Report on the Deliberation Results

March 8, 2018

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

Brand Name	Galafold Capsules 123 mg
Non-proprietary Name	Migalastat Hydrochloride (JAN*)
Applicant	Amicus Therapeutics, Inc.
Date of Application	June 28, 2017

Results of Deliberation

In its meeting held on March 1, 2018, 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 not classified as a biological product or a specified biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, to identify the characteristics of the treated patients and to collect safety and efficacy data of the product early so as to take necessary measures for the proper use of the product.

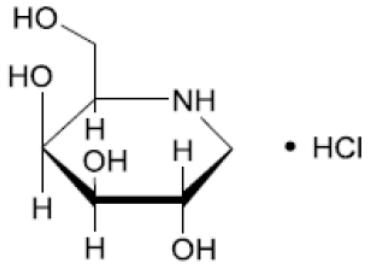
**Japanese Accepted Name (modified INN)*

Review Report

February 15, 2018
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 Galafold Capsules 123 mg
Non-proprietary Name Migalastat Hydrochloride
Applicant Amicus Therapeutics, Inc.
Date of Application June 28, 2017
Dosage Form/Strength Capsules, each containing 150 mg of migalastat hydrochloride (123 mg of migalastat).
Application Classification Prescription drug, (1) Drug with a new active ingredient
Chemical Structure



Molecular formula: $C_6H_{13}NO_4 \cdot HCl$
Molecular weight: 199.63
Chemical name: (2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl)piperidine-3,4,5-triol monohydrochloride

Items Warranting Special Mention Orphan drug (Drug Designation No. 276 [*24 yaku*], PSEHB/PED Notification No. 0414-2 dated April 14, 2017, 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 Fabry disease with migalastat-responsive *GLA* mutations, 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. The safety and the efficacy of the product in patients with renal impairment should be further evaluated.

Indication	Treatment of Fabry disease with migalastat-responsive *GLA* mutations
Dosage and Administration	The usual dosage for patients aged 16 years or older is 123 mg of migalastat orally administered once every other day. Galafold should not be taken at least 2 hours before and 2 hours after a meal.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, to identify the characteristics of the treated patients and to collect safety and efficacy data of the product early so as to take necessary measures for the proper use of the product.

Attachment

Review Report (1)

January 11, 2018

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.

Product Submitted for Approval

Brand Name	Galafold Capsules 123 mg
Non-proprietary Name	Migalastat Hydrochloride
Applicant	Amicus Therapeutics, Inc.
Date of Application	June 28, 2017
Dosage Form/Strength	Capsules, each containing 150 mg of migalastat hydrochloride (123 mg of migalastat).
Proposed Indication	Treatment of Fabry disease with migalastat-responsive *GLA* mutations
Proposed Dosage and Administration	The usual dosage for patients aged 16 years or older is 123 mg of migalastat orally administered once every other day at the same time of day. Galafold should be taken in a fasting state, and food should not be consumed at least 2 hours before and 2 hours after taking Galafold.

Table of Contents

List of Abbreviations

See Appendix.

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

Migalastat, developed by Amicus Therapeutics in the U.S., is an analog of the terminal galactose of glycosphingolipid (e.g., globotriaosylceramide [GL-3]) which is a substrate of alpha-galactosidase A (α-Gal A). Migalastat is a pharmacological chaperone that is designed to bind to the mutant forms of α-Gal A. After binding to α-Gal A, migalastat facilitates the transport of α-Gal A to lysosomes and increase α-Gal A activity in lysosomes.

Fabry disease is an X-chromosome linked genetic disease and is associated with reduced α-Gal A activity due to mutations in *GLA* gene encoding α-Gal A which degrades the glycosphingolipids such as GL-3. The accumulation of substrates such as GL-3 in the lysosomes leads to tissue disorders including neurogenic pain, skin symptoms, ophthalmic symptoms, gastrointestinal symptoms, lung symptoms, renal disorders, cardiomyopathy, and cerebrovascular diseases. Fabry disease can be divided into classic and late-onset phenotypes. Classic Fabry disease occurs mainly in men, and patients with the classic phenotype have non-detectable or very low α-Gal A activity and present with renal, cardiac, and cerebrovascular diseases at early stages (*The Metabolic and Molecular Bases of Inherited Disease 8th edition*. New York; 2001:3733-74). The late-onset phenotype of Fabry disease develops mainly in men with a high residual α-Gal A activity and heterozygous women, and the initial symptoms usually appear in adulthood. The prevalence of Fabry disease is reported to be one per 40,000 to 117,000 persons (*The Metabolic and Molecular Bases of Inherited Disease 8th edition*. New York. 2001:3733-74; *JAMA*. 1999;281: 249-54). In Japan, 315 to 1061 patients have a diagnosis of Fabry disease and receive enzyme replacement therapy (ERT).[1)] Currently, agalsidase beta and agalsidase alfa, products for ERT intravenously administered every 2 weeks, are approved for treatment of Fabry disease: approval was granted for agalsidase beta in January 2004 and for agalsidase alfa in October 2006.

The applicant applied for marketing authorization for the product, claiming that the efficacy and safety of the product have been confirmed in studies including global phase III study.

Outside Japan, the product was first approved in Europe in May 2016 and has gained approval in 36 countries as of December 2017. In the U.S., a new-drug application for the product was submitted in December 2017.

The product was designated as an orphan drug with the proposed indication of treatment of Fabry disease (Drug Designation No. 276 [*24 yaku*], PSEHB/PED Notification No. 0414-2, dated April 14, 2017).

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

2.1 Drug substance

2.1.1 Characterization

1) An epidemiological study of patients with Fabry disease with clinical research personal data sheets (Tuboi K. *Journal of Transportation Medicine*. 2010:64) reported that a total of 315 patients were identified to have Fabry disease between 2003 and 2008, and a total of 1061 certificates for recipients of specific disease treatment were issued for patients with lysosomal storage diseases including Fabry disease as of March 31, 2015 (Japan Intractable Diseases Information Center, Number of Recipient Certificates Issued for Specific Disease Treatment).

The drug substance is a white to pale brown crystalline powder. The properties of the drug substance have been determined, including description, solubility, hygroscopicity, ultraviolet-visible absorption spectrum, specific optical rotation, pH, melting point, dissociation constant, partition coefficient, and particle size distribution.

The chemical structure of the drug substance has been elucidated by single crystal X-ray crystallography, hydrogen and carbon nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C- nuclear magnetic resonance spectrum [NMR]), mass analysis, infrared spectrophotometry (IR), and elemental analysis.

2.1.2 Manufacturing process

The drug substance is synthesized from Substance A as the starting material.

A Quality by Design (QbD) approach was applied to identify [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] ([redacted],[2] [redacted],[3] [redacted],[4] [redacted],[5] and [redacted],[6]) [redacted] ([redacted] and [redacted]), [redacted], and [redacted] as critical quality attributes (CQAs). Based on the quality risk assessment and design of experiments, critical process parameters (CPPs) have been identified, and the control strategy has been examined.

The [redacted] and [redacted] steps are defined as critical steps. [redacted] is controlled as a critical intermediate.

2.1.3 Control of drug substance

The specification for the drug substance consists of content, description, identification (IR, HPLC [high performance liquid chromatography], and chloride), purity (heavy metals [ICP-MS (inductively coupled plasma-mass spectrometry)], palladium [ICP-MS], related substances [HPLC], residual solvents [gas chromatography]), water content, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

Main stability studies performed on the drug product are shown in Table 1. Stability test results demonstrated that the drug substance was stable to light.

Table 1. Stability studies of the drug product

Studies	Reference batches	Temperature	Humidity	Storage form	Storage period
Long-term storage testing	3 production batches [a)]	30°C	65% RH	Low-density polyethylene bag + a polyethylene drum	60 months
	3 production batches [b)]				36 months [c)]
Accelerated testing	3 production batches [a)]	40°C	75% RH		6 months
	3 production batches [b)]				6 months

a) Manufacturing Method A, which was used to manufacture the study drug for phase III studies.
b) Proposed manufacturing method. Changes from the Manufacturing Method A were made to the [redacted] in the [redacted] process and the [redacted] in the [redacted] process. The equivalence of the quality of the drug substance before and after the changes has been verified.
c) The testing was scheduled to be continued for up to 60 months.

2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]
6) [redacted]

Based on the above results, a [redacted]-month re-test period was established for the drug substance when stored in a low-density polyethylene bag placed in a polyethylene drum at room temperature.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is presented as immediate-release hard capsules containing 150 mg of the drug substance (123 mg of migalastat). The drug product contains partially pregelatinized starch and magnesium stearate as excipients.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], encapsulation, and packaging. The [redacted] and [redacted] steps are specified as critical steps. Process controls and action limits have been established for the [redacted] step.

A QbD approach was applied to identify [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as CQAs. Based on the quality risk assessment and design of experiments, CPPs have been identified, and the control strategy has been examined.

2.2.3 Control of drug product

The specification for the drug substance consists of content, description, identification (IR and HPLC), uniformity of dosage units (mass variation test), dissolution (HPLC), microbial limits, and assay (HPLC).

2.2.4 Stability of drug product

Main stability studies of the drug product are shown in Table 2. Stability test results demonstrated that the drug product was stable to light.

Table 2. Stability studies of the drug product

Studies	Reference batches	Temperature	Humidity	Storage form	Storage period
Long-term storage testing	3 production batches	25°C	60% RH	PTP	48 months
Accelerated testing	3 production batches	40°C	75% RH		6 months

Based on the above results, a shelf-life of 48 months was established for the drug product when stored in a press through packaging (PTP) sheet (multilayer films composed of [redacted] and [redacted]/[redacted]-coated aluminum foil) at room temperature.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the review shown below, PMDA concluded that the quality of the drug substance and the drug product have been generally appropriately controlled. The final decision on the quality will be provided in the Review Report (2) in consideration of issues discussed in the section "2.R.1 Control of diastereomers."

2.R.1 Control of diastereomers

The applicant's explanation about the control of diastereomers:

The drug substance contains 4 chiral centers. However, since the starting material is Substance A, which occurs naturally, the appropriate spatial arrangement of the drug substance has been ensured by controlling the optical rotation of the starting material. The optical rotation remained constant in the drug substance batches used in the phase III studies and stability studies, and no changes due to storage were seen. The possibility of epimerization during the manufacturing process for the drug substance was evaluated. Since epimerization is unlikely to occur at 2 or more chiral centers, 4 epimers were deemed to be the potential impurities. The amount of the 4 epimers in crude crystals of migalastat hydrochloride manufactured at commercial scale were measured by NMR and were found to be undetectable for all batches. Among the 4 epimers, C-023988[7)] is converted from C-023987[8)] which is produced in the synthesis process of the intermediates, and therefore the amount of C-02398 in the intermediates is subject to control. As shown above, the control of the optical rotation and the diastereomer impurity amount has not been established.

PMDA has requested the applicant to explain the details of the control strategies to assure that the 4 epimers are constitutively undetectable in the drug substance, including the appropriateness of the control method for the stereoisomers in the starting materials and the adequateness of the control level for C-023987 in the intermediates. The details will be provided in the Review Report (2).

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

In primary pharmacodynamic studies, the investigated were the mechanism of action *in vitro* and the activating action on α-Gal A and the substrate reduction activity *in vivo* in normal animals and animal models of Fabry disease. In secondary pharmacodynamic studies, the effects on various enzymes and receptors were investigated. In safety pharmacology studies, the effects on central nervous, cardiovascular, and respiratory systems were investigated. In pharmacodynamic drug interaction studies, the interaction of migalastat with agalsidase beta and agalsidase alfa was investigated. In this section, the doses and concentrations are expressed as those for the unbound drug. Main study results are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity of migalastat to recombinant human α-Gal A and endogenous (CTD 4.2.1.1.1)

The inhibitory effect of migalastat on α-Gal A was investigated with agalsidase beta and agalsidase alfa spiked with a synthetic fluorescent substrate. The values of dissociation constant for binding of inhibitor to enzyme (Ki) (mean ± standard deviation) were 27.5 ± 7.4 nmol/L (pH4.6), 10.6 ± 0.4 nmol/L (pH5.2), and 16.1 ± 1.0 nmol/L (pH7.0) for agalsidase beta and 10.9 ± 0.6 nmol/L (pH5.2) and 16.5 ± 1.8 nmol/L (pH7.0) for agalsidase alfa.

7) [redacted]
8) [redacted]

The inhibitory effect of migalastat on the endogenous α-Gal A was investigated with crude lysates of 2 human lymphoblast cell lines spiked with a synthetic fluorescent substrate. The IC_{50} value (mean [95% confidence interval (CI)]) was 83 [67, 101] and 93 [81, 107] nmol/L (pH4.6).

3.1.1.2 Effects of migalastat on denaturation of protein of recombinant human α-Gal A (CTD 4.2.1.1.1)

The effects of migalastat on the thermal stability of recombinant human α-Gal A (rhα-Gal A) were investigated with agalsidase beta and agalsidase alfa. The temperature midpoint (Tm) of agalsidase beta and agalsidase alfa under the condition of pH 5.2 was 58°C and 58°C, respectively, in the absence of migalastat and 68°C and 68°C, respectively, in the presence of migalastat 10 μmol/L. The Tm of agalsidase beta and agalsidase alfa under the condition of pH 7.4 was 47°C and 51°C, respectively, in the absence of migalastat and 58°C and 60°C, respectively, in the presence of migalastat 100 μmol/L.

After incubation of agalsidase beta under the conditions of temperature 37°C and pH 7.4, protein denaturation progressed over time with a half-life time of approximately 9 hours for normal protein, whereas protein was stable up to 24 hours later in the presence of migalastat 10 μmol/L or under the condition of pH 5.2.

After incubation of agalsidase beta with human whole blood at 37°C, α-Gal A activity decreased over time with a half-life time of approximately 2 hours, whereas the half-life time was approximately 8 hours in the presence of migalastat.

3.1.1.3 Binding affinity of migalastat to α-Gal A in various animal species (CTD 4.2.1.1.2)

Liver extracts of mice, rats, rabbits, monkeys, and humans were spiked with a synthetic fluorescent substrate (pH 4.6) and were used to investigate the inhibitory effect of migalastat on α-Gal A. The Ki value (mean [95% CI]) for the animal species was 10.6 [9.8, 11.6], 7.7 [7.2, 8.2], 9.4 [8.7, 10.1], 11.4 [10.6, 12.4], and 11.3 [10.0, 12.1] nmol/L, respectively. A similar study was performed for kidney extracts of mice and showed a Ki value of 9.3 [8.4, 10.2] nmol/L.

3.1.1.4 Binding affinity of migalastat to wild-type and mutant forms of α-Gal A (CTD 4.2.1.1.3)

Crude lysates of lymphoblasts obtained from healthy adults and men with Fabry disease were spiked with a synthetic fluorescent substrate and were used to investigate the inhibitory effect of migalastat on wild-type and 26 mutant forms of α-Gal A.[9)] The Ki value for wild-type and mutant forms of α-Gal A was 21 nmol/L and 19 to 254 nmol/L, respectively.

3.1.1.5 Effects of migalastat on wild-type and mutant α-Gal A activity (CTD 4.2.1.1.7 to 8)

Lymphoblasts were obtained from healthy adults and men with Fabry disease and were incubated for 5 days in the presence and absence of migalastat, and the α-Gal A activity was investigated. A concentration-dependent increase in α-Gal A activity was observed in the wild-type form and 49 of 77 mutant forms, and the EC_{50} value (mean) was 0.6 to 1.2 μmol/L for the wild-type and 820 nmol/L to 5510 μmol/L for mutant forms.

9) Except for some cells from persons with wild type or mutant forms of α-Gal A with a sufficiently high α-Gal A activity at baseline, the lymphoblast cells evaluated for the inhibitory effect of migalastat were preincubated for 3 days in the presence of migalastat, and then, α-Gal A activity at baseline was increased after a washout period.

The E_{max} of migalastat on the α-Gal A activity of 49 mutant forms with increased α-Gal A activity elevated to 1.5 to 28 times that in the absence of migalastat and was 1.8% to 140% of E_{max} for the wild-type form. In the remaining mutant forms, the α-Gal A activity was undetectable at baseline, or the α-Gal A activity was not increased by treatment with migalastat. The α-Gal A activity of 77 mutant forms in the absence of migalastat was 0% to 52% of the wild-type α-Gal A activity. In the wild-type α-Gal A and 4 of 49 mutant forms of α-Gal A with increased α-Gal A activity, the western blotting showed increases in the intracellular α-Gal A protein, which was consistent with the increases in the α-Gal A activity. In a further study, the α-Gal A activity was evaluated in a similar manner by using fibroblasts obtained from men with Fabry disease with any of the 4 mutant forms of α-Gal A, and results were obtained similar to those observed for lymphoblasts with the same mutations.

The α-Gal A activity was investigated for genotypes reported to be associated with the classic form and the late-onset form, and the EC_{50} value (mean ± standard error) for the α-Gal A activity was 800 ± 300, 22 ± 15, and 1.9 ± 0.3 μmol/L in the classic, late-onset, and wild-type forms, respectively. The classic, late-onset, and wild-type α-Gal A activity was 0.7 ± 0.2, 4.3 ± 1, and 30 ± 1 nmol/mg protein/h, respectively, in the absence of migalastat and 4.8 ± 1.2, 19 ± 3, and 45 ± 2 nmol/mg protein/h, respectively, in the presence of migalastat, and significant increases were observed in the presence of migalastat as compared with data obtained in the absence of migalastat (7.3 ± 1.1, 7.1 ± 1.3, and 1.5 ± 0.3 times higher than that in the absence of migalastat, respectively). The α-Gal A activity was similarly investigated for the genotype reported to be associated with the cardiac variant phenotype. The α-Gal A activity increased in the presence of migalastat, the EC_{50} value was 0.63 ± 0.3 μmol/L, and the E_{max} was 1.6 ± 0.2 higher than that in the absence of migalastat. The mutant α-Gal A activity of the cardiac variant phenotype in the absence of migalastat was 18% ± 4% of wild-type α-Gal A activity. Similar evaluation was performed for the nonsense mutations resulting in classic form of the disease, and the α-Gal A activity was unmeasurable in the absence of migalastat, and no increase in α-Gal A activity was observed in the presence of migalastat.

The α-Gal A activity was investigated in human embryonic kidney (HEK) -293 cells expressing wild-type and 531 mutant forms of α-Gal A which were incubated for 4 to 5 days in the presence of migalastat. Significant increases in the α-Gal A activity were observed for 316 mutant forms of α-Gal A with EC_{50} values of 0.29 to 2685 μmol/L as compared with that in the absence of migalastat.

3.1.1.6 Sustenance of wild-type and mutant α-Gal A activity after removal of migalastat (CTD 4.2.1.1.4)

Lymphoblasts were obtained from healthy adults and men with Fabry disease and were incubated for 5 days in the presence of migalastat (100 μmol/L), and the α-Gal A activity up to 96 hours after removal of migalastat was investigated with the cells. The half-life time of the wild-type α-Gal A activity (defined as the time to reach 50% of the α-Gal A activity at 0 hour after removal of migalastat) was 110 to 120 hours, which were generally longer than those observed for the mutant α-Gal A activity: among 17 mutant forms of α-Gal A, the half-life time was 10 to 17 hours for 15 mutant forms and 120 to 150 hours for the remaining 2 mutant forms.

3.1.1.7 Substrate reduction activity in fibroblasts obtained from patients with Fabry disease (CTD 4.2.1.1.5)

The effects of migalastat on intracellular GL-3 concentrations were investigated with fibroblasts obtained from healthy adults and men with Fabry disease (3 mutant forms of α-Gal A; amino-acid substitution of R301Q, L300P, and C52S). The intracellular GL-3 concentration in the R301Q, L300P, and C52S cells was 5.3 ± 0.6, 4.9 ± 0.6, and 7.5 ± 1.0 times the GL-3 concentration of normal blast cells, respectively. After incubation of the mutant cells in the presence of migalastat (0 to 1000 μmol/L) for 7 days and then for 3 days in the absence of migalastat, the GL-3 concentrations decreased in a manner dependent on the concentration of migalastat in the R301Q and L300P mutant cells, but no effects of migalastat were observed for the C52S mutant cells. The mutant cells were incubated for 10 days in the presence of migalastat (0 to 1000 μmol/L), and no effects of migalastat were observed for any type of the mutant cells.

3.1.1.8 Half-life time of substrates in normal human fibroblasts (CTD 4.2.1.1.6)

Fibroblasts obtained from healthy adults were incubated for 7 days in the presence of migalastat (0, 300, 1000, and 3000 μmol/L) and were then used to investigate the intercellular GL-3 concentrations up to 0 to 48 hours after the removal of migalastat. In the migalastat arm, the intracellular GL-3 concentration elevated at 0 hour after the removal of migalastat as compared with the control arm. The intracellular GL-3 concentration reached the maximum at 1 hour after the removal, and then decreased to a level similar to that observed in the control arm by 48 hours after the removal. The half-life time of the intracellular GL-3 concentrations (defined as the time from the maximum α-Gal A activity to 50% of the maximum α-Gal A activity) was 2.1, 3.1, and 5.6 hours for migalastat at 300, 1000, and 3000 μmol/L, respectively.

Fibroblast cell lines obtained from healthy adults were incubated in the presence of migalastat (0, 300, 1000, and 3000 μmol/L) for 5 days and then in the presence of migalastat and agalsidase beta (100 nmol/L) for 2 days and were used to investigate the intracellular GL-3 concentrations at 0 to 48 hours after the removal of migalastat. The intracellular GL-3 concentration reached the maximum by 30 min after the removal of migalastat and then decreased to a level generally comparable to that observed in the control group by 48 hours after the removal. The half-life time of the intracellular GL-3 concentrations was 2.7, 3.0, and 3.6 hours for migalastat at 300, 1000, and 3000 μmol/L, respectively.

3.1.2 *In vivo* studies

3.1.2.1 Effects of migalastat on α-Gal A activity in tissues of normal animals (CTD 4.2.1.1.9)

Migalastat (1, 10, or 100 mg/kg/day) or a vehicle[10)] was administered to male mice (8 weeks old, 7 animals per group at each time point) for 28 days through voluntary water intake, and in the control group and the migalastat 100 mg/kg/day group, a vehicle [10)] was additionally administered for another 14 days through voluntary water intake. The activities of α-Gal A, acid α-glucosidase, and acid β-glucosidase in tissues were measured 28 days after administration and 1, 3, 5, 7, and 14 days after the discontinuation. The α-Gal A activity in the heart, kidney, skin, liver, spleen, and brain increased dose-dependently 28 days after the treatment. The α-Gal A activity in the heart, kidney, and liver significantly increased in the migalastat

10) Water.

≥10 mg/kg/day groups, and the α-Gal A activity in the skin, spleen, and brain significantly increased in the migalastat 100 mg/kg/day group, as compared with the control group. In the migalastat 100 mg/kg/day group, the α-Gal A activity in the heart and kidney was significantly higher than that in the control group up to 7 days after discontinuation, and the α-Gal A activity in the skin was significantly higher than that in the control group. In the migalastat 100 mg/kg/day group, the half-life time of α-Gal A activity in the heart, kidney, and skin was 2.7, 3.3, and 4.0 days, respectively. No effects on the activities of tissue acid α-glucosidase or acid β-glucosidase were observed.

3.1.2.2 Effects of migalastat on tissue α-Gal A activity and substrate concentrations in *Gla* KO mice and hR301Q α-Gal A transgenic/KO mice (CTD 4.2.1.1.10 to 12)

GL-3 concentrations in tissues were investigated in male *Gla* knockout (KO) mice lacking the endogenous mouse α-Gal-A gene (7 animals at each time point) and male hR301Q α-Gal A transgenic (Tg)/KO mice lacking the endogenous mouse α-Gal-A gene and expressing human R301Q mutant α-Gal A transgene (7 animals at each time point) at the age of 4, 12, 24, and 48 weeks. In both mouse models, the GL-3 concentrations in the skin, heart, and kidney increased with advancing age, showing no significant differences at any time points between the mouse models. Immunohistochemical examinations revealed an accumulation of GL-3 in the skin fibroblasts, smooth muscle cells in the vessel wall of the skin and heart, and epithelial cells of the distal tubule of the renal cortex.

Migalastat (3, 10, 30, 100, or 300 mg/kg/day) or a vehicle [10)] was administered to the male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 to 21 animals per group) for 4 weeks via voluntary water intake, and the α-Gal A activity and GL-3 concentrations in tissues were investigated.[11)] The α-Gal A activity and GL-3 concentrations were investigated also in wild-type mice (12 weeks old, 7 animals) in a similar manner. In the skin, heart, and kidney, the α-Gal A activity increased dose-dependently, and GL-3 concentrations decreased 4 weeks after the treatment. In comparison with the control group, 4 weeks after treatment, a significant increase in the α-Gal A activity in the skin and heart was observed in the migalastat ≥3 mg/kg/day groups, and a significant increase in the α-Gal A activity in the kidney was observed in the migalastat ≥10 mg/kg/day groups. The α-Gal A activity in the skin in the migalastat 30 mg/kg/day group increased to the level comparable to that observed in wild-type mice, and the α-Gal A activity in the heart in the migalastat 10 mg/kg/day group increased to the level comparable to that observed in wild-type mice. Even in the migalastat 300 mg/kg/day group, the α-Gal A activity in the kidney was about 40% of that in wild-type mice. The western blotting showed a dose-dependent increase in α-Gal A proteins in tissues. In comparison with the control group, the GL-3 concentrations at 4 weeks after treatment significantly decreased in the skin in the migalastat ≥30 mg/kg/day groups, in the heart in the migalastat ≥3 mg/kg/day groups, and in the kidney in the migalastat ≥10 mg/kg/day groups. The GL-3 concentration at 4 weeks after treatment in the migalastat 300 mg/kg/day was higher in all organs than those observed in wild-type mice. Immunohistochemical examinations performed for the migalastat 100 and 300 mg/kg/day groups showed decreases in GL-3 in the skin fibroblasts,

11) Data from 3 independent studies in which migalastat was administered to male hR301Q α-Gal A Tg/KO mice for 4 weeks through voluntary water intake were combined and evaluated.

smooth muscle cells in the vessel wall of the skin and heart, and epithelial cells of the distal tubule of the kidney.

Migalastat (30 mg/kg/day) or a vehicle [10)] was administered by gavage once daily for 28 days to male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 animals per group). The α-Gal A activity in the skin, heart, and kidney increased to 6 ± 1.0 (mean ± standard error), 25 ± 5.0, and 8 ± 1.0 times that observed in the control group, respectively, and the GL-3 concentrations in the skin, heart, and kidney decreased to 71% ± 4%, 52% ± 7%, and 30% ± 7% of that observed in the control group, respectively, showing similar results to those seen with migalastat 30 mg/kg/day administered through voluntary water intake.

Migalastat (100 mg/kg/day) or a vehicle [10)] was administered to male *Gla* KO mice (8 weeks old, 7 animals per group) through voluntary water intake for 4 weeks, and α-Gal A activity and GL-3 concentrations in the plasma, heart, kidney, and skin were investigated. No effects of treatment with migalastat were observed on these parameters.

3.1.2.3 Effects on α-Gal A activity in tissues of hR301Q α-Gal A Tg/KO mice after discontinuation (CTD 4.2.1.1.13)

Migalastat (100 mg/kg/day) or a vehicle [10)] was administered to male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 animals per group at each time point) for 28 days through voluntary water intake, followed by 7-day administration of a vehicle [10)] through voluntary water intake. The α-Gal A activity in tissues was evaluated 28 days after the administration and 1, 3, 5, and 7 days after the discontinuation. The α-Gal A activity in the skin, heart, and kidney significantly increased 28 days after treatment, as compared with the control group. The α-Gal A activity was higher at 1 day after discontinuation than that at 28 days after treatment in all tissues. A time-dependent decrease was observed in α-Gal A activity beginning 1 day after discontinuation, but the α-Gal A activity was significantly higher in the migalastat group than in the control group until 7 days after discontinuation. The half-life time 1 day after discontinuation in the skin, heart, and kidney was 2.4, 2.2, and 2.0 days, respectively. The migalastat concentration (mean ± standard deviation) in the skin, heart, and kidney at 28 days after treatment was 1.8 ± 0.2, 1.1 ± 0.2, and 7.5 ± 1.8 μmol/L, respectively. One day after discontinuation, the migalastat concentrations in these organs decreased to ≤10% of those at 28 days after treatment and were below the limit of quantification at 5 days after discontinuation onward.

3.1.2.4 Effects of dosing frequency on GL-3 concentrations in tissues of hR301Q α-Gal A Tg/KO mice (CTD 4.2.1.1.14)

Migalastat (300 mg/kg/day) was administered to male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 animals per group) through voluntary water intake for 4 weeks with a daily dosing schedule (Group 1, the daily dosing group) or with a schedule of a week cycle of 4 days on and 3 days off (Group 2, the intermittent dosing group). A vehicle [10)] was administered for 4 weeks through voluntary water intake. The rate of decrease in GL-3 concentrations in the skin, heart, kidney, and plasma relative to that in the control group (mean ± standard error) was 64% ± 6%, 72% ± 4%, 26% ± 6%, and 41% ± 8%, respectively, in the Group 1 (the daily dosing group) and 82% ± 2%, 87% ± 3%, 46% ± 7%, and 66% ± 5%, respectively, in the Group 2 (the

intermittent dosing group), showing significantly higher decreases in the GL-3 concentrations in the skin, heart, and plasma in the intermittent group than those in the daily dosing group.

Migalastat (100 or 300 mg/kg/day) was administered to male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 animals per group) through voluntary water intake for 4 weeks with the following dosing schedule: 1) daily administration; 2) a week cycle of 2 days on and 5 days off; 3) a week cycle of 3 days on and 4 days off; and 4) a week cycle of 4 days on and 3 days off. A vehicle [10)] was administered for 4 weeks through voluntary water intake. The GL-3 concentrations in the skin, heart, kidney, and plasma tended to decrease in the intermittent dosing groups (the Groups 2 to 4) as compared with those observed in the daily dosing group.

Migalastat (300 mg/kg/day) was administered to male hR301Q α-Gal A Tg/KO mice (12 weeks old, 7 animals per group) through voluntary water intake for 4 weeks with the following dosing schedule: 1) a week cycle of 4 days on and 3 days off; 2) a week cycle of 1 day on and 6 days off; and 3) a week cycle of 2 days (Monday and Thursday) on and 5 days (Tuesday, Wednesday, Friday, Saturday, and Sunday); 4) a 2-week cycle of 1 day on and 13 days off. A vehicle [10)] was administered for 4 weeks through voluntary water intake. In comparison of the migalastat groups with the control group, a significant decrease in the tissue GL-3 concentrations was observed for the skin in the Group 1 (4 days on and 3 days off) and Group 3 (2 days on and 5 days off), for heart in the Group 1 (4 days on and 3 days off) and Group 2 (1 day on and 6 days off), and for plasma in all migalastat groups. The decrease in GL-3 concentrations was largest in the Group 1 (4 days on and 3 days off) for all tissues. No significant effect of administration of migalastat was observed for the kidney.

Migalastat (300 mg/kg/day) was administered to male hR301Q α-Gal A Tg/KO mice (8 weeks old, 7 animals per group) through voluntary water intake or by gavage for 4 weeks with the following dosing schedule: 1) daily administration; 2) alternate-day administration; and 3) a week cycle of 4 days on and 3 days off. A vehicle [10)] was administered by gavage once daily for 4 weeks. The GL-3 concentrations in the skin, kidney, and plasma significantly decreased in all migalastat groups as compared with the control group, and there were no differences due to the difference in administration methods (voluntary water intake versus gavage). With regard to the dosing interval, the GL-3 concentrations tended to decrease more in Group 2 (alternate-day administration) and Group 3 (4 days on and 3 days off) than in Group 1 (daily administration).

3.1.2.5 Effects of long-term administration of migalastat on GL-3 concentrations in tissues of young and mature Fabry disease model mice (CTD 4.2.1.1.15)

Migalastat (10, 30, or 100 mg/kg/day) or a vehicle [10)] was administered to male hR301Q α-Gal A Tg/KO mice (4 weeks older, 8 animals per group) for 24 weeks through voluntary water intake, and GL-3 concentrations in the tissues and plasma were evaluated. The GL-3 concentrations decreased dose-dependently in the skin, heart, kidney, and plasma. In comparison with the control group, the GL-3 concentrations significantly decreased in the skin, heart, and plasma in the migalastat ≥10 mg/kg/day groups and in the kidney in the migalastat ≥30 mg/kg/day groups. Immunohistochemical examinations showed a significant decrease in the number of cells stained for GL-3 in the glomeruli in the migalastat 30 and 100 mg/kg/day groups, as compared with the control group.

Migalastat (10, 30, 100, or 300 mg/kg/day) was administered to male hR301Q α-Gal A Tg/KO mice (24 weeks old, 7 animals per group at each time point) through voluntary water intake for 12 or 24 weeks with a daily dosing schedule (Group 1) or with a schedule of a week cycle of 4 days on and 3 days off (Group 2), and GL-3 concentrations in the tissues and plasma were evaluated. The GL-3 concentrations in the skin, heart, kidney, and plasma decreased generally dose-dependently at 12 and 24 weeks postdose. The α-Gal A activity and GL-3 concentration in the brain were evaluated at 12 weeks postdose. In comparison with the control group, a significant increase in α-Gal A activity was observed in all migalastat groups, and a significant decrease in GL-3 concentrations was seen in the Group 2 (the intermittent dosing group).

3.2 Secondary pharmacodynamics

3.2.1 Inhibitory effects of migalastat on enzymes and receptors (CTD 4.2.1.1.1, 4.2.1.2.1 to 4.2.1.2.2 [reference data])

The inhibitory effect of migalastat (10 μmol/L) on 9 lysosomal hydrolases[12)] was investigated with crude lysates of normal human fibroblast cell line spiked with a synthetic fluorescent substrate (pH 4.6). The experiments showed 63% ± 1.4% inhibition of α-N-acetylgalactosaminidase (NAGA) and 25% ± 2.4% inhibition of beta-galactosidase, but no inhibition was observed for other lysosomal hydrolases. The IC_{50} value (mean [95% CI]) for NAGA was 6.94 [6.38, 7.56] μmol/L, which was approximately 120 times that for α-Gal A (57.7 [55.4, 60.0] nmol/L).

The inhibitory effect of migalastat (10 μmol/L) on 83 enzymes and receptors was investigated, and no inhibition ≥50% was observed.

The inhibitory effect of migalastat (0 to 100 μmol/L) on 3 enzymes involved in galactose metabolism[13)] was investigated, and no inhibition ≥50% was observed.

3.2.2 Effects of migalastat on human fibroblasts and hepatocytes (CTD 4.2.1.2.3)

The effects of migalastat (0 to 1 mmol/L) on proliferation of normal human fibroblasts and hepatocytes were investigated, and no significant cytotoxicity was identified.

12) Acid α-glucosidase, acid β-glucosidase, β-galactosidase, α-mannosidase, β-mannosidase, α-N-acetylgalactosaminidase, β-N-acetylgalactosaminidase, β-glucuronidase, and α-L-fructosidase.

13) Galactokinase, galactose-1-phosphate uridylic transferase, and UDP-galactose-4-epimerase.

3.3 Safety pharmacology

Table 3. Summary of safety pharmacology studies

Items	Test system	Endpoints, methods, etc.	Dose	Route of administration	Findings	CTD
Central nervous system	SD rats (6 male rats per group)	Irwin method	0, 3, 30, 100 mg/kg	PO	No effects observed	4.2.1.3.1
Cardiovascular system	Beagle dogs (3 dogs per sex per group)	Blood pressure, heart rate, body temperature, electrocardiography (without anesthesia)	0, 3, 30, 100 mg/kg	PO	No effects observed	4.2.1.3.3
	CHO-K1 cells (5 specimens)	hERG current	0, 0.00475, 0.0475, 0.475, 4.75, 47.5 μmol/L	*in vitro*	No effects observed	4.2.1.3.2
Respiratory system	SD rats (8 male rats per group)	Respiratory rate, tidal volume, minute ventilation, inspiratory time, expiratory time, maximal expiratory flow, maximal inspiratory flow, relaxation time and PenH [a)]	0, 3, 30, 100 mg/kg	PO	No effects observed	4.2.1.3.4

PO, orally administered.
a) Enhanced pause: an index for bronchoconstriction.

3.4 Pharmacodynamic drug interactions

3.4.1 *In vitro* studies (CTD 4.2.1.4.2)

Fibroblasts obtained from men with Fabry disease (amino-acid substitution, C52S) was incubated for 5 hours in the presence of migalastat (0.1, 1.0, and 10 μmol/L) and agalsidase beta (0.24 nmol/L) or agalsidase alfa (0.5 nmol/L) and then were incubated for a further 2 days. The intracellular α-Gal A activity significantly increased in the presence of migalastat and the rhα-Gal A as compared with that in the presence of rhα-Gal A alone (2.7 to 4.0 times that in the presence of rhα-Gal A alone). The EC_{50} value (mean ± standard error) for α-Gal A activity was 13.7 ± 2.7 nmol/L in the presence of agalsidase beta and 4.7±0.4 nmol/L in the presence of agalsidase beta and migalastat (100 μmol/L) and 16.7±1.2 nmol/L in the presence of agalsidase alfa alone and 7.5±1.0 nmol/L in the presence of agalsidase alfa and migalastat (100 μmol/L). Similarly, the fibroblasts were incubated for 5 hours in the presence of migalastat (0.1, 1.0, and 10 μmol/L) and agalsidase beta (0.24 nmol/L) or agalsidase alfa (0.5 nmol/L) and then were incubated for a further 10 days. The intracellular GL-3 concentrations significantly decreased in the presence of migalastat and the rhα-Gal A as compared with that in the presence of rhα-Gal A alone: in comparison with untreated control cells, intracellular GL-3 concentrations were lower by 18% in the fibroblasts incubated in the presence of agalsidase beta alone, 40% to 48% in those incubated in the presence of agalsidase beta and migalastat, 14% in those incubated in the presence of agalsidase alfa alone, and 29% to 37% in those incubated in the presence of agalsidase alfa and migalastat. The EC_{50} value for GL-3 concentrations was 0.47 ± 0.16 nmol/L in the presence of agalsidase beta alone, 0.14±0.07 nmol/L in the presence of agalsidase beta and migalastat, 0.73 ± 0.14 nmol/L in the presence of agalsidase alfa alone, and 0.29 ± 0.12 nmol/L in the presence of agalsidase alfa and migalastat.

3.4.2 *In vivo* studies

3.4.2.1 Combined use with agalsidase beta (CTD 4.2.1.4.3, 4.2.1.4.5, 4.2.1.4.7)

A single dose of migalastat (3 mg/kg) or a vehicle[10)] was administered by gavage to male rats (8 weeks old, 3 animals per group), and 30 minutes later, a single dose of agalsidase beta (10 mg/kg) was intravenously administered. Plasma α-Gal A activity was evaluated up to 24 hours after the administration. The half-life time

of α-Gal A activity was approximately 24 and 63 minutes in rats receiving agalsidase beta alone and rats receiving agalsidase beta and migalastat, respectively.

Migalastat (3, 10, or 30 mg/kg) or a vehicle[10)] was administered by gavage to male *Gla* KO mice (12 weeks old, 5 animals per group), and 30 minutes later, a single dose of agalsidase beta (1 mg/kg) was intravenously administered. In comparison with mice receiving agalsidase beta alone, a significant increase in the plasma α-Gal A activity was observed at 1, 2, and 4 hours after treatment in mice receiving agalsidase beta and migalastat. The α-Gal A activity in the skin, heart, and kidney decreased over time 1, 3, and 7 days after treatment and higher at all time points in the mice receiving agalsidase beta and migalastat than in mice receiving agalsidase beta alone. The GL-3 concentration in the skin, heart, kidney, and plasma 7 days after treatment tended to be lower in mice receiving agalsidase beta and migalastat than in mice receiving agalsidase beta alone.

Migalastat (3 or 30 mg/kg) or a vehicle[10)] was administered by gavage three times a week for 4 weeks to male *Gla* KO mice (12 weeks old, 8 animals per group at each time point), and agalsidase beta (1 mg/kg) or a vehicle[14)] was intravenously administered once a week, 30 minutes after the administration of migalastat.[15)] The GL-3 concentration in the skin, heart, and kidney 7 days after the last dosing tended to be lower in mice receiving migalastat and agalsidase beta than in mice receiving agalsidase beta alone. However, no further increase in α-Gal A activity was observed in mice receiving migalastat and agalsidase beta as compared with mice receiving agalsidase beta alone.

3.4.2.2 Combined use with agalsidase alfa (CTD 4.2.1.4.3 to 5)

A single dose of migalastat (1, 3, 10, or 30 mg/kg) or a vehicle[10)] was administered by gavage to male rats (8 weeks old, 3 animals per group), and 30 minutes later, a single dose of agalsidase alfa (0.2 mg/kg) was intravenously administered. Plasma α-Gal A activity was evaluated up to 48 hours after the administration. The half-life time of α-Gal A activity was approximately 11 minutes in rats receiving agalsidase alfa. In rats receiving migalastat and agalsidase alfa, the half-life time of α-Gal A activity was prolonged in proportion to the dose of migalastat and was approximately 33 minutes in rats receiving agalsidase alfa and migalastat 30 mg/kg.

Migalastat (1, 3, or 10 mg/kg) or a vehicle[10)] was administered by gavage once a week for 4 weeks to male *Gla* KO mice (12 weeks old, 6 animals per group), and 30 minutes after the administration of migalastat, agalsidase alfa (0.2, 1, or 2 mg/kg) or a vehicle[14)] was intravenously administered[16)]. The plasma α-Gal A activity at 1, 2, 3, and 4 hours after treatment increased in a proportion to the dose of agalsidase alfa in mice receiving agalsidase alfa alone and further increased in a proportion to the dose of migalastat in mice receiving agalsidase alfa and migalastat. The α-Gal A activity in the skin, heart, and kidney 7 days after the last dosing tended to

14) Physiological saline

15) Death or moribund sacrifice occurred in 1 of 24 mice in the 0/0 mg/kg group (migalastat dose/agalsidase beta dose), 2 of 24 mice in the 0/1 mg/kg group, 1 of 24 mice in the 3/1 mg/kg group, and 2 of 24 mice in the 30/1 mg/kg group.

16) Death occurred 1 of 6 mice in the 0/1 mg/kg group (migalastat dose/agalsidase alfa dose), 2 of 6 mice in the 0/2 mg/kg group, 1 of 6 mice in the 1/1 mg/kg group, 3 of 6 mice in the 1/2 mg/kg group, 1 of 6 mice in the 3/1 mg/kg group, and 2 of 6 mice in the 3/2 mg/kg group.

be higher in mice receiving agalsidase alfa and migalastat than in mice receiving agalsidase alfa alone. The GL-3 and Globotriaosylsphingosine (lyso-Gb_3) concentrations tended to be lower in mice receiving agalsidase alfa and migalastat than in mice receiving agalsidase alfa alone.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of migalastat

The applicant's explanation:

Fabry disease is caused by mutations in the *GLA* gene encoding α-Gal A, a lysosomal enzyme which is required for glycosphingolipid metabolism. Mutations in the *GLA* gene result in a deficiency of α-Gal A or reduction in α-Gal A activity and then, in turn, lead to an accumulation of substrates such as GL-3 and lyso-Gb_3 in the lysosomes. More than 900 mutations of *GLA* gene have been identified as the cause of Fabry disease, and approximately 60% of the mutations are missense mutations resulting in single amino acid substitutions (*Oxford PharmaGenesis*. 2006; Chapter 33, *Genet Med*. 2017;19: 430-8). Some mutant forms of α-Gal A, such as a missense mutation, though having enzyme activity, are physically unstable due to their abnormal protein conformation, and with inefficient trafficking to lysosomes, are degraded and excreted rapidly (*Nat Med*. 1999;5:112-5; *Biochem J*. 2007;406:285-95).

Migalastat, a low molecular weight iminosugar, is an analog of the terminal galactose of GL-3, a substrate of α-Gal A. Migalastat inhibits α-Gal A activity by binding to the active site of α-Gal A. Migalastat also shows resistance to the denaturation and inactivation of protein depending on pH, time, and temperature of α-Gal A and acts as a pharmacological chaperone which facilitate the proper trafficking from endoplasmic reticula to lysosomes through stabilization of the protein structure (CTD 4.2.1.1.1). Migalastat reversibly and selectively binds to wild-type α-Gal A and specific mutant forms of α-Gal A and dissociates from α-Gal A after α-Gal A is transported to lysosomes. The released enzyme binds to the substrates deposited in the lysosomes and exerts its activity. *In vitro* and *in vivo* studies demonstrated that migalastat increased α-Gal A activity and reduced substrates in wild-type α-Gal A and some mutant forms of α-Gal A (CTD 4.2.1.1.5, 4.2.1.1.7 to 8, 4.2.1.1.11, and 4.2.1.1.15). As compared with α-Gal A mutations such as frameshift mutations, truncations, insertions, and deletions that can profoundly affect the enzyme structure or function, the mutant form of α-Gal A with a single base substitution, for instance, a missense mutation, can bind to migalastat and is considered to be highly amenable to migalastat. As discussed above, there are genotypes having and not having activation of α-Gal A and reduction in substrates by migalastat (CTD 4.2.1.1.3, 4.2.1.1.5, and 4.2.1.1.7 to 8). Eligible patients should be selected after it is determined whether or not their genotypes are amenable to migalastat. The washout period for migalastat was found to play an important role in the reduction of substrates based on the following findings: that the enzyme activity of α-Gal A persisted after discontinuation of migalastat (CTD 4.2.1.1.4); that substrate reduction activity was observed after discontinuation (CTD 4.2.1.1.5); the half-life of the increased enzyme activity of α-Gal A was longer than the half-life of migalastat in tissues (CTD 4.2.1.1.13); and that intermittent dosing with lower dosing frequency than the daily dosing resulted in a greater decline in GL-3 concentrations in tissues in studies in Fabry disease model mice (CTD 4.2.1.1.14). This is consistent with the theoretical pharmacological effects that trafficking of migalastat-bound α-Gal A to lysosomes is facilitated in the presence

of high-level migalastat and that after elimination of migalastat, dissociation of migalastat allows α-Gal A to exert its enzyme activity, showing the substrate reduction activity.

As shown the above, it is suggested that migalastat, which is administered intermittently, selectively binds to some mutant forms of α-Gal A and was trafficked to lysosomes, and the dissociation of migalastat in lysosomes restores the α-Gal A activity and leads to the reduction in the accumulated substrates.

Effects of migalastat on enzymes other than α-Gal A: When administered at concentrations comparable to the plasma C_{max} in humans receiving migalastat at a clinically recommended dose, migalastat showed its inhibitory effect on NAGA, but its binding affinity to NAGA in crude lysates of normal fibroblasts and human liver extracts was approximately 1/160 to 1/120 of the binding affinity to α-Gal A (CTD 4.2.1.1.1 to 2). The homology of amino acid sequence for NAGA between mice, rats, and monkeys and humans is approximately 90%, 90%, and 98%, respectively, showing a similar binding affinity of migalastat to NAGA between rats and human (the Ki value was 8 and 7 μmol/L, respectively). In non-clinical toxicity studies in mice, rats, and monkeys, migalastat administered at doses sufficient to inhibit NAGA activity in tissues did not induce general symptoms suggestive of effects on central nervous system and did not cause pathological tissue changes in the peripheral or central nervous system, such as local axonal swelling, spheroids, and lamellar structures reported in NAGA KO mice (CTD 4.2.3.2.1, 4.2.3.2.4, and 4.2.3.2.8; *The Metabolic and Molecular Bases of Inherited Disease 8th edition*. New York; 2001. 3483-505). Schindler's disease, a disease caused by the deficiency of human NAGA gene, is characterized by the nearly complete loss of NAGA activity and an accumulation of glycolipids and is known to cause neurodegeneration and psychomotor disorders (e.g., myoclonic seizure, cortical blindness, spasms, abnormal posturing, mental retardation, peripheral nerve axonal degeneration, and angiokeratoma corporis diffusum universale) (*J Biol Chem*. 2010;285:21560-6). In the phase III studies of migalastat, however, no relevant adverse events occurred. Accordingly, the inhibitory effect of migalastat on NAGA is considered to be unlikely to cause clinically significant safety concerns.

PMDA accepted the applicant's explanation [for the appropriateness of target patient population and the dosage and administration for humans, see Sections "7.R.4 Indications" and "7.R.5 Dosage and administration."].

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

Pharmacokinetics was studied after a single dose of migalastat or ^{14}C-migalastat was intravenously or orally administered to mice and rats. Pharmacokinetics after repeated oral doses of migalastat was investigated based on toxicokinetics (TK) observed in toxicity studies in mice, rats, rabbits, and monkeys. Concentrations of unchanged migalastat in plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 2.5 ng/mL, 50.0 ng/mL, or 10.0 μg/mL[17)] for mice, 29.5 ng/mL for rats, 40.0 ng/mL for rabbits, and 50.0 ng/mL for monkeys. Concentrations of unchanged migalastat in milk in rats were determined by an LC-MS/MS method with a lower limit of quantification of 29.4 ng/mL. Radioactivity in biospecimens was measured by using liquid scintillation counter,

17) The lower limit of quantification was 2.5 ng/mL in a single-dose study (CTD 4.2.2.2.4), 10.0 μg/mL in a 28-day repeated dose study (CTD 4.2.3.2.1), 50.0 ng/mL in a 26-week repeated dose study (CTD 4.2.3.4.1.1), and 2.5 ng/mL in tissue distribution studies (CTD 4.2.2.2.3).

radio HPLC, and microplate counter methods. The doses and concentrations of migalastat and ^{14}C-migalastat are expressed as those for the unbound drug. Main study results are described below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.4)

The pharmacokinetic parameters of plasma unchanged migalastat after a single oral or intravenous dose of migalastat to male mice are shown in Table 4.

Table 4. Pharmacokinetic parameters of plasma unchanged migalastat after a single dose of migalastat

Route of administration	Dose (mg/kg)	Number of animals at each time point	C_{max} (µg/mL)	$AUC_{0\text{-last}}$ (µg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL_{tot} (L/h/kg)	V_{ss} (L/kg)	BA (%)
Intravenous administration	1	4	2.1	0.6	0.08	–	1.72	0.36	–
	3	4	4.0	1.2	0.08	0.9	2.49	0.76	–
	10	4	20.4	5.8	0.08	0.8	1.72	0.38	–
Oral administration	3	4	2.8	1.5	0.25	1.3	–	–	120
	10	4	6.8	4.5	0.25	–	–	–	78
	30	4	8.4	8.1	0.25	1.8	–	–	47[a)]
	100	4	23.5	23.6	0.25	1.6	–	–	41[a)]

Mean. –, not calculated.

C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurement time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL_{tot}, clearance; V_{ss}, volume of distribution at steady state; BA, bioavailability.

a) BA for 30 and 100 mg/kg was calculated based on dose-adjusted data obtained for migalastat 10 mg/kg administered intravenously.

4.1.2 Repeated-dose studies (CTD 4.2.3.2.8, 4.2.3.4.1.2, 4.2.3.5.2.3)

Table 5 shows the pharmacokinetic parameters of unchanged migalastat in plasma after repeated oral doses of migalastat to male and female rats, pregnant rabbits, and male and female monkeys.

Table 5. Pharmacokinetic parameters of plasma unchanged migalastat after repeated doses of migalastat

Animal species	Dose [a] (mg/kg/day)	Number of animals	Time point	C_{max} (μg/mL)[c]		$AUC_{0\text{-last}}$ (μg·h/mL)	
				Male	Female	Male	Female
Rats	41	3 [b]	Initial dosing	4.4	8.3	11.6	12.4
		3 or 6 [b]	Week 29 of treatment	4.7	7.0	12.6	14.9
	164	3 [b]	Initial dosing	10.3	14.7	32.7	34.6
		3 or 6 [b]	Week 29 of treatment	10.0	14.6	29.5	37.1
	656	3 [b]	Initial dosing	14.0	27.5	89.4	101.4
		3 or 6 [b]	Week 29 of treatment	16.9	26.6	89.5	117.2
Pregnant rabbits	98	3	Initial dosing	−	27.3 ± 10.7	−	191.0 ± 52.3
		3	Day 14 of treatment	−	39.2 ± 4.6	−	335.0 ± 122.4
	246	3	Initial dosing	−	50.1 ± 8.7	−	405.2 ± 10.1
		3	Day 14 of treatment	−	78.2 ± 18.1	−	1101.2 ± 349.6
	615	2	Initial dosing	−	103.0, 121.0	−	1008.8, 1217.2
		2	Day 14 of treatment	−	116.0, 140.0	−	1574.0, 2351.3
Monkeys	41	9	Initial dosing	10.1 ± 1.7	11.5 ± 2.3	54.5 ± 7.3	70.6 ± 18.6
		4	Week 39 of treatment	5.8 ± 1.4	9.3 ± 4.8	67.7 ± 11.8	76.0 ± 26.3
	164	9	Initial dosing	29.6 ± 9.1	30.6 ± 8.9	171.2 ± 28.6	192.4 ± 52.5
		4	Week 39 of treatment	20.4 ± 4.3	19.8 ± 4.1	173.4 ± 28.5	196.0 ± 35.9
	410	11	Initial dosing	48.2 ± 16.4	51.6 ± 20.9	318.5 ± 63.7	299.2 ± 65.0
		6	Week 39 of treatment	22.8 ± 5.2	26.1 ± 8.0	314.6 ± 94.3	297.0 ± 82.0

Mean or mean ± standard deviation (individual values are shown when n = 2). −, not applicable.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurement time point.
a) Administered twice daily. b) Number of animals at each time point. c) For rats and pregnant rabbits, the C_{max} is the higher of plasma unchanged migalastat concentration after the initial or second dosing of migalastat administered twice daily for rats and pregnant rabbits. For monkeys, the C_{max} is the maximum plasma unchanged migalastat concentration after the initial dosing of migalastat administered twice daily.

4.2 Distribution (CTD 4.2.2.2.3, 4.2.2.3.1 to 2, 4.2.3.5.3.1)

A single dose of migalastat 100 mg/kg was orally administered to male mice (24 animals in total, 3 animals at each time point), and the concentrations of unchanged migalastat were measured up to 24 hours postdose. The unchanged migalastat concentrations reached the maximum 0.5 hours postdose in the kidney, skin, and heart and 8 hours postdose in the brain. The ratio (mean ± standard error) of the maximum unchanged migalastat concentration in the kidney, skin, heart, and brain to the plasma unchanged migalastat concentration at the corresponding time point was 5.60 ± 0.64, 0.46 ± 0.02, 0.24 ± 0.00, and 8.78 ± 1.62, respectively. The radioactivity concentrations decreased over time, and the elimination half-life in the kidney, skin, heart, and brain was estimated to be 2.3, 3.8, 3.6, and >8 hours, respectively.

Migalastat 100 mg/kg/day was administered to male mice (40 animals in total, 5 animals at each time point) for 7 days through voluntary water intake. After completion of the repeated dosing, concentrations of unchanged migalastat were measured in a 24-hour light-dark cycle (light phase, 0 to 12 hours postdose; dark phase, 12 to 24 hours postdose). The unchanged migalastat concentrations in all tissues reached the maximum at 16 hours postdose in the dark phase, which corresponds to the active phase of mice. The ratio (mean ± standard error) of the unchanged migalastat concentration in the kidney, heart, skin, and brain to the plasma unchanged migalastat concentration at that time was 2.06 ± 0.08, 0.37 ± 0.04, 0.32 ± 0.03, and 0.15 ± 0.22, respectively.

A single dose of ^{14}C-migalastat 41 mg/kg was orally administered to male rats (18 animals in total, 3 animals at each time point), and the radioactivity concentrations were measured up to 72 hours postdose. The radioactivity concentrations in the kidney, liver, skin, spleen, heart, and muscle reached the maximum at 1 hour postdose, and the radioactivity concentration in the brain reached the maximum at 4 hours postdose. The ratio (mean ± standard error) of the maximum radioactivity concentrations in the kidney, liver, skin, spleen, heart, muscle, and brain to the plasma radioactivity at the corresponding time point was 7.72 ± 2.11, 2.61 ± 0.45, 0.54 ± 0.04, 0.32 ± 0.09, 0.27 ± 0.04, 0.20 ± 0.01, and 0.86 ± 0.11, respectively. The radioactivity concentrations decreased over time and were below the lower limit of quantification at 24 hours postdose in all tissues except for the kidney and liver. The radioactivity concentrations became undetectable at 72 hours postdose in the kidney and liver.

Migalastat were repeatedly orally administered at 41, 164, and 820 mg/kg/day, divided into 2 doses, to pregnant rats (day 6 of pregnancy to day 20 postpartum, 3 animals at each time point). The ratio of the plasma unchanged migalastat concentrations on day 20 of pregnancy in the dams and fetuses exposed to migalastat 41, 164, and 820 mg/kg/day, was 0.06, 0.09, and 0.11, respectively, at 1 hour postdose, and 0.85, 0.31, and 0.18, respectively, at 4 hours postdose.

The mean plasma protein non-binding rate of ^{14}C-migalastat (1 to 100 μmol/L), as determined by an equilibrium dialysis method, was 101% to 122% in mice, 91.9% to 114% in rats, and 88.3% to 105% in monkeys.

4.3 Metabolism (CTD 4.2.2.3.2, 4.2.2.4.1)

A single dose of ^{14}C-migalastat 41 mg/kg was orally administered to male rats (3 animals at each time point), and the mean percentage of unchanged migalastat in plasma up to 12 hours postdose to the $AUC_{0\text{-}12h}$ of total radioactivity concentration was 82.6%. Main 12 peaks of radioactivity other than that of unchanged migalastat were observed, and the percentage of them in plasma to the $AUC_{0\text{-}12h}$ of total radioactivity concentration ranged 0.35% to 2.98%.

A single dose of ^{14}C-migalastat 41 mg/kg was orally administered to male and female rats (4 animals per sex), and the mean percentage of unchanged migalastat excreted in urine up to 24 hours postdose to the administered radioactivity was 21.9% in male rats and 22.8% in female rats. Main 6 and 5 radioactivity peaks other than that for unchanged migalastat were observed for male and female rats, respectively, and the percentage of them in urine to the administered radioactivity was 0.06% to 1.81% in male rats and 0.08% to 1.05% in female rats. The percentage of unchanged migalastat excreted in feces up to 48 hours postdose to the administered radioactivity was 51.8% in male rats, and 46.7% in female rats. Main 4 and 3 radioactivity peaks other than that for unchanged migalastat were observed for male and female rats, respectively, and the percentage of them in feces to the administered radioactivity was 0.11% to 4.25% in male rats and 0.25% to 4.03% in female rats.

Frozen liver cells of rats and monkeys were used to evaluate the metabolism of ^{14}C-migalastat 1 and 100 μmol/L. The residual percentage of ^{14}C-migalastat 1 and 100 μmol/L after 4-hour incubation (100% before incubation) was 104% and 102%, respectively, in rats and 101% and 107%, respectively, in monkeys, and no metabolites of migalastat were identified.

4.4 Excretion (CTD 4.2.2.3.2, 4.2.2.5.1, 4.2.3.5.3.1)

A single dose of ^{14}C-migalastat 41 mg/kg was orally administered to male and female rats (4 animals per sex). The cumulative excretion in urine and feces up to 168 hours postdose to the administered radioactivity was 32.61% ± 9.86% and 61.77% ± 10.14%, respectively, in male rats and 29.04% ± 5.56% and 60.82% ± 13.20%, respectively, in female rats.

A single dose of ^{14}C-migalastat 1230 mg/kg was orally administered to male and female rats (1 animal per sex). The cumulative excretion in urine, feces, and expired air up to 24 hours postdose to the administered radioactivity was 23.8%, 50.9%, and 0.10%, respectively, in male rats and 17.5%, 67.4%, and 0.14%, respectively, in female rats.

Migalastat were repeatedly orally administered at 41, 164, and 820 mg/kg/day, divided into 2 doses, to pregnant rats (day 6 of pregnancy to day 20 postpartum, 3 animals at each time point). The ratio of the unchanged migalastat concentration in milk to that in plasma on the 15th day of breastfeeding in the dams exposed to migalastat 41, 164, and 820 mg/kg/day, was 1.13, 0.88, and 0.63, respectively, at 1 hour postdose, and 8.10, 2.56, and 2.46, respectively, at 4 hours postdose.

4.R Outline of the review conducted by PMDA

4.R.1 Effects of migalastat on cerebral accumulation

In tissue distribution studies in male mice and male rats, a transfer to the brain of migalastat or 14C-migalastat was observed, and the elimination from the brain was slower than those in other tissues. In light of the findings, PMDA asked the applicant to discuss the possibility that repeated dosing of migalastat might result in accumulation in the brain or that the transfer to the brain might have any clinically significant effects.

The applicant's explanation:

In the tissue distribution studies in male mice (CTD 4.2.2.2.3), migalastat transferred to the brain more slowly than to other tissues, and the migalastat concentration in the brain reached the peak at 8 hours postdose. The elimination half-life was estimated to be >8 hours, and migalastat was eliminated more slowly in the brain than in other tissues. However, the maximum migalastat concentration in the brain was relatively low, and the total exposure in the brain (AUC0-24h) was approximately 41%, 28%, 28%, and 4% of that in the heart, plasma, skin, and kidney, respectively. The migalastat concentrations in the brain were low over time. The results obtained from the tissue distribution studies in male mice suggest that the cerebral transfer of migalastat is unlikely to produce clinically significant effects. Also, in tissue distribution studies in which ^{14}C-migalastat was administered to male rats (CTD 4.2.2.3.2), radioactivity was detected in the brain, but the radioactivity concentrations were below the lower limit of quantification at 24 and 72 hours postdose, suggesting that

alternate-day dosing of migalastat may not cause the accumulation of migalastat in the brain. In safety pharmacology studies or repeated-dose toxicity studies related to the central nervous system, there were no events possibly related to the transfer of migalastat to the brain.

Safety in humans: Among adverse events in the central nerve system (adverse events classified under the System Organ Class (SOC) of "Nervous system disorders" or "Psychiatric disorders"), the incidence of adverse drug reactions was as follows: 22% (8 of 36 patients) in the migalastat group and 0% (none of 21 patients) in the ERT group in the global phase III study conducted in patients with Fabry disease who were receiving ERT (Study AT1001-01, with an 18-month treatment period); and 12.1% (4 of 33 patients) in the placebo group and 17.6% (6 of 34 patients) in the migalastat group in the foreign phase III study conducted in ERT-naïve patients with Fabry disease (Study AT1001-011, with a 6-month treatment period). The incidence of adverse drug reactions was higher in the migalastat group than in the control group in both studies. Among adverse drug reactions observed in both studies, headache was the most frequently observed adverse drug reaction, followed by dizziness and paresthesia. However, no serious adverse events or adverse events leading to treatment discontinuation occurred, and headache, the most frequently observed adverse event, was mild or moderate in severity in all patients and was well tolerated. In a long-term use studies (a 30-month treatment period in Study AT1001-01 and a 24-month treatment period in Study AT1001-011), a patient in Study AT1001-011 presented with a serious adverse drug reaction (paresthesia) but did not require discontinuation of treatment with migalastat, and there was no tendency toward increases in the incidence of these adverse events, indicating that the transfer of migalastat to the brain is unlikely to have clinically significant effects.

As discussed above, results from the non-clinical studies indicate that migalastat is unlikely to accumulate in the brain and demonstrated that migalastat concentrations remained low in the brain, and no adverse events related to the cerebral transfer of migalastat were reported from data of the safety pharmacology studies and non-clinical toxicity studies. In view of these findings, together with the state of occurrence of adverse events related to the central nervous system in clinical studies, it is considered that treatment with migalastat is unlikely to produce any clinically significant effects.

PMDA accepted the applicant's explanation that data from the non-clinical and clinical studies demonstrated that the transfer of migalastat to the brain would be unlikely to cause any clinically significant effects.

5. Toxicity and Outline of the Review Conducted by PMDA

Single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and phototoxicity testing were conducted for migalastat. Data from some studies conducted as non-GLP studies were submitted as reference data. In this section, the doses and concentrations are expressed as those for the unbound drug.

5.1 Single-dose toxicity (CTD 4.2.3.1.1 to 2)

A single dose of migalastat 1230 mg/kg was orally administered to male and female SD (Sprague-Dawley) rats. No deaths occurred, and no changes in the general conditions or body weights in association with migalastat were observed. The approximate lethal dose was determined to be >1230 mg/kg.

A single dose of migalastat 410 mg/kg was orally administered to male and female beagle dogs. No deaths occurred, and no changes in the general conditions or body weights in association with migalastat were observed. An analysis of the test material revealed that the used test material contained 36.8% sodium chloride and that the actually administered dose was 259 mg/kg. Based on the findings, the approximate lethal dose was determined to be >259 mg/kg.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice for up to 4 weeks, in rats for up to 26 weeks, in beagle dogs for up to 2 weeks, and in cynomolgus monkeys for up to 39 weeks. No consistent toxicity was noted for the target organs. The observed toxicity included mucosal inflammation of the large intestine in mice, soft stools and increased lymphoid follicle of the spleen in rats, but no changes suggestive of toxicity were observed in beagle dogs or cynomolgus monkeys.

5.2.1 Four-week repeated-dose toxicity study in mice (CTD 4.2.3.2.1)

Migalastat 0,[18)] 500, 1000, or 2000 mg/kg/day was orally administered once daily for 4 weeks to male and female CByB6F1 mice to find the dose range for a carcinogenicity study in genetically-modified mice. Acute diffuse mucosal inflammation of the large intestine (cecum, colon, and rectum) in the ≥1000 mg/kg/day groups (male rats in the 1000 mg/kg/day group) and thickening of the cecum and increased apoptosis of the mesenteric lymph node in the 2000 mg/kg/day were observed. These changes in the large intestine was attributed to the local irritation of migalastat.

Based on the above findings, the no-observed-adverse-effect level (NOAEL) was determined to be 500 mg/kg/day for female mice and 1000 mg/kg/day for male mice.

5.2.2 Two-week oral repeated-dose toxicity and 2-week recovery study in rats (CTD 4.2.3.2.3)

Migalastat 0,[19)] 82, 410, or 1230 mg/kg was orally administered once daily for 2 weeks to male and female Sprague-Dawley (SD) rats. A 2-week recovery period was also included in the 0 and 1230 mg/kg/day groups to evaluate the recovery. Increased urine chloride, eosinophil infiltration in the glandular stomach, and edema at the junction of the glandular stomach and forestomach were observed. These changes in the stomach were attributed to the local irritation of migalastat. All changes were reversible at the end of the recovery period.

Based on the above findings, the NOAEL was determined to be 410 mg/kg/day.

[18)] Deionized water.
[19)] Purified water.

5.2.3 Twenty-six-week oral repeated-dose toxicity and 8-week recovery study in rats (CTD 4.2.3.2.4)

Migalastat 0,[20] 41, 205, or 615 mg/kg was orally administered twice daily (0, 82, 410, or 1230 mg/kg/day) for 26 weeks to male and female SD rats. An 8-week recovery period was included in the 0 and 1230 mg/kg/day groups to evaluate the recovery. During the treatment period, a male rat and a female rat in the 1230 mg/kg/day group died due to administration error, and a female rat in the 1230 mg/kg/day group presented with swelling of the right hind limb and was then necropsied. In the female rat, a fracture of the tibia was found at necropsy. In the surviving rats, (slightly or mildly) increased lymphoid follicle of the spleen was observed in ≥82 mg/kg/day groups, and soft stools, acidified urine, and increased spleen weight were observed in the 1230 mg/kg/day group. No histopathological changes in the kidneys were identified in rats with acidified urine, and therefore, the urine acidification was considered to have no toxicological significance. While changes in the spleen were observed in ≥82 mg/kg/day groups ($AUC_{0\text{-}t}$ after administration at 82 mg/kg/day, 30,147 ng·h/mL) in this study, no changes in spleen were observed in the 2-year carcinogenicity study in rats ($AUC_{0\text{-}t}$ after administration at 656 or 984 mg/kg/day, 176,000 ng·h/mL) or the 39-week oral repeated-dose toxicity study in cynomolgus monkeys ($AUC_{0\text{-}t}$ after administration at 410 mg/kg/day, 305,823 ng·h/mL). Therefore, the changes in the spleen observed in this study was not considered to represent any toxicity findings. At the end of the recovery period, changes in the spleen were recovering, and other changes were reversible.

Based on the above findings, the NOAEL was determined to be 410 mg/kg/day.

The exposure ($AUC_{0\text{-}t}$) on Day 181 of administration of migalastat at the NOAEL (410 mg/kg/day) was 96,659 ng·h/mL, which was 21.4 times the exposure after the administration at the clinically recommended dose.[21]

5.2.4 Two-week oral repeated-dose toxicity study in dogs (CTD 4.2.3.2.6)

Migalastat 0,[19] 41, 164, or 410 mg/kg was orally administered once daily for 2 weeks to male and female beagle dogs. Changes in stools (e.g., dark or pale stools and/or liquid feces) and increased urine chloride and potassium concentrations were observed in the 410 mg/kg/day group. Since no changes in organ weights, necropsy, or histopathological examinations were identified, the increases in urine chloride and potassium concentrations were considered to have no toxicological significance.

Based on the above findings, the NOAEL was determined to be 164 mg/kg/day.

5.2.5 Two-week oral repeated-dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2.7)

Migalastat 0,[20] 20.5, 82, or 205 mg/kg was orally administered twice daily (0, 41, 164, or 410 mg/kg/day) for 2 weeks to male and female cynomolgus monkeys. Red blood cells decreased in ≥41 mg/kg/day groups, and the decrease was more marked in these groups than the 164 and 410 mg/kg/day groups. Foamy histiocytes in

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20) Water for injection.

21) $AUC_{0\text{-}48h}$ value (9033 ng·h/mL) estimated on the basis of the population pharmacokinetic analysis on the concentrations of plasma unchanged migalastat after administration of migalastat 150 mg every other day in the foreign phase III study in non-Japanese patients with Fabry disease (CTD 5.3.5.1.2).

the lymph node adjacent to the duodenum and dilatation of the chyle vessels in the duodenum were identified in male monkeys in the 410 mg/kg/day group. The decrease in red blood cells was considered unlikely to be related to migalastat and was regarded toxicologically insignificant based on the following findings: that repeated blood collection was suspected to be responsible for the decrease; that changes in red blood cell counts were small; and no similar findings were seen in the 39-week oral repeated-dose toxicity study in monkeys in which the same migalastat doses were used. Changes in the lymph node adjacent to the duodenum were considered unrelated to migalastat because no similar findings were observed in the 39-week oral repeated-dose toxicity study in monkeys in which the same migalastat doses were used.

Based on the above findings, the NOAEL was determined to be 410 mg/kg/day.

5.2.6 Thirty-nine-week oral repeated-dose toxicity and 8-week recovery study in cynomolgus monkeys (CTD 4.2.3.2.8)

Migalastat 0,[20] 20.5, 82, or 205 mg/kg was orally administered twice daily (0, 41, 164, or 410 mg/kg/day) for 13, 26, or 39 weeks to male and female cynomolgus monkeys. In the 0 and 410 mg/kg/day groups, the 39-week repeated-dose treatment period was followed by an 8-week recovery period to evaluate the recovery. A necropsy was performed in a female monkey in the 164 mg/kg/day group with a fracture of the distal end of the femur with rupture of the epiphyseal cartilage, and the necropsy showed no relationship with migalastat.

Based on the above findings, the NOAEL was determined to be 410 mg/kg/day.

The exposure (AUC_{0-t}) on Days 267 and 268[22] of administration of migalastat at the NOAEL (410 mg/kg/day) was 305,823 ng·h/mL, which was 67.7 times the exposure after administration at the clinically recommended dose.[21]

5.3 Genotoxicity (CTD 4.2.3.3.1.1 to 2, 4.2.3.3.2.1 [reference data])

A reverse mutation study using bacteria and a mouse lymphoma TK study using mammalian cells were conducted and yielded in negative results. A rat bone marrow micronucleus study was performed, and the results of the study suggest that migalastat is unlikely to induce micronucleus formation.

5.4 Carcinogenicity

Oral repeated-dose carcinogenicity studies were conducted in Tg.rasH2 mice and rats. No tumor attributable to migalastat occurred in either species.

5.4.1 Twenty-six-week oral repeated-dose carcinogenicity study in Tg.rasH2 mice (CTD 4.2.3.4.1.1)

Migalastat was orally administered once daily for 26 weeks at 0,[18] 100, 300, or 1000 mg/kg/day to male Tg.rasH2 mice and at 0,[18] 50, 150, or 500 mg/kg/day to female Tg.rasH2 mice. No neoplastic or nonneoplastic changes attributable to migalastat were observed.

[22] Measurement was performed on Day 267 in female animals and on Day 268 in male animals.

Based on the above findings, the non-carcinogenic dose was determined to be 1000 mg/kg/day for male rats and 500 mg/kg/day for female rats.

The exposure (AUC_{0-t}) on Day 182 of administration of migalastat 1000 mg/kg/day to male rats and 500 mg/kg/day to female rats was 121,000 and 94,400 ng·h/mL, respectively, which was 26.8 times and 20.9 times the exposure after administration at the clinically recommended,[21)] respectively.

5.4.2 Hundred-four-week oral repeated-dose carcinogenicity study in rats (CTD 4.2.3.4.1.2)

Migalastat 0,[23)] 20.5, 82, or 328/492 mg/kg was orally administered twice daily (0, 41, 164, or 656 or 984 mg/kg/day) for 104 weeks to male and female SD rats. Initially, the dose of 656 mg/kg/day was set as the highest dose in this study because the dose was expected to result in an approximately 25 times the exposure after the administration at the clinically recommended dose.[21)] The exposure after the initial dosing and at Week 29, however, was below the target exposure level. The dose was thus increased to 984 mg/kg/day at Week 36, and the increased dose was used afterward.

Islet cell adenoma occurred more frequently in male animals in the 656/984 mg/kg/day group (an incidence of 20%) than in the control group (6%). No such increase in the occurrence of islet cell adenoma was observed in male animals. No remarkable nonneoplastic changes were identified. The applicant considered that islet cell adenoma was unlikely to be related to treatment with migalastat, based on the following findings: that although the incidence of islet cell adenoma developing in male animals in the 656/984 mg/kg/day group was higher than the reference incidence, no increase in hyperplasia of the pancreatic islet cells was observed; that migalastat is not genotoxic; that there were no increases in tumors in female animals; that no precancerous changes in the pancreas were observed in oral repeated-dose toxicity studies in rats (26 weeks) and monkeys (39 weeks) that received migalastat at doses resulting in plasma exposure higher than that observed in male animals in the 656/984 mg/kg/day group; that no changes suggestive of carcinogenicity was found in the 26-week carcinogenicity study in Tg.rasH2 rats; that a study reported an incidence of 10% to 20% or higher for the spontaneous occurrence of pancreatic islet cell tumors in male SD rats (*A Glossary for use in Toxicity and Carcinogenicity Studies*. Elsevier; 1992. 118-26; *Toxicol Pathol*. 1994;22:48-55); and that in general, pancreatic islet cell tumors occur more frequently in male animals than in female animals and are late-onset in nature, and the occurrence of the tumors increased at around the end of 24-month studies (*Exp Aging Res*. 1982;8:3-24; *Toxicol Pathol*. 1994;22:48-55).

Based on the above findings, the non-carcinogenic dose was determined to be 656/984 mg/kg/day. The exposure (AUC_{0-t}) on Weeks 29 (656 mg/kg/day) and 37 (984 mg/kg/day) of administration of migalastat at the non-carcinogenic dose (656 or 984 mg/kg/day) was 103,000 and 176,000 ng·h/mL, respectively, which was 22.8 and 39.0 times the exposure after the administration at the clinically recommended dose,[21)] respectively.

[23)] Distilled water. Two vehicle control groups were included in this study.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility and early embryonic development study in rats

5.5.1.1 Fertility and early embryonic development study in male and female rats (CTD 4.2.3.5.1.1)

Migalastat 0,[20] 41, 205, or 615 mg/kg was orally administered twice daily (0, 82, 410, or 1230 mg/kg/day) to male and female SD rats. Female SD rats received migalastat from 2 weeks before the mating to day 7 of pregnancy and were necropsied on day 13 of pregnancy. Male SD rats received migalastat from 4 weeks before the mating, through the mating with migalastat-treated female rats (the first mating) and migalastat-untreated female rats (the second mating), to Day 88 of treatment (the previous day of necropsy). Administration of migalastat was interrupted for 4 weeks in male rats receiving the drug to Day 105 of treatment, and the male rats were mated with untreated female rats (the third mating). The pregnancy rate at the first mating, i.e., the mating in the male and female rats treated with migalastat, was 20%, 5%, and 5% in the 82, 410, 1230 mg/kg/day groups, respectively, as compared with that of 95% in the control group, showing reduced fertility in the migalastat groups. Also, the pregnancy rate at the second mating, i.e., the mating of migalastat-treated male rats with untreated female rats, was 45%, 25%, and 10% in the 82, 410, and 1230 mg/kg/day groups, respectively, as compared with that of 95% in the control group, showing reduced fertility in the migalastat groups. At the third mating, i.e., the mating of male rats after a 4-week recovery period with untreated female rats, the decreased fertility was restored in the migalastat groups. As shown above, the reduced fertility was due to the administration of migalastat to male rats, and the change was considered to be reversible after discontinuation of migalastat. Histopathological examinations on male genital organs revealed no changes related to the administration of migalastat and showed no effects of migalastat on the total sperm count, sperm motility, or sperm morphology. Body weight decreased in female rats in the migalastat groups, which was attributed to the reduced number of litters.

Based on the above findings, the NOAEL for fertility and early embryonic development in male and female rats was determined to be <82 mg/kg/day.

5.5.1.2 Fertility and early embryonic development study in male rats (CTD 4.2.3.5.1.2)

Migalastat 0,[20] 1.025, 4.1, or 10.25 mg/kg was orally administered twice daily (0, 2.05, 8.2, or 20.5 mg/kg/day) to male SD rats from 4 weeks before the mating, through the mating period, to the previous day of necropsy (for 9 weeks in total). The female pregnancy rate was 75%, 85%, and 55% in the 2.05, 8.2, and 20.5 mg/kg/day groups, respectively, as compared with that of 95% in the control group, showing reduced fertility in migalastat groups. Although the pregnancy rate in the 2.05 and 8.2 mg/kg/day groups was slightly lower than the lower limit of the reference data, the changes were considered to be related to the administration of migalastat.

Based on the above findings, the NOAEL for fertility and early embryonic development in male rats was determined to be <2.05 mg/kg/day.

The exposure (AUC_{0-t}) after the administration of migalastat 2.05 mg/kg/day was 736 ng·h/mL, which was 0.163 times the exposure after the administration at the clinically recommended dose.[21)]

5.5.1.3 Fertility and early embryonic development study in female rats (CTD 4.2.3.5.1.3)

Migalastat 0,[20)] 4.1, 41, or 410 mg/kg was orally administered twice daily (0, 8.2, 82, or 820 mg/kg/day) to female SD rats from 2 weeks before the mating to day 7 of pregnancy, and there were no changes related to the administration of migalastat.

Based on the above, the NOAEL for fertility and early embryonic development in female rats was determined to be 820 mg/kg/day.

5.5.2 Embryo-fetal development

5.5.2.1 Embryo-fetal development study in rats (CTD 4.2.3.5.2.1)

Migalastat 0,[20)] 41, 205, or 615 mg/kg was orally administered twice daily (0, 82, 410, or 1230 mg/kg/day) to pregnant SD rats from days 6 to 17 of pregnancy, and there were no changes related to the administration of migalastat.

Based on the above findings, the NOAEL for maternal animals and embryo-fetal development was determined to be 1230 mg/kg/day.

5.5.2.2 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2.3)

Migalastat 0,[20)] 49, 123, or 307.5 mg/kg was orally administered twice daily (0, 98, 246, and 615 mg/kg/day) to pregnant New Zealand White (NZW) rabbits from days 6 to 19 of pregnancy. A dam in the 615 mg/kg/day group died due to administration error on day 11 of pregnancy. In 7 dams in the 615 mg/kg/day group, there were chronic reduction in feed consumption, weight loss, and reduction in feces, which were considered to be related to migalastat, and spontaneous abortion occurred on days 22 to 27 of pregnancy. The 7 dams were necropsied. The following effects on the dams were observed: reduction in body weight gain in the 246 mg/kg/day group; reduction in feces and food consumption and an increase in post-implantation embryonal mortality due to early embryonic resorption in the ≥246 mg/kg/day groups; and weight loss, spontaneous abortion, and reduced number of alive litters in the ≥615 mg/kg/day groups. The observed effects on fetuses were increased incidences of delayed ossification (footpad bone and breastbone) and lumbar rib in the ≥246 mg/kg/day groups and fetal weight loss, unossified parietal bone, mild fusion of the sternebra, abnormal coccygeal position, and nasal sutural bones in ≥615 mg/kg/day groups. Nevertheless, no changes suggestive of teratogenicity were identified.

Based on the above findings, the NOAEL for maternal animals and embryo-fetal development was determined to be 98 mg/kg/day.

The exposure (AUC_{0-t}) on day 19 of pregnancy with the administration of migalastat at the NOAEL (98 mg/kg/day) was 334,988 ng·h/mL, which was 74.2 times the exposure after the administration at the clinically recommended dose.[21)]

5.5.3 Effects on pre- and postnatal development, including maternal function

5.5.3.1 A study for effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3.1)

Migalastat 0,[20)] 20.5, 82, or 410 mg/kg was orally administered twice daily (0, 41, 164, or 820 mg/kg/day) to pregnant rats from day 6 of pregnancy to day 20 postpartum, and there were no changes related to the administration of migalastat.

Based on the above findings, the NOAEL for pre- and postnatal development and maternal function was determined to be 820 mg/kg/day.

The plasma unchanged migalastat concentration 1 hour postdose on day 20 of pregnancy with the administration of migalastat at the NOAEL (820 mg/kg/day) was 21,133 and 2317 ng/mL in the dams (F0) and fetuses (F1), respectively. The plasma and milk unchanged migalastat concentration 1 hour postdose on day 15 postpartum in the dams (F0) was 25,533 and 16,133 ng/mL, respectively.

5.6 Other toxicity studies

5.6.1 Photosafety testing (CTD 4.2.3.7.7.2 [reference data])

Migalastat is considered to have no phototoxicity because the molar absorptivity for migalastat at a wavelength of 290 to 700 nm was <1000 L/mol·cm.

5.R Outline of the review conducted by PMDA

5.R.1 Reduced fertility

PMDA asked the applicant to discuss and describe the relevance to and safety in humans for the reduction in fertility observed in male rats in the fertility studies in male and female rats (CTD 4.2.3.5.1.1) and male rats (CTD 4.2.3.5.1.2).

The applicant's response:

A dose-dependent reduction in fertility was observed in the fertility studies in male and female rats (CTD 4.2.3.5.1.1) and male rats (CTD 4.2.3.5.1.2) but was not in the fertility and early embryonic development study in female rats (CTD 4.2.3.5.1.3). These findings suggest that the reduction was a migalastat-related effect on male fertility. The decreased fertility was confirmed to have recovered after a 4-week recovery period and was a reversible change which could relatively immediately recover.

Glycosphingolipids are reported to play roles in various stages of fertility of sperm, for instance acrosome formation, sperm maturation in the epididymis, acquisition of fertility and acrosome reaction at the oocyte membrane, and activation of oocytes after sperm entry (*Biol reprod*. 2005;72:805-13; *PNAS*.

2002;99:17173-8; *Pharmacogenomics*. 2008;9:717-31). Migalastat stabilizes α-Gal A by binding to the active site of α-Gal A and facilitates their trafficking to lysosomes. As a consequence, migalastat affects the metabolism of glycosphingolipids such as GL-3 through α-Gal released from migalastat in lysosomes and may alter functions relevant to the sperm fertility, leading to the reduction in fertility. Reduced fertility due to decreases in male reproductive ability has been reported for miglustat (Brazaves Capsules 100 mg), an iminosugar (an alkylated iminosugar) which is an approved drug having a similar structure to that of migalastat, and atrophic changes in the testis and epididymis and changes in sperm count, motility, and morphology have been reported for the drug (*Biol Reprod*. 2005;72:805-13; PNAS 2002;99:17173-8; *Pharmacogenomics*. 2008;9:717-31). Miglustat inhibits glycosphingolipid metabolism by blocking β-glucosidase 2 that is a membrane-bound glucosylceramidase outside the lysosomes. Accordingly, both migalastat and miglustat influence the glycosphingolipid metabolism. It is presumed that differences in the mechanism of action of these drugs cause the differences in the effects on fertility. No markedly abnormal sperm morphology, changes in sperm parameters, or abnormal morphology of the testis or epididymis were observed in association with migalastat. It is considered that the observed reduction in fertility was probably the consequence of the effects on the acquisition of fertility or the sperm entry to oocytes resulting from biochemical abnormalities of the acrosome in mature sperm.

As shown above, although the possibility cannot be completely ruled out that the reduction in fertility observed in male rats treated with migalastat may occur in humans, the risk does not outweigh the benefits of migalastat for treatment of Fabry disease in light of the following findings: that there were no effects on the weights or tissues (with pathological examinations) of male genital organs or sperm parameters (count, motility, and morphology), and the observed changes recovered immediately after a 4-week recovery period; and that the conception rate in rats treated with migalastat 20.5 mg/kg/day (equivalent to 1.5 times the exposure after the clinically recommended dose[21)]) was 55%, showing that fertility was still present.

PMDA's view on the relevance to and safety in humans for the reduction in fertility observed in male rats treated with migalastat:
PMDA considers that serious effects, such as infertility, are unlikely to occur in humans with consideration of the following findings: that the mechanism of action is based on a nongenotoxic mechanism; that the reduction was not accompanied by changes in sperm or testicular morphology; that the changes were reversible; and the conception rate in rats treated with migalastat 20.5 mg/kg/day (equivalent to 1.5 times the exposure after the clinically recommended dose) was 55%. However, since it cannot be ruled out that fertility may decrease in humans, the study data thereof should be described appropriately in the package insert.

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

6.1 Biopharmaceutic studies and associated analytical methods

The product formulations used in the clinical studies of migalastat are shown in Table 6.

Table 6. Product formulations used in clinical studies

Product formulation	Development phase (Study name)	
	Japanese studies	Foreign studies (including multiregional clinical studies)
Oral solution	Phase I (MGM115806)	Phase I (AT1001-010, AT1001-014, AT1001-018, FAB-CL-101, FAB-CL-102, FAB-CL-103, FAB-CL-104)
Capsule I (25 mg)	−	Phase I (FAB-CL-103) Phase II (FAB-CL-201, FAB-CL-202, FAB-CL-203, FAB-CL-204, FAB-CL-205)
Capsule II (250 mg)	−	Phase II (FAB-CL-205)
Capsule III (150 mg) [a)]	Phase I (MGM115806)	Phase I (AT1001-015) Phase II (AT1001-013, FAB-CL-205) Phase III (AT1001-011, AT1001-012, AT1001-041)
Capsule IV (150 mg) [a)]	−	Phase I (AT1001-016, AT1001-018) Phase II (AT1001-013, FAB-CL-205) Phase III (AT1001-011, AT1001-012, AT1001-041)

−, not applicable.
a) Capsules III and IV was basically identical in formulation to the proposed commercial drug product, except for the colorant for or the printing on the capsules.

LC-MS/MS was used to determine the concentrations of unchanged migalastat in human biospecimens, and the lower limit of quantitation was 5.88 and 100 ng/mL for plasma and urine specimens, respectively. Liquid scintillation counter and radio-HPLC were used to determine the radioactivity in biospecimens. Liquid scintillation counter or accelerator mass spectrometry was used to determine the radioactivity in a human mass balance study.

For biopharmaceutical evaluation, the applicant submitted data from a study of an intravenous administration and absolute bioavailability (BA) (Study AT1001-018), a study of the absolute BA and food effects (Study FAB-CL-103), and a study of food effects (Study AT1001-016).

6.1.1 Study of intravenous administration and absolute BA (CTD5.3.1.1.1, Study AT1001-018 [March 2014 to June 2014])

A study was conducted to evaluate the safety, pharmacokinetics, and absolute BA of migalastat in non-Japanese healthy adults (a target sample size of 31), consisting a randomized, double-blind, placebo-controlled, dose escalation phase for evaluation of migalastat given intravenously and a randomized, open-label, 2-way crossover phase for evaluation of the absolute BA of migalastat.

For evaluation of the intravenous administration (Cohorts 1 to 3), a single solution dose of placebo or migalastat 0.3, 1.0, or 10 mg/kg was intravenously administered over 2 hours. In each cohort, 2 and 5 of 7 subjects were randomly assigned to placebo and migalastat, respectively. For evaluation of absolute BA (Cohort 4, 5 subjects in each group), a single solution dose of migalastat 150 mg was orally administered in a fasting state or intravenously administered over 2 hours, with a 7-day interval between the treatment.

All 31 subjects who were randomly assigned were included in the safety analysis set. Among them, 25 subjects receiving migalastat were included in the pharmacokinetics analysis set.

The pharmacokinetic parameters of plasma unchanged migalastat after a single intravenous dose of the drugs are shown in Table 7.

Table 7. Pharmacokinetic parameters of plasma unchanged migalastat after a single intravenous dose of migalastat

Parameters	Migalastat 0.3 mg/kg (n = 5)	Migalastat 1.0 mg/kg (n = 5)	Migalastat 10 mg/kg (n = 5)
C_{max} (ng/mL)	609 (5.5)	1760 (5.9)	20,652 (11.4)
$AUC_{0\text{-last}}$ (ng·h/mL)	2282 (7.7)	6861 (14.7)	81,106 (14.5)
t_{max} (h)	1.93 (1.93, 1.95)	1.93 (1.93, 1.97)	1.93 (1.93, 1.93)
$t_{1/2}$ (h)	2.1 (8.9)	3.2 (20.5)	10.0 (3.0)
CL (L/h)	6.6 (4.3)	7.6 (14.7)	7.4 (10.2)
V_z (L)	19.8 (7.4)	34.7 (15.6)	106.3 (11.1)
$Ae_{0\text{-}24h}$ (mg)	10.7 ± 5.4	42.2 ± 4.7	512.0 ± 33.0
$fe_{0\text{-}24h}$ (%)	69.2 ± 34.4	79.7 ± 4.0	85.1 ± 2.0
CL_r (L/h)	4.5 ± 2.2	6.2 ± 1.0	6.4 ± 0.5

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL, total clearance; V_z, volume of distribution at the elimination phase; $Ae_{0\text{-}24h}$, cumulative urinary excretion of unchanged migalastat from 0 to 24 hours; $fe_{0\text{-}24h}$, fraction of urinary excretion of unchanged migalastat from 0 to 24 hours; CL_r, renal clearance.

With regard to the absolute BA, the ratio [90% CI] of the least squares geometric mean $AUC_{0\text{-last}}$ of plasma unchanged migalastat after oral administration to that after intravenous administration (oral administration/intravenous administration) was 0.743 [0.670, 0.823], and the absolute BA was 74.3%.

As for safety, in evaluation of intravenous administration (Cohorts 1 to 3), adverse events occurred in 2 of 6 subjects (6 events) in the placebo group, 1 of 5 subjects (2 events) in the 0.3 mg/kg group, 2 of 5 subjects (5 events) in the 1.0 mg/kg group, and 2 of 5 subjects (3 events) in the 10 mg/kg group. Among the adverse events, 2 events (2 events of external ear pain) in 1 of 6 subjects in the placebo group and 1 event (1 event of dysgeusia) in 1 of 5 subjects in the 10 mg/kg group were considered to be adverse drug reactions. In the evaluation of absolute BA (Cohort 4), adverse events occurred in 2 of 10 subjects (2 events) with oral administration and 1 of 10 subjects (2 events) with intravenous administration. Among these events, 1 event (pruritus) in 1 subject after oral administration was judged to be an adverse drug reaction. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.1.2 Study of relative BA and food effects (CTD 5.3.1.2.1, Study FAB-CL-103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, 3-way crossover study was conducted to evaluate the relative BA of migalastat and food effects in non-Japanese healthy adult men (a target sample size of 15).

In each phase, a single dose of migalastat solution 100 mg or migalastat capsule 100 mg was orally administered in a fasting state, or a single dose of migalastat capsule 100 mg was orally administered within 30 min after a high-fat meal, with a 7-day interval between the phases.

All 15 subjects who were randomly assigned were included in the safety and pharmacokinetics analysis sets.[24)]

[24)] Of 15 subjects randomly assigned, 1 subject was tested positive for amphetamines and was withdrawn from the study, and thus, 14 subjects were included in the safety and pharmacokinetics analyses sets for evaluation of migalastat given with meals.

With regard to pharmacokinetics, the ratio [90% CI] of the least squares geometric mean C_{max} and $AUC_{0\text{-last}}$ of plasma unchanged migalastat for migalastat in the commercial capsule formulation to that for the solution formulation (migalastat capsule/migalastat solution) was 0.97 [0.87, 1.09] and 0.98 [0.89, 1.08], respectively. The ratio [90% CI] of the least squares geometric mean C_{max} and $AUC_{0\text{-last}}$ of plasma unchanged migalastat after the administration of migalastat capsule with a meal to that after the administration of migalastat capsule in a fasting state (administration with a meal/administration in a fasting state) was 0.60 [0.53, 0.67] and 0.63 [0.57, 0.69], respectively.

As for safety, adverse events occurred in 1 of 15 subjects (1 event) with migalastat solution, 1 of 15 subjects (1 event) with migalastat capsule given in a fasting state, and 2 of 14 subjects (2 events) with migalastat capsule given with a meal, and all events were considered to be unrelated to the study drug was ruled out for all events. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.1.3 A study of food effects (CTD 5.3.1.1.2, Study AT1001-016 [October 2011 to December 2011])

A randomized, open-label, 5-way crossover study was conducted to evaluate food effects on migalastat in non-Japanese healthy adults (a target sample size of 20).

Migalastat 150 mg was administered in a fasting state, concomitantly with a glucose drink, 1 hour before a high-fat meal, 1 hour before a light meal, and 1 hour after a light meal with an interval of ≥7 days between each dosing.

All 20 subjects who were randomly assigned were included in the safety analysis set,[25)] and 19 subjects were included in the pharmacokinetics analysis set. One patient who had an adverse event (vomiting) when taking migalastat in a fasting state was excluded from the pharmacokinetics analysis set.

The pharmacokinetic parameters of plasma unchanged migalastat at each administration timing are shown in Table 8.

25) Of 20 subjects randomly assigned, 1 subject, who received migalastat 1 hour after a light meal and then received the drug in a fasting state, discontinued the study due to an adverse event (vomiting) after administration of migalastat in a fasting state. Accordingly, 19 subjects were included in the safety analysis set for evaluation of migalastat which was given concomitantly with a glucose drink, 1 hour before a high-fat meal, and 1 hour before a light meal.

Table 8. Pharmacokinetic parameters of plasma unchanged migalastat at each administration timing

Dosing timing	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	Ratio of least squares geometric mean [a] [90% CI]	
					C_{max}	$AUC_{0\text{-last}}$
In a fasting state	1561 (33.8)	9696 (27.1)	3.0 (1.5, 6.0)	3.9 (11.3)	–	–
Concomitantly with a glucose drink	1408 (29.6)	8342 (29.2)	3.0 (2.0, 4.0)	4.0 (11.8)	0.90 [0.80, 1.02]	0.86 [0.77, 0.97]
1 hour before a high-fat meal	1323 (28.3)	6021 (27.6)	1.5 (1.0, 3.0)	4.9 (20.5)	0.85 [0.75, 0.96]	0.62 [0.56, 0.70]
1 hour before a light meal	1278 (39.6)	5573 (32.0)	2.0 (1.5, 3.1)	4.9 (13.4)	0.82 [0.73, 0.93]	0.58 [0.51, 0.65]
1 hour after a light meal	945 (28.3)	5801 (27.0)	3.0 (1.5, 6.0)	4.3 (10.9)	0.61 [0.54, 0.68]	0.60 [0.54, 0.67]

Geometric mean (coefficient of variation %). Median (range) for t_{max}. –, data not available.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life;
a) Ratio of least squares geometric mean at each dosing timing to that at dosing in a fasting state.

The safety analysis revealed adverse events occurring in 1 of 20 subjects (3 events, vomiting/headache/dizziness) after administration in the fasting state, 1 of 19 subjects (1 event, nausea) after administration 1 hour before a light meal, and 1 of 20 subjects (5 events, nausea/vomiting/abdominal pain/diarrhea/headache) after administration 1 hour after a light meal, and all the events were considered adverse drug reactions. There were no deaths or serious adverse events. An adverse event of vomiting led to treatment discontinuation in 1 subject receiving migalastat in a fasting state.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2 Clinical pharmacology

The evaluation data submitted by the applicant consisted of data from a Japanese study (Study MGM11580) and 10 foreign studies (Studies FAB-CL-101, AT1001-018, AT1001-014, FAB-CL-102, AT1001-015, AT1001-010, FAB-CL-201, FAB-CL-204, AT1001-011, and FAB-CL-205), and the reference data submitted by the applicant are composed of data from 2 foreign studies (Studies FAB-CL-104 and AT1001-013) and results of the population pharmacokinetic analyses. In addition to the above, the applicant submitted data from studies with human biospecimens. Results of the main studies are described below. For the results of Study AT1001-018, a foreign study, see Section "6.1.1. Study of intravenous administration and absolute BA."

6.2.1 Studies with human biospecimens (CTD 4.2.2.2-1 to 2, 4.2.2.3-1, 4.2.2.4-1, 4.2.2.6-1 to 10)

Caco-2 cell monolayers were used to investigate the membrane permeability of migalastat (100 μmol/L). The apparent permeability coefficient (P_{app} [$\times 10^{-6}$ cm/sec; mean ± standard deviation]) in the apical-to-basolateral (A-B) and the B-A directions was 0.61 ± 0.40 and 0.40 ± 0.17, respectively, and the ratio of the P_{app} (B-A/A-B) was 0.65. The P_{app} (mean ± standard deviation) for positive controls, i.e., pindolol (10 μmol/L), minoxidil (10 μmol/L), and atenolol (100 μmol/L), in the A-B direction was 22.3 ± 3.21, 5.33 ± 1.45, and 0.43 ± 0.06, respectively. The permeability of migalastat was investigated by using a medium to which ethylene glycol tetraacetic acid (EGTA) was added to decrease the transepithelial electrical resistance of Caco-2 cell monolayers. Positive controls were Lucifer yellow and atenolol showing their permeability through

paracellular pathways and propranolol showing its permeability through transcellular pathways. The P_{app} (mean) in the A-B direction for migalastat (50 μmol/L), Lucifer yellow (500 μmol/L), atenolol (50 μmol/L), and propranolol (10 μmol/L) in a medium treated with EGTA was 13.4, 2.06, 10.2, and 27.1, respectively, and that in a medium without EGTA was <0.74, 0.19, 0.33, and 21.6, respectively.

The plasma protein non-binding rate (mean, as determined by an equilibrium dialysis method) of ^{14}C-migalastat at 1, 10, or 100 μmol/L was 100%, 98%, and 111%, respectively, in humans.

Frozen human liver cells were used to evaluate the metabolism of ^{14}C-migalastat (1 and 100 μmol/L). The residual percentage of ^{14}C-migalastat 1 and 100 μmol/L after 4-hour incubation (in comparison with pre-incubation) was 105% and 101%, respectively, and no metabolites of migalastat were identified.

Human liver microsomes were used to investigate the inhibitory effects of migalastat (0.5 to 500 μmol/L) on various cytochrome P450 (CYP) molecular species (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5). The IC_{50} value of migalastat was >500 μmol/L for all of the CYP molecular species, and migalastat showed no direct, time-dependent, or metabolism-dependent inhibition of them.

Frozen human liver cells were used to investigate the inductive effects of migalastat (10 to 1000 μmol/L) on CYP1A2 and CYP3A4 and those of migalastat (5 to 500 μmol/L) on CYP2B6. Migalastat showed no inductive effects on any of the CYP molecular species.

Cells expressing breast cancer resistance protein (BCRP), bile salt export pump (BSEP), P-glycoprotein (P-gp), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion protein (MATE) 1, and MATE2-K were used to investigate the inhibitory effects of migalastat (0.69 to 500 μmol/L) on these transporters. Migalastat showed no inhibitory effects on any of the transporters.

Cells expressing BCRP, P-gp, OAT1, OAT3, OCT2, MATE1, and MATE2-K were used to investigate the uptake effects of migalastat (10 to 100 μmol/L). There were no observed uptake effects of migalastat via BCRP, P-gp, OAT1, OCT2, MATE1, or MATE2-K. Cells expressing and not expressing OAT3 were used, and the concentrations of unchanged migalastat taken up in vesicles were measured to calculate the permeability coefficient (cells expressing OAT3/cells not expressing OAT3). The permeability coefficient for migalastat 10 and 100 μmol/L was 0.92 to 1.96 and 1.08 to 15.65, respectively. Cells expressing OAT3 were used to investigate the uptake effects of migalastat (3 to 300 μmol/L). The permeability coefficient was <2 (0.95 to 1.52) for all the studied doses, and no uptake effects of migalastat via OAT3 were seen.

Cells expressing sodium glucose cotransporter (SGLT) 1 were used to investigate the uptake effects of migalastat (412 μmol/L to 100 mmol/L). Migalastat showed concentration-dependent membrane depolarization (with an EC_{50} of >100 mmol/L), and the membrane depolarization induced by migalastat was

inhibited by 73.7% in the presence of phlorizin, an SGLT1 inhibitor. The EC_{50} of methyl-α-D-glucopyranoside, a positive control, was 2.08 mmol/L, and the membrane depolarization was inhibited by 100% in the presence of phlorizin. Cells expressing SGLT1 were incubated with migalastat (0.15 to 150 mmol/L) and methyl-α-D(U-^{14}C)-glucopyranoside to investigate the inhibitory effects of migalastat on SGLT1. Migalastat inhibited the uptake of glucose in a concentration-dependent manner with an IC_{50} value (mean) of 64.7 mmol/L.

Cells expressing SGLT2 were used to investigate the uptake effects of migalastat (10 to 300 μmol/L), and no uptake effects of migalastat via SGLT2 were observed. Cells expressing SGLT2 were used to investigate the inhibitory effects of migalastat (3 to 1000 μmol/L) on SGLTs, and migalastat showed no inhibitory effects on SGLT2.

6.2.2 Investigations in healthy adults

6.2.2.1 Single-dose study in Japanese healthy adults (CTD 5.3.3.1.1, Study MGM115806 [September 2011 to December 2011])

A placebo-controlled, randomized, single-blind, 4-period crossover, dose-escalation study was conducted to evaluate the safety and pharmacokinetics of single oral doses of migalastat in healthy Japanese adult men (a target sample size of 12).

In each phase, a single dose of migalastat solution 50 mg, migalastat capsule 150 mg or 450 mg, or placebo was orally administered in a fasting state with an interval of ≥7 days between each dosing.

All 14 subjects who were randomly assigned were included in the safety and pharmacokinetics analysis sets.[26)]

The pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat are shown in Table 9.

Table 9. Pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat

Parameters	Migalastat 50 mg (n = 14)	Migalastat 150 mg (n = 13)	Migalastat 450 mg (n = 13)
C_{max} (ng/mL)	695 (36.0)	2124 (36.3)	5695 (40.4)
$AUC_{0\text{-last}}$ (ng·h/mL)	3905 (35.0)	11,431 (27.4)	30,454 (34.2)
t_{max} (h)	3.0 (1.5, 5.0)	3.5 (2.0, 5.0)	3.5 (2.5, 5.0)
$t_{1/2}$ (h)	3.2 (22.5)	3.8 (6.6)	4.0 (5.6)
CL/F (L/h)	12.6 (34.6)	13.0 (27.4)	14.6 (34.1)
V_z/F (L)	57.8 (28.8)	71.7 (27.8)	84.7 (37.0)
$Ae_{0\text{-}24h}$ (mg)	25.5 ± 5.8	71.6 ± 15.5	203.9 ± 38.1
$fe_{0\text{-}24h}$ (%)	51.0 ± 11.6	47.7 ± 10.3	45.3 ± 8.5
CL_r (L/h)	6.4 ± 1.3	6.2 ± 1.1	6.1 ± 1.0

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution; $fe_{0\text{-}24h}$, fraction of urinary excretion of unchanged migalastat from 0 to 24 hours; $Ae_{0\text{-}24h}$, cumulative urinary excretion of unchanged migalastat from 0 to 24 hours; CL_r, renal clearance.

The safety analysis revealed adverse events in 5 of 14 subjects (7 events) after administration of placebo, 5 of 14 subjects (10 events) after administration of migalastat solution 50 mg, 4 of 13 subjects (6 events) after

26) One of the 14 subjects who were randomly assigned discontinued the study with withdrawal of consent. Accordingly, 13 subjects were included in the safety and pharmacokinetics analysis sets for dosing of migalastat capsule 150 and 450 mg.

administration of migalastat capsule 150 mg, and 2 of 13 subjects (2 events) after administration of migalastat capsule 450 mg. Among these events, the following events were considered adverse drug reactions: 1 event in 1 subject after administration of placebo (frequent bowel movements); 7 events in 4 subjects after administration of migalastat solution 50 mg (2 events of headache in 2 subjects, seasonal allergy in 1 subject, and headache/hypertension/blood creatine phosphokinase increased/arthralgia in 1 subject); and 2 events in 2 subjects after administration of migalastat capsule 450 mg (2 events of headache in 2 subjects). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

As for changes in laboratory data, low lymphocyte count was reported in 2 of 14 subjects after administration of placebo, 1 of 14 subjects after administration of migalastat 50 mg, 1 of 13 subjects after administration of migalastat capsule 150 mg, and 1 of 13 subjects after administration of migalastat capsule 450 mg, but any of the changes were not considered adverse events.

With regard to vital signs, low diastolic blood pressure was reported in 1 of 14 subjects after administration of placebo and 2 of 13 subjects after administration of migalastat capsule 150 mg, high diastolic blood pressure was reported in 1 of 14 subjects after administration of migalastat solution 50 mg, and high systolic blood pressure was reported in 1 of 13 subjects after administration of migalastat capsule 150 mg. The high diastolic blood pressure observed in 1 subject after administration of migalastat solution 50 mg was regarded as an adverse event and resolved by the end of the study. Regarding electrocardiographic findings, negative T waves were identified in 1 of 14 subjects after administration of placebo and migalastat solution 50 mg. The event was considered to represent an adverse event and resolved by the end of the study.

6.2.2.2 Single-dose study in non-Japanese healthy adults (CTD 5.3.3.1.2, Study FAB-CL-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, dose-escalation study was conducted to evaluate the safety and pharmacokinetics of single oral doses of migalastat in healthy non-Japanese adult men (a target sample size of 32).

A single dose of migalastat solution 25, 75, 225, or 675 mg or placebo was orally administered in a fasting state. Of 8 subjects in each cohort, 2 and 6 subjects were randomly assigned to placebo and migalastat, respectively.

All 32 subjects who were randomly assigned were included in the safety analysis set. Among them, 24 subjects receiving migalastat were included in the pharmacokinetics analysis set.

The pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat are shown in Table 10.

Table 10. Pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat

Parameters	Migalastat 25 mg (n = 6)	Migalastat 75 mg (n = 6)	Migalastat 225 mg (n = 6)	Migalastat 675 mg (n = 6)
C_{max} (ng/mL)	201 (35.5)	685 (16.7)	1997 (56.1)	6492 (24.4)
$AUC_{0\text{-}last}$ (ng·h/mL)	1092 (34.2)	4661 (9.0)	11,177 (59.8)	35,275 (22.3)
t_{max} (h)	3.0 (2.0, 4.0)	3.0 (1.5, 5.0)	3.0 (2.0, 4.0)	2.5 (2.0, 4.0)
$t_{1/2}$ (h)	3.0 (15.4)	4.0 (15.3)	4.6 (15.4)	4.2 (7.61)
CL/F (L/h)	18.1 (33.6)	13.0 (8.6)	16.2 (59.2)	15.5 (22.4)
V_z/F (L)	78.5 (29.7)	74.9 (22.2)	107.0 (75.9)	93.2 (17.4)
$Ae_{0\text{-}24h}$ (mg)	9.3, 3.9 [a)]	26.4 ± 8.4 [b)]	90.7 ± 33.8	267.5 ± 39.8
$fe_{0\text{-}24h}$ (%)	45.6, 18.9 [a)]	43.0 ± 13.7 [b)]	49.3 ± 18.4	48.5 ± 7.2
CL_r (L/h)	5.8, 6.0 [a)]	5.7 ± 1.7 [b)]	7.5 ± 1.3	7.7 ± 1.6

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}. Individual values are shown when n = 2.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-}last}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution; $Ae_{0\text{-}24h}$, cumulative urinary excretion of unchanged migalastat from 0 to 24 hours; $fe_{0\text{-}24h}$, fraction of urinary excretion of unchanged migalastat from 0 to 24 hours (%); CL_r, renal clearance.
a) N = 2. b) N = 4.

Adverse events occurred in 2 of 8 subjects (5 events) in the placebo group, 1 of 6 subjects (2 events) in the migalastat 75 mg group, and 2 of 6 subjects (3 events) in the migalastat 675 mg group. Among these adverse events, 2 events in 1 subject in the placebo group (headache/stools watery), 1 event in 1 subject in the migalastat 75 mg group (headache), and 2 events in 2 subjects in the migalastat 675 mg group (headache and dizziness) were considered adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.2.3 Repeated-dose study in non-Japanese healthy adults (CTD 5.3.3.1.3, Study FAB-CL-102 [[redacted] 20[redacted] to[redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, dose-escalation study was conducted to evaluate the safety and pharmacokinetics of repeated oral doses of migalastat in healthy non-Japanese adult men (a target sample size of 16).

Migalastat solution at a dose of 50 or 150 mg or placebo was orally administered twice daily repeatedly for 7 days. Of 8 subjects in each cohort, 2 and 6 subjects were randomly assigned to placebo and migalastat, respectively.

All 16 subjects who were randomly assigned were included in the safety analysis set. Among them, 12 subjects receiving migalastat were included in the pharmacokinetics analysis set.

The pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat twice daily shown in Table 11.

Table 11. Table 10. Pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat twice daily

Parameters	Migalastat 50 mg BID (n = 6)		Migalastat 150 mg BID (n = 6)	
	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	344 (40.9)	617 (35.1)	1723 (46.6)	1659 (40.5)
$AUC_{0\text{-last}}$ (ng·h/mL)	1897 (48.0)	–	8955 (40.5)	–
$AUC_{0\text{-}\tau}$ (ng·h/mL)	–	3259 (25.6)	–	10,680 (33.6)
t_{max} (h)	2.5 (2.0, 5.0)	2.3 (1.5, 4.0)	3.5 (1.5, 4.0)	2.5 (2.0, 4.0)
$t_{1/2}$ (h)	2.5 (15.0)	–	2.4 (5.4)	–
CL/F (L/h)	20.3 (47.8)	–	12.9 (40.2)	–
V_z/F (L)	74.2 (60.5)	–	45.4 (37.4)	–
Flux1 (%)	–	204 (17.5)	–	160 (21.1)
Flux2 (%)	–	914 (38.1)	–	638 (36.5)
$Ae_{0\text{-}12h}$ (mg)	11.7 ± 5.5 [a)]	19.2 ± 6.5	72.6 ± 24.8	82.3 ± 20.2
$fe_{0\text{-}12h}$ (%)	28.6 ± 13.4 [a)]	47.1 ± 15.8	59.2 ± 20.3	67.1 ± 16.5
CL_r (L/h)	4.5 ± 1.2 [a)]	5.7 ± 1.2	7.6 ± 1.4	7.6 ± 1.5

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}. BID, administered twice daily. –, data not available.

C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; $AUC_{0\text{-}\tau}$, area under the plasma unchanged migalastat concentration-time curve over a dosing interval; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution; Flux1, fraction of the difference between the maximum and minimum plasma concentrations of unchanged migalastat to the mean plasma unchanged migalastat concentration; Flux2, fraction of the difference between the maximum and minimum plasma concentrations of unchanged migalastat to the minimum plasma unchanged migalastat concentration; $Ae_{0\text{-}24h}$, cumulative urinary excretion of unchanged migalastat from 0 to 24 hours; $fe_{0\text{-}12h}$, fraction of urinary excretion of unchanged migalastat from 0 to 12 hours (%); CL_r, renal clearance.

As for safety, 10 adverse events occurred in 4 of 6 subjects in the migalastat 150 mg, and all the events were considered unrelated to the study drug. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.2.4 Mass balance study (CTD5.3.3.1.4, Study AT1001-014 [August 2011 to September 2011])

An open-label, uncontrolled study was conducted to evaluate the pharmacokinetics after a single oral dose of ^{14}C-migalastat in non-Japanese healthy adult men (a target sample size of 6).

A single dose of ^{14}C-migalastat 150 mg was orally administered in a fasting state.

All 6 subjects who received ^{14}C-migalastat were included in the safety and pharmacokinetics analysis sets.

As for pharmacokinetics of total radioactivity and unchanged migalastat in plasma, C_{max} (geometric mean [coefficient of variation]) of them was 2246 ng·eq/mL (27%) and 1516 ng/mL (27%), respectively, $AUC_{0\text{-last}}$ was 18,718 ng·eq·h/mL (14%) and 10,957 ng·h/mL (22%), respectively, t_{max} (median [range]) was 4.00 h [2.00, 6.00] and 4.00 h [2.00, 6.00], respectively, and $t_{1/2}$ (mean ± standard deviation) was 7.68 ± 6.90 h and 6.34 ± 2.50 h, respectively. The proportion of unchanged migalastat to the total radioactivity in plasma up to 24 hours postdose was approximately 77%, and the proportion for *O*-glucuronide conjugates M1, M2, and M3 was 5%, 2%, and 6%, respectively. The ratio of radioactivity in blood and plasma from 2 to 24 hours postdose ranged 0.76 to 1.12. The total radioactivity in urine and feces combined (mean) up to 240 hours postdose accounted for 97.6% of radioactivity administered; 77.2% in urine and 20.4% in feces. The fraction of urinary excretion of unchanged migalastat to administered radioactivity up to 240 hours postdose was 64.5%, and renal clearance

was 7.32 L/h. The fraction of urinary excretion of unchanged migalastat to administered radioactivity up to 12 hours postdose was 55%, and the combined fraction of urinary excretion of the 3 *O*- glucuronide conjugates (M1, M2, and M3) was 5%. No radioactivity was detected in the expiratory air.

As for safety, 6 adverse events occurred in 4 of 6 subjects, and 3 of the 6 events in 2 patients (headache and diarrhea in 1 patient, and headache in the other) were considered to be adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.3 Studies in patients

6.2.3.1 Foreign phase II study in men with Fabry disease (CTD 5.3.4.2.1, Study FAB-CL-201 [January 2006 to January 2008])

An open-label, dose escalation study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese men with Fabry disease (a target sample size of 20) [for details of the study design and its pharmacodynamics and safety results, see Section "7.1.1 Foreign phase II study in men with Fabry disease"].

The pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat twice daily are shown in Table 12.

Table 12. Pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat twice daily

Parameters	Migalastat 25 mg BID		Migalastat 剤 100 mg BID		Migalastat 250 mg BID	
	Day 1 (n = 9)	Day 14 (n = 8)	Day 15 (n = 8)	Day 28 (n = 8)	Day29 (n = 8)	Day 42 (n =8)
C_{max} (ng/mL)	204 (31.3)	263 (46.4)	884 (37.6)	1071 (30.3)	2305 (37.1)	2185 (33.6)
$AUC_{0\text{-}12h}$ (ng·h/mL)	1053 (29.9)	1361 (32.9)	4218 (32.0)	5643 (25.3)	10,881 (32.4)	12,244 (26.0)
t_{max} (h)	2.0 (1.9, 4.0)	3.0 (2.0, 5.0)	2.5 (1.0, 3.0)	3.0 (1.0, 5.0)	3.0 (2.0, 4.1)	3.0 (1.1, 4.1)
$t_{1/2}$ (h)	2.4 (20.0)	2.6 (25.0)	2.5 (19.2)	2.6 (11.9)	2.4 (13.4)	2.7 (17.3)
CL/F (L/h)	18.3 (28.9)	15.0 (32.9)	18.2 (33.3)	14.5 (25.3)	17.8 (31.9)	16.7 (26.0)
V_z/F (L)	63.5 (39.9)	−	66.1 (37.2)	−	60.8 (38.0)	−
Accumulation coefficient [a)]	−	1.3 (53.0)	−	1.3 (30.2)	−	1.1 (37.2)

Geometric mean (coefficient of variation %). Median (range) for t_{max}. BID, administered twice daily. −, data not available.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-}12h}$, area under the plasma unchanged migalastat concentration-time curve from 0 to 12 hours postdose; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution.
a) Calculated based on the ratio of $AUC_{0\text{-}12h}$ after repeated doses (Day 14 for migalastat 25 mg BID, Day 28 for migalastat 100 mg BID, Day 42 for migalastat 250 mg BID) to $AUC_{0\text{-}12h}$ after the initial dose (Day 1 for migalastat 25 mg BID, Day 15 for migalastat 100 mg BID, Day 29 for migalastat 250 mg BID).

With regard to the urinary pharmacokinetic parameters,[27)] Cumulative amount of unchanged drug excreted into urine from time zero to 10-hour urine collection time interval ($Ae_{0\text{-}10h}$) (mean ± standard deviation) on Day 28 (Day 14 of administration of migalastat 100 mg) and Day 42 (Day 14 of administration of migalastat 250 mg) was 38.8 ± 11.3 mg and 91.7 ± 26.1 mg, respectively, $fe_{0\text{-}10h}$ on the days was 47.4% ± 13.8% and 44.9% ± 12.8%, respectively, and CL_r on the days was 6.84 ± 1.24 L/h and 7.92 ± 2.21 L/h, respectively.

27) No urinary pharmacokinetic parameters were presented because unchanged migalastat after administration of migalastat at 25 mg BID was undetectable or the data missed in almost all subjects.

6.2.3.2 Foreign phase II study in women with Fabry disease (CTD5.3.4.2.4, Study FAB-CL-204 [September 2006 to May 2008])

A randomized, open-label study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese women with Fabry disease (a target sample size of 12) [for details of the study design and its pharmacodynamics and safety results, see Section "7.1.4 Foreign phase II study in women with Fabry disease"].

The pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat given once every other day are shown in Table 13.

Table 13. Pharmacokinetic parameters of plasma unchanged migalastat after repeated oral doses of migalastat given once every other day

	Evaluation time point	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL) [a]	t_{max} (h)	$Ae_{0\text{-10 h}}$ (mg)	$fe_{0\text{-10 h}}$ (%)	CL_r (L/h)
Migalastat 50 mg QOD (n = 2)	Day 1	294, 918	1457, 4744	2.0, 2.0	–	–	–
	Day 14	478, 754	2099, 4854	2.3, 4.0	16.8 [b]	41.0 [b]	8.0 [b]
	Day 84	325, 772	1402, 3775	2.0, 2.0	4.2 [b]	10.2 [b]	3.0 [b]
Migalastat 150 mg QOD (n = 4)	Day 1	1691 (22.0)	8942 (32.2)	3.5 (1.0, 4.0)	74.1 ± 32.7 [c]	60.4 ± 26.7 [c]	9.6 ± 7.3 [c]
	Day 14	2029 (40.0)	10,638 (35.6)	3.0 (2.0, 4.0)	73.0 ± 43.1 [c]	59.5 ± 35.1 [c]	9.0 ± 8.2 [c]
	Day 84	1524 (23.3)	8582 (29.7)	3.5 (2.0, 4.0)	41.8 ± 22.7	34.1 ± 18.5	5.4 ± 4.2
Migalastat 250 mg QOD (n = 3)	Day 1	2461 (43.4)	13,217 (30.2)	3.0 (2.0, 5.0)	64.9 ± 32.7	31.8 ± 16.0	4.6 ± 1.3
	Day 14	2663 (22.8)	14,851 (9.6)	3.0 (3.0, 5.0)	79.4 ± 24.7	38.9 ± 12.1	5.5 ± 2.1
	Day 84	1954 (49.1)	9970 (37.8)	3.0 (3.0, 4.0)	60.8 ± 41.0	29.8 ± 20.1	7.0 ± 5.9

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}. Individual values are shown when n = 2. QOD, once every other day; −, data not available.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $Ae_{0\text{-10h}}$, cumulative urinary excretion of unchanged migalastat from 0 to 10 hours; $fe_{0\text{-10h}}$, fraction of urinary excretion of unchanged migalastat from 0 to 10 hours; CL_r, renal clearance.
a) $AUC_{0\text{-10h}}$ (area under the plasma unchanged migalastat concentration-time curve from 0 to 10 hours postdose) for data on Days 14 and 84; b) n = 1; c) n = 3

6.2.4 Investigation of intrinsic factors

6.2.4.1 Pharmacokinetic study in subjects with renal impairment (CTD 5.3.3.3.1, Study AT1001-015 [August 2011 to April 2012])

An open-label study was conducted to evaluate the effects of renal function on the safety and pharmacokinetics of a single oral dose of migalastat in non-Japanese adults (a target sample size of 32).

A single dose of migalastat 150 mg was orally administered in a fasting state.

All 32 subjects who received migalastat were included in the safety and pharmacokinetics analysis sets: 8 subjects with normal renal function[28] (CLcr of ≥90 mL/min); 8 subjects with mild renal impairment (CLcr of ≥60 and <90 mL/min); 8 subjects with moderate renal impairment (CLcr of ≥30 and <60 mL/min); and 8 subjects with severe renal impairment (CLcr of ≥15 and <30 mL/min).

The pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat 150 mg are shown in Table 14. The ratio [90% CI] of the least squares geometric mean C_{max} of plasma unchanged migalastat concentrations in subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function was 1.04 [0.79, 1.38], 0.89 [0.67, 1.18], 0.99 [0.75, 1.31], respectively.

[28] CLcr calculated with the Cockcroft-Gault equation.

The respective corresponding ratio [90% CI] of the least squares geometric mean $AUC_{0-\infty}$ was 1.17 [0.90, 1.53], 1.81 [1.39, 2.36], and 4.53 [3.48, 5.90].

Table 14. Pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat 150 mg

Parameters	Subjects with normal renal function (n = 8)	Subjects with mild renal impairment (n = 8)	Subjects with moderate renal impairment (n = 8)	Subjects with severe renal impairment (n = 8)
C_{max} (ng/mL)	2100 (26.0)	2191 (28.8)	1868 (32.1)	2078 (45.5)
$AUC_{0-\infty}$ (ng·h/mL)	12,397 (27.7)	14,536 (30.7)	22,460 (42.2)	56,154 (24.9)
C_{48h} (ng/mL)	5.70 ± 3.63	9.34 ± 7.57	64.5 ± 68.1	334 ± 126
t_{max} (h)	2.5 (1.5, 3.0)	2.5 (1.5, 4.0)	3.0 (1.5, 4.0)	4.3 (3.0, 8.0)
$t_{1/2}$ (h)	6.4 ± 1.9	7.7 ± 3.0	22.2 ± 14.2	32.3 ± 7.4
CL/F (L/h)	12.1 (27.7)	10.3 (30.7)	6.68 (42.2)	2.67 (24.9)
V_z/F (L)	107.3 (38.0)	107.0 (37.7)	172.8 (102.3)	122.0 (43.7)

Geometric mean (coefficient of variation %). Mean ± standard deviation. Median (range) for t_{max}.
C_{max}, maximum concentration of plasma unchanged migalastat; $AUC_{0-\infty}$, area under the plasma unchanged migalastat concentration-time curve from 0 to infinity; C_{48h}, plasma unchanged migalastat concentration at 48 hours postdose; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution.

The safety analysis revealed adverse events in 3 of 8 subjects with normal renal function (3 events), 4 of 8 subjects with mild renal impairment (5 events), 4 of 8 subjects with moderate renal impairment (9 events), and 3 of 8 subjects with severe renal impairment (4 events). Among these events, 1 event in 1 subject with normal renal function (dry mouth), 3 events in 2 subjects with mild renal impairment (headache/nasal congestion and pollakiuria in 1 each), 3 events in 1 subject with moderate renal impairment (headache, diarrhea, and nightmare), and 2 events in 1 subject with severe renal impairment were considered adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically significant changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.5 Investigation of drug interaction

6.2.5.1 Drug interaction study with agalsidase (CTD 5.3.3.4.1, Study AT1001-013 [February 2011 to October 2012], reference data)

An open-label study was conducted to evaluate the drug interaction between migalastat and agalsidase in non-Japanese men with Fabry disease (a target sample size of 18 to 24).

In the first 14-day period (Period 1) of Stage 1, a single intravenous dose of agalsidase alfa 0.2 mg/kg or agalsidase beta 0.5 or 1.0 mg/kg was administered on Day 1. In the next 14-day period (Period 2), a single oral dose of migalastat 150 mg was administered in a fasting state on Day 1, and then a single intravenous dose of agalsidase alfa 0.2 mg/kg or agalsidase beta 0.5 or 1.0 mg/kg was administered 2 hours after the administration of migalastat. In the following 8-day period (Period 3), a single oral dose of migalastat 150 mg was administered in a fasting state. In the first 14-day period (Period 1) of Stage 2, a single intravenous dose of agalsidase alfa 0.2 mg/kg or agalsidase beta 0.5 or 1.0 mg/kg was administered on Day 1. In the next 14-day period (Period 2), a single oral dose of migalastat 450 mg was administered in a fasting state on Day 1, and then a single intravenous dose of agalsidase alfa 0.2 mg/kg or agalsidase beta 0.5 or 1.0 mg/kg was given 2 hours after the administration of migalastat.

All 23 subjects who received the study drug (12 subjects in Stage 1 and 11 subjects in Stage 2) were included in the safety and pharmacokinetics analysis sets.

Table 15 shows the ratio [90% CI] of the least squares geometric mean C_{max} and $AUC_{0\text{-last}}$ of plasma unchanged migalastat after co-administration of migalastat with agalsidase to those after administration of migalastat 150 mg alone.

Table 15. Comparison of plasma unchanged migalastat concentrations after administration of migalastat 150 mg alone and co-administration of migalastat with agalsidase

Agalsidase dose	C_{max}	$AUC_{0\text{-last}}$
Agalsidase alfa 0.2 mg/kg (n = 4)	1.03 [0.80, 1.31]	1.03 [0.69, 1.53]
Agalsidase beta 0.5 mg/kg (n = 5)	1.01 [0.70, 1.45]	1.11 [0.70, 1.76]
Agalsidase beta 1.0 mg/kg (n = 3)	0.95 [0.46, 1.95]	1.02 [0.65, 1.58]
Overall (n = 12)	1.00 [0.79, 1.26]	1.06 [0.82, 1.37]

Ratio of least squares geometric mean (migalastat co-administered with agalsidase/migalastat 150 mg alone) [90% CI]
C_{max}, maximum concentration of plasma unchanged migalastat (ng/mL); $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point (ng·h/mL).

Table 16 shows the ratio [90% CI] of the least squares geometric mean C_{max} and $AUC_{0\text{-last}}$ of plasma α-Gal A activity and α-Gal A protein concentrations after co-administration of agalsidase with migalastat to those after administration of agalsidase alone.

Table 16. Comparison ofα-Gal A activity and α-Gal A protein concentrations after administration of agalsidase alone and co-administration of agalsidase with migalastat

Migalastat dose	Agalsidase dose	Plasma α-Gal A activity		Plasma α-Gal A protein concentration	
		C_{max}	$AUC_{0\text{-last}}$	C_{max}	$AUC_{0\text{-last}}$
Migalastat 150 mg	Agalsidase alfa 0.2 mg/kg (n = 4)	1.71 [1.44, 2.02]	4.12 [3.26, 5.22]	1.09 [0.93, 1.28]	1.00 [0.97, 1.04]
	Agalsidase beta 0.5 mg/kg (n = 5)	1.73 [1.35, 2.21]	2.83 [2.14, 3.75]	0.94 [0.73, 1.21]	0.93 [0.74, 1.17]
	Agalsidase beta 1.0 mg/kg (n =3)	1.39 [0.97, 2.01]	2.00 [1.49, 2.67]	1.13 [0.83, 1.53]	1.23 [0.88, 1.72]
	Overall (n = 12)	1.63 [1.44, 1.84]	2.94 [2.44, 3.55]	1.03 [0.93, 1.15]	1.03 [0.92, 1.14]
Migalastat 450 mg	Agalsidase alfa 0.2 mg/kg (n = 4)	1.69 [1.26, 2.28]	3.12 [2.02, 4.81]	1.07 [0.97, 1.18]	1.06 [0.94, 1.19]
	Agalsidase beta 0.5 mg/kg (n = 1)	–	–	–	–
	Agalsidase beta 1.0 mg/kg (n = 6)	1.40 [1.04, 1.89]	1.93 [1.29, 2.88]	1.10 [0.93, 1.29]	1.46 [1.01, 2.13]
	Overall (n = 11)	1.55 [1.30, 1.84]	2.35 [1.83, 3.04]	1.06 [0.97, 1.16]	1.26 [1.03, 1.54]

Ratio of least squares geometric mean (agalsidase co-administered with migalastat/agalsidase alone) [90% CI]. −, data not available.
C_{max}, maximum plasma α-Gal A activity (nmol/mL·h) or maximum plasma α-Gal A protein concentration (ng/mL). $AUC_{0\text{-last}}$, are under the plasma α-Gal A activity (nmol·h/mL·h) or plasma α-Gal A protein concentration (ng·h/mL)-time curve from 0 to the last measurable time point.

In Stage 1, adverse events occurred in 1 of 4 subjects receiving agalsidase alfa 0.2 mg/kg alone, 4 of 5 subjects receiving agalsidase beta 0.5 mg/kg alone, 3 of 3 subjects receiving agalsidase beta 1.0 mg/kg alone, 2 of 3 subjects receiving migalastat in combination with agalsidase beta 1.0 mg/kg, and 5 of 12 subjects receiving migalastat 150 mg alone. In Stage 2, adverse events occurred in 3 of 4 subjects receiving agalsidase alfa 0.2 mg/kg alone, 1 of 2 subjects receiving agalsidase beta 0.5 mg/kg alone, 1 of 6 subjects receiving agalsidase beta 1.0 mg/kg alone, 4 of 4 subjects receiving migalastat in combination with agalsidase alfa 0.2 mg/kg, and 1 of 6 subjects receiving migalastat in combination with agalsidase beta 1.0 mg/kg. Adverse events developing in 1 subject receiving agalsidase alfa 0.2 mg/kg alone (post procedural hemorrhage) and 1 subject receiving migalastat in combination with agalsidase alfa 0.2 mg/kg (lethargy/nausea) in Stage 2 were considered adverse drug reactions. A serious adverse event (Fabry disease) occurred in 1 patient receiving agalsidase beta 0.5 mg/kg alone in Stage 2 but was considered unrelated to the study drug. There were no deaths or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.6 Pharmacodynamics

6.2.6.1 Thorough QT/QTc study (CTD 5.3.4.1.1, Study AT1001-010 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo- and moxifloxacin-controlled, randomized, double-blind, 4-arm, cross-over study was conducted to evaluate the effects of a single oral dose of migalastat on QT/QTc interval in non-Japanese healthy adults (a target sample size of 52).

In each period, placebo, a single dose of migalastat solution 150 or 1250 mg, or moxifloxacin (a positive control) 400 mg was orally administered in a fasting state, with a 7-day interval between each period.

All 52 subjects who were randomly assigned were included in the safety and pharmacokinetics analysis sets.[29)]

The pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat are shown in Table 17.

Table 17. Pharmacokinetic parameters of plasma unchanged migalastat after a single oral dose of migalastat

Parameters	Migalastat 150 mg (n = 51)	Migalastat 1250 mg (n = 52)
C_{max} (ng/mL)	1635 (27.3)	12,579 (29.6)
$AUC_{0\text{-last}}$ (ng·h/mL)	10,306 (24.5)	71,200 (27.1)
t_{max} (h)	3.0 (1.0, 6.0)	3.0 (2.0, 4.0)
$t_{1/2}$ (h)	3.8 (9.9)	4.0 (11.2)

Geometric mean (coefficient of variation %). Median (range) for t_{max}.
Cmax, maximum concentration of plasma unchanged migalastat; $AUC_{0\text{-last}}$, area under the plasma unchanged migalastat concentration-time curve from 0 to the last measurable time point; t_{max}, time to maximum plasma unchanged migalastat concentration; $t_{1/2}$, elimination half-life.

As for the estimated changes from baseline in individually corrected QT (QTcI) interval,[30)] the adjusted mean difference[31)] [95% CI] in comparison with placebo reached the maximum 12 hours after administration of migalastat 150 and 1250 mg (0.06 [2.06] milliseconds for migalastat 150 mg and 0.08 [2.06] milliseconds for migalastat 1250 mg), and the upper limit of the 95% CI was below 10 milliseconds. The adjusted mean difference [95% CI] at 2 hours after administration of moxifloxacin in comparison with placebo was 10.85 [9.26] ms, and the lower limit of the 95% CI was above 5 milliseconds.

The incidence of adverse events and adverse drug reactions was as follows: 14% (7 of 51 subjects) and 6% (3 of 51 subjects; headache in 3 subjects) for the placebo, respectively; 12% (6 of 51 subjects) and 0% (none of 51 subjects) for migalastat150 mg, respectively; 15% (8 of 52 subjects) and 10% (5 of 51 subjects; headache in 2, chest pain/feeling hot/hyperhidrosis, constipation, asthenia in 1 each) for migalastat 1250 mg, respectively; and 12% (6 of 51 subjects) and 2% (1 of 51 subjects; abdominal pain lower in 1 subject) for moxifloxacin. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

[29)] Of 52 subjects who were randomly assigned, 1 subject withdrew the consent after the completion of administration of migalastat 1250 mg in Period 1 and before the start of Period 2. Accordingly, 51 subjects were included in the safety and pharmacokinetics analysis sets for the administration of migalastat 150 mg and moxifloxacin.

[30)] QT interval adjusted for baseline QT and corrected for heart rate for each subject.

[31)] Values estimated by using a mixed-effect analysis of covariance model with treatment timing, treatment, and interaction between treatment timing and treatment as fixed effects and subjects as a random effect.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

6.2.7 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

A population pharmacokinetics (PPK) analysis was performed on the data of plasma unchanged migalastat concentrations measured at 4447 time points from 260 subjects (sex, 169 men and 91 women; difference in subjects, 179 healthy adults and 81 patients with Fabry disease; race, 204 Caucasian subjects, 25 black subjects, 24 Asian subjects, and 7 subjects of other races) in a total of 13 phase I, II, and III studies in healthy adults and patients with Fabry disease in and outside of Japan (a Japanese study, Study MGM115806; Foreign studies, Studies FAB-CL-101, FAB-CL-102, FAB-CL-103, FAB-CL-104, AT1001-010, AT1001-014, AT1001-015, AT1001-016, FAB-CL-201, FAB-CL-204, FAB-CL-205, and AT1001-011). A modeling software (NONMEM ver. 7.3) was used.

Age, body weight, and baseline estimated glomerular filtration rate (eGFR) were evaluated as patient characteristics in the PKK analysis, and the median (range) of these parameters was 36 (16, 74) years, 74 (38, 141) kg, and 89.8 (7.1, 236) mL/min/1.73m^2, respectively.

A 2-compartment model with first-order absorption including a depot compartment in which lag time was considered was established as a basic model which integrated eGFR and body weight as covariates for CL/F and body weight as a covariate for V_2/F for the central compartment. In this model, eGFR, CLcr, body weight, subject difference (a healthy adult or a patient with Fabry disease), and race were evaluated as covariates for parameter estimates in individuals by using a stepwise method. In addition to the previously incorporated covariates, eGFR and body weight as covariates for CL/F and body weight as a covariate for V_2/F, the subject difference (a healthy adult or a patient with Fabry disease) was integrated as a covariate for CL/F and V_2/F in the final model. Based on the investigation of the covariates obtained from the final model, the variation range for CL/F was estimated to be 6.01 and 22.32 L/h for eGFR of 30 and 120 mL/min/1.73m^2, respectively, and to be 0.85 and 1.47 L/h for body weight of 50 and 170 kg, respectively. The final model was used to investigate the estimates of parameters for individual healthy adults and patients with Fabry disease in the thorough QT/QTc study (Study AT1001-010) and the foreign phase III study (Study AT1001-011). As a result, C_{max} (geometric mean [coefficient of variation]) and $AUC_{0\text{-}48h}$ for healthy adults and patients with Fabry disease were estimated to be 1539 ng/mL (24.7%) and 1180 ng/mL (32.9%), respectively, and 9682 ng·h/mL (26.1%) and 9033 ng·h/mL (35.1%), respectively.

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

6.R.1 Timing of administration

The applicant's explanation about the timing of administration of migalastat:

In the study of food effects (Study AT1001-016), a comparison of exposure was performed between administration of migalastat 150 mg with a meal and in a fasting state. The C_{max} and $AUC_{0\text{-}last}$ for migalastat

administered 1 hour before a high-fat meal, 1 hour before a light meal, and 1 hour after a light meal decreased by approximately 15%, 18%, and 39%, respectively, and 38%, 43%, and 40%, respectively, as compared with the administration under fasting conditions. In the study, the t_{max} after administration of migalastat in a fasting state was approximately 3 hours, and the plasma unchanged migalastat concentration 2 hours postdose was equivalent to 87.2% of the C_{max}. Based on the findings, it was presumed that food was unlikely to affect the bioavailability of unabsorbed migalastat (12.8% of C_{max}) even when a meal was taken 2 hours postdose. In addition, when a meal is taken 2 hours predose, the residual food is considered to be unlikely to significantly influence the bioavailability of migalastat, though depending on the time to elimination food from the stomach, as compared with migalastat administered concomitantly with a meal or 1 hour after a meal. The exact mechanism of food effects on migalastat remains unclear, and effects of food taken about 2 hours before or 2 hours after administration of migalastat on the pharmacokinetics of migalastat have not been evaluated yet. However, with consideration of these study results, phase III studies were conducted in which migalastat was to be administered 2 hours before or 2 hours after food intake.

It is considered that migalastat, when administered intermittently, binds to some mutant forms of α-Gal A selectively and is transferred to the lysosomes, where dissociation of migalastat allows the recovery of α-Gal A activity, leading to decreases in the deposited substrates [see Section "3.R.1 Mechanism of action of migalastat"]. Accordingly, migalastat should be administered at the same time of the scheduled day, in consideration of administration of migalastat at a regular interval. In tissue distribution studies in which migalastat or ^{14}C-migalastat was administered to male mice and male rats, nearly complete elimination was observed in many tissues after 12 to 24 hours postdose, but in some tissues, concentrations of unchanged migalastat or radioactivity could be detected even 24 hours postdose (CTD 4.2.2.2.3 and 4.2.2.3.2). In light of its elimination half-life, migalastat was expected to be almost completely eliminated from these tissues by 36 hours postdose. Therefore, the following precautions will be provided: if a dose of migalastat is missed for the planned time, the patient should take the missed migalastat dose if it is within 12 hours of the planned time. If more than 12 hours have passed, the patient should resume taking migalastat at the next planned dosing time. No clinical study data are available which support that migalastat can be taken at an interval of more than 36 hours if a dose of migalastat is missed for the planned time. Nevertheless, the specific rules for dosing timing for a missed migalastat dose can help to avoid taking migalastat on 2 consecutive days. Individual patients will be instructed to take migalastat at a regular time, which means in turn that the dosing time can be set appropriately for individual patients, and such instruction will contribute to preventing poor treatment adherence.

PMDA's review:
No concrete data based on pharmacokinetics and supporting the timing of administration proposed by the applicant (administration of migalastat 2 hours before or 2 hours after a meal) are available from clinical studies. However, PMDA considers that the applicant's explanation is acceptable. in light of data available from the study of food effects (Study AT1001-016) and the efficacy and safety data obtained from the phase III studies in which migalastat was administered at the administration timing described above. Based on the pharmacokinetic mechanism of action of migalastat, no specific problems have been identified in the proposed

actions taken for a missed migalastat dose and the proposal for the administration of migalastat at a regular planned time for each patient. Information on the proper use of migalastat in terms of each administration timing should be adequately provided through documents and materials [see Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.5 Dosage and administration"].

6.R.2 Similarity in pharmacokinetics of migalastat between Japanese and non-Japanese populations

The applicant's explanation about the similarity in the pharmacokinetics of migalastat in Japanese and non-Japanese populations:

In Study MGM115806, a single dose of migalastat 150 mg was orally administered to Japanese healthy adults in a fasting state, and the C_{max} and $AUC_{0-\infty}$ (geometric mean [coefficient of variation]) was 2124 ng/mL (36.3%) and 11,519 ng·h/mL (27.4%), respectively. In 5 foreign clinical studies,[32)] a single dose of migalastat 150 mg was orally administered to non-Japanese healthy adults in a fasting state, and the C_{max} and $AUC_{0-\infty}$ ranged from 1516 to 2100 ng/mL (25.9% to 33.8%) and from 9805 to 12,397 ng·h/mL (22.0% to 27.7%), respectively, showing no marked difference in exposure from that observed in Japanese healthy adults. Body weight is suggested to be a covariate affecting the pharmacokinetics of migalastat, but no marked differences in the pharmacokinetic parameters corrected for body weight[33)] were observed between Japanese and non-Japanese healthy adults.

No pharmacokinetic data were obtained from Japanese patients with Fabry disease. Meanwhile, the C_{max} and AUC (geometric mean [coefficient of variation]) in non-Japanese patients with Fabry disease after alternate-day administration of migalastat 150 mg was 1524 to 2029 ng/mL (22.0% to 40.0%) and 8582 to 10,638 ng·h/mL (29.7% to 35.6%), respectively, in individual evaluation periods in Study FAB-CL-20 (Table 13) and 1180 ng/mL (32.9%) and 9033 ng·h/mL (35.1%), respectively, in Study AT1001-011 [see Section "6.2.7 Population pharmacokinetic analysis], showing no marked differences in pharmacokinetics between non-Japanese healthy adults and non-Japanese patients with Fabry disease. These findings suggest that similarly, no marked differences in pharmacokinetics would exist between Japanese and non-Japanese patients with Fabry disease.

Although no pharmacokinetic data are available from Japanese patients with Fabry disease, PMDA accepted the applicant's explanation on the similarity in pharmacokinetics between Japanese and non-Japanese populations, because no marked differences in pharmacokinetics have been identified in Japanese and non-Japanese healthy adults and non-Japanese patients with Fabry disease.

6.R.3 Pharmacokinetics of migalastat administered in patients with renal impairment

In Study AT1001-015 evaluating the effects of renal function on the pharmacokinetics of migalastat in non-Japanese subjects, the exposure ($AUC_{0-\infty}$) and half-life of plasma unchanged migalastat increased in proportion

32) Studies AT1001-010, AT1001-014, AT1001-015, AT1001-016, and AT1001-018.

33) The C_{max} and $AUC_{0-\infty}$ (geometric mean) corrected for body weight was 1928 ng/mL and 10,456 ng· h/mL, respectively, in Japanese healthy adults and 1682 to 2334 ng/mL and 10,737 to 13,778 ng· h/mL, respectively, in non-Japanese healthy adults.

to the severity of renal impairment. PMDA asked the applicant to discuss the factors responsible for the observed tendency.

The applicant's response:
In Study AT1001-015, following a single oral dose of migalastat 150 mg, the ratio of the least squares geometric mean of $AUC_{0-\infty}$ of plasma unchanged migalastat in subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function was 1.17, 1.81, and 4.53, respectively, and increased with increases in severity of renal impairment. The half-life (mean) of plasma unchanged migalastat was 6.4, 7.7, 22.2, and 32.3 hours in the subjects with normal renal function and mild, moderate, and severe renal impairment, respectively, and tended to be prolonged in proportion to the severity of renal impairment. A plausible explanation is as follows: The results from the mass balance study (Study AT1001-014) showed that approximately 77% of administered radioactivity was excreted in urine by 24 hours postdose. In consideration of the results, the plasma clearance was reduced depending on the severity of renal impairment, and the reduction, in turn, delayed the excretion of migalastat and led to an increase in exposure.

In Study AT1001-015, the concentration at 48 hours postdose (C_{48h}) (mean) after a single oral dose of migalastat was 5.70, 9.34, 64.5, and 334 ng/mL in the subjects with normal renal function and mild, moderate, and severe renal impairment, respectively (Table 14). The C_{48h} was around the lower limit of quantification in subjects with normal renal function and was slightly above the lower limit of quantification in subjects with slight renal impairment. These results suggest that plasma unchanged migalastat is unlikely to accumulate after repeated doses of migalastat 150 mg given every other day in patients with normal renal function and those with mild renal impairment. Meanwhile, the C_{48h} was higher in subjects with moderate or severe renal impairment than in subjects with mild renal impairment and was further higher especially in subjects with severe renal impairment. The findings suggest that repeated doses of migalastat may lead to accumulation of unchanged migalastat. Therefore, the plasma unchanged migalastat concentrations after the initial dose and in the steady state after repeated doses of migalastat 150 mg administered every other day in subjects with moderate and severe renal impairment were estimated by using a simulation to evaluate the accumulation. The C_{max}, C_{48h}, and AUC_{0-48h} were estimated to be 1734 ng/mL, 84.3 ng/mL, and 24,552 ng·h/mL, respectively, after the initial dose and 822 ng/mL, 101.1 ng/mL, and 27,191 ng·h/mL, respectively, after repeated doses in subjects with moderate renal impairment. The C_{max}, C_{48h}, and AUC_{0-48h} were estimated to be 1980 ng/mL, 361.9 ng/mL, and 56,502 ng·h/mL, respectively, after the initial dose and 2416 ng/mL, 497.1 ng/mL, and 74,428 ng·h/mL, respectively, after repeated doses in subjects with severe renal impairment. Especially in subjects with severe renal impairment, the magnitude of the increase in exposure after repeated doses of migalastat 150 mg once every other day suggest the possibility of accumulation of migalastat.

As shown above, the results from Study AT1001-01 and the possible accumulation of migalastat in the steady state after its repeated doses were evaluated. In light of the evaluation results, together with the safety and efficacy data obtained from clinical studies [see Section "7.R.6.1 Patients with renal impairment"], it is considered that no significant concerns are raised regarding the alternate-day administration of migalastat 150 mg in patients with Fabry disease and moderate renal impairment. Meanwhile, for patients with Fabry

disease and severe renal impairment, the magnitude of increases in exposure after administration of migalastat 150 mg was higher than that in those with normal renal function, and it is indicated that migalastat may accumulate in the steady state when the drug is repeatedly administered once every other day. The recommended dosage and regimen cannot thus be determined for patients with Fabry disease and severe renal impairment, and there is no clinical study experience with administration of migalastat to patients with Fabry disease and baseline severe renal impairment. In view of these, the alternate-day administration of migalastat 150 mg is not recommended for patients with Fabry disease and severe renal impairment. Based on the above, we plan to conduct a separate clinical study to investigate the administration of migalastat, including regimens, to patients with Fabry disease and severe renal impairment.

PMDA's view:

The kidney is the main organ involved in the elimination of migalastat, and available data suggest that exposure increased in proportion to the decrease in renal function. Therefore, patients with renal impairment should be managed carefully. In patients with moderate renal impairment, the evaluation of the accumulation of migalastat in such patients and the safety and efficacy data available from clinical studies [see Section "7.R.6.1 Patients with renal impairment"] suggest that no significant concerns are raised regarding the alternate-day administration of migalastat 150 mg in such patients. For patients with severe renal impairment, however, the magnitude of the increase in exposure after administration of migalastat 150 mg was higher in subjects with severe renal impairment than in subjects with normal renal function, suggesting the possible accumulation in the steady state after the repeated doses of migalastat administered once every other day. The recommended dose and regimen based on the safety and efficacy for patients with severe renal impairment have not been determined so far. Therefore, as indicated by the applicant, PMDA considers that the package insert should include precautions stating that the alternate-day administration of migalastat 150 mg is not recommended for patients with severe renal impairment. The applicant plans to conduct a clinical study in patients with severe renal impairment and is requested to submit the results immediately after data are available. In addition, the applicant is required to collect information on the safety and efficacy of migalastat in patients with renal impairment after its launch and to re-evaluate the appropriateness of the precautions thereof based on the information obtained. The administration of migalastat to patients with Fabry disease and renal impairment will be discussed also in the next section based on the close review of the safety and efficacy of migalastat [see Section "7.R.6.1 Patients with renal impairment"].

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

Data from the studies listed in Table 18 were submitted as the main evaluation data for the efficacy and safety of migalastat.

Table 18. List of main clinical studies for the efficacy and safety of migalastat

Document category	Region	Study name	Phase	Patient population	Number of subjects enrolled	Outline of dosages and regimens	Main endpoints
Evaluation	Outside Japan	FAB-CL-201	II	Men with Fabry disease	15	Main treatment period: 1) migalastat 25 mg twice daily for 2 weeks, migalastat 100 mg twice daily for 2 weeks, migalastat 250 mg twice daily for 2 weeks, migalastat 25 mg twice daily for 6 weeks; and 2) migalastat 150 mg once daily for 12 weeks Extended treatment period: 1) migalastat 25 mg twice daily; and 2) migalastat 50 mg once daily.	Safety Pharmacokinetics Pharmacodynamics
	Outside Japan	FAB-CL-202	II	Men with Fabry disease	4	Migalastat 150 mg once every other day	Safety Pharmacokinetics Pharmacodynamics
	Outside Japan	FAB-CL-203	II	Men with Fabry disease	5	Migalastat 150 mg once every other day	Safety Pharmacodynamics
	Outside Japan	FAB-CL-204	II	Women with Fabry disease	9	Migalastat 50, 150, or 250 mg once every other day	Safety Pharmacokinetics Pharmacodynamics
	Outside Japan	FAB-CL-205	II	Men and women with Fabry disease	23	Migalastat 150 mg once every other day. Dose escalation period: The 2-month regimen consisted of the administration of migalastat 250 mg once daily for 3 days, followed by a 4-day interval. The subsequent 2-month regimen consisted of administration of migalastat 500 mg once daily for 3 days, with a 4-day interval.	Safety Pharmacokinetics Pharmacodynamics
	Global	AT1001-012	III	Men and women with Fabry disease	57	Migalastat 150 mg once every other day, or an enzyme replacement therapy at its approved dosage and regimen.	Efficacy Safety
	Outside Japan	AT1001-011	III	Men and women with Fabry disease	67	Migalastat 150 mg or placebo once every other day	Efficacy Safety Pharmacokinetics Pharmacodynamics
	Outside Japan	AT1001-041	III	Men and women with Fabry disease	85	Migalastat 150 mg once every other day	Safety Efficacy

Results of the main clinical studies are described below.

7.1 Phase II studies

7.1.1 Foreign phase II study in men with Fabry disease (CTD 5.3.4.2.1, Study FAB-CL-201 [January 2006 to January 2008])

An open-label, dose escalation study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese men with Fabry disease (a target sample size of 20) [for pharmacokinetics, see Section "6.2.3.1 Foreign phase II study in men with Fabry disease"].

The main inclusion criteria included the following: Men between 18 and 55 years of age (inclusive) with a diagnosis of Fabry disease with a *GLA* missense mutation (individual or familial) who had enhanceable α-Gal

A activity[34] and were previously untreated with ERT or substrate depletion therapy or have not received ERT within 28 days before the start of the study treatment.[35]

This study consisted of a screening period (4 weeks), a main treatment period (12 weeks), and optional extension periods 1 (36 weeks) and 2 (48 weeks).

In the main treatment period, the subjects were to receive oral migalastat 25 mg twice daily in Weeks 1 and 2, 100 mg twice daily in Weeks 3 and 4, 250 mg twice daily in Weeks 5 and 6, and 25 mg twice daily in Weeks 7 to 12. In the extension period, migalastat was to be orally administered at 25 mg twice daily. The protocol for this study was revised several times during the study. The protocol was amended to orally administer migalastat 150 mg once daily in the main treatment period and migalastat 50 mg once daily in the extension periods 1 and 2.[36] Changes in dosages and regimens in individual subjects are shown in Table 19.

Table 19. Changes in dosages and regimens of migalastat (main treatment period and extension periods)

Subject No.	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	Weeks 7 to 12	Weeks 13 to 24	Weeks 25 to 36	Weeks 37 to 48	Weeks 49 to 96
01-1	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	25 mg BID	50 mg QD	50 mg QD
01-2	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	25 mg BID	50 mg QD	50 mg QD
01-3	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	25 mg BID	50 mg QD	50 mg QD
01-4	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	25 mg BID	50 mg QD	50 mg QD
01-5	25 mg BID	−	−	−	−	−	−	−
01-6	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	50 mg QD	50 mg QD	50 mg QD
01-7	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	50 mg QD	−	−
01-8	25 mg BID	100 mg BID	250 mg BID	25 mg BID	25 mg BID	50 mg QD	−	−
01-9	25 mg BID	100 mg BID	250 mg BID	250 mg BID	50 mg QD	50 mg QD	50 mg QD	50 mg QD

BID, bis in die (twice daily). QD, quaque die (once daily).−, not applicable.

All 15 subjects who received the study drug were included in the safety analysis set, and all 9 subjects[36] who entered the main treatment period were included in the pharmacokinetics and pharmacodynamics analysis sets. Study treatment was discontinued in 1 subject (for an adverse event) in the main treatment period and 2 subjects (for consent withdrawal in both subjects) during the extension period. No subject was withdrawn from the study in the extension period 2.

Changes in α-Gal A activity in peripheral blood mononuclear cells (PBMCs) and urinary GL-3 concentrations as pharmacodynamic parameters are shown in Table 20. Administration of migalastat increased the α-Gal A activity in PBMCs and yielded no consistent changes in urinary GL-3 concentrations.

[34] Defined as having residual α-Gal A activity of ≥3% of wild-type α-Gal A activity and enhanced α-Gal A activity by ≥20% after incubation with migalastat (20 μmol/L) in the subjects' peripheral blood mononuclear cells (PBMCs). For 6 subjects enrolled in the study after a revision of the protocol, α-Gal A activity was considered to be enhanceable when any of the following was met after determination of α-Gal A activity in the subjects' PBMC following oral administration of migalastat 150 mg once daily:
- Residual α-Gal A activity of <1% of wild-type α-Gal A activity: ≥2% of wild-type α-Gal A activity.
- Residual α-Gal A activity of ≥1% and <3% of wild-type α-Gal A activity: ≥2 times baseline activity.
- Residual α-Gal A activity of ≥3% and <10% of wild-type α-Gal A activity: Higher than baseline by ≥3% of wild-type α-Gal A activity.
- Residual α-Gal A activity of ≥10% of wild-type α-Gal A activity: 1.3 times baseline activity.

[35] Protocol was revised to include patients who were naïve to ERT or who had not previously received within 28 days before the start of the study treatment.

[36] All 6 subjects who were enrolled in the study after the revision of the protocol did not meet the inclusion criterion for α-Gal A (footnote 34). Accordingly, none of them entered the main treatment period.

Table 20. Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations (main treatment period and extension periods)

Endpoints	Subject No.	Baseline	Week 2	Week 4	Week 6	Week 12	Week 24	Week 48	Week 96
α-Gal A activity in PBMCs (nmol/h/mg)	01-1	5.2	14.6	13.3	14.1	17.4	15.5	19.8	20.3
	01-2	4.7	19.7	26.9	27.9	24.6	−	24.7	22.8
	01-3	6.6	16.3	26.8	33.3	24.6	−	26	20.3
	01-4	1.0	11.7	14.5	15.3	14.8	−	9.4	12.8
	01-5	10.7	15.9	−	−	−	−	−	−
	01-6	0.9	5.2	6.6	4.5	3.9	3.5	6.2	1.9
	01-7	0	0.4	0.5	1.4	0.4	0.1	−	−
	01-8 [b)]	0.1	0.9	1.7	1.2	0.9	0.8	−	−
	01-9	0.2	1.6	1.5	2.9	0.3	0.1	0.6	0.2
Urinary GL-3 concentrations (pmol/nmol PC [a)])	01-1	66.5	72.7	155.5	371.0	54.2	55.5	50.8	52.1
	01-2	49.4	38.1	71.7	107.1	47.8	61.0	63.5	39.4
	01-3	64.1	61.4	93.7	110.2	106.3	68.2	49.3	68.3
	01-4	159.0	198.8	272.4	556.4	140.2	139.1	120.6	131.6
	01-5	75.5	69.4	−	−	−	−	−	−
	01-6	851.9	1641.3	2062.3	1816.0	1914.0	1669.2	1750.6	2266.5
	01-7	2212.3	3508.8	2625.8	1845.5	469.9	1435.0	−	−
	01-08 [b)]	4091.0	2653.0	2575.9	1784.9	1368.9	1290.8	−	−
	01-09	457.7	800.5	619.7	984.6	1859.7	−	2647.6	2160.8

−, no measurements available.
a) PC, phosphatidylcholine
b) Subjects determined to have *GLA* mutation nonamenable to migalastat with a Good Laboratory Practice (GLP)-validated HEK assay[37)] in a post-hoc analysis.

The safety analysis revealed that adverse events or adverse drug reactions occurred in all 9 subjects who entered the main treatment period. Adverse events occurring in ≥2 subjects during the main treatment period and the treatment extended periods were headache (5), nausea(4), abdominal pain upper(2), diarrhea (2), dry mouth (2), vertigo (2), pain (2), back pain (2), myalgia (2), pain in extremity (2), and insomnia (2). Adverse drug reactions occurring in ≥2 subjects were headache (5), nausea (3), abdominal pain upper (2), diarrhea (2), dry mouth (2), vertigo (2), pain (2), back pain (2), and myalgia (2). Of 6 subjects who received migalastat 150 mg once daily in the screening period, 5 subjects experienced adverse events. In these subjects, an adverse event occurring in ≥2 subjects was arthralgia (2), and the event was in both subjects was considered an adverse drug reaction.

There were no deaths or serious adverse events. An adverse event (hypertension) in 1 subject (migalastat 25 mg BID) in the main treatment period led to treatment discontinuation and was considered to represent an adverse drug reaction.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.1.2 Foreign phase II study in men with Fabry disease (CTD 5.3.4.2.2, Study FAB-CL-202 [June 2006 to May 2008])

An open-label study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese men with Fabry disease (a target sample size of 8).

[37)] HEK-293 cells expressing a mutant form of α-Gal A were incubated in the presence or absence of migalastat (10 μmol/L). Patients with *GLA* mutation having α-Gal A activity of ≥3% of wild-type α-Gal A activity in the presence of migalastat and ≥1.2 times higher than α-Gal A activity in the absence of migalastat were considered to be "responsive."

The main inclusion criteria included the following: Men between 18 and 65 years of age (inclusive) with a diagnosis of Fabry disease with a *GLA* missense mutation (individual or familial), who had enhanceable α-Gal A activity,[38] were previously untreated with ERT or substrate depletion therapy or could discontinue ERT during the study period, and had clinical symptoms of Fabry disease (abnormal electrocardiogram or left ventricular hypertrophy, or renal impairment, history of stroke, or peripheral nerve dysfunction).

This study consisted of a screening period (4 weeks), a main treatment period (12 weeks), and an optional extension period (36 weeks).

Migalastat 150 mg was orally administered every other day.

All 4 subjects who received the study drug were included in the safety, pharmacokinetics, and pharmacodynamics analysis sets. No subject discontinued the study treatment in the main treatment period, and 1 subject (poor treatment adherence) was withdrawn from the study in the extension period.

Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations as pharmacodynamic parameters are shown in Table 21. Administration of migalastat increased the α-Gal A activity in PBMCs and reduced the urinary GL-3 concentrations in 3 of 4 subjects.

Table 21. Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations (main treatment period and extension period)

Endpoints	Subject No.	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48
α-Gal A activity in PBMCs (nmol/h/mg)	02-1 [b]	0.14	0.14	BLQ	BLQ	0.18	−	0.12
	02-2	0.24	2.23	1.76	2.3	−	−	−
	02-3 [c]	0.21	2.88	3.18	2.43	3.36	BLQ	−
	02-4	0.3	7.53	6.45	7.36	7.12	7.7	6.06
Urinary GL-3 concentrations (pmol/nmol PC [a])	02-1 [b]	2098.9	5794.3	3986.1	2298.3	5052.1	4568.7	4050.4
	02-02	2935.0	1699.6	1357.1	1162.0	−	−	−
	02-3 [c]	2355.6	677.5	470.4	594.7	663.9	928.6	−
	02-4	336.2	258.6	225.2	207.6	138.5	188.9	182.3

BLQ, below the lower limit of quantification. −, no measurements available.
a) PC, phosphatidylcholine
b) Subjects determined to have *GLA* mutation nonamenable to migalastat with a GLP HEK assay[37] in a post-hoc analysis.
c) Subjects had not received the study drug because of problems in the supply of the study drug beginning 69 days before the Week 48 visit (5 days before Week 36 visit).

As for safety, adverse events or adverse drug reactions occurred in 3 of the 4 subjects during the main treatment period and the extension period. An adverse event occurring in ≥2 subjects was the event abdominal pain upper in 2 subjects, and among them, the event in 1 subject was considered to represent an adverse drug reaction.

There were no deaths or adverse events leading to treatment discontinuation. A serious adverse event (atrioventricular block) occurred in 1 subject, and the event was considered to be unrelated to the study drug.

[38] Defined as α-Gal A activity meeting any of the following criteria after incubation with migalastat (20 μmol/L) in the subjects' PBMCs:
- Residual α-Gal A activity of <1% of wild-type α-Gal A activity: ≥2% of wild-type α-Gal A activity.
- Residual α-Gal A activity of ≥1% and <3% of wild-type α-Gal A activity: ≥2 times baseline activity.
- Residual α-Gal A activity of ≥3% and <10% of wild-type α-Gal A activity: Higher than baseline by ≥3% of wild-type α-Gal A activity.
- Residual α-Gal A activity of ≥10% of wild-type α-Gal A activity: 1.3 times baseline activity.

There were no clinically meaningful changes observed in laboratory data or vital signs. As for electrocardiographic findings, atrioventricular block and atrial fibrillation occurred in 1 subject and were considered adverse events.

7.1.3 Foreign phase II study in men with Fabry disease (CTD 5.3.4.2.3, Study FAB-CL-203 [May 2006 to March 2008])

An open-label study was conducted to evaluate the safety and pharmacodynamics of migalastat in non-Japanese men with Fabry disease (a target sample size of 8).

The main inclusion criteria included the following: Men between 18 and 65 years of age (inclusive) with a diagnosis of Fabry disease with a *GLA* missense mutation (individual or familial), who had enhanceable α-Gal A activity,[38)] were previously untreated with ERT or substrate depletion therapy or could discontinue ERT during the study period, and had clinical symptoms of Fabry disease (abnormal electrocardiogram or left ventricular hypertrophy, or renal impairment).

This study consisted of a screening period (4 weeks), a main treatment period (24 weeks), and an optional extension period (24 weeks).

Migalastat 150 mg was orally administered every other day.

All 5subjects who received the study drug were included in the safety and pharmacodynamics analysis sets. No subject was withdrawn from the study.

Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations as pharmacodynamic parameters are shown in Table 22. Administration of migalastat increased the α-Gal A activity in PBMCs and yielded no consistent changes in urinary GL-3 concentrations.

Table 22. Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations (main treatment period and extension period)

Endpoints	Subject No.	Baseline	Week 4	Week 12	Week 24	Week 48
α-Gal A activity in PBMCs (nmol/h/mg)	03-1	0.05	0.1	0.22	0.36	0.1
	03-2 [b)]	0.06	0.08	BLQ	0.13	0.1
	03-3 [b)]	0.14	0.39	BLQ	0.3	0.33
	03-4	3.4	8.46	10.6	10.9	7.4
	03-5	0.18	0.3	0.38	1.32	3.13
Urinary GL-3 concentrations (pmol/nmol PC [a)])	03-1	3875.9	8585.9	6414.6	6240.0	4765.3
	03-2 [b)]	3565.5	4220.1	5677.9	3803.5	3998.2
	03-3 [b)]	1488.7	5439.0	4837.8	4209.3	4347.2
	03-4	170.0	147.4	108.4	135.7	132.1
	03-5	1159.7	1532.0	1081.0	559.1	841.1

BLQ, below the lower limit of quantification.
a) PC, phosphatidylcholine
b) Subjects determined to have *GLA* mutation nonamenable to migalastat with the GLP HEK assay [37)] in a post-hoc analysis.

As for safety, adverse events or adverse drug reactions occurred in all subjects. Adverse events occurring in ≥2 subjects in the main treatment period and the extension period were proteinuria in 2 subjects and headache in 2 subjects. The event proteinuria in 2 subjects was considered to be an adverse drug reaction.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.1.4 Foreign phase II study in women with Fabry disease (CTD 5.3.4.2.4, Study FAB-CL-204 [September 2006 to May 2008])

A randomized, open-label study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese women with Fabry disease (a target sample size of 12) [for pharmacokinetics, see Section "6.2.3.2 Foreign phase II study in women with Fabry disease"].

The main inclusion criteria included the following: Women between 18 and 65 years of age (inclusive) with a diagnosis of Fabry disease with a *GLA* missense mutation (individual or familial), who had enhanceable α-Gal A activity,[38)] were previously untreated with ERT or substrate depletion therapy or could discontinue ERT during the study period, and had clinical symptoms of Fabry disease (abnormal electrocardiogram or left ventricular hypertrophy, or renal impairment, history of stroke, or peripheral nerve dysfunction).

This study consisted of a screening period (4 weeks), a main treatment period (12 weeks), and an optional extension period (36 weeks).

Migalastat 50, 150, or 250 mg was orally administered every other day.

All 9 subjects who received the study drug (2 in the migalastat 50 mg group, 4 in the migalastat 150 mg group, and 3 in the migalastat 250 mg group) were included in the safety, pharmacokinetics, and pharmacodynamics analysis sets. No subject discontinued the study treatment.

Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations as pharmacodynamic parameters are shown in Table 23. Administration of migalastat increased the α-Gal A activity in PBMCs at Week 48 in 8 of 9 subjects and reduced the urinary GL-3 concentrations at Week 48 in 7 of 9 subjects.

Table 23. Changes in α-Gal A activity in PBMCs and urinary GL-3 concentrations (main treatment period and extension period)

Endpoints	Subject No.	Dose	Baseline	Week 8	Week 12	Week 24	Week 36	Week 48
α-Gal A activity in PBMCs (nmol/h/mg)	04-1	Migalastat 50 mg QOD	13.4	1.54	2.46	24.6	22.6	26
	04-2		24.5	33.1	35.8	43.2	51.5	39.6
	04-3	Migalastat 150 mg QOD	25.1	4.45	4.15	33.8	40	–
	04-4		6.39	18.8	18.4	16.6	5.2	16.1
	04-5 [b)]		17.3	0.45	5.85	31.8	21.6	22.2
	04-6 [b)]		24.6	12.1	12.6	37.7	43.8	46.5
	04-7 [b)]	Migalastat 250 mg QOD	3.25	8.41	6.56	9.92	7.71	4.83
	04-8		14.7	18.9	23.3	34.6	30.4	29.2
	04-9 [b)]		13.1	17.4	8.86	23.8	9.93	7.58
Urinary GL-3 concentrations (pmol/nmol PC [a)])	04-1	Migalastat 50 mg QOD	117.8	167.4	196.3	77.2	–	97.9
	04-2		28.1	47.5	29.4	17.6	22.4	17.3
	04-3	Migalastat 150 mg QOD	651.4	–	228.9	213.8	327.3	340.8
	04-4		502.2	413.7	248.0	373.8	267.8	284.6
	04-5 [b)]		51.7	234.3	352.8	151.7	377.5	541.2
	04-6 [b)]		267.0	730.3	94.5	289.2	680.0	673.2
	04-7 [b)]	Migalastat 250 mg QOD	408.7	486.9	365.3	368.5	–	267.7
	04-8		295.5	69.3	189.8	162.4	47.0	42.4
	04-9 [b)]		169.7	338.1	151.9	3449.3	348.7	97.2

QOD, once every other day
a) PC, phosphatidylcholine
b) Subjects determined to have *GLA* mutation nonamenable to migalastat with the GLP HEK assay[37)] in a post-hoc analysis.

As for safety, adverse events occurred in all subjects. The following adverse events occurred in ≥2 subjects in any group: Headache (1 in the migalastat 50 mg group and 3 in the migalastat 150 mg group); arthralgia (1 in the migalastat 50 mg group and 2 in the migalastat 150 mg group); and pain in extremity (2 in the migalastat 150 mg group). Adverse drug reactions occurred in 2 subjects in the migalastat 50 mg group (sinus arrhythmia/electrocardiogram abnormal, and abdominal discomfort in 1 each), 3 subjects in the migalastat 150 mg group (atrioventricular block, myocardial ischemia/nasopharyngitis/ cough/ rash macular/proteinuria, and cardiac murmur/headache/fatigue/pain in extremity/chills/pyrexia in 1 each), and 2 subjects in the migalastat 250 mg group (back pain/constipation/blood glucose increased/feeling abnormal/lower abdominal mass/fungal infection and bronchitis/visual acuity reduced/atrial fibrillation/electrocardiogram abnormal in 1 each). There were no adverse drug reactions occurring in ≥ 2 subjects in any group.

There were no deaths or adverse events leading to treatment discontinuation. A serious adverse event occurred in 1 subject in the migalastat 150 mg group during the main treatment period (musculoskeletal chest pain), but the event was considered to be unrelated to the study drug.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.1.5 Foreign phase II extension study in patients with Fabry disease (CTD 5.3.4.2.5, Study FAB-CL-205 [September 2007 to September 2012])

An open-label, extension study was conducted to evaluate the long-term safety, pharmacokinetics, and pharmacodynamics of migalastat in non-Japanese patients with Fabry disease completing Studies FAB-CL-201, 202, 203, or 204.

Migalastat 150 mg was orally administered every other day. The protocol for this study was revised several times during the study. The protocol was amended to include a dose escalation period (4 months). In the first 2 months of the dose escalation period, migalastat 250 mg was orally administered once daily for 3 days with a 4-day interruption (3/4D regimen). Then, migalastat 500 mg was administered with the 3/4D regimen for the subsequent 2 months[39]. After the dose escalation period, migalastat 500 mg was administered with the 3/4D regimen. Subsequently, another amendment was made to the protocol to administer migalastat 150 mg every other day after the dose escalation period. The dosing regimen was changed to administer migalastat 150 mg every other day from the start of the dose escalation period to Months 18 to 24 to all subjects, excluding 1 subject who received migalastat 300 mg with the 3/4D regimen after the dose escalation period and 4 subjects who were withdrawn from this study during administration of migalastat 500 mg with the 3/4D regimen. Changes in the dosage and regimen of migalastat after the start of dose escalation period are shown in Table 24.

Table 24. Changes in dosage and regimen of migalastat after the start of dose escalation period

		Dosage regimen of migalastat	Months 1 to 2	Months 3 to 4	Months 5 to 8	Months 9 to 11	Months 12 to 14	Months 15 to 17	Months 18 to 20	Months 21 to 23	Months 24 and onward
Amenable	Men (n = 11)	250 mg 3/4D	11	–	1[a)]	2[a), b)]	2[a), b)]	2[a), b)]	2[a), b)]	–	–
		500 mg 3/4D	–	11[a)]	10	9	9	8	4	–	–
		150 mg QOD	–	–	–	–	–	–	3	9[a),]	8[a)]
		300 mg 3/4D	–	–	–	–	–	–	1[c)]	1[c)]	1[c)]
	Women (n = 5)	250 mg 3/4D	5	–	–	–	–	–	–	–	–
		500 mg 3/4D	–	5	5	5	5	5	3	2	–
		150 mg QOD	–	–	–	–	–	–	2	3	4
Nonamenable	Men (n = 3)	250 mg 3/4D	3	–	–	–	–	–	–	–	–
		500 mg 3/4D	–	3	3	3	2	2	–	–	–
	Women (n = 4)	250 mg 3/4D	4	–	–	–	–	–	–	–	–
		500 mg 3/4D	–	4	4	4	4	4	3	1	–
		150 mg QOD	–	–	–	–	–	–	1	3	4

Amenable/nonamenable: A subject with *GLA* mutation amenable or nonamenable to migalastat. At the analysis, the amenability was determined on the basis of the preliminary HEK assay[40] but was confirmed to be the same as determined by the final [37] in a post-hoc analysis.
QOD, once every other day; 3/4D, administered once daily for 3 days with a 4-day interruption
a) Migalastat dose was increased to 500 mg with the 3/4D regimen at Month 2, and migalastat was administered for 1 month. At Month 3, the regimen was changed to administer migalastat 250 mg with the 3/4D regimen. A further change was made to the dosing regimen at Month 21: migalastat 150 mg was to be administered every other day, and after Month 42, migalastat 150 mg was to be administered once every 4 days.
b) After the dose escalation period, migalastat 250 mg was administered with the 3/4D regimen.
c) After the dose escalation period, migalastat 300 mg was administered with the 3/4D regimen.

All 23 subjects (14 men consisting of 6 from Study FAB-CL-201, 3 from Study FAB-CL-202, and 5 from Study FAB-CL-203; 9 women from Study FAB-CL-204) were included in the safety and pharmacodynamics analysis sets. Of 23 patients, 16 patients (11 men and 5 women) were confirmed to be amenable to migalastat as assessed by the preliminary HEK assay.[40] Six patients were withdrawn from the study because of an adverse event in 1 patient, consent withdrawal in 1 patient, and other reasons (including lack of efficacy) in 4 patients. The median duration of treatment in this study was 4.1 years (range, 1.0 to 4.7 years). In this section, the measurement time points are expressed as the treatment duration from the start of dose escalation period in this study.

[39] For subjects who were already enrolled and received migalastat 150 mg every other day in the study at the time of the amendment to the protocol, the dose escalation period was to be started at the next visit.
[40] HEK assay for which its basic analysis methods and criteria for determination of amenability were similar to those of the GLP HEK assay [see the footnote 37] and which had not been validated in terms of quality control, rigor, precision, and consistency.

Changes over time from baseline in α-Gal A activity in PBMCs and urinary GL-3 concentrations as pharmacodynamic parameters are shown in Table 25.

Table 25. Changes over time from baseline in α-Gal A activity in PBMCs and urinary GL-3 concentrations (pharmacodynamics analysis set)

	Baseline [a]	Dose escalation period			Extension period			
		Month 1	Month 2	Month 4	Month 12	Month 24	Month 36	Month 42
α-Gal A activity in PBMCs (nmol/h/mg)								
Amenable								
Men (n = 11)	0.9 (0.1, 6.6)	5.7 [c] (0.3, 14.7)	5.0 (0.2, 15.1)	4.9 [c] (0.3, 14.3)	6.5 (0.1, 20.9)	9.9 [d] (0.3, 19.2)	7.3 [d] (−2.1, 19.0)	9.2 [e] (−1.7, 21.2)
Women (n = 5)	14.7 (6.4, 25.1)	8.3 (5.2, 14.6)	5.0 (1.4, 9.4)	7.5 (2.4, 37.8)	8.6 (−10.1, 19.8)	13.8 [d] (−13.4, 29.1)	8.5 [d] (2.8, 17.4)	10.4 [g] (9.9, 34.7)
Nonamenable								
Men (n = 3)	0.1 (0.1, 0.1)	0.1 (0.0, 0.3)	0.0 (−0.1, 0.3)	0.0 (0.0, 0.2)	0.3 [h] (0.2, 0.4)	—	—	—
Women (n = 4)	15.3 (3.3, 24.7)	3.1 (0.3, 8.4)	3.7 (2.0, 6.3)	4.6 (−1.6, 15.0)	9.4 (3.9, 24.6)	19.7 (11.3, 32.6)	6.2 (3.5, 12.0)	9.2 (4.4, 16.3)
Urinary GL-3 concentrations (pmol/nmol PC [b])								
Amenable								
Men and women (n = 16)	315.8 (28.1, 3875.9)	−20.1 (−795.7, 2914.3)	−16.8 (−1703.1, 934.5)	−17.8 (−1131.5, 1204.4)	3.4 (−1566.9, 1206.8)	−3.3 [i] (−279.8, 1553.0)	13.4 [j] (−180.9, 3161.6)	53.8 [j] (−45.5, 1001.5)
Nonamenable								
Men and women (n = 7)	408.7 (51.7, 3565.5)	491.2 (−53.9, 2714.9)	148.4 (−81.5, 2379.8)	518.0 (−11.6, 3136.2)	582.5 [k] (−50.7, 3399.6)	392.2 [f] (33.8, 2442.7)	180.3 [f] (92.0, 626.2)	727.8 [f] (43.6, 1001.5)

Amenable/nonamenable: A subject with *GLA* mutation amenable or nonamenable to migalastat. At the analysis, the amenability was determined on the basis of the preliminary HEK assay [40] but was confirmed to be the same as determined by the final [37] in a post-hoc analysis.
Median (range). −, no measurements available.
a) The last measurement in the previous study; b) PC, phosphatidylcholine
c) n = 10; d) n = 9; e) n = 7; f) n = 4; g) n = 3; h) n = 2; i) n = 13; j) n = 12; k) n = 6

The changes from baseline in α-Gal A activity in PBMCs and urinary GL-3 concentrations in subjects with the *GLA* mutation responsive to migalastat are shown in Table 26. Administration of migalastat 150 mg every other day increased the α-Gal A activity in PBMCs and reduced the urinary GL-3 concentrations. No significant changes were identified after switching to administration of migalastat 250 or 500 mg, once daily, with the 3/4D regimen.

Table 26 Changes from baseline in α-Gal A activity in PBMCs and urinary GL-3 concentrations in subjects with the *GLA* mutation responsive to migalastat [a] (Pharmacodynamics analysis set)

Endpoints	Subject No.	Baseline [b]	Last dosing of migalastat 150 mg QOD [c]	8 weeks after initial dosing of migalastat 250 mg with the 3/4D regimen	8 weeks after initial dosing of migalastat 500 mg with the 3/4D regimen	Last dosing of migalastat 500 mg with the 3/4D regimen [d]
α-Gal A activity in PBMCs (nmol/h/mg)	01-1	5.23	8.15	10.21	13.52	16.08
	01-2	4.7	14.54	15.02	12.70	30.10
	01-3	6.58	13.68	15.15	14.26	18.66
	01-4	0.98	2.98	5.05	11.64	−0.92
	01-6	0.91	−0.11	2.12	2.91	−
	01-9	0.23	0.35	0.74	1.95	1.31
	02-4	0.31	8.02	9.17	6.93	20.70
	03-4	3.44	6.04	6.07	0.27	−0.11
	03-5	0.18	1.32	0.84	2.16	−
	04-4	6.39	5.54	6.61	6.67	12.18
	04-2	24.55	5.50	5.02	7.53	−13.44
	04-8	14.73	3.79	4.36	2.35	18.34
Urinary GL-3 concentrations (pmol/nmol PC [e])	01-1	66.5	−21.2	−8.3	−2.8	10.2
	01-2	49.4	−8.7	4.0	−1.7	22.6
	01-3	64.1	−30.1	−22.6	−28.7	−13.4
	01-4	159	−70.0	−39.6	−48.6	−33.0
	01-6	851.9	686.4	934.5	1204.4	−
	01-9	457.7	−8.2	435.7	312.2	405.6
	02-4	336.2	−276.2	−212.4	−291.0	132.3
	03-4	170	7.9	−71.2	−16.4	109.1
	03-5	1159.7	196.0	−48.2	132.9	3203.2
	04-4	502.2	−284.9	−411.4	−248.8	−75.1
	04-2	28.1	2.6	−13.1	−19.1	12.4
	04-8	295.5	−229.1	−20.5	−191.4	29.5

QOD, once every other day; 3/4D, administered once daily for 3 days with a 4-day interruption. −, no measurements available.
a) Subjects who were enrolled in this study before the amendment to the protocol to include a dose escalation period and were determined to be responsive to migalastat. At the analysis, the amenability was determined on the basis of the preliminary HEK assay [40] but was confirmed to be the same as determined by the final [37] in a post-hoc analysis.
b) The last measurement in the previous study.
c) At the last dose of migalastat 150 mg which was administered every other day before the dose escalation period (migalastat 150 mg once daily every other day for about 8 to 120 weeks).
d) At the last dose of migalastat 500 mg with the 3/4D regimen (migalastat 500 mg was administered with the 3/4D regimen for about 12 to 20 months).
e) PC, phosphatidylcholine.

The safety analysis revealed that adverse events occurred in all subjects. The following adverse events occurred in ≥ 3 subjects: arthralgia (9), fatigue (8), back pain (8), influenza (6), pain in extremity (6), headache (6), palpitations (5), diarrhea (5), abdominal pain upper (5), nasopharyngitis (5), sinusitis (5), myalgia (5), vomiting (4), abdominal pain (4), upper respiratory tract infection (4), urinary tract infection (4), dizziness (4), gastroesophageal reflux disease (4), insomnia (4), vision blurred (3), edema peripheral (3), pyrexia (3), flank pain (3, muscle spasms (3), paresthesia (3), depression (3), oropharyngeal pain (3), and cough (3). The number of adverse drug reactions was: 5 in 4 of 18 subjects with migalastat 150 mg every other day (0.12 events per person-year), 9 in 5 of 23 subjects with migalastat 250 mg with the 3/4D regimen (1.48 events per person-year), and 23 in 10 of 23 subjects with migalastat 500 mg with the 3/4D regimen (0.73 events per person-year). Adverse drug reactions occurring in ≥ 2 subjects were dizziness (3), dry mouth (2), weight increased (2), and muscle twitching (2).

There were no deaths. Serious adverse events occurred in 7 of 23 subjects (ventricular fibrillation/cerebrovascular accident dehydration/malnutrition/pneumonia aspiration, sensation of foreign body/atrial flutter/ atrial fibrillation/atrioventricular block/cardiac failure congestive/epistaxis, atrial

fibrillation, dyspepsia/post procedural hemorrhage, hyperthyroidism, transient ischemic attack, and ankle fracture/syncope in 1 each. A causal relationship with the study drug was ruled out for all serious events. Adverse events in 1 of 23 subjects led to the treatment discontinuation (ventricular fibrillation/cerebrovascular accident), and the subject was withdrawn from the study. However, a causal relationship with the study drug was ruled out. Adverse events in 2 of 23 subjects resulted in the dose reduction (muscle twitching and confusional state/intention tremor/arthralgia/myalgia/dizziness in 1 each). All events except dizziness were assessed as adverse drug reactions.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.2 Phase III studies

7.2.1 Global phase III study in patients with Fabry disease currently receiving ERT including Japanese patients (CTD 5.3.5.1.1, Study AT1001-012 [September 2011 to May 2015])

A randomized, open-label, parallel-group study to evaluate the efficacy and safety of migalastat in comparison to ERT in Japanese and non-Japanese[41)] patients with Fabry disease who were currently receiving ERT (a target sample size of 50).

The main inclusion criteria included the following: Male or women between 16 and 74 years of age (inclusive) with a diagnosis of Fabry disease with migalastat-responsive *GLA* mutations as determined by the preliminary HEK assay[40)] who were receiving ERT for ≥12 months before the randomization, in whom the dose level and regimen of ERT had been stable for 3 months before the randomization,[42)] and who had an $eGFR_{MDRD}$[43)] of ≥30 mL/min/1.73 m^2.

This study consisted of a screening period (2 months), a main treatment period (18 months), and an optional extension period (12 months).

In the main treatment period, migalastat 150 mg was orally administered every other day, or an ERT drug (agalsidase alfa or agalsidase beta) was administered with its approved dose and regimen.[44)] In the extension period, migalastat 150 mg was orally administered every other day to all subjects. When data including those obtained from the extension period are shown, the subgroup of patients who received migalastat in both the main treatment period and the extension period is referred to as the "migalastat-migalastat group", and the subgroup of patients who received ERT in the main treatment period and migalastat in the treatment extension group is referred to as the "ERT-migalastat group".

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41) Australia, Austria, Belgium, Brazil, Denmark, France, Italy, UK, and US.
42) At least 80% of the dose and regimen specified in the package insert.
43) Estimated glomerular filtration rate (eGFR) by the MDRD equation: eGFR (mL/min/1.73 m^2) $=175\times (\text{serum creatinine})^{-1.154}\times (\text{age})^{-0.203}\times 1.212$ [if black or African American] × 0.742 [if female]
44) In general, agalsidase beta was to be administered at a dose of 1 mg/kg intravenously by drip infusion once every other week, and agalsidase alfa was to be administered at a dose of 0.2 mg/kg intravenously by drip infusion once every other week.

All 57 subjects (36 subjects, including 2 Japanese subjects, in the migalastat group and 21 subjects, including 2 Japanese subjects, in the ERT group) who received the study drug were included in the safety analysis set. Of the 57 subjects, 52 subjects (34 subjects, including 5 Japanese subjects, in the migalastat group and 18 subjects, including a Japanese subject, in the ERG group) who had the *GLA* mutation responsive to migalastat as determined by the GLP HEK assay[37)] and had data of glomerular filtration rate measured by the plasma clearance of unlabelled iohexol ($mGFR_{iohexol}$) [45)] at and after baseline and $eGFR_{CKD\text{-}EPI}$ [46)] after baseline were included in the modified intent-to-treat (mITT) population, which was used as the primary efficacy analysis set. In the main treatment period, 5 subjects (2 in the migalastat group and 3 in the ERT group) were withdrawn from the study, and their reason for discontinuation was withdrawal of consent in all the subjects. Of 52 subjects who completed the main treatment period, 48 subjects (33 including 5 Japanese, in the migalastat-migalastat group and 15 subjects, including a Japanese subject, in the ERT-migalastat group) entered the extension period. Of the 48 subjects, 46 subjects (31 including 5 Japanese, in the migalastat-migalastat group and 15 subjects, including a Japanese subject, in the ERT-migalastat group) had the *GLA* mutation responsive to migalastat as determined by the GLP HEK assay. In the extension period, 6 subjects (3 in the migalastat-migalastat group and 3 including 1 Japanese, in the ERT-migalastat group) discontinued the study for the reasons including withdrawal of consent in 2 subjects (1 in the migalastat -migalastat group and 1 in the ERT-migalastat group), decision by the physician in 1 subject (1 Japanese in the ERT-migalastat group), lack of efficacy in 1 subject (in the migalastat -migalastat group), lost to follow-up in 1 subject (in the ERT-migalastat group), and pregnancy in 1 subject (in the migalastat-migalastat group).

The annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ up to Month 18 of treatment in the mITT population are the primary efficacy endpoints and are shown in Table 27. In the overall population, the pre-specified criteria for comparability[47)] were met in the migalastat and ERG groups.

Table 27. Annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ up to Month 18 of treatment (main treatment period [18 months of treatment], mITT population)

	Endpoints	Migalastat group	ERT group	Intergroup difference [a)]	Percentage of overlap of the 95% CI of each group
Overall population	$eGFR_{CKD\text{-}EPI}$ [b)]	−0.40±0.93 [−2.27, 1.48] (n = 34)	−1.03±1.29 [−3.64, 1.58] (n = 18)	0.63	100%
	$mGFR_{iohexol}$ [b)]	−4.35±1.64 [−7.65, −1.06] (n = 34)	−3.24±2.27 [−7.81, 1.33] (n = 18)	−1.11	100%
Japanese subgroup	$eGFR_{CKD\text{-}EPI}$	−1.78 [−6.61, 3.04] (n = 5)	1.56 (n = 1)		
	$mGFR_{iohexol}$	−7.59 [−15.56, 0.37] (n = 5)	−6.42 (n = 1)		

Unit, mL/min/1.73 m^2/year.
For the entire study population, least squares mean ± standard error [95% C]. For the Japanese subgroup, mean [95% CI]. The value is shown when n = 1.
a) Least squares mean. b) An analysis of covariance (ANCOVA) with baseline $eGFR_{CKD\text{-}EPI}$ or $mGFR_{iohexol}$, sex, age, and baseline 24-hour urine protein as covariates.

Results of the main secondary endpoints are shown in Table 28.

45) Glomerular filtration rate (mL/min/1.73 m^2) measured by the plasma clearance of unlabelled iohexol
46) Estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration equation: eGFR (mL/min/1.73 m^2) $= 141 \times \text{minimum (serum creatinine } /\kappa, 1)^{\alpha} \times \text{maximum (serum creatinine } /\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.1018$ [if female] × 1.159 [if black] (J Am Soc Nephrol 2009;20:2305-13); κ, 0.7 [if female] or 0.9 [if male]; α, −0.329 [if female] or −0.411 [if male].
47) Difference of the annualized changes (least squares mean) in GFR within 2.2 mL/min/1.73 m^2, and >50% overlap of the 95% CI for the annualized changes in GFR between the migalastat and ERT groups. With regard to the difference of the least squares mean, a value of 2.2 mL/min/1.73m^2/year was selected as the threshold for the comparability between the migalastat and ERT groups, based on data (the upper limit of confidence interval) from a published literature describing a study in which agalsidase alfa was administered for ≥6 months and the mean annualized changes in eGFR [90% CI] was estimated to be −3.6 [−5.0, −2.2] mL/min/1.73m^2/year (Nephrol Dial Transplant 2006;21:345-54).

Table 28. Results of main secondary endpoints (main treatment period [18 months of treatment], mITT population)

Endpoints		Overall population		Japanese subgroup	
		Migalastat (n = 34)	ERT (n = 18)	Migalastat (n = 5)	ERT (n = 1)
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Baseline	88.70 ± 20.22	94.71 ± 20.20	82.41 ± 27.06	44.83
	Changes	−3.17 ± 1.33 [a)] [−5.84, −0.49]	−4.30 ± 1.90 [a), j)] [−8.11, −0.48]	−4.78 ± 4.73	4.97
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Baseline	82.28 ± 16.88	81.43 ± 23.91	84.64 ± 27.71	33.00
	Changes	−6.49 ± 2.47 [a)] [−11.47, −1.51]	−3.16 ± 3.67 [a), k)] [−10.56, 4.24]	−11.82 ± 10.97	−6.30 [b)]
Left ventricular mass index (g/m^2)	Baseline	95.30 ± 22.75 [g)]	92.90 ± 25.67 [k)]	111.33 ± 35.79	85.34
	Changes	−6.58 ± 12.08 [h)] [−11.01, −2.15]	−2.02 ± 14.86 [l)] [−10.99, 6.96]	−13.82 ± 8.53 [n)]	12.54
α-Gal A activity in PBMCs (nmol/h/mg)	Baseline	9.94 (0.16, 34.30) [g)]	7.29 (0.10, 21.45)	1.69 (1.23, 22.42)	13.64
	Changes	5.07 (−3.83, 15.33) [h)]	−0.97 (−7.82, 2.06) [j)]	5.07 (0.74, 13.06)	−6.31
Plasma lyso-Gb_3 (nmol/L)	Baseline	6.35 (0.80, 59.07) [i)]	9.65 (0.85, 73.4) [j)]	3.22 (1.38, 14.50)	10.93
	Changes	0.550 (−2.27, 28.30) [h)]	−0.04 (−11.90, 2.57) [m)]	0.28 (−1.11, 0.77)	−
Composite clinical outcomes [c)] (%)		29 (10/34)	44 (8/18)	20 (1/5)	100 (1/1)
Renal events [d)] (%)		24 (8/34)	33 (6/18)	20 (1/5)	0 (0/1)
Cardiac events [e)] (%)		6 (2/34)	17 (3/18)	0 (0/5)	100 (1/1)
Cerebrovascular events [f)] (%)		0 (0/34)	6 (1/18)	0 (0/5)	0 (0/1)

Mean ± standard deviation [95% CI]. Median (range). Incidence % (number of subjects with events/number of subjects evaluated). −, data not available

a) Least squares mean ± standard error [95% CI] (an ANCOVA with treatment group as a fixed effect and baseline $eGFR_{CKD-EPI}$ or $mGFR_{iohexol}$, sex, age, baseline 24-hour urine protein as covariates). b) At Month 12

c) Number of subjects with renal events, cardiac events, cerebrovascular events, or death. No deaths occurred

d) Defined as follows: 1) A decrease in $eGFR_{CKD-EPI}$ ≥15 mL/min/1.73 m^2, with the decreased $eGFR_{CKD-EPI}$ <90 mL/min/1.73 m^2 relative to baseline; or 2) an increase in 24-hour urine protein ≥33%, with the increased 24-hour urine protein ≥300 mg relative to baseline

e) Defined as myocardial infarction, unstable cardiac angina (according to the treatment guidelines by the American College of Cardiology and the American Heart Association), new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), or congestive cardiac failure (New York Heart Association Class III or IV)

f) Defined as stroke or transient ischemic attack

g) n = 33; h) n = 31; i) n = 32; j) n = 17; k) n = 16; l) n = 13; m) n = 15; n) n = 4

Efficacy results observed up to the extension period (Month 30 of treatment) are shown in Table 29.

Table 29. Efficacy results up to the extension period (main treatment period + extension period [30 months of treatment], subgroup of patients with GLA mutation responsive to migalastat who continued treatment)

Endpoints		Entire study population		Japanese subgroup	
		Migalastat-migalastat (n = 31)	ERT-migalastat (n = 15)	Migalastat-migalastat (n = 5)	ERT-migalastat (n = 1)
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Baseline	89.68 ± 20.87	96.05 ± 21.00	82.41 ± 27.06	44.83
	Changes (Months 0 to 18)	−3.80 ± 5.23 [−5.72, −1.89]	−5.55 ± 12.48 [−12.46, 1.36]	−4.78 ± 4.73	4.97
	Annualized changes (Months 0 to 18)	−1.069 ± 3.116 [−2.212, 0.074]	−2.039 ± 6.653 [−5.723, 1.646]	−1.783 ± 3.886	1.557
	Changes (Months 0/18 to 30)	−3.69 ± 8.88 [f] [−7.01, −0.38]	−0.05 ± 11.76 [i] [−6.84, 6.74]	−7.09 ± 6.83	−17.60
	Annualized changes (Months 0/18 to 30)	−1.718 ± 2.550 [−2.653, −0.782]	−2.131 ± 12.430 [−9.015, 4.752]	−2.939 ± 2.930	−20.262
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Baseline	82.77 ± 17.55	81.18 ± 25.91	84.64 ± 27.71	33.00
	Changes (Months 0 to 18)	−7.11 ± 14.62 [−12.47, −1.75]	−0.14 ± 15.67 [i] [−9.19, 8.90]	−11.82 ± 10.97	−6.30 [a]
	Annualized changes (Months 0 to 18)	−4.979 ± 9.536 [−8.476, −1.481]	−0.653 ± 9.369 [−5.842, 4.535]	−7.594 ± 6.418	−6.424
	Changes (Months 0/18 to 30)	−6.37 ± 14.49 [f] [−11.78, −0.96]	−3.86 ± 15.05 [j] [−15.43, 7.71]	−7.92 ± 6.06	−6.30[a]
	Annualized changes (Months 0/18 to 30)	−2.746 ± 5.532 [f] [−4.812, −0.681]	−3.857 ± 15.091 [j] [−15.457, 7.743]	−3.385 ± 2.523	–
Left ventricular mass index (g/m^2)	Baseline	94.65 ± 22.42 [f]	88.51 ± 25.64 [k]	111.33 ± 35.79	85.34
	Changes (Months 0 to 18)	−7.66 ± 12.53 [f] [−12.34, −2.98]	−2.76 ± 15.26 [l] [−12.46, 6.93]	−10.73 ± 10.12	12.54
	Changes (Months 0/18 to 30)	−3.77 ± 13.15 [g] [−8.87, 1.33]	−0.32 ± 11.54 [m] [−8.58, 7.93]	−13.31 ± 10.22	0.72
α-Gal A activity in PBMCs (nmol/h/mg)	Baseline	7.79 (0.16, 34.30)	9.42 (0.11, 21.45)	1.69 (1.23, 22.42)	13.64
	Changes (Months 0 to 18)	5.91 [h] (−2.21, 15.33)	−1.40 (−7.82, 2.06)	5.07 (0.74, 13.06)	−6.31
	Changes (Months 0/18 to 30)	3.48 (−5.22, 22.31)	7.36 [i] (0.06, 21.92)	3.48 (1.02, 15.15)	16.98
Plasma lyso-Gb_3 (nmol/L)	Baseline	6.21 (0.80, 59.07)	7.80 (0.85, 49.60)	3.22 (1.38, 14.50)	10.93
	Changes (Months 0 to 18)	0.54 [f] (−2.27, 28.30)	−0.03 [i] (−11.90, 2.57)	0.28 (−1.11, 0.77)	–
	Changes (Months 0/18 to 30)	0.81 [h] (−2.33, 71.60)	1.46 [j] (−2.36, 35.67)	0.73 (−2.13, 1.05)	–
Composite clinical outcomes [b] (%)	Months 0 to 18	23 (7/31)	40 (6/15)	20 (1/5)	100 (1/1)
	Months 0/18 to 30	32 (10/31)	40 (6/15)	40 (2/5)	100 (1/1)
Renal events [c] (%)	Months 0 to 18	19 (6/31)	27 (4/15)	20 (1/5)	0 (0/1)
	Months 0/18 to 30	29 (9/31)	40 (6/15)	40 (2/5)	100 (1/1)
Cardiac events [d] (%)	Months 0 to 18	3 (1/31)	20 (3/15)	0 (0/5)	100 (1/1)
	Months 0/18 to 30	3 (1/31)	7 (1/15)	0 (0/5)	100 (1/1)
Cerebrovascular events [e] (%)	Months 0 to 18	0 (0/31)	7 (1/15)	0 (0/5)	0 (0/1)
	Months 0/18 to 30	0 (0/31)	0 (0/15)	0 (0/5)	0 (0/1)

Mean ± standard deviation [95% CI]. Median (range). Incidence (number of subjects with events/number of subjects evaluated). −, data not available
Months 0/18 to 30: Changes, annualized changes, and incidence from baseline for the migalastat-migalastat group and those from Month 18 for the ERT-migalastat group

a) At Month 12

b) Number of subjects with renal events, cardiac events, cerebrovascular events, or death. No deaths occurred.

c) Defined as follows: 1) A decrease in $eGFR_{CKD-EPI}$ ≥15 mL/min/1.73 m^2, with the decreased $eGFR_{CKD-EPI}$ <90 mL/min/1.73 m^2 relative to baseline; or 2) an increase in 24-hour urine protein ≥33%, with the increased 24-hour urine protein ≥300 mg relative to baseline

d) Defined as myocardial infarction, unstable cardiac angina (according to the treatment guidelines by the American College of Cardiology and the American Heart Association), new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), or congestive cardiac failure (New York Heart Association Class III or IV)

e) Defined as stroke or transient ischemic attack

f) n = 30; g) n = 28; h) n = 29; i) n = 14; j) n = 9; k) n = 13; l) n = 12; m) n = 10

Individual subject characteristics and results of the primary endpoints and main secondary endpoints in Japanese subgroup are shown in Table 30.

Table 30. Individual subject characteristics and results of the primary and main secondary endpoints in Japanese subgroup (main analysis period + extension period [30 months of treatment], Japanese subgroup)

Treatment groups		Migalastat-migalastat (n = 5)					ERT-migalastat (n = 2)	
No. of subject		Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6 [a)]	Subject 7
Age (years)		48	56	57	52	46	53	70
Sex		Men	Men	Women	Women	Men	Women	Women
Duration of disease (years)		19.74	4.63	4.78	17.31	4.20	10.73	26.82
Use of ACEI/ARB		Used	Used	Not used	Used	Used	Not used	Not used
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Baseline	51.33	99.74	97.73	108.34	54.91	106.85	44.83
	Changes (Months 0 to 18)	−11.93	0	−6.99	−2.14	−2.85	−7.43	4.97
	Annualized changes (Months 0 to 18)	−6.97	2.25	−4.25	1.53	−1.48	−1.77	1.56
	Changes (Months 0/18 to 30)	−17.66	0.58	−8.65	−3.48	−6.26	–	–
	Annualized changes (Months 0/18 to 30)	−5.82	0.10	−6.26	−0.73	−1.98	–	−20.26
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Baseline	56.20	99.80	107.60	106.80	52.80	108.00	33.00
	Changes (Months 0 to 18)	−10.5	−20.0	−25.8	−1.1	−1.7	−4.2	−6.3 [b)]
	Annualized changes (Months 0 to 18)	−7.22	−11.40	−16.32	−1.93	−1.11	−4.70	−6.42 [b)]
	Changes (Months 0/18 to 30)	−15.1	−13.1	−0.4	−5.4	−5.6	–	–
	Annualized changes (Months 0/18 to 30)	−6.02	−5.85	−0.11	−2.27	−2.68	–	–
Left ventricular mass index (g/m^2)	Baseline	102.64	165.73	87.83	74.83	125.63	122.49	85.34
	Changes (Months 0 to 18)	−7.74	−26.23	1.63	−8.72	−12.59	−23.97	12.54
	Changes (Months 0/18 to 30)	−17.96	−24.46	−0.12	−18.86	−5.13	–	13.26
α-Gal A activity in PBMCs (nmol/h/mg)	Baseline	1.69	1.48	22.42	17.61	1.23	11.91	13.64
	Changes (Months 0 to 18)	6.86	0.74	5.07	13.06	2.25	3.57	−6.31
	Changes (Months 0/18 to 30)	3.48	1.02	13.44	15.15	2.86	–	10.67
Plasma lyso-Gb_3 (nmol/L)	Baseline	2.247	11.500	3.220	1.380	14.500	13.133	10.933
	Changes (Months 0 to 18)	0.767	−1.107	0.277	0.550	−0.200	−2.367	−0.567 [b)]
	Changes (Months 0/18 to 30)	1.050	−2.127	0.967	0.733	−0.833	–	–

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin II receptor blocker
Months 0/18 to 30: Changes and annualized changes from baseline for the migalastat-migalastat group and those from Month 18 for the ERT-migalastat group
a) The subject was determined to have the *GLA* mutation nonamenable to migalastat as assessed by the GLP HEK assay and was excluded from the mITT population. b) At Month 12.

Table 31 shows adverse events occurring during the main treatment period in ≥10% of subjects in either group and those considered adverse drug reactions. Adverse events occurred in all subjects in the Japanese subgroup (5 in the migalastat group and 2 in the ERT group), and all the events were assessed as unrelated to the study drug. The adverse event nasopharyngitis occurred in ≥2 subjects in either treatment group of the Japanese subgroup (4 subjects in the migalastat group and 1 subject in the ERT group).

Table 31. Adverse events occurring in ≥10% of subjects in either group and those considered adverse drug reactions (main treatment period [18 months of treatment], safety analysis set)

	Migalastat group (n = 36)		ERT group (n = 21)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any adverse events	94.4 (34)	38.9 (14)	95.2 (20)	14.3 (3)
Nasopharyngitis	33.3 (12)	0 (0)	33.3 (7)	0 (0)
Headache	25.0 (9)	16.7 (6)	23.8 (5)	0 (0)
Dizziness	16.7 (6)	5.6 (2)	9.5 (2)	0 (0)
Diarrhea	13.9 (5)	8.3 (3)	9.5 (2)	0 (0)
Abdominal pain	13.9 (5)	5.6 (2)	9.5 (2)	0 (0)
Nausea	13.9 (5)	5.6 (2)	9.5 (2)	0 (0)
Influenza	13.9 (5)	0 (0)	19.0 (4)	0 (0)
Upper respiratory tract infection	11.1 (4)	0 (0)	4.8 (1)	0 (0)
Urinary tract infection	11.1 (4)	0 (0)	4.8 (1)	0 (0)
Back pain	11.1 (4)	0 (0)	14.3 (3)	0 (0)
Vomiting	8.3 (3)	0 (0)	14.3 (3)	0 (0)
Sinusitis	8.3 (3)	0 (0)	14.3 (3)	0 (0)
Cough	8.3 (3)	0 (0)	23.8 (5)	5 (1)
Bronchitis	5.6 (2)	0 (0)	14.3 (3)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions). MedDRA/J ver.15.1.

Table 32 shows adverse events occurring during the extension period in ≥10% of subjects in either group and those considered adverse drug reactions. Adverse events occurred in all subjects in the Japanese subgroup (5 in the migalastat-migalastat group and 1 in the ERT-migalastat group), and all the events were assessed as unrelated to the study drug. The adverse event nasopharyngitis occurred in ≥2 Japanese subjects (4 subjects in the migalastat-migalastat group).

Table 32. Adverse events and adverse drug reactions occurring in ≥10% of subjects in either group (main treatment period + extension period [30 months of treatment], safety analysis set)

	Migalastat-migalastat (n = 33)		ERT-migalastat (n = 15)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any adverse events	97.0 (32)	42.4 (14)	100.0 (15)	26.7 (4)
Nasopharyngitis	42.4 (14)	0 (0)	33.3 (5)	0 (0)
Headache	36.4 (12)	18.2 (6)	20.0 (3)	0 (0)
Influenza	27.3 (9)	0 (0)	20.0 (3)	0 (0)
Diarrhea	18.2 (6)	6.1 (2)	26.7 (4)	6.7 (1)
Nausea	18.2 (6)	6.1 (2)	13.3 (2)	0 (0)
Cough	18.2 (6)	0 (0)	6.7 (1)	0 (0)
Dizziness	15.2 (5)	3.0 (1)	13.3 (2)	6.7 (1)
Urinary tract infection	15.2 (5)	0 (0)	6.7 (1)	0 (0)
Myalgia	15.2 (5)	3.0 (1)	6.7 (1)	0 (0)
Blood creatine phosphokinase increased	15.2 (5)	9.1 (3)	13.3 (2)	0 (0)
Abdominal pain	15.2 (5)	6.1 (2)	13.3 (2)	0 (0)
Protein urine present	12.1 (4)	0 (0)	0 (0)	0 (0)
Sinusitis	12.1 (4)	0 (0)	0 (0)	0 (0)
Vomiting	12.1 (4)	0 (0)	26.7 (4)	6.7 (1)
Pain	12.1 (4)	3.0 (1)	6.7 (1)	0 (0)
Pyrexia	12.1 (4)	3.0 (1)	13.3 (2)	0 (0)
Arthralgia	12.1 (4)	0 (0)	13.3 (2)	0 (0)
Bronchitis	9.1 (3)	0 (0)	13.3 (2)	0 (0)
Fatigue	6.1 (2)	3.0 (1)	13.3 (2)	0 (0)
Neuralgia	6.1 (2)	0 (0)	13.3 (2)	6.7 (1)
Muscle spasms	6.1 (2)	3.0 (1)	13.3 (2)	6.7 (1)
Diabetes mellitus	0 (0)	0 (0)	13.3 (2)	0 (0)
Poor quality sleep	0 (0)	0 (0)	13.3 (2)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions) MedDRA/J ver.15.1
The main treatment period + extension period (Months 0 to 30) for the migalastat -migalastat group and the extension period (Months 18 to 30) for the ERT-migalastat group.

There were no deaths or adverse events leading to treatment discontinuation in any treatment period. In the main treatment period, serious adverse events occurred with an incidence of 19% (7 of 36 subjects) in the migalastat group (chest pain in 2, ventricular tachycardia/chest pain, bile duct stone, pneumonia, upper limb fracture/pheochromocytoma, and obesity in 1 each) and an incidence of 33% (7 of 21 subjects) in the ERG group (cardiac failure chronic, vertigo, hernial eventration, device malfunction, transient ischemic attack/abdominal pain, asthenia/mental status change of unknown etiology/bilateral filmy vision of unknown etiology/numbness of the left face and dyspnea/atrial fibrillation in 1 each). None of these events were assessed as related to the study drug. In the extension period, serious adverse events occurred with an incidence of 18% (6 of 33 subjects) in the migalastat-migalastat group (proteinuria, suicidal ideation, embolic stroke, hemoptysis, obesity, and perineal abscess in 1 each) and an incidence of 20% (3 of 15 subjects) in the ERT-migalastat group (atelectasis/hernial eventration, transient ischemic attack, and dyspnea in 1 each). The event proteinuria in a subject in the migalastat-migalastat group was considered an adverse drug reaction.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.2.2 Foreign phase III study in previously untreated patients with Fabry disease (CTD 5.3.5.1.2, Study AT1001-011 [October 2009 to January 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and pharmacodynamics of migalastat in non-Japanese ERT-naïve patients with Fabry disease (a target sample size of 60).

The main inclusion criteria included the following: Men or women between 16 and 74 years of age (inclusive) with a diagnosis of Fabry disease with migalastat-responsive *GLA* mutations as determined by the preliminary HEK assay[40] who were ERT-naïve or had not received ERT for ≥6 months before screening and had $eGFR_{MDRD}$ of ≥30 mL/min/1.73 m^2 and urinary GL-3 concentrations of ≥4 times the upper limit of the normal range.

This study consisted of a screening period (2 months), a main treatment period (6 months), an extension period 1 (6 months), and an optional extension period 2 (12 months).

In the main treatment period, placebo or migalastat 150 mg was orally administered every other day. In the extension periods 1 and 2, migalastat 150 mg was orally administered every other day to all subjects in an open-label manner. When data including those obtained from the extension period are shown, the subgroup of patients who received placebo in the main treatment period and migalastat in the extension period is referred to as the "placebo-migalastat group", and the subgroup of patients who received migalastat in both the main treatment period and the extension period is referred to as the "migalastat-migalastat group."

All 67 subjects who were randomly assigned (33 subjects in the placebo group and 34 subjects in the migalastat group) were included in the ITT population, which was used as the primary efficacy analysis set. All subjects in the ITT population received ≥1 dose of the study drug and were included in the safety analysis set. In the main treatment period, 3 subjects (all in the placebo group) were withdrawn from the study because of withdrawal of consent (in 2 subjects in the placebo group) and pregnancy (in 1 subject in the placebo group). Of 64 subjects who completed the main treatment period, 63 subjects (30 in the placebo group and 33 in the migalastat group) entered the extension period 1. In the extension period 1, 3 subjects (1 in the placebo-migalastat group and 2 subjects in the migalastat-migalastat group) were withdrawn from the study because of adverse events in 2 subjects (1 in the placebo-migalastat group and 1 in the migalastat-migalastat group) and withdrawal of consent in 1 subject (in the migalastat-migalastat group). Of 60 subjects who completed the extension period 1, 57 subjects (28 in the placebo-migalastat group and 29 subjects in the migalastat-migalastat group) entered the extension period 2. In the extension period 2, 3 subjects (1 in the placebo-migalastat group and 2 in the migalastat-migalastat group) were withdrawn from the study because of withdrawal of consent in 1 subject (in the placebo-migalastat group), pregnancy in 1 subject (in the migalastat-migalastat group), and lost to follow-up in 1 subject (in the migalastat-migalastat group). In the extension periods 1 and 2, the subgroup of subjects with *GLA* gene responsive to migalastat as determined by

the GLP HEK assay[37] was included in the efficacy analysis set. In the main treatment period, a post-hoc analysis was performed in subjects with *GLA* gene responsive to migalastat as determined by the GLP HEK assay.

The primary endpoint was the mean number of GL-3 inclusions per interstitial capillary[48] (IC) (the number of kidney IC GL-3 inclusions) at Month 6 of treatment in the ITT population. The percentage of subjects with ≥50% reduction from baseline in the mean number of kidney IC GL-3 inclusions was 28.1% (9 of 32 patients) in the placebo group and 40.6% (13 of 32 subjects) in the migalastat group (p=0.300, the Cochran-Mantel-Haenszel test stratified by sex).

Results of the primary endpoint and the main secondary endpoints are shown in Table 33.

Table 33. Results of the primary endpoint and the main secondary endpoints (main treatment period [6 months of treatment], ITT population)

Endpoints		Placebo (n = 33)	Migalastat (n = 34)
Percentage of subjects with ≥50% reduction from baseline in the mean number of kidney IC GL-3 inclusions (%)		28.1 (9/32)	40.6 (13/32)
Number of kidney IC GL-3 inclusions	Baseline	0.23 (0.03, 2.77) (n = 30)	0.18 (0.02, 5.96) (n = 30)
	Percent change up to Month 6 (%)	−5.6 (−94.4, 285.1) (n = 30)	−40.8 (−90.4, 433.8) (n = 30)

Percentage of subjects % (number of applicable subjects/number of evaluated subjects); Median (range)

Changes in the number of the kidney IC GL-3 inclusions in the main treatment period and the extension period 1 (12 months of treatment) are shown in Table 34.

Table 34. Changes in the number of the kidney IC GL-3 inclusions (main treatment period and extension period 1)

		ITT population[a]		ITT population of subjects with *GLA* mutations responsive to migalastat[a, b]	
		Placebo-migalastat (n = 33)	Migalastat-migalastat (n = 34)	Placebo-migalastat (n = 22)	Migalastat-migalastat (n = 28)
Number of kidney IC GL-3 inclusions [b]	Baseline	0.576 ± 0.697 (n = 30)	0.895 ± 1.604 (n = 30)	0.493 ± 0.594 (n = 20)	0.649 ± 1.229 (n = 25)
	Month 6	0.655 ± 0.949 (n = 30)	0.799 ± 1.556 (n = 32)	0.565 ± 0.975 (n = 20)	0.389 ± 0.792 (n = 26)
	Changes (Months 0 to 6)	0.079 ± 0.499(n = 30)	−0.176 ± 0.515 (n = 30)	0.071 ± 0.563 (n = 20)	−0.250 ± 0.513 (n = 25)
	Month 12	0.658 ± 1.219 (n = 26)	0.631 ± 1.301 (n = 26)	0.312 ± 0.628 (n = 17)	0.429 ± 0.861 (n = 22)
	Changes (Months 0/6 to 12)	−0.079 ± 0.795 (n = 26)	−0.141 ± 0.524 (n = 26)	−0.330 ± 0.626 (n = 17)	−0.239 ± 0.500 (n = 22)

Mean ± standard deviation.
Months 0/6 to 12: Changes from Month 6 for the placebo-migalastat group and changes from baseline for the migalastat-migalastat group.
a) For the extension period 1, subjects who completed the primary treatment period and then entered the extension period 1 in the ITT population were evaluated.
b) The ITT population was used as the efficacy analysis set for the main treatment period (from baseline to Month 6), and an analysis was conducted as a post-hoc analysis in the ITT population of subjects with *GLA* mutations responsive to migalastat as determine by the GLP HEK assay.

Main efficacy results up to the extension period 2 (24 months of treatment) are shown in Table 35.

[48] The number of kidney IC GL-3 inclusions was evaluated with renal biopsy specimens by 3 independent pathologists in a blinded manner and was quantified by using the Barisoni method (Barisoni Lipid Inclusion Scoring System to score the specimen slides with standard digital images; Arch Pathol Lab Med 2012;136:816-24).

Table 35. Main efficacy results
(main treatment period + extension periods 1 and 2 [24 months of treatment], ITT population of subjects with *GLA* mutations responsive to migalastat [a])

Endpoints		Placebo-migalastat (n = 22)	Migalastat-migalastat (n = 28)
Urinary GL-3 concentrations (ng/mg creatinine)	Baseline	1165.0 ± 1439.0 (n = 20)	916.7 ± 1269.9 (n = 27)
	Changes (Months 0 to 6)	−147.3 ± 968.8 (n = 20)	−361.3 ± 878.1 (n = 27)
	Changes (Months 0/6 to 12)	−469.1 ± 787.5 (n = 19)	−304.4 ± 693.0 (n = 25)
	Changes (Months 0/6 to 24)	−459.8 ± 719.9 (n = 6)	−84.2 ± 641.1 (n = 11)
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Baseline	90.2 ± 17.8 (n = 20)	96.2 ± 25.6 (n = 27)
	Changes (Months 0 to 6)	1.2 ± 7.9 (n = 20)	1.2 ± 8.3 (n = 27)
	Annualized changes (Months 0 to 6)	2.0 ± 15.4 (n = 20)	0.7 ± 17.2 (n = 27)
	Changes (Months 0/6 to 12)	−1.3 ± 8.7 (n = 19)	0.9 ± 8.3 (n = 25)
	Annualized changes (Months 0/6 to 12)	−3.8 ± 18.7 (n = 19)	−0.5 ± 7.9 (n = 25)
	Changes (Months 0/6 to 24)	0.9 ± 6.6 (n = 19)	−0.5 ± 11.5 (n = 22)
	Annualized changes (Months 0/6 to 24)	−0.2 ± 4.4 (n = 19)	−0.4 ± 4.2 (n = 22)
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Baseline	83.7 ± 20.8 (n = 18)	88.9 ± 21.6 (n = 23)
	Changes (Months 0 to 6)	1.1 ± 11.7 (n = 18)	−5.4 ± 17.1 (n = 23)
	Annualized changes (Months 0 to 6)	0.9 ± 20.0 (n = 18)	−11.3 ± 35.1 (n = 23)
	Changes (Months 0/6 to 12)	−1.5 ± 11.3 (n = 17)	−7.1 ± 20.7 (n = 22)
	Annualized changes (Months 0/6 to 12)	3.0 ± 23.1 (n = 17)	−7.1 ± 20.7 (n = 22)
	Changes (Months 0/6 to 24)	−4.6 ± 11.3 (n = 17)	−1.0 ± 16.7 (n = 20)
	Annualized changes (Months 0/6 to 24)	−4.2 ± 7.7 (n = 17)	0.7 ± 7.9 (n = 20)
Left ventricular mass index (g/m^2)	Baseline	104.05 ± 37.19 (n = 17)	93.98 ± 30.13 (n = 24)
	Changes (Months 0 to 6)	−1.46 ± 6.59 (n = 16)	0.53 ± 8.22 (n = 24)
	Changes (Months 0/6 to 12)	4.54 ± 16.55 (n = 15)	−1.76 ± 11.88 (n = 21)
α-Gal A activity in PBMCs [b] (nmol/h/mg)	Baseline	0.513 ± 0.498 (n = 9)	1.511 ± 3.334 (n = 7)
	Changes (Months 0 to 6)	−0.102 ± 0.356 (n = 9)	0.890 ± 5.041 (n = 7)
	Changes (Months 0/6 to 12)	3.602 ± 3.544 (n = 9)	−0.034 ± 5.528 (n = 5)
	Changes (Months 0/6 to 24)	4.831 ± 3.121 (n = 7)	−0.438 ± 4.907 (n = 5)

Mean ± standard deviation.
Months 0/6 to 12, Months 0/6 to 24: Changes or annualized changes from Month 6 for the placebo-migalastat group and those from baseline for the migalastat-migalastat group.
a) For the extension period 1 and 2, subjects who completed the previous treatment period and entered the extension period 1 or 2 in the ITT population were evaluated.
b) Only for men.

Table 36 shows adverse events occurring during the main treatment period (6 months of treatment) in ≥10% of subjects in either group and those considered adverse drug reactions.

Table 36. Adverse events occurring in ≥10% of subjects in either group and those considered adverse drug reactions (main treatment period [6 months of treatment], safety analysis set)

	Placebo (n = 33)		Migalastat (n = 34)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any adverse events	90.9 (30)	27.3 (9)	91.2 (31)	44.1 (15)
Headache	21.2 (7)	9.1 (3)	35.3 (12)	2.9 (1)
Nasopharyngitis	6.1 (2)	0 (0)	17.6 (6)	0 (0)
Fatigue	12.1 (4)	6.1 (2)	11.8 (4)	0 (0)
Paresthesia	12.1 (4)	0 (0)	11.8 (4)	5.9 (2)
Nausea	6.1 (2)	0 (0)	11.8 (4)	5.9 (2)
Pyrexia	3.0 (1)	0 (0)	11.8 (4)	0 (0)
Pain in extremity	12.1 (4)	3.0 (1)	0 (0)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions). MedDRA/J ver.15.1

As for safety up to the extension period 2 (Month 24), Table 37 shows adverse events occurring in ≥10% of subjects in either group and those considered adverse drug reactions.

Table 37. Adverse events occurring in ≥10% of subjects in either group and those considered adverse drug reactions (Main treatment period + extension periods 1 and 2 [24 months of treatment], safety analysis set)

	Placebo-migalastat (n = 33)		Migalastat-migalastat (n = 34)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any adverse events	84.8 (28)	30.3 (10)	100.0 (34)	55.9 (19)
Headache	24.2 (8)	12.1 (4)	41.2 (14)	2.9 (1)
Nasopharyngitis	12.1 (4)	0 (0)	23.5 (8)	0 (0)
Paresthesia	6.1 (2)	3.0 (1)	23.5 (8)	8.8 (3)
Diarrhea	9.1 (3)	3.0 (1)	20.6 (7)	11.8 (4)
Urinary tract infection	6.1 (2)	0 (0)	20.6 (7)	0 (0)
Bronchitis	9.1 (3)	0 (0)	14.7 (5)	0 (0)
Procedural pain	9.1 (3)	0 (0)	14.7 (5)	0 (0)
Back pain	9.1 (3)	0 (0)	14.7 (5)	0 (0)
Myalgia	0 (0)	0 (0)	14.7 (5)	2.9 (1)
Depression	6.1 (2)	3.0 (1)	14.7 (5)	2.9 (1)
Oropharyngeal pain	9.1 (3)	0 (0)	14.7 (5)	0 (0)
Cough	0 (0)	0 (0)	14.7 (5)	0 (0)
Nausea	15.2 (5)	6.1 (2)	11.8 (4)	5.9 (2)
Constipation	3.0 (1)	3.0 (1)	11.8 (4)	5.9 (2)
Fatigue	12.1 (4)	3.0 (1)	11.8 (4)	2.9 (1)
Pyrexia	0 (0)	0 (0)	11.8 (4)	0 (0)
Upper respiratory tract infection	12.1 (4)	0 (0)	11.8 (4)	0 (0)
Vitamin D deficiency	3.0 (1)	0 (0)	11.8 (4)	0 (0)
Arthralgia	12.1 (4)	0 (0)	11.8 (4)	0 (0)
Proteinuria	15.2 (5)	0 (0)	11.8 (4)	2.9 (1)

Incidence % (number of subjects with adverse events or adverse drug reactions). MedDRA/J ver.15.1
For the migalastat-migalastat group, the main treatment period + the extension periods 1 and 2 (Months 0 to 24).
For the placebo-migalastat group, the extension periods 1 and 2 (Months 6 to 24).

No deaths occurred in any treatment periods. In the main treatment period, the incidence of serious adverse events was 12.1% (4 of 33 subjects; bacterial infection, meningitis viral, post procedural hemorrhage in 1 each, and anaplastic large cell lymphoma T- and null-cell types in 1) in the placebo group and 5.9% (2 of 34 subjects; post procedural hematoma and hydronephrosis in 1 each) in the migalastat group. In the extension period 1, the incidence of serious adverse events was 6.7% (2 of 30 subjects; bone cyst and pulmonary embolism/deep vein thrombosis in 1 each) in the placebo-migalastat group and an incidence of 9.1% (3 of 33 subjects; ventricular tachycardia, amyotrophic lateral sclerosis/cerebral hemorrhage/pulmonary embolism, and bulimia nervosa in 1 each) in the migalastat-migalastat group. In the extension period 2, the incidence of serious adverse events was 25.0% (7 of 28 subjects; abdominal pain lower, non-cardiac chest pain, helicobacter gastritis, multiple fractures, meningioma, fatigue/paresthesia, and syncope in 1 each) in the placebo-migalastat group and 17.2% (5 of 29 subjects; palpitations, constipation, malaise, transient ischemic attack, and pneumothorax in 1 each) in the migalastat-migalastat group. Among them, the events occurring in the subject in the placebo-migalastat group during the extension period 2 were considered adverse drug reactions. The study treatment was discontinued in 1 of 33 subjects in the placebo group in the main treatment period (anaplastic large cell lymphoma T- and null-cell types) and in 1 of 33 subjects in the migalastat-migalastat group in the extension period 1 (amyotrophic lateral sclerosis). Both adverse events were assessed as unrelated to the study drug.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.2.3 Foreign phase III extension study (CTD 5.3.5.2.1, Study AT1001-041 [October 2011 to February 2016])

An open-label, extension study was conducted to evaluate the long-term safety and efficacy of migalastat in non-Japanese patients with Fabry disease who completed the Studies FAB-CL-205, AT1001-012, or AT1001-011.

Migalastat 150 mg was orally administered every other day without maximum treatment duration.

All 85 subjects (33 men and 52 women) who received the study drug were included in the safety analysis set. Of the 85 subjects, 68 subjects who had the *GLA* mutation responsive to migalastat as determined by the GLP HEK assay[37)] were included in the efficacy analysis set. A total of 20 subjects were withdrawn from the study, and their reason for discontinuation included withdrawal of consent in 8 subjects, decision by their physicians in 4 subjects, non-compliance with the study drug in 3 subjects, deaths in 2 subjects, adverse events in 1 subject, pregnancy in 1 subject, and lack of efficacy in 1 subject. Patients who were receiving migalastat in the study were allowed to participate in the open-label extension study (Study AT1001-042[49)]) after the completion of this study. The median treatment duration was 23.4 months (range, 0.69 to 42.4 months).

Results of the main efficacy endpoints are shown in Table 38.

Table 38. Results of main efficacy endpoints (efficacy analysis set)

Endpoints		Migalastat group (n = 68)
Annualized changes in $eGFR_{CKD-EPI}$ (mL/min/1.73 m^2/year) [a)]		1.54 ± 10.79 [−1.63, 4.71] (n = 47)
Annualized changes in $eGFR_{MDRD}$ (mL/min/1.73 m^2/year) [a)]		1.40 ± 15.46 [−3.14, 5.94] (n = 47)
Left ventricular mass index (g/m^2)	Baseline [b)]	90.87 ± 28.66 (n = 68)
	Changes up to Month 12	−0.76 ± 13.44 [−5.31, 3.79] (n = 36)
	Changes up to Month 24	−0.47 ± 11.67 [−4.99, 4.06] (n = 28)
	Changes up to Month 36	−4.82 ± 3.58 [−10.51, 0.87] (n = 4)

Mean ± standard deviation [95% CI]
a) Annualized changes from baseline that was the last measurement in the previous study.
b) The last measurement in the previous study.

Adverse events occurring in ≥10% of subjects and those considered adverse drug reactions are shown in Table 39.

[49)] An open-label, extension study to evaluate the long-term safety and efficacy of migalastat in Japanese and non-Japanese patients with Fabry disease who completed Study AT1001-012 or AT1001-041. Migalastat 150 mg was orally administered every other day. A total of 83 patients (including 5 Japanese patients) were enrolled, and the study is ongoing as of December 2017.

Table 39. Adverse events occurring in ≥10% of subjects and those considered adverse drug reactions (safety analysis set)

	Migalastat group (n = 85)	
	Adverse events	Adverse drug reactions
Any adverse events	87.1 (74)	16.5 (14)
Diarrhea	15.3 (13)	3.5 (3)
Arthralgia	12.9 (11)	0 (0)
Pain in extremity	12.9 (11)	0 (0)
Headache	12.9 (11)	0 (0)
Nausea	11.8 (10)	1.2 (1)
Fatigue	10.6 (9)	1.2 (1)
Influenza	10.6 (9)	0 (0)
Nasopharyngitis	10.6 (9)	0 (0)
Dizziness	10.6 (9)	1.2 (1)

Incidence % (number of subjects with adverse events or adverse drug reactions. MedDRA/J ver.15.1

Deaths occurred in 2 subjects (death in 1 subject and breast cancer metastatic in 1 subject) but were assessed as unrelated to the study drug in both subjects. Serious adverse events occurred in 25.9% (22 of 85) of subjects, and all serious adverse events were assessed as unrelated to the study drug. Serious adverse events occurring in ≥2 subjects were atrial fibrillation in 2 subjects, pneumonia in 2 subjects, and implantable defibrillator insertion in 2 subjects. Of 85 subjects, a subject was withdrawn from the study due to an adverse event (squamous cell carcinoma with metastasis), but the adverse event was assessed as unrelated to the study drug.

There were no clinically meaningful changes observed in laboratory data, vital signs, or electrocardiographic findings.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation:

Fabry disease is a progressive X-linked genetic disease due to mutations in the *GLA* gene and affects males and females. A deficiency or insufficiency of α-Gal A activity results in the accumulation of glycosphingolipid substrates (e.g., GL-3 and lyso-Gb_3), which leads to disorders including neurogenic pain, skin symptoms, ophthalmic symptoms, gastrointestinal symptoms, lung symptoms, renal disorders, cardiomyopathy, and cerebrovascular diseases.

Agalsidase beta and agalsidase alfa, which are genetic recombinant α-Gal A, have been approved for treatment of Fabry disease. These ERT products require to be administered intravenously every other week over a lifetime and are reported to be associated with hypersensitivity and administration-related reactions. In addition, it is suggested that their therapeutic effects may be reduced by the production of neutralizing antibodies against α-Gal A. Migalastat, an oral drug product, is associated with less burden and a small risk of reactions related to intravenous drip infusion and production of antibodies as compared with ERT products requiring patients to visit hospital once every 2 weeks to receive intravenous drip infusion of the products. In addition, while ERT is a therapy to replace deficient enzymes, migalastat is a pharmacological chaperone that is designed to bind to α-Gal A and to facilitate the transport of α-Gal A to lysosomes by stabilizing the proteins. The Fabry Disease: Diagnosis and Management Handbook for Japanese 2015 (edited by the editorial committee for the Fabry Disease: Diagnosis and Management Handbook for Japanese, 2015) states that a chaperone therapy, such

as migalastat, is expected to offer a new therapy option to cover the disadvantages of ERT. Based on the above, migalastat is expected to be a new option for treatment of Fabry disease.

PMDA's view:
Migalastat is an orally available capsule product, and the chaperone therapy with migalastat has a mechanism of action and a route of administration which both differ from those of existing enzyme replacement therapy. An approval of migalastat will make it possible to select a therapy according to the condition of individual patients, and migalastat can serve as a new therapeutic option for patients with Fabry disease.

7.R.2 Efficacy

Fabry disease is a rare disease, and the number of patients with Fabry disease in Japan is reported to be 315 to 1061.[1)] In the global phase III study (Study AT1001-012) in which Japanese patients were enrolled, only 7 Japanese patients participated.[50)] Based on the above facts, PMDA decided to investigate the efficacy of migalastat also in individual Japanese patients.

7.R.2.1 Efficacy of migalastat in patients with a history of ERT

The applicant's explanation:
Progressive decline in renal function is a major complication of Fabry disease and may result in end-stage renal failure or require dialysis or kidney transplantation (*Nephrol Dial Transplant*. 2009;24:2102-11; *Clin Genetics*. 2014;86:301-9; *Nat Clin Pract Nephrol*. 2008;4:327-36; *Genet Med*. 2009;11:790-6). In addition, the decline in renal function in patients with Fabry disease is suggested to be a major risk factor for cardiac events, and therefore, slowing of progression of renal function decline is an important therapeutic goal (*J Am Coll Cardiol*. 2011;57:1093-9). GFR is a standard parameter for renal function, and the assessment of eGFR based on serum creatinine values is a standard parameter to monitor the progression of chronic kidney diseases, including treatment of Fabry disease (*N Engl J Med*. 2006;354:2473-83; *J Am Soc Nephrol*. 2014;837-49). In the main treatment period of the global phase III study (Study AT1001-012) in patients with Fabry disease who were receiving ERT, the intergroup difference of least squares mean of annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$, the primary composite endpoint, was ≤2.2 mL/min/1.73 m^2 with an overlap of the 95% CI of ≥50%, meeting the prespecified criterion for comparability in the subgroup of patients with *GLA* mutations responsive to migalastat (Table 27). No clinically meaningful differences in annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were observed in the migalastat group as compared with the ERT group. Even in the extension period, renal function remained stable during treatment with migalastat (Table 29). Cardiac complication is frequently observed and is the leading cause of death in patients with Fabry disease (*Genet Med*. 2009;11:790-6). The most common cardiac symptom is left ventricular hypertrophy, which is known to be a main risk factor of cardiac events (*J Am Coll Cardiol*. 2011;57:1093-9). In Study AT1001-012, the left ventricular mass index, a parameter of cardiac function used as a secondary endpoint, began to decrease at

[50)] In the Basic Principles on Global Clinical Trials (PFSB/ELD Notification No. 0928010, dated September 28, 2007), the percentage of approximately 15% to 20% is suggested as reference for the target sample size and the proportion of Japanese patients in a global study. However, Fabry disease is a rare disease, and there is a difficulty in enrolling patients. Therefore, in the global phase III study (Study AT1001-012), patient enrollment was conducted based on the feasibility of the study, and the planned sample size of Japanese patients was not determined from the point of view of the consistency of results between the entire study population and Japanese subgroup.

Month 18 and remained decreased even at Month 30 in the migalastat group (Table 28 and Table 29). In the ERG group, decreases from baseline in the parameter began to be observed, but the magnitude was small. Plasma lyso-Gb_3 as the disease substrate showed low levels up to Month 30 and was suggested to remain low even if therapy was switched from ERT to migalastat (Table 29).

PMDA asked the applicant to discuss the differences in intrinsic and extrinsic ethnic factors and patient characteristics between the Japanese and non-Japanese patients and to explain the efficacy in Japanese patients.

The applicant's response:
Fabry disease is caused by a mutation of *GLA* gene on the X chromosome and is classified into 2 main phenotypes, "classic" and "late-onset," based on the α-Gal A activity and clinical symptoms. The etiology and the disease type classification do not differ between Japan and other countries. Common diagnosis methods are used in Japan and other countries, and genetic testing is used to determine α-Gal A activity and to identify the mutant form of *GLA* gene adjunctively. More than 900 mutations of *GLA* gene have been identified as the cause of Fabry disease so far, and about 60% of the mutations are missense mutations with single amino-acid substitution. In Japan, 66 mutations of *GLA* gene have been reported,[51)] and similarly, 69% of the mutations are missense mutations. Approximately 85% of *GLA* gene mutations, including missense mutations, are single base mutations and are identified in nearly all gene coding regions (*Fabry Disease - Update*. Kato Bunmeisha. 2014). At this time, approximately 46% and 48% of *GLA* gene mutations reported in the entire population and Japanese subgroup of patients with Fabry disease, respectively, are found to be responsive to migalastat. Symptoms in patients with Fabry disease include cardiac, renal, neurological, cutaneous, ocular, ear, digestive symptoms. Although severity and onset age substantially vary among patients, but these symptoms themselves are common between Japanese and non-Japanese patients. ERT is the only available therapy for patients with Fabry disease in Japan and other countries, except for some countries in which migalastat has been approved, and the dosage and regimen of ERT approved in Japan are the same as those approved in other countries. The pharmacokinetics of migalastat does not substantially differ between the Japanese and non-Japanese patients even taking into account the differences in body weight [see Section "6.R.2 Similarity in pharmacokinetics of migalastat between Japanese and non-Japanese populations"].

Because of the small size of Japanese patients, the interpretation of the results of efficacy comparison between the entire study population and Japanese subgroup is limited, but the patient characteristics did not largely differ between the entire study population and Japanese subgroup in Study 1001-012 (Table 40).

[51)] fabry-database.org (http://fabry-database.org/, Meiji Pharmaceutical University)

Table 40. Patient characteristics in the entire study population and Japanese subgroup in Study AT1001-012 (safety analysis set)

		Entire study population		Japanese subgroup	
		Migalastat (n = 36)	ERT (n = 21)	Migalastat (n = 5)	ERT (n = 2)
Sex	Male	44 (16)	43 (9)	60 (3)	0 (0)
	Female	56 (20)	57 (12)	40 (2)	100 (2)
Age (years)		54.0 (18, 70)	48.0 (18, 72)	52.0 (46, 57)	61.5 (53, 70)
Height (cm)		168.7 (150.0, 187.5)	168.3 (152.5, 186.7)	166.4 (153.1, 170.5)	156.5 (155.3, 157.6)
Body weight (kg)		70.0 (43.3, 142.9)	80.2 (50.3, 117.8)	55.3 (43.3, 67.5)	51.4 (50.3, 52.4)
BMI (kg/m^2)		24.5 (18.4, 55.1)	26.56 (19.7, 42.4)	20.3 (18.5, 24.4)	21.0 (20.3, 21.7)
Disease duration (year)		4.5 (1, 43)	9.4 (1, 39)	4.6 (4, 20)	18.5 (11, 26)
Urine protein (mg/day)		129 (0, 2282)	108 (0, 3154)	602 (0, 2282)	23 (0, 46)
Renal function	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	85.9 (51.3, 145.1)	96.8 (44.8, 129.5)	97.7 (51.3, 108.3)	75.8 (44.8, 106.9)
	$eGFR_{MDRD}$ (mL/min/1.73 m^2)	78.5 (47, 131)	88.0 (43, 124)	91.0 (47, 119)	79.0 (43, 115)
	$mGFR_{iohexol}$ (mL/min/1.73 m^2)	81.3 (51.7, 124.0)	85.1 (33.0, 132.2)	99.8 (52.8, 107.6)	70.5 (33.0, 108.0)
History of treatment with renin-angiotensin system inhibitors		44 (16)	52 (11)	80 (4)	0 (0)
ERT product type	Agalsidase beta	31 (11)	38 (8)	40 (2)	50 (1)
	Agalsidase alfa	24 (67)	62 (13)	60 (3)	50 (1)
GLP HEK assay "amenable"		94 (34)	90 (19)	100 (5)	50 (1)

GLP HEK assay "amenable": A subject with *GLA* mutations responsive to migalastat as determined by the GLP HEK assay.
Percentage of subjects % (Number of subjects). Median (range)

In both migalastat and ERT groups, the mean annualized changes in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ up to Month 18, the primary endpoints (Table 27), in the Japanese subgroup fell within the 95% CI for the least squares mean for the entire study population, showing no large difference between the populations. In the migalastat group of Japanese patients, as with the entire study population, the changes in left ventricular mass index, a main secondary endpoint, decreased beginning baseline to Month 18 months (Table 28). Other endpoints, including plasma lyso-Gb_3 as the disease substrate remained stable from baseline to Month 30 in the migalastat-migalastat group of Japanese patients, showing no distinct difference as compared with the entire study population (Table 29).

As for the long-term efficacy, the mean annualized changes [95% CI] in $eGFR_{CKD-EPI}$ from baseline to Month 48 was −1.08 [−1.93, −0.22] mL/min/1.73 m^2/year (in 14 subjects), showing stable changes in the subjects who entered Study AT1001-045, an extension study of Study AT1001-012.[49)]

7.R.2.2 Efficacy of migalastat in untreated patients (patients without a history of ERT)

The applicant's explanation:

Renal disorder in patients with Fabry disease is considered to be caused by the damage to the glomeruli due to the accumulation of GL-3 in the kidney cells including renal interstitial capillary cells, glomerular podocytes, and renal tubular cells (*Proc Natl Acad Sci USA*. 2008;105:2812-7; *CJASN*. 2010;5:365-70). The decline in GL-3 in renal tissues is regarded as an outcome of treatment (*Orphanet J Rare Dis*. 2010;5:30; *Am J Hum Genet*. 2001;68:711-22) and was used as a primary endpoint in clinical studies of agalsidase beta (Review Report for Fabrazyme, 2003). In the foreign phase III study (Study 1001-011) in ERT-naïve patients with Fabry disease, the percentage of kidney IC GL-3 responders (defined as subjects with ≥50% reduction from baseline in the mean number of kidney IC GL-3 inclusions) at Month 6 in the ITT population, the primary endpoint, was 28% (9 of 32) of subjects in the placebo group and 41% (13 of 32) of subjects in the migalastat group, showing no statistically significant differences. A discussion was held with the Food and Drug Administration (FDA) before the start of the study, and the FDA requested to include not only men with high baseline kidney

IC GL-3 inclusions but also patients having a low baseline kidney IC GL-3 inclusions, including women. It was considered difficult to demonstrate a clinically meaningful effects in a responder analysis in subjects including those with low baseline kidney IC GL-3 inclusions. Therefore, an analysis on percent change from baseline in kidney IC GL-3 inclusions was prespecified, and the effects of migalastat were comprehensively evaluated. The median percent change of kidney IC GL-3 inclusions, a secondary endpoint, was −5.6% in the placebo group and −40.8% in the migalastat group (Table 33). In a post-hoc analysis in subjects excluding 17 subjects with *GLA* mutations nonamenable to migalastat as determined by the GLP HEK assay, the changes in kidney IC GL-3 inclusions in the main treatment period decreased in the migalastat group as compared with the placebo group (Table 34). At the end of the extension period 1 (Month 12), the decrease in the changes in kidney IC GL-3 inclusions at Month 6 was maintained in the migalastat-migalastat group, and further decrease from Month 6 was observed with a similar magnitude of decline in the placebo-migalastat group, showing a similar decline to that in the main treatment period in the migalastat-migalastat group (Table 34).

As for renal function, in the extension period 2 (Months 0 to 24 for the migalastat-migalastat group, Months 6 to 24 for the placebo-migalastat group), the mean annualized changes in GFR was −0.30 and 0.79 mL/min/1.73m^2 for $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$, respectively, which were good results in comparison with the annualized changes in eGFR of −1.1 to −12.2 mL/min/1.73m^2 in treatment-naïve patients with Fabry disease reported in the published literature (*Nephrol Dial Transplant*. 2009;24:2102-11; *Clin Nephrol*. 2006;66:77-84; *Clin J Am Soc Nephrol*. 2010;5:2220-8; *Medicine*. 2002;81:122-38; *J Am Nephrol*. 2007;18:2609-17; *J Am Nephrol*. 2009;20:1132-9). With regard to cardiac function, a decline in the left ventricular mass index from baseline to Month 12 was observed in the migalastat-migalastat group (Table 35).

With regard to the long-term efficacy of migalastat, the mean annualized changes [95% CI] in $eGFR_{CKD\text{-}EPI}$ was −0.81 [−2.00, 0.37] mL/min/1.73 m^2/year and remained stable after long-term administration of migalastat (3 years in average; range, 1.5 to 4.5 years) in patients who entered the foreign phase III extension study (Study AT1001-041) from Study AT1001-011 (n = 40). As for cardiac function, the mean changes [95% CI] in the left ventricular mass index from baseline to Month 30 or 36 was −17.0 g/m^2 [−26.2, −7.9] (n = 15) and showed a further decrease from the end of Study AT1001-011.

PMDA's view:

It was confirmed that no substantial differences existed between the migalastat and ERT groups in the annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$, the primary endpoints of the entire study population in the global phase III study (Study AT1001-012) in which Japanese patients were also included. Although the investigation was limited due to the small sample size, no clinically significant differences were identified between the Japanese subgroup and the entire study population. Therefore, the data can be interpreted to demonstrate the efficacy of migalastat in patients with Fabry disease with migalastat-responsive *GLA* mutations who were previously treated with ERT. In addition, no statistically significant results were observed for the primary endpoint in the foreign phase III study (Study AT1001-011), but reduction in the mean number of kidney IC GL-3 inclusions was seen in subjects with *GLA* mutation responsive to migalastat as determined by the GLP HEK assay, who were the proposed target patients of migalastat therapy. In light of these findings, it

can be concluded that migalastat is expected to be effective even in ERT-naïve patient. Nevertheless, it is necessary to continue collecting data even after the market launch because very limited number of Japanese patients were evaluated and because the efficacy of migalastat has not been studied in ERT-naïve Japanese patients. A final decision on the above matters will be made on the basis of comments from the Expert Discussion.

7.R.3 Safety

The applicant's explanation:

Adverse events observed in the global phase III study (Study AT1001-012) conducted in patients who were receiving ERT are shown in Table 41. Overall, no events, except for adverse drug reactions, tended to occur with a higher incidence in the migalastat group than in the ERT group during the main treatment period. Adverse events with a higher incidence in the entire study population were nasopharyngitis and headache in both groups (Table 32). The majority of adverse events were mild or moderate in severity, and no marked differences in the incidence of adverse events by severity were found between the groups. Adverse drug reactions occurred with a higher incidence in the migalastat group than in the ERT group. Headache was the most frequently observed adverse drug reaction in the migalastat group (16.7% [6 of 36] of subjects in the migalastat group and 0% [0 of 22] of subjects in the ERT group) but was mild or moderate in severity. Among them, there were no serious events or events leading to treatment discontinuation. Although the interpretation was limited due to the small sample size of the Japanese subgroup and the entire study population, no substantial differences in the status of occurrence of adverse events were observed in the main treatment period and the extension period, and no Japanese patient-specific concerns were identified.

Table 41. Occurrence of adverse events in Study AT1001-012 (safety analysis set)

	Main treatment period (18 months of treatment)				Main treatment period ＋ extension period (30 months of treatment)			
	Entire study population		Japanese subgroup		Entire study population		Japanese subgroup	
	Migalastat (n = 36)	ERT (n = 21)	Migalastat (n = 5)	ERT (n = 2)	Migalastat-migalastat (n = 33)	ERT-migalastat[a)] (n = 15)	Migalastat-migalastat (n = 5)	ERT-migalastat[a)] (n =1)
Adverse events	94.4 (34)	95.2 (20)	100.0 (5)	100.0 (2)	97.0 (32)	100.0 (15)	100.0 (5)	100.0 (1)
Adverse drug reactions	38.9 (14)	14.3 (3)	0 (0)	0 (0)	42.4 (14)	26.7 (4)	0 (0)	0 (0)
Serious adverse events	19.4 (7)	33.3 (7)	0 (0)	50.0 (1)	33.3 (11)	20.0 (3)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild adverse events	30.6 (11)	33.3 (7)	60.0 (3)	0 (0)	30.3 (10)	33.3 (5)	80.0 (4)	100.0 (1)
Moderate adverse events	55.6 (20)	52.3 (11)	40.0 (2)	50.0 (1)	48.5 (16)	53.3 (8)	20.0 (1)	100.0 (1)
Severe adverse events	8.3 (3)	9.5 (2)	0 (0)	50.0 (1)	18.2 (6)	13.3 (2)	0 (0)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions)
a) The extension period for the ERT-migalastat group (Months 18 to 30)

Adverse events observed in the foreign phase III study (Study AT1001-011) conducted in ERT-naïve patients are shown in Table 42. No marked difference in the incidence of adverse events, except for adverse drug reactions, during the main treatment period (6 months of treatment) was found between the placebo and migalastat groups. Adverse events occurring at a ≥10 percentage point higher incidence in the migalastat group than the placebo group were headache (21% [7 of 33] of subjects in the placebo group

and 35% [12 of 34] of subjects in the migalastat group) and nasopharyngitis (6% [2 of 33] of subjects in the placebo group and 18% [6 of 34] of subjects in the migalastat group). The incidence of adverse drug reactions was higher in the migalastat group than in the placebo group. Adverse drug reactions occurring with a higher incidence in the migalastat group than in the placebo group were nausea, diarrhea, weight increased, torticollis, and paresthesia (6.1% [2 of 33] of subjects in the migalastat group and 0% [0 of 34] of subjects in the placebo group for each reaction) but were mild in severity. Among them, there were no serious events or events leading to treatment discontinuation. With regard to effects of a history of ERT on the safety of migalastat, no obvious difference in the occurrence of adverse events was observed between Study AT1001-012 enrolling patients who were receiving ERT and Study AT1001-011 enrolling ERT-naïve patients.

Table 42. Occurrence of adverse events in Study AT1001-011 (safety analysis set)

	Main treatment period (6 months of treatment)		Main treatment period + extension periods 1 and 2 (24 months of treatment)	
	Placebo (n = 33)	Migalastat (n = 34)	Placebo-migalastat[a)] (n = 33)	Migalastat-migalastat (n = 15)
Adverse events	91.0 (30)	91.2 (31)	84.8 (28)	100.0 (34)
Adverse drug reactions	27.3 (9)	44.1 (15)	30.3 (10)	55.9 (19)
Serious adverse events	12.0 (4)	5.9 (2)	21.2 (7)	23.5 (8)
Adverse events leading to treatment discontinuation	3.0 (1)	0 (0)	0 (0)	2.9 (1)
Mild adverse events	45.5 (15)	47.1 (16)	45.5 (15)	32.4 (11)
Moderate adverse events	39.4 (13)	35.3 (12)	24.2 (8)	44.1 (15)
Severe adverse events	6.1 (2)	8.8 (3)	15.2 (5)	23.5 (8)

Incidence % (number of subjects with adverse events or adverse drug reactions)
a) The extension periods 1 and 2 for the placebo-migalastat group (Months 6 to 24).

Adverse events by treatment period in Study AT1001-012 are shown in Table 43. The incidence was highest before Month 6, and no increase in the incidence was observed with an increase in the duration of treatment in any adverse events.

Table 43. Occurrence of adverse events by treatment period in the global study, Study AT1001-012 (safety analysis set)

	Months 1 to 6 (n = 51)	Months 7 to 12 (n = 49)	Months 13 to 18 (n = 45)	Months 19 to 24 (n = 34)	Months 25 to 30 (n = 32)	>Months 30 (n = 14)
Adverse events	88.2 (45)	71.4 (35)	82.2 (37)	73.5 (25)	59.4 (19)	42.9 (6)
Adverse drug reactions	35.3 (18)	12.2 (6)	6.7 (3)	14.7 (5)	9.4 (3)	7.1 (1)

Incidence % (number of subjects with adverse events or adverse drug reactions)
The treatment periods with migalastat in the migalastat-migalastat and ERT-migalastat groups only

With regard to the long-term safety of migalastat, Table 44 shows adverse events observed in the foreign phase III extension study (Study AT1001-041) and Study AT1001-042,[49)] the extension study for Studies AT1001-012 and AT1001-041, (data cutoff date, February 10, 2017; the median treatment duration of 1.5 years [range, 0.1 to 2.3 years]). In Study AT1001-041, deaths occurred in 2 subjects and were assessed as unrelated to the study drug. One of the fatal cases concerns a 64-year-old woman in whom grade 3 metastatic breast cancer (invasive), which was the cause of death, was diagnosed 3 months before her death, and she had been treated with migalastat for 2 years at the time of her death. The other case concerns a 63-year-old who was found dead in his home 21 days after treatment. The death certificate listed coronary artery disease and diabetes mellitus as the cause of death, but the exact cause of death could not be determined because no autopsy was performed. At the time of his death, the patient received migalastat for 2 years, and his medical history included transient ischemic attack, obesity, type 2 diabetes mellitus, hypercholesterolemia, cardiac stent placement, triple bypass surgery, and cardiac pacemaker insertion. In Study AT1001-042, the adverse event nasopharyngitis occurred in ≥10% of subjects (in 10 of 84 subjects [11.9%]). Serious adverse events occurred in 17 subjects and were

all assessed as unrelated to the study drug. Among the serious adverse events, the event atrial fibrillation occurred in ≥2 subjects. Adverse events occurred in 80.0% (4 of 5) of Japanese subjects. As for adverse events occurring in ≥2 subjects, the event nasopharyngitis occurred in 2 Japanese subjects, and there were no serious events.

Table 44. Occurrence of adverse events in Studies AT1001-041 and AT1001-042

	AT1001-041	AT1001-042	
	Entire study population (n = 85)	Entire study population (n = 84)	Japanese subgroup (n = 5)
Adverse events	87.1 (74)	85.7 (72)	80.0 (4)
Adverse drug reactions	16.5 (14)	11.9 (10)	0 (0)
Serious adverse events	25.9 (22)	20.2 (17)	0 (0)
Adverse events leading to treatment discontinuation	1.2 (1)	0 (0)	0 (0)
Deaths	2.4 (2)	2.4 (2)	0 (0)
Mild adverse events	25.9 (22)	29.8 (25)	40.0 (2)
Moderate adverse events	47.1 (40)	42.9 (36)	40.0 (2)
Severe adverse events	14.1 (12)	13.1 (11)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions)

In phase I studies, headache was the most frequently observed adverse event (10% [24 of 242] of subjects) and occurred during the treatment with migalastat in 19 subjects. There was no clear tendency related to the dose or administration route of migalastat in the incidence of the event headache. As for other adverse events, each event occurred only in a subject per study. No serious adverse events occurred. In phase II studies (Studies AT1001-013, FAB-CL-201, FAB-CL-202, FAB-CL-203, and FAB-CL-204), the following adverse events occurred with an incidence of ≥25% in each of them: headache and nausea in Study FAB-CL-201; abdominal pain upper in Study FAB-CL-202; and headache and proteinuria in Study FAB-CL-203. Adverse events occurring with an incidence of ≥25% in Study FAB-CL-205, an extension study for Studies FAB-CL-201, -202, -203, and -204, were arthralgia, fatigue, back pain, pain in extremity, influenza, and headache. Serious adverse events occurred in a total of 13 subjects in these phase II studies (including screening periods and periods after treatment discontinuation) but were all assessed as unrelated to the study drug.

In the foreign post-marketing data, 24 adverse drug reactions were reported during the period between May 26, 2016 and May 25, 2017 (a total exposure period of 14,448 day-person). As for the system organ class (SOC), adverse drug reactions were most frequently reported in the SOCs “General disorders and administration site conditions,” “Injury, poisoning and procedural complications,” and “Nervous system disorders” (6 reactions for each SOC). Headache was the only event (preferred term) reported in ≥2 subjects. Six serious adverse reactions were reported in 3 subjects (discomfort, fatigue, swelling, and paresthesia in 1 subject; spinal fracture in 1 subject; and cerebrovascular accident in 1 subject). The post-marketing safety profile of migalastat was similar to that in clinical studies, and no new safety concerns have been identified.

As shown above, headache was the most common adverse event in the clinical studies of migalastat. In general, the event headache was mild to moderate in severity and manageable and did not require treatment. No clinically significant adverse events were observed after short- or long-term treatment with migalastat, suggesting the favorable tolerability of migalastat.

PMDA’s view:

The safety profile of migalastat is acceptable because no clinically significant risk has been identified in the Japanese and non-Japanese clinical studies or the foreign post-marketing data so far. It is necessary to continue to collect data on the safety of migalastat because very limited number of Japanese patients were evaluated.

7.R.4 Indication

7.R.4.1 *GLA* mutations responsive to migalastat

The applicant's explanation:

Since the efficacy and safety of migalastat in patients with Fabry disease with migalastat-responsive *GLA* mutations have been confirmed in phase III studies of migalastat, it is considered that migalastat should be indicated for the treatment of Fabry disease with migalastat-responsive *GLA* mutations.

In early clinical studies (Studies FAB-CL-201 to -204), patients with migalastat-enhanceable α-Gal A activity were enrolled on the basis of α-Gal A activity in the subjects' PBMCs.[34),38)] However, because of the co-existence of both wild-type and mutant forms of α-Gal A in PBMCs from females, even if there were any mutant forms of *GLA* responsive to migalastat, it was not useful to detect the amenability of migalastat to *GLA* mutations in women because wild-type GLA was predominant in the cells. Afterward, a preliminary HEK assay using HEK cells expressing specific mutant forms of *GLA* was developed as an assay which required no subject specimens, could be performed only with information on mutant forms of *GLA*, and was applicable to both males and females. The HEK assay was used to determine the eligibility for inclusion criteria of phase III studies. If the presence of amenability of *GLA* mutations to migalastat can be determined by using this method, the results are applicable to patients having the same mutant form.

Patients were considered to be responsive to migalastat with the preliminary HEK assay when α-Gal A activity was ≥3% of wild-type α-Gal A activity after incubation with migalastat 10 μmol/L and increased by ≥1.2 times from the baseline. The rationale is described below, and the migalastat concentration of 10 μmol/L was determined as a concentration equivalent to the C_{max} after administration of migalastat 150 mg to patients with Fabry disease. Increases in α-Gal A activity up to approximately 1% to 5% of wild-type α-Gal A activity in patients with Fabry disease are considered clinically meaningful (*J Inherit Eng Metab*. 2004;27:385-410). In addition, the use of a threshold of relative increase from baseline was examined to show a greater absolute increase in patients with mutant forms having relatively high baseline α-Gal A activity. Various combinations of thresholds were examined with an index of the amenability of α-Gal A activity in subjects' PBMCs in 19 mutant forms in men with Fabry disease who received migalastat in phase II studies (Studies FAB-CL-201, FAB-CL-202, and FAB-CL-203). A combination of 3% of wild-type α-Gal A activity and a relative increase of 1.2 times baseline α-Gal A activity was chosen as a threshold for optimal sensitivity and specificity.

During the conduct of the phase III studies, the GLP HEK assay to which the preliminary HEK assay was modified was established (*Genet Med*. 2017; 9:430-8). A strong correlation was observed between the amenability to migalastat as determined by the GLP HEK assay and the α-Gal A activity in PBMCs derived

from 51 men with Fabry disease who received migalastat 150 mg orally every other day in phase II and III studies.[52)]

Among subjects enrolled in the phase III studies based on the results of the preliminary HEK assay, 17 of 67 subjects (11 in the placebo group and 6 in the migalastat group) in Study AT1001-01 (the ITT population) and 4 of 60 subjects (2 in the migalastat group and 2 in the ERT group) in Study AT1001-012 (the ITT population) were identified to have *GLA* mutations nonamenable to migalastat as determined by the GLP HEK assay. In Study AT1001-011, the changes in the number of kidney IC GL-3 inclusions from baseline to Month 6 of treatment in 50 subjects with migalastat-responsive *GLA* mutations as determined by the GLP HEK assay was 0.071 ± 0.563 in the placebo group and −0.250 ± 0.513 in the migalastat group, showing a tendency toward decreasing in the migalastat group, and the changes from Month 6 to Month 12 in the placebo-migalastat group in the extension period 1 was −0.330±0.626, showing a similar decrease to that observed in the migalastat group in the main treatment period. Meanwhile, in 17 subjects with GLA mutations nonamenable to migalastat as determined by the GLP HEK assay, changes in the mean number of kidney IC GL-3 inclusions from baseline to Month 6 was 0.09 ± 0.37 in the placebo group (n = 10) and 0.20 ± 0.37 in the migalastat group (n = 5), showing no decrease during treatment with migalastat. Figure 1 shows the changes in plasma lyso-Gb_3 from baseline to Month 18 in 4 subjects (2 in the migalastat group and 2 in the ERT group) with *GLA* mutations nonamenable to migalastat as determined by the GLP HEK assay in Study AT1001-012. Despite the small number of subjects evaluated, plasma lyso-Gb_3 levels elevated in the migalastat group after switching from ERT to migalastat at the start of this study, and distinct differences were seen in comparison with subjects with *GLA* mutations amenable to migalastat as determined by the GLP HEK assay.

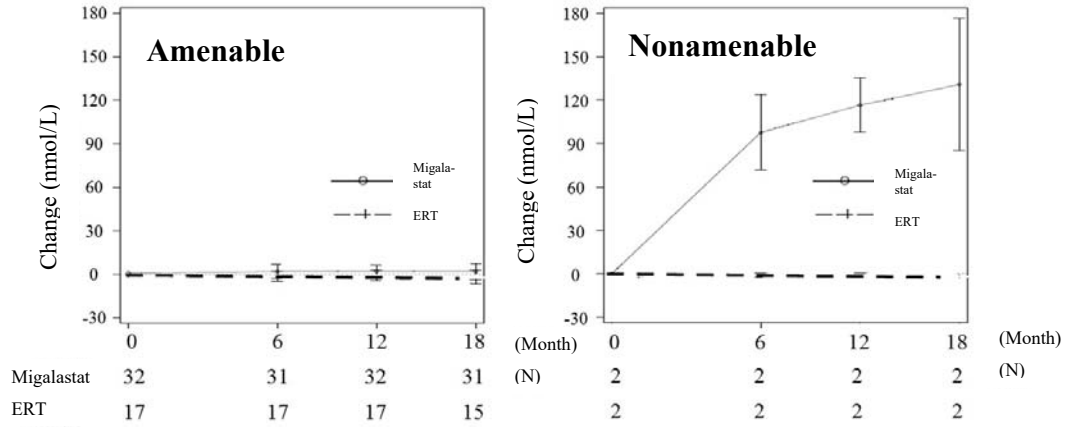

Figure 1. Changes in plasma lyso-Gb_3 in subjects with and without amenability to migalastat as determine by the GLP HEK assay
(mean ± standard deviation) (Study AT1001-012, ITT population)

As described above, migalastat should be indicated for patients with Fabry disease with *GLA* mutations amenable to migalastat as determined by the GLP HEK assay, and sufficient information thereof is to be

[52)] When the α-Gal A activity in PBMCs of subjects elevated by ≥2% of wild-type α-Gal A activity, the case was defined as a case having "increased *in vivo* activity," and the sensitivity, specificity, positive predictive value, and negative predictive value were analyzed. The predictive values were estimated as follows: sensitivity, 1.0 (number of responsive subjects/ number of subjects with increased *in vivo* activity); specificity, 0.88 (number of nonresponders /number of subjects without increased *in vivo* activity); positive predictive value, 0.95 (number of subjects with increased *in vivo* activity/number of responsive subjects); and negative predictive value, 1.0 (number of subjects without increased *in vivo* activity/number of nonresponders).

provided in materials including the package insert. Information on the amenability of individual *GLA* mutations to migalastat is to be adequately provided to healthcare professionals in medical practice by using materials for healthcare professionals and lists on the dedicated website and is to be updated regularly.

PMDA's view:
In a global phase III study (Study AT1001-012) enrolling patients with Fabry disease previously treated with ERT, the efficacy of migalastat was demonstrated in patients with Fabry disease with migalastat-responsive *GLA* mutations as determined by the GLP HEK assay. Similarly, based on the data obtained from the foreign phase III study (Study AT1001-011) conducted in ERT-naive patients, migalastat is expected to be effective in patients with Fabry disease with migalastat-responsive *GLA* mutations as determined by the GLP HEK assay, and the safety of treatment with migalastat is acceptable. Therefore, it is appropriate that migalastat is indicated for the treatment of Fabry disease with migalastat-responsive GLA mutations.

In addition, since the use of migalastat is restricted to patients with migalastat-responsive GLA mutations, the amenability of *GLA* mutations to migalastat must be confirmed prior to the start of treatment with migalastat. Precautions thereof and information on the amenability of individual GLA mutations to migalastat should be provided to healthcare professionals in a timely and appropriate manner, by using, for example, information materials and a dedicated website as proposed by the applicant. A final conclusion on the details of measures to ensure the proper use of migalastat will be made on the basis of comments from the Expert Discussion.

7.R.4.2 Phenotype

The applicant's explanation:
Table 45 shows the efficacy of migalastat in patients with individual phenotypes (men with classic type[53)] and men and women with non-classic type) in the phase III studies (Studies AT1001-012 and AT1001-011. Although the interpretation of the results is limited because of the small sample size, the data suggest that migalastat is expected to be effective for the $eGFR_{CKD\text{-}EPI}$, $mGFR_{iohexol}$, left ventricular mass index, and plasma lyso-Gb_3 concentrations. The numerically higher changes in some parameters in men with classic phenotype in the migalastat group were attributable to the higher baseline levels in them than that in the men and women subjects with non-classic phenotype.

[53)] In Study AT1001-011, a patients with classic phenotype was defined as a male patient who had Fabry disease-related clinical signs in multiple organs and had α-Gal A activity of <3% of wild-type α-Gal A activity (*Ann Intern Med*. 2003;138:338-46; *Molecular Genetics and Metabolism*. 2008;93:112-28; *Biochimica et Biophysica Acta*. 2010;1802:741-8; *J Inherited Metabolic Disease*. 2009;32:424-40). In Study AT1001-012, a patient with classic phenotype was defined as a male patient who had Fabry disease-related clinical signs in multiple organs, because, in the study, the most recent ERT prior to the start of the study had an influence on the baseline α-Gal A activity.

Table 45. Efficacy of migalastat in patients with individual phenotypes (Study AT1001-012 [18 months of treatment], Study AT1001-011 [24 months of treatment [a)]])

		Study AT1001-012 (mITT population)				Study AT1001-011 (ITT population of subjects with migalastat-responsive *GLA* mutations)	
		Men with classic type		Men and women with non-classic type		Men with classic type (n = 14)	Men and women with non-classic type (n = 36)
		Migalastat (n = 12)	ERT (n = 8)	Migalastat (n = 22)	ERT (n = 11)		
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Baseline	87.1 ± 23.3	95.7 ± 17.1	89.7 ± 19.2 [e)]	93.3 ± 22.3	87.8 ± 33.6	95.3 ± 19.6 [i)]
	Annualized changes	−2.4 ± 3.3 [−4.5, −0.2]	−1.5 ± 7.6 [−7.8, 4.9]	−0.6 ± 4.7 [−2.6, 1.5]	−5.6 ± 12.1 [−13.7, 2.5]	−0.3 ± 3.8 [b)] [−2.8, 2.3]	−0.3 ± 4.5 [j)] [−2.0, 1.5]
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Baseline	78.0 ± 13.4	82.1 ± 14.6	84.6 ± 18.4	79.8 ± 28.9	78.6 ± 22.9 [b)]	88.2 ± 22.0 [k)]
	Annualized changes	−1.8 ± 6.8 [−6.2, 2.5]	−5.5 ± 5.8 [−10.3, −0.6]	−5.9 ± 10.4 [−10.5, −1.3]	0.5 ± 10.8 [g)] [−7.2, 8.2]	−3.0 ± 6.0 [g)] [−7.7, 1.6]	−1.0 ± 8.7 [l)] [−4.4, 2.3]
Left ventricular mass index (g/m^2)	Baseline	108.7 ± 26.4 [b)]	109.8 ± 21.6	88.6 ± 17.8	78.3 ± 17.5 [g)]	114.3 ± 27.3	88.2 ± 32.3 [j)]
	Changes	−11.8 ± 12.2 [b)] [−20.0, −3.6]	4.1 ± 18.5 [d)] [−15.4, 23.5]	−4.6 ± 12.1 [−9.9, 0.8]	−7.2 ± 9.4 [c)] [−15.9, 1.5]	−16.7 ± 18.6 [g)] [−31.1, −2.4]	−3.2 ± 18.7 [m)] [−12.5, 6.1]
	Annualized changes	−7.9 ± 8.1 [b)] [−13.3, −2.4]	2.7 ± 12.3 [d)] [−10.2, 15.6]	−3.1 ± 8.0 [−6.6, 0.5]	−4.8 ± 6.3 [c)] [−10.6, 1.0]	−10.4 ± 11.8 [g)] [−19.5, −1.4]	−1.7 ± 10.9 [m)] [−7.1, 3.8]
Plasma Lyso-Gb_3 (nmol/L)	Baseline	14.3 ± 16.0	36.0 ± 21.5 [c)]	5.9 ± 3.8 [f)]	4.8 ± 3.7 [h)]	99.8 ± 35.3 [c)]	29.3 ± 48.3 [n)]
	Annualized changes	3.5 ± 9.1 [b)] [−2.6, 9.7]	−5.0 ± 6.8 [d)] [−12.2, 2.2]	0.7 ± 1.1 [f)] [0.2, 1.3]	0.1 ± 0.8 [g)] [−0.5, 0.8]	−36.8 ± 35.8 [c)] [−69.9, −3.7]	−7.7 ± 20.3 [o)] [−16.6, 1.3]

Mean ± standard deviation [95% CI]
a) Months 6 to 24 for the placebo-migalastat group and Months 0 to 24 for the migalastat-migalastat group.
b) n = 11; c) n = 7; d) n = 6; e) n = 21; f) n = 20; g) n = 9; h) n = 10; i) n = 34; j) n = 30; k) n = 31; l) n = 28; m) n = 18; n) n = 24; o) n = 22

As for safety, no substantial differences in the occurrence of adverse events after the administration of migalastat existed between the phenotypes (Table 46). In Study AT1001-011, serious adverse events occurred more frequently in men with classic phenotype than in men and women with non-classic phenotype, and all serious adverse events but those occurring in 1 patient (paresthesia and fatigue) were assessed as unrelated to the study drug. In the patient with the adverse drug reactions (paresthesia and fatigue), treatment was continued, and the patient recovered.

Table 46. Safety in patients with individual phenotypes (Study AT1001-012 [18 months of treatment], Study AT1001-011 [24 months of treatment [a)]]: safety analysis set)

	Study AT1001-012				Study AT1001-011	
	Men with classic type		Men and women with non-classic type		Men with classic type (n = 19)	Men and women with non-classic type (n = 48)
	Migalastat (n = 14)	ERT (n = 8)	Migalastat (n = 22 例)	ERT (n = 13)		
Adverse events	92.9 (13)	100.0 (8)	100.0 (22)	92.3 (12)	94.7 (18)	91.7 (44)
Adverse drug reactions	35.7 (5)	12.5 (1)	45.5 (10)	15.4 (2)	26.3 (5)	50.0 (24)
Serious adverse events	28.6 (4)	25.0 (2)	40.9 (9)	38.5 (5)	31.6 (6)	18.8 (9)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	5.3 (1)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions).
a) Months 6 to 24 for the placebo-migalastat group and Months 0 to 24 for the migalastat-migalastat group.

A patient with the cardiac variant phenotype[54)] was defined as a patient with the N215S mutation, a *GLA* mutation considered to manifest the cardiac variant Fabry disease, and 10 subjects (7 in the migalastat group and 3 in the ERT group) were enrolled in Study AT1001-012. Of the 10 subjects, 7 (6 in the migalastat group and 1 in the ERT group) had cardiac diseases at baseline, including left ventricular hypertrophy, coronary artery diseases, and cardiac conduction disorders. In the 7 subjects, treatment with migalastat stabilized $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ and decreased the left ventricular mass index and

54) A total of 10 subjects (7 subjects in the migalastat group and 3 subjects in the ERT group) with N215S genotype with *GLA* mutations presenting with the cardiac variant were included (*Heart*. 2015;101(12):961-6), and patients with IVS4+919G>A variant were not included (*Cardiovascular Genetics*. 2009;2(5):450-6) in Study AT1001-012. Patients with these mutations were not included in Study AT1001-011.

plasma lyso-Gb_3 levels. Adverse events and adverse drug reactions occurred in 7 of 7 subjects and 5 of 7 subjects, respectively, in the migalastat group and 3 of 3 subjects and 1 of 3 subjects, respectively, in the ERG group. There were no adverse events leading to treatment discontinuation. Serious adverse events occurred in 2 of 7 subjects in the migalastat group (ventricular tachycardia/chest pain and hemoptysis in 1 each) and were all assessed as unrelated to the study drug. The cardiac variant of Fabry disease is generally defined as a condition having main signs of cardiac symptoms alone. However, it is difficult to strictly identify patients with cardiac variant based on their genotype, and the majority of the subjects had multiple organ disorders including left ventricular hypertrophy.

As shown above, migalastat is expected to be effective in patients with migalastat-responsive *GLA* mutations regardless of phenotypes, and there are no events warranting special safety concerns for individual phenotypes.

PMDA's view:
No particular problems are found in the applicant's opinions. However, because of the limited number of patients evaluated in the clinical studies, it is necessary to continue to collect data on the safety and efficacy concerning the phenotypes even after the market launch. The final decision will be made on the basis of comments from the Expert Discussion.

7.R.4.3 Use of migalastat in combination with ERT

The applicant's explanation:
The efficacy and safety of migalastat in combination with ERT have not been evaluated, and it is not assumed to use migalastat in combination with ERT in the post-marketing setting. It has been demonstrated that a single dose of migalastat in combination with an ERT product increased the exposure to the ERT product (the AUC of plasma α-Gal A activity) by 1.9 to 4.1 times higher than that observed after the administration of the ERT product alone (Table 16). Therefore, as practiced overseas, the Japanese package insert should warn that the efficacy and safety of migalastat in combination with ERT have not been established.

PMDA accepted the applicant's explanation on the condition that appropriate precautionary statements are included in the package insert.

7.R.5 Dosage and administration

The applicant's explanation:
Results of the non-clinical studies suggest that the decrease in GL-3 levels is greater after the daily administration of migalastat than that after the administration of migalastat at a longer interval, for instance, an alternate-day administration. This is consistent with the pharmacological activity of migalastat: Migalastat binds to mutant forms of α-Gal A and is transported to the lysosomes, where dissociation of migalastat restores the α-Gal A activity [see Section "3.R.1 Mechanism of action of migalastat"].

In 5 phase II studies (Studies FAB-CL-201 to -205), the following dosages and regimens were evaluated: 25, 100, and 250 mg, twice daily; 50 and 150 mg, once daily; 50, 150, and 250 mg, once every other day; and 250

and 500 mg, once daily for 3 days with a 4-day interruption (3/4D regimen). In Study FAB-CL-201 conducted in men with Fabry disease, dose escalation of migalastat (25, 100, and 250 mg twice daily and 50 mg once daily) was evaluated, and no consistent decreases in urinary GL-3 concentrations were observed (Table 20). Meanwhile, in Studies FAB-CL-202 and FAB-CL-203 conducted in men with Fabry disease, migalastat 150 mg was administered once every other day, and a tendency toward decreases in the urinary GL-3 concentrations was observed in subjects with *GLA* mutations amenable to migalastat as determined by the GLP HEK assay (Table 21 and Table 22). In Study FAB-CL-204 enrolling women with Fabry disease in which migalastat 50, 150, and 250 mg was administered once every other day, a tendency toward decreases in the urinary GL-3 concentrations was observed with all dosages, and the urinary GL-3 concentrations decreased in 5 subjects with *GLA* mutations responsive to migalastat as determined by the GLP HEK assay (Table 23). In Study FAB-CL-205, an extension study for Studies FAB-CL-201 to -204, the administration of migalastat 150 mg once every other day decreased the urinary GL-3 concentrations generally and increased α-Gal A activity in PBMCs (Table 26). In the extension study, no clear changes were identified in α-Gal A activity or urinary GL-3 concentrations in subjects who were switched from migalastat 150 mg once every other day to migalastat 250 or 500 mg with the 3/4D regimen (Table 26). No significant safety issues were raised, and migalastat was well-tolerated, for any of the dosages and regimens evaluated. However, the incidence of adverse drug reactions adjusted by exposure was 0.12 events/year for migalastat 150 mg once every other day, 1.48 events/year for migalastat 250 mg with the 3/4D regimen, and 0.73 events/year for migalastat 500 mg with the 3/4D regimen, illustrating that the incidence was lower with migalastat 150 mg once every other day than that with migalastat 250 or 500 mg with the 3/4D regimen.

Based on the above findings, migalastat 150 mg once every other day was chosen for the dosage and regimen to be evaluated in the phase III studies. Since the results obtained from the phase III studies (Studies AT1001-012 and AT1001-011) and extension studies have demonstrated the efficacy and safety of migalastat in patients with Fabry disease with migalastat-responsive *GLA* mutations, it is considered that migalastat 150 mg once every other day should be recommended for its clinical use. Information on the following is to be appropriately provided in the documents including the package insert: that migalastat should be administered with consideration of food effects; that migalastat should be administered at the same time on the scheduled day in principle; and measures taken for the missed dose [see Section “6.R.1 Timing of administration”].

PMDA asked the applicant to discuss the measures relevant to the safety in patients accidentally overdosing on migalastat and the proper use of migalastat because the drug is administered once every other day.

The applicant’s response:
In clinical studies (Studies FAB-CL-205, AT1001-012, AT1001-011, and AT1001-042 [data cutoff date, February 10, 2017]), 12 events of overdose of migalastat were reported in 9 subjects: one overdose event occurred in 1 subject receiving migalastat 250 mg once every other day, and the remaining 11 events occurred in 8 subjects receiving migalastat 150 mg once every other day. No adverse events were reported by the investigators to be related to the overdose of migalastat. No overdose case was reported in the foreign post-marketing data (from May 26, 2016 to May 25, 2017). In foreign studies (Studies AT1001-010 and FAB-

CL-104[55]), a single oral dose of migalastat 1250 or 2000 mg was administered to healthy adults. In these studies, headache and dizziness were the most frequently observed adverse events, and migalastat was well tolerated. Based on the above, even if migalastat is accidentally administered every day, the administered dose fells within the range confirmed to be tolerable in clinical studies. Therefore, there would be no clinically significant safety issues even in the case of accidental overdose of migalastat. Information on the dosage and administration of migalastat is to be appropriately provided with the use of materials for healthcare professionals and patients. On the blister pack for migalastat, there is a field for entering the scheduled administration date, and the packaging design allows users to push the drug through the blister foil on the administration date and to make a punch hole at the field for the administration date on the following day. Including these, measures are taken to ensure the proper use of migalastat.

PMDA's view:
No problems have been found for migalastat 150 mg once every other day because the efficacy and safety of the dosage and regimen have been confirmed in the phase III studies (Studies AT1001-012 and AT1001-011) [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. The applicant answered that information on the proper use of migalastat in relation to its dosage and administration, including those described in Section "6.R.1 Timing of administration," would be provided with the use of the package insert, product packaging, and materials for healthcare professionals and patients. No particular problem has been found in the applicant's answer. However, the final decision on the measures taken to ensure the proper use will be made on the basis of comments from the Expert Discussion.

7.R.6 Special patient population

7.R.6.1 Patients with renal impairment

The applicant's explanation:
In a pharmacokinetic study in subjects with renal impairment (Study AT1001-015), the exposure after the administration of a single oral dose of migalastat 150 mg increased with the severity of renal impairment, and the ratio of the geometric mean of $AUC_{0-\infty}$ in subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function was 1.17, 1.81, and 4.53, respectively.

Patients with Fabry disease and moderate renal impairment (baseline eGFR of ≥30 and <60 mL/min/1.73m^2):
In the global phase III study (Study AT1001-012) conducted in patients who were receiving ERT, a total of 3 patients (2 patients in the migalastat-migalastat group and 1 patient in the ERT-migalastat group) met the criterion for moderate renal impairment (baseline $eGFR_{CKD-EPI}$ of ≥30 and <60 mL/min/1.73m^2). As for safety in the patient subgroup, adverse events occurred in all subjects with moderate renal impairment, but there were no adverse drug reactions or adverse events leading to treatment discontinuation. A serious adverse event (chronic cardiac failure) occurred in a subject in the ERT-migalastat group. However, a relationship between the serious adverse event and the study drug was ruled out because the event occurred during ERT. Table 47 shows adverse events occurring in subjects with moderate renal impairment (baseline $eGFR_{MDRD}$ of ≥30 and

[55] Study FAB-CL-104: A placebo-controlled, double-blind, parallel-group study to evaluate the safety, tolerability, and pharmacokinetics of a single oral dose of migalastat 500, 1250, or 2000 mg in non-Japanese healthy men and women.

<60 mL/min/1.73m^2) in the foreign phase III study (Study AT1001-011) enrolling ERT-naïve patients. Serious adverse events occurred during the treatment with migalastat in 3 subjects with moderate renal impairment in the migalastat-migalastat group (amyotrophic lateral sclerosis/cerebral hemorrhage/pulmonary embolism, hydronephrosis, and pneumothorax in 1 each) and 2 subjects in the placebo-migalastat group (pulmonary embolism/deep vein thrombosis and syncope in 1 each). All the serious adverse events were assessed to be unrelated to the study drug. Because of the small size of subjects with moderate renal impairment in these studies, the interpretation of the results is limited, but no particular safety issue has been found.

Table 47. Occurrence of adverse events by the severity of renal impairment ($eGFR_{MDRD}$) in Study AT1001-001 (safety analysis set)

	Main treatment period (6 months of treatment)				Main treatment period + extension periods 1 and 2 (24 months of treatment)			
	≥30 and <60		≥60		≥30 and <60		≥60	
	Placebo (n = 4)	Migalastat (n = 5)	Placebo (n = 29)	Migalastat (n = 29)	Migalastat-migalastat (n = 5)	Placebo-migalastat (n = 4)	Migalastat-migalastat (n = 29)	Placebo-migalastat (n = 29)
Adverse events	100.0 (4)	100.0 (5)	89.7 (26)	89.7 (26)	100.0 (5)	75.0 (3)	100.0 (29)	86.2 (25)
Adverse drug reactions	25.0 (1)	40.0 (2)	27.6 (8)	44.8 (13)	60.0 (3)	0 (0)	55.2 (16)	34.5 (10)
Serious adverse events	0 (0)	20.0 (1)	13.8 (4)	3.4 (1)	60.0 (3)	50.0 (2)	17.2 (5)	17.2 (5)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	3.4 (1)	0 (0)	20.0 (1)	0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with adverse events or adverse drug reactions)

In Study AT1001-015, there was no correlation between the occurrence of adverse events and the severity of renal impairment [see Section "6.2.4.1 Pharmacokinetic study in subjects with renal impairment"].

With regard to the efficacy of migalastat, it is thought that after elimination of migalastat, the released α-Gal A degrades the substrates. In consideration of the results from Study AT1001-015 suggesting that C_{48h} elevates with the severity of renal impairment, the plasma unchanged migalastat concentrations at 2, 3, 4, and 8 hours postdose in Study AT1001-011 were used to compare and evaluate the relationship between the C_{48h} at steady state estimated based on the results of a population pharmacokinetic analysis and the mean changes in the kidney IC GL-3 and plasma lyso-Gb_3 from baseline to Month 12 in patients with moderate renal impairment (baseline $eGFR_{MDRD}$ of ≥30 and <60 mL/min/1.73m^2) and those with $eGFR_{MDRD}$ of ≥60 mL/min/1.73m^2. The results illustrated that C_{48h} tended to be higher in patients with $eGFR_{MDRD}$ of ≥30 and <60 mL/min/1.73m^2 than in patients with $eGFR_{MDRD}$ of ≥60 mL/min/1.73m^2.[56] However, the magnitude of the increase in C_{48h} in patients with moderate renal impairment seemed to have no influence on the efficacy because no marked differences in individual efficacy endpoints were observed between the groups. In patients with moderate renal impairment ($eGFR_{MDRD}$ of ≥30 and <60 mL/min/1.73m^2) in Study AT1001-01, the changes (mean ± standard deviation) in the number of kidney IC GL-3 inclusions from baseline to Month 6 were 0.036 ± 0.144 (in 2 subjects) in the placebo group and −0.390 ± 0.616 (in 3 subjects) in the migalastat group, showing decreases in the number of kidney IC GL-3 inclusions in the migalastat group as compared with the placebo group, as with the subjects

[56] The mean estimated C_{48h} was 34.59 to 52.7 ng/mL in subjects with $eGFR_{MDRD}$ of ≥30 and <60 mL/min/1.73m^2 and 7.55 to 7.94 ng/mL in subjects with $eGFR_{MDRD}$ of ≥60 mL/min/1.73m^2.

with $eGFR_{MDRD}$ of ≥60 mL/min/1.73m^2 (0.068 ± 0.613 in 18 subjects in the placebo group and −0.295 ± 0.621 in 22 subjects in the migalastat group).

As described above, data suggest that the safety and efficacy of migalastat in patients with Fabry disease and moderate renal impairment do not differ from those in patients with normal or mildly decreased renal function.

Patients with Fabry disease and severe renal impairment (eGFR of <30 mL/min/1.73m^2) were excluded and did not evaluated in phase III studies. In Studies AT1001-012, AT1001-011, and AT1001-042, GFR decreased below 30 mL/min/1.73m^2 during treatment with migalastat in 3 subjects (1 subject in each study). An adverse drug reaction (overdose) occurred in the subject in Study AT1001-011, and the reaction was mild in severity. Two serious adverse events (endocarditis/embolic stroke) occurred in the subject in Study AT1001-012, and the serious adverse events resolved and were assessed as unrelated to migalastat. The subject in Study AT1001-011 withdrew the informed consent, and the subject in Study AT1001-042 met the discontinuation criterion of decreased renal function (GFR of <30 mL/min/1.73m^2). The study drug was discontinued at Month 6 in these subjects. The remaining subject in Study AT1001-012 was a patient with a *GLA* mutation nonamenable to migalastat and was withdrawn from the study because of lack of efficacy. Although no safety concerns were found in subjects in whom GFR decreased below 30 mL/min/1.73m^2 during treatment with migalastat, results of a simulation based on the data from Study AT1001-015 suggest the possible accumulation of migalastat after repeated dosing of migalastat 150 mg every other day in patients with severe renal impairment [see Section "6.R.3 Pharmacokinetics of migalastat administered in patients with renal impairment"]. No recommended dosage regimen have been determined for patients with severe renal impairment because of the efficacy and safety concerns. Based on these, at this point, the proposed package insert in Japan, as with that in Europe, does not recommend the use of migalastat in patients with severe renal impairment. With regard to the use of migalastat in patients with severe renal impairment, the implementation of a clinical study in such patients, including investigation of migalastat regimens, is under consideration outside of Japan, and it is planned to be discuss the enrollment of Japanese patients in the study.

PMDA's view:

No clinically significant tendency toward increasing risks has been identified in patients with moderate renal impairment receiving migalastat 150 mg once every other day as compared with patients with normal or mildly impaired renal function. According to the applicant's explanation, there was no clear tendency toward reduction in the efficacy in patients with moderate renal impairment. Therefore, PMDA considers that there are no major problems in administration of migalastat 150 mg once every other day in patients with mild or moderate renal impairment without dose adjustment. Meanwhile, for patients with severe renal impairment, increased exposure and accumulation after repeated dosing are suggested, and thus no recommended dosage regimen have been determined for these patients because of the efficacy and safety concerns. Migalastat has not been administered to patients with Fabry disease and severe renal impairment at baseline in clinical studies, and thus there is no clinical experience in such patients. In light of these facts, at this time, there are no problems in the applicant's view that the use of migalastat is not recommended for patients with severe renal impairment.

The applicant plans to conduct a clinical study in patients with severe renal impairment and is required to submit data from the clinical study immediately when data are available. After the market launch of migalastat, the applicant is also required to collect information on the safety and efficacy in patients with severe renal impairment and re-evaluate the appropriateness of the precautions thereof based on the data obtained. A final decision on the specific measures for provision of precautions for patients with renal impairment will be made on the basis of comments from the Expert Discussion.

7.R.6.2 Pediatric use

PMDA asked the applicant to explain their pediatric development plan because of the known onset of Fabry disease in childhood.

The applicant answered that the implementation of a pediatric clinical study outside of Japan was under discussion including enrollment of Japanese patients in the pediatric clinical study.

PMDA accepted the applicant's answer.

7.R.7 Post-marketing investigations

The applicant's explanation:

A drug use-results survey is planned to be conducted in all patients treated with migalastat to collect information on the safety and efficacy. The planned enrollment period is 6 years or until reaching the target sample size of 160 patients, whichever comes first. The planned survey period is 8 years or until the end of the observation period for the last enrolled patient (≥2 years), whichever comes first.

Given the very limited number of evaluable Japanese patients treated with migalastat, PMDA finds no special problems for the implementation of a post-marketing surveillance encompassing all patients treated with migalastat. PMDA also considers that information on the safety and efficacy especially in patients with renal impairment, as well as information on the safety and efficacy with the use of migalastat, should be collected. The final decision about the details of the post-marketing surveillance will be made on the basis of 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

Compliance assessment is now under way, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

Compliance assessment is now under way, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that migalastat has efficacy in the treatment of Fabry disease with migalastat-responsive *GLA* mutations and that migalastat has acceptable safety in view of its benefits. Migalastat, a pharmacological chaperone of α-Gal A, offers a new therapeutic option for Fabry disease and has clinical significance. PMDA considers that further discussion is necessary on the measures to ensure the proper use of migalastat and to provide precautions for patients with renal impairment.

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

Review Report (2)

February 14, 2018

Product Submitted for Approval

Brand Name	Galafold Capsules 123 mg
Non-proprietary Name	Migalastat Hydrochloride
Applicant	Amicus Therapeutics, Inc.
Date of Application	June 28, 2017

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

1.1 Efficacy

PMDA's view:

It has been confirmed that there were no significant differences between the migalastat group and ERT group in the annualized changes in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$, which are the primary endpoints of the entire study population in the global phase III study (Study AT1001-012) including Japanese patients. Although the small sample size allows only limited interpretation, no clinically significant differences were identified between the Japanese subgroup and the entire study population, and the results suffice to demonstrate the efficacy of migalastat in patients with Fabry disease with *GLA* mutations responsive to migalastat. The foreign phase III study (Study AT1001-011) failed to yield statistically significant results in the primary endpoint However, the mean number of kidney IC GL-3 inclusions decreased in subjects with *GLA* mutations responsive to migalastat as determined by the GLP HEK assay, who are the target patients for migalastat, and this allows to consider that migalastat has efficacy even in ERT-naïve patients. Nevertheless, it is necessary to continue to collect data in the post-marketing setting because extremely limited number of Japanese patients were evaluated and the efficacy of migalastat has not been investigated in ERT-naïve Japanese patients.

The expert advisors supported the above PMDA's conclusion.

1.2 Safety

PMDA's view:

The safety profile of migalastat is acceptable based on the Japanese and foreign clinical study data and the foreign post-marketing data showing no significant risks. Because of extremely limited number of Japanese patients evaluated, safety data of migalastat should be collected further in the post-marketing setting.

The expert advisors supported the above PMDA's conclusion.

1.3 Indication

1.3.1 *GLA* mutations responsive to migalastat

PMDA's view:

In the global phase III study (Study AT1001-012) conducted in patients previously treated with ERT, the efficacy of migalastat has been confirmed in patients with Fabry disease with *GLA* mutations responsive to migalastat as determined by the GLP HEK assay. The data obtained from the foreign phase III study (Study AT1001-011) in ERT-naïve patients suggest that migalastat is expected to have efficacy and its safety profile is acceptable in patients with Fabry disease with GLA mutations responsive to migalastat as determined by the GLP HEK assay. Therefore, Fabry disease with migalastat-responsive GLA mutations is the appropriate indication for migalastat.

The use of migalastat is restricted to patients with migalastat-responsive *GLA* mutations. Healthcare professionals should be advised to check the amenability of *GLA* mutations to migalastat prior to migalastat therapy. As explained by the applicant, the amenability of different *GLA* mutations to migalastat should be communicated to the healthcare professionals in a timely and appropriate manner via written materials and web sites.

The expert advisors supported the above PMDA's conclusion.

PMDA instructed the applicant to modify the descriptions of the "Indication" and "Precautions for Indication" sections of the package insert as shown below, and confirmed that the applicant responded appropriately to the instruction.

Indication

Treatment of Fabry disease with migalastat-responsive *GLA* mutations

Precautions for Indication

1. Migalastat should be used for patients with a confirmed diagnosis of Fabry disease.
2. The amenability of the patient's *GLA* mutations to migalastat should be determined prior to migalastat therapy.

1.3.2 Phenotype

PMDA's view:

The applicant's views, i.e., migalastat is expected to have efficacy for patients with migalastat-responsive *GLA* mutations regardless of the phenotypes, and there have been no adverse events of particular safety concerns among the phenotypes, are acceptable. On the other hand, the clinical studies were conducted in only limited number of patients, phenotype-based safety and efficacy data should be further collected in the post-marketing setting.

The expert advisors supported the above PMDA's conclusion.

1.4 Dosage and administration

PMDA's view:

The efficacy and safety of migalastat have been confirmed at the dose of 150 mg administered once every other day in the phase III studies (Studies AT1001-012 and AT1001-011), and there is no problem with the use of this dosage regimen [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. Further, there are no particular concerns in the applicant's explanation, i.e., information on the proper use of migalastat in relation to its dosage regimen, including the details in Section "6.R.1 Timing of administration" in the Review Report (1), to be provided via the package insert, the product package, and written materials for healthcare professionals and patients.

The expert advisors supported the above PMDA's conclusion.

PMDA instructed the applicant to modify the descriptions of the "Dosage and Administration" and Precautions for Dosage and Administration" sections of the package insert as shown below and confirmed that the applicant responded appropriately to the instruction.

Dosage and administration

The usual dosage for patients aged 16 years or older is 123 mg of migalastat orally administered once every other day. Galafold should not be taken at least 2 hours before and 2 hours after a meal.

Precautions for dosage and administration

1. Migalastat exposure is affected by food intake. Galafold should not be taken 2 hours before and 2 hours after a meal.
2. Galafold should be administered at the same time of day as a rule. If a dose is missed, the dose must be taken within 12 hours after the scheduled time. When >12 hours have passed, the therapy should be resumed with the next dose as scheduled.

1.5 Special populations (patients with renal impairment)

PMDA's view:

Migalastat 150 mg administered once every other day did not cause patients with moderate renal impairment to have increased clinically significant risk as compared with patients with normal or mildly impaired renal function. According to the applicant's explanation, the efficacy of migalastat also did not tend to be reduced in

patients with moderate renal impairment. Based on the findings, PMDA considers that there are no major problems in treating patients with mild or moderate renal impairment with migalastat 150 mg once every other day without dose adjustment. In patients with severe renal impairment, because of suggested increased exposure and accumulation of migalastat after repeated dosing, no specific dosage regimen is recommended in view of efficacy and safety. Migalastat has not been administered to patients with Fabry disease and severe renal impairment at baseline in the clinical studies. In light of these facts, the applicant's intention not to recommend the use of migalastat for patients with severe renal impairment at present is reasonable. The applicant is required to submit data from an upcoming clinical study in patients with severe renal impairment immediately whenever available. The applicant is also required to collect safety and efficacy data from patients with renal impairment in the post-marketing setting and review the appropriateness of the warning based on the data obtained.

The expert advisors supported the above PMDA's conclusion.

PMDA instructed the applicant to give appropriate cautionary advice in the package insert and confirmed that the applicant had taken an appropriate action [for post-marketing investigations, see Section "1.6 Risk management plan (draft)"].

1.6 Risk management plan (draft)

In view of the discussions in "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for migalastat should include the safety and efficacy specifications presented in Table 48 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 49 and Table 50.

Table 48. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	・Administration to patients with *GLA* mutations nonamenable to migalastat. ・Decreased fertility in men after administration	・Long-term safety ・Safety in patients with renal impairment
Efficacy specification		
・Long-term efficacy		

Table 49. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・Drug use-results survey (all-case surveillance) ・Post-marketing clinical study[a)]	・Preparation and distribution of information materials for healthcare professionals. ・Setting up of a website for healthcare professionals to check the amenability to migalastat. ・Provision of information through early post-marketing phase vigilance

a) The ongoing Study AT1001-042, an extension study for Study AT1001-012 and other studies, will be reclassified as a post-marketing clinical study after marketing approval.

Table 50. Outline of use results-survey (draft)

Objective	To evaluate the safety and efficacy of migalastat in routine clinical practice.
Survey method	Central registration
Patient population	All patients treated with migalastat.
Observation period	From the start of treatment with migalastat through the end of the survey period (≥3 years [up to 8 years])
Planned sample size	All patients treated with migalastat.
Main survey items	Patient characteristics, status of treatment with migalastat, concomitant medications, safety evaluation (e.g., adverse events), efficacy evaluation (e.g., eGFR, cardiac function parameters).

1.7 Control of diastereomers

The applicant's explanation about the strategy for control of diastereomers:

In addition to optical rotation, stereoisomers of the starting material are controlled in consideration of the state of formation and removal of epimers in the manufacturing process of the starting material and the state of removal of epimers in the manufacturing process of the drug substance. In theory, Substance A, the starting material, may contain epimers, namely Substances B, C, and D. Substance B is produced during the process for [redacted], is then degraded to [redacted] before being removed. The residual Substance B can be detected by an assay (HPLC) for the related substances of Substance A and is controlled with the control value for the total related substances. It has been confirmed that Substance B is removed during the manufacturing process of the drug substance even if its amount in Substance A exceeds the control value. Meanwhile, Substances C and D are naturally almost absent, and they are unlikely to coexist in the raw materials of lactose or to be produced in the manufacturing process of the starting material. Accordingly, there was no need to quantitatively control Substances C and D in Substance A.

Crude crystals of migalastat hydrochloride may theoretically contain epimers, namely, C-023988,[7)] GSK3037281A,[57)] GSK3022152B,[58)] and GR86643A.[59)] These epimers were added to the crude crystals of migalastat hydrochloride for recrystallization. The removal of GR86643A was insufficient, whereas C-023988, GSK3037281A, and GSK3022152B were efficiently removed. Only C-023988 was actually confirmed to be produced in the manufacturing process of the drug substance and is controllable by the control value for C-023987,[8)] which is a precursor of C-023988, in the intermediate. It has been confirmed that even following the addition of C-023988 of an amount exceeding the control value to the crude crystals of migalastat hydrochloride, C-023988 is removed through the subsequent recrystallization. Meanwhile, the 3 epimers except C-023988 are potential impurities. The amount of the 3 epimers were measured in the 6 batches of crude crystals of migalastat hydrochloride produced at commercial scale by NMR and were all found to be undetectable. Based on the above findings, it has been concluded that no quantitative control is required for these epimers in the drug substance or intermediates. Among the 3 epimers, GSK3037281A and GR86643A can be detected by the purity test for the drug substance [the related substance (HPLC)], but none of them were identified in the drug substance which was stored under the long-term storage condition (for 48 months).

57) [redacted]
58) [redacted]
59) [redacted]

The above findings indicate that the constitutive removal of epimers from the drug substance can be ensured by the control in the manufacturing processes for the starting material and the drug substance.
Given the insufficient removal of GR86643A in the spiking experiments during the manufacturing process for the drug substance, PMDA asked the applicant about the method to verify the removal. According to the applicant, when GR86643A of >[redacted]% is detected in the drug substance purity test [the related substance (HPLC)], recrystallization is performed to confirm the removal. PMDA accepted the applicant's explanation.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

3. Overall evaluation

Based on the above review, PMDA has concluded that the product may be approved with the following condition after the proposed indication and dosage and administration are modified as shown below. Since the product is designated as an orphan drug, the re-examination period of the product is 10 years. The product is not classified as a biological product or a specified biological product. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

Indication

Treatment of Fabry disease with migalastat-responsive *GLA* mutations

Dosage and Administration

The usual dosage for patients aged 16 years or older is 123 mg of migalastat orally administered once every other day. Galafold should not be taken at least 2 hours before and 2 hours after a meal.

(Underlines denote amendment.)

Conditions of Approval

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

2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, to identify the characteristics of the treated patients and to collect safety and efficacy data of the product early so as to take necessary measures for the proper use of the product.

Appendix

List of Abbreviations

Adverse drug reaction	An adverse event for which a causal relationship to the study drug cannot be ruled out
$Ae_{0\text{-}10h}$	Cumulative amount of unchanged drug excreted into urine from time zero to 10-hour urine collection time interval
ANCOVA	Analysis of covariance
AUC	Area under the drug plasma concentration-time curve
BA	Bioavailability
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
C_{48h}	Concentration at 48 hours postdose
CHO	Chinese hamster ovary
CLcr	Creatinine clearance
CL/F	Apparent total clearance
CL_r	Renal clearance
C_{max}	Maximum plasma concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P450
EC_{50}	Concentration yielding 50% of the maximal effect
eGFR	Estimated glomerular filtration rate
$eGFR_{CKD\text{-}EPI}$	Estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation
$eGFR_{MDRD}$	Estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation
EGTA	Ethylene glycol tetraacetic acid
E_{max}	Maximum effect
ERT	Enzyme replacement therapy
$fe_{0\text{-}10h}$	Percent of the migalastat excreted in urine from time zero to 10-hour urine collection time interval
α-Gal A	α-Galactosidase A
GFR	Glomerular filtration rate
GL-3	Globotriaosylceramide
hERG	Human ether-a-go-go related gene
HEK	Human embryonic kidney
HPLC	High performance liquid chromatography
IC	Interstitial capillary
IC_{50}	Half maximal inhibitory concentration
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IR	Infrared absorption spectrum
ITT	Intent-to-treat
Ki	Dissociation constant for binding of inhibitor to enzyme
KO	Knockout
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
lyso-Gb_3	Globotriaosylsphingosine
MATE	Multidrug and toxin extrusion protein
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
$mGFR_{iohexol}$	Glomerular filtration rate measured by the plasma clearance of unlabelled iohexol
mITT	Modified intent-to-treat
NAGA	α-N-acetylgalactosaminidase
NMR	Nuclear magnetic resonance spectrum
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide

OCT	Organic cation transporter
P_{app}	Apparent permeability
PBMC	Peripheral blood mononuclear cell
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PTP	Press through packaging
QbD	Quality by Design
QTcI	Individually corrected QT interval
rhα-Gal A	Recombinant human α-Gal A
SD	Sprague-Dawley
SGLT	Sodium glucose cotransporter
SOC	System organ class
Tg	Transgenic
TK	Toxicokinetics
Tm	Temperature midpoint
t_{max}	Time to reach the maximum drug plasma concentration following drug administration
V_2/F	Central compartment volume of distribution
3/4D	Regimen of once daily for 3 days with a 4-day interruption