Report on the Deliberation Results

September 7, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Nexviazyme for I.V. Infusion 100 mg
Non-proprietary Name	Avalglucosidase Alfa (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	January 19, 2021

Results of Deliberation

In its meeting held on August 30, 2021, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 6, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Nexviazyme for I.V. Infusion 100 mg
Non-proprietary Name	Avalglucosidase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	January 19, 2021
Dosage Form/Strength	Lyophilized powder for injection: Each vial contains 103 mg of avalglucosidase alfa (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Avalglucosidase alfa is a glycoengineered alglucosidase alfa analog (molecular weight: ca. 124,000) which is oxidized and its average of 5-9 *N*-acetylneuraminic acid portions are chemically modified to 5-acetamido-3,5,7-trideoxy-7-[(*E*)-(2-oxo-2-{2-[4-({*O*-(6-*O*-phosphono-α-D-mannopyranosyl)-(1→2)-*O*-α-D-mannopyranosyl-(1→6)-*O*-α-D-mannopyranosyl-(1→6)-*O*-[*O*-(6-*O*-phosphono-α-D-mannopyranosyl)-(1→2)-*O*-α-D-mannopyranosyl-(1→3)]-β-D-mannopyranosyl}oxy)butanoyl]hydrazinyl}ethoxy)imino]-β-L-arabino-2-heptulo-2,6-pyranosylonic acid groups.

Structure

Amino acid sequence:

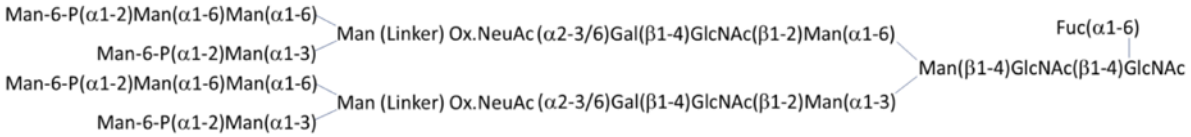
QQGASRPGPR DAQAHPGRPR AVPTQCDVPP NSRFDCAPDK AITQEQCEAR
GCCYIPAKQG LQGAQMGQPW CFFPPSYPSY KLENLSSSEM GYTATLTRTT
PTFFPKDILT LRLDVMMETE NRLHFTIKDP ANRRYEVPLE TPRVHSRAPS
PLYSVEFSEE PFGVIVHRQL DGRVLLNTTV APLFFADQFL QLSTSLPSQY
ITGLAEHLSP LMLSTSWTRI TLWNRDLAPT PGANLYGSHP FYLALEDGGS
AHGVFLLNSN AMDVVLQPSP ALSWRSTGGI LDVYIFLGPE PKSVVQQYLD
VVGYPFMPPY WGLGFHLCRW GYSSTAITRQ VVENMTRAHF PLDVQWNDLD
YMDSRRDFTF NKDGFRDFPA MVQELHQGGR RYMMIVDPAI SSSGPAGSYR
PYDEGLRRGV FITNETGQPL IGKVWPGSTA FPDFTNPTAL AWWEDMVAEF
HDQVPFDGMW IDMNEPSNFI RGSEDGCPNN ELENPPYVPG VVGGTLQAAT
ICASSHQFLS THYNLHNLYG LTEAIASHRA LVKARGTRPF VISRSTFAGH
GRYAGHWTGD VWSSWEQLAS SVPEILQFNL LGVPLVGADV CGFLGNTSEE
LCVRWTQLGA FYPFMRNHNS LLSLPQEPYS FSEPAQQAMR KALTLRYALL
PHLYTLFHQA HVAGETVARP LFLEFPKDSS TWTVDHQLLW GEALLITPVL
QAGKAEVTGY FPLGTWYDLQ TVPIEALGSL PPPPAAPREP AIHSEGQWVT
LPAPLDTINV HLRAGYIIPL QGPGLTTTES RQQPMALAVA LTKGGEARGE
LFWDDGESLE VLERGAYTQV IFLARNNTIV NELVRVTSEG AGLQLQKVTV
LGVATAPQQV LSNGVPVSNF TYSPDTKVLD ICVSLLMGEQ FLVSWC

N indicates a glycosylation site

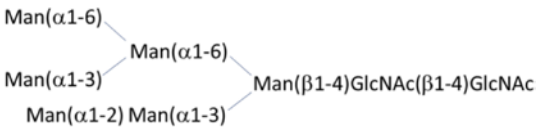
Disulfide bridges: C26–C53, C36–C52, C47–C71, C477–C502, C591–C602, and C882–C896

Major glycan structure:

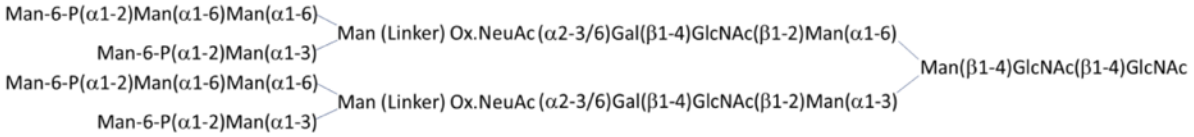
N84



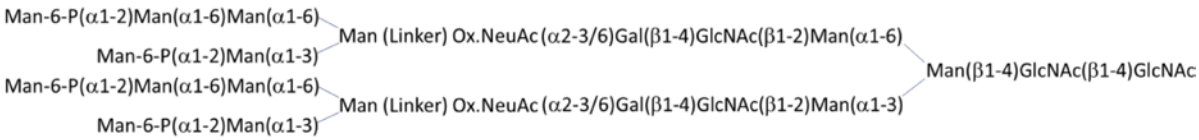
N177



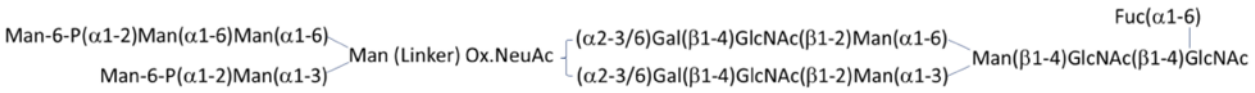
N334



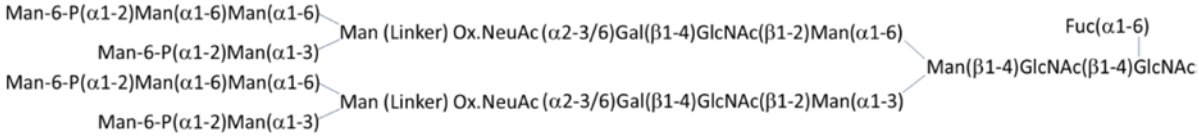
N414



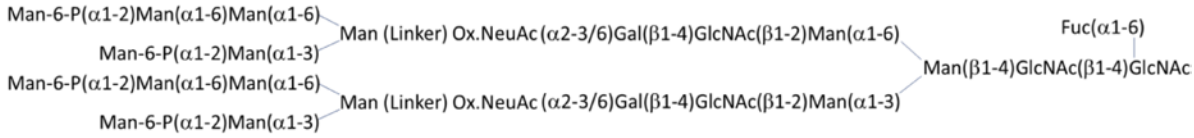
N596



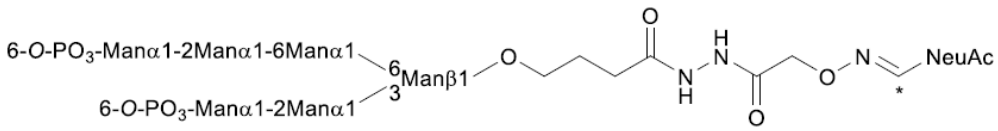
N826



N869



Modified glycan structure:



* Carbon atom 7 of NeuAc

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

Molecular formula: $C_{4490}H_{6818}N_{1197}O_{1299}S_{32}$ (protein moiety)

Molecular weight: 99,371 (protein moiety)

Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 492 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 1125-9 dated November 25, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

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

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

Indication

Pompe disease

Dosage and Administration

For patients with late-onset Pompe disease, the usual dosage is 20 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion.

For patients with infantile-onset Pompe disease, the usual dosage is 40 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion.

Approval condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

July 2, 2021

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

Product Submitted for Approval

Brand Name	Nexviazyme for I.V. Infusion 100 mg
Non-proprietary Name	Avalglucosidase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	January 19, 2021
Dosage Form/Strength	Lyophilized powder for injection: Each vial contains 103 mg of avalglucosidase alfa (genetical recombination).

Proposed Indication

Pompe disease (glycogen storage disease type II)

Proposed Dosage and Administration

The usual dosage for patients with Pompe disease (excluding patients with infantile-onset Pompe disease) is 20 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion. The usual dosage for patients with infantile-onset Pompe disease is 40 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion.

Table of Contents

List of Abbreviations

See Appendix.

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

Nexviazyme is a powder for injection containing the active ingredient Avalglucosidase Alfa (Genetical Recombination) (hereinafter referred to as "avalglucosidase alfa") which is a glycoengineered analog of alglucosidase alfa (genetical recombination) (hereinafter referred to as "ALGLU"; its brand name is Myozyme 50 mg for intravenous drip infusion). ALGLU is approved in Japan for the treatment of glycogen storage disease type II.

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive inherited disorder caused by inherited deficiency of acid alpha-glucosidase (GAA), an enzyme essential for lysosomal degradation of glycogen, or decreased GAA activity, which results in accumulation of undegraded glycogen in the lysosomes of cardiac muscles, liver, skeletal muscles, and other tissues. Pompe disease is classified into 2 phenotypes: infantile-onset Pompe disease (IOPD), which presents in early infancy (in the first few months of life), and late-onset Pompe disease (LOPD), which manifests after infancy. Infantile-onset Pompe disease presents with cardiac hypertrophy, hepatomegaly, and muscular weakness, and untreated patients with IOPD usually die within the first year of life (*Orphanet J Rare Dis.* 2016;11:65). The clinical course of LOPD varies from patient to patient, with the typical initial symptom being muscle weakness in the lower limbs and other symptoms including respiratory dysfunction and exercise intolerance (*Muscle Nerve.* 2008;38:1236-45). Additionally, loss of muscular strength accompanying disease progression will decrease mobility, hampering the ability to independently perform the activities of daily living, which results in deterioration in quality of life (*Neurology.* 2005;63:1688-92, *Brain.* 2005;128:671-7).

The results of a newborn screening program for Pompe disease in Japan have reported that the estimated incidence of IOPD is less than 1 in approximately 103,000 births while that of LOPD is less than 1 in approximately 34,000 births (*J Hum Genet.* 2019;64:741-55). According to the nationwide epidemiological survey conducted from 2013 to 2016, an estimated 134 patients have Pompe disease in Japan (*Japanese Journal of Clinical Medicine.* 2019;77:1245-8).

In Japan, ALGLU, approved in April 2007, is currently available as enzyme replacement therapy for Pompe disease. Avalglucosidase alfa is designed to increase cellular uptake of the enzyme, compared to ALGLU. Avalglucosidase alfa has hexamannose structures conjugated to oxidized sialic acid residues on ALGLU, thereby increasing mannose-6-phosphate (M6P) levels on the enzyme molecules, which is assumed to increase uptake of the enzyme into the diaphragm and other skeletal muscles via M6P receptors.

Recently, the applicant filed an application for marketing approval based on data that demonstrated the efficacy and safety of avalglucosidase alfa in the treatment of Pompe disease. The data came from several studies including global clinical studies in patients with IOPD or LOPD (Studies ACT14132 and EFC14028).

Outside Japan, marketing applications for avalglucosidase alfa were filed in the US and Europe in [redacted] and in [redacted] in [redacted], and the applications are currently under review. As of June 2021, avalglucosidase alfa has not been approved in any country or region.

Avalglucosidase alfa was granted orphan drug designation status for the intended indication of "glycogen storage disease type II" (Orphan Drug Designation No. 492 of 2020 [*R2 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The master cell bank (MCB) and working cell bank (WCB) for the production of avalglucosidase alfa are identical to those for the production of ALGLU.

Both the MCB and WCB are stored in the gas phase above liquid nitrogen. No renewal of MCB and WCB is planned.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: (a) production and purification of a pre-oxidization intermediate of ALGLU, a critical intermediate; (b) manufacturing of glycan E13,[1)] a critical intermediate; and (c) production of avalglucosidase alfa through conjugation of ALGLU with glycan E13 and purification. The manufacturing process for the pre-oxidization intermediate of ALGLU is identical to the [redacted] step and preceding steps for the drug substance of ALGLU.

(a) Pre-oxidization intermediate of ALGLU

The manufacturing process for the pre-oxidization intermediate of ALGLU consists of the following steps: thawing WCB, seed culture, expansion culture, production culture, harvest, [redacted], [redacted] chromatography [redacted], [redacted] chromatography, [redacted] chromatography/[redacted] virus inactivation treatment, [redacted], [redacted] chromatography, and [redacted].

[redacted], [redacted], [redacted] chromatography [redacted], [redacted] chromatography/[redacted] virus inactivation treatment, [redacted], [redacted] chromatography, and [redacted] are defined as critical steps.

[redacted], [redacted], [redacted], and [redacted] have been identified as control items for the pre-oxidization intermediate of ALGLU.

1) [redacted]

(b) Glycan E13

Glycan E13 is synthesized using [redacted][2] and [redacted][3] as the starting materials.

(c) Avalglucosidase alfa

The manufacturing process of avalglucosidase alfa consists of the following steps: oxidation and [redacted] of the pre-oxidization intermediate of ALGLU, conjugation with glycan E13, [redacted] chromatography [redacted], [redacted]/virus removal filtration, formulation, filling, and testing/storage.

[redacted] and [redacted], [redacted], [redacted] virus removal filtration, and [redacted] are defined as critical steps.

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

2.1.3 Adventitious agents safety evaluation

Raw materials of biological origin used in the manufacturing process of the drug substance are Chinese hamster ovary (CHO) cell lines, which are the host cells, bovine serum (sourced from New Zealand), and trypsin from porcine pancreas (sourced from the US or Canada), all of which conform to the requirements of the Standard for Biological Ingredients.

The MCB, WCB, and end-of-production (EOP) cells were tested for purity, and the results were evaluated (see the Review Report of "Myozyme 50 mg for intravenous drip infusion" published in April 2007). The mycoplasma testing, *in vitro* virus testing, and vesivirus testing on pre-harvest unprocessed bulk have been specified as in-process controls.

Virus clearance studies were performed with model viruses for the purification process. The results showed that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})							
	Minute virus of mice		Reovirus type 3		Xenotropic murine leukemia virus		Pseudorabies virus	
Manufacturing process [redacted]								
[redacted] chromatography								
[redacted] chromatography	[redacted][a]	[redacted][a]						
chromatography/ [redacted] virus inactivation treatment	[redacted]	[redacted]	[redacted]	[redacted]	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
[redacted] chromatography[b]	[redacted]		[redacted]		[redacted]		[redacted]	
Virus removal filtration	≥[redacted]		≥[redacted]		≥[redacted]		≥[redacted]	
Overall virus reduction factor	≥16.17	≥15.85	≥17.14	≥17.28	≥15.45	≥16.35	≥18.16	≥18.11

a) [redacted]

b) [redacted].

2) [redacted]

3) [redacted]

2.1.4 Manufacturing process development

The major changes made to the manufacturing process during the development of the drug substance are shown below (the manufacturing processes are referred to as Processes A, B, C1, C2A, and C2B [proposed commercial process]). In the phase II study (ACT14132) and phase III study (EFC14028), a formulation produced with the drug substance manufactured by Process C1, C2A, or C2B was used.

- Process A → Process B: [redacted]
- Process B → Process C1: Changes to [redacted], [redacted], and [redacted]
- Process C1 → Process C2A: [redacted], addition of [redacted]
- Process C2A → Process C2B: [redacted]

Comparability studies were conducted following the above manufacturing process changes, and their impacts on the quality attributes were assessed. The results demonstrated the comparability of the pre- and post-change drug substances.

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

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 summarizes characterization tests performed.

Table 2. Evaluation items for characterization

Primary/higher-order structure	Amino acid sequence, deamidated variants, disulfide bonds, secondary structure, tertiary structure, free thiol
Physicochemical properties	Molecular weight, [redacted], molecular variants ([redacted], macromolecules/aggregates, deamidation variants, oxidants)
Glycan structure	M6P content, oligosaccharide profile, [redacted], monosaccharide composition
Biological properties	Enzyme activity, cellular uptake activity, binding affinity for M6P receptor

The results of characterization tests for the biological properties are summarized as follows:

- Enzyme activity was measured using [redacted] and [redacted] as substrates. When [redacted] was used, [redacted] was [redacted] to [redacted] mmol/L and [redacted] was [redacted] to [redacted] U/mg. When [redacted] was used, [redacted] was [redacted] to [redacted] mg/mL and [redacted] was [redacted] to [redacted] nmol/mg/min.
- The cellular uptake activity was measured using [redacted]. The relationship between the content of M6P and cellular uptake was evaluated using avalglucosidase alfa samples with a range of M6P content. The results showed that avalglucosidase alfa was taken up into cells in a M6P content-dependent manner, and a plateau was reached at a M6P content[4)] of [redacted] mol/mol.
- The affinity for M6P receptors was evaluated by surface plasmon resonance (SPR) and high performance liquid chromatography (HPLC) with an M6P receptor affinity column.

4) [redacted]

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization tests in Section "2.1.5.1 Structure and characterization," Impurity A, macromolecules/aggregates, deamidated variants and oxidants were identified as product-related impurities.

Of the product-related impurities, Impurity A, Impurity B/Impurity C, and Impurity D are controlled by the specifications for the drug substance and drug product. Impurity E is not controlled by the specifications because it is considered to be indirectly controllable through the control of Impurity C. No product-related substances have been identified.

2.1.5.3 Process-related impurities

Host cell proteins (HCPs), protein derived from bovine serum (bovine serum albumin [BSA], bovine immunoglobulin G [IgG]), host cell DNA, Impurities F, G, H, I, J, K, L, M, N, O, P, Q, R, and S were identified as process-related impurities. All the process-related impurities were confirmed to be adequately removed during the manufacturing process. Impurities K and P are controlled by the specifications for the drug substance. Impurities N and O are controlled through the control of Impurity T.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping, sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE]), pH, purity (size exclusion-high performance liquid chromatography [SE-HPLC], SDS-PAGE, Impurity K [SPR], residue E11 [HPLC]), bacterial endotoxins, bioburden, [redacted] (enzyme activity), M6P receptor affinity (SPR), and assay (ultraviolet visible absorption spectroscopy).

The M6P receptor affinity was specified during the review process [see Section 2.R.1 "Biological activity testing"].

2.1.7 Stability of drug substance

Table 3 summarizes main stability studies for the drug substance.

Table 3. Summary of main stability studies for the drug substance

	Manufacturing process	Number of batches	Storage condition	Test period	Storage package
Long-term	[redacted]	3	[redacted] ± [redacted] °C	[redacted] months	[redacted] bag
Accelerated	[redacted]	3	[redacted] ± [redacted] °C/ [redacted] ± [redacted] % RH	[redacted] weeks	
Photostability	[redacted]	1	Overall illumination of ≥1.2 million lux·h, and integrated near ultraviolet energy of ≥200 W·h/m^2		Tightly capped [redacted]

The long-term testing showed increases in Impurities K and U.

The above change seen in the long-term testing was more prominent in the accelerated testing.

The photostability testing showed that the drug substance was photolabile.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance when stored at [redacted] ± [redacted]°C in a [redacted] bag protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a vial (20 mL) containing 103 mg of avalglucosidase alfa. Excipients contained in the drug product are L-histidine, L-histidine hydrochloride hydrate, glycine, D-mannitol, and polysorbate 80. Each vial is overfilled to ensure that the labeled amount (100 mg) of avalglucosidase alfa can be withdrawn after reconstitution with 10 mL of water for injection.

2.2.2 Manufacturing process

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

[redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

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

2.2.3 Manufacturing process development

Changes were made to [redacted], [redacted], and [redacted] during the development of the drug product.

Comparability studies were conducted following the manufacturing process changes, and their impacts on the quality attributes were assessed. The results demonstrated the comparability of the pre- and post-change drug products.

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

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmolality, pH, purity (SE-HPLC, SDS-PAGE, Impurity K [SPR], residue E11 [HPLC]), water content, bacterial endotoxins, foreign insoluble matter, insoluble particulate matter, sterility, M6P receptor affinity (SPR), [redacted], [redacted] (enzyme activity), and assay (ultraviolet visible spectroscopy).

The M6P receptor affinity was specified during the review process [see Section 2.R.1 “Biological activity testing”].

2.2.5 Stability of drug product

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

Table 4. Summary of main stability studies for the drug product

	Manufacturing process for drug substance	Number of batches	Storage condition	Test period	Storage package
Long-term	Process [redacted]	4	5 ± 3°C	48 months	Primary packaging: chlorobutyl rubber stopper and glass vial Secondary packaging: paper carton
	Process [redacted]	2		30 months[a)]	
	Process [redacted]	3		24 months[a), b)]	
Accelerated	Process [redacted]	3	25 ± 2°C/60 ± 5% RH	6 months	
Photostability	Process [redacted]	1	Overall illumination of ≥1.2 million lux·h, and integrated near ultraviolet energy of ≥200 W·h/m^2		Chlorobutyl rubber stopper and glass vial

a) The stability testing is ongoing for up to [redacted] months.
b) The stability testing for [redacted] of the batches has been performed for [redacted] months

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

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

Based on the above, a shelf life of 48 months has been proposed for the drug product when stored at 5 ± 3°C in a glass vial with a chlorobutyl rubber stopper.

2.3 QbD

Information on the quality attributes of avalglucosidase alfa, including product-related impurities [see Section "2.1.5.2 Product-related substances/Product-related impurities"] and process-related impurities [see Section "2.1.5.3 Process-related impurities"], was obtained during the development of avalglucosidase alfa. Based on the information, the following critical quality attributes (CQAs) were identified.

CQAs: enzyme activity, [redacted], identification, M6P content, [redacted], water content, insoluble particulate matter, [redacted], sterility, [redacted], bacterial endotoxins, bioburden, mycoplasma, viruses, foreign insoluble matter

• Process characterization

Process parameters (input) and performance indices (output) were classified based on the risk assessment, and the characterization of each process was performed.

• Development of control strategy

Control strategy for the quality attributes of avalglucosidase alfa was established based on the process knowledge (including the above characterization), batch analysis data, stability and other data. The quality attributes are controlled by a combination of the control of process parameters/performance indices, in-process controls, and specifications [see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities" for the control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following review, PMDA concluded that the quality of the drug substance and drug product had been adequately controlled.

2.R.1 Biological activity testing

Since avalglucosidase alfa binds to M6P receptors on the cell surface and is internalized to exert its effect, PMDA requested the applicant to select either of the following options for the specifications for the drug substance and drug product: (i) cellular uptake activity and (ii) testing that can control a surrogate indicator shown to be correlated to cellular uptake activity.

The applicant' response:

M6P receptor affinity will be included, as the indicator for cellular uptake activity, in the specifications for the drug substance and drug product because M6P receptor affinity studies demonstrated correlation between cellular uptake and M6P receptor affinity.

PMDA accepted the applicant's explanation.

2.R.2 Novel excipient

The drug product contains glycine in an amount exceeding that previously used for intravenous infusion, and glycine is therefore handled as a novel excipient.

2.R.2.1 Specifications and stability

PMDA concluded that the use of glycine would not affect the specifications or stability of the drug product because it conforms to the requirements specified in the Japanese Pharmacopoeia.

2.R.2.2 Safety

Based on the submitted data, PMDA concluded that there is no safety-related problems with the amount of glycine used at the proposed dosage.

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

A primary pharmacodynamic study was conducted *in vivo* to investigate glycogen clearance in GAA knockout (GAAKO) mice. Safety pharmacology was evaluated by investigating the effects on the central nervous system (CNS), cardiovascular system, and respiratory system in toxicity studies. No secondary pharmacodynamic or pharmacodynamic drug interaction studies were conducted. Results from the main studies are presented in the following sections.

3.1 Primary pharmacodynamics

3.1.1 Investigation of glycogen clearance in GAAKO mice (CTD 4.2.1.1-2)

Avalglucosidase alfa (4, 12, or 20 mg/kg), ALGLU (20, 60, or 100 mg/kg), or vehicle[5)] was administered intravenously to GAAKO mice (aged 3-6 months; n = 11-12/group) once weekly for 4 weeks. To prevent hypersensitivity, mice were pre-treated with diphenhydramine (DPH) 5.0 mg/kg intraperitoneally 10 to 20 minutes before the administration of the second, third, and fourth doses.

Glycogen content in the heart, triceps, quadriceps, psoas muscle, and diaphragm was measured using a biochemical glycogen assay. Glycogen content in the heart and quadriceps decreased dose-dependently both in the avalglucosidase alfa and ALGLU groups, with a similar extent of glycogen reduction between the dose levels of the avalglucosidase alfa group and those of the ALGLU group.[6)] Glycogen content in triceps, psoas muscle, and diaphragm in the avalglucosidase alfa and ALGLU groups tended to decrease in an almost similar manner to that in the heart and quadriceps, while glycogen levels in these tissues following treatment with avalglucosidase alfa 20 mg/kg were similar to those following treatment with avalglucosidase alfa 12 mg/kg, and glycogen levels in triceps and psoas muscle were higher than those following treatment with ALGLU 100 mg/kg.

3.2 Safety pharmacology

The effects of avalglucosidase alfa on the CNS, cardiovascular system, and respiratory system were evaluated in repeated-dose toxicity studies [see Section "5.2 Repeated-dose toxicity"]. Table 5 summarizes the results.

Table 5. Summary of results of safety pharmacology studies

Organ system	Test system	Evaluation parameter/method	Dosage regimen of avalglucosidase alfa	Route of administration	Findings	CTD
CNS	Cynomolgus monkey (males and females, N = 6/group)	CNS evaluation, core body temperature	0, 50, or 200 mg/kg 26 weeks (every other week)	Intravenous	No findings	4.2.3.2-4
Cardiovascular system	Cynomolgus monkey (males and females, N = 6/group)	Electrocardiography, heart rate	0, 50, or 200 mg/kg 26 weeks (every other week)	Intravenous	No findings	4.2.3.2-4
Respiratory system	Cynomolgus monkey (males and females, N = 6/group)	Respiratory rate	0, 50, or 200 mg/kg 26 weeks (every other week)	Intravenous	No findings	4.2.3.2-4

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of avalglucosidase alfa

The applicant's explanation:

GAA is an enzyme that degrades glycogen in lysosomes. Avalglucosidase alfa has bis-M6P conjugated to oxidized sialic acid residues on ALGLU that is a recombinant human GAA. With an enhanced cellular uptake, avalglucosidase alfa is expected to have a more potent effect than ALGLU.

In the study that measured the glycogen content in the heart, triceps, quadriceps, psoas muscle, and diaphragm following 4-week administration of avalglucosidase alfa or ALGLU to GAAKO mice (CTD 4.2.1.1-2),

5) 10 mmol/L L-histidine, 2% w/v glycine, 2% w/v mannitol, and 0.01% polysorbate 80 (pH6.5)

6) The glycogen content was compared in the following pairs: avalglucosidase alfa 4 mg/kg vs. ALGLU 20 mg/kg, avalglucosidase alfa 12 mg/kg vs. ALGLU 60 mg/kg, and avalglucosidase alfa 20 mg/kg vs. ALGLU 100 mg/kg.

glycogen content decreased in all the tissues of animals treated with avalglucosidase alfa or ALGLU. The results suggested that the extent of glycogen clearance in avalglucosidase alfa-treated mice was greater than that in ALGLU-treated mice on a dose-for-dose basis. In the heart and quadriceps, glycogen content decreased in a dose-dependent manner following treatment with avalglucosidase alfa; in contrast, in triceps, psoas muscle, and diaphragm, the extent of glycogen clearance in the 12 mg/kg group was similar to that in the 20 mg/kg group, indicating that the extent of glycogen clearance tended to vary across tissues. Avalglucosidase alfa was designed to improve binding to the cation-independent mannose-6-phosphate receptor (CIMPR) compared to ALGLU, thereby increasing cellular uptake and subsequent delivery to lysosomes. It has been suggested that CIMPR expression level is higher in the heart than in skeletal tissues (*Mol Genet Metab.* 2011;103:107-12). In contrast, CIMPR expression level is low in triceps muscle fiber and psoas muscle, which are primarily composed of type II muscle fibers ; therefore, when high dose levels of avalglucosidase alfa or ALGLU are administered, CIMPR binding may become saturated. The glycogen content in the diaphragm decreased to values closer to the lower limit of quantitation at 12 mg/kg and 20 mg/kg.

PMDA's view:

Based on the results of the study comparing the glycogen clearance by avalglucosidase alfa with that by ALGLU in various tissues from GAAKO mice following 4-week intravenous treatment, and given that avalglucosidase alfa is ALGLU conjugated with bis-M6P, avalglucosidase alfa is assumed to be able to reduce glycogen content in various organs, and the effect is likely to be more potent than that of ALGLU. However, mice used in the *in vivo* study were GAAKO mice aged <6 months, which did not present clear signs of muscle weakness, and the effect of avalglucosidase alfa on reversal or stabilization of the phenotype was not evaluated in the study. Therefore, the efficacy of avalglucosidase alfa in the treatment of Pompe disease in humans will be discussed in Section "7.R.1 Efficacy."

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

The pharmacokinetic data were evaluated after single intravenous administration of avalglucosidase alfa in mice. The pharmacokinetic data after repeated intravenous administration of avalglucosidase alfa were evaluated based on the toxicokinetics in mouse and monkey toxicity studies. The concentrations of avalglucosidase alfa in serum and biological samples were determined by enzyme activity assay.[7)] The lower limits of quantitation for serum avalglucosidase alfa concentrations were 320 to 2200 ng/mL in mice and 100 to 125 ng/mL in monkeys. Anti-avalglucosidase alfa antibodies were measured by enzyme-linked immunosorbent assay (ELISA). The results of the main studies are presented in the following sections.

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2-1)

A single intravenous dose of avalglucosidase alfa or ALGLU was administered to male and female GAAKO mice. Table 6 shows pharmacokinetic parameters of avalglucosidase alfa or ALGLU in serum.

7) Fluorometric detection using 4-methylumbelliferyl-α-glucoside (4-MUG) as a substrate for avalglucosidase alfa to generate 4-methylumbelliferon (4-MU).

Table 6. Pharmacokinetic parameters following single intravenous administration of avalglucosidase alfa or ALGLU

Treatment	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)
Avalglucosidase alfa	20 mg/kg	M	5	646 ± 46	671 ± 46	0.70 ± 0.09	30.0 ± 1.9	30.2 ± 2.7
		F	5	494 ± 53	554 ± 75	0.53 ± 0.09	36.6 ± 4.8	27.8 ± 5.0
ALGLU	20 mg/kg	M	5	446 ± 35	723 ± 19	2.24 ± 0.31	27.7 ± 0.8	89.6 ± 12.9
		F	5	447 ± 19	672 ± 81	2.60 ± 0.51	30.1 ± 3.2	111.1 ± 8.7

Mean ± standard deviation

C_{max}, maximum serum concentration; $AUC_{0\text{-}inf}$, area under the serum concentration-time curve from time 0 extrapolated to infinity; $t_{1/2}$, elimination half-life; CL, total body clearance; V_d, volume of distribution

4.1.2 Repeated-dose studies (CTD 4.2.3.2-2, 4.2.3.2-4, 4.2.3.5.4-1)

Table 7 shows pharmacokinetic parameters of avalglucosidase alfa in serum in mouse and monkey studies. Avalglucosidase alfa was administered once weekly intravenously to male and female mice, and every other week intravenously[8)] to male and female monkeys. Anti-avalglucosidase alfa antibodies in serum, which were measured after the fourth dose in mice and after the seventh and 13th doses in monkeys, were detected at all the time points in all animals treated with avalglucosidase alfa.

Table 7. Pharmacokinetic parameters following repeated intravenous administration of avalglucosidase alfa

Animal	Dose (mg/kg)	Evaluation time point	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h)	V_z (mL)
Mouse	4	Initial dose	M	2	81.3, 87.8	48.8, 66.5	0.316, 0.420	82.0, 60.1	37.4, 36.5
			F	3	89.7 ± 9.66	71.8 ± 8.0	0.513 ± 0.049	56.2 ± 6.5	41.3 ± 0.95
		Fourth dose	M	2	68.8[a)]	50.0[a)]	0.315[a)]	80.0[a)]	36.3[a)]
			F	3	—[b)]	—[b)]	—[b)]	—[b)]	—[b)]
	40	Initial dose	M	3	1005 ± 101.6	1309 ± 49.0	0.715 ± 0.124	30.6 ± 1.16	31.5 ± 5.44
			F	3	880 ± 28.7	1304 ± 51.8	0.820 ± 0.049	30.7 ± 1.21	36.3 ± 2.70
		Fourth dose	M	3	841 ± 42	1737 ± 228	0.778 ± 0.344	23.3 ± 2.87	25.2 ± 7.60
			F	3	1056 ± 168	1259 ± 339	0.725 ± 0.163	33.6 ± 10.30	34.2 ± 7.80
	120	Initial dose	M	3	2505 ± 122	5106 ± 249	1.25 ± 0.026	23.5 ± 1.2	42.5 ± 3.0
			F	2	2277, 2793	4332, 5984	1.11, 1.29	27.7, 20.1	44.4, 37.4
		Fourth dose	M	2	2282, 2185	4960, 4762	1.13, 1.01	24.2, 25.2	39.4, 36.7
			F	3	3287±439	4282±695	0.852 ± 0.018	28.5 ± 4.51	35.0 ± 5.14
Monkey[c)]	50	Initial dose	M	6	610 ± 201	2603 ± 845	0.526 ± 0.086	21.2 ± 8.04	15.5 ± 3.80
			F	6	523 ± 96.6	2244 ± 481	0.523 ± 0.106	23.3 ± 5.95	17.0 ± 2.34
		Seventh dose	M	5	880 ± 174	3646 ± 643	0.648 ± 0.107	14.1 ± 2.59	13.0 ± 2.75
			F	6	767 ± 177	3087 ± 786	0.518 ± 0.089	17.1 ± 4.34	12.4 ± 2.15
		13th dose	M	6	884 ± 217	3870 ± 1087	0.830 ± 0.250	14.1 ± 5.18	15.7 ± 2.90
			F	4	825 ± 162	3473 ± 876	0.598 ± 0.095	15.0 ± 3.13	12.8 ± 3.00
	200	Initial dose	M	6	3944 ± 592	19208 ± 3770	1.49 ± 0.181	10.7 ± 2.07	22.9 ± 3.83
			F	6	3840 ± 456	18248 ± 1818	1.30 ± 0.204	11.1 ± 1.11	20.6 ± 2.73
		Seventh dose	M	6	4452 ± 1210	24272 ± 8061	1.71 ± 0.137	8.79 ± 2.04	21.4 ± 4.23
			F	5	4221 ± 365	20291 ± 2486	1.73 ± 0.035	10.0 ± 1.23	24.9 ± 3.12
		13th dose	M	4	6177 ± 1457	29105 ± 13468	2.02 ± 0.310	7.90 ± 3.13	22.3 ± 7.23
			F	4	4392 ± 769	27218 ± 9115	1.96 ± 0.182	7.86 ± 2.03	22.0 ± 5.22

Mean ± standard deviation

Individual values are presented for N ≤2.

"—": not calculated

C_{max}, maximum serum concentration; $AUC_{0\text{-}inf}$, area under the serum concentration-time curve from time 0 extrapolated to infinity; $t_{1/2}$, elimination half-life; CL, total body clearance; V_z, volume of distribution

a) One animal

b) Pharmacokinetic parameters were unable to be calculated with serum concentration data obtained from any of the 3 animals.

c) Administered by continuous intravenous infusion.

Avalglucosidase alfa 20, 50, or 100 mg/kg was administered every other week intravenously to male and female juvenile mice (n = 9/sex, n = 3/time point) from post-natal day 21 to post-natal day 77. The $AUC_{0\text{-}24\,h}$ (mean) of serum avalglucosidase alfa on post-natal day 77 were 550, 2730, and 8140 μg·h/mL, respectively, in males; and 469, 1490, and 5400 μg·h/mL, respectively, in females. Anti-avalglucosidase alfa antibodies in serum were detected in all animals on post-natal day 76.

8) Administered by continuous intravenous infusion.

4.2 Distribution (CTD 4.2.2.3-1, 4.2.2.3-2)

A single intravenous dose of avalglucosidase alfa 20 mg/kg or ALGLU 20 mg/kg was administered to male and female GAAKO mice. Table 8 shows the concentrations of avalglucosidase alfa or ALGLU in the liver, heart, quadriceps, and triceps at 1, 6, and 24 hours post-dose.

Table 8. Tissue concentrations after single intravenous administration of avalglucosidase alfa or ALGLU

Tissue	Measurement time point	Avalglucosidase alfa	ALGLU
Liver	1 hour post-dose	99.25 ± 19.098 [a)]	133.89 ± 11.470
	6 hours post-dose	215.58 ± 43.583	159.87 ± 9.237
	24 hours post-dose	184.75 ± 51.447	178.95 ± 11.403
Heart	1 hour post-dose	7.11 ± 2.087	6.90 ± 2.037
	6 hours post-dose	5.58 ± 0.909	4.07 ± 0.622
	24 hours post-dose	5.99 ± 1.248	3.74 ± 0.430
Quadriceps	1 hour post-dose	1.32 ± 0.382	0.90 ± 0.375
	6 hours post-dose	1.36 ± 0.418	0.94 ± 0.238
	24 hours post-dose	0.72 ± 0.127	0.87 ± 0.430
Triceps	1 hour post-dose	0.86 ± 0.425	1.17 ± 0.611
	6 hours post-dose	0.97 ± 0.429	0.80 ± 0.122
	24 hours post-dose	0.86 ± 0.289	0.68 ± 0.134

N = 36 (N = 6/time point)
Mean ± standard deviation
Unit: μg/g
a) N = 5

Avalglucosidase alfa 50 mg/kg was administered intravenously to male and female GAAKO mice (n = 4/sex/time point). The concentrations of avalglucosidase alfa in bone marrow (mean ± standard deviation) were 87.1 ± 33.9 and 121.2 ± 27.9 μg/g at 6 and 24 hours post-dose, respectively, while the concentrations after the second and third doses, administered 4 hours apart, were 218.9 ± 58.2 and 369.1 ± 70.5 μg/g, respectively, at 24 hours after the first dose.

4.3 Metabolism

No studies on metabolism have been conducted.

4.4 Excretion

No studies on excretion have been conducted.

4.R Outline of the review conducted by PMDA

4.R.1 Tissue distribution of avalglucosidase alfa

The applicant's explanation:

In the tissue distribution study, following administration of the same dose level of avalglucosidase alfa or ALGLU to GAAKO mice, both avalglucosidase alfa and ALGLU were distributed primarily in the liver, and to a lesser extent in the heart and skeletal muscles. There was no significant difference in the degree of tissue distribution between avalglucosidase alfa and ALGLU (CTD 4.2.2.3-1). Avalglucosidase alfa has bis-M6P conjugated to oxidized sialic acid residues on ALGLU. With an enhanced cellular uptake, avalglucosidase alfa is expected to have a more potent effect than ALGLU; however, the details of the factors responsible for the small differences in the degree of tissue distribution are unknown. On the other hand, the results of a non-clinical pharmacology study in GAAKO mice (CTD 4.2.1.1-2), which compared the pharmacodynamics of avalglucosidase alfa with that of ALGLU, showed that avalglucosidase alfa at a lower dose level than ALGLU achieved a similar degree of glycogen clearance to that achieved by ALGLU. The activity of avalglucosidase

alfa is expected to be similar to that of ALGLU after their internalization into lysosomes, and increases in the levels of these enzymes in the lysosomes are likely to enhance glycogen clearance. Therefore, while tissue distribution data for avalglucosidase alfa evaluated in the tissue distribution study in GAAKO mice are similar to those for ALGLU, CIMPR-mediated cellular uptake and lysosomal entry of avalglucosidase alfa are likely to increase compared with ALGLU, leading to avalglucosidase alfa having a more potent effect than ALGLU [see Section "3.R.1 Mechanism of action of avalglucosidase alfa"].

The results of the tissue distribution study showed that avalglucosidase alfa was distributed predominantly in the liver (37.91% to 82.35% of the amount of avalglucosidase alfa administered at 1-24 hours post-dose) (CTD 4.2.2.3-1). However, given that no liver-related toxicity findings associated with avalglucosidase alfa were reported in the toxicity studies, this is unlikely to pose a safety concern.

PMDA accepted the applicant's explanation about the tissue distribution of avalglucosidase alfa. The efficacy and safety of avalglucosidase alfa compared with ALGLU will be further discussed in Sections "7.R.1 Efficacy" and "7.R.2 Safety."

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted the following toxicity studies of avalglucosidase alfa: repeated-dose toxicity studies, reproductive and developmental toxicity studies, and other toxicity studies (those investigating the toxicity of impurities contained in avalglucosidase alfa). In the control group, vehicle (10 mmol/L L-histidine, 2% w/v glycine, 2% w/v mannitol, 0.01% polysorbate 80 [pH6.2 ± 0.5]) was administered.

5.1 Single-dose toxicity

Although no single dose toxicity studies were conducted, the acute toxicity of avalglucosidase alfa was evaluated based on the data following the initial dose in the repeated-dose toxicity studies in mice (non-GLP) and monkeys (Table 9). There were no deaths or signs of acute toxicity, and the approximate lethal dose of avalglucosidase alfa was determined to be >120 mg/kg in mice and >200 mg/kg in cynomolgus monkeys.

Table 9. Summary of data after the initial dose in repeated-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female mice (CD-1)	Intravenous	0, 4, 40, 120	None	>120	Reference data 4.2.3.2-2
Male/female cynomolgus monkeys	Intravenous[a)]	0, 50, 200	None	>200	4.2.3.2-4

a) Administered by continuous intravenous infusion.

5.2 Repeated-dose toxicity

Exploratory repeated-dose toxicity studies (non-GLP) were conducted in mice and cynomolgus monkeys. Because hypersensitivity associated with avalglucosidase alfa was observed in the mouse study, a repeated-dose study under GLP-compliant conditions was conducted in cynomolgus monkeys only (Table 10).

Although anti-avalglucosidase alfa antibodies associated with avalglucosidase alfa treatment were detected in all animals, no particular toxicity findings were noted. Cynomolgus monkeys were treated with avalglucosidase

alfa at 200 mg/kg, which is the no-observed adverse effect level (NOAEL), every other week for 26 weeks. The exposure to avalglucosidase alfa in animals was 5284 μg/mL (C_{max}) and 28162 μg·h/mL ($AUC_{0\text{-}inf}$), which are approximately 13.1-fold (C_{max}) and 10.7-fold ($AUC_{0\text{-}inf}$) the exposures [9)] in patients treated with avalglucosidase alfa at the maximum clinical dose (40 mg/kg).

Table 10. Summary of repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg/2 weeks)	Major findings	NOAEL (mg/kg/2 weeks)	CTD
Male/female cynomolgus monkeys	Intravenous[a)]	26 weeks (every other week) + 4-week recovery period	0, 50, 200	No toxicity findings	200	4.2.3.2-4

a) Administered by continuous intravenous infusion.

5.3 Genotoxicity

No genotoxicity studies have been conducted for avalglucosidase alfa.

5.4 Carcinogenicity

No carcinogenicity studies have been conducted. The applicant's explanation about the carcinogenic risk of avalglucosidase alfa:

Toxicity studies of avalglucosidase alfa indicated no findings suggestive of carcinogenicity. The investigation of [redacted] contained in avalglucosidase alfa also suggests that it is unlikely to involve carcinogenicity. Additionally, there were no reports of events suggestive of carcinogenic risk associated with the clinical use of ALGLU. Based on the above information, the carcinogenic risk of avalglucosidase alfa is considered to be low.

5.5 Reproductive and developmental toxicity

A study on fertility and early embryonic development to implantation in mice, embryo-fetal development studies in mice and rabbits, and a study for effects on pre- and postnatal development including maternal function in mice were conducted (Table 11). Because substantial differences in dosing interval between the non-clinical and clinical studies preclude direct comparison of avalglucosidase alfa exposures (AUC) in animals with those in humans, an estimated exposure for 2 weeks (daily exposure multiplied by the number of doses in 2 weeks) was used to adjust to the exposure ($AUC_{0\text{-}2w}$) at human dosing intervals. In the mouse embryo-fetal development study, avalglucosidase alfa exposures (C_{max} and $AUC_{0\text{-}2w}$) at the NOAEL for the parent animal's general toxicity (50 mg/kg) were 1440 μg/mL (C_{max}) and 20,800 μg·h/mL ($AUC_{0\text{-}2w}$), corresponding to a safety margin of 5.3-fold and 17-fold, respectively, the clinical exposures, [10)] while avalglucosidase alfa exposures (C_{max} and $AUC_{0\text{-}2w}$) at the NOAEL for maternal fertility and embryo-fetal development (20 mg/kg) were 454 μg/mL (C_{max}) and 5820 μg·h/mL ($AUC_{0\text{-}2w}$), corresponding to a safety margin of 1.7-fold and 4.8-fold, respectively, the clinical exposures.[10)] In the rabbit embryo-fetal development study, avalglucosidase alfa exposures (C_{max} and $AUC_{0\text{-}2w}$) at the NOAEL for the parent animal's general toxicity (30 mg/kg) were 772 μg/mL and 17,640 μg·h/mL, corresponding to a safety margin of 2.8-fold and 14.5-fold, respectively, the clinical exposures,[10)] while avalglucosidase alfa exposures (C_{max} and $AUC_{0\text{-}2w}$) at

9) Exposures in patients with IOPD treated with avalglucosidase alfa 40 mg/kg every other week as an intravenous infusion (mean C_{max}, 403 μg/mL; mean $AUC_{0\text{-}2w}$, 2630 μg·h/mL).

10) Estimated exposure following administration of intravenous avalglucosidase alfa 20 mg/kg every other week, calculated by the population pharmacokinetic analysis using plasma avalglucosidase alfa concentration data in patients with LOPD (mean C_{max}, 273 μg/mL; mean $AUC_{0\text{-}2w}$, 1220 μg·h/mL).

the NOAEL for maternal fertility and embryo-fetal development (100 mg/kg) were 2530 μg/mL (C_{max}) and 110,740 μg·h/mL ($AUC_{0\text{-}2w}$), corresponding to a safety margin of 9.3-fold and 91-fold, respectively, the clinical exposures.[10)] The majority of the toxicity findings were thought to have been caused by immune response resulting from administration of a foreign protein or occurred secondarily, suggesting the findings were unlikely to be relevant to humans.

A juvenile animal study was conducted, and the results suggested that the toxicity profile in juvenile animals would not differ from that in adult animals.

Table 11. Summary of reproductive and developmental toxicity study results

Study type	Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Fertility and early embryonic development to implantation	Male mice (CD-1)	Intravenous	10 weeks prior to mating, during mating (until sacrifice)	0, 0,[a)] 10, 20, 50 Once every 2 days In the avalglucosidase alfa group, DPH 5 mg/kg was administered intraperitoneally from the 6th dose onward to males and from the 2nd dose onward to females, as necessary	Parent animals: Died[b)] at 10 mg/kg (4 of 22 animals), at 20 mg/kg (7 of 22 animals), and at 50 mg/kg (3 of 22 animals) Decreased spontaneous activity, prostrate while walking, tremor, ataxia, labored breathing, tactile hyperesthesia, hunchback position	Parent animals (general toxicity): 50 Parent animals (reproductive): 50	4.2.3.5.1-1
	Female mice (CD-1)		2 weeks prior to mating until gestation day 7		Parent animals: Died/sacrificed moribund[b)] at 10 mg/kg (2 of 22 animals), at 20 mg/kg (4 of 22 animals), and at 50 mg/kg (1 of 22 animals) Decreased spontaneous activity, ataxia, labored breathing, loss of righting reflex Embryos/fetuses: No toxicity findings	Parent animals (general toxicity): 50 Parent animals (reproductive): 50 Early embryonic development: 50	
Embryo-fetal development	Female mice (CD-1)	Intravenous	Gestation days 6-15	0, 0,[a)] 10, 20, 50 Once daily In the avalglucosidase alfa group, DPH was planned to be administered as necessary, but was not administered	Parent animals: Died[b)] at 50 mg/kg (2 of 22 animals) At ≥10 mg/kg, inanimation[c)] Fetuses: At 50 mg/kg, high postimplantation loss,[c)] increased late embryo resorption[c)]	Parent animals (general toxicity): 50 Parent animals (reproductive): 20 Embryo-fetal: 20	4.2.3.5.2-1
	Female rabbits (NZW)	Intravenous[d)]	Gestation days 6-19	0, 30, 60, 100 Once daily	Parent animals: Died[b)] at 30 mg/kg (1 of 24 animals) At 100 mg/kg, low body weight At ≥60 mg/kg, reduced body weight gain, low food consumption Fetuses: No toxicity findings	Parent animals (general toxicity): 30 Parent animals (reproductive): 100 Embryo-fetal: 100	4.2.3.5.2-4
Prenatal and postnatal development and maternal function	Female mice (CD-1)	Intravenous	Gestation day 6 to postnatal day 20	0, 0,[a)] 10, 20, 50 Once every 2 days In the avalglucosidase alfa group, DPH 5 mg/kg was administered intraperitoneally from the fifth dose onward	Parent animals: Died/sacrificed moribund[b)] at 10 mg/kg (2 of 25 animals), at 20 mg/kg (1 of 22 animals), at 50 mg/kg (1 of 22 animals[e)]) No toxicity findings Live F1 offspring: Died/sacrificed moribund[b)] at 0 mg/kg (1 of 25 female animals), at 0[a)] mg/kg (1 of 25	Parent animals (general toxicity): 50 Parent animals (reproductive): 50 Live F1 offspring: 50	4.2.3.5.3-1

					male animals), at 20 mg/kg (1 of 25 female animals) No toxicity findings		
Juvenile animals	Male/ female juvenile mice (CD-1)	Intravenous	Post-natal day 21 to post-natal day 77 or 91 + 4-week recovery period	0, 0,[a] 25/20,[f] 50, 100 Every other week In the avalglucosidase alfa group, DPH 5 mg/kg was administered intraperitoneally from the 2nd dose onward	Died/sacrificed moribund[b] at 0 mg/kg (1 of 35 male animals, 1 of 35 female animals), at 20/25 mg/kg (6 of 35 male animals, 5 of 35 female animals), at 50 mg/kg (2 of 35 male animals, 1 of 35 female animals) At ≥50 mg/kg, elevated white blood cell parameters[c]	100	4.2.3.5.4-1

a) Vehicle + DPH (5 mg/kg)
b) It is considered that animals died or were sacrificed moribund due to causes unrelated to avalglucosidase alfa treatment, or due to anaphylaxis or other immune response to avalglucosidase alfa treatment.
c) These are likely to be immune response-related findings, or findings secondary to immune responses.
d) Administered by continuous intravenous infusion.
e) Sacrificed in association with spontaneous abortion.
f) Only males in the main study group received 25 mg/kg; and animals in the recovery group, fertility evaluation group, and TK group received 20 mg/kg.

5.6 Local tolerance

The local tolerance of intravenous avalglucosidase alfa was evaluated as part of the repeated-dose toxicity study in cynomolgus monkeys. No findings suggestive of irritation caused by avalglucosidase alfa were noted at the injection site; therefore, intravenous avalglucosidase alfa is considered to have no local irritant effect.

5.7 Other toxicity studies

5.7.1 Evaluation of potential mutagenic impurities

A total of 13 potential impurities for the drug substance were identified according to the ICH M7 Guidelines. The applicant explained that the impurities are to be adequately controlled at levels below the threshold of toxicological concern by establishing specification limits. A bacterial reverse mutation assay was performed on Impurity U, which was identified as being a structural alert by the *in silico* evaluation. The tests returned negative results (Table 12).

Table 12. Summary of genotoxicity study results for Impurity U

Study type	Test system	Metabolic activation (treatment)	Concentration (μg/plate)	Test result	CTD
Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537, and TA102	S9−	0,[a] 5, 16, 50, 160, 500, 1600, 5000	Negative	4.2.3.7.6-1
		S9+	0,[a] 5, 16, 50, 160, 500, 1600, 5000		

a) Water for injection

5.7.2 Evaluation of impurities/degradation products

Impurity T, an impurity contained in the drug product, was evaluated in the 13-week repeated-dose toxicity study in monkeys (Table 13), bacterial reverse mutation assay, and mammalian cell chromosomal aberration assay (Table 14). The results did not raise any particular safety concerns in relation to the clinical use of Nexviazyme.

Table 13. Summary of repeated-dose toxicity study results for Impurity T

Test system	Route of administration	Treatment duration	Dose: avalglucosidase alfa + Impurity T (mg/kg/2 weeks)	Major findings	NOAEL (mg/kg/2 weeks)	CTD
Male/female cynomolgus monkeys	Intravenous[a)]	13 weeks + 4-week recovery period	0, 50 + 3, 50 + 6, 50 + 12.55	No toxicity findings except for hypersensitivity-related findings caused by administration of avalglucosidase alfa	50 + 12.55	4.2.3.7.6-2

a) Administered by continuous intravenous infusion

Table 14. Summary of genotoxicity study results for Impurity T

Study type	Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL)	Test result	CTD
Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537, and TA102	S9−	0,[a)] 5, 16, 50, 160, 500, 1600, 5000	Negative	4.2.3.7.7-1
		S9+	0,[a)] 5, 16, 50, 160, 500, 1600, 5000		
Mammalian cell chromosomal aberration assay	Cultured human peripheral blood lymphocytes	S9− (3 hours)	0,[a)] 1 to 500	Negative	4.2.3.7.7-2
		S9− (20 hours)	0,[a)] 3 to 500		
		S9+ (3 hours)	0,[a)] 1-500 or 10-500		

a) Water for injection

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that there are no particular concerns with the clinical use of avalglucosidase alfa from a toxicological viewpoint.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Formulations used in the major clinical studies of avalglucosidase alfa are presented in Table 15. Changes were made to the manufacturing processes for the drug substance and the drug product. Comparability studies were performed to assess the impact of the changes on the quality attributes, and the results demonstrated the comparability of the drug substances or drug products before and after the changes [see Sections “2.1.4 Manufacturing process development” and “2.2.3 Manufacturing process development”].

Table 15. Formulations used in major clinical studies

Manufacturing process of drug substance	Phase (study ID)	
	Global study	Foreign study
Process A	—	Phase I/II study (Study TDR12857)
Process B	—	Extension study (Study LTS13769)
Process C1	Phase II study (Study ACT14132) Phase III study (Study EFC14028)	Extension study (Study LTS13769)
Process C2A	Phase II study (Study ACT14132) Phase III study (Study EFC14028)	Extension study (Study LTS13769)
Process C2B[a)]	Phase II study (Study ACT14132) Phase III study (Study EFC14028)	Extension study (Study LTS13769)

“—,” not applicable
a) Proposed commercial process

Plasma avalglucosidase alfa concentrations were determined by the enzyme activity assay.[7)] The lower limit of quantitation of avalglucosidase alfa ranged from 0.012 to 0.0125 μg/mL. Both anti-avalglucosidase alfa antibodies and anti-ALGLU antibodies in serum were measured by ELISA and radioimmunoprecipitation assay (RIP). Neutralizing antibodies were detected by the enzyme activity assay or cell-based assay.

6.2 Clinical pharmacology

The evaluation data submitted were the results from a global phase II study (Study ACT14132), a global phase III study (Study EFC14028), and a population pharmacokinetic analysis. The reference data submitted were the results from a foreign phase I/II study (Study TDR12857) and its extension study (Study LTS13769[11)]). Results from a study using human biological samples were also submitted. Results from the main studies are presented in the following sections.

6.2.1 Study using human biological samples (CTD 5.3.2.2-1 [reference data])

Human hepatocytes were incubated with avalglucosidase alfa (4 μmol/L) or Impurity T (40 μmol/L), an impurity contained in the drug product, for up to 48 hours; or human plasma was incubated with avalglucosidase alfa (0.4 or 4 μmol/L) for up to 24 hours, to evaluate whether the [redacted] of Impurity T and compounds containing a hydrazine structure ([redacted], [redacted], and [redacted]) were released. The results showed that the [redacted] of Impurity T, [redacted], [redacted], and [redacted] were below the lower limit of quantitation.

6.2.2 Investigation in patients

6.2.2.1 Foreign phase I/II study in patients with LOPD (CTD 5.3.3.2-1, Study TDR12857 [August 2013 to February 2015])

An open-label study was conducted to investigate the safety, pharmacokinetics, and pharmacodynamics of avalglucosidase alfa administered intravenously in multiple doses to non-Japanese patients[12)] with LOPD who were naïve to ALGLU or previously treated with ALGLU (target sample size, 21 subjects; Group 1 [treatment-naïve], n = 3/group at 5, 10, and 20 mg/kg; Group 2 [previously treated with ALGLU], n = 3/group at 5 and 10 mg/kg, n =6/group at 20 mg/kg).

Main inclusion criteria were patients aged ≥18 years with LOPD who were naïve to ALGLU (Group 1), or those who had been previously treated with ALGLU for ≥9 months (Group 2). Eligible patients had to: (1) have histologically confirmed GAA enzyme deficiency and/or GAA gene mutation; (2) no past history of cardiac hypertrophy; (3) be able to ambulate 50 meters without stopping and without an assistive device; and (4) have a % predicted forced vital capacity (FVC) ≥50% in the upright position.

The study consisted of the screening period (up to 90 days), treatment period (24 weeks), post-treatment evaluation period (2 weeks), and end-of-study evaluation period (2 weeks).

Subjects received avalglucosidase alfa 5, 10, or 20 mg/kg every other week as an intravenous infusion. The starting infusion rate was 1 mg/kg/h, and the infusion rate was to be increased gradually if there were no signs of infusion-associated reactions (IARs). The infusion rate could be increased to 7 mg/kg/h.

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11) An open-label, extension study that enrolled patients with LOPD who had completed Study TDR12857, with an aim to evaluate the long-term safety and pharmacokinetics of avalglucosidase alfa following continuous administration of intravenous avalglucosidase alfa every other week.

12) Patients in the US, France, Belgium, Denmark, the Netherlands, the UK, and Germany

All 24 subjects who received avalglucosidase alfa (4 subjects [5 mg/kg], 3 subjects [10 mg/kg], and 3 subjects [20 mg/kg] for Group 1; 4 subjects [5 mg/kg], 4 subjects [10 mg/kg], and 6 subjects [20 mg/kg] for Group 2) were included in the full analysis set (FAS), safety analysis set, and pharmacokinetic analysis set.

Table 16 shows pharmacokinetic parameters of multiple intravenous doses of avalglucosidase alfa 5, 10, or 20 mg/kg.

Table 16. Pharmacokinetic parameters after multiple intravenous doses of avalglucosidase alfa every other week

Prior ALGLU	Dose	Measurement time point	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
Treatment-naïve	5 mg/kg	Initial dose	4	82.3 ± 6.69	259 ± 37.6	1.71 [1.47, 2.58]	0.784 ± 0.369	1.26 ± 0.203	2.62 ± 0.396
		Week 13	4	98.7 ± 38.9	285 ± 82.9	1.60 [1.50, 1.80]	1.34 ± 1.05	1.22 ± 0.307	2.65 ± 0.803
		Week 25	3	89.1 ± 11.0	264 ± 50.2	1.43 [1.43, 1.62]	0.777 ± 0.0455	1.23 ± 0.229	2.40 ± 0.316
	10 mg/kg	Initial dose	3	190 ± 40.1	529 ± 79.6	2.30 [2.23, 2.30]	0.833 ± 0.493	1.24 ± 0.386	2.48 ± 0.626
		Week 13	3	151 ± 29.7	529 ± 41.8	2.33 [1.48, 2.35]	0.738 ± 0.133	1.28 ± 0.261	3.02 ± 0.766
		Week 25	3	162 ± 26.5	565 ± 89.8	2.35 [2.35, 2.45]	0.856 ± 0.235	1.18 ± 0.176	2.67 ± 0.109
	20 mg/kg	Initial dose	3	302 ± 107	1520 ± 806	3.83 [3.75, 4.00]	0.778 ± 0.217	0.989 ± 0.278	2.90 ± 0.439
		Week 13	3	357 ± 185	1660 ± 1030	3.92 [3.75, 4.00]	1.34 ± 0.753	0.954 ± 0.335	2.91 ± 0.661
		Week 25	3	350 ± 105	1560 ± 637	3.92 [3.75, 4.50]	1.03 ± 0.242	0.917 ± 0.214	2.93 ± 0.233
Treatment-experienced	5 mg/kg	Initial dose	4	77.4 ± 22.4	246 ± 81.5	1.84 [1.38, 2.60]	0.668 ± 0.299	1.57 ± 0.362	3.71 ± 1.52
		Week 13	4	103 ± 42.8	296 ± 84.2	1.64 [1.52, 2.58]	0.656 ± 0.253	1.29 ± 0.319	2.83 ± 0.762
		Week 25	4	97.1 ± 36.4	306 ± 79.9	1.97 [1.50, 2.62]	1.53 ± 0.520	1.24 ± 0.342	2.88 ± 0.704
	10 mg/kg	Initial dose	4	168 ± 36.8	631 ± 118	2.27 [1.75, 2.43]	1.03 ± 0.628	1.28 ± 0.246	3.21 ± 0.839
		Week 13	4	171 ± 45.1	668 ± 186	2.44 [2.28, 2.72]	0.838 ± 0.214	1.28 ± 0.448	3.28 ± 1.08
		Week 25	4	164 ± 19.1	642 ± 46.9	2.51 [2.25, 3.35]	0.712 ± 0.103	1.23 ± 0.0563	3.06 ± 0.114
	20 mg/kg	Initial dose	6	321 ± 125	1500 ± 502	3.83 [3.68, 4.73]	0.876 ± 0.232	1.06 ± 0.198	3.31 ± 0.731
		Week 13	6	327 ± 90.2	1430 ± 529	3.86 [3.58, 4.23]	0.849 ± 0.254	1.16 ± 0.321	3.51 ± 0.952
		Week 25	5	299 ± 47.5	1530 ± 434	3.83 [3.68, 5.58]	1.06 ± 0.435	0.998 ± 0.204	3.29 ± 0.755

Mean ± standard deviation
t_{max} is median [range].
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal phase elimination half-life; CL, total body clearance; V_{ss}, steady-state volume of distribution

Pharmacodynamics following multiple intravenous doses of avalglucosidase alfa 5, 10, or 20 mg/kg was evaluated. Table 17 shows percent change from baseline in urine glucose tetrasaccharide (HEX4) levels and glycogen content in quadriceps muscle.

Table 17. Urine HEX4 levels and glycogen content in quadriceps muscle at baseline, and percent change from baseline in those parameters following continuous intravenous infusion of multiple doses of avalglucosidase alfa

Endpoint	Prior ALGLU	Dose	Baseline	Week 13	Week 25 or 27[a)]
Urine HEX4 level	Treatment-naïve	5 mg/kg	7.0 ± 3.92 (4)	−16.0 ± 19.19 (4)	−30.3 ± 18.63 (3)
		10 mg/kg	13.0 ± 4.75 (3)	−34.3 ± 16.37 (3)	−36.0 ± 6.87 (3)
		20 mg/kg	5.4 ± 4.30 (3)	−27.0 ± 8.63 (3)	−13.2 ± 40.63 (3)
	Treatment-experienced	5 mg/kg	7.0 ± 3.77 (4)	4.3 ± 8.82 (4)	−7.5 ± 38.77 (4)
		10 mg/kg	3.9 ± 1.87 (4)	−9.9 ± 21.13 (4)	−12.0 ± 29.72 (4)
		20 mg/kg	7.5 ± 8.31 (6)	−31.0 ± 9.70 (6)	−20.5 ± 27.77 (5)
Glycogen content in quadriceps muscle	Treatment-naïve	5 mg/kg	7.0 ± 11.41 (4)	—	38.5 ± 77.79 (4)
		10 mg/kg	7.6 ± 3.72 (3)	—	−16.0, 14.3 (2)
		20 mg/kg	3.1 ± 0.81 (3)	—	13.6 ± 39.56 (3)
	Treatment-experienced	5 mg/kg	8.6 ± 10.89 (4)	—	−18.9 ± 26.03 (3)
		10 mg/kg	3.0 ± 2.23 (3)	—	47.7 ± 10.14 (3)
		20 mg/kg	6.7 ± 8.16 (6)	—	−28.5 ± 30.78 (3)

Baseline units: mmol/mol for urine HEX4 level; % for glycogen content in quadriceps muscle; and % for change from baseline
Mean ± standard deviation (n)
Individual values are presented for N ≤2.
"—": not applicable
a) Urine HEX4 levels at Week 25, and glycogen content in quadriceps muscle at Week 27

Safety data were analyzed. In Group 1, adverse events occurred in 4 of 4 subjects in the 5 mg/kg group, 3 of 3 subjects in the 10 mg/kg group, and 1 of 3 subjects in the 20 mg/kg group; and adverse drug reactions occurred

in 3 of 4 subjects in the 5 mg/kg group, 2 of 3 subjects in the 10 mg/kg group, and 1 of 3 subjects in the 20 mg/kg group. In Group 2, adverse events occurred in 4 of 4 subjects in the 5 mg/kg group, 2 of 4 subjects in the 10 mg/kg group, and 6 of 6 subjects in the 20 mg/kg group; and adverse drug reactions occurred in 3 of 4 subjects in the 5 mg/kg group, 1 of 4 subjects in the 10 mg/kg group, and 3 of 6 subjects in the 20 mg/kg group. There were no deaths. Serious adverse events occurred in 1 subject (respiratory distress/chest discomfort) in the 5 mg/kg group in Group 1 and in 1 subject (gastrointestinal haemorrhage) in the 5 mg/kg group in Group 2. The former events (respiratory distress/chest discomfort) in 1 subject were classified as adverse drug reactions. An adverse event leading to treatment discontinuation occurred in 1 subject (respiratory distress/chest discomfort) in the 5 mg/kg group of Group 1.

Anti-drug antibody status was as follows: before the start of treatment with avalglucosidase alfa, no subjects tested positive for anti-avalglucosidase alfa antibodies in Group 1, while 1 of 4 subjects in the 5 mg/kg group, 3 of 4 subjects in the 10 mg/kg group, and 1 of 6 subjects in the 20 mg/kg group tested positive for anti-avalglucosidase alfa antibodies in Group 2. By Week 29, 4 of 4 subjects in the 5 mg/kg group, 2 of 3 subjects in the 10 mg/kg group, and 3 of 3 subjects in the 20 mg/kg group became positive for anti-avalglucosidase alfa antibodies in Group 1; and 2 of 4 subjects in the 5 mg/kg group, 3 of 4 subjects in the 10 mg/kg group, and 2 of 6 subjects in the 20 mg/kg group became positive for anti-avalglucosidase alfa antibodies in Group 2. One subject[13)] in the 5 mg/kg group in Group 1 developed neutralizing antibodies to avalglucosidase alfa. In Group 2, 3 of 4 subjects in the 5 mg/kg group, 4 of 4 subjects in the 10 mg/kg group, and 3 of 6 subjects in the 20 mg/kg group became positive for anti-ALGLU antibodies by Week 29.

6.2.2.2 Global phase III study (CTD 5.3.5.1-2, Study EFC14028 [ongoing since November 2016, data cut-off in March 2020])

A double-blind, parallel-group, active-controlled study was conducted to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of avalglucosidase alfa or ALGLU, administered every other week intravenously in multiple doses to Japanese and non-Japanese patients with LOPD who were naïve to ALGLU (target sample size, 96 subjects) [see Section "7.1 Global phase III study" for details of the study design, and efficacy and safety data].

Table 18 shows the pharmacokinetic parameters of plasma avalglucosidase alfa in subjects receiving multiple intravenous doses of avalglucosidase alfa 20 mg/kg every other week.

Table 18. Pharmacokinetic parameters in subjects receiving multiple intravenous doses of avalglucosidase alfa every other week

Measurement time point	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
Initial dose	49	259 ± 72.3	1290 ± 420	4.02 [2.53, 6.33]	1.34 ± 0.561[a)]	1.22 ± 0.332[a)]	6.66 ± 1.87[a)]
Week 49	48	242 ± 81.4	1250 ± 433	4.03 [2.20, 7.33]	1.55 ± 0.887	1.38 ± 0.522[a)]	7.63 ± 2.33[a)]

Mean ± standard deviation
t_{max} is median [range].
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal phase elimination half-life; CL, total body clearance; V_{ss}, steady-state volume of distribution
a) N = 47

13) The subject tested positive for neutralizing antibodies (that inhibit cellular uptake) at Week 27.

Pharmacodynamics was evaluated in subjects receiving multiple intravenous doses of avalglucosidase alfa or ALGLU 20 mg/kg every other week. Table 19 shows percent change from baseline in urine HEX4 levels.

Table 19. Urine HEX4 levels at baseline, and percent change from baseline in subjects receiving multiple intravenous doses of avalglucosidase alfa or ALGLU

Treatment	Baseline	Week 25	Week 49	Week 73	Week 97	Week 145
Avalglucosidase alfa continuous treatment	12.71 ± 10.10 (51)	−53.56 ± 17.47 (51)	−53.90 ± 24.03 (51)	−57.25 ± 20.79 (37)	−65.00 ± 17.85 (21)	−56.99 ± 29.90 (11)
ALGLU/avalglucosidase alfa[a)]	8.74 ± 5.04 (49)	−24.22 ± 18.04 (45)	−10.76 ± 32.33 (41)	−49.66 ± 21.46 (30)	−58.34 ± 11.97 (21)	−29.39 ± 75.55 (8)

Unit of baseline value: mmol/mol
Change from baseline: %
Mean ± standard deviation (n)
a) At Week 49, patients switched from ALGLU to avalglucosidase alfa 20 mg/kg every other week

Anti-drug antibody (ADA) status was as follows: At baseline, 2 of 51 subjects (avalglucosidase alfa) and 2 of 48 subjects (ALGLU) tested ADA-positive; by Week 49, 49 of 51 subjects (avalglucosidase alfa) and 46 of 48 subjects (ALGLU) became ADA-positive. Among these subjects, 13 subjects in the avalglucosidase alfa group developed neutralizing antibodies[14)] to avalglucosidase alfa and 21 subjects in the ALGLU group developed neutralizing antibodies[14)] to ALGLU.

6.2.2.3 Global phase II study (CTD 5.3.5.1-1, Study ACT14132 [ongoing since October 2017, data cut-off in September 2019])

An open-label study was conducted to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamics of avalglucosidase alfa, administered every other week intravenously in multiple doses to Japanese and non-Japanese patients with IOPD who had been previously treated with ALGLU (target sample size, ≥20 subjects) [see Section "7.2 Global phase II study" for details of the study design, and efficacy and safety study data].

Table 20 shows the pharmacokinetic parameters of plasma avalglucosidase alfa in subjects receiving multiple intravenous doses of avalglucosidase alfa 20 or 40 mg/kg every other week.

Table 20. Pharmacokinetic parameters of plasma avalglucosidase alfa in subjects receiving multiple intravenous doses of avalglucosidase alfa every other week

Treatment	Measurement time point	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
Cohort 1[a)] Avalglucosidase alfa 20 mg/kg	Initial dose	5	189 ± 56.7	923 ± 352	4.43 [3.90, 5.33]	0.703 ± 0.291	0.673 ± 0.222	3.55 ± 0.927
	Week 25	5	175 ± 65.9	805 ± 295	3.97 [3.77, 4.75]	0.601 ± 0.256	0.696 ± 0.203	3.52 ± 1.18
Cohort 2[a)] Avalglucosidase alfa 40 mg/kg	Initial dose	4	403 ± 171	2630 ± 972	7.00 [6.00, 7.25]	1.15 ± 0.523	0.562 ± 0.152	4.50 ± 0.882
	Week 25	5	297 ± 60.1	1930 ± 348	7.13 [5.67, 7.98]	1.04 ± 0.248	0.683 ± 0.345	5.35 ± 2.27
Cohort 3[b)] Avalglucosidase alfa 40 mg/kg	Initial dose	4	250 ± 45.1	1720 ± 255	6.83 [6.65, 7.22]	0.806 ± 0.248	0.529 ± 0.150	4.30 ± 1.42
	Week 25	5	356 ± 84.7	2200 ± 533	6.87 [5.03, 7.43]	1.19 ± 0.472	0.526 ± 0.125	4.02 ± 1.39

Mean ± standard deviation
t_{max} is median [range].
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal phase elimination half-life; CL, total body clearance; V_{ss}, steady-state volume of distribution
a) Patients who demonstrated clinical decline after receiving treatment with a stable dose of ALGLU for at least 6 months
b) Patients who demonstrated a sub-optimal clinical response after receiving treatment with a stable dose of ALGLU for at least 6 months

14) Subjects who developed "neutralizing antibodies that inhibit enzyme activity" or "neutralizing antibodies that inhibit cellular uptake."

Pharmacodynamics in subjects receiving multiple intravenous doses of avalglucosidase alfa (20 mg/kg or 40 mg/kg every other week) or ALGLU (ranging from 20 mg/kg every other week to 40 mg/kg weekly) was evaluated. Table 21 shows percent change from baseline in urine HEX4 levels.

Table 21. Urine HEX4 levels at baseline, and percent change from baseline in subjects receiving multiple intravenous doses of avalglucosidase alfa or ALGLU

Treatment	Baseline	Week 25	Week 49	Week 73	Week 97
Cohort 1[a)] Avalglucosidase alfa 20 mg/kg	80.25 ± 48.38 (6)	0.34 ± 42.09 (6)	−22.98 ± 22.75 (6)	−20.01 ± 25.13 (6)	−31.41 ± 19.33 (3)
Cohort 2[a)] Avalglucosidase alfa 40 mg/kg	63.43 ± 30.71 (5)	−40.95 ± 16.72 (5)	−19.19 ± 78.01 (5)	−68.9, −80.3 (2)	—
Cohort 3[b)] Avalglucosidase alfa 40 mg/kg	54.81 ± 50.41 (5)	−37.48 ± 17.16 (5)	—	—	—
Cohort 3[b)] ALGLU	52.16 ± 33.93 (6)	15.65 ± 87.20 (5)	—	—	—

Unit of baseline value: mmol/mol
Change from baseline: %
Mean ± standard deviation (n)
Individual values are presented for N ≤2.
"—": not applicable
a) Patients who demonstrated clinical decline after receiving treatment with a stable dose of ALGLU for at least 6 months
b) Patients who demonstrated a sub-optimal clinical response after receiving treatment with a stable dose of ALGLU for at least 6 months

Anti-drug antibody (ADA) status was as follows: At baseline, 1 of 6 subjects (avalglucosidase alfa) and 4 of 6 subjects (ALGLU) were ADA-positive in Cohort 1; and 0 of 5 subjects (avalglucosidase alfa) and 1 of 5 subjects (ALGLU) were ADA-positive in Cohort 2. In Cohort 3, 1 of 5 subjects (avalglucosidase alfa) and 3 of 5 subjects (ALGLU) in the avalglucosidase alfa group were ADA-positive while 1 of 6 subjects (avalglucosidase alfa) and 3 of 6 subjects (ALGLU) in the ALGLU group were ADA-positive. By Week 25, 1 of 6 subjects (avalglucosidase alfa) and 6 of 6 subjects (ALGLU) became ADA-positive in Cohort 1; and 1 of 5 subjects (avalglucosidase alfa) and 1 of 5 subjects (ALGLU) became ADA-positive in Cohort 2. In Cohort 3, 4 of 5 subjects (avalglucosidase alfa) and 4 of 5 subjects (ALGLU) in the avalglucosidase alfa group became ADA-positive while 2 of 6 subjects (avalglucosidase alfa) and 4 of 6 subjects (ALGLU) in the ALGLU group became ADA-positive. No subjects developed neutralizing antibodies to avalglucosidase alfa. On the other hand, 3 subjects in the avalglucosidase alfa group and 2 subjects in the ALGLU group in Cohort 3 developed neutralizing antibodies to ALGLU.[14)]

6.2.3 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis was performed using plasma avalglucosidase alfa concentration data from 3 studies (Studies TDR12857, LTS13769,[12)] and EFC14028) in patients with LOPD (software, NONMEM ver.7.4.1). The data were from 75 subjects (39 males and 36 females), measured at 2057 time points (race, Caucasian [68], black [2], Asian [3], and other [2]; prior ALGLU treatment, experienced [14] and naïve [61]; anti-avalglucosidase alfa antibody status at baseline, positive [7], negative [67], and unknown [1]; anti-avalglucosidase alfa antibody status during study period,[15)] positive [69] and negative [6]).

The characteristics of the subjects included in the population pharmacokinetic analysis were as follows: age, 46.0 [19.5, 78.3] years (mean [95% confidence interval (CI)], the same shall apply hereinafter in this paragraph); body weight, 75.9 [43.4, 126] kg; blood albumin level, 44.2 [35.9, 50.0] g/L; alkaline phosphatase

15) Subjects who had tested positive for anti-avalglucosidase alfa antibodies at least once during the study period were counted as "positive."

(ALP), 69.0 [40.6, 115] IU/L; alanine aminotransferase (ALT), 71.6 [19.9, 245] IU/L; aspartate aminotransferase (AST), 72.1 [26.6, 226] IU/L; total bilirubin, 8.98 [3.36, 22.3] μmol/L; creatine kinase, 676 [123, 2400] IU/L; creatinine clearance, 164 [62.5, 287] mL/min; and glomerular filtration rate (GFR), 143 [66.3, 268] mL/min.

A 3-compartment model comprising the transfer between the central compartment and peripheral compartment C2 (Q2); transfer from peripheral compartment C2 to peripheral compartment C3 (Q3); and transfer from peripheral compartment C3 to the central compartment (Q4) was developed as the base model with zero-order absorption, nonlinear Michaelis-Menten elimination, and linear elimination. Values obtained in the evaluation of plasma avalglucosidase alfa concentration data from Study TDR12857 were used for modeling to determine volume of distribution in the peripheral compartments (V2 and V3), Q2, and Q3. For all parameters, sex, race, age, body weight, blood albumin level, ALP, ALT, AST, total bilirubin, creatin kinase, creatinine clearance, eGFR, and anti-avalglucosidase alfa antibody status were evaluated as covariates by stepwise covariate modeling; however, none of these were incorporated into the final model.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations

The applicant's explanation about the differences in pharmacokinetics between Japanese and non-Japanese populations:

Table 22 shows pharmacokinetic parameters in Japanese and non-Japanese patients receiving multiple intravenous doses of avalglucosidase alfa every other week in Studies EFC14028 and ACT14132, which both enrolled Japanese patients. No significant differences in pharmacokinetics were observed between Japanese and non-Japanese patients.

Table 22. Pharmacokinetic parameters in patients receiving multiple intravenous doses of avalglucosidase alfa every other week

Study	Dose	Measurement time point	Subject	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
EFC14028 (LOPD)	20 mg/kg	Initial dose	Japanese	1	262	1330	4.12	1.17
			Non-Japanese	48	259 ± 73.1	1290 ± 425	4.01 [2.53, 6.33]	1.34 ± 0.566[a)]
		Week 49	Japanese	1	251	1270	4.02	1.02
			Non-Japanese	47	242 ± 82.3	1250 ± 438	4.03 [2.20, 7.33]	1.56 ± 0.893
ACT14132 (IOPD)	20 mg/kg	Week 25	Japanese	1	182	783	3.97	0.569
			Non-Japanese	4	174 ± 76	810 ± 340	4.06 [3.77, 4.75]	0.609 ± 0.295
	40 mg/kg	Initial dose	Japanese	1	212	1580	7.25	0.818
			Non-Japanese	3	467 ± 140	2980 ± 820	6.97 [6.00, 7.02]	1.26 ± 0.582
		Week 25	Japanese	1	237	1630	7.43	0.974
			Non-Japanese	4	312 ± 57.5	2000 ± 352	6.96 [5.67, 7.98]	1.06 ± 0.283

Mean ± standard deviation
t_{max}, is median [range].
Individual values are presented for N = 1.
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal phase elimination half-life;
a) N = 46

Table 23 shows percent change from baseline in urine HEX4 levels, one of the pharmacodynamic indicators of avalglucosidase alfa. The trend for Japanese patients was similar to that for non-Japanese patients.

Table 23. Urine HEX4 levels at baseline, and percent change from baseline in patients receiving continuous intravenous infusion of multiple doses of avalglucosidase alfa

Study	Dose	Subject	N	Baseline	Week 13	Week 25	Week 49	Week 73
EFC14028 (LOPD)	20 mg/kg	Japanese	1	14.44	−53.88	−74.17	−68.42	−74.58
		Non-Japanese	50	12.68 ± 10.20	−35.65 ± 56.22[a)]	−53.15 ± 17.40	−53.61 ± 24.18	−56.77 ± 20.87[b)]
ACT14132 (IOPD)	20 mg/kg	Japanese	1	124.30	−17.38	−4.10	−47.18	—
		Non-Japanese	5	71.43 ± 48.41	−9.59 ± 26.23	1.22 ± 46.99	−18.14 ± 21.71	—
	40 mg/kg	Japanese	1	71.31	−39.71	−54.75	−63.44	—
		Non-Japanese	4	61.46 ± 35.10	−28.59 ± 24.74	−37.50 ± 17.13	−8.13 ± 85.43	—

Unit of baseline value: mmol/mol
Change from baseline: %
Mean ± standard deviation
Individual values are presented for N = 1.
"—": not applicable
a) N = 49
b) N = 36

PMDA's view:

Although only a limited number of Japanese patients were treated with avalglucosidase alfa, the submitted data did not show clearly different trends in pharmacokinetics and pharmacodynamics between Japanese patients and non-Japanese patients.

6.R.2 Impact of anti-drug antibodies on pharmacokinetics

The applicant's explanation:

Table 24 shows avalglucosidase alfa exposure in plasma (C_{max} and AUC_{last}) in ALGLU treatment-naïve patients with LOPD (Group 1 in Study TDR12857 and Study EFC14028) following administration of avalglucosidase alfa, by anti-avalglucosidase alfa antibody or neutralizing antibody status at each time point. There were no substantial differences in pharmacokinetic parameters between those who tested positive versus those who tested negative for anti-avalglucosidase alfa antibodies or anti-neutralizing antibodies.

Table 24. Pharmacokinetic parameters in ALGLU treatment-naïve patients with LOPD, anti-avalglucosidase alfa antibody-negative vs. positive (neutralizing antibody negative/positive)

Study	Dose	Measurement time point	C_{max} (μg/mL)			AUC_{last} (μg·h/mL)		
			Negative for anti-avalglucosidase alfa antibodies	Positive for anti-avalglucosidase alfa antibodies		Negative for anti-avalglucosidase alfa antibodies	Positive for anti-avalglucosidase alfa antibodies	
				Neutralizing antibody-negative	Neutralizing antibody-positive[a)]		Neutralizing antibody-negative	Neutralizing antibody-positive[a)]
TDR12857 (LOPD, treatment-naïve)	5 mg/kg[b)]	Initial dose	82.3 ± 6.69 (4)	—	—	259 ± 37.6 (4)	—	—
		Week 13	—	98.7 ± 38.9 (4)	—	—	285 ± 82.9 (4)	—
		Week 25	—	89.1 ± 11.0 (3)	—	—	264 ± 50.2 (3)	—
	10 mg/kg	Initial dose	190 ± 40.1 (3)	—	—	529 ± 79.6 (3)	—	—
		Week 13	158 (1)	118, 176 (2)	—	484 (1)	535, 567 (2)	—
		Week 25	139 (1)	156, 191 (2)	—	462 (1)	612, 622 (2)	—
	20 mg/kg	Initial dose	302 ± 107 (3)	—	—	1520 ± 806 (3)	—	—
		Week 13	—	357 ± 185 (3)	—	—	1660 ± 1030 (3)	—
		Week 25	—	350 ± 105 (3)	—	—	1560 ± 637 (3)	—
EFC14028 (LOPD, treatment-naïve)	20 mg/kg	Initial dose	258 ± 73.7 (47)	293 (1)	271 (1)	1290 ± 428 (47)	1070 (1)	1360 (1)
		Week 49	256 ± 82.7 (6)	241 ± 84.1 (40)	226, 236 (2)	1380 ± 510 (6)	1230 ± 435 (40)	1180, 1260 (2)

Mean ± standard deviation (n)
Individual values are presented for N ≤2.
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point
a) Subjects who developed "neutralizing antibodies that inhibit enzyme activity" or "neutralizing antibodies that inhibit cellular uptake."
b) One of the subjects tested positive for neutralizing antibodies at Week 27; however, this subject tested negative for neutralizing antibodies at Week 25, when pharmacokinetic parameters were measured.

Table 25 shows avalglucosidase alfa exposure in plasma (C_{max} and AUC_{last}) in ALGLU treatment-experienced patients with LOPD (Group 2 in Study TDR12857) and ALGLU treatment-experienced patients with IOPD (Study ACT14132) following administration of avalglucosidase alfa, by anti-avalglucosidase alfa antibody status at each time point. In Group 2 of Study TDR12857 and Study ACT14132, no subjects developed neutralizing antibodies. There were no substantial differences in pharmacokinetic parameters of avalglucosidase alfa between ADA-negative subjects versus ADA-positive subjects (and those who tested negative for neutralizing antibodies).

Table 25. Pharmacokinetic parameters in ALGLU treatment-experienced patients who tested negative or positive for anti-avalglucosidase alfa antibodies

Study	Dose	Measurement time point	C_{max} (μg/mL)		AUC_{last} (μg·h/mL)	
			Negative for anti-avalglucosidase alfa antibodies	Positive for anti-avalglucosidase alfa antibodies (Neutralizing antibody-negative)	Negative for anti-avalglucosidase alfa antibodies	Positive for anti-avalglucosidase alfa antibodies (Neutralizing antibody-negative)
TDR12857 (LOPD, treatment-experienced)	5 mg/kg	Initial dose	86.8 ± 15.1 (3)	49.3 (1)	274 ± 72.3 (3)	162 (1)
		Week 13	108, 157 (2)	53.0, 95.8 (2)	300, 414 (2)	228, 243 (2)
		Week 25	111, 135 (2)	48.7, 93.5 (2)	353, 393 (2)	227, 250 (2)
	10 mg/kg	Initial dose	169 (1)	168 ± 45.1 (3)	623 (1)	633 ± 144 (3)
		Week 13	185 (1)	166 ± 54 (3)	668 (1)	667 ± 228 (3)
		Week 25	184 (1)	157 ± 16.5 (3)	597 (1)	657 ± 44.4 (3)
	20 mg/kg	Initial dose	336 ± 133 (5)	242 (1)	1590 ± 508 (5)	1070 (1)
		Week 13	324 ± 104 (4)	270, 398 (2)	1460 ± 630 (4)	1050, 1680 (2)
		Week 25	309 ± 60.4 (3)	262, 309 (2)	1520 ± 539 (3)	1240, 1830 (2)
ACT14132 (IOPD, treatment-experienced)	Cohort 1[a)] 20 mg/kg	Initial dose	205 ± 52.0 (4)	128 (1)	1010 ± 343 (4)	587 (1)
		Week 25	175 ± 65.9 (5)	—	805 ± 295 (5)	—
	Cohort 2[a)] 40 mg/kg	Initial dose	403 ± 171 (4)	—	2630 ± 972 (4)	—
		Week 25	306 ± 65.3 (4)	261 (1)	1990 ± 362 (4)	1660 (1)
	Cohort 3[b)] 40 mg/kg	Initial dose	248 ± 55.0 (3)	256 (1)	1750 ± 302 (3)	1620 (1)
		Week 25	443 (1)	334 ± 80.0 (4)	2680 (1)	2080 ± 533 (4)

Mean ± standard deviation (n)
Individual values are presented for N ≤2.
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point
a) Patients who demonstrated clinical decline after receiving treatment with a stable dose of ALGLU regularly for at least 6 months
b) Patients who demonstrated a sub-optimal clinical response after receiving treatment with a stable dose of ALGLU regularly for at least 6 months

Based on the above, the development of anti-avalglucosidase alfa antibodies or neutralizing antibodies is not likely to impact the pharmacokinetic parameters of avalglucosidase alfa.

PMDA's view:

The results of the clinical studies conducted suggest that patients treated with avalglucosidase alfa may develop anti-avalglucosidase alfa antibodies and neutralizing antibodies. On the other hand, it was confirmed that the pharmacokinetic parameters in subjects who tested positive for anti-avalglucosidase alfa antibodies (those who tested negative and those who tested positive for neutralizing antibodies) did not differ markedly from the pharmacokinetic parameters in subjects who tested negative for anti-avalglucosidase alfa antibodies, although the limited number of subjects who tested positive for anti-avalglucosidase alfa antibodies and neutralizing antibodies preclude strict comparison. Given the fact that many patients with LOPD or IOPD treated with avalglucosidase alfa developed anti-avalglucosidase alfa antibodies, the impact of antibody development on the safety and efficacy of avalglucosidase alfa will be further discussed in Section "7.R.2.2 Impact of antibody development."

6.R.3 Effects of body weight on pharmacokinetics and pharmacodynamics of avalglucosidase alfa

The applicant's explanation:

Based on the population pharmacokinetic analysis, steady-state plasma avalglucosidase alfa exposure in patients with LOPD treated with avalglucosidase alfa 20 mg/kg was estimated by body weight (<50 kg, ≥50 kg and <100 kg, and ≥100 kg). Results are shown in Table 26. Avalglucosidase alfa exposure tended to be lower in patients with lower body weight than in patients with higher body weight.

Table 26. Pharmacokinetic parameters in subjects receiving multiple intravenous doses of avalglucosidase alfa every other week

Body weight	N	C_{max} (μg/mL)	$AUC_{0\text{-}2w}$ (μg·h/mL)
<50 kg	5	174 [135, 196]	790 [582, 820]
≥50 kg and <100 kg	55	261 [157, 370]	1160 [667, 2100]
≥100 kg	10	387 [318, 432]	1640 [1150, 2370]

Median [range]
C_{max}, maximum plasma concentration; $AUC_{0\text{-}2w}$, area under the plasma concentration-time curve from time 0 to Week 2

Table 27 shows percent change from baseline in urine HEX4 levels (one of the pharmacodynamic indicators) by quartiles of body weight (≤59.0 kg, >59.0 kg and ≤75.9 kg, >75.9 kg and ≤91.8 kg, and >91.8 kg) in the global phase III study (Study EFC14028) involving patients with LOPD. The differences among the body weight subgroups are not substantial.

Table 27. Urine HEX4 levels at baseline, and percent change from baseline in subjects receiving multiple intravenous doses of avalglucosidase alfa or ALGLU

Treatment	Body weight	Baseline	Week 25	Week 49	Week 73	Week 97	Week 145
Avalglucosidase alfa continuous treatment	≤59.0 kg	16.97 ± 12.05 (13)	−52.89 ± 13.77 (13)	−54.67 ± 19.03 (13)	−55.36 ± 25.56 (8)	−69.93 ± 10.31 (5)	−61.87 ± 21.12 (3)
	>59.0 kg and ≤75.9 kg	12.06 ± 12.01 (13)	−55.85 ± 14.70 (13)	−46.22 ± 33.31 (13)	−49.71 ± 22.73 (11)	−61.81 ± 14.08 (6)	−55.12 (1)
	>75.9 kg and ≤91.8 kg	12.11 ± 8.64 (13)	−54.37 ± 18.74 (13)	−55.70 ± 20.60 (13)	−65.63 ± 16.98 (9)	−57.04 ± 42.57 (3)	−53.81 ± 56.52 (3)
	>91.8 kg	9.47 ± 5.69 (12)	−50.92 ± 23.39 (12)	−59.45 ± 21.18 (12)	−59.76 ± 16.47 (9)	−67.62 ± 12.31 (7)	−56.16 ± 22.73 (4)
ALGLU/avalglucosidase alfa[a)]	≤59.0 kg	9.57 ± 5.86 (6)	−24.15 ± 22.07 (5)	−26.79 ± 14.24 (6)	−64.81 ± 7.34 (3)	−63.47 ± 11.82 (3)	−77.79 (1)
	>59.0 kg and ≤75.9 kg	9.92 ± 6.89 (16)	−24.42 ± 21.68 (14)	0.42 ± 31.41 (13)	−51.17 ± 12.25 (9)	−55.05 ± 8.31 (5)	−51.67 ± 28.02 (3)
	>75.9 kg and ≤91.8 kg	8.32 ± 3.64 (16)	−24.03 ± 16.59 (15)	−3.20 ± 35.29 (13)	−47.76 ± 22.08 (9)	−60.43 ± 14.89 (7)	−48.0, 151.7 (2)
	>91.8 kg	7.18 ± 2.83 (11)	−24.28 ± 15.51 (11)	−27.14 ± 31.00 (9)	−45.01 ± 30.01 (9)	−56.06 ± 12.53 (6)	−64.7, −41.3 (2)

Unit of baseline value: mmol/mol
Change from baseline: %
Mean ± standard deviation (n)
Individual values are presented for N ≤2.
a) At Week 49, patients were switched from ALGLU to avalglucosidase alfa 20 mg/kg every other week.

IOPD patients with lower body weight tended to have lower exposure in the global phase II study (Study ACT14132) involving patients with IOPD. This trend is similar to that in patients with LOPD. Table 28 shows steady-state plasma avalglucosidase alfa exposure in patients with LOPD and IOPD. Individual values in patients with IOPD treated with avalglucosidase alfa 20 mg/kg were generally within the distribution range of exposure seen in patients with LOPD, but the former patient population tended to have lower exposure than the latter patient population. The difference in body weight between the LOPD and IOPD patient populations may be partly attributable to the trend toward lower exposure in patients with IOPD than in patients with LOPD.

Table 28. Pharmacokinetic parameters in subjects receiving multiple intravenous doses of avalglucosidase alfa every other week

Study	Dose	Measurement time point	N	Body weight (kg)	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)
EFC14028 (LOPD)	20 mg/kg	Week 49	48	77.7 [42, 132]	240.5 [95, 467]	1226.4 [314, 2444]
ACT14132 (IOPD)	20 mg/kg[b)]	Week 25	5	18.2 [14, 50]	182 [72.3, 241]	783 [383, 1110]
	40 mg/kg[b)]	Week 25	5	25.8 [13, 69]	275 [237, 388]	1740 [1630, 2340]
	40 mg/kg[c)]	Week 25	5	31.5 [15, 46]	352 [252, 443]	2470 [1480, 2680]

Median [range]
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve to the last measurable time point
a) Patients who demonstrated clinical decline after receiving treatment with a stable dose of ALGLU regularly for at least 6 months
b) Patients who demonstrated a sub-optimal clinical response after receiving treatment with a stable dose of ALGLU regularly for at least 6 months

PMDA's view:

While avalglucosidase alfa exposure tended to be lower in patients with lower body weight following administration avalglucosidase alfa, the percent change from baseline in urine HEX4 levels (one of the

pharmacodynamic indicators) in patients with LOPD did not differ substantially regardless of body weight, though the reason for this finding have yet to be clearly identified due to the small number of patients studied. Exposure varies more among patients with IOPD than among patients with LOPD, and the variability is likely to be attributable to differences in body weight. Given this, the dosage regimen of avalglucosidase alfa will be further discussed in Section "7.R.4 Dosage and administration."

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

The applicant submitted efficacy and safety evaluation data in the form of results data from 2 global studies as summarized in Table 29. The applicant also submitted the results of 2 foreign clinical studies as reference data.

Table 29. List of efficacy and safety evaluation data

Data	Geographical region	Study ID	Phase	Patient Population	Number of subjects treated	Summary of dosage regimen	Major endpoint
Evaluation	Global	EFC14028	III	Patients with LOPD	N = 100	Primary analysis period: Avalglucosidase alfa or ALGLU 20 mg/kg every other week as an intravenous infusion Extension treatment period: Avalglucosidase alfa 20 mg/kg every other week intravenously	Efficacy Safety Pharmacokinetics Pharmacodynamics
		ACT14132	II	Patients with IOPD	Stage 1: N = 11 Stage 2: N = 11	Stage 1: Avalglucosidase alfa 20 mg/kg (Cohort 1) or 40 mg/kg (Cohort 2) every other week for 25 weeks as an intravenous infusion Stage 2: Avalglucosidase alfa 40 mg/kg every other week, or a stable dose of ALGLU as an intravenous infusion for 25 weeks (Cohort 3) Extension treatment period: Avalglucosidase alfa 20 mg/kg (Cohort 1) or 40 mg/kg (Cohorts 2 and 3) every other week as an intravenous infusion	Safety Efficacy Pharmacokinetics Pharmacodynamics

The following sections provide the results of major studies.

7.1 Global phase III study (CTD 5.3.5.1-2, Study EFC14028 [ongoing since November 2016, data cut-off on March 19, 2020])

A double-blind, parallel-group, active-controlled study was conducted to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of intravenous avalglucosidase alfa versus ALGLU in ALGLU treatment-naïve patients with LOPD[16] including Japanese patients (target sample size, 96 subjects[17]; 48 in the avalglucosidase alfa group and 48 in the ALGLU group) [see Section "6.2.2.2 Global phase III study" for details of pharmacokinetics and pharmacodynamics].

Main inclusion criteria: patients had a histologically confirmed diagnosis of LOPD (GAA enzyme deficiency or 2 GAA gene mutations); and aged ≥3 years who had never received ALGLU or other therapies for Pompe disease.

16) Japan, the UK, the US, Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, South Korea, Taiwan, Mexico, the Netherlands, Poland, Portugal, Russia, Spain, Switzerland, China, and Turkey

17) The sample size required to verify the non-inferiority of avalglucosidase alfa to ALGLU was determined to be 96 patients when the following were assumed: between-group difference in change in FVC (% predicted) of 2.0%, common standard deviation of 5.1%, 2-sided significance level of 5%, power of 80%, and percentage of patients with missing data of 10%.

The exclusion criteria: patient had cardiomyopathy associated with Pompe disease; is wheelchair-dependent; is not able to ambulate 40 meters without stopping and without an assistive device; requires invasive ventilation; or is not able to achieve FVC percent of predicted values (FVC [% predicted]) within the range of ≥30% and ≤85% (calculated on the basis of sex, race, age, and height) for repeated FVC measurements in the upright position.

This study consisted of the 2-week screening period, 49-week double-blind primary analysis period, and extension treatment period of a maximum of 144 weeks.

In the primary analysis period, subjects received avalglucosidase alfa 20 mg/kg or ALGLU 20 mg/kg every other week as an intravenous infusion. In the extension treatment period, subjects in both groups received avalglucosidase alfa 20 mg/kg. The starting infusion rate was 1 mg/kg/h, and if there were no signs of IAR, the infusion rate was to be increased gradually. The infusion rate could be increased up to 7 mg/kg/h.

All 100 randomized subjects (51 subjects [including 1 Japanese subject] to avalglucosidase alfa and 49 subjects to ALGLU) received the study drug, and were included in the safety analysis set and the modified intent-to-treat (mITT) set. The mITT set was defined as the primary efficacy analysis set. Of the 100 subjects, 95 (including 1 Japanese subject) entered the extension treatment period. In the primary analysis period, 5 subjects were withdrawn from the study (5 subjects in the ALGLU group ["adverse events" for 4 subjects; "other reasons" for 1 subject]). In the extension treatment period, 4 subjects were withdrawn from the study (3 subjects in the avalglucosidase alfa continuous treatment group ["adverse events" for 2 subjects; "other reasons" for 1 subject], and 1 subject in the ALGLU/avalglucosidase alfa group ["adverse events" for 1 subject]).

Table 30 shows the change in FVC (% predicted) from baseline to Week 49, the primary endpoint. The lower bound of the 2-sided 95% CI for the difference between avalglucosidase alfa and ALGLU was greater than −1.1%,[18)] demonstrating the non-inferiority of avalglucosidase alfa to ALGLU. A similar analysis was performed in the per protocol population (46 subjects in the avalglucosidase alfa group and 39 subjects in the ALGLU group). The difference between avalglucosidase alfa and ALGLU in change in FVC (% predicted) from baseline to Week 49 [95% CI] was 2.69% [−0.06, 5.44], demonstrating the robustness of the results of the primary analysis in the mITT population.

Table 30. FVC (% predicted) from baseline to Week 49 (Study EFC14028 [primary analysis period], mITT)

Treatment	Baseline	Week 49	Change from baseline[a)]	Difference of avalglucosidase alfa − ALGLU [95% CI][a)]	*P*-value[a), b)]
Avalglucosidase alfa	62.55 ± 14.39 (51)	65.49 ± 17.42 (49)	2.89 ± 0.88	2.43 [−0.13, 4.99]	0.0074
ALGLU	61.56 ± 12.40 (49)	61.16 ± 13.49 (43)	0.46 ± 0.93		

Unit, %; mean ± standard deviation
Change from baseline: least squares mean ± standard error
Between group difference: least squares mean [95% CI]
a) A mixed model for repeated measures (MMRM) with age, sex, treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline FVC (% predicted) as a covariate
b) Two-sided significance level of 5%

18) Based on the study results for the comparator ALGLU, a value that is approximately 50% of the lower bound of 80% CI for the treatment effect of ALGLU versus placebo was selected.

Table 31 shows the results for key secondary endpoints from baseline to Week 49.

Table 31. Results for key secondary endpoints from baseline to Week 49 (Study EFC14028 [primary analysis period], mITT)

Endpoint	Measurement time point	Avalglucosidase alfa (N = 51)	ALGLU (N = 49)
6MWT (m)	Baseline	399.30 ± 110.93 (51)	378.09 ± 116.22 (49)
	Change at Week 49[a)]	32.21 ± 9.93	2.19 ± 10.40
MIP (% predicted)	Baseline	59.88 ± 47.10 (50)	60.65 ± 41.05 (49)
	Change at Week 49[a)]	−0.29 ± 3.84	−2.87 ± 4.04
MEP (% predicted)	Baseline	65.77 ± 38.97 (50)	74.83 ± 35.22 (49)
	Change at Week 49[a)]	2.39 ± 4.00	5.00 ± 4.20
Lower extremity HHD composite score[19)]	Baseline	1330.45 ± 625.44 (50)	1466.16 ± 604.91 (46)
	Change at Week 49[a)]	260.69 ± 46.07	153.72 ± 48.54
QMFT total score[20)]	Baseline	41.29 ± 10.15 (51)	42.30 ± 10.58 (46)
	Change at Week 49[a)]	3.98 ± 0.63	1.89 ± 0.69

Baseline values: mean ± standard deviation (n)
Change from baseline: least squares mean ± standard error
a) An MMRM model with age, sex, treatment, visit, and treatment-by-visit interaction as fixed effects, and adjusted baseline value for each endpoint and FVC (% predicted) at baseline (excluding MIP [% predicted] and MEP [% predicted]) as covariates

Table 32 shows results for the key efficacy endpoints in the primary analysis period and extension treatment period (up to Week 145).

19) Two measurements are taken per side for flexion, extension, abduction, and adduction of the hip joint, flexion and extension of the knee joint, dorsiflexion and plantarflexion of the ankle joint, and values indicating greater gain in muscle strength from the 2 measurements are summed to obtain the total score.

20) The quick motor function test (QMFT) comprises 16 items to assess movements specifically difficult for patients with Pompe disease. The items are scored individually on a 5-point scale by an assessor

Table 32. Results for key efficacy endpoints (change from baseline, Study EFC14028 [primary analysis period and extension treatment period], mITT)

Endpoint	FVC (% predicted)		6MWT (m)	
Treatment	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)
Baseline	62.55 ± 14.39 (51)	61.56 ± 12.40 (49)	399.30 ± 110.93 (51)	378.09 ± 116.22 (49)
Change from baseline at Week 25	3.27 ± 6.30 (51)	0.22 ± 5.23 (45)	29.19 ± 51.56 (49)	9.22 ± 100.66 (45)
Change from baseline at Week 49	3.02 ± 6.83 (49)	−0.03 ± 5.83 (43)	37.86 ± 52.81 (48)	−1.73 ± 85.16 (43)
Change from baseline at Week 61	1.97 ± 6.58 (41)	1.05 ± 6.14 (35)	27.22 ± 69.99 (42)	−2.38 ± 88.56 (36)
Change from baseline at Week 73	1.66 ± 7.18 (36)	0.62 ± 7.78 (29)	35.59 ± 62.03 (38)	−1.56 ± 95.26 (29)
Change from baseline at Week 97	1.60 ± 7.72 (24)	1.64 ± 8.97 (21)	37.34 ± 68.41 (24)	25.71 ± 71.31 (22)
Change from baseline at Week 121	−0.45 ± 8.54 (17)	0.00 ± 7.54 (15)	34.51 ± 85.54 (17)	14.14 ± 63.54 (13)
Change from baseline at Week 145	−1.27 ± 8.08 (11)	−4.90 ± 8.14 (9)	2.67 ± 42.84 (10)	40.46 ± 56.43 (9)
Endpoint	MIP (% predicted)[a)]		MEP (% predicted)[a)]	
Treatment	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)
Baseline	51.74 ± 24.85 (48)	53.71 ± 23.47 (47)	59.17 ± 21.60 (48)	70.21 ± 27.32 (47)
Change from baseline at Week 25	7.46 ± 13.81 (48)	1.65 ± 18.40 (43)	9.09 ± 15.61 (48)	4.44 ± 14.30 (43)
Change from baseline at Week 49	9.21 ± 18.11 (46)	3.70 ± 10.86 (41)	11.30 ± 17.84 (46)	8.11 ± 21.65 (41)
Change from baseline at Week 61	12.14 ± 16.49 (39)	5.32 ± 11.30 (31)	15.72 ± 17.30 (39)	7.07 ± 11.68 (31)
Change from baseline at Week 73	11.77 ± 21.28 (34)	4.31 ± 11.84 (27)	17.43 ± 23.29 (34)	10.32 ± 14.58 (27)
Change from baseline at Week 97	15.12 ± 24.72 (22)	5.08 ± 15.32 (19)	20.21 ± 25.86 (22)	8.85 ± 15.17 (19)
Change from baseline at Week 121	14.23 ± 26.59 (15)	5.52 ± 11.27 (13)	17.98 ± 25.80 (15)	13.49 ± 17.98 (13)
Change from baseline at Week 145	6.51 ± 18.31 (9)	9.17 ± 7.56 (7)	9.64 ± 21.23 (9)	12.18 ± 14.14 (7)
Endpoint	Lower extremity HHD composite score		QMFT total score	
Treatment	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)	Avalglucosidase alfa continuous treatment (N = 51)	ALGLU/ avalglucosidase alfa (N = 49)
Baseline	1330.45 ± 625.44 (50)	1466.16 ± 604.91 (46)	41.29 ± 10.15 (51)	42.30 ± 10.58 (46)
Change from baseline at Week 25	219.67 ± 336.35 (47)	98.80 ± 229.60 (41)	3.44 ± 4.31 (50)	1.86 ± 4.00 (42)
Change from baseline at Week 49	275.41 ± 361.93 (46)	145.77 ± 279.34 (40)	4.41 ± 4.88 (49)	1.77 ± 3.98 (39)
Change from baseline at Week 61	272.04 ± 384.79 (39)	180.22 ± 290.23 (34)	4.33 ± 6.17 (43)	1.39 ± 6.02 (33)
Change from baseline at Week 73	159.63 ± 500.50 (35)	207.06 ± 295.98 (28)	4.37 ± 5.14 (38)	2.89 ± 5.31 (27)
Change from baseline at Week 97	177.20 ± 520.02 (25)	218.78 ± 371.96 (21)	4.80 ± 5.91 (25)	2.95 ± 5.92 (20)
Change from baseline at Week 121	126.31 ± 557.10 (17)	256.97 ± 307.35 (13)	5.29 ± 6.45 (17)	1.67 ± 5.47 (12)
Change from baseline at Week 145	345.71 ± 469.01 (11)	270.73 ± 440.93 (9)	5.36 ± 5.30 (11)	2.22 ± 4.94 (9)

Mean ± standard deviation (n)

a) Baseline MIP and MEP exceeded 200 cmH_2O in 2 subjects each in the avalglucosidase alfa group and ALGLU group. These data were excluded due to wrong use of instruments or data entry errors.

Table 33 shows the baseline patient characteristics of 1 Japanese subject (avalglucosidase alfa group) and Table 34 shows changes from baseline over time for key efficacy endpoints (up to Week 121).

Table 33. Baseline patient characteristics (Study EFC14028; Japanese subject)

	Subject 1
Sex	Male
Age (years)	6[redacted]
Body weight (kg)	8[redacted]
BMI (kg/m^2)	30.4
Duration of disease (months)	3.6

Table 34. Changes from baseline over time for key efficacy endpoints (Study EFC14028 [primary analysis period and extension treatment period], Japanese subject)

Measurement time point	FVC (% predicted)	6MWT (m)	MIP (% predicted)	MEP (% predicted)	Lower extremity HHD composite score	QMFT total score
Baseline	48.04	365	28.40	54.23	1140	35
Change from baseline at Week 25	−4.786	16.0	2.168	14.797	−27.0	5.0
Change from baseline at Week 49	0.432	55.0	0.117	15.012	−91.0	4.0
Change from baseline at Week 61	−1.387	53.0	13.892	11.049	−174.0	10.0
Change from baseline at Week 73	7.666	96.0	1.232	−1.116	−169.0	3.0
Change from baseline at Week 97	7.263	56.0	4.472	12.166	−195.0	9.0
Change from baseline at Week 121	−0.439	55.0	4.540	11.557	−51.0	2.0

Table 35 shows the incidence of adverse events occurring in ≥3 subjects in either group during the primary analysis period and the incidence of these events classified as adverse drug reactions. Adverse events (nasopharyngitis/pain in extremity) occurred in 1 Japanese subject in the avalglucosidase alfa group. Both were non-serious and their causal relationship to the study drug was ruled out.

Table 35. Adverse events occurring in ≥3 subjects (Study EFC14028 [primary analysis period], safety analysis set)

Events	Avalglucosidase alfa (N = 51)		ALGLU (N = 49)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Subjects with any event	86.3 (44)	45.1 (23)	91.8 (45)	49.0 (24)
Nasopharyngitis	23.5 (12)	2.0 (1)	24.5 (12)	0 (0)
Back pain	23.5 (12)	0 (0)	10.2 (5)	0 (0)
Headache	21.6 (11)	5.9 (3)	32.7 (16)	12.2 (6)
Fatigue	17.6 (9)	5.9 (3)	14.3 (7)	6.1 (3)
Influenza	17.6 (9)	0 (0)	4.1 (2)	0 (0)
Pain in extremity	15.7 (8)	0 (0)	14.3 (7)	0 (0)
Fall	13.7 (7)	0 (0)	20.4 (10)	2.0 (1)
Nausea	11.8 (6)	5.9 (3)	14.3 (7)	10.2 (5)
Diarrhoea	11.8 (6)	3.9 (2)	16.3 (8)	0 (0)
Dizziness	9.8 (5)	2.0 (1)	8.2 (4)	4.1 (2)
Myalgia	9.8 (5)	2.0 (1)	14.3 (7)	0 (0)
Contusion	9.8 (5)	2.0 (1)	8.2 (4)	0 (0)
Arthralgia	9.8 (5)	0 (0)	16.3 (8)	2.0 (1)
Pruritus	7.8 (4)	7.8 (4)	8.2 (4)	8.2 (4)
Vomiting	7.8 (4)	3.9 (2)	6.1 (3)	0 (0)
Upper respiratory tract infection	7.8 (4)	0 (0)	4.1 (2)	0 (0)
Urticaria	5.9 (3)	5.9 (3)	2.0 (1)	2.0 (1)
Dyspnoea	5.9 (3)	2.0 (1)	8.2 (4)	4.1 (2)
Dyspepsia	5.9 (3)	2.0 (1)	6.1 (3)	0 (0)
Erythema	5.9 (3)	2.0 (1)	6.1 (3)	4.1 (2)
Muscle spasms	5.9 (3)	2.0 (1)	10.2 (5)	2.0 (1)
Influenza like illness	5.9 (3)	2.0 (1)	2.0 (1)	0 (0)
Oedema peripheral	5.9 (3)	2.0 (1)	6.1 (3)	2.0 (1)
Cystitis	5.9 (3)	0 (0)	0 (0)	0 (0)
Paraesthesia	5.9 (3)	0 (0)	4.1 (2)	2.0 (1)
Non-cardiac chest pain	5.9 (3)	0 (0)	0 (0)	0 (0)
Rash	3.9 (2)	3.9 (2)	8.2 (4)	6.1 (3)
Cough	3.9 (2)	2.0 (1)	8.2 (4)	0 (0)
Alanine aminotransferase increased	3.9 (2)	2.0 (1)	6.1 (3)	2.0 (1)
Oropharyngeal pain	3.9 (2)	0 (0)	10.2 (5)	0 (0)
Abdominal pain upper	3.9 (2)	0 (0)	6.1 (3)	0 (0)
Pain	3.9 (2)	0 (0)	10.2 (5)	2.0 (1)
Pyrexia	3.9 (2)	0 (0)	8.2 (4)	2.0 (1)
Chills	2.0 (1)	2.0 (1)	6.1 (3)	4.1 (2)
Nasal congestion	2.0 (1)	0 (0)	10.2 (5)	0 (0)
Hypertension	2.0 (1)	0 (0)	6.1 (3)	4.1 (2)
Flushing	0 (0)	0 (0)	6.1 (3)	6.1 (3)
Muscular weakness	0 (0)	0 (0)	6.1 (3)	2.0 (1)
Infusion site extravasation	0 (0)	0 (0)	6.1 (3)	0 (0)

Incidence: % (n); Medical dictionary for regulatory activities (MedDRA)/J ver.22.1

One subject in the ALGLU group died of acute myocardial infarction, and its causal relationship to the study drug was ruled out. Serious adverse events occurred in 8 subjects in the avalglucosidase alfa group (hypoventilation, respiratory failure, syncope, breast cyst, calculus urinary/hydronephrosis, renal colic, dyspnoea, and pneumonia), and 12 subjects in the ALGLU group (dyspnoea in 2 subjects; pneumonia, brain stem stroke/cerebellar ischaemia, acute myocardial infarction, diaphragmatic paralysis/abdominal pain upper, dizziness/visual impairment/hypotension/cold sweat/chills, pulmonary embolism/gastrointestinal haemorrhage/haemoglobin decreased, sepsis/nephrolithiasis, angina pectoris, inappropriate antidiuretic hormone secretion, and supraventricular tachycardia in 1 subject each). Among these, the following adverse events were classified as adverse drug reactions: dyspnoea (1 subject) in the avalglucosidase alfa group; dyspnoea (2 subjects) and dizziness/visual impairment/hypotension/cold sweat/chills (1 subject) in the ALGLU group. Adverse events leading to treatment discontinuation occurred in 4 subjects in the ALGLU group (dyspnoea, acute myocardial infarction, urticaria, and arthritis). Among these, events in 2 subjects (dyspnoea and urticaria) were classified as adverse drug reactions.

Table 36 shows the incidence of adverse events occurring in ≥3 subjects in either group during the primary analysis period and extension treatment period, as well as the incidence of these events classified as adverse drug reactions. Adverse events (nasopharyngitis/pain in extremity/dyslipidaemia/hyperuricaemia/dental caries/skin papilloma) occurred in 1 Japanese subject in the avalglucosidase alfa continuous treatment group. All these events were non-serious, and their causal relationship to the study drug was ruled out.

Table 36. Adverse events occurring in ≥3 subjects (Study EFC14028 [primary analysis period and extension treatment period], safety analysis set)

Events	Avalglucosidase alfa continuous treatment (N = 51)		ALGLU/avalglucosidase alfa[a)] (N = 44)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Subjects with any event	94.1 (48)	49.0 (25)	79.5 (35)	43.2 (19)
Nasopharyngitis	31.4 (16)	2.0 (1)	22.7 (10)	2.3 (1)
Back pain	29.4 (15)	0 (0)	13.6 (6)	0 (0)
Headache	25.5 (13)	7.8 (4)	25.0 (11)	6.8 (3)
Influenza	25.5 (13)	0 (0)	6.8 (3)	0 (0)
Nausea	23.5 (12)	9.8 (5)	11.4 (5)	2.3 (1)
Diarrhoea	19.6 (10)	3.9 (2)	22.7 (10)	0 (0)
Pain in extremity	19.6 (10)	2.0 (1)	11.4 (5)	2.3 (1)
Arthralgia	19.6 (10)	0 (0)	11.4 (5)	0 (0)
Fatigue	17.6 (9)	5.9 (3)	11.4 (5)	6.8 (3)
Dizziness	17.6 (9)	2.0 (1)	4.5 (2)	2.3 (1)
Fall	15.7 (8)	0 (0)	11.4 (5)	0 (0)
Myalgia	13.7 (7)	2.0 (1)	6.8 (3)	2.3 (1)
Contusion	13.7 (7)	2.0 (1)	2.3 (1)	0 (0)
Vomiting	11.8 (6)	3.9 (2)	13.6 (6)	2.3 (1)
Muscle spasms	11.8 (6)	3.9 (2)	6.8 (3)	0 (0)
Influenza like illness	11.8 (6)	3.9 (2)	0 (0)	0 (0)
Upper respiratory tract infection	11.8 (6)	0 (0)	13.6 (6)	0 (0)
Pruritus	9.8 (5)	9.8 (5)	15.9 (7)	13.6 (6)
Rash	9.8 (5)	3.9 (2)	11.4 (5)	4.5 (2)
Pyrexia	9.8 (5)	0 (0)	4.5 (2)	0 (0)
Urticaria	7.8 (4)	7.8 (4)	9.1 (4)	9.1 (4)
Chills	7.8 (4)	7.8 (4)	4.5 (2)	4.5 (2)
Erythema	7.8 (4)	3.9 (2)	0 (0)	0 (0)
Abdominal pain upper	7.8 (4)	2.0 (1)	2.3 (1)	0 (0)
Oedema peripheral	7.8 (4)	2.0 (1)	0 (0)	0 (0)
Musculoskeletal pain	7.8 (4)	0 (0)	11.4 (5)	0 (0)
Urinary tract infection	7.8 (4)	0 (0)	4.5 (2)	0 (0)
Vitamin D deficiency	7.8 (4)	0 (0)	2.3 (1)	0 (0)
Abdominal pain	7.8 (4)	0 (0)	2.3 (1)	0 (0)
Cough	5.9 (3)	2.0 (1)	6.8 (3)	2.3 (1)
Dyspnoea	5.9 (3)	2.0 (1)	4.5 (2)	0 (0)
Alanine aminotransferase increased	5.9 (3)	2.0 (1)	4.5 (2)	0 (0)
Dyspepsia	5.9 (3)	2.0 (1)	0 (0)	0 (0)
Oropharyngeal pain	5.9 (3)	0 (0)	4.5 (2)	0 (0)
Peripheral swelling	5.9 (3)	0 (0)	4.5 (2)	2.3 (1)
Paraesthesia	5.9 (3)	0 (0)	1 (2.3)	0 (0)
Syncope	5.9 (3)	0 (0)	0 (0)	0 (0)
Hypotension	5.9 (3)	0 (0)	0 (0)	0 (0)
Viral upper respiratory tract infection	5.9 (3)	0 (0)	0 (0)	0 (0)
Cystitis	5.9 (3)	0 (0)	0 (0)	0 (0)
Renal colic	5.9 (3)	0 (0)	0 (0)	0 (0)
Non-cardiac chest pain	5.9 (3)	0 (0)	0 (0)	0 (0)
Pain	3.9 (2)	0 (0)	13.6 (6)	4.5 (2)
Conjunctival haemorrhage	0 (0)	0 (0)	6.8 (3)	0 (0)
Bronchitis	0 (0)	0 (0)	6.8 (3)	0 (0)
Infusion site extravasation	0 (0)	0 (0)	6.8 (3)	2.3 (1)

Incidence: % (n); MedDRA/J ver.22.1

a) The list includes only events that occurred during treatment with avalglucosidase alfa in the extension treatment period

In the extension treatment period, 1 subject in the ALGLU/avalglucosidase alfa group died of adenocarcinoma pancreas. Its causal relationship to the study drug was ruled out. Serious adverse events occurred in 8 subjects in the avalglucosidase alfa continuous treatment group (cholecystitis/cholelithiasis, respiratory failure, VIIIth nerve injury, moyamoya disease/subarachnoid haemorrhage, nausea, renal oncocytoma/headache/skin discolouration/pelvi-ureteric obstruction/chills/blood pressure increased/body temperature increased/heart rate increased/oxygen saturation decreased, hyponatraemia/acute myocardial infarction, and bacteraemia/pneumonia/respiratory acidosis) and 5 subjects in the ALGLU/avalglucosidase alfa group (vertigo, angina pectoris, bipolar disorder, hip fracture, and adenocarcinoma pancreas). Events in 2 subjects in the avalglucosidase alfa continuous treatment group (nausea and headache/skin discolouration/chills/blood pressure increased/body temperature increased/heart rate increased/oxygen saturation decreased) were

classified as adverse drug reactions. Adverse events leading to treatment discontinuation occurred in 2 subjects in the avalglucosidase alfa continuous treatment group (ocular hyperaemia/erythema and acute myocardial infarction), of which ocular hyperaemia/erythema in 1 subject were classified as adverse drug reactions.

7.2 Global phase II study (CTD 5.3.5.1-1, Study ACT14132 [ongoing since October 2017, data cut-off in September 2019])

An open-label study was conducted to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of intravenous avalglucosidase alfa in patients with IOPD[21)] including Japanese patients who had demonstrated clinical decline or a sub-optimal clinical response while on treatment with ALGLU (target sample size, 20 subjects [10 subjects each in Stages 1 and 2]) [see Section "6.2.2.3 Global phase II study" for the details of pharmacokinetics and pharmacodynamics].

Main inclusion criteria: patients aged <18 years, who had a definitive diagnosis of IOPD with confirmed GAA enzyme deficiency by blood, skin, or muscle tissue testing; had cardiomyopathy at the time of Pompe disease diagnosis; had received a stable dose of ALGLU for at least 6 months. Furthermore, in Stages 1 and 2. Eligible patients had to show clinical decline (Stage 1) or a sub-optimal clinical response (Stage 2) in at least 1 of the prespecified parameters in at least the last 2 consecutive assessments by the investigator, performed ≥2 weeks apart prior to study entry. The parameters, (a) through (c), are shown in Table 37. Patients with persistently high anti-ALGLU antibody titers[22)] were excluded.

Table 37. Main inclusion criteria (Study ACT14132; Stages 1 and 2)

Stage 1: Patients who demonstrated clinical decline	Stage 2: Patients who demonstrated a sub-optimal clinical response
(a) Respiratory function New development or worsening of respiratory failure requiring the use or increased use of ventilatory assistance (invasive or non-invasive). (ventilatory assistance of ≥4 weeks is required)	(a) Respiratory function Sustained decline in relative change in FVC (% predicted) ≥15%, or new onset of non-invasive ventilatory assistance (ventilatory assistance of ≥4 weeks is required).
(b) Motor skills • For patients ≤2 years of age: Failure to acquire at least 2 new age-appropriate gross motor milestones ≥6 months prior to study enrolment. • For patients >2 years of age: Muscle weakness is demonstrated by a loss of one of the following: independent running, independent ascending and descending stairs, independent walking, walking with an assistive device, transitions from the floor to standing, crawling, independent sitting, transitioning in and out of sitting, holding head up while sitting, functional use of upper extremities.	(b) Motor skills Developmental plateau or decrease on the Gross Motor Function Measure-88 (GMFM-88)[23)] and/or in scaled score of Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI),[24)] Functional Skills Scale: Mobility Domain, or in other motor scale and/or clinical developmental evaluation.
(c) Cardiac parameters Left ventricular mass (LVM) Z score ≥6 or LVM index ≥150 g/m^2	(c) New onset of eyelid ptosis Confirmed occurrence of ptosis (drooping eyelids).

In this study, each of Stages 1 and 2 consisted of the 14-day screening period, 25-week primary analysis period, and the extension treatment period of a maximum of 226 weeks.

21) Japan, France, Taiwan, the UK, and the US

22) Patients who had high antibody titer (anti-ALGLU antibody titer of ≥25600-fold) at 2 consecutive time points not less than 1 month apart.

23) The GMFM-88 consists of 88 items divided into 5 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping), which are regarded as part of healthy physical development. The classification system was developed to detect quantitative changes in gross motor function based on the quality of movements for 88 items.

24) The Pompe-PEDI is comprised of a Functional Skills Scale and a Caregiver Assistance Scale, and both scales have 3 domains: Self Care, Mobility, and Social Function. The purpose of the system is to assess functional capabilities and performance in pediatric patients from young age to adolescence.

During the primary analysis period in Stage 1, subjects received avalglucosidase alfa 20 mg/kg (Cohort 1) or 40 mg/kg (Cohort 2) every other week as an intravenous infusion. Because the maximum tolerated dose for avalglucosidase alfa was determined to be 40 mg/kg in Stage 1, subjects enrolled in Stage 2 (Cohort 3), during the primary analysis period, were to receive intravenous avalglucosidase alfa 40 mg/kg every other week or ALGLU at the stable dosage regimen[25)] that had been administered prior to study enrollment. Patients who had been treated in either Stage 1 or 2 were allowed to enter the extension treatment period. During the extension treatment period, subjects in Cohort 1 continued to receive avalglucosidase alfa 20 mg/kg, and those who had demonstrated clinical decline, as shown in Table 37, in 2 consecutive assessments could receive 40 mg/kg. Subjects in Cohorts 2 and 3 were to receive avalglucosidase alfa 40 mg/kg. The starting infusion rate was 1 mg/kg/h, and if there were no signs of IAR, the infusion rate was to be increased gradually. The infusion rate could be increased up to 7 mg/kg/h in the avalglucosidase alfa 20 mg/kg group and ALGLU group, and up to 10 mg/kg/h in the avalglucosidase alfa 40 mg/kg group.

A total of 22 subjects received treatment (6 subjects including 1 Japanese subject [avalglucosidase alfa 20 mg/kg] and 5 subjects including 1 Japanese subject [avalglucosidase alfa 40 mg/kg] in Stage 1; and 5 subjects [avalglucosidase alfa 40 mg/kg] and 6 subjects [ALGLU] in Stage 2), and all of them were included in the safety analysis set and mITT, and the mITT was defined as the primary efficacy analysis set. All subjects completed the primary analysis period (Stage 1 or 2), and entered the extension treatment period. No subjects were withdrawn from the study as of the time of data cut-off.

Table 38 shows the results of key efficacy endpoints in the primary analysis period.

25) The actual dosage regimen administered to the subjects in this study was as follows: 20 mg/kg every other week; 20 mg/kg once weekly; 40 mg/kg every other week; 30 mg/kg once weekly; or 40 mg/kg once weekly.

Table 38. Results of key efficacy endpoints from baseline to the measurement time point (Study ACT14132 [primary analysis period], mITT)

Endpoint	Measurement time point	Stage 1 (Patients demonstrating clinical decline)		Stage 2 (Patients demonstrating a sub-optimal clinical response)	
		Avalglucosidase alfa 20 mg/kg (N = 6)	Avalglucosidase alfa 40 mg/kg (N = 5)	Avalglucosidase alfa 40 mg/kg (N = 5)	ALGLU (N = 6)
GMFM-88 total percent score	Baseline	56.25 [0.8, 86.2] (6)	86.63 [19.1, 96.3] (5)	82.76 [52.6, 96.6] (4)	59.63 [5.1, 73.4] (6)
	Change from baseline at Week 25	1.68 [−7.7, 19.4] (6)	0.83 [−0.8, 12.8] (5)	3.55 [0.1, 9.6] (4)	7.68 [0.8, 9.9] (6)
QMFT total score	Baseline	25.00 [1.0, 41.0] (6)	38.00 [10.0, 52.0] (5)	33.00 [11.0, 46.0] (4)	24.00 [3.0, 36.0] (6)
	Change from baseline at Week 25	−0.50 [−7.0, 6.0] (6)	2.00 [−2.0, 10.0] (5)	4.50 [0.0, 8.0] (4)	4.00 [1.0, 13.0] (6)
Pompe-PEDI Functional Skills Scale: Mobility Domain	Baseline	49.83 [0.0, 61.8] (6)	57.93 [35.1, 78.1] (5)	57.93 [0.0, 64.8] (5)	39.44 [18.4, 57.3] (6)
	Change from baseline at Week 25	1.97 [−2.1, 25.9] (6)	0.00 [0.0, 9.3] (5)	3.09 [0.7, 4.0] (3)	1.77 [1.0, 12.9] (6)
LVM index (g/m^2)	Baseline	55.31 [52.5, 77.1] (6)	64.53 [64.3, 108.5] (3)	64.40 [52.9, 71.8] (5)	64.80 [52.9, 73.5] (5)
	Change from baseline at Week 25	3.01 [−29.1, 26.3] (5)	−19.2, 0.4 (2)	−5.63 [−15.1, 4.6] (5)	11.77 [−16.7, 28.1] (5)
LVM Z score	Baseline	−1.30 [−2.0, 0.9] (6)	−0.60 [−1.8, 2.8] (3)	−0.70 [−1.8, −0.1] (5)	0.00 [−1.8, 0.1] (4)
	Change from baseline at Week 25	0.20 [−3.2, 1.9] (5)	−1.1, −0.1 (2)	−0.70 [−1.3, 0.3] (5)	0.70 [−1.4, 2.1] (3)
IPFD left non-flash (mm)	Baseline	9.50 [5.5, 10.0] (6)	7.50 [6.0, 8.5] (5)	8.00 [5.5, 9.0] (5)	8.00 [6.5, 10.0] (6)
	Change from baseline at Week 25	−0.50 [−3.0, 1.5] (6)	1.50 [−0.5, 3.5] (5)	1.00 [0.5, 2.5] (5)	−0.50 [−1.5, 0.5] (6)
MRD-1 left (mm)	Baseline	2.75 [0.0, 4.5] (6)	2.50 [0.5, 3.0] (4)	2.50 [1.0, 4.5] (4)	2.00 [0.5, 3.5] (6)
	Change from baseline at Week 25	0.75 [−2.5, 1.0] (6)	−0.25 [−1.5, 0.5] (4)	1.00 [−0.5, 2.0] (4)	0.00 [−0.5, 1.5] (6)
6MWT[a)] (m)	Baseline	259.50 [105.8, 364.7] (4)	420.00 [315.8, 452.0] (3)	370.00 [253.0, 397.6] (3)	213.00 [180.0, 253.0] (3)
	Change from baseline at Week 25	−25.45 [−119.6, 27.0] (3)	38.92 [30.0, 59.0] (3)	39.42 [−33.0, 96.0] (3)	−13.00 [−17.8, −0.9] (3)

Median [range] (n)
Individual values are presented for N ≤2.
a) Only patients who were able to ambulate ≥40 meters without stopping and without an assistive device were evaluated.

Table 39 shows the results of key efficacy endpoints in the primary analysis period and extension treatment period (up to Week 97).

Table 39. Results of key efficacy endpoints from baseline to the measurement time points (Study ACT14132 [primary analysis period and extension treatment period], mITT)

Endpoint	Measurement time point	Stage 1 (Patients demonstrating clinical decline)	
		Avalglucosidase alfa 20 mg/kg (N = 6)	Avalglucosidase alfa 40 mg/kg (N = 5)
GMFM-88 total percent score	Baseline	56.25 [0.8, 86.2] (6)	86.63 [19.1, 96.3] (5)
	Change from baseline at Week 25	1.68 [−7.7, 19.4] (6)	0.83 [−0.8, 12.8] (5)
	Change from baseline at Week 49	1.20 [−7.2, 30.5] (6)	3.54 [−1.4, 22.1] (4)
	Change from baseline at Week 73	−1.07 [−6.8, 35.3] (6)	−2.6, 3.4 (2)
	Change from baseline at Week 97	0.00 [−2.1, 6.0] (3)	—
QMFT total score	Baseline	25.00 [1.0, 41.0] (6)	38.00 [10.0, 52.0] (5)
	Change from baseline at Week 25	−0.50 [−7.0, 6.0] (6)	2.00 [−2.0, 10.0] (5)
	Change from baseline at Week 49	1.00 [−8.0, 7.0] (6)	6.50 [−6.0, 12.0] (4)
	Change from baseline at Week 73	−1.00 [−12.0, 8.0] (6)	−1.0, 10.0 (2)
	Change from baseline at Week 97	0.00 [−2.0, 3.0] (3)	—
Pompe-PEDI Functional Skills Scale: Mobility Domain	Baseline	49.83 [0.0, 61.8] (6)	57.93 [35.1, 78.1] (5)
	Change from baseline at Week 25	1.97 [−2.1, 25.9] (6)	0.00 [0.0, 9.3] (5)
	Change from baseline at Week 49	2.60 [−1.8, 22.2] (6)	1.74 [0.7, 6.5] (4)
	Change from baseline at Week 73	2.49 [−4.2, 26.7] (6)	1.1, 6.9 (2)
	Change from baseline at Week 97	6.31 [−1.7, 27.5] (3)	—
LVM index (g/m^2)	Baseline	55.31 [52.5, 77.1] (6)	64.53 [64.3, 108.5] (3)
	Change from baseline at Week 25	3.01 [−29.1, 26.3] (5)	−19.2, 0.4 (2)
	Change from baseline at Week 49	12.25 [−5.2, 19.4] (5)	−12.81 [−30.4, 57.5] (3)
	Change from baseline at Week 73	3.98 [−14.1, 14.8] (6)	−3.12 (1)
	Change from baseline at Week 97	−4.48 [−4.7, 12.9] (3)	—
LVM Z score	Baseline	−1.30 [−2.0, 0.9] (6)	−0.60 [−1.8, 2.8] (3)
	Change from baseline at Week 25	0.20 [−3.2, 1.9] (5)	−1.1, −0.1 (2)
	Change from baseline at Week 49	0.60 [−0.8, 1.4] (5)	−1.30 [−1.9, 3.1] (3)
	Change from baseline at Week 73	0.20 [−1.3, 1.1] (6)	−0.50 (1)
	Change from baseline at Week 97	−0.60 [−0.7, 0.9] (3)	—
6MWT[a)] (m)	Baseline	259.50 [105.8, 364.7] (4)	420.00 [315.8, 452.0] (3)
	Change from baseline at Week 25	−25.45 [−119.6, 27.0] (3)	38.92 [30.0, 59.0] (3)
	Change from baseline at Week 49	−64.7, −11.4 (2)	59.70 [−29.0, 113.0] (3)
	Change from baseline at Week 73	−30.43 [−113.5, 13.8] (3)	89.00 (1)
	Change from baseline at Week 97	−30.00 (1)	—

Median [range] (n); data for patients in Stage 2 have not been collected
a) Data were evaluated in the same manner as described in Note a) to Table 38.

Table 40 shows the baseline patient characteristics of 2 Japanese subjects, and Table 41 shows changes from baseline over time for key efficacy endpoints (up to Week 145).

Table 40. Baseline patient characteristics (Study ACT14132, Japanese subjects)

	Subject 1	Subject 2
Sex	Male	Female
Age (years)	[redacted]	1[redacted]
Body weight (kg)	1[redacted]	2[redacted]
BMI (kg/m^2)	13.2	12.0
Duration of disease (years)	6.5	9.8

Table 41. Changes from baseline over time for key efficacy endpoints (Study ACT14132 [primary analysis period and extension treatment period], Japanese subjects)

Measurement time point	GMFM-88 total % score	QMFT total score	Pompe-PEDI Functional Skills Scale: Mobility Domain	LVM index (g/m^2)	LVM Z score	IPFD left non-flash (mm)	MRD-1 left (mm)	6MWT (m)
Subject 1 (Stage 1: Avalglucosidase alfa 20 mg/kg)								
Baseline	57.56	19	49.83	52.451	−1.4	5.5	0	105.84[a)]
Change from baseline at Week 25	2.96	−2	0.3	7.635	0.6	0	1	—
Change from baseline at Week 49	2.39	2	−0.3	12.829	1	0	1	—
Change from baseline at Week 73	−2.14	−2	−2.97	14.783	1.1	1.5	0.5	—
Change from baseline at Week 97	−2.99	−1	−2.97	12.585	0.9	—	—	—
Change from baseline at Week 121	−0.69	−2	0	2.045	0	—	—	—
Change from baseline at Week 145	−1.18	1	−0.57	7.215	0.4	—	—	—
Subject 2 (Stage 1: Avalglucosidase alfa 40 mg/kg)								
Baseline	96.29	52	78.14	64.266	−0.6	6	2.5	452
Change from baseline at Week 25	0.83	2	0	0.417	−0.1	1.5	−1.5	59
Change from baseline at Week 49	1.46	5	1.98	−12.811	−1.3	0.5	−1.5	113
Change from baseline at Week 73	3.43	10	6.93	−3.117	−0.5	1.5	0	89
Change from baseline at Week 97	2.36	12	5.64	−7.902	−1.1	1.5	−1.5	78
Change from baseline at Week 121	2.64	8	2.76	—	—	2	−0.5	59
Change from baseline at Week 145	3.2	10	4.56	—	—	—	—	96

"—": not measured

a) This subject was using an assistive device. The measurement was taken only at baseline when the subject was walking with an assistive device to stabilize the gait.

Table 42 shows the incidence of adverse events occurring in ≥2 subjects in any group during the primary analysis period, as well as the incidence of these events classified as adverse drug reactions. Of the 2 Japanese subjects, the one that was treated with avalglucosidase alfa 40 mg/kg had adverse events (skin abrasion/ligament sprain/arthropod sting/sunburn/arthralgia/musculoskeletal pain/erythema/injection site swelling/abdominal pain/thermal burn/contusion/oropharyngeal pain). However, all the events were non-serious and their causal relationship to the study drug was ruled out.

Table 42. Adverse events occurring in ≥2 subjects (Study ACT14132 [primary analysis period], safety analysis set)

Event	Stage 1				Stage 2			
	Avalglucosidase alfa 20 mg/kg (N = 6)		Avalglucosidase alfa 40 mg/kg (N = 5)		Avalglucosidase alfa 40 mg/kg (N = 5)		ALGLU (N = 6)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Subjects with any event	83.3 (5)	0 (0)	100 (5)	40.0 (2)	100 (5)	20.0 (1)	83.3 (5)	16.7 (1)
Rash	0 (0)	0 (0)	20.0 (1)	20.0 (1)	40.0 (2)	20.0 (1)	16.7 (1)	20.0 (1)
Pyrexia	33.3 (2)	0 (0)	20.0 (1)	0 (0)	40.0 (2)	0 (0)	16.7 (1)	0 (0)
Cough	16.7 (1)	0 (0)	20.0 (1)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)
Diarrhoea	0 (0)	0 (0)	20.0 (1)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	20.0 (1)	0 (0)	40.0 (2)	0 (0)	50.0 (3)	0 (0)
Upper respiratory tract infection	33.3 (2)	0 (0)	0 (0)	0 (0)	40.0 (2)	0 (0)	16.7 (1)	0 (0)
Headache	16.7 (1)	0 (0)	0 (0)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)
Eye irritation	0 (0)	0 (0)	0 (0)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)
Rhinorrhoea	0 (0)	0 (0)	0 (0)	0 (0)	40.0 (2)	0 (0)	16.7 (1)	0 (0)
Device occlusion	0 (0)	0 (0)	0 (0)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)
Eyelid ptosis	0 (0)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	0 (0)	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fall	33.3 (2)	0 (0)	20.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	33.3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)	0 (0)
Viral infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33.3 (2)	0 (0)

Incidence: % (n); MedDRA/J ver.22.0

There were no deaths. In Stage 1, serious adverse events occurred in 1 subject (respiratory tract infection viral) in the avalglucosidase alfa 20 mg/kg group and 3 subjects (eyelid ptosis in 2 subjects and respiratory distress/pyrexia in 1 subject) in the avalglucosidase alfa 40 mg/kg group. In Stage 2, serious adverse events occurred in 2 subjects in the ALGLU group (pneumonia/lung consolidation/urinary tract infection and lung infection pseudomonal/joint dislocation). A causal relationship to the study drug was ruled out for all these events. No adverse events led to treatment discontinuation.

Table 43 shows the incidence of adverse events occurring in ≥2 subjects in either group during the primary analysis period and extension treatment period, as well as the incidence of these events classified as adverse drug reactions. Both Japanese subjects experienced adverse events. One of the subjects with a starting dose level of avalglucosidase alfa 20 mg/kg experienced dental caries/myalgia/presyncope/lymph node pain/alopecia areata while the other subject with a starting dose level of avalglucosidase alfa 40 mg/kg experienced skin abrasion/ligament sprain/arthropod sting/sunburn/arthralgia/musculoskeletal pain/erythema/injection site swelling/abdominal pain/thermal burn/contusion/oropharyngeal pain/vomiting/back pain/headache/foot deformity/epistaxis. However, all the events were non-serious and their causal relationship to the study drug was ruled out.

Table 43. Adverse events occurring in ≥2 subjects (Study ACT14132 [primary analysis period and extension treatment period], safety analysis set)

Event	Avalglucosidase alfa 20 mg/kg (initial dose level)[a] (N = 6)		Avalglucosidase alfa 40 mg/kg (initial dose level)[b] (N = 13)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
Subjects with any event	100 (6)	16.7 (1)	100 (13)	38.5 (5)
Rash	16.7 (1)	16.7 (1)	38.5 (5)	23.1 (3)
Vomiting	16.7 (1)	0 (0)	30.8 (4)	0 (0)
Pyrexia	33.3 (2)	0 (0)	30.8 (4)	0 (0)
Upper respiratory tract infection	33.3 (2)	0 (0)	23.1 (3)	0 (0)
Fall	33.3 (2)	0 (0)	23.1 (3)	0 (0)
Cough	16.7 (1)	0 (0)	23.1 (3)	0 (0)
Abdominal pain	16.7 (1)	0 (0)	23.1 (3)	0 (0)
Diarrhoea	16.7 (1)	0 (0)	23.1 (3)	0 (0)
Tachypnoea	0 (0)	0 (0)	15.4 (2)	7.7 (1)
Epistaxis	16.7 (1)	0 (0)	15.4 (2)	0 (0)
Pain in extremity	16.7 (1)	0 (0)	15.4 (2)	0 (0)
Eye irritation	0 (0)	0 (0)	15.4 (2)	0 (0)
Eyelid ptosis	0 (0)	0 (0)	15.4 (2)	0 (0)
Oropharyngeal pain	0 (0)	0 (0)	15.4 (2)	0 (0)
Rhinorrhoea	0 (0)	0 (0)	15.4 (2)	0 (0)
Device occlusion	0 (0)	0 (0)	15.4 (2)	0 (0)
Pneumonia	50.0 (3)	0 (0)	7.7 (1)	0 (0)
Otitis media	33.3 (2)	0 (0)	7.7 (1)	0 (0)
Urinary tract infection	33.3 (2)	0 (0)	7.7 (1)	0 (0)
Bronchitis	33.3 (2)	0 (0)	0 (0)	0 (0)

Incidence: % (n); MedDRA/J ver.22.0

a) Results obtained from Cohort 1 subjects treated in the primary analysis period and extension treatment period

b) The data consist of the results in the following subjects: Cohort 2 or 3 subjects assigned to avalglucosidase alfa during the primary analysis period and extension treatment period, and three Cohort 3 subjects who were initially assigned to ALGLU and switched from ALGLU to avalglucosidase alfa in the extension treatment period.

There were no deaths. Serious adverse events occurred in 4 subjects with a starting dose level of avalglucosidase alfa 20 mg/kg (influenza/pneumonia/tympanic membrane perforation; pneumonia; respiratory tract infection viral/adenoidal hypertrophy/tonsillar hypertrophy/otitis media/device malfunction/atrial thrombosis; post procedural haemorrhage) and 4 subjects with a starting dose level of avalglucosidase alfa 40 mg/kg (strabismus/pneumonia; eyelid ptosis; respiratory distress/pyrexia/gastroenteritis; joint dislocation/lung infection pseudomonal/femur fracture). A causal relationship to the study drug was ruled out for all these events. No adverse events led to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in patients with LOPD

The applicant's explanation:

Patients with LOPD have a clinical course characterized by progressive disorder of respiratory function due to weakening of the diaphragm and other accessory muscles of respiration. Respiratory failure is one of the major causes of death in these patients (e.g., *Orphanet J Rare Dis*. 2011;6:34, *J Neurol*. 2005;252:875-84). According to a report on the assessments of the respiratory function in patients with LOPD, the mean decline in FVC (% predicted) among untreated patients was 2.3% after 12 months, and 6.2% after 4 years when the predicted values were calculated on the basis of sex, race, age, and height (*J Neurol*. 2017;264:621-30). In the global phase III study in ALGLU treatment-naïve patients with LOPD (Study EFC14028), the change from baseline to Week 49 in FVC (% predicted), the primary endpoint, (least squares mean ± standard error) was 2.89 ± 0.88% in the avalglucosidase alfa group and 0.46 ± 0.93% in the ALGLU group. The least squares mean difference for avalglucosidase alfa versus ALGLU and the 95% CI is 2.43% [−0.13, 4.99]. The lower bound

of the 2-sided 95% CI is greater than the predefined non-inferiority threshold of −1.1, demonstrating the non-inferiority of avalglucosidase alfa to ALGLU (Table 30). The minimal clinically important difference of 2% to 6% reported in a study in 1156 patients with idiopathic pulmonary fibrosis (IPF) (*Orphanet J Rare Dis.* 2013;8:160). IPF is a progressive restrictive pulmonary disease, and the mortality rate of patients with IPF is dependent on respiratory function. Based on this report, the change from baseline in FVC (% predicted) observed in the avalglucosidase alfa group was thought to be a clinically significant improvement. In the extension treatment period, improved FVC (% predicted) was maintained in patients who had continued to receive avalglucosidase alfa. On the other hand, patients who were switched from ALGLU to avalglucosidase alfa after Week 49 showed improvement in FVC (% predicted) after switching treatment (Table 32).

In patients with LOPD, progressive loss of skeletal muscle strength gradually reduces mobility and hampers activities of daily living, ultimately resulting in the use of assistive devices in walking. In Study EFC14028, the 6-minute walk test (6MWT) was selected as an endpoint for motor function. The change from baseline to Week 49 in 6MWT (mean ± standard deviation) was 37.86 ± 52.81 m in the avalglucosidase alfa group and −1.73 ± 85.16 m in the ALGLU group, demonstrating improved motor function in the avalglucosidase alfa group compared to the ALGLU group (Table 31). In the above-mentioned, large-scale study in patients with idiopathic pulmonary fibrosis, a minimal clinically important difference of 24 to 54 m was reported for 6MWT (*Orphanet J Rare Dis.* 2013;8:160). This information suggests that the change from baseline and between-group difference observed in Study EFC14028 are clinically significant. In addition, other motor function endpoints, namely, changes from baseline to Week 49 in lower extremity hand-held dynamometry (HHD) composite score, and QMFT total score, improved in the avalglucosidase alfa group compared to the ALGLU group (Table 31). In the extension treatment period, improvements in 6MWT, lower extremity HHD composite score, and QMFT total score were maintained in patients who continued to receive avalglucosidase alfa. In patients who were switched from ALGLU to avalglucosidase alfa after Week 49, 6MWT remained around the same level as baseline at Weeks 61 and 73 but tended to improve at Week 97 and thereafter. The lower extremity HHD composite score and QMFT total score tended to improve after switching treatment (Table 32).

Efficacy in Japanese patients was compared to that for the entire study population. Table 44 shows the patient characteristics in the entire study population and 1 Japanese subject in Study EFC14028.

Table 44. Patient characteristics in the entire study population and a Japanese subject in Study EFC14028 (mITT)

		Avalglucosidase alfa (N = 51)	ALGLU (N = 49)	Japanese subject (N = 1, avalglucosidase alfa)
Sex	Male	52.9% (n =27)	51.0% (n =25)	Male
	Female	47.1% (n = 24)	49.0% (n =24)	
Age (years)		46.0 ± 14.5	50.3 ± 13.7	6[redacted]
Body weight (kg)		77.8 ± 22.1	79.3 ± 18.2	8[redacted]
BMI (kg/m^2)		26.39 ± 6.79	26.69 ± 5.42	30.4
Duration of disease (months)		15.60 ± 32.06	26.52 ± 59.86	3.6

Mean ± standard deviation; % (n) for each sex
Individual values are shown for the Japanese subject data.

The change from baseline to Week 49 in FVC (% predicted), the primary endpoint, was 0.432% in the Japanese subject (Table 34), which tends to be lower than that in the entire study population (least squares mean and its 95% CI, 2.89% [1.13, 4.65]). However, the change from baseline in FVC (% predicted) improved to 3.64% at Week 37 and 7.67% at Week 73, showing the variability among the evaluation time points. This Japanese

subject had a past history of pneumonia and tracheostomy approximately 4 months prior to the screening visit, and presented with severe respiratory function disorder, with baseline FVC (% predicted) of 48.04%, MIP (% predicted) of 28.40%, and MEP (% predicted) of 54.23%. The change from baseline to Week 49 in 6MWT, a secondary endpoint, improved in the Japanese subject in a manner similar to that in the entire study population, and the change in QMFT total score also improved (Table 31). There have been no reports indicating relevant variations in the pathophysiology of Pompe disease or response to enzyme replacement therapy between different regions (*Aging.* 2020;12:15856-74, *Hum Mutat.* 2021;42:119-34). In addition, the efficacy of enzyme replacement therapy with ALGLU has been demonstrated in Japanese patients with Pompe disease. Based on the above findings, it is not likely that the efficacy of avalglucosidase alfa in Japanese patients differs from that in non-Japanese patients.

PMDA's view:
It is reasonable to select a respiratory function-related measure of FVC (% predicted) as the primary endpoint of Study EFC14028 which was conducted in ALGLU treatment-naïve patients with LOPD. The study has demonstrated the non-inferiority of avalglucosidase alfa to ALGLU for the change from baseline to Week 49 in FVC (% predicted). In addition to the primary endpoint, the efficacy of avalglucosidase alfa tended to be higher than that of ALGLU for motor function endpoints such as 6MWT. Patients who switched from ALGLU to avalglucosidase alfa in the extension treatment period tended to have improvements in respiratory and motor functions after switching treatment. Based on the above, avalglucosidase alfa is expected to be effective both in ALGLU treatment-naïve patients and in patients who switch from ALGLU to avalglucosidase alfa. However, due to the limited number of Japanese patients enrolled in Study EFC14028, the applicant should continue to collect efficacy data in the post-marketing setting.

7.R.1.2 Efficacy in patients with IOPD

The applicant's explanation:
Infantile-onset Pompe disease, which presents in the first few months of life, is characterized by severe cardiomyopathy and respiratory failure, and untreated patients with IOPD usually die within the first year of life (*Orphanet J Rare Dis.* 2016;11:65). In Study ACT14132, a global phase II study involving patients with IOPD who demonstrated clinical decline (Stage 1) or a sub-optimal clinical response (Stage 2) after treatment with ALGLU, the cardiac function in 1 subject (Stage 1, avalglucosidase alfa 40 mg/kg) who had had an abnormal LVM Z score (>2) at baseline improved to the normal range by Week 25. All other patients with evaluable echocardiography had a normal LVM Z score at baseline, which remained stable through Week 25. Respiratory function testing was not performed in subjects who were unable to be tested correctly or who were on invasive ventilatory assistance. Only subjects who were able to have their respiratory function tested were evaluated for FVC (% predicted). Consequently, only a small number of subjects were able to undergo testing (evaluable at Week 25: 2 subjects each in Cohorts 1 and 2, and 2 subjects in the avalglucosidase alfa group and 1 subject in the ALGLU group in Cohort 3). The results did not show consistent trends in any group in Stages 1 and 2. Motor function was evaluated using the GMFM-88 total percent score and QMFT total score. The GMFM-88 total percent score tended to improve from baseline to Week 25 in all groups in Stages 1 and 2, while in patients who had demonstrated a sub-optimal clinical response to ALGLU (Stage 2), change from

baseline was smaller in the avalglucosidase alfa group than in the ALGLU group (Table 38). In patients who had demonstrated clinical decline after ALGLU treatment (Stage 1), the QMFT total score decreased slightly from baseline to Week 25 in the avalglucosidase alfa 20 mg/kg group, while it tended to improve in the avalglucosidase alfa 40 mg/kg group. In patients who had demonstrated a sub-optimal clinical response to ALGLU (Stage 2), the QMFT total score tended to improve in both the avalglucosidase alfa 40 mg/kg group and the ALGLU group. In Stage 2, the extent of improvement in GMFM-88 total percent score was lower in the avalglucosidase alfa group than in the ALGLU group. This may be attributable to the following factors: subjects in the ALGLU group were younger; and many of the subjects were enrolled because of new onset of eyelid ptosis, resulting in a smaller proportion of subjects presenting with a sub-optimal clinical response in motor function. In all cohorts, there was a general tendency toward an increase in the scaled score of Pompe-PEDI (Functional Skills Scale: Mobility Domain) from baseline to Week 25 in individual subjects, suggesting an increase in the number of acquired mobility-related functional skills. The 6MWT was to be performed only for subjects who were able to ambulate ≥40 meters without stopping and without an assistive device. Although the between-subject variation was large, the mean change from baseline in 6MWT distance significantly increased in the avalglucosidase alfa 40 mg/kg group in Stages 1 and 2 compared with that in the avalglucosidase alfa 20 mg/kg group in Stage 1 or the ALGLU group in Stage 2. The values for eyelid levator muscle-related endpoints, i.e., interpalpebral fissure distance (IPFD) and margin reflex distance-1 (MRD-1) in the avalglucosidase alfa 20 mg/kg group in Stage 1 and the ALGLU group in Stage 2 either remained unchanged or decreased, while those in the avalglucosidase alfa 40 mg/kg group in Stages 1 and 2 tended to increase. Regarding the data obtained during the extension treatment period, data from subjects enrolled in Stage 1 were available as of the data cut-off date. The GMFM-88 total percent score, QMFT total score, and other values tended to be maintained at a constant level in these subjects.

Efficacy data in Japanese patients were compared to those in the entire study population. Table 45 shows the baseline patient characteristics of the entire study population and 2 Japanese subjects in Study ACT14132. As shown in the efficacy results in Table 41, the GMFM-88 total percent score, QMFT total score, 6MWT, and other values improved in the subject in the 40 mg/kg group.

Table 45. Baseline patient characteristics (Study ACT14132, entire study population and Japanese subpopulation)

Patient characteristics		Stage 1 (Patients who demonstrated clinical decline after treatment with ALGLU)			
		Cohort 1 (avalglucosidase alfa 20 mg/kg) (N = 6)		Cohort 2 (avalglucosidase alfa 40 mg/kg) (N = 5)	
		Entire study population	Japanese subject (1)	Entire study population	Japanese subject (1)
Sex	Male	83.3% (5)	Male	60.0% (3)	Female
	Female	16.7% (1)		40.0% (2)	
Age (years)		8.2 [2, 11]	[redacted]	9.8 [1, 12]	1[redacted]
Body weight (kg)		24.5 [13, 50]	1[redacted]	23.4 [10, 64]	2[redacted]
BMI (kg/m^2)		17.02 [13.0, 22.8]	13.2	16.52 [12.0, 26.9]	12.0
Age at diagnosis (months)		1.10 [0.3, 5.5]	1.6	4.47 [0.3, 8.7]	7.2
Age at onset of symptoms (months)		0.34 [0.0, 4.4]	0.0	4.40 [0.1, 6.5]	6.5
Age at start of ALGLU (months)		2.41 [0.4, 5.7]	1.7	4.63 [0.5, 10.4]	10.4
Duration of disease (years)		7.92 [2.1, 10.8]	6.5	9.44 [0.7, 11.9]	9.8

Median [range]; % (n) for each sex
Individual values are shown for the Japanese subject data.

PMDA's view:

Although a small number of enrolled subjects precludes strict evaluation, the results of the global phase II study in patients with IOPD (Study ACT14132) showed a trend toward improvement in motor function endpoints when subjects who had demonstrated clinical decline after treatment with ALGLU were treated with avalglucosidase alfa 40 mg/kg. A trend toward improvement in motor function endpoints was also observed when subjects who had demonstrated a sub-optimal clinical response to ALGLU were treated with avalglucosidase alfa 40 mg/kg. In addition, there is a trend toward increasing efficacy compared to ALGLU, especially for 6MWT, eyelid levator muscle-related endpoints (IPFD and MRD-1), and other endpoints. The change from baseline in GMFM-88 total percent score was smaller than that in the ALGLU group. As discussed by the applicant, this may have been attributable to the following and other factors: subjects in the ALGLU group were younger than those in the avalglucosidase alfa group; and the proportion of subjects presenting with a sub-optimal clinical response in motor function was smaller in the ALGLU group. The values of cardiac function, as measured by the LVM Z score, were normalized or remained stable in the normal range in the avalglucosidase alfa group. In the extension treatment period, there was no trend toward diminishing efficacy for motor function and other endpoints. The above results indicate that avalglucosidase alfa is expected to be effective in patients with IOPD who demonstrated clinical decline or a sub-optimal clinical response after treatment with ALGLU. However, given that only a limited number of patients with IOPD were evaluated, the applicant should continue to collect data in the post-marketing setting.

7.R.2 Safety

The applicant's explanation:

Table 46 shows the incidence of adverse events reported in Study EFC14028, a global phase III study in treatment-naïve patients with LOPD and in Study ACT14132, a global phase II study in patients with IOPD who demonstrated clinical decline or a sub-optimal clinical response after treatment with ALGLU. There was no trend toward an increasing incidence of adverse events in the avalglucosidase alfa group compared to the ALGLU group during the primary analysis period of each study. Most of the adverse events reported were either mild or moderate in severity, with no marked difference across treatment groups in the incidence of adverse events by severity. In Study ACT14132, the incidence of adverse events in the avalglucosidase alfa 40 mg/kg group did not differ substantially from that in the 20 mg/kg group. While the incidence of serious adverse events varied between cohorts, there were no severe events or serious adverse drug reactions. In Study ACT14132, no patients needed dose reduction for safety reasons. During the extension treatment period, the dose was increased from 20 mg/kg to 40 mg/kg in 2 subjects due to a sub-optimal clinical response to avalglucosidase alfa at 20 mg/kg, but there was no trend toward a significant increase in the number of adverse events in these subjects after the dose increase. Adverse events occurred in Japanese subjects (1 subject in Study EFC14028 and 2 subjects in Study ACT14132), and these events were all mild in severity. None of the adverse events were classified as adverse drug reactions or serious adverse events, or led to discontinuation of the study drug.

Table 46. Summary of adverse events reported in Studies EFC14028 and ACT14132 (primary analysis period, safety analysis set)

Events		EFC14028		ACT14132			
		Avalglucosidase alfa (N = 51)	ALGLU (N = 49)	Stage 1 (Clinical decline after ALGLU)		Stage 2 (Cohort 3) (Sub-optimal clinical response to ALGLU)	
				Cohort 1 (Avalglucosidase alfa 20 mg/kg) (N = 6)	Cohort 2 (Avalglucosidase alfa 40 mg/kg) (N = 5)	Avalglucosidase alfa 40 mg/kg (N = 5)	ALGLU (N = 6)
All adverse events		86.3 (44)	91.8 (45)	83.3 (5)	100 (5)	100 (5)	83.3 (5)
All adverse drug reactions		45.1 (23)	49.0 (24)	0 (0)	40.0 (2)	20.0 (1)	16.7 (1)
Serious adverse events		15.7 (8)	24.5 (12)	16.7 (1)	60.0 (3)	0 (0)	33.3 (2)
Deaths		0 (0)	2.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation		0 (0)	8.2 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Severity	Mild	29.4 (15)	22.4 (11)	33.3 (2)	40.0 (2)	40.0 (2)	33.3 (2)
	Moderate	45.1 (23)	55.1 (27)	50.0 (3)	20.0 (1)	60.0 (3)	33.3 (2)
	Severe	11.8 (6)	14.3 (7)	0 (0)	40.0 (2)	0 (0)	16.7 (1)

Incidence: % (n)

A pooled analysis was performed using data from all 141 subjects who had received avalglucosidase alfa in the following studies: Studies EFC14028, ACT14132, TDR12857 (a foreign phase I/II study in treatment-naïve or ALGLU treatment-experienced patients with LOPD), and LTS13769 (an extension study of TDR12857). Table 47 summarizes the incidence of adverse events. The incidence of adverse events was analyzed in pediatric versus adult patients, and treatment-naïve versus treatment-experienced patients. While the incidence of serious adverse events was higher in the pediatric subgroup than in the adult subgroup, a causal relationship to avalglucosidase alfa was ruled out for all events occurring in the pediatric subgroup. There was no other significant difference in the incidence of adverse events between patient subgroups. Table 48 shows the incidence of individual adverse events and adverse drug reactions in the pooled analysis. The events observed were similar to those observed in ALGLU-treated patients (Tables 35 and 42).

Table 47. Summary of adverse events in subjects treated with avalglucosidase alfa
(primary analysis period and extension treatment period, safety analysis set; data cut-off on July 17, 2020)

Events		Treatment-naïve (N = 61)	Treatment-experienced (N = 80)[a)]	Adult (N = 118)	Pediatric (N = 23)[a)]	All subjects treated with avalglucosidase alfa (N = 141)[a)]
All adverse events		96.7 (59)	95.0 (76)	94.9 (112)	100 (23)	95.7 (135)
All adverse drug reactions		52.5 (32)	47.5 (38)	52.5 (62)	34.8 (8)	49.6 (70)
Serious adverse events		34.4 (21)	26.3 (21)	27.1 (32)	43.5 (10)	29.8 (42)
Deaths		0 (0)	1.3 (1)	0.8 (1)	0 (0)	0.7 (1)
Adverse events leading to treatment discontinuation		6.6 (4)	1.3 (1)	4.2 (5)	0 (0)	3.5 (5)
Severity	Mild	93.4 (57)	87.5 (70)	89.0 (105)	95.7 (22)	90.1 (127)
	Moderate	78.7 (48)	66.3 (53)	72.0 (85)	69.6 (16)	71.6 (101)
	Severe	24.6 (15)	23.8 (19)	23.7 (28)	26.1 (6)	24.1 (34)
IAR		34.4 (21)	33.8 (27)	34.7 (41)	30.4 (7)	34.0 (48)
Treatment-induced anti-avalglucosidase alfa antibodies[b)]		94.9 (56)	50.0 (16)	87.7 (64)	44.4 (8)	79.1 (72)
Treatment-boosted anti-avalglucosidase alfa antibodies[c)]		100 (2)	50.0 (23)	55.6 (25)	0 (0)	52.1 (25)
Treatment-emergent anti-avalglucosidase alfa antibodies[d)]		95.1 (58)	50.0 (39)	75.4 (89)	38.1 (8)	69.8 (97)

Incidence: % (n)

a) Two cross-reacting immunologic material (CRIM)-negative pediatric patients who had received immune tolerance induction therapy were excluded from the evaluation of anti-avalglucosidase alfa antibodies.

b) Treatment-induced: subjects tested negative for anti-avalglucosidase alfa antibodies at baseline but became positive after treatment. Incidence = (number of subjects with treatment-induced anti-avalglucosidase alfa antibodies) / (number of subjects with anti-avalglucosidase alfa antibodies-negative at baseline) × 100

c) Treatment-boosted: subjects tested positive for anti-avalglucosidase alfa antibodies at baseline and had treatment-boosted anti-avalglucosidase alfa antibodies with increased titers by ≥4-fold. Incidence = (number of subjects with treatment-boosted anti-avalglucosidase alfa antibodies) / (number of subjects with anti-avalglucosidase alfa antibodies-positive at baseline) × 100

d) Incidence = (number of subjects with treatment-induced or treatment-boosted anti-avalglucosidase alfa antibodies) / (number of evaluable subjects) × 100

Table 48. Adverse events occurring in ≥10% of all subjects treated with avalglucosidase alfa
(primary analysis period and extension treatment period, safety analysis set; data cut-off on July 17, 2020)

Events	Treatment-naïve (N = 61)		Treatment-experienced (N = 80)		Adult (N = 118)		Pediatric (N = 23)		All subjects treated with avalglucosidase alfa (N = 141)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Subjects with any adverse event	96.7 (59)	52.5 (32)	95.0 (76)	47.5 (38)	94.9 (112)	52.5 (62)	100 (23)	34.8 (8)	95.7 (135)	49.6 (70)
Headache	32.8 (20)	8.2 (5)	28.8 (23)	7.5 (6)	31.4 (37)	8.5 (10)	26.1 (6)	4.3 (1)	30.5 (43)	7.8 (11)
Nasopharyngitis	36.1 (22)	0 (0)	26.3 (21)	0 (0)	34.7 (41)	0 (0)	8.7 (2)	0 (0)	30.5 (43)	0 (0)
Diarrhoea	27.9 (17)	3.3 (2)	23.8 (19)	1.3 (1)	26.3 (31)	2.5 (3)	21.7 (5)	0 (0)	25.5 (36)	2.1 (3)
Back pain	32.8 (20)	0 (0)	18.8 (15)	1.3 (1)	26.3 (31)	0 (0)	17.4 (4)	4.3 (1)	24.8 (35)	0.7 (1)
Fall	21.3 (13)	0 (0)	23.8 (19)	0 (0)	22.0 (26)	0 (0)	26.1 (6)	0 (0)	22.7 (32)	0 (0)
Nausea	29.5 (18)	11.5 (7)	15.0 (12)	5.0 (4)	22.9 (27)	8.5 (10)	13.0 (3)	4.3 (1)	21.3 (30)	7.8 (11)
Arthralgia	26.2 (16)	0 (0)	17.5 (14)	0 (0)	23.7 (28)	0 (0)	8.7 (2)	0 (0)	21.3 (30)	0 (0)
Rash	14.8 (9)	4.9 (3)	22.5 (18)	11.3 (9)	16.1 (19)	6.8 (8)	34.8 (8)	17.4 (4)	19.1 (27)	8.5 (12)
Pain in extremity	23.0 (14)	1.6 (1)	16.3 (13)	2.5 (2)	19.5 (23)	1.7 (2)	17.4 (4)	4.3 (1)	19.1 (27)	2.1 (3)
Upper respiratory tract infection	14.8 (9)	0 (0)	22.5 (18)	0 (0)	16.1 (19)	0 (0)	34.8 (8)	0 (0)	19.1 (27)	0 (0)
Influenza	26.2 (16)	0 (0)	10.0 (8)	0 (0)	17.8 (21)	0 (0)	13.0 (3)	0 (0)	17.0 (24)	0 (0)
Fatigue	21.3 (13)	8.2 (5)	12.5 (10)	6.3 (5)	17.8 (21)	7.6 (9)	8.7 (2)	4.3 (1)	16.3 (23)	7.1 (10)
Pyrexia	18.0 (11)	1.6 (1)	15.0 (12)	0 (0)	13.6 (16)	0.8 (1)	30.4 (7)	0 (0)	16.3 (23)	0.7 (1)
Myalgia	19.7 (12)	3.3 (2)	12.5 (10)	2.5 (2)	17.8 (21)	3.4 (4)	4.3 (1)	0 (0)	15.6 (22)	2.8 (4)
Vomiting	14.8 (9)	1.6 (1)	16.3 (13)	2.5 (2)	13.6 (16)	1.7 (2)	26.1 (6)	4.3 (1)	15.6 (22)	2.1 (3)
Muscle spasms	21.3 (13)	4.9 (3)	10.0 (8)	1.3 (1)	17.8 (21)	3.4 (4)	0 (0)	0 (0)	14.9 (21)	2.8 (4)
Musculoskeletal pain	11.5 (7)	0 (0)	16.3 (13)	0 (0)	15.3 (18)	0 (0)	8.7 (2)	0 (0)	14.2 (20)	0 (0)
Pruritus	13.1 (8)	13.1 (8)	13.8 (11)	10.0 (8)	16.1 (19)	13.6 (16)	0 (0)	0 (0)	13.5 (19)	11.3 (16)
Dizziness	19.7 (12)	3.3 (2)	7.5 (6)	2.5 (2)	15.3 (18)	3.4 (4)	0 (0)	0 (0)	12.8 (18)	2.8 (4)
Contusion	18.0 (11)	1.6 (1)	8.8 (7)	0 (0)	13.6 (16)	0.8 (1)	8.7 (2)	0 (0)	12.8 (18)	0.7 (1)
Urinary tract infection	18.0 (11)	0 (0)	8.8 (7)	0 (0)	12.7 (15)	0 (0)	13.0 (3)	0 (0)	12.8 (18)	0 (0)
Abdominal pain	13.1 (8)	0 (0)	11.3 (9)	0 (0)	10.2 (12)	0 (0)	21.7 (5)	0 (0)	12.1 (17)	0 (0)

Incidence: % (n)

One subject receiving avalglucosidase alfa died of adenocarcinoma pancreas. The event was assessed as unrelated to the study drug. In Study LTS13769, 1 subject died of acute respiratory failure after completion of treatment with avalglucosidase alfa 20 mg/kg. The event was assessed as unrelated to avalglucosidase alfa. Serious adverse events occurred in 42 of 141 subjects (29.8%), and the following events in 8 subjects were classified as adverse drug reactions: chills/pyrexia, respiratory distress/chest discomfort, nausea, dyspnoea, headache/skin discolouration/chills/blood pressure increased/body temperature increased/heart rate increased/oxygen saturation decreased, urticaria, respiratory distress/tongue oedema, and pruritus. While some required treatment, all events were resolving within the day of onset. Adverse events led to treatment discontinuation in 5 subjects (pregnancy [2 subjects], ocular hyperaemia/erythema [1 subject], acute myocardial infarction [1 subject], respiratory distress/chest discomfort/nausea/cough/flushing [1 subject]). Among these, events in 2 subjects (ocular hyperaemia/erythema; and respiratory distress/chest discomfort) were classified as adverse drug reactions. In Study ACT14132, the incidence of adverse events in subjects treated with avalglucosidase alfa 20 mg/kg was similar to that in subjects treated with 40 mg/kg (Table 46). The incidences of serious adverse events and severe adverse events (in severity grading scale) in the avalglucosidase alfa 40 mg/kg group in Stage 1 differ from those in the avalglucosidase alfa 40 mg/kg group in Stage 2, showing no consistent trends between the same dose levels (Table 46).

Long-term safety was evaluated using the pooled analysis of data from Studies EFC14028, ACT14132, TDR12857, and LTS13769. Table 49 shows the incidence of adverse events and adverse drug reactions by timing of onset in subjects treated with avalglucosidase alfa in these studies. A majority of severe adverse

events and serious adverse events reported in patients treated with avalglucosidase alfa for ≥36 months were considered to be unrelated to avalglucosidase alfa, but were rather related to comorbidity or underlying diseases. There was no trend toward a significant change in the incidence of events with an increase in the duration of treatment.

Table 49. Incidence of adverse events in all subjects treated with avalglucosidase alfa by timing of onset (primary analysis period and extension treatment period, safety analysis set; data cut-off on July 17, 2020)

Time to onset		All subjects (N = 141)	0-6 months (N = 141)	6-12 months (N = 139)	12-18 months (N = 135)	18-24 months (N = 107)	24-30 months (N = 80)	30-36 months (N = 58)	>36 months (N = 36)
All adverse events		95.7 (135)	52.5 (74)	66.2 (92)	80.7 (109)	69.2 (74)	76.3 (61)	69.0 (40)	77.8 (28)
All adverse drug reactions		49.6 (70)	22.0 (31)	15.1 (21)	25.2 (34)	12.1 (13)	12.5 (10)	3.4 (2)	11.1 (4)
Serious adverse events		29.8 (42)	7.1 (10)	10.8 (15)	11.1 (15)	9.3 (10)	3.8 (3)	5.2 (3)	22.2 (8)
Adverse events leading to treatment discontinuation		3.5 (5)	1.4 (2)	0 (0)	1.5 (2)	0.9 (1)	0 (0)	0 (0)	0 (0)
Severity	Mild	90.1 (127)	51.1 (72)	59.0 (82)	65.9 (89)	56.1 (60)	67.5 (54)	55.2 (32)	69.4 (25)
	Moderate	71.6 (101)	24.8 (35)	33.8 (47)	44.4 (60)	34.6 (37)	33.8 (27)	32.8 (19)	61.1 (22)
	Severe	24.1 (34)	5.7 (8)	7.9 (11)	8.9 (12)	7.5 (8)	2.5 (2)	6.9 (4)	22.2 (8)
IAR[a)]		34.0 (48)	12.1 (17)	8.6 (12)	20.0 (27)	9.3 (10)	10.0 (8)	3.4 (2)	2.8 (1)

Incidence: % (n)

a) Adverse events that occurred during the infusion or the observation period (2 hours) following the infusion and which were considered to be related or possibly related to the study drug. Adverse events occurring after the completion of the post-infusion observation period can also be included in the assessment at the discretion of the investigator.

Based on the above, adverse events reported in the clinical studies are similar to those that occurred after treatment with ALGLU; therefore, the safety profile of avalglucosidase alfa does not differ significantly from that of ALGLU.

PMDA's view:

In light of the incidence of adverse events in the clinical studies, the safety of avalglucosidase alfa 20 mg/kg every other week in patients with LOPD and avalglucosidase alfa 40 mg/kg every other week in patients with IOPD is acceptable, provided that appropriate cautionary advice is given regarding the events, the details of which will be discussed later. However, because of the limited number of patients evaluated in the clinical studies, the applicant should continue to collect data on the safety and other aspects of avalglucosidase alfa in the post-marketing setting. The details of the events will be further discussed in Sections 7.R.2.1 and 7.R.2.2.

7.R.2.1 IARs (including anaphylaxis)

The applicant's explanation:

In the primary analysis period of Study EFC14028, the incidence of IAR[26)] was 25.5% (13 of 51 subjects) in the avalglucosidase alfa group and 32.7% (16 of 49 subjects) in the ALGLU group, indicating that there were no substantial differences between the treatment groups. In the primary analysis period of Study ACT14132, IARs occurred in 0 of 6 subjects in the avalglucosidase alfa 20 mg/kg group and in 2 of 5 subjects in the avalglucosidase alfa 40 mg/kg group in Stage 1. Although the incidence was higher in the 40 mg/kg group, this result does not necessarily indicate a clear relationship to the dose levels because of the limited number of subjects who had IARs. In Stage 2 of Study ACT14132, the incidence of IARs was 20.0% (1 of 5 subjects) in the avalglucosidase alfa group and 16.7% (1 of 6 subjects) in the ALGLU group, showing no substantial differences between the treatment groups.

26) Adverse events that occurred during the infusion or the observation period (2 hours) following the infusion and which were considered to be related or possibly related to the study drug. Adverse events occurring after the completion of the post-infusion observation period can also be included in the assessment at the discretion of the investigator.

In the pooled data analysis of avalglucosidase alfa-treated subjects from Studies EFC14028, ACT14132, TDR12857, and LTS13769, the incidence of IARs was 34.0% (48 of 141 subjects), and the incidence was similar between the patient subgroups, i.e., pediatric versus adult patients, and treatment-naïve versus treatment-experienced patients (Table 47). The following IARs occurred more frequently: pruritus (11.3%, 16 of 141 subjects), rash (7.8%, 11 of 141 subjects), urticaria (7.1%, 10 of 141 subjects), headache (6.4%, 9 of 141 subjects), nausea (6.4%, 9 of 141 subjects), chills (5.7%, 8 of 141 subjects), and erythema (5.7%, 8 of 141 subjects). IARs led to treatment discontinuation in 1 subject in Study EFC14028 (ocular hyperaemia/erythema) and 1 subject in Study TDR12857 (dizziness/flushing/rash/cough/respiratory distress/nausea/chest discomfort); IARs led to dose reduction of avalglucosidase alfa in 2 subjects in Study EFC14028 (rash, pruritus/rash). All these events resolved with appropriate treatment.

In the primary analysis period of Study EFC14028, the incidence of anaphylaxis[27)] was 3.9% (2 of 51 subjects) in the avalglucosidase alfa group and 4.1% (2 of 49 subjects) in the ALGLU group. A serious adverse event occurred in 1 subject in the ALGLU group (dyspnoea). In the extension treatment period, anaphylaxis occurred in 4 subjects. In Study ACT14132, no anaphylaxis occurred. In the pooled analysis of data from subjects treated with avalglucosidase alfa in Studies EFC14028, ACT14132, TDR12857, and LTS13769, anaphylaxis occurred in 9 subjects, of which 3 subjects were considered to have had anaphylaxis based on the Sampson's criteria (*J Allergy Clin Immunol.* 2006;117:391-7), severity/seriousness of the event, and specific treatment given. The details of the events in the 3 subjects are as follows: the first subject (a participant in Study TDR12857), who was an ALGLU treatment-naïve patient, had respiratory distress, chest discomfort, flushing, cough, dizziness, and nausea during the infusion of avalglucosidase alfa 5 mg/kg on Day 109 (Week 16). The symptoms improved after discontinuation of avalglucosidase alfa and appropriate treatments; however, the patient was withdrawn from the study. This subject had tested negative for anti-avalglucosidase alfa antibodies at baseline, and developed anti-avalglucosidase alfa antibodies during treatment. The subject tested negative for neutralizing antibodies. The second subject (a participant in Study LTS13769), who was an ALGLU treatment-experienced patient, had erythema, palmar erythema, swollen tongue, lip swelling, breath sounds abnormal, and ventricular extrasystoles during treatment with avalglucosidase alfa 20 mg/kg on Day 351 (Week 51). The symptoms resolved after interruption of avalglucosidase alfa and appropriate treatments. On Day 373 (Week 54), this subject again had lip swelling, pruritus, palmar erythema, oxygen saturation decreased, and swollen tongue. The symptoms resolved after interruption of avalglucosidase alfa and appropriate treatments. After that, no similar events occurred when avalglucosidase alfa was administered. This subject had tested positive for anti-avalglucosidase alfa antibodies at baseline, and then had treatment-boosted anti- antibody titer [28)] during treatment with avalglucosidase alfa. This subject tested negative for neutralizing antibodies. The third subject (a participant in Study EFC14028), who was an ALGLU treatment-naïve patient, had erythema, tongue oedema, respiratory distress, nausea, dysphagia, and chest discomfort during treatment with avalglucosidase alfa 20 mg/kg on Day 665 (Week 95). The symptoms improved after discontinuation of avalglucosidase alfa and

27) Events coded to anaphylactic reaction (broad) and those coded to anaphylactic reaction (narrow) in MedDRA Standardized MedDRA query (SMQ).

28) Treatment-boosted anti-avalglucosidase alfa antibodies were defined as the case where a patient tested positive for anti-avalglucosidase alfa antibodies at baseline and the antibody titer increased by ≥4-fold during treatment.

appropriate treatments. This subject had tested positive for anti-avalglucosidase alfa antibodies at baseline, and then had treatment-boosted antibody titer during treatment with avalglucosidase alfa. This subject tested negative for neutralizing antibodies. The other 6 subjects whose IARs were not classified as anaphylaxis were in a non-serious condition. While some required treatments, all these events resolved.

In summary, although IARs and anaphylaxis occurred in some subjects treated with avalglucosidase alfa in the clinical studies, all cases were well managed by appropriate treatments and other measures. However, cautionary statements regarding IARs including anaphylaxis will be included in the package insert; in addition, data will continue to be collected in the post-marketing setting.

PMDA's view:
Analyses of the data from Studies EFC14028 and ACT14132 did not show clearly different trends between patients treated with avalglucosidase alfa and those treated with ALGLU in terms of the incidence of IARs and anaphylaxis. Given that all IARs and anaphylaxis events reported in the clinical studies were well managed by appropriate treatments and other measures, the risk for IARs and anaphylaxis is acceptable. However, patients should be carefully monitored for the risk of IARs and anaphylaxis during treatment with avalglucosidase alfa. The applicant should provide appropriate cautionary statements regarding these events in the package insert.

7.R.2.2 Impact of antibody development

The applicant's explanation:
Study EFC14028 was conducted in ALGLU treatment-naïve patients. In the avalglucosidase alfa group (n = 51), 49 subjects tested negative for anti-avalglucosidase alfa antibodies at baseline, of which 47 subjects (95.9%) became positive during treatment (primary analysis period). At baseline, 2 subjects tested positive for anti-avalglucosidase alfa antibodies, and both subjects had treatment-boosted antibody titers during treatment with avalglucosidase alfa (primary analysis period). In the ALGLU group (n = 48), 46 subjects tested negative for anti-ALGLU antibodies at baseline, of which 44 subjects (95.7%) became positive during treatment. Study ACT14132 was conducted in ALGLU-treatment-experienced patients. Of the 20 subjects with evaluable anti-avalglucosidase alfa antibody data, 17 subjects tested negative at baseline, of which 7 subjects became positive during treatment (primary analysis period). Three subjects who tested positive for anti-avalglucosidase alfa antibodies at baseline did not have treatment-boosted antibody titers during treatment with avalglucosidase alfa (primary analysis period).

According to the pooled data analysis of avalglucosidase alfa-treated subjects from Studies EFC14028, ACT14132, TDR12857, and LTS13769, 69.8% (97 of 139) of subjects in the anti-drug antibody evaluation set developed anti-avalglucosidase alfa antibodies. Table 50 shows the incidence of adverse events by anti-avalglucosidase alfa antibody status in the pooled analysis. Although a small number of subjects precludes strict interpretation, the incidence of total adverse events and that of total serious adverse events did not differ substantially between subjects who tested positive and those who tested negative for anti-avalglucosidase alfa antibodies.

Table 50. Incidence of adverse events in subjects with and without anti-avalglucosidase alfa antibodies (analysis of pooled data from Studies EFC14028, ACT14132, TDR12857, and LTS13769, anti-avalglucosidase alfa antibody evaluation set; data cut-off on July 17, 2020)

	Treatment-naïve (N = 61)		Treatment-experienced (N = 78)		Adult (N = 118)		Pediatric (N = 21)	
Anti-avalglucosidase alfa antibody status (positive vs negative)	Positive (N = 58)	Negative (N = 3)	Positive (N = 62)	Negative (N = 16)	Positive (N = 109)	Negative (N = 9)	Positive (N = 11)	Negative (N = 10)
All adverse events	96.6 (56)	100 (3)	93.5 (58)	100 (16)	94.5 (103)	100 (9)	100 (11)	100 (10)
All serious adverse events	34.5 (20)	33.3 (1)	21.0 (13)	43.8 (7)	27.5 (30)	22.2 (2)	27.3 (3)	60.0 (6)
IARs[a)]	34.5 (20)	33.3 (1)	37.1 (23)	25.0 (4)	36.7 (40)	11.1 (1)	27.3 (3)	40.0 (4)
Anaphylaxis	5.2 (3)	33.3 (1)	8.1 (5)	0 (0)	6.4 (7)	11.1 (1)	9.1 (1)	0 (0)

Incidence; % (n)
Positive: subjects who tested positive for anti-avalglucosidase alfa antibodies at one or more time points post-baseline
Negative: anti-avalglucosidase alfa antibodies were not detected at any of the time points post-baseline
a) The same definition as described in Note a) to Table 49

An analysis of the efficacy endpoints, i.e., FVC (% predicted), MIP (% predicted), MEP (% predicted), and 6MWT, by peak titer of anti-avalglucosidase alfa antibodies indicates no impact of anti-avalglucosidase alfa antibodies on efficacy (Table 51).

Table 51. Results for efficacy endpoints in ALGLU treatment-naïve patients by peak titer of anti-avalglucosidase alfa antibodies (change from baseline to Week 49[a)])

Endpoints	Negative (N = 3)	Peak titer, 100-800 (N = 14)	Peak titer, 1600-6400 (N = 29)	Peak titer ≥12800 (N = 13)
FVC (% predicted)	1.1, 4.1 (2)	3.93 ± 10.87 (13)	2.49 ± 5.89 (27)	2.77 ± 5.43 (13)
MIP (% predicted)	6.1, 21.5 (2)	12.26 ± 19.08 (13)	−9.98 ± 58.83 (26)	8.76 ± 13.88 (13)
MEP (% predicted)	−6.4, 41.8 (2)	7.84 ± 18.45 (13)	−2.36 ± 48.69 (26)	9.03 ± 11.64 (13)
6MWT (m)	−20.0, −3.0 (2)	44.07 ± 52.95 (13)	33.16 ± 60.96 (27)	34.73 ± 43.26 (12)

Mean ± standard deviation (n)
Individual values are presented for N ≤2.
a) The Study LTS13769 data used were the change from baseline to Week 52

As shown above, development of anti-avalglucosidase alfa antibodies does not appear to have an impact on the therapeutic effect of avalglucosidase alfa. While the development of anti-avalglucosidase alfa antibodies may be associated with the risk of IARs and hypersensitivity, the events reported were manageable and did not prevent continuation of treatment.

PMDA's view:

In the clinical studies conducted in and outside Japan, development of anti-avalglucosidase alfa antibodies associated with administration of avalglucosidase alfa has been reported. In the ALGLU treatment-experienced patient group, the incidence of IARs was higher in anti-avalglucosidase alfa antibodies-positive subjects than in negative subjects. However, due to the limited number of patients studied and given that the IARs reported were well managed by appropriate treatments and other measures, the currently available data do not indicate any clear safety concerns that could be caused by anti-avalglucosidase alfa antibodies. The efficacy data by peak titer so far do not indicate any particular impacts of anti-avalglucosidase alfa antibodies on the data, albeit the number of subjects studied was limited as with other analyses. However, the applicant should continuously collect the results of anti-avalglucosidase alfa antibody tests, if available, in the post-marketing setting, so as to accrue information on the impact of anti-avalglucosidase alfa antibodies on the safety and efficacy of avalglucosidase alfa.

7.R.3 Clinical positioning and indication

The applicant's explanation:

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive inherited disorder caused by gene mutations of GAA, a glycogen-degrading lysosomal enzyme. Decreased GAA activity or GAA deficiency leads to accumulation of glycogen, a substrate of GAA, in lysosomes, causing muscle weakness, cardiomyopathy, and other symptoms, which result in respiratory failure. IOPD presents in the first few months of life and is characterized by severe cardiomyopathy, systemic myopathy, and respiratory failure. Untreated patients with IOPD usually die within the first year of life. On the other hand, LOPD manifests after infancy, and is characterized by progressive decline in the strength of the skeletal and respiratory muscles. Symptoms of Pompe disease vary from patient to patient. The most common cause of death is respiratory failure.

In Japan, ALGLU, a recombinant human GAA, is available for the treatment of Pompe disease; however, it cannot completely prevent the progression of muscle weakness and respiratory dysfunction. This is likely to be attributable to the inadequate uptake of ALGLU into skeletal muscles. Avalglucosidase alfa has bis-M6P conjugated to oxidized sialic acid residues on ALGLU, thereby increasing uptake of the enzyme into cells. With the enhanced cellular uptake, avalglucosidase alfa is expected to more effectively improve the symptoms of muscle weakness and respiratory dysfunction.

In Study EFC14028 involving patients with LOPD, respiratory function was evaluated using FVC (% predicted) and other endpoints. The results showed improvement in respiratory function following treatment with avalglucosidase alfa compared to baseline, demonstrating the non-inferiority of avalglucosidase alfa to ALGLU in change from baseline to Week 49 in FVC (% predicted), the primary endpoint. Motor function, as measured by 6MWT and other parameters, also tended to improve compared to baseline. In Study ACT14132 involving patients with IOPD, the LVM Z score was normalized or remained stable in the normal range, with improvement in motor function, as measured by GMFM-88 total percent score, QMFT total score, and other parameters. In Study EFC14028 involving patients with LOPD, the trend toward improvement in clinical symptoms was greater in the avalglucosidase alfa group than in the ALGLU group for some efficacy endpoints. In Study ACT14132, patients with IOPD who had demonstrated clinical decline or a sub-optimal clinical response to ALGLU received avalglucosidase alfa, and in particular, those treated with the regimen of 40 mg/kg every other week had stable or improved clinical symptoms. In addition, the results of Studies EFC14028 and ACT14132 suggest that the safety profile of avalglucosidase alfa is not substantially different from that of ALGLU. Although no clinical studies have been conducted in patients with IOPD who had no prior treatment or in patients with IOPD whose condition has been stable on ALGLU, avalglucosidase alfa is also expected to be effective in treatment-naïve patients with IOPD and patients with IOPD whose condition has been stable on ALGLU, based on the results of the clinical studies conducted in patients with LOPD who were naïve to ALGLU or had no prior treatment, and in treatment-experienced patients with LOPD. Therefore, avalglucosidase alfa will be beneficial for treatment of a wide range of symptoms of Pompe disease. After the launch, the expectation is that avalglucosidase alfa will replace ALGLU as treatment for Pompe disease in the future.

In 2007 when ALGLU was approved, the term “glycogen storage disease type II” was widely used. Since ALGLU entered the market, “Pompe disease” has become the term more commonly used in treatment guidelines and among healthcare professionals in Japan. “Pompe disease (glycogen storage disease type II)” is therefore considered more appropriate for the indication of avalglucosidase alfa.

PMDA’s view:
The efficacy of avalglucosidase alfa was evaluated based on the data from Studies EFC14028 and ACT14132. Only a small number of patients were enrolled especially in Study ACT14132 involving patients with IOPD. Although the limited number of patients precludes strict interpretation, avalglucosidase alfa is expected to have a certain level of efficacy in the treatment of compromised respiratory and motor functions, as well as cardiac hypertrophy in both patients with LOPD and patients with IOPD. To evaluate the efficacy of avalglucosidase alfa versus ALGLU, point estimates were compared in Study EFC14028 involving patients with LOPD. The results showed that respiratory and motor function endpoints tended to indicate higher efficacy in the avalglucosidase alfa group than in the ALGLU group. In Stage 1 of Study ACT14132 involving patients with IOPD, there was a trend toward improvement in motor function endpoints, compared to baseline, following treatment with avalglucosidase alfa 40 mg/kg in subjects who had demonstrated clinical decline after treatment with ALGLU. The results in Stage 2 which included patients who had demonstrated a sub-optimal clinical response to ALGLU also suggested a trend toward higher efficacy in the avalglucosidase alfa 40 mg/kg group than in the ALGLU group [see Section “7.R.1 Efficacy”]. In addition, the safety profile of avalglucosidase alfa is similar to that of ALGLU and therefore acceptable [see Section “7.R.2 Safety”]. Based on these and other factors, it is reasonable to provide healthcare professional and patients s with access to avalglucosidase alfa as a new treatment option for Pompe disease, replacing ALGLU. Based on the recent circumstances of healthcare practice in Japan, the use of the term “Pompe disease” may be acceptable; however, a decision on the term used for the indication will be made after taking into account the comments from the Expert Discussion.

7.R.4 Dosage and administration

The applicant’s explanation about the dosage regimen for patients with LOPD:
Table 52 shows the results for key efficacy endpoints in Study TDR12857, a foreign phase I/II study in treatment-naïve or ALGLU treatment-experienced patients with LOPD. The results showed slight increases or no significant changes from baseline in FVC (% predicted) and 6MWT in both treatment-naïve patients and ALGLU treatment-experienced patients, and no clear dose-response relationship was noted across the dose levels (5 mg/kg, 10 mg/kg, and 20 mg/kg every other week). In treatment-naïve subjects, however, improvement in FVC (% predicted) and 6MWT was slightly greater in the avalglucosidase alfa 20 mg/kg group than in the other treatment groups.

Table 52. Results for key efficacy endpoints (Study TDR12857, FAS)

	Endpoint	Time point	5 mg/kg	10 mg/kg	20 mg/kg
Group 1 (treatment-naïve)	FVC (% predicted)	Baseline	57.5 [50.7, 80.0] (4)	81.1 [56.4, 109.8] (3)	53.3 [52.8, 84.0] (3)
		Change from baseline to Week 25	−0.8 [−12.3, 5.1] (3)	4.0 [−0.5, 9.3] (3)	6.1 [3.0, 9.3] (3)
	6MWT (m)	Baseline	374.5 [208.0, 507.0] (4)	510.0 [470.0, 540.0] (3)	555.0 [360.0, 593.0] (3)
		Change from baseline to Week 25	12.0 [−9.0, 33.0] (3)	−15.0 [−31.0, 0.0] (3)	25.0 [1.0, 47.0] (3)
Group 2 (treatment-experienced)	FVC (% predicted)	Baseline	72.9 [65.3, 92.0] (4)	73.3 [65.5, 117.2] (4)	70.3 [49.6, 95.1] (6)
		Change from baseline to Week 25	−2.3 [−3.3, 5.9] (4)	−2.9 [−3.5, 1.3] (4)	0.3 [−4.3, 10.1] (5)
	6MWT (m)	Baseline	350.5 [201.0, 428.0] (4)	542.5 [260.0, 591.0] (4)	482.5 [331.0, 657.0] (6)
		Change from baseline to Week 25	3.0 [−47.0, 25.0] (4)	4.0 [−4.0, 13.0] (4)	16.0 [−104.0, 56.0] (5)

Median [range] (n)

Based on the above results, the regimen of avalglucosidase alfa 20 mg/kg every other week was chosen for Study EFC14028, a global phase III study involving patients with LOPD. In Study EFC14028, the changes from baseline in the efficacy endpoints, including respiratory function and motor function, showed an improvement in subject treated with avalglucosidase alfa 20 mg/kg every other week. In addition, there was a trend toward greater improvement in subjects receiving avalglucosidase alfa 20 mg/kg every other week than in subjects receiving ALGLU 20 mg/kg every other week. The safety profile of avalglucosidase alfa 20 mg/kg every other week did not differ substantially from that of ALGLU 20 mg/kg every other week [see Section "7.1 Global phase III study"]. Based on the above analyses, the applicant considered that the recommended clinical dose of avalglucosidase alfa for patients with LOPD should be 20 mg/kg every other week.

The applicant's explanation about the dosage regimen for patients with IOPD:
Patients with IOPD have a more severe GAA deficiency than patients with LOPD. In clinical practice, patients with IOPD are treated with ALGLU at a dose higher than 20 mg/kg every other week, the approved dosage regimen of ALGLU (in some cases, the dosage of a maximum of 40 mg/kg once weekly is used). Patients with IOPD treated with ALGLU 40 mg/kg every other week presented with a higher antibody response than those treated with ALGLU 20 mg/kg every other week, and tended to have a higher incidence of IARs (*Neurology.* 2007;68:99-109, *Genet Med.* 2009;11:210-9); however, these events were manageable. Following the administration of ALGLU at a higher dose or higher dosing frequency to patients with IOPD who had a sub-optimal clinical response or clinical decline at the approved dosage regimen of ALGLU, there was improvement in gross motor function measures, pulmonary function indicators, and biochemical markers (e.g., *Genet Med.* 2020;22:898-907, *J Inherit Metab Dis.* 2020;43:1243-53). Another publication has reported that a higher dose regimen is required for patients with IOPD to match the blood concentrations of recombinant human GAA seen in adult patients (*Genet Med.* 2020;22:898-907). Based on the above ALGLU data in the clinical setting and reports, in Study ACT14132, a global phase II study in patients with IOPD who had demonstrated clinical decline or a sub-optimal clinical response to ALGLU (within the range of 20 mg/kg every other week to 40 mg/kg once weekly), avalglucosidase alfa 40 mg/kg every other week was also evaluated in addition to 20 mg/kg every other week. The results of the study showed that motor function in patients who had previously had a sub-optimal clinical response to ALGLU improved in both the avalglucosidase alfa 40 mg/kg group and the ALGLU group. The point estimates for the change in GMFM-88

were greater in the ALGLU group than in the avalglucosidase alfa group. This result may be attributable to the following factors: The patients enrolled in the ALGLU group were younger and had lower baseline scores than those enrolled in the avalglucosidase alfa group. The change from baseline to Week 25 in GMFM-88 total percent score was classified as “improved,” “unchanged,” and “worsening” with respect to a predefined minimal clinically important difference. In the avalglucosidase alfa 20 mg/kg group (n = 6), 3 subjects were classified as “improved,” 1 subject as “unchanged,” and 2 subjects as “worsening”; in the avalglucosidase alfa 40 mg/kg group (n = 9), 4 subjects were classified as “improved,” 5 subjects as “unchanged,” and 0 subjects as “worsening.” More subjects receiving avalglucosidase alfa 40 mg/kg every other week had improved or unchanged motor function, with fewer subjects with worsened motor function, compared to those receiving avalglucosidase alfa 20 mg/kg every other week. The results in subjects evaluable for 6MWT in the avalglucosidase alfa 40 mg/kg group improved while those in the avalglucosidase alfa 20 mg/kg and ALGLU groups either remained unchanged or worsened. The assessment according to the Pompe-PEDI did not indicate any particular dose-dependent trend. The results for eyelid levator muscle-related endpoints (IPFD and MRD-1) tended to improve in the avalglucosidase alfa 40 mg/kg group while those in the avalglucosidase alfa 20 mg/kg and ALGLU groups either remained unchanged or worsened.

The safety data showed that the incidence of IARs and the proportion of anti-avalglucosidase alfa antibody-positive subjects were higher in the avalglucosidase alfa 40 mg/kg group than in the 20 mg/kg group. However, none of the adverse events were classified as severe in severity, nor were any serious adverse events considered related to avalglucosidase alfa. Neutralizing antibodies were detected only in a limited number of subjects who received avalglucosidase alfa regardless of dose levels. Based on these findings, the safety profile of avalglucosidase alfa 40 mg/kg every other week was considered to be acceptable.

In patients with severe IOPD, characterized by rapid progression of musculoskeletal involvement, initiation of enzyme replacement therapy at a higher dose level is recommended at an earlier stage of the disease to prevent irreversible muscle damage in a wider area, which leads to loss of function. The clinical study of avalglucosidase alfa showed favorable efficacy in subjects treated with avalglucosidase alfa 40 mg/kg every other week than in those treated with avalglucosidase alfa 20 mg/kg, and the dosage regimen has acceptable safety. The applicant therefore considered that the recommended clinical dose of avalglucosidase alfa for patients with IOPD should be 40 mg/kg every other week.

In the clinical studies, the starting infusion rate of avalglucosidase alfa was 1 mg/kg/h, and the infusion rate was to be increased gradually up to 7 or 10 mg/kg/h. Modification of the specified infusion rate for safety reasons occurred in 31.6% of subjects in Study EFC14028 (30 of 95 subjects; for 57 out of a total of 4407 doses), and 31.8% of subjects in Study ACT14132 (7 of 22 subjects; for 21 out of a total of 1057 doses). Adverse events leading to treatment discontinuation occurred in only 3.5% (5 of 141) of all subjects who received avalglucosidase alfa. The majority of patients were able to continue treatment with avalglucosidase alfa; therefore, there would be no problems with the infusion rate specified for the clinical studies. Furthermore, in the clinical studies, 3 subjects experienced repeated hypersensitivity reactions (1 subject in Study EFC14028 and 2 subjects in Study ACT14132). Temporary dose interruption, dose reduction, or reduced infusion rate of

avalglucosidase alfa mitigated IARs, and subsequently these subjects were able to receive avalglucosidase alfa at the recommended dose level. Based on the above investigation, the package insert will include the following cautionary statements that (i) if a severe hypersensitivity reaction or anaphylaxis occurs, avalglucosidase alfa treatment should be discontinued immediately and the event should be treated appropriately; and (ii) treatment with avalglucosidase alfa may be resumed at a dose level lower than the recommended dose and at a reduced infusion rate only after assessment of the risks and benefits of retreatment with avalglucosidase alfa.

PMDA's view:

Based on the efficacy and safety data of avalglucosidase alfa in the clinical study results submitted [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"], the dosage and administration of avalglucosidase alfa for patients with LOPD can be set at 20 mg/kg every other week as an intravenous infusion, which is the same as the dosage regimen employed in Study EFC14028. On the other hand, not only the severity of GAA deficiency but also body weight may affect exposure to avalglucosidase alfa in patients with IOPD, i.e., those who have lower body weight tend to have lower exposure to avalglucosidase alfa [see Section "6.R.3 Effects of body weight on pharmacokinetics and pharmacodynamics of avalglucosidase alfa"]. Taking account of the above findings, it is reasonable that initiation of treatment with higher-dose avalglucosidase alfa at an earlier stage of IOPD is important, as discussed by the applicant. The results of Study ACT14132 in patients with IOPD showed that avalglucosidase alfa 40 mg/kg every other week as an intravenous infusion tended to be more effective than avalglucosidase alfa 20 mg/kg every other week as an intravenous infusion. In addition, the data indicate no particular safety concerns about the 40 mg/kg regimen compared to the 20 mg/kg regimen; therefore, avalglucosidase alfa 40 mg/kg every other week as an intravenous infusion may be selected as the dosage regimen for patients with IOPD. However, because of the limited number of subjects evaluated in the clinical study, especially patients with IOPD treated with avalglucosidase alfa 40 mg/kg every other week, the applicant should continue to collect data on the safety and other aspects of avalglucosidase alfa by phenotype and dose level in the post-marketing setting. Furthermore, although the infusion rate was modified in some cases for safety reasons, patients were generally able to receive infusions at the specified infusion rate, and in fact, adverse events led to the discontinuation of avalglucosidase alfa only in a limited number of patients. For these reasons, it is appropriate to provide a cautionary statement in the package insert regarding the infusion rate of avalglucosidase alfa based on that specified in the clinical studies. Given that some participants in the clinical studies underwent temporary dose interruption, dose reduction, or reduced infusion rate of avalglucosidase alfa for safety reasons, and subsequently they were able to receive avalglucosidase alfa at the recommended dose level without major safety issues; a cautionary statement may be provided to the effect that treatment with avalglucosidase alfa should be resumed at a dose level lower than the recommended dose and at a reduced infusion rate in patients who had severe hypersensitivity or anaphylaxis. At the same time, the applicant should continue to collect data on the safety of avalglucosidase alfa at the reduced dose and the safety of resuming treatment with avalglucosidase alfa at the recommended dose level in the post-marketing setting.

7.R.5 Post-marketing investigations

The applicant's explanation:

Because of the limited number of patients with Pompe disease treated with avalglucosidase alfa, the applicant has planned to conduct a specified use-results survey to evaluate the long-term safety and efficacy of avalglucosidase alfa. The observation period is from the survey enrollment to the completion of the survey (expected duration of at least 1 year to a maximum of 6 years) for each patient. Patients will be enrolled into the survey until the planned sample size (n = 50) is achieved. Safety data to be collected include hypersensitivity reactions (including anaphylaxis and IARs), impacts of the development of anti-avalglucosidase alfa antibodies on the safety and efficacy of avalglucosidase alfa, and incidence of other adverse drug reactions. Efficacy data to be collected include FVC (% predicted) and 6MWT. Based on the experience in the use results survey conducted for ALGLU, the efficacy of avalglucosidase alfa for the treatment of Pompe disease in routine clinical practice can be evaluated more accurately by utilizing a registry established by physicians specialized in Pompe disease; accordingly, a database survey will be conducted by making use of the registry. The survey will use a patient registry owned by the "Research group for development and implementation of the system for high-quality and appropriate healthcare for lysosomal storage diseases and peroxisome diseases" that is a project supported by Grant-in-Aid for Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan. Data on FVC (% predicted) and 6MWT will be collected to perform a comparison of efficacy of treatment before and after switching from ALGLU to avalglucosidase and other investigations.

PMDA's view:

Because of the limited number of patients with Pompe disease treated with avalglucosidase alfa and other reasons, the applicant should collect long-term data from as many patients as possible in the post-marketing setting, and continue to evaluate the safety and efficacy of avalglucosidase alfa by phenotype and dose level. The applicant should conduct a specified use-results survey as planned. The database survey utilizing the registry, planned by the applicant, would also be useful. The details of post-marketing surveys to be conducted will be finalized taking into account the comments from the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1 and 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including

Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that avalglucosidase alfa has efficacy in the treatment of Pompe disease, and that avalglucosidase alfa has acceptable safety in view of its benefits. Avalglucosidase alfa, which showed an increased cellular uptake compared to the existing drug, is clinically meaningful because it offers a new treatment option for patients with Pompe disease.

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

Review Report (2)

August 5, 2021

Product Submitted for Approval

Brand Name	Nexviazyme for I.V. Infusion 100 mg
Non-proprietary Name	Avalglucosidase Alfa (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	January 19, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

1.1.1 Efficacy in patients with LOPD

PMDA's view:

Study EFC14028, a global phase III study involving patients with LOPD, demonstrated the non-inferiority of avalglucosidase alfa to ALGLU in change from baseline to Week 49 in FVC (% predicted), the primary endpoint. Motor function, as measured by 6MWT and other parameters, also tended to improve compared to the baseline level. In patients who switched from ALGLU to avalglucosidase alfa in the extension treatment period, respiratory function and motor function tended to improve after the switch. Based on the above, avalglucosidase alfa is expected to be effective in patients with LOPD.

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

1.1.2 Efficacy in patients with IOPD

PMDA's view:

In the primary analysis period of Study ACT14132, a global phase II study involving patients with IOPD, there was a trend toward improvement in the motor function-related endpoints following administration of avalglucosidase alfa at 40 mg/kg in patients who had demonstrated clinical decline while on ALGLU. There was also a trend toward improvements in the motor function-related endpoints following administration of

avalglucosidase alfa at 40 mg/kg to patients who had had a sub-optimal clinical response to ALGLU. The results for each endpoint generally indicated a trend toward higher efficacy in the avalglucosidase alfa group than in the ALGLU group. Given that there is no trend toward decreasing efficacy in the extension treatment period, together with the results for cardiac function, avalglucosidase alfa is expected to be effective in patients with IOPD.

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

1.2 Safety

PMDA's view:

In light of the incidence of adverse events in the clinical studies, the safety profile of avalglucosidase alfa does not differ substantially from that of ALGLU. The safety of avalglucosidase alfa 20 mg/kg every other week in patients with LOPD and avalglucosidase alfa 40 mg/kg every other week in patients with IOPD is acceptable provided that appropriate cautionary advice is given regarding IARs including anaphylaxis as well as development of antibodies, both of which are adverse events of special interest for treatment with avalglucosidase alfa. However, because of the limited number of patients evaluated in the clinical studies, the applicant should continue to collect data on the safety and other aspects of avalglucosidase alfa in the post-marketing setting.

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

1.3 Clinical positioning and indication

PMDA's view:

The efficacy of avalglucosidase alfa was evaluated based on the data from Studies EFC14028 and ACT14132. Avalglucosidase alfa is expected to have a certain level of efficacy in the treatment of compromised respiratory and motor functions as well as cardiac hypertrophy in both patients with LOPD and patients with IOPD. Comparison of avalglucosidase alfa with ALGLU was performed in Study EFC14028 involving patients with LOPD, and the results of endpoints for respiratory function and motor function tended to indicate higher efficacy in the avalglucosidase alfa group than in the ALGLU group. In Study ACT14132 involving patients with IOPD, following administration of avalglucosidase alfa 40 mg/kg to subjects who had demonstrated clinical decline on ALGLU, there was a trend toward improvement in motor function-related endpoints compared to the baseline level. The results in patients who had demonstrated a sub-optimal clinical response to ALGLU also suggested a trend toward higher efficacy in the avalglucosidase alfa 40 mg/kg group than in the ALGLU group. In addition, the safety profile of avalglucosidase alfa is acceptable and not substantially different from that of ALGLU. Based on these and other factors, it may be reasonable to provide healthcare professionals and patients with access to avalglucosidase alfa as a new treatment option for Pompe disease, replacing ALGLU. Based on the recent circumstances of healthcare practice in Japan, the use of the term "Pompe disease" for the indication may be acceptable.

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

- The applicant should continue to collect data on the efficacy of avalglucosidase alfa versus ALGLU in routine clinical practice.
- As for the term used for the indication, this disease is classified as "muscle glycogen storage disorder" type II under the designated intractable disease classification system. While there is an option of putting "Pompe disease" side by side with "glycogen storage disease type II," which is the indication of ALGLU, the use of "Pompe disease" alone, the term used in "Practical guideline for the management of Pompe disease 2018" (Japanese Society for Inherited Metabolic Diseases), would not cause major confusion among healthcare professionals.

Based on the above, PMDA requested the applicant to modify the indication as shown below. The applicant took appropriate action.

Indication

Pompe disease

1.4 Dosage and administration

PMDA's view:

Based on the efficacy and safety data of avalglucosidase alfa in the submitted clinical study results, the dosage regimen for avalglucosidase alfa for patients with LOPD can be set at 20 mg/kg every other week as an intravenous infusion, which is the same as the dosage regimen employed in Study EFC14028. On the other hand, the severity of GAA deficiency is more severe in patients with IOPD than in patients with LOPD, and patients with IOPD who have lower body weight tend to have decreased exposure to avalglucosidase alfa. Furthermore, the results of Study ACT14132 involving patients with IOPD showed that avalglucosidase alfa 40 mg/kg every other week as an intravenous infusion is more effective than avalglucosidase alfa 20 mg/kg every other week as an intravenous infusion; additionally, the submitted data have indicated no particular safety concerns about the 40 mg/kg regimen compared to the 20 mg/kg regimen. For these reasons, avalglucosidase alfa 40 mg/kg every other week as an intravenous infusion may be selected as the dosage regimen for patients with IOPD. However, because of the limited number of subjects evaluated in the clinical study, especially patients with IOPD treated with avalglucosidase alfa 40 mg/kg every other week, the applicant should continue to collect data on the safety and other aspects of avalglucosidase alfa by phenotype and dose level in the post-marketing setting. Moreover, it is appropriate to provide a cautionary statement in the package insert regarding the infusion rate of avalglucosidase alfa based on that specified in the clinical studies. Given that some participants in the clinical studies underwent temporary dose interruption, dose reduction, or reduced infusion rate of avalglucosidase alfa for safety reasons, and subsequently they were able to receive avalglucosidase alfa at the recommended dose level without major safety issues; a cautionary statement may be provided to the effect that treatment with avalglucosidase alfa should be resumed at a dose level lower than the recommended dose and at a reduced infusion rate in patients who had severe hypersensitivity or anaphylaxis. At the same time, the applicant should continue to collect data on the safety of avalglucosidase alfa at reduced dose and the

safety of resuming treatment with avalglucosidase alfa at the recommended dose level in the post-marketing setting.

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

- Study ACT14132 was conducted in patients aged <12 years with IOPD. Given this and other factors, whether the 40 mg/kg regimen is appropriate for patients aged ≥12 years with IOPD needs to be addressed in future studies.
- The applicant plans to provide a cautionary statement to the effect that treatment with avalglucosidase alfa should be resumed at a dose level lower than the recommended dose and at a reduced infusion rate in patients who had severe hypersensitivity or anaphylaxis. It would be advisable to add specific dose levels and infusion rates at the time of resuming the treatment as a guide.

Based on the above, PMDA asked the applicant to consider providing specific dose levels and infusion rates for resuming the treatment in patients who had severe hypersensitivity or anaphylaxis. The applicant responded that it would provide such information using information materials, and PMDA accepted the response.

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion as set out in Section "7.R.5 Post-marketing investigations" in Review Report (1). PMDA has concluded that the risk management plan (draft) for avalglucosidase alfa should include the safety and efficacy specifications presented in Table 53, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and risk minimization activities presented in Tables 54 and 55.

Table 53. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction • Hypersensitivity reactions including anaphylaxis	• Immunogenicity	None
Efficacy specification		
• Efficacy in clinical practice		

Table 54. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey • Post-marketing clinical study[a)]	• Specified use-results survey • Database survey utilizing the patient registry for lysosomal storage disease/peroxisome disease	• Disseminate data gathered during early post-marketing phase vigilance

a) The ongoing Studies EFC14028 and ACT14132 will be reclassified as post-marketing clinical studies after approval granted, which will continue until avalglucosidase alfa is supplied to medical institutions.

Table 55. Outline of specified use-results survey (draft)

Objective	To assess the safety and efficacy of avalglucosidase alfa in routine clinical practice
Survey method	Central registry
Population	Patients with Pompe disease
Observation period	From the start of treatment with avalglucosidase alfa to the end of the survey period (expected duration of at least 1 year to a maximum of 6 years)
Planned sample size	50 patients
Main survey items	Patient characteristics, treatment status with avalglucosidase alfa, adverse events, hypersensitivity (including anaphylaxis, IARs), impacts of the development of anti-avalglucosidase alfa antibodies on the safety and efficacy of avalglucosidase alfa, efficacy evaluation (FVC [% predicted], 6MWT)

2. Overall Evaluation

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

Indication

Pompe disease

Dosage and Administration

For patients with late-onset Pompe disease, the usual dosage is 20 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion.

For patients with infantile-onset Pompe disease, the usual dosage is 40 mg/kg (of body weight) of avalglucosidase alfa (genetical recombination) administered every other week as an intravenous infusion.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

4-MU	4-methylumbelliferon
4-MUG	4-methylumbelliferyl-α-glucoside
6MWT	6-minute walk test
ALGLU	Alglucosidase alfa
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
AST	Aspartate aminotransferase
Avalglucosidase alfa	Avalglucosidase Alfa (Genetical Recombination)
BMI	Body mass index
CHO	Chinese hamster ovary
CIMPR	Cation-independent mannose-6-phosphate receptor
CNS	Central nervous system
CQA	Critical quality attributes
CRIM	Cross-reacting immunologic material
DPH	Diphenhydramine
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FVC	Forced vital capacity
GAA	Acid alpha-glucosidase
GAAKO	GAA knockout
GFR	Glomerular filtration rate
GMFM-88	Gross motor function measure-88
HCP	Host cell protein
HEX4	Glucose tetrasaccharide
HHD	Hand-held dynamometry
HPLC	High performance liquid chromatography
IAR	Infusion associated reaction
ICH M7 Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use M7 Guidelines: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3, dated November 10, 2015)
IOPD	Infantile-onset Pompe disease
IPFD	Interpalpebral fissure distance
K_m	Michaelis constant
LOPD	Late-onset Pompe disease
LVM	Left ventricular mass
M6P	Mannose-6-phosphate
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
mITT	Modified intent-to-treat
MRD-1	Margin reflex distance-1
Nexviazyme	Nexviazyme for I.V. Infusion
NZW	New Zealand White
PMDA	Pharmaceuticals and Medical Devices Agency
Pompe-PEDI	Pompe pediatric evaluation of disability inventory

QbD	Quality by design
QMFT	Quick motor function test
RIP	Radioimmunoprecipitation assay
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE-HPLC	Size exclusion-high performance liquid chromatography
SMQ	Standardized MedDRA query
SPR	Surface plasmon resonance
V_{max}	Maximum rate of reaction
WCB	Working cell bank