebo group and 30.6% (11 of 36 subjects) in the sebelipase alfa group, demonstrating the superiority of sebelipase alfa over placebo.

As baseline age (min., 4 years; max., 58 years; median, 13 years) and baseline liver disease severity (liver volume: min., 0.83 MN[55]; max., 2.91 MN; median, 1.405 MN and ALT value: min., 50 U/L; max., 237 U/L; median, 87 U/L) considerably varied for subjects enrolled in the clinical study, subgroup analyses were performed according to baseline age (<12 years, 12-18 years, ≥19 years), baseline liver volume (<1.25 MN, ≥1.25 MN and <1.58 MN, ≥1.58 MN), and baseline ALT value (<3×ULN, ≥3×ULN) (Table 19).

The subgroup analysis by age group showed a trend towards higher efficacy in the sebelipase alfa group than in the placebo group for all endpoints across all age groups, and efficacy tended to be higher in ≥12 year-old patients than in <12 year-old patients. The subgroup analysis by liver disease severity also showed a trend towards higher efficacy in the sebelipase alfa group than in the placebo group for all endpoints, regardless of baseline liver volume and baseline ALT values. While the proportion of subjects who achieved ALT normalization tended to decrease with higher baseline ALT values, there were no major differences in the results of other endpoints regardless of baseline ALT values.

[54] The "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) provide a reference guide to sample size determination for a global clinical trial. The notification recommends that the proportion of Japanese subjects be 15% to 20% of the total sample size. However, given the rarity of LAL deficiency and the difficulty of patient enrollment, the multiregional phase III study (LAL-CL02) was designed to enroll patients from the feasibility standpoint. For this reason, the Japanese sample size was not intended to obtain consistent results between the entire population and the Japanese population.

[55] MN (multiples of normal): Liver volume measured by abdominal MRI was adjusted for body weight to take into account differences in liver volume between the age groups (liver volume adjusted for body weight (%) = volume (cc)/body weight (g)×100) and reported as multiples of normal (normal liver volume was set as 2.5% of the body weight).

Table 19. Efficacy results, from baseline to Week 24, by baseline characteristics (Study LAL-CL02; overall population)

Baseline characteristics			Placebo	Sebelipase alfa
Age	<12 years	ALT normalization	0.0 (0/10)	21.4 (3/14)
		AST normalization	0.0 (0/10)	35.7 (5/14)
		Percent change from baseline in LDL-C	-0.74 ± 11.10 (n = 10)	-17.03 ± 24.68 (n = 14)
		Percent change from baseline in Non-HDL-C	-0.69 ± 8.89 (n = 10)	-17.99 ± 19.86 (n = 14)
		Percent change from baseline in liver volume	0.93 ± 10.69 (n = 10)	-13.49 ± 11.79 (n = 13)
	≥12 and <18 years	ALT normalization	7.1 (1/14)	11.1 (1/9)
		AST normalization	7.7 (1/13)	55.6 (5/9)
		Percent change from baseline in LDL-C	-8.86 ± 12.65 (n = 14)	-32.09 ± 17.29 (n = 9)
		Percent change from baseline in non-HDL-C	-9.94 ± 10.27 (n = 14)	-33.49 ± 13.99 (n = 9)
		Percent change from baseline in liver volume	-3.30 ± 9.26 (n = 13)	-13.05 ± 9.85 (n = 8)
	≥18 years	ALT normalization	16.7 (1/6)	53.8 (7/13)
		AST normalization	0.0 (0/6)	38.5 (5/13)
		Percent change from baseline in LDL-C	-9.34 ± 15.93 (n = 6)	-38.16 ± 18.10 (n = 13)
		Percent change from baseline in non-HDL-C	-10.34 ± 12.56 (n = 6)	-34.91 ± 16.16 (n = 13)
		Percent change from baseline in liver volume	-9.59 ± 9.52 (n = 4)	-4.97 ± 7.71 (n = 12)
Baseline liver volume	<1.25 MN[a)]	ALT normalization	0.0 (0/7)	42.9 (6/14)
		AST normalization	14.3 (1/7)	42.9 (6/14)
		Percent change from baseline in LDL-C	-8.10 ± 13.96 (n = 7)	-34.38 ± 19.22 (n = 14)
		Percent change from baseline in non-HDL-C	-7.09 ± 10.99 (n = 7)	-33.01 ± 17.44 (n = 14)
		Percent change from baseline in liver volume	-1.95 ± 7.07 (n = 7)	-5.67 ± 10.68 (n = 13)
	≥1.25 MN and <1.58 MN	ALT normalization	0.0 (0/10)	27.3 (3/11)
		AST normalization	0.0 (0/10)	45.5 (5/11)
		Percent change from baseline in LDL-C	-10.21 ± 15.83 (n = 10)	-29.32 ± 17.37 (n = 11)
		Percent change from baseline in non-HDL-C	-11.30 ± 12.92 (n = 10)	-28.53 ± 13.42 (n = 11)
		Percent change from baseline in liver volume	-1.32 ± 12.30 (n = 10)	-8.28 ± 10.11 (n = 9)
	≥1.58 MN	ALT normalization	9.1 (1/11)	18.2 (2/11)
		AST normalization	0.0 (0/10)	36.4 (4/11)
		Percent change from baseline in LDL-C	-1.59 ± 10.08 (n = 11)	-19.94 ± 28.80 (n = 11)
		Percent change from baseline in non-HDL-C	-3.16 ± 9.04 (n = 11)	-21.01 ± 23.41 (n = 11)
		Percent change from baseline in liver volume	-4.51 ± 10.21 (n = 10)	-17.37 ± 6.95 (n = 11)

Mean ± SD, proportion of subjects who achieved ALT or AST normalization (%) (number of subjects/number of evaluable subjects), percent change (%)
a) MN, multiples of normal

Table 19. Efficacy results, from baseline to Week 24, by baseline characteristics (Study LAL-CL02: overall population) (continued)

Baseline ALT	<3×ULN	ALT normalization	9.1 (2/22)	38.5 (10/26)
		AST normalization	4.8 (1/21)	42.3 (11/26)
		Percent change from baseline in LDL-C	-6.22 ± 11.23 (n = 22)	-27.72 ± 23.99 (n = 26)
		Percent change from baseline in non-HDL-C	-6.71 ± 8.95 (n = 22)	-27.43 ± 19.79 (n = 26)
		Percent change from baseline in liver volume	-2.55 ± 9.54 (n = 19)	-10.47 ± 10.45 (n = 25)
	≥3×ULN	ALT normalization	0.0 (0/8)	10.0 (1/10)
		AST normalization	0.0 (0/8)	40.0 (4/10)
		Percent change from baseline in LDL-C	-6.34 ± 17.99 (n = 8)	-30.25 ± 18.18 (n = 10)
		Percent change from baseline in non-HDL-C	-7.55 ± 15.91 (n = 8)	-29.39 ± 16.01 (n = 10)
		Percent change from baseline in liver volume	-2.94 ± 12.05 (n = 8)	-9.70 ± 11.42 (n = 8)

Mean ± SD, proportion of subjects who achieved ALT or AST normalization (%) (number of subjects/number of evaluable subjects), percent change (%)

PMDA asked the applicant to explain the following findings: (1) The proportion of sebelipase alfa-treated subjects who achieved ALT normalization tended to decrease with larger liver volume at baseline and (2) the percent change in liver volume was smaller in the sebelipase alfa group than in the placebo group for subjects ≥18 years of age.

The applicant's response:

The proportion of subjects who achieved ALT normalization tended to decrease with larger liver volume at baseline. The baseline ALT (mean) in the subgroups classified by baseline liver volume (<1.25 MN, ≥1.25 MN and <1.58 MN, ≥1.58 MN) varied, i.e. 98.9, 113.1, and 105.1, respectively, whereas the percent changes in ALT in the subgroups were similar, i.e. 53%, 56%, and 56%, respectively. The percent change in liver volume was smaller in the subgroup of subjects ≥18 years of age possibly because liver volume was already relatively near-normal at baseline in the subgroup. This is on the grounds that baseline liver volume (mean) in the sebelipase alfa group was 4% smaller in the subjects ≥18 years of age than in the subjects ≥12 and <18 years of age and 21% smaller in the subjects ≥18 years of age than in the subjects <12 years of age.

PMDA asked the applicant to explain the following findings: In Study LAL-CL02, while reductions in transaminases, liver fat content, and liver volume were greater in the sebelipase alfa group than in the placebo group in the double-blind period, there were no major differences in improvement in liver histopathology between the treatment groups.

The applicant's response:

In Study LAL-CL02, improvement in liver histopathology (a ≥5% decrease in hepatic steatosis score) was assessed as a secondary endpoint. The results of endpoints are shown in Table 9. While a trend towards improvements in transaminases, liver fat content, and liver volume was observed, there were no major differences in improvement in liver histopathology between the treatment groups. As many of the subjects were children, only 39% of subjects in the FAS underwent liver biopsy at both baseline and Week 20 (16 of 36 subjects in the sebelipase alfa group, 10 of 30 subjects in the placebo group). Thus, the finding may be attributable to the small number of evaluable subjects. The correlation between liver fat content as measured by MRI and hepatic steatosis score as assessed by morphometry of H&E stained sections of the liver was analyzed for subjects with available data at both baseline and the end of the double-blind period. As a result, both liver fat content as measured by MRI and hepatic steatosis score on biopsy were found to be reduced in 56% (9 of 16 subjects) of subjects in the sebelipase alfa group and 29% (2 of 7 subjects) of subjects in the placebo group, demonstrating that the majority of subjects in the sebelipase alfa group had reductions in liver fat content and hepatic steatosis score. Inconsistency between serum chemistry parameters and hepatic histopathological findings may be partly because histological improvement takes longer, compared with improvement in parameters such as serum transaminases.

The efficacy of sebelipase alfa in the open-label period was evaluated in 65 subjects who completed the double-blind period and then entered the open-label period in Study LAL-CL02. In the sebelipase alfa group, reductions in serum ALT values were observed promptly after the initiation of treatment with sebelipase alfa and ALT remained reduced in the open-label period (Figure 1). Also in the placebo/sebelipase alfa group, reductions in serum ALT values were observed after the initiation of treatment with sebelipase alfa. A similar trend was observed for AST values. Lipid parameters in the sebelipase alfa group were evaluated. There were transient increases in both LDL-C and non-HDL-C at Week 2, and the 2 parameters returned to baseline levels between Week 4 and Week 6 (Table 20). Subsequent rapid declines were observed in LDL-C and non-HDL-C

and the improvements were sustained in the open-label period (Figure 1). In the placebo/sebelipase alfa group, transient increases in LDL-C and non-HDL-C after the initiation of treatment with sebelipase alfa were observed, with subsequent improvements (Figure 1).

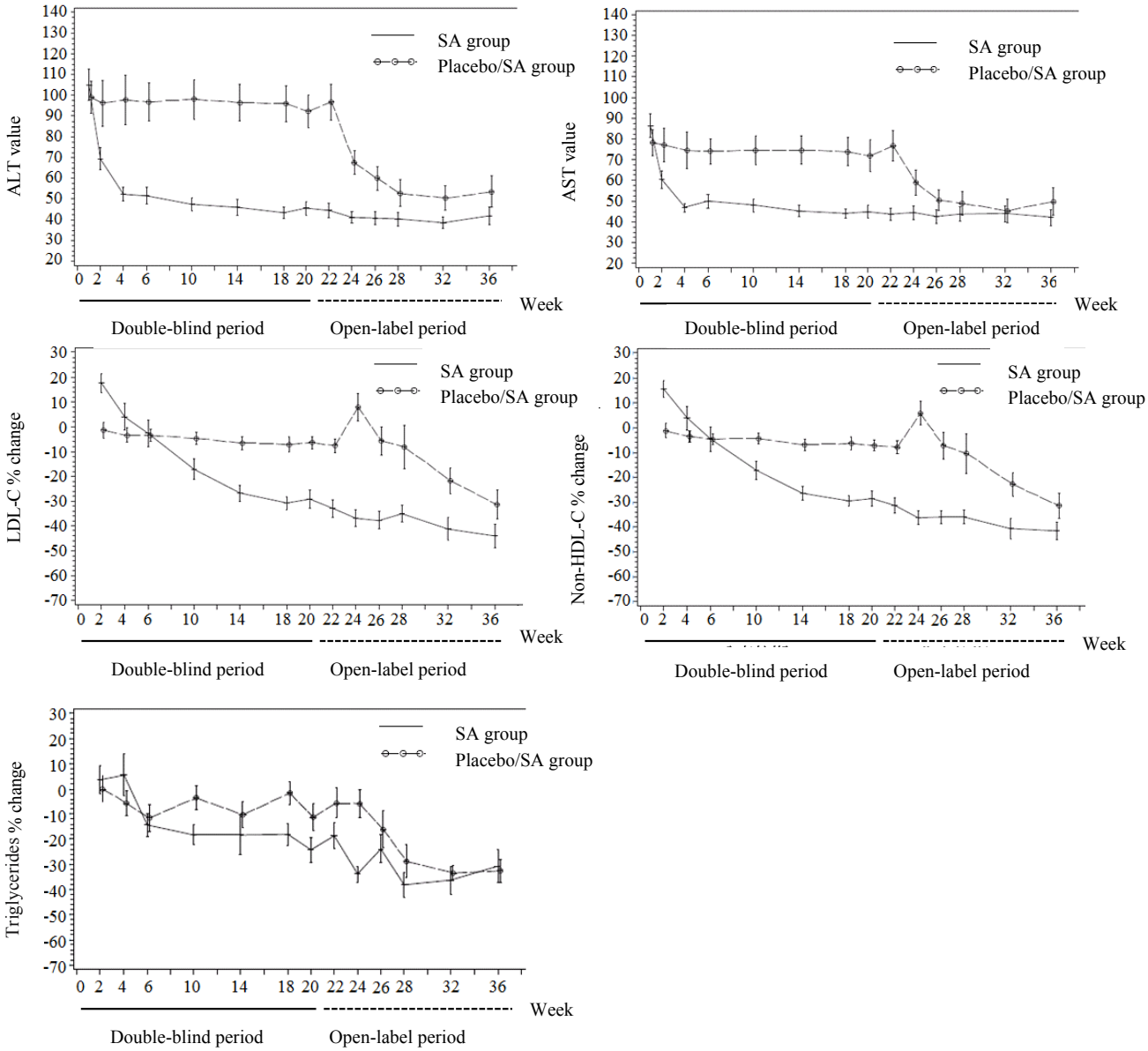

Figure 1. Liver enzyme and lipid parameters over time in the double-blind period and in the open-label period in the sebelipase alfa (SA) and placebo/SA groups (Study LAL-CL02)
(Mean ± standard error)

Table 20. Lipid parameters over time in early phase of treatment (Study LAL-CL02)

Endpoint		Baseline	Week 2	Week 4	Week 6	Week 10
LDL-C[a)] (mg/dL)	Placebo (n = 30)	229.5 ± 69.95 (n = 30)	224.1 ± 74.72 (n = 30)	221.7 ± 77.26 (n = 30)	220.7 ± 73.90 (n = 30)	218.7 ± 71.88 (n = 30)
	Sebelipase alfa (n = 36)	189.9 ± 57.16 (n = 36)	219.2 ± 70.37 (n = 36)	198.6 ± 88.08 (n = 35)	183.8 ± 78.95 (n = 35)	156.1 ± 58.81 (n = 35)
Non-HDL-C (mg/dL)	Placebo (n = 30)	263.8 ± 75.48 (n = 30)	258.9 ± 79.24 (n = 30)	254.3 ± 80.62 (n = 30)	251.0 ± 79.29 (n = 30)	251.9 ± 76.77 (n = 30)
	Sebelipase alfa (n = 36)	220.5 ± 61.48 (n = 36)	250.6 ± 75.03 (n = 36)	229.4 ± 93.14 (n = 35)	209.3 ± 84.77 (n = 35)	180.9 ± 62.26 (n = 35)
Triglyceride (mg/dL)	Placebo (n = 30)	174.4 ± 65.90 (n = 30)	176.2 ± 90.42 (n = 30)	163.7 ± 75.86 (n = 30)	152.0 ± 72.62 (n = 30)	166.0 ± 69.29 (n = 30)
	Sebelipase alfa (n = 36)	152.8 ± 54.43 (n = 36)	157.4 ± 76.44 (n = 36)	159.1 ± 84.10 (n = 35)	128.1 ± 54.15 (n = 35)	123.8 ± 47.20 (n = 35)

Mean ± SD
a) Calculated using the Friedewald formula.

The results of different endpoints in the open-label period for Japanese subjects are shown in Table 21. Reductions from baseline in liver enzymes, liver fat content, and liver volume were observed in both subjectsand these effects were largely sustained at Week 50. Reductions from baseline in LDL-C and non-HDL-C at the end of the double-blind period were observed in Subject 1 receiving lipid-lowering medication. Subject 2 not receiving lipid-lowering medication showed no reductions in LDL-C and non-HDL-C at the end of the double-blind period, but experienced improvements in the lipid parameters at Week 50. Subject 1 remained on a dose of 1 mg/kg every other week. In Subject 2, the dose was escalated to 3 mg/kg every other week at Week 74 due to persistent increases in ALT and LDL-C, and improvements in the parameters such as ALT, LDL-C, and non-HDL-C were observed at Week 100.

Table 21. Results of primary, secondary, and other endpoints in individual subjects (Study LAL-CL02; Japanese subgroup)

Endpoint	Subject number	Baseline	End of double-blind period	Week 50 or 52 [a)]	Week 64	Week 100
ALT (U/L)	Subject 1	116	51 (-56.0%)	47 (-59.5%)	23 (-80.2%)	20 (-82.8%)
	Subject 2	91	48 (-47.3%)	68 (-25.3%)	75 (-17.6%)	37 (-59.3%)
AST (U/L)	Subject 1	96	43 (-55.2%)	38 (-60.4%)	29 (-69.8%)	29 (-69.8%)
	Subject 2	69	39 (-43.5%)	49 (-29.0%)	58 (-15.9%)	33 (-52.2%)
LDL-C (mg/dL)[b)]	Subject 1	222	114 (-48.6%)	156 (-29.7%)	95 (-57.2%)	131 (-41.0%)
	Subject 2	239	348 (45.6%)	212 (-11.3%)	240 (0.4%)	195 (-18.4%)
Non-HDL-C (mg/dL)	Subject 1	244	138 (-43.4%)	177 (-27.5%)	115 (-52.9%)	156 (-36.1%)
	Subject 2	280	378 (35.0%)	235 (-16.1%)	274 (-2.1%)	213 (-23.9%)
HDL-C (mg/dL)	Subject 1	48	72 (50.0%)	68 (41.7%)	55 (14.6%)	57 (18.8%)
	Subject 2	27	32 (18.5%)	35 (29.6%)	36 (33.3%)	38 (40.7%)
Triglyceride (mg/dL)	Subject 1	109	119 (9.2%)	105 (-3.7%)	101 (-7.3%)	122 (11.9%)
	Subject 2	207	149 (-28.0%)	115 (-44.4%)	170 (-17.9%)	92 (-55.6%)
Liver fat content [c)] (%)	Subject 1	10.76	7.44 (-30.9%)	7.74 (-28.1%)	—	—
	Subject 2	7.69	5.18 (-32.6%)	5.64 (-26.7%)	—	—
Liver volume[c)] (MN[d)])	Subject 1	1.04	1.14 (9.6%)	0.94 (-9.6%)	—	—
	Subject 2	2.91	2.36 (-18.9%)	2.29 (-21.3%)	—	—
Spleen volume[c)] (MN[d)])	Subject 1	1.64	1.4 (-14.6%)	1.36 (-17.1%)	—	—
	Subject 2	8.17	7.00 (-14.3%)	6.00 (-26.6%)	—	—

Value (percent change from baseline); —, not measured
a) Week 50 for blood test parameters, Week 52 for parameters as measured by MRI
b) Calculated using the Friedewald formula.
c) Assessed by multi-echo gradient-echo MRI (MEGE-MRI) (abdominal MRI).
d) MN, multiples of normal

4.(iii).B.(2).2) Efficacy in patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease)

The applicant's explanation:

In order to assess the efficacy of sebelipase alfa in patients with infantile-onset, rapidly progressive LAL deficiency, the results from Study LAL-CL03 were compared with those from Study LAL-1-NH01, which served as a historical control. Patient characteristics in Studies LAL-CL03 and LAL-1-NH01 are shown in Table 22.

Table 22. Comparison of subject characteristics in infant studies (Study LAL-CL03, Study LAL-1-NH01)

	Study LAL-CL03 (n = 9)	Study LAL-1-NH01 (no history of hematopoietic stem cell or liver transplantation, and early growth failure) (n = 21)	Study LAL-1-NH01 (no history of hematopoietic stem cell or liver transplantation) (n = 25)
Sex (Male %)	5/9 (55.6%)	10/21 (47.6%)	13/25 (52.0%)
Age at onset (months of age)	1.61 ± 1.71 (1.24) (n = 8)	1.39 ± 1.07 (1.08) (n = 21)	1.29 ± 1.02 (1.15) (n = 25)
Age at diagnosis (months of age)	2.44 ± 1.81 (2.00) (n = 9)	2.75 ± 0.95 (2.63) (n = 21)	3.43 ± 3.23 (2.63) (n = 25)
Growth failure with onset before 6 months of age	8/9 (88.9%)	21/21 (100.0%)	21/25 (84.0%)
Weight-for-age Z-score	−4.35 ± 1.62 (−4.45) (n = 9)	−2.11 ± 1.73 (−2.64) (n = 20)	−0.47 ± 1.26 (−0.17) (n = 25)
ALT (U/L)	130 ± 96 (145) (n = 9)	176 ± 252 (63) (n = 16)	162 ± 241 (56) (n = 18)
AST (U/L)	294 ± 256 (125) (n = 9)	497 ± 774 (350) (n = 12)	447 ± 723 (279) (n = 14)

Number of subjects/Number of evaluable subjects (Proportion %), Mean ± SD (Median)

In Study LAL-CL03 in patients with growth failure with onset before 6 months of age or other evidence of rapidly progressive LAL deficiency, the proportion of sebelipase alfa-treated infants surviving to 12 months of age was 66.7% (6 of 9 subjects) (95% confidence interval [CI]: 29.9%, 92.5%). Analyses were performed for a historical control group from Study LAL-1-NH01 because the patient baseline characteristics were similar to those of the LAL-CL03 patient population ("patients who had early growth failure, but who did not have a hematopoietic stem cell or liver transplant, etc. at ≤6 months of age"). Of the 21 historical control infants analyzed, none survived beyond 8 months of age. The proportion of these infants surviving to 12 months of age was 0% (0 of 21 patients) (95% CI: 0%, 16.1%), which was lower than the survival in the subjects evaluated in Study LAL-CL03 (Figure 2). Furthermore, analyses were performed for a historical control group defined as "patients with or without early growth failure who did not have a hematopoietic stem cell or liver transplant, etc. at ≤6 months of age," and 25 historical control infants were analyzed for survival at 12 months of age. The proportion of surviving infants in the historical control group was 4.0% (1 of 25 patients) (95%CI: 0.10%, 20.35%), which was lower than the survival in the subjects in Study LAL-CL03.

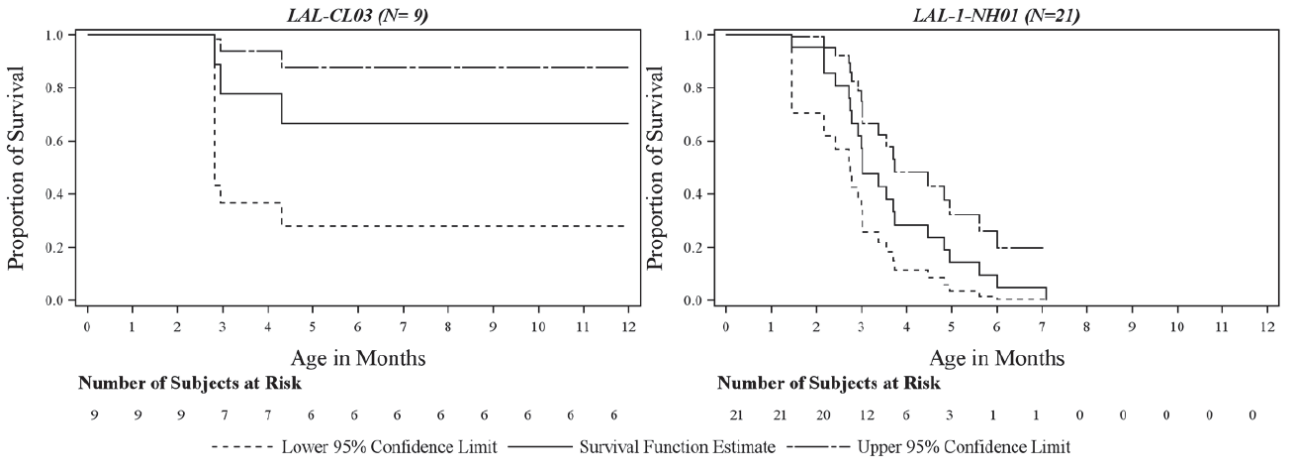

Figure 2. Kaplan-Meier survival analysis from birth up to Month 12 in Studies LAL-CL03 and LAL-1-NH01

In Study LAL-CL03, sebelipase alfa doses were escalated to 3 mg/kg in all of 6 subjects surviving at 12 months of age and the dose was escalated to 5 mg/kg in 1 of these 6 subjects. Neutralizing antibodies were detected in the subject who required a dose increase to 5 mg/kg. All of the 3 subjects who died during Study LAL-CL03 had a history suggestive of multi-system organ failure syndrome. At the time of death, 2 subjects were receiving sebelipase alfa at a dose of 0.35 mg/kg and the remaining 1 subject was receiving sebelipase alfa at a dose of 1 mg/kg. The cause of death in all cases was complications secondary to disease progression, etc. and its causal relationship to study drug was ruled out.

All of the 6 subjects surviving to 12 months of age in Study LAL-CL03 remained on treatment and the duration of exposure was up to 38 months. Patient status beyond 12 months of age is shown in Table 23.

Table 23. Patient status beyond 12 months of age (Study LAL-CL03 [Data cutoff in [redacted]])

	12 months of age	18 months of age	24 months of age	30 months of age	36 months of age
Alive and on treatment	6 (66.7)	3 (33.3)	2 (22.2)	1 (11.1)	1 (11.1)
Died	3 (33.3)	3 (33.3)	3 (33.3)	3 (33.3)	3 (33.3)
Alive, but not reached the age specified for the analysis	0 (0.0)	3 (33.3)	4 (44.4)	5 (55.6)	5 (55.6)

n (Proportion, %)

Table 15 shows growth and liver enzyme parameters over time in Study LAL-CL03, indicating that increases in weight-for-age and height-for-age and decreases in liver enzyme parameters were observed after treatment with sebelipase alfa.

As described above, sebelipase alfa-treated patients with infantile-onset, rapidly progressive LAL deficiency demonstrated clinically meaningful improvement in survival as well as improvements in growth and liver enzyme parameters. Analyses were performed for a historical control group of untreated patients with LAL deficiency who had early growth failure within the first 6 months of life. None of the 21 historical control subjects survived beyond 8 months of age, and the proportion of subjects surviving to 12 months of age was 0% (0 of 21 subjects) (95% CI: 0%, 16.1%).

PMDA's view on the discussions presented in 4.(iii).B.(2).1) and 4.(iii).B.(2).2):
A multiregional phase III study in patients with late-onset LAL deficiency (CESD) demonstrated the superiority of sebelipase alfa over placebo for the proportion of subjects who achieved ALT normalization (the primary

endpoint). Improvements in lipid parameters (the secondary endpoints) were also observed in the study. In individual Japanese subjects in the sebelipase alfa group, a trend towards improvements in liver enzyme and lipid parameters was observed and the effects of treatment were sustained. There are limitations to comparison of sebelipase alfa-treated patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) in Study LAL-CL03 and a historical control group, but the analysis revealed a trend towards improvement in survival in sebelipase alfa-treated patients. Based on the above, it can be interpreted that the efficacy of sebelipase alfa in patients with LAL deficiency has largely been demonstrated. Because of the limited number of patients studied, information on the efficacy of sebelipase alfa should continue to be collected via post-marketing surveillance. The above decisions will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(3) Safety

The applicant's explanation:

The occurrence of adverse events in each clinical study was analyzed based on the pooled data (data cutoff in [redacted]). The results are shown in Table 24. Most adverse events were mild or moderate in severity, except for those reported in Studies LAL-CL03 and LAL-CL08.[56] Events reported by ≥10% of subjects in the pooled safety set were diarrhoea, pyrexia, headache, nasopharyngitis, cough, vomiting, rhinitis, upper respiratory tract infection, abdominal pain, nausea, oropharyngeal pain, rhinorrhoea, upper abdominal pain, and gastroenteritis (in descending order of incidence). The system organ classes of adverse events occurring more frequently in Studies LAL-CL03 and LAL-CL08 conducted in patients with infantile-onset, rapidly progressive LAL deficiency than in Studies LAL-CL02, LAL-CL04, and LAL-CL06[57] conducted in patients with late-onset LAL deficiency were "blood and lymphatic system disorders," "cardiac disorders," "investigations," "metabolism and nutrition disorders," and "skin and subcutaneous tissue disorders."

A total of 64 serious adverse events occurred in 19 subjects, and of the events, 58 occurred in 14 subjects in Studies LAL-CL03 and LAL-CL08 in patients with infantile-onset, rapidly progressive LAL deficiency. Serious adverse events reported by ≥2 subjects were pyrexia (4 subjects); tachycardia and device related infection (3 subjects); and catheter site infection, sepsis, viral infection, and dehydration (2 subjects). Although a causal relationship to study drug was ruled out for many of the serious adverse events, the following 9 events reported by 4 subjects were classified as adverse drug reactions: 1 event reported by 1 subject in Study LAL-CL02 (infusion related reaction), 4 events reported by 1 subject in Study LAL-CL03 (tachycardia, pallor, chills, and pyrexia), 1 event reported by 1 subject in Study LAL-CL06 (anaphylactic reaction), and 3 events reported by 1 subject in Study LAL-CL08 (respiratory distress, tachycardia, and urticaria). There were 5 deaths; all occurred in the studies in patients with infantile-onset, rapidly progressive LAL deficiency (Studies LAL-CL03 and LAL-CL08), and their causal relationship to study drug was ruled out.

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[56] Study LAL-CL08: An open-label, uncontrolled study in <8-month-old patients with infantile-onset, rapidly progressive LAL deficiency. Sebelipase alfa was to be administered at a dose of 1 mg/kg once weekly and a dose escalation to 3 mg/kg once weekly after at least 4 infusions at a dose of 1 mg/kg was permitted in subjects exhibiting a suboptimal treatment response. An option for dose escalation to 5 mg/kg once weekly was given to subjects who had evidence for a continued suboptimal response or loss of efficacy in association with the presence of anti-drug antibodies.

[57] Study LAL-CL06: An open-label, uncontrolled study in ≥8-month-old patients with LAL deficiency who were ineligible for other trials. Sebelipase alfa was to be administered at a dose of 1 mg/kg once every other week and a dose escalation to 3 mg/kg once every other week was permitted in subjects exhibiting a suboptimal treatment response. The dosage was to be increased to 3 mg/kg once weekly in subjects with continued suboptimal response. Dose reduction to 0.35 mg/kg once every other week was permitted in the event of poor tolerability.

Table 24. Occurrence of adverse events (Pooled data, data cutoff in [redacted])

	LAL-CL02 (N = 66[a])	LAL-CL03 (N = 9[b])	LAL-CL04 (N = 9[c])	LAL-CL06 (N = 17[d])	LAL-CL08 (N = 5[e])	Total (N = 106[f])
Adverse events	62 (93.9)	9 (100.0)	9 (100.0)	4 (23.5)	5 (100.0)	89 (84.0)
Mild adverse events	31 (47.0)	0 (0.0)	1 (11.1)	3 (17.6)	0 (0.0)	35 (33.0)
Moderate adverse events	26 (39.4)	0 (0.0)	6 (66.7)	1 (5.9)	2 (40.0)	35 (33.0)
Severe adverse events	5 (7.6)	9 (100.0)	2 (22.2)	0 (0.0)	3 (60.0)	19 (17.9)
Serious adverse events	3 (4.5)	9 (100.0)	1 (11.1)	1 (5.9)	5 (100.0)	19 (17.9)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Adverse drug reactions	15 (22.7)	5 (55.6)	5 (55.6)	3 (17.6)	3 (60.0)	31 (29.2)
Serious adverse drug reactions	1 (1.5)	1 (11.1)	0 (0.0)	1 (5.9)	1 (20.0)	4 (3.8)
Deaths	0 (0.0)	4 (44.4)	0 (0.0)	0 (0.0)	1 (20.0)	5 (4.7)

n (Incidence, %)
a) 2.00-12.00 years, N = 24; 12.01-17.99 years, N = 23; ≥18 years, N = 19
b) <2 years, N = 9
c) ≥18 years, N = 9
d) 2.00-12.00 years, N = 7; 12.01-17.99 years, N = 3; ≥18 years, N = 5; Unknown, N = 2
e) <2 years, N = 5
f) <2 years, N = 14; 2.00-12.00 years, N = 31; 12.01-17.99 years, N = 26; ≥18 years, N = 33; Unknown, N = 2

The occurrence of adverse events by time period is shown in Table 25. There were no differences in the occurrence of adverse events according to time period.

Table 25. Occurrence of adverse events by time period (Pooled data, data cutoff in [redacted][a])

Time period (Week)	0-3	4-11	12-25	26-37	38-51	52-77	78-103	104-129	130-155	156-181
N	104	94	88	80	66	48	16	10	9	7
Adverse events	51 (49.0)	58 (61.7)	64 (72.7)	53 (66.3)	41 (62.1)	27 (56.3)	10 (62.5)	7 (70.0)	7 (77.8)	2 (28.6)
Serious adverse events	9 (8.7)	7 (7.4)	8 (9.1)	4 (5.0)	2 (3.0)	2 (4.2)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse drug reactions	11 (10.6)	10 (10.6)	10 (11.4)	7 (8.8)	7 (10.6)	5 (10.4)	1 (6.3)	2 (20.0)	2 (22.2)	1 (14.3)
Serious adverse drug reactions	1 (1.0)	1 (1.1)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)
a) One subject was treated for ≥182 weeks, but the data are omitted.

Adverse events by dose at onset are shown in Table 26. The incidences of serious adverse events and serious adverse drug reactions were higher in subjects receiving 3 mg/kg than in subjects receiving 0.35 or 1 mg/kg. This is considered attributable to the fact that the majority of the subjects receiving 3 mg/kg (8 of the 12 subjects) had infantile-onset, rapidly progressive LAL deficiency.

Table 26. Adverse events by dose at onset (Pooled data, data cutoff in [redacted])

	0.35 mg/kg (N = 11)	1 mg/kg (N = 101)	3 mg/kg (N = 12)	Total (N = 106)
Adverse events	10 (90.9)	83 (82.2)	11 (91.7)	89 (84.0)
Serious adverse events	2 (18.2)	15 (14.9)	7 (58.3)	19 (17.9)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	1 (9.1)	0 (0.0)	0 (0.0)	1 (0.9)
Adverse drug reactions	2 (18.2)	29 (28.7)	5 (41.7)	31 (29.2)
Serious adverse drug reactions	0 (0.0)	3 (3.0)	1 (8.3)	4 (3.8)
Deaths	2 (18.2)	2 (2.0)	1 (8.3)	5 (4.7)

n (Incidence, %)

Based on the occurrence of adverse events and adverse drug reactions in clinical studies in patients with late-onset LAL deficiency (CESD) or patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease), PMDA considers that the safety of sebelipase alfa is acceptable, provided that appropriate precautions are advised. Individual events have been further analyzed.

4.(iii).B.(3).1) Hypersensitivity (including anaphylaxis)

The applicant's explanation:

The occurrence of hypersensitivity-related events[58] in each clinical study was analyzed based on the pooled data (data cutoff in [redacted]). The results are shown in Table 27. The incidence of hypersensitivity-related events was high in clinical studies in patients with infantile-onset, rapidly progressive LAL deficiency (Studies LAL-CL03 and LAL-CL08). Serious events in the SMQ "hypersensitivity" occurred in 1 subject (anaphylactic reaction) in Study LAL-CL06 and 1 subject (respiratory distress and urticaria) in Study LAL-CL08. Serious events in the SMQ "anaphylactic reaction" occurred in 1 subject (cardiac arrest) in Study LAL-CL03, 1 subject (anaphylactic reaction, the same subject as the subject with a serious event in the SMQ "hypersensitivity") in Study LAL-CL06, and 2 subjects (hypotension; respiratory distress and urticaria [the same subject as the subject with serious events in the SMQ "hypersensitivity"]) in Study LAL-CL08. One subject who died in Study LAL-CL03 (4.3-month-old) had anaemia and thrombocytopenia after the first infusion of sebelipase alfa at a dose of 0.35 mg/kg once weekly and serum ferritin increased after the second infusion. This subject experienced "cardiac arrest," an event in the SMQ "anaphylactic reaction" after 2 infusions at a dose of 1 mg/kg once weekly, but its causal relationship to study drug was ruled out.

[58] Events identified by SMQ "hypersensitivity" and SMQ "anaphylactic reaction."

Table 27. Occurrence of hypersensitivity-related events (Pooled data, data cutoff in [redacted])

		LAL-CL02 (N = 66)	LAL-CL03 (N = 9)	LAL-CL04 (N = 9)	LAL-CL06 (N = 17)	LAL-CL08 (N = 5)	Total (N = 106)
SMQ "Hypersensitivity"	Adverse events	16 (24.2)	6 (66.7)	3 (33.3)	1 (5.9)	5 (100.0)	31 (29.2)
	Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (20.0)	2 (1.9)
	Severe adverse events	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (1.9)
	Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SMQ "Anaphylactic reaction"	Adverse events	25 (37.9)	6 (66.7)	5 (55.6)	2 (11.8)	5 (100.0)	43 (40.6)
	Serious adverse events	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.9)	2 (40.0)	4 (3.8)
	Severe adverse events	1 (1.5)	2 (22.2)	0 (0.0)	0 (0.0)	2 (40.0)	5 (4.7)
	Deaths	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)

The occurrence of hypersensitivity-related events by time period is shown in Table 28. There were no differences in the occurrence of hypersensitivity-related events according to time period.

Table 28. Occurrence of hypersensitivity-related events by time period (Pooled data, data cutoff in [redacted] a))

Time period (Week)	0-3	4-11	12-25	26-37	38-51	52-77	78-103	104-129	130-155	156-181
N	104	94	88	80	66	48	16	10	9	7
SMQ "Hypersensitivity"										
Adverse events	11 (10.6)	8 (8.5)	12 (13.6)	10 (12.5)	6 (9.1)	6 (12.5)	1 (6.3)	2 (20.0)	1 (11.1)	1 (14.3)
Serious adverse events	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe adverse events	1 (1.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SMQ "Anaphylactic reaction"										
Adverse events	11 (10.6)	12 (12.8)	10 (11.4)	13 (16.3)	9 (13.6)	13 (27.1)	2 (12.5)	2 (20.0)	1 (11.1)	2 (28.6)
Serious adverse events	1 (1.0)	2 (2.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe adverse events	3 (2.9)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)
a) One subject was treated for ≥182 weeks, but the data are omitted.

Hypersensitivity-related events by dose at onset are shown in Table 29. The incidence of hypersensitivity was higher in subjects receiving 3 mg/kg than in subjects receiving 0.35 or 1 mg/kg. This is considered attributable to the fact that the majority of the subjects receiving 3 mg/kg (8 of the 12 subjects) had infantile-onset, rapidly progressive LAL deficiency.

Table 29. Hypersensitivity-related events by dose at onset (Pooled data, data cutoff in [redacted])

		0.35 mg/kg (N = 11)	1 mg/kg (N = 101)	3 mg/kg (N = 12)	Total (N = 106)
SMQ "Hypersensitivity"	Adverse events	1 (9.1)	27 (26.7)	9 (75.0)	31 (29.2)
	Serious adverse events	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.9)
	Severe adverse events	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.9)
	Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SMQ "Anaphylactic reaction"	Adverse events	1 (9.1)	39 (38.6)	8 (66.7)	43 (40.6)
	Serious adverse events	0 (0.0)	4 (4.0)	0 (0.0)	4 (3.8)
	Severe adverse events	1 (9.1)	4 (4.0)	0 (0.0)	5 (4.7)
	Deaths	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.9)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)

Among hypersensitivity-related events, "hypersensitivity reactions" were identified by reviewing a temporal relationship of the adverse event with sebelipase alfa infusion, concurrent associated adverse events, causality assessment by the investigator, and by other means. Of 106 subjects in the pooled safety set, 21 subjects experienced "hypersensitivity reactions," including 9 infants and 12 children/adults.

Many of the hypersensitivity reactions occurred during infusion or within 4 hours after infusion and were reported as IARs by the investigator. The management of hypersensitivity reactions included temporarily interrupting the study infusion, lowering the infusion rate, and treatment with antihistamines, antipyretic analgesics, and corticosteroids. There was no early discontinuation of treatment with sebelipase alfa due to "hypersensitivity reactions."

In clinical studies, premedication with antihistamines or antipyretic analgesics, etc. was not routinely administered unless a subject experienced an IAR. If a subject experienced an IAR, the subject received premedication with oral antihistamines or antipyretic analgesics, etc. prior to the next infusion.

Based on the pooled data (data cutoff in [redacted]) and subsequent data, "hypersensitivity reactions" including anaphylaxis presenting with respiratory symptoms such as dyspnoea, cardiovascular symptoms such as decreased blood pressure, and neurologic symptoms such as consciousness clouding occurred in 10 subjects (2 subjects in Study LAL-CL02, 2 subjects in Study LAL-CL03, 1 subject in Study LAL-CL04, 2 subjects in Study LAL-CL06, and 3 subjects in Study LAL-CL08). Of these 10 subjects, 6 experienced severe events.

The 6 subjects with severe "hypersensitivity reactions" consisted of 2 subjects in Study LAL-CL02, 1 subject in Study LAL-CL03, 1 subject in Study LAL-CL04, 1 subject in Study LAL-CL06, and 1 subject in Study LAL-CL08. Of the 6 subjects,3 (1 each in Studies LAL-CL02, LAL-CL06, and LAL-CL08) were considered to have anaphylaxis.

The details of the 6 subjects with severe "hypersensitivity reactions" were as follows:
The first subject in Study LAL-CL02 was a [redacted]-year-old boy who received placebo during the double-blind period and sebelipase alfa 1 mg/kg once every other week during the open-label period. The subject developed anaphylaxis (hyperaemia, chest discomfort, and pruritus [mild to moderate]) during sebelipase alfa infusion at Week 56 of the open-label period (Week 78 from the start of the study). The subject received premedication with an antihistamine and an antipyretic analgesic prior to the next infusion, but developed anaphylaxis

(pruritus [mild], hyperaemia [severe], dyspnoea [moderate], and chest discomfort [moderate]) during sebelipase alfa infusion. The symptoms resolved following cessation of sebelipase alfa infusion and administration of a corticosteroid, and the subsequent doses of study drug were discontinued. The second subject in Study LAL-CL02 was a [redacted]-year-old boy who was randomized to receive sebelipase alfa during the double-blind period. The subject experienced mild hypersensitivity (rash) after the first infusion of sebelipase alfa at 1 mg/kg once every other week and was therefore premedicated with an antihistamine and a corticosteroid prior to the second infusion. Approximately 8.5 hours after the second infusion, the subject had severe hypersensitivity with dyspnea (rash, chest discomfort, nausea, dyspnoea, laryngeal oedema, anxiety, body temperature increased). Following administration of an antihistamine and an antacid, the subject recovered. This reaction was assessed as an IAR and treatment was interrupted. One year and 8 months later, the subject resumed treatment with sebelipase alfa at a reduced dose of 0.35 mg/kg once every other week and the dose was escalated to 1 mg/kg once every other week after 2 infusions at 0.35 mg/kg once every other week. Since then, the subject has been receiving sebelipase alfa 1 mg/kg once every other week without recurrence of an IAR.

In Study LAL-CL03, a [redacted]-month-old infant (boy) had severe tachycardia and moderate pyrexia on the day of escalating the dose to 3 mg/kg once weekly at Week 6. The events resolved within 2 hours without treatment. At Week 12, the infusion was interrupted due to the occurrence of severe pallor and tachycardia and moderate chills and pyrexia during sebelipase alfa infusion. The symptoms improved following fluid therapy and oxygen inhalation, and the subject resumed treatment. Despite premedication with an antipyretic analgesic and an antihistamine at Week 34, the subject had a moderate IAR (chills, pyrexia, oxygen saturation decreased) during sebelipase alfa infusion. The subject experienced mild chills, tachycardia, hypertension, hypotonia, and pyrexia, also at Week 58.

In Study LAL-CL04, a 2[redacted]-year-old man experienced moderate hyperaemia and chills during sebelipase alfa infusion (1 mg/kg weekly) at Week 36. The subject was therefore premedicated with an antihistamine and an antipyretic analgesic at Week 38, but had IARs (moderate hypersensitivity, mild laryngeal oedema, moderate abdominal pain, mild chills, and moderate nausea) including severe dizziness and hyperaemia during sebelipase alfa infusion. The symptoms resolved following administration of an antihistamine and epinephrine. Study drug administration was interrupted from Week 40 until Week 88 and treatment with sebelipase alfa was resumed at a dose of 0.35 mg/kg at Week 90 with a reduced infusion rate after premedication with an antihistamine and an antipyretic analgesic. The dose was escalated to 1 mg/kg once weekly at Week 98. The subject received infusions without premedication and without recurrence of IARs at Week 116. The subject tested negative for anti-sebelipase alfa antibodies and anti-egg white antibodies.

In Study LAL-CL06, a 4[redacted]-year-old man experienced serious anaphylaxis (pruritic rash, tachycardia, tachypnoea, conjunctival hyperaemia, and rhinorrhoea) during sebelipase alfa infusion at 1 mg/kg once every other week on Day 86, and the infusion was thus interrupted. The subject was premedicated with an antipyretic analgesic and an antihistamine prior to the next infusion, but experienced recurrent anaphylaxis (systemic and pruritic rash, tachypnoea, conjunctival hyperaemia, and rhinorrhoea) after the start of the infusion. Sebelipase alfa infusion was interrupted and the symptoms resolved following administration of an antihistamine and a

corticosteroid. The subject had a positive intradermal test to sebelipase alfa. Therefore, the subject has been receiving sebelipase alfa doses according to the desensitization protocol (sebelipase alfa was diluted into three concentrations and the solutions were infused over long hours in order of increasing concentration. If there were no problems, the infusion time was reduced). The subject experienced non-serious IARs (mild urticaria [6 events after 4 infusions] and moderate generalised rash and conjunctival hyperaemia).

In Study LAL-CL08, a [redacted]-month-old infant (boy) experienced anaphylaxis associated with severe respiratory distress, urticaria, and tachycardia during sebelipase alfa infusion at 1 mg/kg once weekly at Week 5. The symptoms resolved several hours later following treatment with an antihistamine, a corticosteroid, epinephrine, an antipyretic analgesic, fluid therapy, and oxygen inhalation. For subsequent infusions, the subject was premedicated with a corticosteroid, an antipyretic analgesic, and an antihistamine, but experienced a non-serious IAR (moderate agitation, tachycardia, and urticaria). Since then, the subject has been receiving sebelipase alfa without recurrence of an IAR.

As described above, hypersensitivity-related events occurred following sebelipase alfa infusion and were more common in infants, but these events were managed by reducing the infusion rate, interrupting the infusion, and administering antihistamines and/or antipyretic analgesics. Hypersensitivity including anaphylaxis will be listed in the contraindications, careful administration, important precautions, and clinically significant adverse reactions sections of the package insert.

PMDA's view:
It is necessary to appropriately call attention to the occurrence of hypersensitivity-related events including anaphylaxis in clinical studies and continue to collect information on the occurrence of hypersensitivity via post-marketing surveillance. The appropriateness of warnings and precautions in the package insert will be determined, taking account of comments from the Expert Discussion.

4.(iii).B.(3).2) Infusion Associated Reaction (IAR)
The applicant's explanation:
In accordance with the provisions of the protocol, any infusion associated reactions (IARs) were reported by the investigator, regardless of onset time after infusion. However, at the time of analyses of clinical studies, an IAR was defined as any event that occurred during the infusion or within 4 hours after the end of the infusion and was assessed by the Investigator (sub-investigator) as related to treatment.

In Study LAL-CL02 (data cutoff in [redacted]), the incidence of IARs was 6.1% (4 of 66 subjects) and the IARs were mild and non-serious in 3 of the 4 subjects. The IAR observed in the remaining 1 subject was considered to be severe and serious, leading to treatment interruption. Then, the subject resumed treatment with sebelipase alfa at a reduced dose of 0.35 mg/kg once every other week. No new IAR has been reported since the resumption of infusion (the [redacted]-year-old boy referred in "4.(iii).B.(3).1) Hypersensitivity (including anaphylaxis)").

In Study LAL-CL03 (data cutoff in [redacted]), the incidence of IARs was 44.4% (4 of 9 subjects) and 47 IARs (mild only in 1 subject, mild to moderate in 2 subjects, mild to severe in 1 subject) were reported.

Although 3 of the 4 subjects experienced multiple IARs (including 8 moderate events and 3 severe events), most events were mild in severity. Moderate to severe events occurred at a dose of 3 mg/kg [see "4.(iii).B.(3).1) Hypersensitivity (including anaphylaxis)" for the details of the subject with 3 severe events].

The occurrence of adverse events such as IARs in each clinical study was analyzed based on the pooled data (data cutoff in [redacted]). The results are shown in Table 30. The incidences of IARs were higher in clinical studies in patients with infantile-onset, rapidly progressive LAL deficiency (Studies LAL-CL03 and LAL-CL08). Many of the IARs were mild or moderate in severity. There was consistency between adverse events/adverse drug reactions that occurred during the infusion or within 4 hours after the end of the infusion and adverse events/adverse drug reactions that occurred during the infusion or within 24 hours after the end of the infusion.

Table 30. Occurrence of adverse events such as IARs (Pooled data, data cutoff in [redacted])

	LAL-CL02 (N = 66)	LAL-CL03 (N = 9)	LAL-CL04 (N = 9)	LAL-CL06 (N = 17)	LAL-CL08 (N = 5)	Total (N = 106)
IARs	7 (10.6)	4 (44.4)	2 (22.2)	1 (5.9)	2 (40.0)	16 (15.1)
Adverse events that occurred during the infusion or within 4 hours after the end of the infusion	29 (43.9)	7 (77.8)	7 (77.8)	2 (11.8)	5 (100.0)	50 (47.2)
Adverse events that occurred during the infusion or within 24 hours after the end of the infusion	34 (51.5)	8 (88.9)	9 (100.0)	4 (23.5)	5 (100.0)	60 (56.6)
Adverse drug reactions that occurred during the infusion or within 4 hours after the end of the infusion	7 (10.6)	4 (44.4)	3 (33.3)	2 (11.8)	2 (40.0)	18 (17.0)
Adverse drug reactions that occurred during the infusion or within 24 hours after the end of the infusion	9 (13.6)	4 (44.4)	3 (33.3)	3 (17.6)	2 (40.0)	21 (19.8)

n (Incidence, %)

Adverse events such as IARs by dose at onset are shown in Table 31. The incidences of IARs, adverse events that occurred during the infusion or within 4 hours after the end of the infusion, and adverse events that occurred during the infusion or within 24 hours after the end of the infusion were higher in subjects receiving 3 mg/kg than in subjects receiving 0.35 or 1 mg/kg. This is considered attributable to the fact that the majority of the subjects receiving 3 mg/kg (8 of 12 subjects) had infantile-onset, rapidly progressive LAL deficiency. There were no differences in the occurrence of IARs according to time period.

Table 31. Occurrence of adverse events such as IARs by dose at onset (Pooled data, data cutoff in [redacted])

	0.35 mg/kg (N = 11)	1 mg/kg (N = 101)	3 mg/kg (N = 12)	Total (N = 106)
IARs	0 (0.0)	16 (15.8)	3 (25.0)	16 (15.1)
Adverse events that occurred during the infusion or within 4 hours after the end of the infusion	4 (36.4)	46 (45.5)	8 (66.7)	50 (47.2)
Adverse events that occurred during the infusion or within 24 hours after the end of the infusion	8 (72.7)	54 (53.5)	10 (83.3)	60 (56.6)
Adverse drug reactions that occurred during the infusion or within 4 hours after the end of the infusion	0 (0.0)	18 (17.8)	3 (25.0)	18 (17.0)
Adverse drug reactions that occurred during the infusion or within 24 hours after the end of the infusion	2 (18.2)	21 (20.8)	3 (25.0)	21 (19.8)

n (Incidence, %)

Based on the pooled data (data cutoff in [redacted]), 6 of 84 subjects (3 infants [<2 years]; 1 child [≥4 years]; 2 adults [≥18 years]) experienced moderate or severe IARs. In the subsequent data, 4 subjects (2 in Study LAL-CL02, 1 each in Studies LAL-CL06 and LAL-CL08) were found to have moderate or severe IARs.

Based on the pooled data (data cutoff in [redacted]) and subsequent data, 6 subjects (2 in Study LAL-CL02, 1 each in Studies LAL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08) experienced severe IARs, which were all categorized as "hypersensitivity reactions," including anaphylaxis in 3 subjects [see "4.(iii).B.(3).1) Hypersensitivity (including anaphylaxis)"].

Four subjects experienced moderate IARs, including 1 subject with "hypersensitivity reaction" in Study LAL-CL03 (about [redacted]-month-old boy). The subject received premedication with an antihistamine and an H_2-blocker at Week 23 (when the dose was escalated to 3 mg/kg once weekly), but experienced moderate urticaria during sebelipase alfa infusion. Following interruption of the infusion and administration of an antihistamine, the symptoms resolved. Subsequently, the subject experienced mild IAR twice (at Week 27 and Week 48).While receiving premedication with a corticosteroid, an antihistamine, and an H_2-blocker, the subject has been on treatment with sebelipase alfa.

The details of the 3 cases of moderate IARs that were not categorized as "hypersensitivity reactions" are as follows:
The first case occurred in 3[redacted]-year-old man in Study LAL-CL02. The subject experienced moderate nausea after the end of the infusion at Week 24 (1 mg/kg once every other week), and this event was categorized as an IAR. The IAR resolved without treatment and no new IAR was reported. The second case occurred in an about 4-month-old boy in Study LAL-CL03. The subject had moderate infusion site oedema after the start of the infusion at Week 142 (3 mg/kg once weekly), and this event was categorized as an IAR. The oedema resolved following topical application of dextrose solution and no IAR was reported after that. The remaining 1 case occurred in a 2[redacted]-year-old woman in Study LAL-CL04. The subject experienced moderate paraesthesia (left arm, left hand, left leg) after the infusion at Week 36 (0.35 mg/kg once weekly), and this event was categorized as an IAR. MRI findings were all normal and the symptoms resolved without medical treatment.

As described above, although IARs occurred following sebelipase alfa infusion, the reactions were largely mild to moderate in severity and were managed by reducing the infusion rate, interrupting the infusion, administering antihistamines and/or antipyretic analgesics, and by other means.

PMDA's view:
As IARs including anaphylaxis have been reported, it is necessary to appropriately advise precautions against IARs and continue to collect information via post-marketing surveillance.

4.(iii).B.(3).3) Impact of antibody formation

The applicant's explanation:
In Studies LAL-CL02, LAL-CL03, and LAL-CL01/LAL-CL04, of 82 sebelipase alfa-treated subjects (66 in Study LAL-CL02, 7 in Study LAL-CL03,[51] 9 in Study LAL-CL01/LAL-CL04) assessed for antibodies, 11 (6 in Study LAL-CL02, 4 in Study LAL-CL03, 1 in Study LAL-CL01/LAL-CL04) tested positive for anti-

sebelipase alfa antibodies at ≥1 time point. In Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency, the proportion of subjects who were antibody-positive were high (4 of 7 subjects). Antibody development was possibly associated with the following factors: sebelipase alfa was administered more frequently in patients with infantile-onset, rapidly progressive LAL deficiency (once weekly) than in patients with late-onset LAL deficiency (once every other week); and sebelipase alfa was administered at a higher dose in patients with infantile-onset, rapidly progressive LAL deficiency (mainly 3 mg/kg) than in patients with late-onset LAL deficiency (mainly 1 mg/kg every other week).

In Study LAL-CL02, subjects in the placebo group had undetectable antibody titers. Of the 66 subjects who received sebelipase alfa in either the sebelipase alfa group or placebo/sebelipase alfa group, 6 (9%) tested positive at some time point, of whom, 3 had ≥2 consecutive positive antibody assessments. Of the 6 antibody-positive subjects, 5 were tested positive during the double-blind period, but none of them remained antibody-positive through the last assessment. One of the 5 subjects who tested positive in the double-blind period was antibody-positive also in the open-label period. One subject was antibody-positive in the open-label period only. Of the 6 antibody-positive subjects, 4 had low antibody titers, which became undetectable by the last assessment. The remaining 2 subjects tested positive for neutralizing antibodies that inhibit LAL cellular uptake, but had undetectable neutralizing antibodies that inhibit LAL enzyme activity. The antibody titers were low and not persistently positive. One of 2 Japanese subjects was antibody-positive.

In Study LAL-CL03, of 7 subjects assessed for antibodies, 4 tested positive at some time point. Three of the 4 subjects had ≥2 consecutive positive antibody assessments and the remaining 1 subject was found to have undetectable titers after becoming antibody-positive at Week 8. In all of the 3 subjects with ≥2 consecutive positive antibody assessments, the maximum antibody titers decreased with continued treatment, and 2 of the 3 subjects tested negative at the last assessment. Two of the 4 antibody-positive subjects tested positive for neutralizing antibodies that inhibit LAL enzyme activity and inhibition of LAL enzyme activity was observed at the time point at which antibody positivity was initially reported.

In Study LAL-CL01/LAL-CL04, 1 of the 9 subjects with antibody assessments tested positive at Week 4 only and tested negative at all subsequent time points.

The impact of antibody formation on safety

The occurrence of adverse events by antibody status is shown in Table 32. While the incidence of serious adverse events was higher in the subgroup of antibody-positive subjects than in the subgroup of antibody-negative subjects, there were no deaths, adverse events leading to treatment discontinuation, or adverse events leading to study discontinuation in antibody-positive subjects. The adverse event profile in antibody-positive subjects was similar to that in the overall study population. The occurrence of hypersensitivity-related events by antibody status is shown in Table 33. There was no clear association between antibody status and hypersensitivity-related events. However, only 12 subjects were antibody-positive and their antibody status differed at different time points and the proportion of patients with infantile-onset, rapidly progressive LAL deficiency among antibody-positive subjects was 41.7% (5 of 12 subjects), which was higher than that among antibody-negative subjects, 8.4% (7 of 83 subjects). Thus, the impact of antibody formation on the occurrence of adverse events could not be assessed.

Table 32. Occurrence of adverse events by antibody status (Pooled data, data cutoff in [redacted])

	Antibody-positive (N = 12)	Antibody-negative (N = 83)	Total (N = 106[a)])
Adverse events	12 (100.0)	74 (89.2)	89 (84.0)
Mild adverse events	2 (16.7)	13 (15.7)	15 (14.2)
Moderate adverse events	2 (16.7)	8 (9.6)	10 (9.4)
Severe adverse events	1 (8.3)	4 (4.8)	5 (4.7)
Serious adverse events	5 (41.7)	12 (14.5)	19 (17.9)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	0 (0.0)	1 (1.2)	1 (0.9)
Adverse drug reactions	5 (41.7)	26 (31.3)	31 (29.2)
Serious adverse drug reactions	1 (8.3)	3 (3.6)	4 (3.8)
Deaths	0 (0.0)	4 (4.8)	5 (4.7)
IARs	6 (50.0)	10 (12.0)	16 (15.1)

n (Incidence, %)
a) Including 11 subjects without antibody assessment.

Table 33. Occurrence of hypersensitivity-related events by antibody status (Pooled data, data cutoff in [redacted])

		Antibody-positive (N = 12)	Antibody-negative (N = 83)	Total (N = 106[a)])
SMQ "Hypersensitivity"	Adverse events	6 (50.0)	24 (28.9)	31 (29.2)
	Serious adverse events	0 (0.0)	2 (2.4)	2 (1.9)
	Severe adverse events	0 (0.0)	2 (2.4)	2 (1.9)
	Deaths	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
SMQ "Anaphylactic reaction"	Adverse events	8 (66.7)	33 (39.8)	43 (40.6)
	Serious adverse events	0 (0.0)	3 (3.6)	4 (3.8)
	Severe adverse events	0 (0.0)	3 (3.6)	5 (4.7)
	Deaths	0 (0.0)	1 (1.2)	1 (0.9)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)
a) Including 11 subjects without antibody assessment.

The impact of neutralizing antibodies on safety

Two subjects who were positive for neutralizing antibodies that inhibit LAL enzyme activity in Study LAL-CL03 experienced serious adverse events, all of which were IARs (e.g., tachycardia, pallor) or events considered associated with their underlying disease. Overall, the profile of adverse events in subjects who tested positive for neutralizing antibodies was not markedly different from that of adverse events in subjects who tested positive for anti-sebelipase alfa antibodies and who tested negative for neutralizing antibodies or subjects who tested negative for anti-sebelipase alfa antibodies. The presence of neutralizing antibodies was considered to have no impact on the safety profile of sebelipase alfa.

The impact of antibody formation on efficacy

Reductions from baseline in ALT and AST were observed in all of 5 sebelipase alfa-treated subjects who tested positive for anti-sebelipase alfa antibodies in the double-blind period of Study LAL-CL02 in patients with late-onset LAL deficiency. The proportion of subjects who achieved ALT normalization during the double-blind period was 40% (2 of 5 subjects) in antibody-positive subjects and 30% (9 of 30 subjects) in antibody-negative subjects, and the presence of antibodies did not contribute to a lower proportion of subjects who achieved ALT normalization. Reductions from baseline in LDL-C and non-HDL-C were observed in all of the 5 antibody-positive subjects and the mean percent changes from baseline at the end of the double-blind period were −45% and −40%, respectively. A 10% increase in HDL-C from baseline at the end of the double-blind period was

also observed in the 5 subjects. Reductions from baseline in liver fat content and liver volume at the end of the double-blind period were observed and the mean percent changes from baseline were −49% and −4%, respectively. Of these 5 antibody-positive subjects, only 2 underwent liver biopsy for liver histopathology assessments at baseline and at the end of the double-blind period, and both subjects showed improvement in liver histopathology.

In Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency, 4 subjects were antibody-positive and 2 of them tested positive for neutralizing antibodies that inhibit LAL enzyme activity. Suboptimal growth rate was observed in 1 subject, suggesting the possibility of a continued suboptimal treatment response in association with the presence of neutralizing antibodies, while other clinical parameters were unaffected by antibody development. There was no association between the development of anti-drug antibodies and clinical parameters in the other subject who developed neutralizing antibodies.

In Study LAL-CL01, none of 9 subjects developed anti-sebelipase alfa antibodies. In Study LAL-CL04, 1 of 8 subjects was antibody-positive at Week 4 only, without changes in serum transaminases, serum lipids, and macrophage activity.

As described above, the proportion of antibody-positive subjects was low across clinical studies of sebelipase alfa, and the incidence of antibody development was higher in patients with infantile-onset, rapidly progressive LAL deficiency than in patients with late-onset LAL deficiency. There was no clear association between antibody positivity and safety profile. Efficacy parameters were unaffected by antibody formation in patients with late-onset LAL deficiency. Although some effects on efficacy were observed in 1 antibody-positive patient with infantile-onset, rapidly progressive LAL deficiency, whether these effects were attributable to antibody formation could not be determined.

PMDA accepts the applicant's explanation that there was no clear association between antibody positivity and safety profile, but considers that it is necessary to continue to collect information on the impact of antibody formation via post-marketing surveillance because (1) sebelipase alfa-treated subjects developed antibodies, (2) the possibility that antibody formation affects the efficacy of the drug could not be ruled out for 1 subject, and (3) the number of patients assessed in clinical studies in Japan and overseas was limited.

4.(iii).B.(4) Indication

The applicant's explanation on the proposed indication:

Infantile-onset, rapidly progressive LAL deficiency is historically called Wolman disease and late-onset LAL deficiency is historically called cholesteryl ester storage disease (CESD). Although these two conditions were previously regarded as two different diseases, it has recently been recognized that Wolman disease and CESD are categorized as the same disease caused by mutations in the LIPA gene encoding lysosomal acid lipase. LAL deficiency results in accumulation of cholesteryl esters and triglycerides in the lysosomes of various tissues and cells throughout the body, and sebelipase alfa-treated patients have demonstrated improvements in disease-related symptoms in clinical studies. Sebelipase alfa has been approved for the indication of LAL deficiency in the EU. There are no differences in diagnostic methods between Japan and other countries. The disease

condition is related to the deficiency of a lysosomal enzyme, irrespective of genotype, and there has been no clear relationship between LIPA gene mutation status and the disease condition/severity. The clinical signs and symptoms are highly variable from patient to patient, and this is common both in and outside Japan. In addition, no differences in genotype between the Japanese and other ethnic groups have been reported.

Based on the above, sebelipase alfa should be indicated for "lysosomal acid lipase deficiency."

PMDA's view:
There is no particular problem with the claimed indication of "lysosomal acid lipase deficiency," but the appropriateness of the wording of the indication will be determined, taking account of comments from the Expert Discussion, as LAL deficiency is called Wolman disease or cholesteryl ester storage disease in clinical practice.

4.(iii).B.(5) Dosage and administration

4.(iii).B.(5).1) Dosage and administration

The applicant's explanation:
In a phase I/II study in adult patients with LAL deficiency (LAL-CL01), sebelipase alfa 0.35, 1, or 3 mg/kg was administered once weekly for 4 weeks. At all 3 dose levels, improvements in serum transaminases (ALT and AST) and serum lipid parameters were observed. While marked improvements in serum lipid parameters were seen in 3 subjects treated with sebelipase alfa 3 mg/kg once weekly, there was no dose dependency for serum transaminases (ALT and AST). In Study LAL-CL04 (an extension study of LAL-CL01), subjects who received sebelipase alfa 0.35 or 1 mg/kg qw in Study LAL-CL01 were transitioned to dosing at 1 mg/kg qow, and subjects who received sebelipase alfa 3 mg/kg qw in Study LAL-CL01 were transitioned to dosing at 3 mg/kg qow. The duration of treatment was up to 104 weeks. There were no clear differences in changes in serum transaminases and lipid parameters between 1 mg/kg qow and 3 mg/kg qow.

Study LAL-CL02 in patients with late-onset LAL deficiency (CESD) was conducted based on the results from Studies LAL-CL01 and LAL-CL04. In this study, subjects received 1 mg/kg qow during the double-blind period, and dose escalation to 3 mg/kg qow or dose reduction to 0.35 mg/kg qow was permitted according to the patient's condition during the open-label period. As shown in Table 9, normalization of serum transaminases (ALT and AST), improvements in lipid parameters, and other changes were observed in the sebelipase alfa group relative to the placebo group during the double-blind period. During the open-label period, the majority of subjects received 1 mg/kg once every other week, the effects of sebelipase alfa (Table 10), while the dose was escalated to 3 mg/kg once every other week in 6 subjects (including 1 Japanese patient). This Japanese patient showed improvements in lipid parameters and serum transaminases after the dose escalation (Table 21). Treatment was interrupted in 1 subject who experienced an IAR during the double-blind period, and the dose was reduced from 1 mg/kg once every other week to 0.35 mg/kg once every other week.

In Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease), subjects received a starting dose of 0.35 mg/kg of sebelipase alfa once weekly and then the dose was escalated to 1 mg/kg once weekly. Further dose increase to 3 mg/kg once weekly was permitted in subjects exhibiting a

suboptimal treatment response, contingent upon acceptable safety of preceding infusions. After at least 24 weeks of treatment at a stable dose, change to an every-other-week dosing schedule at the same dose per infusion was permitted. Of 9 sebelipase alfa-treated subjects, 8 received a starting dose of 0.35 mg/kg of sebelipase alfa once weekly. Of the 8 subjects, 2 died after receiving the first dose of 0.35 mg/kg and 6 had their dose escalated to 1 mg/kg once weekly after 2 infusions at a dose of 0.35 mg/kg once weekly. The remaining 1 subject treated with sebelipase alfa received a starting dose of 0.2 mg/kg once weekly, and the dose was escalated to 0.3 mg/kg at Week 1, 0.5 mg/kg at Week 2, 0.75 mg/kg at Week 3, and 1 mg/kg at Week 4. All of the 7 subjects treated with 1 mg/kg once weekly showed improvements in liver enzymes and other changes, of whom, 6 subjects were dose-escalated to 3 mg/kg once weekly due to a suboptimal treatment response. The main reason for dose escalation was suboptimal improvement in weight-for-age, and many subjects consistently showed persistent improvements in height-for-age and weight-for-age after dose escalation. For 1 of the 6 subjects who had their dose escalated to 3 mg/kg once weekly, there was concern about the effects of neutralizing antibodies. Thus, the dose was further increased to 5 mg/kg once weekly at Week 88 (23.2 months of age), but the weight-for-age percentile remained low at the next time point, Week 92. In this subject, confounding factors possibly affecting growth, such as the use of a corticosteroid for the management of an IAR, were identified. No subjects had their dose reduced due to tolerability issues. The effects of dosing frequency were examined in subjects who received long-term sebelipase alfa treatment in Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency. One subject was treated with 3 mg/kg once weekly for 31 weeks and then transitioned to 3 mg/kg once every other week. However, this subject reverted to once weekly dosing schedule due to worsening of liver enzymes and lipid parameters. These results indicated that once-weekly dosing is needed to control accumulation of lysosomal lipids to a level where disease can be managed in patients with infantile-onset, rapidly progressive LAL deficiency.

As described above, in Study LAL-CL02 in patients with late-onset LAL deficiency, subjects treated with sebelipase alfa 1 mg/kg once every other week experienced improvements in liver enzymes and lipid parameters, etc. as compared with subjects in the placebo group. During the open-label period, a higher dose was considered necessary for some patients including a Japanese patient due to worsening of liver enzymes and lipid parameters, and then the dose was escalated to 3 mg/kg once every other week. The Japanese subject showed improvements in lipid parameters and serum transaminases after dose escalation. In Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency, despite improvements in liver enzyme parameters in subjects treated with 1 mg/kg once weekly, a higher dose was considered necessary in order to produce greater benefits in terms of some clinical parameters such as weight-for-age. After dose escalation to 3 mg/kg, persistent improvements in parameters such as weight-for-age and height-for-age, were consistently observed. Dose escalation to 5 mg/kg was studied in only 1 subject. Since only limited information is available from the study results, the effects of the increased dose are not clear at present.

PMDA asked the applicant to explain the reason for selecting the regimen of 1 mg/kg once weekly, which was not studied in Study LAL-CL03, as the proposed starting dosage regimen for patients with infantile-onset, rapidly progressive LAL deficiency.

The applicant's response:
As Study LAL-CL03 was the first study in patients with infantile-onset, rapidly progressive LAL deficiency, the minimum effective dose of 0.35 mg/kg once weekly was chosen as the starting dosage for safety considerations. Sebelipase alfa 1 mg/kg once weekly demonstrated clinically meaningful effects in the study. Most subjects were dose-escalation to 3 mg/kg once weekly without marked increases in adverse events, and persistent improvements were observed. Five subjects enrolled in ongoing Study LAL-CL08 in patients with infantile-onset, rapidly progressive LAL deficiency and 2 compassionate use patients received a starting dose of 1 mg/kg once weekly. There are no particular trends toward differences between safety data from these patients and the data from Study LAL-CL03, and rapid improvements in disease-related abnormalities such as liver dysfunction (ALT), body weight gain, and stable clinical status have been observed.

Based on the above, the starting dosage should be 1 mg/kg once weekly for patients with infantile-onset, rapidly progressive LAL deficiency, and the dose may be increased to 3 mg/kg once weekly according to the patient's condition.

4.(iii).B.(5).2) Infusion rate
In Study LAL-CL03 in patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease), the study drug was diluted to a final concentration of 0.1 to 1.5 mg/mL. The diluted solution was infused over approximately 2 hours at a rate of 5 mL/hr for the 0.35 or 1 mg/kg dose or at a rate of 10 mL/hr for the 3 mg/kg dose. The infusion rate was adjusted according to the subject's body weight, with a maximum rate of 4 mL/kg/hr. Four of 9 subjects experienced IARs, and all IARs were managed by interrupting the infusion, reducing the infusion rate, and administering antipyretic analgesics, antihistamines, corticosteroids, or other supportive treatments (e.g., oxygen inhalation).

In Study LAL-CL02 in patients with late-onset LAL deficiency (CESD), the study drug was diluted to a final concentration of 0.1 to 1.5 mg/mL, and the diluted solution was infused over approximately 2 hours at a rate of 50 to 150 mL/hr between Week 0 and Week 22 and over approximately 1 hour from Week 24 onward. The infusion rate was adjusted according to the subject's body weight, with a maximum rate of 4 mL/kg/hr. As of data cutoff in [redacted], 40 subjects (19 in the placebo/sebelipase alfa group, 21 in the sebelipase alfa group) received at least one infusion administered over approximately 1 hour. The subjects in the placebo/sebelipase alfa group received placebo during the double-blind period and sebelipase alfa during the open-label period. One subject in the placebo/sebelipase alfa group was premedicated with an antihistamine prior to study drug infusion and experienced an IAR (mild urticaria) after the start of the second infusion of sebelipase alfa (Week 2 of the open-label period, Week 24 of the study). This subject received the first infusion of sebelipase alfa at a rate of 50 mL/hr and the infusion rate was changed to 100 mL/hr for the second infusion. However, the infusion rate was decreased from 100 mL/hr to 50 mL/h due to the occurrence of the IAR and the infusion was completed. The sebelipase alfa infusion with premedication with an antihistamine was continued, and the

subject received 4 infusions at a rate of 100 mL/hr without recurrence of an IAR. No IARs occured in other subjects receiving doses of sebelipase alfa infused over approximately 1 hour.

Based on the above clinical study results, sebelipase alfa should be diluted to a final concentration of 0.1 to 1.5 mg/mL and the diluted solution should be administered as an intravenous infusion over approximately 2 hours at a rate of ≤4 mL/kg/hr while the patient's condition is monitored. A 1-hour infusion may be considered after patient tolerability is established.

PMDA asked the applicant to explain the reason why the infusion time can be shortened also in patients with infantile-onset, rapidly progressive LAL deficiency although the shorter infusion duration (1-hour infusion) was not investigated in Studies LAL-CL03 and LAL-CL08.

The applicant's response:
Studies LAL-CL03 and LAL-CL08 did not require changing the infusion time from 2 hours to 1 hour, but shortening the infusion time at the discretion of the investigator was permitted in anticipation of long-term treatment. If sebelipase alfa infusions are well tolerated and clinical symptoms are stabilized during long-term treatment with sebelipase alfa, there is no problem with shortening the infusion time, as long as the physician considers that the infusion time can be reduced from 2 hours to 1 hour.

PMDA's views on discussions presented in 4.(iii).B.(5).1) and 4.(iii).B.(5).2):
Since (1) only 2 Japanese patients were treated with sebelipase alfa and (2) no Japanese patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) were included in the clinical studies the appropriateness of the dosage regimens in Japanese patients cannot be evaluated fully. However, there is no particular problem with the proposed dosage regimens based on the results from clinical studies conducted in Japan and overseas (The dosage in patients with late-onset LAL deficiency [CESD] is 1 mg/kg of sebelipase alfa administered once every other week as an intravenous infusion. For patients with an inadequate treatment response, the dose may be increased to 3 mg/kg according to their condition. The dosage in patients with infantile-onset, rapidly progressive LAL deficiency [Wolman disease] is 1 mg/kg of sebelipase alfa administered once weekly as an intravenous infusion. For patients with an inadequate treatment response, the dose may be increased to 3 mg/kg according to their condition.). There is no major problem with the applicant's explanation that the dosage and the infusion rate should be adjusted according to the patient's condition. The appropriateness of the dosage and administration and the precautions for dosage and administration will be determined, taking account of comments from the Expert Discussion.

4.(iii).B.(6) Special populations

Pediatric patients

The applicant's explanation:

In the clinical studies in patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) (Studies LAL-CL03 and LAL-CL08), 3 mg/kg once weekly was the most common dosage and was followed by 1 mg/kg once weekly. Among patients with late-onset LAL deficiency (CESD), 2- to 17-year-old patients (Studies LAL-CL02 and LAL-CL06) mostly received 1 mg/kg once every other week and only 1 patient ([redacted] years) in Study LAL-CL02 was dose-escalated to 3 mg/kg once every other week. Patients aged ≥18 years (Studies LAL-CL02 and LAL-CL06) mostly received 1 mg/kg once every other week. In Study LAL-CL04, 1 mg/kg once every other week was the most common dosage and was followed by 3 mg/kg once every other week.

Safety was analyzed by age group. The occurrence of adverse events by age group based on the pooled data (data cutoff in [redacted]) is shown in Table 34. The incidences of adverse events were higher in patients aged <2 years than in other age groups, especially for events of tachycardia, bradycardia, and pyrexia. The most common events were pyrexia, diarrhoea, and vomiting in the <2-year-old age group, headache and cough in the 2- to 12-year-old age group, diarrhoea and pyrexia in the 13- to 17-year-old age group, and nasopharyngitis, diarrhoea, and abdominal pain in the ≥18-year-old age group. The incidence of adverse drug reactions was also higher in the <2-year-old age group.

Table 34. Occurrence of adverse events by age group (Pooled data, data cutoff in [redacted])

	<2 years (N = 14)	2.00-12.00 years (N = 31)	12.01-17.99 years (N = 26)	≥18 years (N = 33)	Total (N = 104)
Adverse events	14 (100.0)	25 (80.6)	23 (88.5)	27 (81.8)	89 (85.6)
Adverse drug reactions	8 (57.1)	5 (16.1)	5 (19.2)	13 (39.4)	31 (29.8)
Serious adverse events	14 (100.0)	0 (0.0)	1 (3.8)	4 (12.1)	19 (18.3)
Serious adverse drug reactions	2 (14.3)	0 (0.0)	1 (3.8)	1 (3.0)	4 (3.8)
Deaths	5 (35.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.8)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

n (Incidence, %)

As of data cutoff in [redacted], the occurrence of adverse events by age group in main clinical studies (Studies LAL-CL02, LAL-CL03, and LAL-CL04) is shown in Table 35. The incidence of serious adverse events was higher in patients aged <2 years than in other age groups.

Table 35. Occurrence of adverse events by age group in main clinical studies (Studies LAL-CL03, LAL-CL02, and LAL-CL04)

	LAL-CL03	LAL-CL02			LAL-CL04
	<2 years (N = 9)	2.00-12.00 years (N = 24)	12.01-17.99 years (N = 23)	≥18 years (N = 19)	≥18 years (N = 9)
Adverse events	9 (100.0)	24 (100.0)	22 (95.7)	16 (84.2)	9 (100.0)
Adverse drug reactions	5 (55.6)	5 (20.8)	4 (17.4)	6 (31.6)	5 (55.6)
Serious adverse events	9 (100.0)	0 (0.0)	1 (4.3)	2 (10.5)	1 (11.1)
Serious adverse drug reactions	1 (11.1)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)
Deaths	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to treatment discontinuation	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)

The occurrences of hypersensitivity-related events and IARs by age group are shown in Table 36 and Table 37, respectively. While the incidences of hypersensitivity-related events and IARs were higher in patients aged <2 years than in other age groups, no major differences were observed among the other age groups.

Table 36. Occurrence of hypersensitivity-related events by age group (Pooled data, data cutoff in [redacted])

		<2 years (N = 14)	2.00-12.00 years (N = 31)	12.01-17.99 years (N = 26)	≥18 years (N = 33)	Total (N = 104)
SMQ "Hypersensitivity"	Adverse events	11 (78.6)	7 (22.6)	5 (19.2)	8 (24.2)	31 (29.8)
	Serious adverse events	1 (7.1)	0 (0.0)	0 (0.0)	1 (3.0)	2 (1.9)
	Severe adverse events	1 (7.1)	0 (0.0)	1 (3.8)	0 (0.0)	2 (1.9)
	Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SMQ "Anaphylactic reaction"	Adverse events	11 (78.6)	11 (35.5)	10 (38.5)	11 (33.3)	43 (41.3)
	Serious adverse events	3 (21.4)	0 (0.0)	0 (0.0)	1 (3.0)	4 (3.8)
	Severe adverse events	4 (28.6)	0 (0.0)	1 (3.8)	0 (0.0)	5 (4.8)
	Deaths	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
	Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (Incidence, %)

Table 37. Occurrence of IARs by age group (Pooled data, data cutoff in [redacted])

	<2 years (N = 14)	2.00-12.00 years (N = 31)	12.01-17.99 years (N = 26)	≥18 years (N = 33)	Total (N = 104)
IARs	6 (42.9)	3 (9.7)	3 (11.5)	4 (12.1)	16 (15.4)
Adverse events that occurred during the infusion or within 4 hours after the end of the infusion	12 (85.7)	14 (45.2)	6 (23.1)	18 (54.5)	50 (48.1)
Adverse events that occurred during the infusion or within 24 hours after the end of the infusion	13 (92.9)	15 (48.4)	9 (34.6)	23 (69.7)	60 (57.7)
Adverse drug reactions that occurred during the infusion or within 4 hours after the end of the infusion	6 (42.9)	2 (6.5)	4 (15.4)	6 (18.2)	18 (17.3)
Adverse drug reactions that occurred during the infusion or within 24 hours after the end of the infusion	6 (42.9)	2 (6.5)	5 (19.2)	8 (24.2)	21 (20.2)

n (Incidence, %)

Table 38 shows adverse events by age group and dose at onset (1 mg/kg and 3 mg/kg) in main clinical studies (Studies LAL-CL02, LAL-CL03, and LAL-CL04) as of data cutoff in [redacted]. At both 1 mg/kg and 3 mg/kg, the incidences of adverse drug reactions, serious adverse events, and IARs tended to be higher in patients aged <2 years than in other age groups.

Table 38. Adverse events by age group and dose at onset

	1 mg/kg				3 mg/kg			
	<2 years (N = 12)	2.00-12.00 years (N = 31)	12.01-17.99 years (N = 26)	≥18 years (N = 30)	<2 years (N = 8)	2.00-12.00 years (N = 1)	12.01-17.99 years (N = 0)	≥18 years (N = 3)
Adverse events	11 (91.7)	25 (80.6)	23 (88.5)	24 (80.0)	8 (100.0)	0 (0.0)	－	3 (100.0)
Adverse drug reactions	7 (58.3)	5 (16.1)	5 (19.2)	12 (40.0)	4 (50.0)	0 (0.0)	－	1 (33.3)
Serious adverse events	11 (91.7)	0 (0.0)	1 (3.8)	3 (10.0)	6 (75.0)	0 (0.0)	－	1 (33.3)
Serious adverse drug reactions	1 (8.3)	0 (0.0)	1 (3.8)	1 (3.3)	1 (12.5)	0 (0.0)	－	0 (0.0)
IARs	6 (50.0)	3 (9.7)	3 (11.5)	4 (13.3)	3 (37.5)	0 (0.0)	－	0 (0.0)
Deaths	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	－	0 (0.0)
Adverse events leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	－	0 (0.0)
Adverse events leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	－	0 (0.0)

n (Incidence, %)

As described above, the incidence of adverse events tended to be higher in patients aged <2 years than in other age groups. This is considered attributable to the fact that patients aged <2 years had rapidly progressive LAL deficiency and received a higher dose of sebelipase alfa more frequently.

PMDA considers that information on safety in pediatric patients should continue to be collected via post-marketing surveillance because the incidence of adverse events tended to be higher in patients aged <2 years and the number of patients studied was limited.

4.(iii).B.(7) Post-marketing investigations

The applicant's explanation:

Because of the very limited number of patients studied in Japan, a specified drug use-results survey (survey period, approximately 9 years; registration period, approximately 8.5 years), covering all patients treated with the product, will be conducted in order to determine the safety and efficacy of the product in routine clinical settings. Information about hypersensitivity and the factors that affect the safety and efficacy of the product (the impact of antibody formation, etc.) will be collected via the survey.

PMDA's view:

Because of the very limited number of sebelipase alfa-treated patients studied in Japan, etc., it is appropriate to collect information on the safety and efficacy of the product in all patients treated with the product. The details of the survey (e.g., the survey method, the survey period, and the information to be collected) will be finalized, taking account of comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act) for the data submitted in the new drug application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the PMD Act for the data submitted in the new drug application (5.3.5.1.1). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of sebelipase alfa in the treatment of patients with lysosomal acid lipase deficiency has been demonstrated and its safety is acceptable in view of its observed benefits. Sebelipase alfa can become a therapeutic option for patients with lysosomal acid lipase deficiency and is of clinical significance. PMDA considers that further investigation of hypersensitivity, IARs, and the impact of antibody formation, evaluation of the long-term safety and efficacy of sebelipase alfa, and other activities should be continued in post-marketing surveillance.

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

Review Report (2)

February 3, 2016

I. Product Submitted for Registration

[Brand name] Kanuma Intravenous Infusion 20 mg
[Non-proprietary name] Sebelipase Alfa (Genetical Recombination)
[Applicant] Synageva BioPharma Japan K.K. (a predecessor of Alexion Pharma Godo Kaisha)
[Date of application] May 22, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, 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) Efficacy

PMDA's view:

A multiregional phase III study in non-Japanese and Japanese patients with late-onset lysosomal acid lipase (LAL) deficiency (cholesteryl ester storage disease) demonstrated the superiority of sebelipase alfa over placebo for the proportion of subjects who achieved ALT normalization (the primary endpoint), and improvements in lipid parameters (the secondary endpoints) were also observed. Also in individual Japanese subjects in the sebelipase alfa group, a trend towards improvements in liver enzyme and lipid parameters was observed and the effects of treatment were sustained. There are limitations to comparison of sebelipase alfa-treated patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) in Study LAL-CL03 and a historical control group, but the analysis revealed a trend towards improvement in survival in sebelipase alfa-treated patients. Based on the above, it can be interpreted that the efficacy of sebelipase alfa in patients with LAL deficiency (cholesteryl ester storage disease and Wolman disease) has largely been demonstrated. Because of the limited number of patients studied, information on the efficacy of sebelipase alfa should continue to be collected via post-marketing surveillance.

The above conclusions by PMDA were supported by the expert advisors.

(2) Safety

Hypersensitivity (including anaphylaxis)

PMDA's view:

There were 6 subjects who experienced severe hypersensitivity reactions presenting with dyspnoea, cardiovascular symptoms, or neurologic symptoms (including 3 subjects with anaphylaxis). Two of the 3

subjects with anaphylaxis continued to receive sebelipase alfa after treatment of hypersensitivity (including infusion associated reactions). It is necessary to appropriately call attention to the occurrence of hypersensitivity-related events including anaphylaxis in clinical studies and continue to collect information on the occurrence of hypersensitivity via post-marketing surveillance.

The above conclusions by PMDA were supported by the expert advisors. The expert advisors commented that given the seriousness of LAL deficiency and non-availability of alternative treatment options, sebelipase alfa should not be contraindicated in any patient population, but a warning regarding anaphylaxis should be included in the "Warnings" section of the package insert.

PMDA accordingly instructed the applicant to take action regarding a warning in the package insert and confirmed that appropriate action was taken [see "(6) Draft drug risk management plan" for post-marketing investigations].

(3) Indication

PMDA's view:

There is no particular problem with the proposed indication of "lysosomal acid lipase deficiency." However, the indication should be determined, taking also account of the following issues: (1) LAL deficiency is called Wolman disease or cholesteryl ester storage disease in clinical practice, and (2) as shown in the next section "Dosage and administration," different dosage regimens have been proposed for patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) and others (cholesteryl ester storage disease).

PMDA's view described above was supported by the expert advisors. The expert advisors commented that cholesteryl ester storage disease and Wolman disease, along with LAL deficiency, should also be listed in the "Indication" section.

PMDA accordingly instructed the applicant to modify the indication statement as shown below and confirmed that appropriate action was taken.

[Indication]

Lysosomal acid lipase deficiency (cholesteryl ester storage disease, Wolman disease)

(4) Dosage and administration

PMDA's view:

Only 2 Japanese patients were treated with sebelipase alfa in the clinical study and no Japanese patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) were studied. Therefore the appropriateness of the dosage regimens in Japanese patients cannot be evaluated fully. However, there is no particular problem with the proposed dosage and administration based on the results from clinical studies in Japan and overseas (The dosage in patients with late-onset LAL deficiency [cholesteryl ester storage disease] is 1 mg/kg of sebelipase alfa administered once every other week as an intravenous infusion. For patients with

an inadequate treatment response, the dose may be increased to 3 mg/kg according to their condition. The dosage in patients with infantile-onset, rapidly progressive LAL deficiency (Wolman disease) is 1 mg/kg of sebelipase alfa administered once weekly as an intravenous infusion. For patients with an inadequate treatment response, the dose may be increased to 3 mg/kg according to their condition.). There is no major problem with the applicant's explanation that the dosage and the infusion rate should be adjusted according to the patient's condition.

The above conclusions by PMDA were supported by the expert advisors. The expert advisors made the following comments:

- Sebelipase alfa is an enzyme replacement therapy that replaces the missing enzyme and its mechanism of action is clear.
- Although lysosomal acid lipase deficiency is known as cholesteryl ester storage disease or Wolman disease in clinical practice, these diseases cannot be distinguished from each other precisely and the clinical manifestation of each disease is highly variable. Patients with cholesteryl ester storage disease may also have rapidly progressive liver dysfunction, and such severe patients require weekly dosing.
- Given that infantile-onset, rapidly progressive lysosomal acid lipase deficiency (Wolman disease) is serious disease and that sebelipase alfa has been administered at a dose of 5 mg/kg once weekly in an ongoing clinical study, patients may require 5 mg/kg once weekly depending on their disease condition or symptoms also in the post-marketing setting.

Based on the above, PMDA concluded that the dosage and administration and related precautions should be modified as shown below.

PMDA instructed the applicant to modify the dosage and administration and related precautions and confirmed that appropriate action was taken.

[Dosage and administration]

The usual dosage is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once every other week as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once every other week or once weekly as an intravenous infusion.

The dosage in patients with infantile-onset, rapidly progressive LAL deficiency is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once weekly as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once weekly as an intravenous infusion.

The dosage should be adjusted according to the patient's condition.

[Precautions for dosage and administration]

(1) Infusion rate: Since infusion associated reactions are likely to occur at a higher infusion rate, intravenous infusions should be administered over at least 2 hours while monitoring the patient's condition. Intravenous infusions may be administered over at least 1 hour in those patients receiving the 1 mg/kg dose who tolerate the infusion, but the infusion rate should not exceed 4 mL/kg/h.

(2) Dilution method: The volume of the solution needed, which is calculated based on the patient's body weight, should be diluted with Isotonic Sodium Chloride Solution (JP) to a final Sebelipase Alfa (Genetical Recombination) concentration of 0.1 to 1.5 mg/mL.

(3) In patients with severe cholesteryl ester storage disease who have rapidly progressive liver dysfunction, the dosage may be increased to 3 mg/kg once weekly. In the clinical studies, no patients with cholesteryl ester storage disease were treated with sebelipase alfa at a dosage exceeding 3 mg/kg once weekly and no patients with infantile-onset, rapidly progressive Wolman disease were treated with sebelipase alfa at a dosage exceeding 5 mg/kg once weekly.

(5) Special populations

PMDA considered that since the incidence of adverse events tended to be higher in patients aged <2 years and the number of patients studied was limited, information on safety in pediatric patients should continue to be collected via post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors [see "(6) Draft drug risk management plan" for post-marketing investigations].

(6) Draft drug risk management plan

Based on the review in Section "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA considers that the risk management plan should include the following additional issue.

● Safety of sebelipase alfa in pediatric patients

PMDA asked the applicant to take action regarding the above issue. The applicant presented a summary of the draft risk management plan (Table 39, Table 40) and the outline of the draft specified drug use-results survey plan (Table 41) as shown below and PMDA confirmed that there are no problems with the contents of these plans.

Table 39. Safety and efficacy specifications in the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
・ Hypersensitivity including anaphylaxis	・ Impact of anti-sebelipase alfa antibody formation ・ Transmission of infections derived from raw materials	・ Safety of sebelipase alfa in pediatric patients ・ Safety of sebelipase alfa in patients with egg allergies
Efficacy specification		
・ Long-term efficacy		

Table 40. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
・ Early Post-marketing Phase Vigilance (EPPV) ・ Specified drug use-results survey (all-case surveillance)	・ Develop and distribute materials for healthcare providers ・ Provide information from EPPV

Table 41. Outline of the draft specified drug use-results survey plan

Objective	To evaluate the long-term efficacy and safety of sebelipase alfa in routine clinical settings.
Survey method	All-case surveillance
Population	All patients treated with sebelipase alfa [a)]
Observation period	From registration until the end of survey period (registered within approximately 8.5 years after the market launch)
Planned sample size	All patients treated with sebelipase alfa
Main survey items	Patient characteristics, use of sebelipase alfa, concomitant medications, safety evaluation (hypersensitivity including anaphylaxis), efficacy evaluation (liver function tests [ALT, AST, etc.], lipid parameters [LDL-C, non-HDL-C, etc.), patient growth and development, impact of anti-sebelipase alfa antibody formation, safety in patients with egg allergies

a) Patients with a diagnosis of lysosomal acid lipase deficiency who are not receiving sebelipase alfa will also be surveyed only if the medical institution is agreed to the survey and the patient's consent is obtained.

(7) Designation as a specified biological product

PMDA's view on the potential risk of infections associated with the product containing human serum albumin as an excipient:

Given that sebelipase alfa is an enzyme replacement therapy and is intended to be used over longer periods, the total administered amount of human serum albumin contained as an excipient in the drug product may exceed the total dose of an approved human serum albumin preparation administered at the recommended dose. Thus, the product (Kanuma) should be classified as a specified biological product. Furthermore, the package insert, etc. should appropriately contain the following information: Human serum albumin used in the product conforms to the Standard for Biological Ingredients and safety measures to prevent infections are taken by the applicant, but as with currently available human serum albumin preparations, the potential risk of infections associated with the product cannot be ruled out completely.

The above conclusions by PMDA were supported by the expert advisors.

PMDA instructed the applicant to take action accordingly and confirmed that appropriate action was taken.

III. Overall Evaluation

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

[Indication]

Lysosomal acid lipase deficiency (cholesteryl ester storage disease, Wolman disease)

[Dosage and administration]
The usual dosage is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once every other week as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once every other week or once weekly as an intravenous infusion.

The dosage in patients with infantile-onset, rapidly progressive LAL deficiency is 1 mg/kg of Sebelipase Alfa (Genetical Recombination) administered once weekly as an intravenous infusion. For patients with an inadequate treatment response, the dosage should be increased to 3 mg/kg administered once weekly as an intravenous infusion.

The dosage should be adjusted according to the patient's condition.

[Conditions for approval]
- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients studied in Japan, the applicant is required to conduct a post-marketing drug use-results survey, covering all patients treated with the product during the re-examination period, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.