Report on the Deliberation Results

March 2, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Cerdelga Capsules 100 mg
[Non-proprietary name]	Eliglustat Tartrate (JAN*)
[Applicant]	Genzyme Japan K.K.
[Date of application]	June 30, 2014

[Results of deliberation]
In the meeting held on February 20, 2015, 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 re-examination period is 10 years, the drug substance and the drug product are both classified as a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:
1. Develop and appropriately implement a risk management plan.
2. Conduct a post-marketing drug use-results survey covering all patients treated with the product during the reexamination period to obtain characteristics of the patients since the number of subjects in the clinical study in Japan was very limited; and at the same time, ensure that safety and efficacy data on the product is collected without delay and that necessary measures are taken to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

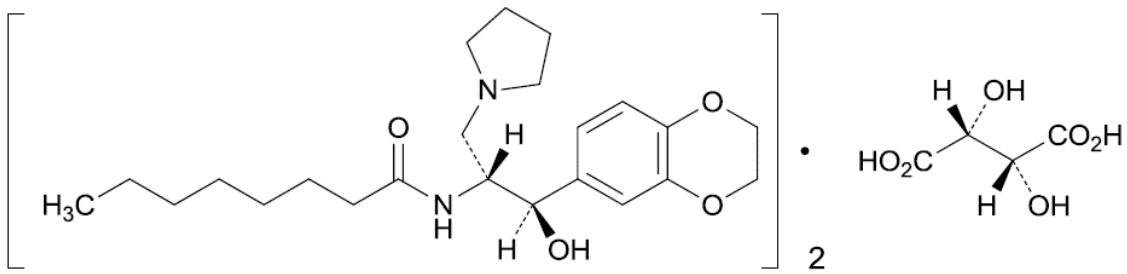
Review Report

February 6, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Cerdelga Capsules 100 mg
[Non-proprietary name]	Eliglustat Tartrate
[Applicant]	Genzyme Japan K.K.
[Date of application]	June 30, 2014
[Dosage form/Strength]	Each capsule contains 100 mg of eliglustat tartrate.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $(C_{23}H_{36}N_2O_4)_2 \cdot C_4H_6O_6$
Molecular weight: 959.17
Chemical name: *N*-[(1*R*,2*R*)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl]octanamide hemi-(2*R*,3*R*)-tartrate

[Items warranting special mention]	Orphan drug (Drug Designation No. 241 of 2011 [*23 yaku*], Notification 0309-11 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 9, 2011)
[Reviewing office]	Office of New Drug I

Review Results

February 6, 2015

[Brand name] Cerdelga Capsules 100 mg
[Non-proprietary name] Eliglustat Tartrate
[Applicant] Genzyme Japan K.K.
[Date of application] June 30, 2014
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in treatment of patients with Gaucher disease has been demonstrated and its safety is acceptable in view of its observed benefits. Proarrhythmic risk, safety by CYP2D6 phenotype, long-term safety, and other issues must be further evaluated through post-marketing surveillance.

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

[Indication] Alleviation of symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, and skeletal pathology)

[Dosage and administration] The usual dosage for adults who are CYP2D6 extensive or intermediate metabolizers is 100 mg of eliglustat tartrate administered orally, twice daily. The dose should be reduced according to the condition of the patient.

[Conditions for approval]
The applicant is required to:
1. Develop and appropriately implement a risk management plan.
2. Conduct a post-marketing drug use-results survey covering all treated patients with the product during the reexamination period to obtain characteristics of the patients since the number of subjects in the clinical study in Japan was very limited; and at the same time, ensure that safety and efficacy data on the product is collected without delay and that necessary measures are taken to facilitate the proper use of the product.

Review Report (1)

January 5, 2015

I. Product Submitted for Registration

[Brand name] Cerdelga Capsules 100 mg

[Non-proprietary name] Eliglustat Tartrate

[Applicant] Genzyme Japan K.K.

[Date of application] June 30, 2014

[Dosage form/Strength] Each capsule contains 100 mg of eliglustat tartrate.

[Proposed indication] Gaucher disease type 1

[Proposed dosage and administration]

The usual dosage for adults is 100 mg of eliglustat tartrate administered orally, twice daily. Before initiation of treatment with the product, patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. The product is to be administered only to patients who are CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs)

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

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

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

Cerdelga capsules contain eliglustat tartrate, as an active ingredient, which is a compound developed by Genzyme Corporation (the United States). Eliglustat tartrate resembles the ceramide moiety of glucosylceramide, and inhibits the synthesis of glucosylceramide by inhibiting glucosylceramide synthase.

Gaucher disease is an autosomal recessive disorder in which a mutation in the gene for glucocerebrosidase responsible for breaking down glucosylceramide results in reduced glucocerebrosidase activity, and as a result, glucosylceramide progressively accumulates primarily in macrophages, damaging the tissues of the liver, spleen, bone marrow, lungs, and other organs.[1] Gaucher disease is classified into 3 types: types 1, 2, and 3. Type 1 does not involve the central nervous system (CNS), while types 2 and 3 feature CNS involvement. Type 2 (acute neuropathic form occurring in infancy and leading to premature death) and type 3 (chronic neuropathic form occurring from late infancy onward and having a life span that may extend into adulthood) are classified according to severity.[2] Gaucher disease has a prevalence of 1 in 100,000 people.[3] In Japan, 51 patients with

[1] Pastores GM, et al., *Semin Hematol*, 2004; 41:4-14

[2] Grabowski, 2010, *The Online Metabolic and Molecular Bases of Inherited Disease*

[3] Meikle PJ, et al., *J Am Med Assoc*, 1999, 281(3):249-54, Pinto R, et al., *Eur J Hum Genet*, 2004; 12:87-92, Poorthuis BJHM, et al., *Hum Genet*, 1999; 105:151-6, *Orphanet reports Series*, 2013, Grabowski, 2010, *The Online Metabolic and Molecular Bases of Inherited Disease*

Gaucher disease[4] received financial assistance for medical expenses in the fiscal years 2003 to 2006, and 43 patients[5] were in the Gaucher disease registry as of fiscal year 2008. The product was designated as an orphan drug with the expected indication of Gaucher disease type 1 (Drug Designation No. 241-2011 [*23 yaku*]).

Imiglucerase (Genetical Recombination) (hereinafter referred to as "imiglucerase") and Velaglucerase Alfa (Genetical Recombination) (hereinafter referred to as "velaglucerase alfa") were approved in March 1998 and July 2014, respectively, for the treatment of Gaucher disease. Both of them are enzyme replacement therapies (ERTs) administered by intravenous infusion every other week.

The applicant has filed a marketing application claiming that the efficacy and safety of the product in treatment of Gaucher disease type 1 have been demonstrated in phase III and other clinical studies.

The product was approved in August 2014 in the United States. As of December 2014, it was not approved in any other country.[6]

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to pale yellow-brown crystalline powder whose description, solubility, pH, dissociation constant, partition coefficient, hygroscopicity, and particle size distribution have been characterized.

Its chemical structure has been elucidated by elemental analysis, infrared (IR) spectrophotometry, ultraviolet (UV) spectroscopy, nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR and ^{1}H-^{1}H and ^{1}H-^{13}C correlation), tandem liquid-chromatography-mass spectrometry (HPLC-MS), X-ray diffraction (single crystals and powder), differential scanning calorimetry, polarized light microscopy, thermogravimetry, moisture analysis, and hygroscopicity.

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

[redacted][7] [redacted]

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4 FY 2007 Summary and Partial Research Reports, Epidemiological Research on Specified Diseases, Research Project for Overcoming Intractable Diseases, supported by the Health and Labour Sciences Research Grant

5 FY 2009 Report, Post-Legislation Research on Registration, Management, Evaluation, and Information Provision Medical Aid for Specific Chronic Pediatric Diseases, Research on Children and Families, supported by the Health and Labour Sciences Research Grant

6 A marketing application was filed in the European Union in September 2013 and is now under review. (The Committee for Medicinal Products for Human Use [CHMP] recommended approval in November 2014.)

7 [redacted]

Purity and impurities were identified as critical quality attributes (CQAs) through the application of quality by design (QbD) approach. Critical process parameters (CPPs) were identified, and control strategies for the CPPs were also investigated through quality risk assessment and design of experiments.

All processes are defined as critical steps. [redacted][8] [redacted][9] [redacted] [redacted][10] [redacted]

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include strength, description, identification (IR spectrophotometry and liquid chromatography [HPLC]), purity (impurities) (HPLC), purity (optical isomers) (HPLC), counter ion (tartrate) (HPLC), residual solvents (gas chromatography), thermal analysis (differential scanning calorimetry), residue on ignition, heavy metals (inductively coupled plasma-mass spectrometry), and assay (HPLC).

2.A.(1).4) Stability of drug substance

Table 1 shows the results of stability studies of the drug substance. Photostability testing showed that the drug substance is photostable.

Table 1. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term testing	4 pilot batches	25ºC	60% RH	Polyethylene bag (double-bagged) / metal drum	[redacted] months
Accelerated testing	4 pilot batches	40ºC	75% RH		[redacted] months

Based on the above results, the retest period of the drug substance, when stored in double polyethylene bags in a metal drum at room temperature, is [redacted] months.

2.A.(2) Drug product

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

The drug product is a hard capsule containing 100 mg of eliglustat tartrate (84 mg as eliglustat free base). The drug product contains microcrystalline cellulose, lactose monohydrate, hypromellose, and glycerol esters of fatty acids as excipients.

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

The drug product manufacturing process consists of the steps of weighing, granulation, drying/blending, capsule filling, and packaging. Weighing, granulation, and capsule filling are defined as critical steps. Process control parameters and process control values are defined for the drying/blending, capsule filling, and packaging steps.

8 [redacted]
9 [redacted]
10 [redacted]

QbD approach was used to identify dissolution, appearance, assay, content uniformity, individual specified degradation products, and primary packaging integrity for moisture protection as CQAs. CPPs were identified, and control strategies for the CPPs were investigated on the basis of quality risk assessment and design of experiments.

2.A.(2).3) Control of drug product

[redacted]

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

Table 2 shows the results of stability studies of the drug product. Photostability testing showed that the drug product was photostable.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term testing	3 pilot batches	25ºC	60% RH	Blister packaging	36 months
Accelerated testing	3 pilot batches	40ºC	75% RH		[redacted] months

[redacted]

2.B Outline of the review by PMDA

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

2.B.(1) Policy for controlling enantiomers

PMDA asked the applicant to justify controlling enantiomers only in the drug substance.

The applicant explained that enantiomer control was not necessary for the drug product because drug substance enantiomers were below the detection limit in the initial batch of the drug product, no increase in enantiomers was detected in long-term testing, and racemization does not occur under normal storage conditions.

PMDA accepted the applicant's response.

2.B.(2) Control strategy for drug substance

PMDA asked the applicant to explain how they established the control strategy for drug substance.

The applicant responded as follows:

Potential CPPs identified by preliminary failure mode analysis were evaluated through design of experiments studies, reaction conditions were evaluated, and impurity spiking studies were also performed. [redacted] Control strategies for the critical quality attributes of the drug substance were selected based on these evaluations.

PMDA considers as follows:

[redacted] However, this is not a major concern for the drug product control strategy because over the range investigated, appropriate in-process control parameters have been established and the specifications are appropriate.

2.B.(3) Control strategy for drug product

The applicant provided the following explanation about the control strategy for the drug product:

A quality target product profile (QTPP) was established, and CQAs affecting the QTPP were identified. [redacted][11] It was decided that Test Parameter 1 for the granules following granulation and appearance and mass after capsule filling were controlled in the process controls to ensure process monitoring and specification compliance.

[redacted]

The applicant responded as follows:

[redacted]. No significant increase in hygroscopicity after drying was observed under the long-term condition (25°C/60% RH) or intermediate condition (30°C/75% RH).[redacted]

Accordingly, Test Parameter 1 need not be established in the specifications of the drug product.

PMDA considers as follows:

[redacted]

11 [redacted]

[redacted]. In light of the above, the control strategy for the drug product is acceptable.

2.B.(4) Novel excipients

Candurin silver fine pearl effect color, which contains the novel excipient aluminum potassium silicate, is included in the capsule shell used for the drug product.

2.B.(4).1) Specification and stability

PMDA finds the specification and stability of Candurin silver fine acceptable.

2.B.(4).2) Safety

PMDA finds that the amount of Candurin silver fine used presents no safety concerns.

In conclusion, PMDA finds no specific problems with the excipients used in the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The primary pharmacodynamic studies included evaluations of the mechanism of action *in vitro* and the suppression of glucosylceramide accumulation and other factors in normal animals and animal models of Gaucher disease *in vivo*. The inhibitory effect on receptors and other entities was evaluated in secondary pharmacodynamic studies. Effects on the cardiovascular system, central nervous system, respiratory system, renal function, and the gastrointestinal system were evaluated in safety pharmacology studies. Some of the studies on effects on human ether-à-go-go-related gene (hERG) current and sodium and calcium channels were conducted under non-Good Laboratory Practice (GLP) conditions.[12] Unless otherwise specified, eliglustat tartrate (hereinafter referred also to as "eliglustat" in this section) was used in the pharmacology studies.

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

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

(a) Inhibition of glucosylceramide synthase by eliglustat (4.2.1.1-1, 4.2.1.1--2)

The inhibitory effect of eliglustat on human glucosylceramide synthase[13] was evaluated in microsomes prepared from a human melanoma cell line (A375 cells). The 50% inhibitory concentration (IC_{50}, mean ± standard deviation) was 19.6 ± 0.68 nmol/L (approximately 7.9 ng/mL as eliglustat free base).

The inhibitory effect of eliglustat on the cell surface expression of galactosyl-N-acetylgalactosaminyl

[12] Six studies investigating the effects of metabolites on ion channels (4.2.1.3-2, -3, -4, -6, -8, and -9) and a study to investigate the effects of eliglustat on calcium channels (4.2.1.3-7) were conducted as non-GLP studies. Although "Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" (PFSB/ELD Notification No. 1023-(4) dated October 23, 2009) was not effective when some of these studies were conducted, all these studies were properly performed.

[13] UDP-glucose binding to nitrobenzoxadiazole (NBD)-C6-ceramide labeled with fluorescent NBD was measured.

-(N-acetylneuraminyl)-galactosylglucosylceramide (GM1)[14] was evaluated in a human erythroleukemia cell line (K562 cells) and a canine macrophage cell line (DH82 cells) to determine glucosylceramide synthase inhibition in different types of cells, and the mean IC_{50} was 28[15] and 78 nmol/L,[15] respectively. The inhibitory effect of eliglustat on the cell surface expression of (N-acetylneuraminyl)-galactosylglucosylceramide (GM3)[16] was evaluated in B16 mouse melanoma cells, and the IC_{50} was 56.7 ± 22.7 nmol/L.

(b) Inhibition of glucosylceramide synthase by human metabolites of eliglustat (4.2.1.1-3)

The inhibition of glucosylceramide synthase were evaluated using 10 metabolites of eliglustat (major metabolites [4-carboxy metabolite, 5-carboxy metabolite, 6-carboxy metabolite], 5 other oxides [7-hydroxyl metabolite, 7-ketone metabolite, 6-ketone metabolite, 6-hydroxyl metabolite, 5-hydroxyl metabolite], primary amine formed by oxidative dealkylation of pyrrolidine moiety [amino metabolite], and N-oxide [N-oxide metabolite]).

The inhibitory effects of the metabolites on glucosylceramide synthase were evaluated with human A375 cell-derived microsomes,[13] and IC_{50} values[15] (μmol/L) were >30 for the 5-carboxy, 6-carboxy, and 4-carboxy major metabolites, 9.45 for the N-oxide metabolite, 6.87 for the amino metabolite, 1.09 for the 7-ketone metabolite, 1.35 for the 7-hydroxyl metabolite, 1.78 for the 6-ketone metabolite, 2.92 for the 6-hydroxyl metabolite, and 2.14 for the 5-hydroxyl metabolite.

The inhibitory effects of the metabolites on cell surface GM3 expression were evaluated in mouse B16 cells,[16] and IC_{50} values[15] (μmol/L) were >10 for the 5-carboxy, 6-carboxy, and 4-carboxy metabolites, 2.24 for the N-oxide metabolite, 4.97 for the amino metabolite, 1.87 for the 7-ketone metabolite, 3.81 for the 7-hydroxyl metabolite, 3.25 for the 6-ketone metabolite, 1.54 for the 6-hydroxyl metabolite, and 2.47 for the 5-hydroxyl metabolite.

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

(a) Studies in mouse model of Gaucher disease

i) Oral administration study (4.2.1.1-4)

Glucosylceramide levels and the number of Gaucher cells were determined in tissues collected from male and female D409V/null mice[17] (7 months of age, 16 per group [8 per time point]) after 5 or 10 weeks of once daily oral administration of eliglustat (as tartrate) 150 mg/kg/day or vehicle.[18] Five male and female D409V/null mice were used for baseline measurements. Glucosylceramide levels and the number of Gaucher cells in tissues

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14 Indirectly measured with fluorescent-labeled antibodies by detecting cholera toxin binding to cell surface ganglioside.

15 Mean values were calculated from 2 runs.

16 Indirectly measured with fluorescent-labeled antibodies by detecting cell surface ganglioside.

17 The D409V/null mouse, a compound heterozygous transgenic murine model of Gaucher disease type 1, is created by introducing a glucocerebrosidase D409V missense mutation into the *gba* locus and then mating homozygous D409V/D409V mice with heterozygous *gba* wild type (wt)/null mice (Xu YH, et al., *Am J Pathol*, 2003; 163(5):2093-101). Residual glucocerebrosidase levels amount to approximately 5% in the peripheral tissues and approximately 21% in the brain. Glucosylceramide begins accumulating in the liver, spleen, and lungs at 3 months of age, and Gaucher cells appear by 4 months of age. The mouse model is considered to show no glucosylceramide accumulation in the central nervous system or neurological pathologies because of remaining glucocerebrosidase activity in the brain. Although D409V/null mice show large biological variability, glucosylceramide levels in the peripheral tissues rise to 16 times wild-type levels and many Gaucher cells accumulate particularly in the liver and lungs at 1 year of age.

18 Water for injection.

were determined at baseline and Week 10 in male and female heterozygous (D409V/wt) mice (7 months of age, 10 animals [5 per time point]). Baseline glucosylceramide was 4-fold higher in the liver, 5-fold higher in the spleen, and 16-fold higher in the lungs in the D409V/null mice than in the D409V/wt mice. The neutrophil count in the bronchoalveolar lavage fluid (BALF) collected at baseline from the D409V/null mice was approximately 15-fold that from the D409V/wt mice.

In the D409V/null mice, the tissue glucosylceramide levels at Weeks 5 and 10 in the eliglustat group were determined and their percent changes relative to the vehicle control group were 43% and 35%, respectively, in the liver, 55% and 60%, respectively, in the spleen, and 56% and 51%, respectively, in the lungs. Glucosylceramide accumulation was significantly inhibited in the eliglustat group relative to the vehicle control group at Week 10 in the liver and at both time points in the spleen and lungs. Gaucher cell counts were determined in Alcian blue/PAS stained liver tissue. The count in the eliglustat group relative to the vehicle control group was 34% at Week 5 and 28% at Week 10, indicating a reduction in Gaucher cells in the eliglustat group. Neutrophil counts in BALF in the eliglustat group relative to the vehicle control group were 35% at Week 5 and 67% at Week 10, indicating a reduction in BALF neutrophil counts in the eliglustat group.

ii) Oral administration and dietary administration studies (4.2.1.1-5, 4.2.1.1-6)

Glucosylceramide levels and the number of Gaucher cells were determined in tissues collected from male and female D409V/null mice (10 weeks of age, 6 per group) after 8 weeks of once daily repeated oral administration of eliglustat (as tartrate; 150 mg/kg/day) or 8 weeks of dietary administration of eliglustat (as tartrate; approximately 450 mg/kg/day). Untreated male and female D409V/null mice (10 weeks of age, 6 animals) were caged for 8 weeks as a control. Six male and female D409V/null mice were used for baseline measurements. The glucosylceramide levels in tissues of the D409V/null mice in the eliglustat dietary administration group were determined and their percent changes relative to the control group were 29% in the liver, 28% in the spleen, and 27% in the lungs, indicating that glucosylceramide accumulation in the dietary administration group was significantly inhibited as compared with the control group. Tissue glucosylceramide levels in the eliglustat oral administration group were determined, and the percent changes relative to the control group were 86% in the liver, 64% in the spleen, and 51% in the lungs. Gaucher cells in the liver were stained with the macrophage marker CD68, and the positively stained area was measured. The area with positive staining was significantly reduced from the baseline in both eliglustat dietary administration and oral administration groups and was significantly lower in the eliglustat dietary administration group in comparison to the control group.

Male and female D409V/null mice (10 weeks of age, 6 per group) were given eliglustat tartrate (150, 300, 450 mg/kg/day) by dietary administration for 7 weeks or eliglustat (as tartrate; 150 mg/kg/day) orally for 7 weeks. A control group received standard feed. Tissue glucosylceramide levels in the eliglustat dietary administration group were inhibited in a dose-dependent manner, and the percent changes in the glucosylceramide levels in the 150, 300, and 450 mg/kg/day groups relative to the control group were 42%, 16%, and 11%, respectively, in the liver; 42%, 21%, and 26%, respectively, in the lungs; and 41%, 20%, and 17%, respectively, in the spleen. Glucosylceramide accumulation was significantly inhibited in the 300 and 450 mg/kg/day groups relative to

the control group. Analysis of area found positive for CD68 staining in the liver revealed a significant reduction in the stained area in the 450 mg/kg/day group in comparison to the control group. The glucosylceramide levels in the eliglustat tartrate oral administration group were determined, and their percent changes relative to the control group were 40% in the liver, 60% in the lungs, and 62% in the spleen. A significant reduction in the area positive for CD68 staining in the liver was noted in comparison to the control group.

iii) Studies of pretreatment with imiglucerase enzyme replacement therapy (ERT) (4.2.1.1-7, 4.2.1.1-8)
Male and female D409V/null mice (4.5 to 6 months of age, 4 to 6 per group) were given a total of 4 intravenous doses of imiglucerase 10 mg/kg or vehicle[18] once every 3 days and then given eliglustat (as tartrate; approximately 150 mg/kg/day) in diet or standard diet (no eliglustat) beginning on the day after the end of imiglucerase administration (12 days after the first dose). Glucosylceramide levels and the number of Gaucher cells in tissues were determined after the fourth imiglucerase dose and at 5 and 10 weeks after the start of eliglustat administration. The glucosylceramide levels in tissues following the fourth imiglucerase dose were determined, and their percent changes relative to the vehicle control group were 21% in the liver, 66% in the spleen, and 105% in the lungs. Accumulation of glucosylceramide was not reduced in the lungs.

The glucosylceramide levels in the liver and spleen from the animals treated with 4 doses of imiglucerase and then with no eliglustat (standard diet) for 5 or 10 weeks were compared with the level achieved after 4 doses of imiglucerase, showing higher glucosylceramide levels in the former group of animals for both treatment periods.

The glucosylceramide levels in the liver and spleen from the animals treated with 4 doses of imiglucerase and then treated with eliglustat for 5 weeks remained at the level comparable to that achieved after 4 doses of imiglucerase. The glucosylceramide levels in the liver and spleen from the animals treated with 4 doses of imiglucerase and then treated with eliglustat for 10 weeks were lower than those in the control (animals which received imiglucerase and then standard diet), but a greater amount of glucosylceramide was accumulated in the former group of animals than in the latter group of animals.

The glucosylceramide levels in the liver and spleen from the animals treated with eliglustat (for 5 or 10 weeks) and without imiglucerase pretreatment were lower than those in the control (animals which received vehicle and then standard diet[no eliglustat]), and were comparable to the level achieved in the animals treated with 4 doses of imiglucerase and then no eliglustat.

Glucosylceramide accumulation in the lungs did not decrease in the animals treated with 4 doses of imiglucerase only or those treated with 4 doses of imiglucerase and then with no eliglustat (for 5 or 10 weeks). In contrast, in the animals treated with 4 doses of imiglucerase and then eliglustat (for 5 or 10 weeks), glucosylceramide levels in the lungs from the animals in both 5- and 10-week eliglustat treatment groups were comparable to those achieved after 4 doses of imiglucerase, and no increase in glucosylceramide level was observed. In the animals receiving eliglustat (for 5 and 10 weeks) without imiglucerase pretreatment, the

glucosylceramide level tended to be lower than that observed in the control (animals which received vehicle and then standard diet [no eliglustat]).

Analysis of area found positive for CD68 staining in the liver revealed a reduction in stained area after the fourth imiglucerase dose in comparison to the vehicle control. The stained area increased after treatment with 4 doses of imiglucerase and then with no eliglustat (for 10 weeks) as compared to that after the fourth imiglucerase dose. After treatment with 4 doses of imiglucerase and then with eliglustat for 10 weeks, the decrease seen in stained area was comparable to that after the fourth imiglucerase dose. In the animals receiving eliglustat for 10 weeks without imiglucerase pretreatment, stained area decreased relative to the control (animals which received vehicle and then standard diet [no eliglustat]) and were comparable to that after 4 doses of imiglucerase.

Male and female D409V/null mice (2 to 3 months of age, 4 to 6 per group) were given a total of 8 intravenous doses of 10 mg/kg of imiglucerase or vehicle[18] in 2 weeks (with dosing intervals of ≥48 hours) and then given eliglustat (as tartrate; approximately 150 mg/kg/day or approximately 450 mg/kg/day) in diet or standard diet beginning the day after the end of imiglucerase administration. Glucosylceramide levels and the number of Gaucher cells were determined in tissues collected after 2 weeks of imiglucerase administration and 5 and 10 weeks after the start of eliglustat administration. The glucosylceramide levels after 2 weeks of imiglucerase administration were 24% in the liver, 41% in the spleen, and 62% in the lungs compared to those in the vehicle control group, indicating decreased glucosylceramide levels in all the tissues.

In comparison to the levels after 2 weeks of imiglucerase administration, glucosylceramide levels in the liver, lungs, and spleen were higher in the animals treated with imiglucerase for 2 weeks and then no eliglustat for 5 or 10 weeks.

Glucosylceramide levels in the liver and spleen of the animals treated with imiglucerase for 2 weeks and then eliglustat for 5 weeks decreased to the levels comparable to or lower than those in the animals treated with imiglucerase for 2 weeks,. The results were similar in the 2 eliglustat dose groups. However, glucosylceramide levels in the lungs showed a decrease only in the eliglustat 450 mg/kg/day group, and no decrease in glucosylceramide levels in the 150 mg/kg/day group. Glucosylceramide levels in the spleen and lungs of the animals treated with imiglucerase for 2 weeks and then eliglustat for 10 weeks decreased to the levels comparable to or lower than those in the animals treated with imiglucerase for 2 weeks. The results were similar in the 2 eliglustat dose groups. Glucosylceramide levels in the liver in the eliglustat 450 mg/kg/day group were comparable to those after 2 weeks of imiglucerase administration. In the 150 mg/kg/day group, glucosylceramide levels in the liver were lower than those in the control (animals which received imiglucerase and then standard diet [no eliglustat]), but glucosylceramide levels were higher than those after 2 weeks of imiglucerase administration.

In the animals receiving eliglustat for 10 weeks without imiglucerase pretreatment, glucosylceramide levels in the liver, lungs, and spleen were lower than those in the control (animals which received vehicle and then

standard diet), and glucosylceramide levels decreased in the 450 mg/kg/day group to the levels comparable to or lower than those after 2 weeks of imiglucerase administration.

Analysis of area found positive for CD68 staining in the liver after 2 weeks of imiglucerase administration revealed a reduction in stained area in comparison to the vehicle control. When mice were given imiglucerase for 2 weeks and then eliglustat for 10 weeks, a greater area was stained as compared to that seen after 2 weeks of imiglucerase administration. When treated with imiglucerase for 2 weeks and then with eliglustat for 10 weeks, the stained area reduced at both doses of eliglustat to the similar extent to the control (animals receiving standard diet after imiglucerase administration). When eliglustat was administered for 10 weeks in mice without imiglucerase pretreatment, stained areas decreased relative to the control group (animals receiving standard diet after vehicle administration).

(b) Studies in normal animals (4.2.1.1-9, 4.2.1.1-10)

In male SD rats (4 per group), eliglustat (as tartrate; 10, 25, and 50 mg/kg/day) or vehicle[18] was orally administered for 4 days. The glucosylceramide levels in plasma of the eliglustat groups were at most 26%, 23%, and 30%, respectively, lower than that in the vehicle control group.[19]

In male and female beagle dogs (2 to 4 per group), eliglustat (as tartrate; 2.5, 5, and 12.5 mg/kg) or vehicle[18] was orally administered twice daily for 28 days. The glucosylceramide levels in the liver of the eliglustat groups were 50%, 47%, and 60% lower than that in the vehicle control group. The vehicle control group and eliglustat 12.5 mg/kg group were also evaluated after a 14-day recovery period following the 28-day dosing period. The glucosylceramide level in the 12.5 mg/kg group was 13% lower than that in the vehicle control group.

Eliglustat (as tartrate; 10 mg/kg) or vehicle[18] was orally administered once daily for 13 weeks to male beagle dogs (4 per group). The glucosylceramide level in the liver in the eliglustat group significantly lowered (32% to 55%) compared with the vehicle control group.

3.(i).A.(2) Secondary pharmacodynamics

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

(a) Inhibitory effects on different receptors, ion channels, transporters, and enzymes (4.2.1.2-1, 4.2.1.2-2)

The inhibitory effect of 10 μmol/L of eliglustat was evaluated on 80 types of receptors, transporters, and ion channels. Ligand binding was inhibited by at least 50% in dopamine receptors D3 and D4.4, the serotonin receptors 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_6, the μ-opioid receptor, the non-specific σ-receptor, and the Ca^{2+} ion channel (L, verapamil site). The inhibitory effects of major metabolites (6-carboxy, 5-carboxy, and 4-carboxy metabolites) were also evaluated. None of these metabolites showed significant inhibition of ligand binding up to a concentration of 10 μmol/L.

[19] The applicant attributed the smaller decreases to the rapid elimination of eliglustat from the plasma and the short half-life of eliglustat.

(b) Assay of agonist activity at serotonin 5-HT_{2B} receptor (4.2.1.2-3)

Evaluation of 5-HT_{2B} receptor agonist activity[20] revealed no activation of 5-HT_{2B} receptor up to a concentration of 100 μmol/L of eliglustat.

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

3.(i).A.(3).1) Cardiovascular effects

(a) *In vitro* studies

i) Effects on hERG channels (4.2.1.3-1 to 4.2.1.3-4)

The effects of eliglustat tartrate (0.01, 0.1, 0.3, 1, 10, and 100 μg/mL [0.021, 0.209, 0.626, 2.09, 20.9, and 209 μmol/L, respectively]), E-4031 (positive control, 100 nmol/L), and the vehicle[21] on hERG current were evaluated in HEK293 cells stably expressing hERG channels. Eliglustat inhibited hERG currents in a concentration-dependent manner, producing significant inhibition at concentrations of eliglustat tartrate of 0.1 μg/mL and above and complete inhibition at 10 and 100 μg/mL. IC_{50} value was 0.35 μg/mL (0.730 μmol/L), and IC_{25} and IC_{75} values were 0.11 μg/mL (0.229 μmol/L) and 1.02 μg/mL (2.127 μmol/L), respectively. E-4031 inhibited hERG current by 97.0%.

The effects of major metabolites (4-carboxy and 5-carboxy metabolites, both at 10 and 300 μmol/L) and cisapride (positive control: 90 nmol/L) on hERG current were also investigated. The hERG current inhibition rate (mean ± standard error) at 10 and 300 μmol/L was 1.3% ± 0.3% and 2.0% ± 0.4%, respectively, for the 4-carboxy metabolite and 0.1% ± 0.4% and 0.7% ± 0.3%, respectively, for the 5-carboxy metabolite. Cisapride inhibited hERG current by approximately 80%.

Effects of the following 9 metabolites on hERG current were also evaluated: amino, 7-ketone, 7-hydroxyl, 5-hydroxyl, 6-hydroxyl, and N-oxide metabolites (all at 0.1 to 30 μmol/L), 6-carboxy and 6-ketone metabolites (all at 1.0, 10, and 30 μmol/L), and 5-carboxy metabolite (at 0.3, 1.0, and 3.0 μmol/L). IC_{50} values were calculated only for the metabolites showing inhibition of at least 50%. Only the amino metabolite inhibited hERG current in a concentration-dependent manner, and the IC_{50} was 1.8 μg/mL (5.1 μmol/L). The 6-carboxy and 5-carboxy metabolites showed no inhibitory effect up to 30 μmol/L and 3 μmol/L, respectively. The 7-ketone, 7-hydroxyl, 5-hydroxyl, 6-hydroxyl, N-oxide, and 6-ketone metabolites showed a slight concentration-dependent inhibitory effect (with approximately 20% inhibition of hERG current at 30 μmol/L).

ii) Effects on sodium channels (4.2.1.3-5, 4.2.1.3-6)

This study evaluated the effects of eliglustat tartrate (0.3, 1, 3, 10, and 100 μg/mL [0.742, 2.47, 7.4, 25, and 247 μmol/L, respectively] as free base), the 6-carboxy metabolite (30 μg/mL [75 μmol/L]), the 5-carboxy metabolite (5 μg/mL [12.5 μmol/L], limit of solubility), flecainide (positive control, 100 μmol/L), and the vehicle[21] on human cardiac sodium channel (hNav1.5) current in HEK293 cells stably expressing hNav1.5. Eliglustat inhibited hNav1.5 current in a concentration-dependent manner with an IC_{50} of 5.2 μg/mL (12.9

[20] Determined by measuring inositol-1-phosphate release. Activation of the 5-HT_{2B} receptors has been reported to be strongly associated with drug-induced valvular heart disease (Rothman RB, et al., *Expert Opin Drug Saf*, 2009; 8(3):317-29).

[21] 0.1% dimethyl sulfoxide (DMSO)

μmol/L as eliglustat free base). Eliglustat tartrate at 1 μg/mL and above showed significant inhibition as compared to the vehicle control. The 5-carboxy and 6-carboxy metabolites did not show a significant inhibitory effect. Flecainide inhibited hNav1.5 current by 95%.

Effects on hNav1.5 current were also evaluated with 8 other metabolites (4-carboxy, 7-ketone, 7-hydroxyl, 5-hydroxyl, 6-hydroxyl, and N-oxide metabolites [all at 10 and 100 μmol/L], amino metabolite [9, 27, and 90 μmol/L], and 6-ketone metabolite [at 14 and 144 μmol/L]), lidocaine (positive control, at 2 mmol/L), and the vehicle.[22] IC_{50} values were calculated only for the metabolites showing inhibition of at least 50%. Only the amino metabolite, a trace metabolite, inhibited hNav1.5 current in a concentration-dependent manner, and the IC_{50} was 37 μmol/L. The other 7 metabolites did not show an inhibitory effect. Lidocaine inhibited hNav1.5 current by 85.0%.

iii) Effects on calcium channels (4.2.1.3-7 to 4.2.1.3-9)

This study evaluated the effects of eliglustat tartrate (4.0, 12.1, and 40 μg/mL [10, 30, and 100 μmol/L, respectively] as free base), nifedipine (positive control, at 0.1 μmol/L), or the vehicle[22] on human Cav1.2 calcium channels (hCav1.2: L-type voltage-dependent calcium channels) in Chinese hamster ovary (CHO) cells expressing the α1C subunit of hCav1.2. Eliglustat inhibited hCav1.2 current in a concentration-dependent manner with an IC_{50} of 10.0 μg/mL (24.8 μmol/L as eliglustat free base). The hCav1.2 current inhibition rate (mean ± standard error) at concentrations of 10, 30, and 100 μmol/L of eliglustat was 30.2% ± 2.6%, 48.9% ± 1.6%, and 88.0% ± 3.2%, respectively. Nifedipine inhibited hCav1.2 current by 73.8%.

The effects of major metabolites (6-carboxy and 5-carboxy metabolites, both at 10, 30 and 100 μmol/L), nifedipine (positive control, at 0.1 μmol/L), and the vehicle[23] on hCav1.2 were also investigated. The hCav1.2 current inhibition rate was 0.5% ± 0.2% at 10 μmol/L, 0.1% ± 0.0% at 30 μmol/L, and 5.4% ± 0.1% at 100 μmol/L for the 6-carboxy metabolite and 0.6% ± 0.2%, 0.8% ± 0.8%, and 12.3% ± 0.4%, respectively, for the 5-carboxy metabolite. Nifedipine inhibited hCav1.2 current by 79.3%.

Effects on hCav1.2 current were also evaluated with 8 other metabolites (4-carboxy, 7-ketone, 7-hydroxyl, 5-hydroxyl, 6-hydroxyl, N-oxide, and 6-ketone metabolites [all at 10 and 100 μmol/L] and amino metabolite [10, 30, and 100 μmol/L]), nifedipine (positive control, at 0.1 μmol/L), and the vehicle[22]. Only the amino metabolite, a trace metabolite, inhibited hCav 1.2 current in a concentration-dependent manner, showing inhibition rate at 10, 30, and 100 μmol/L was 3.6% ± 0.9%, 24.5% ± 1.2%, and 81.5% ± 1.9%, respectively. The IC_{50} was 50 μmol/L. The other 7 metabolites did not show an inhibitory effect. Nifedipine inhibited hCav1.2 current by 85.0%.

iv) Effects on action potential parameters in isolated canine cardiac Purkinje fiber (4.2.1.3-10)

This study evaluated the effects of eliglustat tartrate (0.03, 0.1, 0.3, 1, 10, and 100 μg/mL), *dl*-sotalol hydrochloride (positive control, 50 μmol/L), and the vehicle[21] on action potential parameters (action potential

[22] 0.3% DMSO

[23] 0.3% DMSO or HB-PS buffer (for 5-carboxy metabolite only)

duration at 90% of repolarization [APD_{90}], action potential duration at 60% of repolarization [APD_{60}], maximum rate of depolarization [MRD], resting membrane potential [RMP], and upstroke amplitude [UA]) in Purkinje fibers isolated from male and female beagle dogs and stimulated at a frequency of 1 or 0.5 Hz. At the concentrations of 0.03 and 0.1 µg/mL, eliglustat did not affect any action potential parameter. APD_{90} was unaffected at eliglustat tartrate concentrations up to 0.3 µg/mL, but shortening was observed at 1 µg/mL and above (at 1 Hz and 0.5 Hz, shortening of 12% and 8% at 1 µg/mL eliglustat tartrate and 35% and 39% at 10 µg/mL eliglustat tartrate). APD_{60} was shortened at eliglustat tartrate concentrations of 0.3 µg/mL and above: at 1 and 0.5 Hz, APD_{60} was shortened by 12% and 10%, respectively, at 0.3 µg/mL eliglustat tartrate, 19% and 17%, respectively, at 1 µg/mL eliglustat tartrate, and 55% and 61%, respectively, at 10 µg/mL eliglustat tartrate. MRD was unaffected at eliglustat tartrate concentrations up to 0.3 µg/mL but decreased slightly at 1 µg/mL (13% and 9% at 1 and 0.5 Hz, respectively) and decreased at 10 µg/mL (53% and 47% at 1 and 0.5 Hz, respectively). Analysis of RMP showed mild depolarization at 10 µg/mL. UA was unaffected at eliglustat tartrate concentrations up to 1 µg/mL and decreased at 10 µg/mL (24 and 19 mV at 1 and 0.5 Hz, respectively). In summary, action potential parameters were affected in a concentration-dependent manner at concentrations of eliglustat tartrate of 0.3 µg/mL and above, and cardiac ion channels were blocked with no action potential induction at 100 µg/mL.

The effects of eliglustat tartrate (0.3 µg/mL) on MRD were investigated with the fibers stimulated at a frequency of 3 Hz to evaluate whether frequency-dependent interactions with cardiac sodium channels[24] are present. When the frequency of stimulation was increased to 3 Hz, MRD decreased by 2.8% for the vehicle control and 13% for eliglustat tartrate 0.3 µg/mL. The lack of effects on MRD at eliglustat tartrate 0.3 µg/mL and 1 Hz stimulation suggests that eliglustat tartrate might block cardiac sodium channels at a concentration of 0.3 µg/mL.

The control *dl*-sotalol hydrochloride prolonged APD_{60} (57% and 81% at 1 and 0.5 Hz, respectively) and APD_{90} (53% and 74% at 1 and 0.5 Hz, respectively).

(b) *In vivo* studies

i) Effects in conscious animals (4.2.1.3-15)

Single oral doses of eliglustat (as tartrate; 0 [vehicle[25]], 10, 25, 50, and 80 mg/kg) were administeredin an escalating manner to conscious male beagle dogs (n = 4).[26] Also single oral doses of eliglustat (as tartrate; 0, 1, and 3 mg/kg) were administeredin an escalating manner to conscious male beagle dogs (n = 4, dosing interval of 3 to 4 days). Telemetry was used to evaluate the effects of the doses on blood pressure, heart rate, and lead II electrocardiography parameters (PR, RR, and QT intervals and QRS interval) from 30 minutes before to approximately 6 hours after administration. No effects on arterial pressure (systolic and diastolic blood pressure and mean blood pressure) were noted at any dose.

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[24] Increased stimulation frequency promotes cardiac sodium channel blockage, enhancing the effects of test articles on parameters such as MRD and UA (Gintant GA, et al., *Pflugers Arch*, 1984; 400(2):121-9).

[25] Reverse osmosis water

[26] The dosing intervals were 3 to 4 days up to 50 mg/kg and 11 days at 50 and 80 mg/kg in 3 animals and 3 to 4 days up to 80 mg/kg in 1 animal.

Heart rate was unaffected at doses up to 50 mg/kg of eliglustat but was higher at 30 to 90 minutes postdose at 80 mg/kg as compared with the vehicle control.

An evaluation of electrocardiographic parameters showed no effects on QT or QTcF[27] interval at any dose. RR interval was unaffected at doses up to 50 mg/kg of eliglustat but tended to be shorter at 30 to 90 minutes postdose at 80 mg/kg as compared with the vehicle control. PR interval was unaffected at doses up to 25 mg/kg of eliglustat but tended to be prolonged in a dose-dependent manner at 30 to 120 minutes postdose at 50 and 80 mg/kg, with maximum prolongation of 19.2 ms (at 120 minutes postdose) at 50 mg/kg and 21 ms (at 60 minutes postdose) at 80 mg/kg. QRS interval was unaffected at the doses of 1 and 3 mg/kg of eliglustat but was prolonged in a dose-dependent manner at 10, 25, 50, and 80 mg/kg as compared with the vehicle control, with maximum prolongation of 3.0, 4.0, 5.8, and 10.7 ms, respectively.

No abnormal behavior was noted at the doses of 1 to 25 mg of eliglustat, but vomiting was found in all animals at 80 mg/kg and three-fourths of the animals at 50 mg/kg.

ii) Effects in anesthetized animals (4.2.1.3-16)

Intravenous doses of eliglustat (as tartrate; 1, 2.5, and 5 mg/kg) were administered (with 40-minute intervals) in an escalating manner to anesthetized male beagle dogs (n = 6). The vehicle[18] was administered with 40-minute intervals to 5 animals in the same manner. Effects on arterial pressure, heart rate, and lead II electrocardiographic parameters (PR, RR, and QT intervals and QRS interval) were evaluated 15 minutes and 5 minutes before the first dose and 2, 5, 15, and 35 minutes after each dose. Arterial pressure was unaffected at 1 mg/kg of eliglustat. Mean arterial pressure and left ventricular systolic blood pressure decreased slightly in a dose-dependent manner at 2.5 and 5 mg/kg, but the decreases were not significant as compared with the vehicle control. Heart rate decreased in a dose-dependent manner at ≥1 mg/kg of eliglustat. Eliglustat significantly decreased heart rate as compared with the vehicle control. Analysis of the electrocardiographic parameters revealed prolongation of the RR interval in a dose-dependent manner beginning at 1 mg/kg of eliglustat. Eliglustat caused significant prolongation as compared with the vehicle control. The other electrocardiographic parameters were unaffected at 1 mg/kg of eliglustat but were prolonged at 2.5 and 5 mg/kg. The PR interval and QTcF interval were significantly prolonged at 2.5 and 5 mg/kg as compared with the vehicle control, and significant QRS prolongation was noted at 5 mg/kg. Atrioventricular and intraventricular conduction times were prolonged in a dose-dependent manner at 1, 2.5, and 5 mg/kg of eliglustat. The maximum rate of left ventricular pressure rise (dP/dt_{max}) was significantly lower at any dose in comparison to the vehicle control.

3.(i).A.(3).2) Effects on CNS (4.2.1.3-11)

Eliglustat (as tartrate; 20, 100, and 400 mg/kg), chlorpromazine (positive control, 20 mg/kg), or the vehicle[25] was orally administered as a single dose to male rats (6 animals per group). The method of Irwin was used to

[27] Corrected with Fridericia's formula.

evaluate clinical signs and behavior as well as autonomic nervous system functions including body temperature, salivation, respiration, and pupil diameter at 30, 90, 150 and 240 minutes postdose. No treatment-related effects were noted. Chlorpromazine dosing resulted in effects consistent with its known pharmacologic actions.

Pharmacokinetic parameters were measured at 30, 60, and 120 minutes after administration of a single oral dose of eliglustat (as tartrate; 20, 100, and 400 mg/kg) to male rats (3 animals per group). The plasma eliglustat concentration peaked at 30 minutes postdose. Plasma concentrations of unchanged eliglustat at 30 minutes postdose were 121 ± 44.9 ng/mL at 20 mg/kg, 1125 ± 161 ng/mL at 100 mg/kg, and 1494 ± 263 ng/mL at 400 mg/kg. These values were 2.7-fold, 25.4-fold, and 33.7-fold the expected[28] maximum plasma concentration (C_{max}) of unchanged eliglustat at the clinical dose.

3.(i).A.(3).3) Respiratory effects (4.2.1.3-12)

This plethysmography study evaluated the effects on respiratory rate and tidal volume at baseline and 30 and 120 minutes postdose in male rats (7 to 8 animals per group) in which eliglustat (as tartrate; 20, 100, 400 mg/kg) or the vehicle[25] was orally administered, or morphine (positive control, 20 mg/kg) was intravenously administered. No significant effects on respiratory rate or tidal volume were noted at any time point in the eliglustat 20 or 100 mg/kg group as compared with the vehicle control. The respiratory rate decreased in the 400 mg/kg group at 30 minutes postdose (by 27% compared with the vehicle control), but no decreases were observed at 120 minutes postdose. Morphine injection reduced respiratory rate and tidal volume from baseline at 30 and 120 minutes postdose. The C_{max} of unchanged eliglustat in plasma following a 100 mg/kg dose was estimated to be 1125 ng/mL, which is approximately 25-fold the estimated C_{max}[28] of unchanged eliglustat in plasma at the clinical dose.

3.(i).A.(3).4) Effects on renal function (4.2.1.3-13)

Male SD rats (8 animals per group) received an oral load of physiological saline (approximately 20 mL/kg) followed 30 minutes later by a single oral dose of eliglustat (as tartrate; 20, 100, 400 mg/kg), furosemide (positive control, 20 mg/kg), or the vehicle.[25] Urine was collected during the periods of 0 to 3 hours, 3 to 6 hours, and 6 to 24 hours postdose. The animals were not allowed to drink from approximately 2 hours before saline loading to 6 hours after the start of urine collection. In the eliglustat 20 mg/kg group, no significant change in urine volume, urine pH, or urinary electrolytes[29] (Na, K, Cl) was seen as compared with the vehicle control at any time point. In the eliglustat 100 mg/kg group, urine volume and urinary electrolytes were not significantly changed, but urine pH increased in the samples collected from 3 to 6 hours postdose. In the eliglustat 400 mg/kg group, urine volume and urinary Na were unaffected at any time point, but K and Cl decreased in the samples collected from 6 to 24 hours postdose, and urine pH increased in the samples collected from 0 to 3 hours and 3 to 6 hours postdose. Furosemide dosing markedly increased urine volume, decreased urine pH, and also affected electrolyte excretion.

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[28] The mean estimated C_{max} (44.3 ng/mL) at steady state following oral dose of 100 mg twice daily in CYP2D6 extensive metabolizers and intermediate metabolizers, 50 mg twice daily in poor metabolizers, and 150 mg twice daily in ultra-rapid metabolizers, as determined with population pharmacokinetic analysis.

[29] Urinary electrolytes per unit body weight were calculated as follows:
Urinary electrolytes = electrolyte concentration in urine (mmol/L)/body weight (g) × urine volume (mL).

3.(i).A.(3).5) Gastrointestinal effects (4.2.1.3-14)

Male rats (8 animals per group) received a single oral dose of eliglustat (as tartrate; 20, 100, and 400 mg/kg), morphine (positive control, 20 mg/kg), or the vehicle.[25] Approximately 30 minutes later, the animals were given a suspension of powdered charcoal orally. Gastrointestinal transport of powdered charcoal (relative distance of intestinal movement at 30 minutes after administration of powdered charcoal[30]) and gastric emptying (stomach weight) were unaffected in the eliglustat 20 mg/kg group, but in the 100 and 400 mg/kg groups, gastrointestinal transport of powdered charcoal was inhibited (relative distance of intestinal movement [mean ± standard error] was 0.0% ± 0.00% and 3.6% ± 2.79%, respectively), and emptying of gastric contents was delayed (stomach weight was 73% and 113%, respectively, higher than that in the vehicle control). Gastrointestinal tract transport and gastric emptying were delayed in the morphine group.

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

3.(i).B.(1) Mechanism of action

The applicant explained as follows:

Glucosylceramide synthesis is the rate-limiting step in the metabolism of ganglioside and neutral glycosphingolipid. Glycosphingolipids are broken down by specific catabolic enzymes in lysosomes and are therefore normally at low concentrations in lysosomes. In many lysosomal disorders, an abnormality in the genes that code for these catabolic enzymes causes a decrease in catabolic activity and a consequent accumulation of the corresponding substrate in lysosomes. In patients with Gaucher disease type 1, a deficiency of glucocerebrosidase, an enzyme that catabolizes glucosylceramide into ceramide and glucose, results in reduced glucosylceramide hydrolysis and a consequent accumulation of glucosylceramide in lysosomes of the liver, spleen, and bone marrow.

Eliglustat is an inhibitor of glucosylceramide synthase, which is widely expressed in cells and tissues. By suppressing glucosylceramide synthesis, it suppresses glucosylceramide accumulation to be in step with the reduced rate of catabolism in affected patients. Eliglustat is a small molecule drug and may be beneficial even in cells deficient in the mannose receptor,[31] which contributes to cellular uptake in ERT.

Published data on the effects of eliglustat on the synthesis of substrates other than glucosylceramide are as follows: The compound showed no inhibitory effects on intestinal glycosidases (lactase, maltase, sucrase), α-glucosidase I and II, and cytosolic debranching enzyme (1,6-α-glucosidase) up to concentrations of 2,500 μmol/L (1.01 mg/mL as eliglustat free base) and showed very weak inhibitory activity (IC_{50} of approximately 1,600 μmol/L [647 μg/mL as eliglustat free base]) on non-lysosomal β-glucosidase (GBA2).[32]

[30] Relative distance of intestinal movement = distance of intestinal movement of charcoal powder from pyloric sphincter/total length of intestine

[31] Mistry PK, et al., *Proc Natl Acad Sci*, 2010: 107(45):19473-8

[32] McEachern KA, et al., *Mol Genet Metab*, 2007; 91(3):259-67

PMDA asked the applicant to discuss the possibility of cellular accumulation of ceramide and other sphingolipids caused by the inhibition of glucosylceramide synthase by eliglustat, including possible effects of such accumulation.

The applicant responded as follows:
It has been reported that glucosylceramide, GM3, and phosphatidylglycerol levels are elevated, while sphingomyelin, ceramide, and dihexosylceramide levels are decreased in patients with Gaucher disease.[33] Since treatment-naïve patients with Gaucher disease have deficient glucocerebrosidase activity for converting glucosylceramide into ceramide and glucose, glucosylceramide is not further broken down to generate ceramide in lysosomes, and in turn ceramide is unavailable for the synthesis of sphingomyelin and other sphingolipids. Eliglustat inhibits glucosylceramide synthase to reduce glucosylceramide levels, making ceramide to be used in the synthesis of sphingomyelin and other sphingolipids. ERT to prompt the production of ceramide and glucose from glucosylceramide produces a similar effect. Treatment with eliglustat and ERT are thus both believed to maintain sphingomyelin levels slightly high but within the normal range.

Clinical studies of eliglustat in patients with Gaucher disease type 1 were conducted to evaluate the effects of eliglustat treatment on sphingolipid intermediates of glucosylceramide and GM3 (sphingomyelin and ceramide). Treatment with eliglustat did not greatly alter plasma ceramide levels, which are generally within normal range in patients with Gaucher disease type 1. In Study ENGAGE in treatment-naïve patients, plasma ceramide levels were within the normal range in all patients. In a phase II study, plasma ceramide levels were high in 2 patients but only slightly above the normal range and not clinically significant. In Study ENCORE in patients with a history of ERT, plasma ceramide levels were either normal or changed in a clinically insignificant manner in all patients.

Plasma sphingomyelin levels are generally normal in patients with Gaucher disease type 1. In the phase II study and Study ENGAGE in treatment-naïve patients, the mean plasma sphingomyelin levels increased following eliglustat administration but were within the normal range in all patients. In the phase II study, the mean plasma sphingomyelin levels still remained within the normal range even 4 years later. Also in Study ENCORE in patients with a history of ERT, plasma sphingomyelin levels were within the normal range in all patients at baseline and 1 year later.

Based on the above results, inhibition of glucosylceramide synthase by eliglustat is unlikely to result in abnormal accumulation of physiologically important lipids synthesized from ceramide.

PMDA accepted the responses of the applicant.

[33] Meikle PJ, et al., *Blood Cells Mol Dis*, 2008; 40(3):420-7

3.(i).B.(2) Gastrointestinal symptoms

Since inhibition of dopamine, serotonin, μ-opioid, and other receptors was observed in the secondary pharmacodynamic studies, PMDA asked the applicant to discuss safety in humans.

The applicant responded as follows:

At the maximum concentration of 10 μmol/L (4.0 μg/mL as eliglustat free base) studied in the relevant secondary pharmacodynamic study (4.2.1.2-2), eliglustat inhibited the μ-opioid receptor by 53%, the dopamine D3 receptor by 69%, the 5-HT_{1A} receptor by 65%, the 5-HT_{2A} receptor by 62%, the 5-HT_{2B} receptor by 55%, and the 5-HT_6 receptor by 73%. Since opioid receptor inhibition can cause constipation,[34] effects on the gastrointestinal tract may be related to actions on these receptors. Suppression of gastrointestinal transport may manifest as constipation or obstruction in humans. Salivation in a dose-dependent manner was observed in a toxicity study in rats. Effects on gastrointestinal transport were observed at 100 mg/kg in a pharmacology study in rats (4.2.1.3-14). In addition, vomiting occurred frequently at 25 mg/kg and above in a toxicity study in dogs (4.2.3.1-3).

The 10 μmol/L concentration studied in the secondary pharmacology studies is approximately 100-fold the estimated C_{max}[28] of plasma unchanged eliglustat at the clinical dose. In the study investigating gastrointestinal transport (4.2.1.3-14), C_{max}[35] following administration of eliglustat at 100 mg/kg was 25-fold the estimated C_{max}[28] of plasma unchanged eliglustat at the clinical dose. In the toxicity study in dogs, the estimated C_{max}[36] following a dose of eliglustat at 25 mg/kg was approximately 50-fold the estimated C_{max}[28] of plasma unchanged eliglustat at the clinical dose. Accordingly, inhibition of these receptors are likely to have small impacts on humans treated with the drug.

The incidences of gastrointestinal adverse events in a pooled analysis data of phase II/III studies[37] were 9.9% (39 of 393 patients) for diarrhea, 5.9% (23 of 393 patients) for constipation, and 4.3% (17 of 393 patients) for vomiting, but most events were mild in severity. Most gastrointestinal disorders were non-serious and transient in nature, and none of them led to treatment discontinuation or dose adjustment (reduction). Exposure was not correlated with gastrointestinal events over the dose range investigated in the clinical studies.

PMDA considers as follows:

Gastrointestinal effects are a concern because eliglustat inhibits dopamine, serotonin, and μ-opioid receptors. Although the safety margin is 25-fold or greater, gastrointestinal effects such as those seen in rats and dogs could occur in humans exposed to a high level of eliglustat. Therefore, effects in humans will be reviewed in the clinical section of this report [see "4.(iii).B.(3).3) Gastrointestinal symptoms"].

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34 Holzer P., *Regul Pept*, 2009; 155:11–7

35 C_{max} (1125 ng/mL) in a safety pharmacology study investigating the effects on CNS (4.2.1.3-11)

36 C_{max} (2234 ng/mL: 2598 ng/mL in men; 1871 ng/mL in women) following administration of eliglustat at 25 mg/kg/day (12.5 mg/kg twice daily) was estimated under the assumption of linearity of C_{max} (2078 ng/mL in men; 1497 ng/mL in women) at 10 mg/kg in the 13-week repeated-dose oral toxicity study in dogs (4.2.3.2-8).

37 Eliglustat was administered for up to 6.5 years. A total of 349 subjects (89%), including 10 Japanese subjects, received eliglustat for at least 0.5 years and 204 subjects (52%), including 6 Japanese subjects, received eliglustat for at least 1 year. The duration of exposure to eliglustat (mean ± standard deviation) was 1.4 ± 1.19 years, and the total duration was 535.0 patient-years.

3.(i).B.(3) Cardiovascular effects

PMDA asked the applicant to discuss the proarrhythmic risk of eliglustat, given that eliglustat inhibits hERG, sodium, and calcium channels.

The applicant responded as follows:

Effects of eliglustat on action potential parameters were evaluated at concentrations up to 100 μg/mL in cardiac Purkinje fibers isolated from male and female dogs that were stimulated at different frequencies (0.5, 1, and 3 Hz) (4.2.1.3-10). The frequency of 3 Hz was used to investigate the presence of frequency-dependent interactions between eliglustat and cardiac sodium channels, and 0.5 Hz was used to promote repolarization abnormalities. In the study, eliglustat was found to have no proarrhythmic effects because no inverse frequency dependency was identified and action potential durations were not prolonged. QTcF intervals were unaffected at any dose studied in the study on cardiovascular effects in conscious beagle dogs (4.2.1.3-15). PR intervals tended to be prolonged in a dose-dependent manner at 30 to 120 minutes after administration of doses of 50 mg/kg and above, and dose-dependent QRS interval prolongation was seen at doses of 10 mg/kg and above as compared with the vehicle control. C_{max} values at 10, 25, and 50 mg/kg were 1.0, 1.8, and 4.0 μg/mL, respectively, and were 25- to 100-fold higher than the estimated C_{max}[28] of plasma unchanged eliglustat at the clinical dose.

Thus, there is little proarrhythmic risk occurring in clinical use of eliglustat.

PMDA considers as follows:

Eliglustat is a multi-channel-blocking drug with inhibitory effect on hERG, sodium, and calcium channels. Some multi-channel-blocking drugs cause torsades de pointes (TdP), and some are unlikely to (Kramer J, et al., *Sci Rep*, 2013; 3:2100). Eliglustat prolonged QTcF, QRS, and PR intervals in the study in anesthetized dogs. Eliglustat is metabolized by CYP2D6 and CYP3A4 and could therefore similarly prolong QTcF, QRS, and PR intervals in humans exposed to high levels of eliglustat due to drug-drug interactions. Therefore, the effects in humans will be reviewed in the clinical section of this report [see "4.(ii).B.(2) QT/QTc prolongation and proarrhythmic risk" and "4.(iii).B.(3).1) Proarrhythmic risk"].

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics were evaluated in mice, rats, rabbits, dogs, and monkeys given intravenous, subcutaneous, or oral doses of eliglustat tartrate, ^{14}C-labeled eliglustat tartrate, or ^{14}C-labeled eliglustat free base. Repeat oral dose pharmacokinetics based on toxicokinetics in toxicity studies was also evaluated. High-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to determine concentrations of unchanged eliglustat in plasma and urine. The lower limits of quantification of unchanged eliglustat in plasma were 0.5, 2.5, or 5.0 ng/mL in mice, 0.5 or 5.0 ng/mL in rats, rabbits, and dogs, and 0.5 ng/mL in monkeys. The lower limit of quantification of unchanged eliglustat in urine was 50 ng/mL in the rats and dogs. LC-MS/MS was also used to determine metabolites in plasma. The lower limit of quantification was 0.5 ng/mL in

rats, rabbits, dogs, and monkeys. Radioactivity in biological samples was determined by liquid scintillation counter. The lower limit of quantification was 0.082 μg equivalents/g (μg Eq/g). Unless otherwise specified, the doses of eliglustat tartrate and ^{14}C-labeled eliglustat tartrate used in the pharmacokinetic studies are expressed as eliglustat tartrate equivalent doses. The results from the main studies are described below.

3.(ii).A.(1) Absorption (4.2.2.2-3 to 4.2.2.2-6, 4.2.2.4-11, 4.2.2.7-1 to 4.2.2.7-3, 4.2.3.2-6, 4.2.3.2-8, 4.2.3.7.5-3)

Table 3 shows the pharmacokinetic parameters of unchanged eliglustat in plasma following a single intravenous or oral dose in male and female mice, a murine model of Gaucher disease (male and female mice), male and female rats, female rabbits, male and female dogs, and male monkeys.

Table 3. Pharmacokinetic parameters of unchanged eliglustat in plasma following single doses of eliglustat

Species	Route of adm.	Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL_{tot} (mL/min/kg)	Vd_{ss} (mL/kg)	BA (%)
Mice	i.v.	1	M	3[a)]	-	-	0.55	146	96.0	2.07	-
			F	3[a)]	-	-	0.56	52.5	268	9.44	-
	p.o.	3	M	3[a)]	115	0.08	0.21	20.5	-	-	4.68
Murine model of Gaucher disease	p.o.	150	M	3	1450 ± 429	0.67 ± 0.29	0.98 ± 0.18	4230 ± 1590	-	-	-
			F	3	1420 ± 211	0.25 ± 0.00	1.16 ± 0.21	2600 ± 1770	-	-	-
Rats	i.v.	1	M	3	-	-	0.27 ± 0.06	436 ± 61.4	32.7 ± 4.48	0.56 ± 0.10	-
			F	3	-	-	0.24 ± 0.06	670 ± 108	21.4 ± 3.70	0.30 ± 0.01	-
	p.o.	3	M	4	109 ± 52.0	0.29 ± 0.14	0.41 ± 0.05	114 ± 34.0	-	-	8.70 ± 2.60
			F	4	381 ± 150	0.25 ± 0.00	0.37 ± 0.09	237 ± 66.8	-	-	11.8 ± 3.32
		10	M	4	643 ± 127	0.44 ± 0.13	0.46 ± 0.20	616 ± 102	-	-	14.1 ± 2.34
			F	4	1130 ± 311	0.50 ± 0.00	0.50 ± 0.10	1230 ± 362	-	-	18.4 ± 5.40
Rabbits	p.o.	30	F	4	88.5 ± 144	0.71 ± 0.88	3.90 ± 2.08	128 ± 128	-	-	-
Dogs	i.v.	1	M	3	-	-	1.03 ± 0.26	459 ± 63.9	31.1 ± 4.42	2.38 ± 0.85	-
			F	3	-	-	0.83 ± 0.29	371 ± 63.4	38.6 ± 6.90	2.37 ± 1.04	-
	p.o.	3	M	3	66.2 ± 40.7	0.58 ± 0.38	1.39 ± 0.63	171 ± 79.8	-	-	12.3 ± 4.68
			F	3	69.9 ± 33.8	0.31 ± 0.17	0.74 ± 0.18	90.6 ± 34.7	-	-	7.92 ± 1.93
Monkeys	i.v.	1.18	M	3	-	-	1.43 ± 0.16	222 ± 48.6	77.8 ± 17.9	5.13 ± 0.76	-
	p.o.	3.57	M	3	4.66 ± 2.65	0.25 ± 0.00	0.74 ± 0.03	4.74 ± 0.49	-	-	0.80 ± 0.07

Mean or mean ± standard deviation; -, not calculated

C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma; $t_{1/2}$, elimination half-life; $AUC_{0-\infty}$, area under the plasma concentration of unchanged eliglustat-time curve (extrapolated to infinity); CL_{tot}, total clearance; Vd_{ss}, distribution volume at steady state; BA, bioavailability

a) 3 animals/time point

The 5-carboxy metabolite (M24), a metabolite accounting for >10% of the area under the plasma concentration-time curve (AUC) for radioactivity in human plasma, was administered as a single intravenous, oral, or subcutaneous dose to male rats (2 to 3 animals per group). Table 4 shows the pharmacokinetic parameters of the 5-carboxy metabolite in plasma.

Table 4. Pharmacokinetic parameters of 5-carboxy metabolite in plasma following single doses of 5-carboxy metabolite

Route of adm.	Dose (mg/kg)	n	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL_{tot} (mL/min/kg)	Vd_{ss} (mL/kg)	BA (%)
i.v.	3	2	-	-	0.89, 1.13	1740, 1440	28.7, 34.7	330, 343	-
p.o.	10	3	19.4 ± 10.7	1.50 ± 0.87	9.71 ± 7.19	109 ± 19.7	-	-	1.44 ± 0.20
	30	3	63.9 ± 18.8	0.58 ± 0.38	5.08 ± 1.65	297 ± 58.8	-	-	1.64 ± 0.41
s.c.	1	3	716 ± 157	0.25 ± 0.00	0.53 ± 0.08	685 ± 49.3	-	-	-
	5	3	2240 ± 453	0.25 ± 0.00	0.65 ± 0.03	2500 ± 386	-	-	-
	25	3	13,400 ± 3300	0.19 ± 0.10	2.01 ± 0.17	13,400 ±2350	-	-	-

Mean ± standard deviation except for i.v. (individual values); -, not calculated
C_{max}, maximum concentration of 5-carboxy metabolite in plasma; t_{max}, time to maximum concentration of 5-carboxy metabolite in plasma; $t_{1/2}$, elimination half-life; $AUC_{0-\infty}$, area under the plasma concentration of 5-carboxy metabolite-time curve extrapolated to infinity; CL_{tot}, total clearance; Vd_{ss}, distribution volume at steady state; BA, bioavailability

Pharmacokinetics were investigated in a repeated-dose toxicity study in which eliglustat (as tartrate; 5, 15, or 50 mg/kg) was orally administered once daily for 26 weeks to male and female rats. Compared with Day 1, C_{max} and AUC_{0-t} at Week 26 were increased by 1.6- to 2.2-fold and 1.5- to 2.1-fold, respectively, in the males and by 1.4- to 5.3-fold and 1.7- to 3.7-fold, respectively, in the females, indicating accumulation. No accumulation was observed in male and female dogs orally dosed with 2, 5, or 10 mg/kg of eliglustat tartrate once daily for 13 weeks. No accumulation was noted in male and female rats subcutaneously dosed with 1, 3, or 6 mg/kg of the 5-carboxy metabolite once daily for 13 weeks.

3.(ii).A.(2) Distribution (4.2.2.3-1 to 4.2.2.3-3, 4.2.2.3-6, 4.2.2.3-7)

A single oral dose of 125 mg/kg of ^{14}C-labeled eliglustat free base was administered to untreated normal male mice, male mice pretreated with a single oral dose of 50 mg/kg cyclosporine A as a P-glycoprotein (P-gp) inhibitor, and untreated P-gp deficient mice (2 animals per group per time point). In all groups, high concentrations of radioactivity were observed in the gall bladder, bladder, stomach, small intestine, liver, and kidneys at 0.5 to 2 hours postdose. In addition, approximately 10-fold increase in radioactivity was observed in the brain tissue of the untreated P-gp deficient mice, compared to untreated normal mice, which suggest that unchanged eliglustat is a substrate of mouse P-gp.

In male pigmented rats (1 animal per time point) dosed with a single oral dose of 50 mg/kg ^{14}C-labeled eliglustat tartrate, radioactivity peaked at 0.5 hours postdose in most tissues including the liver, lungs, adrenals, renal medulla, renal cortex, spleen and at 2 hours postdose in the pigmented skin and uveal tract. Radioactivity was not found in the CNS tissues (cerebellum, medulla oblongata, rhinencephalon, spinal cord) at any time point of blood sample collection. By 168 hours postdose, radioactivity decreased to below the detection limit in most tissues but was still measurable in the liver, pigmented skin, eyes, and uveal.

A single 30 mg/kg dose of ^{14}C-labeled eliglustat tartrate was orally administered to pregnant rats (2 animals per time point) on days 12 and 17 of gestation. Radioactivity in the fetuses of each pregnant rat amounted to 0.18 to 0.23 µg Eq/g and 0.46 to 0.47 µg Eq/g at 2 hours postdose and was below the lower limit of quantification and 0.09µg Eq/g at 24 hours postdose, which indicates that eliglustat is distributed to the fetuses.

The mean plasma protein binding of eliglustat free base (0.1 to 10 µmol/L), by rapid equilibrium dialysis, ranged from 95.3% to 98.9% in mice, from 79.7% to 99.0% in rats, from 91.5% to 98.2% in dogs, and from 80.7% to 92.2% in monkeys. When ^{14}C-labeled eliglustat tartrate (0.1 to 10 µmol/L) was added to rat and dog blood samples, the mean partition coefficients between red blood cell and plasma were 0.7 to 1.8 in rat blood and 0.8 to 1.4 in dog blood.

3.(ii).A.(3) Metabolism (4.2.2.4-7 to 4.2.2.4-9, 4.2.2.4-11, 4.2.2.4-13)

Identified as major *in vivo* eliglustat metabolites in plasma of rats and dogs were M5 (7-hydroxyl metabolite), M6 (6-hydroxyl metabolite), M7 (5-hydroxyl metabolite), and M40 as hydroxyl metabolites of the octanoyl moiety, M43 as a glucuronide produced from hydroxyl metabolites, the ketone metabolites M17 (7-ketone metabolite) and M18, the carboxy metabolite M24 (5-carboxy metabolite), the mono-oxidation products M9 and M10 and di-oxidation products M15 and M16 as metabolites of the 2,3-dihydro-1,4-benzodioxane moiety, and M2, M4, M33, M34, M37, M39, M44, M54, M55, M56, M59, and M64 with oxidation at multiple locations of the octanoyl and 2,3-dihydro-1,4-benzodioxane moieties. Metabolites M60 and M68, which are produced by methylation, M50, M52, M61, and M63, which are produced by glucuronidation, and M51, M53, and M62, which are produced by methylation and glucuronidation subsequent to oxidative dealkylation of the 2,3-dihydro-1,4-benzodioxane moiety, were identified as metabolites specific to the rat. The carboxy metabolites M31 (4-carboxy metabolite), M35, and M36, not identified in plasma of rats or dogs, were observed in plasma of rabbits and monkeys.

Male and female rats (5 animals per sex per time point) were orally dosed with 50 mg/kg/day of eliglustat tartrate for 13 days and then orally dosed with 50 mg/kg/day of ^{14}C-labeled eliglustat tartrate on Day 14. The mean proportion of unchanged eliglustat to radioactivity in plasma was 24.8% in males and 41.5% in females at 1 hour postdose and 31.6% in males and 43.5% in females at 4 hours postdose. No metabolite accounted for more than 10% of the radioactivity present in plasma.

Male and female dogs (4 animals per sex) were orally dosed with 50 mg/kg/day of eliglustat tartrate for 13 days and then orally dosed with 10 mg/kg/day of ^{14}C-labeled eliglustat tartrate on Day 14. The mean proportion of unchanged eliglustat to radioactivity in plasma was 22.2% in males and 16.2% in females at 1 hour postdose and 16.3% in the males and 3.2% in females at 4 hours postdose. The metabolites accounting for >10% of the radioactivity in plasma[38] were M5 (7-hydroxyl metabolite) and M17 (7-ketone metabolite). M5 accounted for 14.4% in males and 9.2% in females at 1 hour postdose and 12.2% and 5.6%, respectively, at 4 hours postdose,

[38] As metabolites accounting for >10% of the radioactivity in plasma, M32 was identified, besides M5 and M17, to account for 22.8% in females 4 hours postdose.

and M17 accounted for 16.3% and 19.7%, respectively, at 1 hour postdose and 16.8% and 15.4%, respectively, at 4 hours postdose.

3.(ii).A.(4) Excretion (4.2.2.3-4, 4.2.2.5-1, 4.2.2.5-2)

In male and female rats (5 animals per sex) given a single intravenous dose of 10 mg/kg of ^{14}C-labeled eliglustat tartrate, the cumulative excretion (mean ± standard deviation) of the administered radioactivity over 168 hours postdose was, in urine, 11.4% ± 3.6% in males and 14.2% ± 1.6% in females and, in feces, 82.1% ± 1.1% in males and 81.3% ± 1.6% in females. In male and female rats (5 animals per sex) given a single oral dose of 100 mg/kg of ^{14}C-labeled eliglustat tartrate, the cumulative excretion of the administered radioactivity over 168 hours postdose was, in urine, 16.6% ± 1.1% in males and 12.5% ± 0.6% in females and, in feces, 77.0% ± 1.4% in males and 83.2% ± 1.2% in females. In 4 bile-duct cannulated male rats given a single intravenous dose of 10 mg/kg of ^{14}C-labeled eliglustat tartrate, the cumulative excretion of the administered radioactivity in the bile over 24 hours postdose was 53.4% ± 19.9%.

In male and female dogs (3 animals per sex) given a single intravenous dose of 2.5 mg/kg of ^{14}C-labeled eliglustat tartrate, the cumulative excretion of the administered radioactivity over 168 hours postdose was, in urine, 25.6% ± 3.0% in males and 25.0% ± 4.8% in females and, in feces, 63.9% ± 4.9% in males and 66.5% ± 6.2% in females. In male and female dogs (3 animals per sex) given a single oral dose of 25 mg/kg of ^{14}C-labeled eliglustat tartrate, the cumulative excretion of the administered radioactivity over 168 hours postdose was, in urine, 30.0% ± 8.6% in males and 25.6% ± 4.8% in females and, in feces, 49.7% ± 3.0% in males and 56.5% ± 6.1% in the females.

A single oral dose of 30 mg/kg of ^{14}C-labeled eliglustat tartrate was administered on day 11 of postpartum to lactating rats (3 animals per time point), and cumulative excretion in milk was evaluated on the basis of the level of radioactivity in the gastrointestinal contents of the pups. The mean ratios of radioactivity in milk to that in the maternal plasma at 2, 4, and 24 hours postdose were 0.44, 1.05, and 16.33, respectively. The total cumulative excretion of radioactivity in milk over 24 hours postdose was estimated to be 0.23%.

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

PMDA asked the applicant to discuss the safety of eliglustat in humans (specifically long-term safety in the skin and eyes of Japanese patients) in light of the fact that eliglustat showed melanin affinity, selectively binding to pigmented skin, the uveal, and other melanin-containing tissues in a tissue-distribution study in pigmented rats.

The applicant responded as follows:

Radioactivity was detected in the pigmented skin, eyes, and uveal tract but not in the lens in male pigmented rats given a single oral dose of 50 mg/kg of ^{14}C-labeled eliglustat tartrate. Radioactivity reached a maximum in the pigmented skin, eyes, and uveal tract at 2 hours postdose and subsequently decreased over time. The radioactivity administered had been almost completely eliminated from most tissues by 168 hours postdose, but a detectable amount remained in the liver, pigmented skin, eyes, and uveal tract even at 168 hours postdose.

These findings suggest that ^{14}C-labeled eliglustat selectively binds to melanin-containing tissues in the uveal tract and pigmented skin but does not irreversibly bind to melanin. There were no findings of skin or eye toxicity in the toxicity studies.

An evaluation of skin and eye safety in the clinical studies based on a pooled analysis data from 393 patients in the phase II/III studies, which included 10 Japanese patients,[37] indicated that the relatively common adverse events in the system organ class (SOC) "skin and subcutaneous tissue disorders" were rash (8 patients), pruritus (7 patients), dermatitis contact (6 patients), and dry skin (6 patients). The only adverse events in the high-level group term "pigmentation disorders" in the SOC "skin and subcutaneous tissue disorders" were skin hyperpigmentation (2 patients) and skin hypopigmentation (1 patient). A causal relationship with the study drug was ruled out in each case. No adverse event regarded as a pigmentation disorder occurred in any Japanese patient. The relatively common adverse events in the SOC "eye disorders" were cataract (3 patients) and chalazion (2 patients). None of them were considered to be an adverse event associated with the binding of eliglustat to melanin. The only adverse events of eye disorders reported in the Japanese patients were diabetic retinopathy (1 patient), age-related macular degeneration (1 patient), and vitreous floaters (1 patient), and a causal relationship with the study drug was ruled out for all of them.

In summary, the findings of the tissue-distribution study in pigmented rats indicate that eliglustat selectively binds to melanin-containing tissues in the uveal tract and pigmented skin but that the binding is not irreversible. No findings of toxicity or adverse events have been reported in the skin or eyes in relation to distribution to melanin-containing tissues in the toxicity and clinical studies conducted to the present. Eliglustat, moreover, is not thought to accumulate substantially in the tissues because the drug is rapidly metabolized and has a short elimination half-life. Long-term administration of eliglustat in humans therefore poses minimal safety concerns.

Having considered the nonclinical and clinical study findings, PMDA accepted the applicant's response, i.e., safety issues attributable to the melanin affinity of eliglustat are unlikely to occur.

3.(iii) Summary of toxicology studies

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

The applicant submitted the results of single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other toxicity studies (toxicity study of metabolites, toxicity study of impurities, pilot study to compare the behavioral outcomes following drug-induced peripheral neuropathy). The results of the non-GLP studies were submitted as reference data. The results from the main studies are described below. The eliglustat doses in the toxicity studies are expressed as eliglustat tartrate equivalent doses.

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

3.(iii).A.(1).1) Single-dose intravenous infusion toxicity study in rats (4.2.3.1-1)

A single 1-hour intravenous infusion of 0 (vehicle[39]), 3, 10, or 20 mg/kg of eliglustat tartrate was administered to male and female SD rats. There were no deaths or treatment-related toxic signs.

Based on the above, the no observed adverse effect level (NOAEL) was determined to be 20 mg/kg.

3.(iii).A.(1).2) Single-dose and 10-day repeated-dose oral toxicity study in rats (4.2.3.1-2)

Eliglustat tartrate was given to male and female SD rats as single oral doses of 400, 800, 900, and 1000 mg/kg. Two of 6 animals in the 800 mg/kg group (1 each at 7 and 8 days post-dose), 1 of 6 animals in the 900 mg/kg group (2 days post-dose), and 2 of 6 animals in the 1000 mg/kg group (1 each at 2 and 6 days post-dose) died or were sacrificed due to poor general condition.

Eliglustat tartrate was given to male and female SD rats for 10 days as repeated oral doses of 200 and 400 mg/kg once daily. One of 10 animals (Day 2) in the 400 mg/kg/day group died, and the other animals showed toxic signs including abnormal breathing, salivation, wet fur, and abdominal distension, and eliglustat administration was thus discontinued in all surviving animals on Day 3. One of 10 animals (Day 6) in the 200 mg/kg/day group was sacrificed.

Based on the above, the approximate lethal dose was determined to be 400 mg/kg.

3.(iii).A.(1).3) Dose-escalating and 10-day repeated-dose oral toxicity study in dogs (4.2.3.1-3)

Oral doses of eliglustat tartrate were administered to male and female beagle dogs at 50 mg/kg (under fasted conditions) on Day 1, 100 mg/kg (fasted) on Day 3, 35 mg/kg (fasted) on Day 7, 35 mg/kg (under fed conditions) on Day 9, and 25 mg/kg (fed) on Day 11. Vomiting was observed at all doses.

Vomiting was observed after a single oral dose of eliglustat 25 mg/kg was administered to male and female beagle dogs under fasted conditions.

Vomiting was not observed after repeated oral doses of eliglustat 25 mg/kg were administered once daily for 10 days to male and female beagle dogs fed *ad libitum*.

Based on the above, the NOAEL was determined to be <25 mg/kg under fasted conditions and 25 mg/kg with *ad libitum* feeding.

[39] Physiological saline

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

3.(iii).A.(2).1) Toxicity studies by dietary administration in mice (4.2.3.2-4) (4.2.3.2-1 to 4.2.3.2-3: reference data)

Male and female ICR mice were given eliglustat tartrate daily by dietary administration at concentrations of 0% (standard feed), 1%, 3%, and 5%.[40] Since animals in the eliglustat groups died or were sacrificed due to poor general condition beginning on at 3 days post-dose, the surviving animals in the 3% and 5% groups were sacrificed at 4 or 5 days post-dose, and the surviving animals in the control group and 1% group were sacrificed at 8 days post-dose. At necropsy, black gastrointestinal contents and black deposits were found in the eliglustat groups. Based on the above, all feed concentrations used in the study were determined to exceed the maximum tolerable dose.

Eliglustat tartrate was given by dietary administration for 4 days to male and female ICR mice at doses of 100, 250, 500, and 1000 mg/kg/day.[41] No animal died or showed poor general condition during the administration period, but mild weight loss was seen at ≥100 mg/kg/day and substantial weight loss was observed in the 1000 mg/kg/day group.

Eliglustat tartrate was given by dietary administration for 14 days to male and female ICR mice at doses of 0 (standard diet), 50, 150, and 450 mg/kg/day.[42] Three of the 10 animals in the 450 mg/kg/day group were sacrificed due to poor general condition at Week 2, but no toxic findings were found at necropsy. Four of the 7 surviving animals in this group began to exhibit poor general condition by at earliest Day 6 and, at latest, the end of administration, but no toxic findings were found at necropsy. Based on the above, the maximum tolerated dose was determined to be 150 mg/kg/day.

Eliglustat tartrate was given by dietary administration for 13 weeks to male and female ICR mice at doses of 0 (standard feed), 50, 150, and 350 mg/kg/day.[43] Reduced food consumption was seen in females in the eliglustat groups, and reduced body weight gain and food consumption were observed in males in the 350 mg/kg/day group. Liver weight was increased in males at ≥150 mg/kg/day, and adrenal weight was increased in males at 350 mg/kg/day. However, these findings are considered to be of minimal toxicological significance because no associated blood biochemical or histopathological changes were noted.

3.(iii).A.(2).2) Twenty-eight-day repeated-dose oral toxicity study in rats (4.2.3.2-5)

Eliglustat tartrate was orally administered for 28 days to male and female SD rats at the doses of 0 (vehicle[44]), 10, 30, and 100 mg/kg/day[45] divided into 2 doses per day. Findings included reduced body weight gain in

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40 The actual doses for these concentrations of 1%, 3%, and 5% were calculated to be 2.2, 4.5, and 10.2 g/kg/day, respectively, for the males and 2.4, 3.7, and 17 g/kg/day, respectively, for the females.

41 The actual doses for these nominal doses of 100, 250, 500, and 1000 mg/kg/day were calculated to be 106.2, 266.1, 540.2, and 1274.8 mg/kg/day, respectively, for the males and 104.5, 323.8, 501.3, and 1586.0 mg/kg/day, respectively, for the females.

42 The actual doses for these nominal doses of 50, 150, and 450 mg/kg/day were calculated to be 61, 178, and 769 mg/kg/day, respectively, for the males and 60, 215, and 646 mg/kg/day, respectively, for the females.

43 The actual doses for these nominal doses of 50, 150, and 350 mg/kg/day were calculated to be 49.6, 146.4, and 349.5 mg/kg/day, respectively, for the males and 50.4, 147.3, and 350.7 mg/kg/day, respectively, for the females.

44 Deionized water

45 Doses of 0, 5, 15, and 50 mg/kg were orally administered twice daily, 6 hours apart.

females at ≥30 mg/kg/day, salivation, increased platelet count and platelet volume, and increased blood alanine aminotransferase (ALT), sodium, potassium, chloride, and phosphorus at ≥100 mg/kg/day, decreased blood hemoglobin and hematocrit in males at 100 mg/kg/day, and decreased food consumption and prolonged prothrombin time in females at 100 mg/kg/day.

Reversibility after the 14-day recovery period was evaluated in the 0 and 100 mg/kg/day groups, and all the findings were reversible at the end of the recovery period.

On the basis of above results, although reduced body weight gain was noted at 30 mg/kg/day, the NOAEL was determined to be 30 mg/kg/day because necropsy, organ weights, and histopathological evaluation revealed no findings of toxicity.

3.(iii).A.(2).3) Twenty-six-week repeated-dose oral toxicity study in rats (4.2.3.2-6)

Male and female SD rats were orally treated with 0 (vehicle[46]), 5, 15, or 50 mg/kg/day of eliglustat tartrate once daily for 26 weeks. One of 20 females at 50 mg/kg/day died during the treatment period. At necropsy, vacuolated cortical cells of the adrenals were found in this animal but were unlikely related to the treatment because no toxicological findings indicating the cause of death were identified. Salivation noted at 50 mg/kg/day was first thought to be related to eliglustat or the dosing solution, but this finding was later determined not to be a sign of toxicity because it is frequently noted in rats dosed by oral gavage, and no related pathological changes were observed. Reversibility after the 8-week recovery period was evaluated in the 0 and 50 mg/kg/day groups, and no findings of toxicity were identified.

On the basis of above findings, the NOAEL was determined to be 50 mg/kg/day because no findings of toxicity were identified in laboratory tests, necropsy, or histopathological examination of the other animals in the 50 mg/kg/day group although an animal died of an unknown cause in the group. The area under the plasma unchanged eliglustat concentration-time curve ($AUC_{0\text{-}t}$) at Week 26 in the 50 mg/kg/day group was 2341 ng·h/mL in males and 3787 ng·h/mL in females, which were 8 and 12 times, respectively, the estimated exposure to unchanged eliglustat in plasma in clinical use.[47]

3.(iii).A.(2).4) Twenty-eight-day repeated-dose oral toxicity study in dogs (4.2.3.2-7)

Eliglustat tartrate was orally administered for 28 days to male and female beagle dogs at the doses of 0 (vehicle[44]), 5, 10, and 25 mg/kg/day[48] divided into 2 doses per day. Atrophy of the thymus, lymph nodes, and gut-associated lymphoid tissue was noted at ≥10 mg/kg/day. Reversibility after a 14-day recovery period was evaluated in the 0 and 25 mg/kg/day groups, and atrophy in the lymphoid tissues was reversible at the end of the recovery period.

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46 Purified water

47 Estimated mean $AUC_{0\text{-}12\ h}$ (307 ng·h/mL) of the plasma unchanged eliglustat at steady state in the overall population as estimated with a pharmacokinetic simulation in patients with CYP2D6 phenotype, a representative phenotype of the study patient population (5.3.3.5-4).

48 Doses of 0, 2.5, 5, and 12.5 mg/kg were administered twice daily, 6 hours apart.

On the above basis, the NOAEL was determined to be 5 mg/kg/day.

3.(iii).A.(2).5) Thirteen-week repeated-dose oral toxicity study in dogs (4.2.3.2-8)

Eliglustat tartrate was orally administered once daily for 13 weeks to male and female beagle dogs at the doses of 0 (vehicle[46]), 2, 5, and 10 mg/kg/day. Reduced body weight gain was noted in males in the eliglustat groups and females at 2 and 10 mg/kg/day, and low thymus weight and lymphoid depletion were seen at 10 mg/kg/day. Reversibility after a 4-week recovery period was evaluated in the 0 and 10 mg/kg/day groups, and the findings were reversible at the end of the recovery period.

On the above basis, the NOAEL was determined to be 5 mg/kg/day because reduced body weight gain did not show dose dependency.

3.(iii).A.(2).6) Fifty-two week repeated-dose oral toxicity study in dogs (4.2.3.2-9)

Eliglustat tartrate was orally administered once daily for 52 weeks to male and female beagle dogs at the doses of 0 (vehicle[46]), 2, 5, and 10 mg/kg/day. There were no findings of toxicity in clinical observation, body weight, food consumption, electrocardiographic evaluation, ophthalmological evaluation, hematology, blood biochemistry, urinalysis, necropsy, or histopathological evaluation in the study. Reversibility after an 8-week recovery period was evaluated in the 0 and 10 mg/kg/day groups, and no findings of toxicity were identified.

On the above basis, the NOAEL was determined to be 10 mg/kg/day. At Week 52, exposure to unchanged eliglustat in plasma at 10 mg/kg/day was 4489 ng·h/mL in males and 3130 ng·h/mL in females, which were 15 and 10 times, respectively, the estimated exposure to unchanged eliglustat in plasma in clinical use.[47]

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

With or without metabolic activation, eliglustat did not show genotoxicity in a reverse mutation assay in bacteria or a chromosome aberration test in human peripheral lymphocytes. No increase in micronucleated polychromatic erythrocytes was observed in a bone marrow micronucleus test in which male and female Swiss mice were orally given eliglustat tartrate 0 (vehicle[18]), 68.75, 137.5, or 275 mg/kg/day once daily for 2 days. On the above basis, eliglustat was determined to have no genotoxicity.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) Two-year carcinogenicity study by dietary administration in mice (4.2.3.4.1-1)

Eliglustat tartrate was given to male and female ICR mice for 105 weeks by dietary administration with 0 (control 1,[49] standard feed), 0 (control 2, standard feed), 10, 25, or 75 mg/kg/day.[50] The numbers of surviving male and female animals at final necropsy in the respective groups were 30 of 60, 26 of 60, 27 of 60, 22 of 60, and 23 of 60 males; and 18 of 60, 24 of 60, 29 of 60, 21 of 60, and 20 of 60 females.

[49] Controls 1 and 2 were identically treated. Two control groups were used to check for a difference in the mortality rate between the control groups.

[50] These nominal doses of 10, 25, and 75 mg/kg/day were calculated to be 49.6, 146.4, and 349.5 mg/kg/day, respectively, for males and 50.4, 147.3, and 350.7 mg/kg/day, respectively, for females in terms of actual doses.

Cortical adenoma in the adrenal cortex in males at 75 mg/kg/day and pheochromocytoma of the adrenal medulla and fibrosarcoma of the skin in females at 75 mg/kg/day were noted as tumor lesions, and the incidence of these lesions was higher in this group yet it fell within the range of laboratory's historical data, and these lesions were not associated with precancerous lesions. The tumor lesions were therefore considered to be unrelated to treatment with eliglustat.

Dose-dependent hepatocellular hypertrophy was observed as a non-tumor lesion in the eliglustat groups. Hepatocellular hypertrophy is thought to be an adaptive change secondary to induction of liver metabolizing enzymes and to be of minimal toxicological significance because in mice, eliglustat was rapidly metabolized by CYP in the liver and was thus rapidly eliminated following oral administration (4.2.2.3-8, 4.2.2.4-14).

The non-carcinogenic dose was thus determined to be 75 mg/kg/day.

3.(iii).A.(4).2) Two-year carcinogenicity study in rats (4.2.3.4.1-2)

Eliglustat tartrate was orally administered once daily for 105 weeks to male SD rats at doses of 0 (control 1, vehicle[46]), 0 (control 2, vehicle[46]), 10, 25, and 75 mg/kg/day and once daily for 103 weeks to female SD rats at doses of 0 (control 1), 0 (control 2), 5, 15, and 50 mg/kg/day. The numbers of surviving male and female animals at final necropsy in respective groups were 18 of 50, 24 of 50, 22 of 50, 20 of 50, and 24 of 50 males and 24 of 50, 21 of 50, 15 of 50, 15 of 50, and 25 of 50 females.

Higher incidences of tumor lesions were noted: granulocytic leukemia in males at 10 mg/kg/day; odontoma in males at 25 mg/kg/day; and mammary gland adenomas in females at ≥15 mg/kg/day. The incidences of granulocytic leukemia and odontoma slightly exceeded the range of historical data from the testing laboratory or animal supplier but showed no dose dependency. The incidence of mammary gland adenomas exceeded the range of laboratory's historical data but was within the range of animal supplier's historical data. The overall incidence of the mammary gland tumors (mammary gland adenocarcinomas, fibroadenomas, and fibromas) was consistent among the groups including the control groups. These tumors were therefore determined to be unlikely related to treatment with eliglustat.

Observed non-tumor lesions included squamous metaplasia in the endometrium in females at 50 mg/kg/day and swollen spermatids and inflammation in the coagulating glands in males at 75 mg/kg/day. Abnormal breath sounds and/or dyspnea, granulomas in the lungs, chronic bronchioalveolar inflammation, and bronchiectasis occurring in males at 75 mg/kg/day were attributed to aspiration of foreign matter.

On the basis of above findings, the non-carcinogenic dose was determined to be 75 mg/kg/day in males and 50 mg/kg/day in females. At Week 13, exposure to unchanged eliglustat in plasma in males at 75 mg/kg/day and in females at 50 mg/kg/day was 1135 and 825 ng·h/mL, respectively, which were 4 and 3 times, respectively, the estimated exposure to unchanged eliglustat in plasma in clinical use[47].

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-1)

Eliglustat tartrate at doses of 0 (vehicle[46]), 10, 30, and 100 mg/kg/day were orally administered once daily to male SD rats from 29 days before mating, through the mating period, and until the day before necropsy and to female SD rats from 15 days before mating, through the mating period, and until day 7 of gestation. Males and females in the same dose group were mated. Salivation was noted at ≥30 mg/kg/day but was determined to be of minimal toxicological significance because this finding is often observed following oral gavage. Subacute inflammation of the coagulating glands was observed in males at 100 mg/kg/day. There were no treatment-related effects on male reproductive function (days prior to mating, copulation rate, conception rate, epididymis sperm count, sperm motility, sperm morphology, testicular sperm count, and sperm production), female reproductive function (estrus cycle, days prior to mating, copulation rate, pregnancy rate, number of corpora lutea, number of implantations, and pre-implantation loss), and early embryonic development (surviving embryos and early and late resorptions).

On the basis of above findings, the NOAEL was determined to be 30 mg/kg/day for general toxicity and 100 mg/kg/day for fertility toxicity in males and females and early embryonic development toxicity.

3.(iii).A.(5).2) Study of embryo-fetal development in rats (4.2.3.5.2-2)

Eliglustat tartrate was orally administered once daily to pregnant SD rats from days 6 to 17 of gestation at the doses of 0 (vehicle[46]), 10, 30, and 120 mg/kg/day, and caesarean section was performed on day 20 of gestation. Effects on dams included salivation, reduced body weight gain, low food consumption, and small placenta at 120 mg/kg/day. Effects on embryo-fetal development included increased post-implantation loss, low fetal weight, cerebral ventricle dilatation, delayed ossification, and abnormal numbers of ribs and lumbar vertebrae at 120 mg/kg/day.

On the above basis, the NOAEL was determined to be 30 mg/kg/day for maternal toxicity and embryo-fetal developmental toxicity.

3.(iii).A.(5).3) Study of embryo-fetal development in rabbits (4.2.3.5.2-4)

Eliglustat tartrate was orally administered once daily to pregnant New Zealand white rabbits from days 6 to 18 of gestation at the doses of 0 (vehicle[46]), 10, 30, and 100 mg/kg/day, and caesarean section was performed on day 29 of gestation. Effects on dams included slightly reduced body weight gain and low food consumption at 100 mg/kg/day. No effects on embryo-fetal development were observed in any group.

On the basis of above findings, the NOAEL was determined to be 30 mg/kg/day for maternal toxicity and 100 mg/kg/day for embryo-fetal developmental toxicity. The exposure to unchanged eliglustat in plasma on day 18 of gestation in the 100 mg/kg/day group was 1163 ng·h/mL, which was 4 times the estimated exposure to unchanged eliglustat in plasma in clinical use.[47]

3.(iii).A.(5).4) Study of pre- and postnatal development and maternal function in rats (4.2.3.5.3-1)

Eliglustat tartrate was orally administered once daily to pregnant SD rats from day 6 of gestation to day 21 of lactation at the doses of 0 (vehicle[46]), 10, 30, and 100 mg/kg/day. Effects on dams included salivation (during pregnancy and lactation), reduced body weight gain (days 12 to 20 of gestation), low food consumption, and high post-implantation loss at 100 mg/kg/day. Reduced body weight gain was attributed to high post-implantation loss and low number of delivered pups. Effects on the offspring included low body weight and reduced body weight gain at 100 mg/kg/day, but no effects were observed on physical development, reflexes, learning/memory, spontaneous locomotor activity, pupil constriction, sexual maturity, testes descent, or reproductive function.

On the above basis, the NOAEL was determined to be 30 mg/kg/day for maternal toxicity and developmental toxicity in offspring.

3.(iii).A.(5).5) Testicular toxicity study in rats (4.2.3.5.1-2)

In response to the finding of inflammation in coagulating glands in males in the study on rat fertility and early embryonic development to implantation (4.2.3.5.1-1), an exploratory toxicity study was conducted to evaluate the toxicity of eliglustat on sperm morphology and the male reproductive organs.

Eliglustat tartrate was orally administered for 4 weeks to male SD rats at the doses of 0 (vehicle[46]), 30, 100, and 200 mg/kg/day[51] divided into 2 doses per day. Five animals in each group were necropsied at the end of the treatment period. Five animals each in the 0, 30, and 100 mg/kg/day groups were necropsied after the recovery period of 3, 6, 9, or 12 weeks, and 5 animals in the 200 mg/kg/day group were necropsied after the recovery period of 3, 6, 9, or 14 weeks. The remaining animals were sacrificed at 135 or 136 days post-dose. Hunched posture, piloerection, abnormal breath sounds, incomplete eyelid opening, and emaciation were observed at 200 mg/kg/day. At 11 and 14 days post-dose, 2 of 35 animals died, and 3 of 35 were moribund.[52] The treatment was discontinued in the 200 mg/kg/day group on Day 15. The surviving animals in this group showed weight loss during the treatment period but recovered with the discontinuation.

Findings during or at the end of treatment included reduced body weight gain and low food consumption at 100 mg/kg/day; salivation, increased ALT, reduced prostate weight, germ cell necrosis in the testes, and acute inflammation and epithelial hyperplasia of the coagulating glands at ≥100 mg/kg/day; and low sperm viability, high sperm head separation, and sloughed cells in the epididymis at 200 mg/kg/day.

Findings after the 3-week recovery period included sloughed cells in the epididymis and acute inflammation and epithelia hyperplasia of the coagulating glands at ≥100 mg/kg/day and low testis weight, reduced spermatid count, spermatid degeneration, and swelling of and dense/concentrated darkly colored matters in cytoplasm at 200 mg/kg/day. After the 6-week recovery period, no effects of eliglustat treatment were noted at 100 mg/kg/day, and lesions in the testes, epididymides, and coagulating glands persisted but were resolving at 200 mg/kg/day. These lesions were not observed after the 9-week- recovery period.

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[51] Doses of 15, 50, and 100 mg/kg were administered twice daily, 4 hours apart.

[52] Three animals were sacrificed moribund on Days 11, 14, and 16.

On the above basis, the NOAEL was determined to be 30 mg/kg/day. On Day 28, exposure to unchanged eliglustat in plasma at 30 mg/kg/day was 518 ng·h/mL, which was 2 times the estimated exposure to unchanged eliglustat in plasma in clinical use.[47]

3.(iii).A.(5).6) Testicular toxicity study in monkeys (4.2.3.5.1-3: reference data)

Eliglustat tartrate was orally administered for 4 weeks to male cynomolgus monkeys at the dose of 72 mg/kg/day[53] divided into 2 doses per day. Analysis of sperm parameters revealed no treatment-related effects on sperm motility, morphology, viability, concentration, or total live sperm count, although there were variations among animals.

3.(iii).A.(5).7) Toxicity studies in juvenile animals (4.2.3.5.4-1, 4.2.3.5.4-2)

In a dose-ranging study, eliglustat tartrate was orally administered for 28 days to male and female SD rats of 22 days of age at the doses of 0 (vehicle[44]), 30, 60, and 100 mg/kg/day[54] divided into 2 doses per day. Two of 20 animals at 60 mg/kg/day and 5 of 20 animals at 100 mg/kg/day died just after dosing on the postnatal day 22 or 23 and were therefore replaced. Two of 20 animals at 100 mg/kg/day died after dosing on the postnatal day 27 or 28. One of 20 animals at 100 mg/kg/day and 1 of 20 animals at 60 mg/kg/day died after convulsions just after dosing on the postnatal days 33 and 35, respectively.[55] Elevated blood phosphorus was observed at 100 mg/kg/day, but there were no other treatment-related findings.

In the main study, eliglustat tartrate was orally administered for 10 weeks to male and female SD rats of 22 days of age at the doses of 0 (vehicle[44]), 10, 30, and 50 mg/kg/day[56] divided into 2 doses per day. The following findings were noted at the end of the treatment: increased red blood cell count, decreased mean platelet volume, increased blood glucose and phosphorus, increased urine volume, and decreased urinary specific gravity at ≥30 mg/kg/day; and increased neutrophil count and lymphocyte count, decreased platelet distribution width, decreased blood potassium, increased blood urea and creatinine, submandibular adenopathy, increased liver weight, and lymphoid hyperplasia and increased histiocytic foci in the mandibular lymph nodes at 50 mg/kg/day.

Reversibility after a 4-week recovery period was evaluated in the 0 and 50 mg/kg/day groups, and the observed effects were reversible at the end of the recovery period.

On the above basis, the NOAEL was determined to be 30 mg/kg/day because many of the blood biochemical examination and urinalysis findings at 30 mg/kg/day were mild in severity and toxicologically insignificant. According to the toxicokinetic evaluation performed in the dose range-finding study, the exposure to unchanged eliglustat in plasma on Day 49 in the 30 mg/kg/day was 110 ng·h/mL in males and 170 ng·h/mL in

53 A dose of 36 mg/kg was administered twice daily, 6 hours apart.

54 Doses of 0, 15, 30, and 50 mg/kg were administered twice daily, 6 hours apart.

55 These deaths were very likely attributable to gavage accidents rather than neurotoxicity of eliglustat because abnormal tracheal contents were found during the necropsy of the 2 animals dying after convulsions and the deaths were related to the timing of administration.

56 Doses of 0, 5, 15, and 25 mg/kg were administered twice daily, 6 hours apart.

females, which were 0.36 and 0.55 times, respectively, the estimated exposure to unchanged eliglustat in plasma in clinical use.[47]

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Toxicity studies of metabolites

General toxicity and genotoxicity evaluations were conducted on the 5-carboxy metabolite, which was present in human plasma at a concentration higher than that present in rat or dog plasma.

(a) 13-week repeated-dose subcutaneous toxicity study in rats (4.2.3.7.5-3)

The 5-carboxy metabolite was subcutaneously administered once daily for 13 weeks to male and female SD rats at the doses of 0 (vehicle[57]), 1, 3, and 6 mg/kg/day. There were no findings related to 5-carboxy metabolite treatment with the exception of local reactions (e.g., injection site swelling and hematoma). Reversibility after a 4-week recovery period was evaluated in the 0 and 6 mg/kg/day groups. No findings of toxicity were identified.

On the above basis, the NOAEL of the 5-carboxy metabolite was determined to be 6 mg/kg/day.

(b) Genotoxicity (4.2.3.7.5-1, 4.2.3.7.5-2)

With or without metabolic activation, the 5-carboxy metabolite was found to have no genotoxicity in a reverse mutation assay in bacteria or *in vitro* chromosome aberration test in human lymphocytes.

3.(iii).A.(6).2) Toxicity studies of impurities (4.2.3.7.6-1, 4.2.3.7.6-2)

Genz-256146 and Genz-684453 were identified as impurities of genotoxic concern in *in silico* evaluation. In a reverse mutation assay in bacteria, both impurities were found to have no genotoxicity with or without metabolic activation.

3.(iii).A.(6).3) Pilot study to compare the behavioral outcomes following drug-induced peripheral neuropathy (4.2.3.7.7-1: reference data)

Eliglustat tartrate was orally administered for 35 days to male SD rats at the doses of 0 (vehicle[44]) and 150 mg/kg/day divided into 2 doses per day. Poor general condition was observed at 150 mg/kg/day, and the dose was then reduced to 100 mg/kg/day on Day 5 and thereafter.[58] Serious toxicities (e.g., decreased locomotor activity, wheezing) and deaths (2 of 8 animals) were observed at the eliglustat dose of 150 mg/kg/day, and deaths (3 of 8 animals) and wheezing were also observed after dose reduction to 100 mg/kg/day. Decreased activity in the eliglustat group was observed in an open field test[59] and was attributed to poor general condition or toxicity of eliglustat. Reduced motor coordination was noted in a foot fault test[60] and was likewise attributed

[57] 50 mmol/L phosphate buffered saline (pH 7.4)

[58] Administered twice daily 75 mg/kg until 4 days post-dose and 50 mg/kg from 5 days post-dose onward (dosing interval unknown).

[59] Distance moved in an open field was measured.

[60] The number of times that a foot slip occurred in any paw on a plastic grid and the number of paw missteps on the grid were recorded.

to poor general condition. No treatment-related findings of toxicity were identified in thermal paw stimulation for pain sensitivity, force plate analysis of spontaneous tremor,[61] or histopathological examination of the dorsal ganglia of the lumbar vertebra, the sciatic nerve, and hind paw dermis. As eliglustat was found not to induce peripheral neuropathy at above the maximum tolerated dose, no additional testing was performed.

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

Use in pregnancy

The applicant explained as follows about the use of eliglustat in pregnancy:

In nonclinical studies, maternal toxicity (e.g., reduced body weight gain, reduced food consumption) and embryo-fetal toxicity (e.g., increased post-implantation loss, low fetal body weight, cerebral ventricle dilatation, abnormal numbers of ribs and lumbar vertebrae) were observed in the 120 mg/kg/day group in the embryo fetal development study in rats (4.2.3.5.2-2). Other findings included fetal transfer of 0.034% of the dose administered in a placental transfer study in which 30 mg/kg of ^{14}C-labeled eliglustat tartrate was orally administered to pregnant SD rats (4.2.2.3-7), and transfer to neonates via the milk at 0.23% of the dose administered in a milk transfer study (4.2.2.5-2) in which 30 mg/kg of ^{14}C-labeled eliglustat tartrate was orally administered to lactating SD rats.

Given these nonclinical findings, eliglustat should not be used in women who are or may be pregnant because ERT is now clinically available with imiglucerase and velaglucerase alfa as drugs for the treatment of Gaucher disease type 1.

PMDA considers the applicant's view above is appropriate because toxicities suggestive of teratogenicity were identified in nonclinical studies, albeit at doses producing maternal toxicity.

4. Clinical data

Unless otherwise specified, concentrations of eliglustat in studies with human biological samples and doses of the drug product containing eliglustat and ^{14}C-labeled eliglustat used in clinical studies are expressed as eliglustat tartrate equivalent (eliglustat tartrate and eliglustat are hereinafter referred to as "eliglustat" in this section).

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

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

Five different capsule formulations were used in the clinical development of the drug product except in certain treatment groups[62] in a mass balance study (Study GZGD02107). The formulations used in the clinical studies are shown in Table 5.

[61] The number of tremors in the hindlimbs was counted.

[62] A formulation for intravenous injection was prepared from eliglustat powder, and an oral solution was prepared from radiolabeled powder.

Table 5. Formulations used in clinical studies

Formulation type	Study no.
Phase Ia study formulation [a] (500 mg)	GZGD00103
Phase Ib study formulation (50 and 100 mg)	GZGD00204, GZGD00404
Phase II study formulation (50 mg)	GZGD01807, GZGD02007, GZGD00304
Phase III study formulation (50 and 100 mg)	GZGD01707, GZGD02107, GZGD01907, GZGD02407, GZGD02707, GZGD03610, GZGD03811, GZGD00304, GZGD02507, GZGD02607, GZGD03109
Proposed commercial formulation [b] (50, 100[c], and 150 mg)	GZGD03610, GZGD04112, GZGD03811, GZGD00304, GZGD02507, GZGD02607, GZGD03109

a) Capsules filled with liquid drug formulation.
b) The common blend formulation is used so that the 50, 100, and 150 mg capsules have the same quantitative composition (i.e., eliglustat and excipients).
c) Proposed commercial formulation.

LC-MS/MS was used to determine the levels of unchanged eliglustat (eliglustat free base) and its metabolites in human biological samples. The lower limit of quantification of unchanged eliglustat in plasma was 0.2 or 0.5 ng/mL.[63] The lower limit of quantification was 0.5 ng/mL for unchanged eliglustat in urine and 0.339 or 0.5 ng/mL[64] for metabolites in plasma.

The results of a food effect study (Study GZGD00404) and a relative bioavailability study (Study GZGD03811) have been submitted as biopharmaceutical reference data.

4.(i).A.(1) Food effect (5.3.1.1-1: Study GZGD00404 [[redacted] to [redacted]], reference data)

A randomized, open-label, 2-period, crossover study was conducted to evaluate the effects of food on pharmacokinetics following a single oral dose of eliglustat in healthy non-Japanese men (target sample size, 24).

In each period, a single oral dose of 300 mg eliglustat was administered under fasted conditions (in the fasted state) or immediately after a high-fat diet (in the fed state). The treatment periods were separated by a 6-day washout period.

All 24 treated subjects were included in the pharmacokinetics and safety analysis populations. CYP2D6 gene polymorphism was not characterized.

Pharmacokinetic analyses revealed the maximum plasma concentration of unchanged eliglustat following administration in the fed and fasted states (C_{max}) (mean ± standard deviation) to be 88.3 ± 76.2 and 79.1 ± 65.9 ng/mL, respectively. The area under the plasma unchanged eliglustat concentration-time curve to the last quantifiable time point ($AUC_{0\text{-last}}$) was 606 ± 585 ng·h/mL and 678 ± 638 ng·h/mL, respectively. The elimination half-life ($t_{1/2}$) was 6.68 ± 1.09 and 6.11 ± 1.37 hours, respectively. The median time to the maximum plasma unchanged eliglustat concentration (t_{max}) (minimum, maximum) was 2.00 (0.95, 4.00) and 3.00 (1.00,

63 The lower limit of quantification of the analytical procedure was 0.5 ng/mL initially. Following improvements in the procedure, the lower limit of quantification was changed to 0.2 ng/mL.

64 0.339 ng/mL for Study GZGD00304, 0.5 ng/mL for Studies GZGD02107 and GZGD02407

6.00) hours, respectively. The geometric mean ratios of C_{max} and $AUC_{0\text{-last}}$ (fed/fasted) with their 90% confidence intervals were 0.852 [0.679, 1.069] and 1.047 [0.888, 1.234], respectively.

Safety evaluation revealed 7 adverse events in 3 of 24 subjects treated under fasted conditions and 14 adverse events in 7 of 24 subjects treated under fed conditions. Of these adverse events, those for which a causal relationship with the study drug was not ruled out (adverse drug reactions) were 4 events (soft stool [2 events], flatulence [1], and nausea [1]) in 2 of 24 subjects treated under fasted conditions and 3 events (flatulence [2] and soft stool [1]) in 2 of 24 subjects treated after a meal. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

4.(i).A.(2) Relative bioavailability (5.3.1.2-1: Study GZGD03811 [October to November 2011], reference data)

A randomized, open-label, 2-arm, 4-period crossover study was conducted to evaluate pharmacokinetics following a single dose of the phase III study formulation and the proposed commercial formulation of eliglustat in healthy non-Japanese men and women (target sample size, 22).

In each period, 3 capsules of the 50 mg phase III study formulation (150 mg) or 150 mg of the proposed commercial formulation was administered as a single oral dose[65] under fasted conditions, with a 7-day washout period between treatment periods.

All 22 treated subjects (20 with the CYP2D6 extensive metabolizer [EM] phenotype and 2 with the intermediate metabolizer [IM] phenotype) were included in the pharmacokinetics and safety analysis populations.

Pharmacokinetic analysis showed that the geometric mean ratios of C_{max} and $AUC_{0\text{-last}}$ of unchanged eliglustat in plasma (proposed commercial formulation /phase III study formulation) with their 90% confidence intervals were 1.021 [0.946, 1.102] and 1.006 [0.941, 1.075], respectively.

Safety evaluation revealed 2 adverse events in 2 of 22 subjects receiving 150 mg of the proposed commercial formulation. Of the 2 events, 1 (nausea) occurred in 1 of 22 subjects and was assessed as an adverse drug reaction. No death, serious adverse event, or adverse event leading to treatment discontinuation was reported.

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

PMDA asked the applicant to discuss the effects of food on the final formulation.

The applicant responded as follows:

[65] The proposed commercial formulation, phase III study formulation, proposed commercial formulation, and phase III study formulation were administered in this order as treatment order 1. The phase III study formulation, proposed commercial formulation, phase III study formulation, and proposed commercial formulation were administered in this order as treatment order 2.

In the food effect study (Study GZGD00404) in which the phase Ib study formulation was used, the geometric mean ratios of C_{max} and $AUC_{0\text{-last}}$ (fed/fasted) with their 90% confidence intervals were 0.852 [0.679, 1.069] and 1.047 [0.888, 1.234], respectively, which indicated no food effects. The phase Ib, phase II, and phase III study formulations and the proposed commercial formulation contain the same ingredients. In the phase Ib, phase II, and phase III study formulations, the percent changes in the fillers (microcrystalline cellulose and lactose monohydrate) and binder (hypromellose) are <5% and <0.5%, respectively. These represent minor changes under the formulation change criteria and are not thought to have a detectable impact on the quality or performance of the formulations. Although the percent changes in the excipients between the phase III study formulation (50 mg) and the proposed commercial formulation exceed 5%, these formulations dissolved rapidly at pH 1.0, 4.5, and 6.8 and their dissolution profiles were similar. The phase Ib and phase II study formulations contain the same ingredients at similar proportions as the phase III study formulation, thus, dissolution of the phase Ib and phase II study formulations at pH 1.0, 4.5, and 6.8 is thought to be similar to that of the proposed commercial formulation. The timing of administration was not specified in the phase III studies, and no information on meals was collected. Comparison of exposures to eliglustat following different meal timing was not performed. Nevertheless, the final formulation is not thought to be affected by meals because eliglustat has high solubility and membrane permeability, and because the phase Ib study formulation was unaffected by meals.

PMDA accepted the applicant's response even though the effects of food on the final formulation were not evaluated because no major food effects were observed in the food effect study with the phase Ib study formulation (Study GZGD00404), in light of the solubility, membrane permeability, and physicochemical and pharmacokinetic characteristics of eliglustat, and because no major clinical concerns were identified in evaluations of the efficacy and safety of the final formulation in the phase III studies, even though information on meals was not collected.

4.(ii) Summary of clinical pharmacology studies

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

Submitted as evaluation data were the results of a global phase III study in Japanese and non-Japanese patients with Gaucher disease (Study GZGD03109), non-Japanese phase III studies in non-Japanese patients with Gaucher disease (Studies GZGD00304, GZGD02507, and GZGD02607), and a study to evaluate QT/QTc in healthy non-Japanese adult subjects (Study GZGD01707). Submitted as reference data were the results of 11 non-Japanese clinical studies (Studies GZGD00103, GZGD00204, GZGD02107, GZGD01807, GZGD02007, GZGD02407, GZGD01907, GZGD03610, GZGD04112, GZGD02707, and GZGD03310) and the results of pharmacokinetic analyses (5.3.3.5-1 to 5.3.3.5-5 and 5.3.5.3-1). The results of studies using human biomaterials were also submitted. The findings of major studies are described below.

4.(ii).A.(1) Studies using human biomaterials (4.2.2.2-1, 4.2.2.2-2, 4.2.2.3-1, 4.2.2.3-2, 4.2.2.4-5, 5.3.2.2-5 to 5.3.2.2-12, 5.3.2.3-2, 5.3.2.3-6)

The membrane permeability of eliglustat free base (12.5 to 1250 μmol/L) was investigated in the Caco-2 human adenocarcinoma epithelial cell line. The apparent permeability coefficient (P_{app} [$\times 10^{-6}$ cm/s]) in the apical to

basolateral (A to B) direction and the basolateral to apical (B to A) direction was 22 to 23 and 13 to 24, respectively. The P_{app} of the highly permeable control labetalol (10 μmol/L) was 11 to 13 in the A to B direction and 7.7 to 12 in the B to A direction.

The intestinal permeability of eliglustat (6.0, 60, and 600 μg/mL) was evaluated using rat intestine. The membrane permeability coefficient ($\times 10^4$ cm/s) of eliglustat 6.0, 60, and 600 μg/mL was 0.030, 0.168, and 0.263, respectively, which were 0.19, 1.50, and 1.64 times, respectively, the intestinal permeability of the highly permeable control metoprolol (68 μg/mL) (eliglustat/metoprolol).

The human plasma protein binding of eliglustat free base (0.01 to 1 μmol/L) (mean, determined by rapid equilibrium dialysis) ranged from 76.4% to 82.9%. ^{14}C-labeled eliglustat (0.1 to 10 μmol/L) was added to human blood samples, and the mean partition coefficients between red blood cells and plasma were 1.68 to 1.86.

The proportions present of 11 metabolites were investigated following the incubation of ^{14}C-labeled eliglustat tartrate with recombinant human CYP isozymes (CYP2C19, 2D6, and 3A4). The 7-hydroxyl metabolite M5 (CYP2D6, 47.3%; CYP3A4, 3.4%; CYP2C19, 4.5%), the 6-hydroxyl metabolite M6 (CYP2D6, 11.0%; CYP3A4, 16.4%), and the 7-ketone metabolite M17 (CYP2D6, 7.7%) were produced as major metabolites by oxidation of the octanoyl moiety. Trace metabolites were the following: M9 (CYP2C19, 1.1%), M10 (CYP2C19, 1.6%), and M69 (CYP2C19, 1.7%) produced from oxidation of the 2,3-dihydro-1,4-benzodioxane moiety; M2 (CYP2D6, 22.1%), M3 (CYP2D6, 2.2%), M4 (CYP2D6, 7.5%), and M59 (CYP2D6, 2.3%) produced from oxidation of both the octanoyl moiety and the 2,3-dihydro-1,4-benzodioxane moiety; and amino metabolite (M11) (CYP3A4, 2.4%; CYP2C19, 9.6%) produced from metabolism of the pyrrolidine moiety.

In humans, eliglustat was metabolized primarily by CYP2D6 into the 7-hydroxyl metabolite M5 and also by CYP3A4 into the 5-hydroxyl metabolite M7 and the amino metabolite M11. These hydroxyl metabolites were further oxidized by CYP enzymes into the 7-ketone metabolite M17 and the 6-ketone metabolite M18. It was presumed that the ketone metabolites were oxidized into carboxy metabolites, the 6-carboxy metabolite M25 and 5-carboxy metabolite M24 were produced from the 7-ketone metabolite M17, and the 5-carboxy metabolite M24 and the 4-carboxy metabolite M31 were produced from the 6-ketone metabolite M18.

The ability of eliglustat (0.01 to 10 μmol/L) to induce CYP1A2, 2B6, and 3A4 was investigated in human primary cultured hepatocytes (n = 3). With no effects on mRNA or enzyme activity noted, eliglustat was shown not to induce CYP1A2, 2B6, or 3A4. Eliglustat metabolites[66] likewise did not induce CYP1A2, 2B6, or 3A4.

The inhibitory effect of eliglustat free base (0 to 50 μmol/L) on CYP isoforms was investigated using human liver microsomes spiked with probe substrates of the isoforms. Eliglustat competitively inhibited CYP2D6 (probe substrate: dextromethorphan) and CYP3A (midazolam) with inhibition constants (Ki) of 5.8 and 27.0

[66] The investigation used the metabolites M5 (2.38 μmol/L), M6 (2.38 μmol/L), M7 (0.238 μmol/L), M11 (0.286 μmol/L), M12 (0.238 μmol/L), M17 (2.39 μmol/L), M18 (2.39 μmol/L), M24 (12.3 μmol/L), M25 (2.38 μmol/L), and M31 (2.55 μmol/L).

μmol/L, respectively. Ki exceeded 50 μmol/L in CYP1A2, 2C8, 2C9, 2C19, and 3A4 (testosterone), and IC_{50} exceeded 50 μmol/L in CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, and 2J2. Eliglustat showed time-dependent inhibition of CYP2D6. The 7-hydroxyl metabolite (M5) and amino metabolite (M11) also competitively inhibited CYP2D6 with Ki values of 31.1 and 0.399 μmol/L, respectively. M11 also inhibited CYP3A (using midazolam and testosterone as probe substrates) with Ki values of 8.51 and 10.2 μmol/L. The N-oxide metabolite (M12) showed time-dependent inhibition of CYP2D6 and 3A.

Cell transport of eliglustat (1 μmol/L) was investigated in MDCKII cells expressing P-gp. Eliglustat was found to be a P-gp substrate because the ratio of the apparent membrane permeability coefficient in the apical to basolateral (A to B) direction to that in the basolateral to apical (B to A) direction ($P_{appBtoA}/P_{appAtoB}$) decreased (from 4.9-7.1 to 0.9-1.4) in the presence of the P-gp inhibitor PSC833 (10 μmol/L) or verapamil (60 μmol/L).

Eliglustat showed an inhibitory effect on the efflux transporter P-gp (IC_{50}, 22 μmol/L) in an investigation of the inhibitory effect of eliglustat (3.1 to 250 μmol/L) on substrate uptake by P-gp. Eliglustat showed no inhibitory effect on substrate uptake by the efflux transporters BCRP, BSEP, MRP1, MRP2, MRP3, MRP4, and MRP5 or the uptake transporters OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, and OCT2. Likewise, eliglustat metabolites[66] showed no inhibitory effect on substrate uptake by P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Non-Japanese single dose study (5.3.3.1-1: Study GZGD00103 [to], reference data)

A randomized, double-blind, placebo-controlled, dose escalation study was conducted to evaluate the safety and pharmacokinetics of eliglustat following a single oral administration in healthy non-Japanese men (target sample size, 104).

The subjects received a single oral dose of placebo or eliglustat 0.01, 0.03, 0.1, 0.3, 1, 2, 3, 5, 7, 10, 15, 20, or 30 mg/kg under fasted conditions. At the 30 mg/kg step, 1 subject was randomized to the placebo group and 2 to the eliglustat group while at the other dose steps, 2 subjects were randomized to the placebo group and 6 subjects to the eliglustat group.

All 99 treated subjects were included in the safety analysis population. Of those, all 74 subjects treated with eliglustat were included in the pharmacokinetic analysis population. CYP2D6 gene polymorphism was not characterized.

The pharmacokinetic parameters of unchanged eliglustat in plasma following a single oral dose of eliglustat are shown in Table 6.

Table 6. Pharmacokinetic parameters of unchanged eliglustat in plasma following single oral dose of eliglustat

Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/min)	V_Z/F (L)	CL_r (mL/min)	$fe_{0-8\ h}$ (%)
0.01	-	-	-	-	-	-	-	0.38 ± 0.44
0.03	-	-	-	-	-	-	34.5	0.16 ± 0.04
0.1	-	-	-	-	-	-	360 ± 254	0.18 ± 0.16
0.3	2.68 ± 1.65[a)]	1.50[a)] (0.75, 1.50)	28.1 ± 16.8[b)]	4.83 ± 0.37[b)]	15.7 ± 10.8[b)]	6350 ± 3880[b)]	222 ± 260	0.34 ± 0.25
1	10.4 ± 7.63	2.25 (0.75, 6.00)	151 ± 156[b)]	6.54 ± 1.93[b)]	15.9 ± 16.5[b)]	8050 ± 7900[b)]	101 ± 46.5	0.66 ± 0.74
2	13.3 ± 11.5	1.75 (0.75, 3.00)	112 ± 101	6.35 ± 1.56	34.6 ± 25.0	17,600 ± 10,200	85.0 ± 21.4	0.20 ± 0.12
3	82.4 ± 68.7	1.75 (0.75, 2.00)	633 ± 582	7.52 ± 1.92	9.4 ± 6.75	6140 ± 5140	84.3 ± 31.6	0.96 ± 0.87
5	91.1 ± 86.2	1.50 (0.75, 4.00)	692 ± 913	6.15 ± 1.30	21.0 ± 16.6	10,400 ± 8150	133 ± 51.6	0.78 ± 0.76
7	58.8 ± 38.5	1.75 (1.00, 3.00)	324 ± 207[c)]	5.05 ± 0.27[c)]	30.6 ± 13.7[c)]	13,500 ± 6390[c)]	137 ± 48.8	0.44 ± 0.29
10	267 ± 210	1.00 (0.75, 1.50)	1560 ± 1070	6.09 ± 1.08	15.9 ± 19.5	7460 ± 7900	81.0 ± 24.8	0.72 ± 0.48
15	503 ± 332	1.00 (1.00, 4.00)	3040 ± 1250	6.42 ± 0.75	6.50 ± 2.82	3580 ± 1390	127 ± 44.5	1.34 ± 0.40
20	557 ± 212	1.50 (1.00, 6.00)	4400 ± 1480	6.05 ± 0.56	6.16 ± 3.44	3150 ± 1580	108 ± 31.8	1.31 ± 0.59
30[d)]	1090, 2610	0.75, 3.00	6660, 14,400	5.87, 7.63	2.18, 5.29	1440, 2690	68.9, 90.0	0.93, 1.58

n = 6; mean ± standard deviation (individual values at 30 mg/kg); t_{max} is expressed as median (minimum, maximum); -, not determined;
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
$AUC_{0-\infty}$, area under the plasma unchanged eliglustat concentration-time curve extrapolated to infinity; $t_{1/2}$, elimination half-life;
CL/F, apparent total body clearance; V_Z/F, apparent volume of distribution; CL_r, renal clearance;
$fe_{0-8\ h}$, cumulative urinary excretion to 8 hours postdose.
a) n = 5, b) n = 3, c) n = 4, d) n = 2

Safety evaluation revealed adverse events in 9 of 25 subjects in the placebo group and 67 of 74 subjects in the eliglustat (0.01 to 30 mg/kg) groups. Of these, events identified as adverse drug reactions occurred in 3 of 25 subjects in the placebo group, and in eliglustat groups as follows: 3 of 6 subjects in the 0.01 mg/kg group; 1 of 6 in the 0.03 mg/kg group; 3 of 6 in the 0.1 mg/kg group; 5 of 6 in the 0.3 mg/kg group; 4 of 6 in the 1 mg/kg group; 4 of 6 in the 2 mg/kg group; 6 of 6 in the 3 mg/kg group; 6 of 6 in the 5 mg/kg group; 6 of 6 in the 7 mg/kg group; 6 of 6 in the 10 mg/kg group; 6 of 6 in the 15 mg/kg group; 6 of 6 in the 20 mg/kg group; and 2 of 2 in the 30 mg/kg group. Common adverse drug reactions in the eliglustat groups were dysgeusia (48 of 74 subjects, 64.9%), throat irritation (21 of 74, 28.4%), and abdominal pain (7 of 74, 9.5%). No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

4.(ii).A.(2).2) Foreign repeated-dose study (5.3.3.1-2: Study GZGD00204 [[redacted] to [redacted] [redacted]], reference data)

A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of eliglustat following repeated oral administration in healthy non-Japanese men and women (target sample size, 36).

The subjects orally received placebo or eliglustat (50, 200, or 350 mg) once daily on Days 1, 2, and 12 and twice daily on Days 3 to 11 (100, 400, or 700 mg/day). In each step, 4 subjects were randomized to the placebo group, and 8 subjects to the eliglustat groups.

All 36 treated subjects (all CYP2D6 EMs) were included in the pharmacodynamic and safety analysis populations. All of the 24 subjects treated with eliglustat were additionally included in the pharmacokinetic analysis population.

The pharmacokinetic parameters of unchanged eliglustat in plasma following repeated oral doses of eliglustat are shown in Table 7.

Table 7 Pharmacokinetic parameters of unchanged eliglustat in plasma following repeated oral doses of eliglustat

Dose	Time points	C_{max} (ng/mL)	t_{max} (h)	AUC (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/min)	V_Z/F (L)
50 mg BID	Day 1	2.48 ± 0.83	1.50 (0.50, 3.00)	19.1 ± 7.84[b)]	3.69 ± 1.23[b)]	44.8 ± 26.6[b)]	12,600 ± 3680[b)]
	Day 10	7.35 ± 4.51	1.50 (1.50, 2.02)	39.3 ± 23.2	4.27 ± 1.05[a)]	37.1 ± 48.4	7330 ± 4510[a)]
	Day 12	7.64 ± 4.48	2.00 (0.50, 3.00)	41.9 ± 28.4	5.80 ± 2.73	27.4 ± 21.6	12,400 ± 9220
200 mg BID	Day 1	32.9 ± 30.0	1.75 (1.00, 4.00)	294 ± 323[a)]	5.36 ± 1.34[a)]	38.5 ± 45.6[a)]	13,900 ± 13,800[a)]
	Day 10[a)]	119 ± 81.2	1.50 (1.00, 3.00)	697 ± 590	4.09 ± 0.78	12.5 ± 14.7	4010 ± 4770
	Day 12[a)]	142 ± 99.2	1.50 (1.50, 2.00)	747 ± 608	6.01 ± 1.00	12.1 ± 16.3	5320 ± 5860
350 mg BID	Day 1	107 ± 59.1	2.50 (1.00, 3.07)	678 ± 425	5.65 ± 0.40	11.7 ± 9.14	5930 ± 4910
	Day 10[b)]	231 ± 88.8	2.50 (2.00, 4.00)	1450 ± 682	4.08 ± 0.77	4.13 ± 1.93	1420 ± 571
	Day 12[c)]	278 ± 62.0	1.00 (1.00, 2.00)	1290 ± 428	5.58 ± 0.12	4.08 ± 1.17	1980 ± 600

n = 8; mean ± standard deviation except for t_{max} (median [minimum, maximum]); BID, twice daily dosing;
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
AUC, area under the plasma unchanged eliglustat concentration-time curve ($AUC_{0-\infty}$ for 50 mg BID, AUC_{0-12h} for 200 and 350 mg BID);
$t_{1/2}$, Elimination half-life; CL/F, apparent total body clearance; V_Z/F, apparent volume of distribution.
a) n = 7, b) n = 6, c) n = 3.

Pharmacodynamic evaluation revealed that the percent reduction in plasma glucosylceramide from baseline (100%) to Day 12 (mean ± standard deviation) was 88.3% ± 10.9% in the placebo group, 50.5% ± 11.8% in the 50 mg group, 20.9% ± 12.5% in the 200 mg group, and 13.1% ± 2.82% in the 350 mg group.

Safety evaluation revealed adverse events in 9 of 12 subjects in the placebo group, and in the eliglustat groups as follows: 7 of 8 subjects in the 50 mg group; 7 of 8 in the 200 mg group; and 8 of 8 in the 350 mg group. Of these, events identified as adverse drug reactions were reported in 3 of 12 in the placebo group, and in the eliglustat groups as follows: 4 of 8 in the 50 mg group, 5 of 8 in the 200 mg group, and 7 of 8 in the 350 mg group. Common adverse drug reactions occurring in the eliglustat groups were nausea (11 of 24 subjects, 45.8%), headache (6 of 24, 25.0%), constipation (4 of 24, 16.7%), vomiting (4 of 24, 16.7%), and decreased appetite (4 of 24, 16.7%). No deaths or serious adverse events were reported. Adverse events leading to treatment discontinuation amounted to 1 event (ventricular tachycardia) in 1 of 12 subjects in the placebo group, 1 event (tachyarrhythmia) in 1 of 8 subjects in the 200 mg group, and 6 events (vomiting [4 events], dizziness postural [1], and scotoma [1]) in 5 of 8 subjects in the 350 mg group. All these events other than ventricular tachycardia in the placebo group and scotoma in the 350 mg group were considered to be adverse drug reactions.

4.(ii).A.(2).3) Mass balance study (5.3.3.1-3: Study GZGD02107 [to], reference data)

An open-label, uncontrolled study was conducted to evaluate the disposition of eliglustat in healthy non-Japanese men (target sample size, 10).

The subjects received 50 mg of eliglustat as a single 1-hour intravenous infusion on Day 1, a single oral dose of 100 mg eliglustat on Day 8, repeated oral dose of 100 mg eliglustat twice daily (200 mg/day) from the evening of Day 9 to Day 14, and a single oral dose of 100 mg of ^{14}C-labeled eliglustat on Day 15.

All 10 treated subjects (9 CYP2D6 EM phenotype and 1 IM phenotype) were included in the pharmacokinetics and safety analysis population.

The pharmacokinetic parameters of unchanged eliglustat in plasma following eliglustat administration are shown in Table 8. Absolute bioavailability (mean ± standard deviation) was 4.49% ± 4.13% when the value was calculated from the area under the plasma unchanged eliglustat concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) corrected by the single intravenous dose and single oral dose of eliglustat.

Table 8. Pharmacokinetic parameters of unchanged eliglustat in plasma following eliglustat administration

Dose	Time points	Number of subjects	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_Z (L)
50 mg i.v.	Day 1	10	107 ± 25.0	1.00 (0.50, 1.50)	499 ± 65.7	6.59 ± 0.45	85.8 ± 10.4	816 ± 117
100 mg p.o.	Day 8	10	5.48 ± 5.01	1.76 (1.00, 4.00)	47.2 ± 52.5	5.47 ± 1.39	3490 ± 2360[b)]	24,400 ± 12,800
^{14}C-labeled 100 mg p.o.	Day 15	8	12.1 ± 5.11	2.00 (1.50, 2.07)	76.3 ± 28.1[a)]	6.48 ± 0.69	1290 ± 545[b)]	11,900 ± 4650

Mean ± standard deviation except for t_{max} (median [minimum, maximum]).
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
$AUC_{0-\infty}$, area under the plasma unchanged eliglustat concentration-time curve extrapolated to infinity; $t_{1/2}$, elimination half-life;
CL, total body clearance; V_Z, volume of distribution (p.o.: V_Z/F [apparent volume of distribution]);
a) AUC_{0-12h}; b) CL/F (apparent total body clearance).

Following administration of ^{14}C-labeled eliglustat (100 mg), the cumulative urinary excretion of unchanged eliglustat was 0.47% ± 0.18% of the administered radioactivity at 12 hours postdose, and the cumulative fecal excretion of unchanged eliglustat was 0.13% ± 0.11% of the administered radioactivity at 24 hours postdose. At 240 hours after administration of 100 mg ^{14}C-labeled eliglustat, the cumulative excretion of total radioactivity in urine and feces was 41.8% ± 5.12% and 51.4% ± 3.96% of the administered radioactivity, respectively.

In investigation of the metabolism profile, 21 metabolites were identified in plasma following administration of 100 mg ^{14}C-labeled eliglustat. The 5-carboxy metabolite M24 was the only metabolite with an exposure (AUC) of ≥10% relative to total plasma radioactivity and accounted for 15.9% of AUC of the total plasma radioactivity. M24 exposure was 8.78-fold higher than that of unchanged eliglustat.

Safety evaluation revealed adverse events in 1 of 10 subjects following a single intravenous infusion of eliglustat, 1 of 10 subjects following an oral dose of 100 mg eliglustat, and 3 of 8 subjects following an oral dose of 100 mg ^{14}C-labeled eliglustat. Of these adverse events, there were 2 adverse drug reactions in 1 of 10

subjects following a single intravenous infusion of eliglustat (feeling hot [1 event], restlessness [1]) and 3 adverse drug reactions in 2 of 8 subjects following an oral dose of 100 mg ^{14}C-labeled eliglustat (abdominal pain [2] and headache [1]). No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

4.(ii).A.(3) Studies in patients

4.(ii).A.(3).1) Phase II study in treatment-naïve patients with Gaucher disease type 1 (5.3.5.2-1: Study GZGD00304 [June 2006 to [redacted] data cutoff])

An open-label study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in non-Japanese patients with Gaucher disease type 1 [for more information on the study design and efficacy and safety data, see "4.(iii).A.(2).1) Phase II study in treatment-naïve patients with Gaucher disease type 1"].

The pharmacokinetic parameters[67] of unchanged eliglustat in plasma following repeated oral doses of eliglustat are shown in Table 9.

Table 9. Pharmacokinetic parameters of unchanged eliglustat in plasma following repeated oral doses of eliglustat

Dose	Time points	Number of subjects	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}12\,h}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/min)
50 mg QD	Day 1	26	8.91 ± 6.45	1.50 (1.00, 4.00)	43.7 ± 34.6	6.12 ± 2.94	1240 ± 1040[a)]
50 mg BID	Day 10	24	13.3 ± 10.6	2.00 (1.00, 3.00)	98.3 ± 87.2	-	734 ± 479

Mean ± standard deviation except for t_{max} (median [minimum, maximum]); -, not calculated;
QD, once daily; BID, twice daily;
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
$AUC_{0\text{-}12h}$, area under the plasma unchanged eliglustat concentration-time curve to 12 hours postdose; $t_{1/2}$, elimination half-life;
CL/F, apparent total body clearance.
a) n = 23.

Mean C_{max} and $AUC_{0\text{-}12h}$ of unchanged eliglustat in plasma on Day 1 of administration of 50 mg eliglustat were 8.75 ng/mL and 42.3 ng·h/mL, respectively, in 23 subjects with the CYP2D6 EM phenotype and 22.4 ng/mL and 143 ng·h/mL, respectively, in 1 subject with CYP2D6 poor metabolizer (PM) phenotype. These values were 2.56-fold and 3.38-fold higher in the PM than in the EMs.

Pharmacodynamic evaluation revealed the percent reduction in glucosylceramide from baseline (100%) to Week 52 (mean ± standard deviation) was 78.5% ± 7.87%.

4.(ii).A.(3).2) Global phase III study in Japanese and non-Japanese patients with Gaucher disease (5.3.5.1-3: Study GZGD03109 [EDGE] [June 2010 to [redacted] data cutoff])

An open-label study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in Japanese and non-Japanese patients with Gaucher disease type 1 [for more information on the study design and

[67] Pharmacokinetic analysis of unchanged eliglustat in plasma was performed by determining trough concentrations at 1, 10, 20, and 30 days postdose and at Weeks 13, 26, 39, 52, 53, 65, 78, 91, and 104 and then once every 12 months thereafter. Blood samples for analysis were collected by 24 hours after the very first dose, by 2 hours postdose at Weeks 62 and 91, by 6 hours postdose at 10 and 20 days after the very first dose and at Weeks 13, 39, 52, 78, and 104, and by 12 hours postdose at 30 days after the very first dose and at Week 26.

efficacy and safety data, see "4.(iii).A.(1) Global phase III study in Japanese and non-Japanese patients with Gaucher disease"].

The pharmacokinetic parameters[68] of unchanged eliglustat in plasma at the end of the open-label lead-in period of open-label treatment are shown by CYP2D6 phenotype in Table 10.

Table 10. Pharmacokinetic parameters of unchanged eliglustat in plasma by CYP2D6 phenotype (at end of open-label lead-in period)

Dose	50 mg BID			100 mg BID			150 mg/100 mg BID
CYP2D6 phenotype	PM	IM	EM	IM	EM	URM	EM
Number of subjects	3	11	4	7	99	3	6
C_{max} (ng/mL)	48.8 ± 10.4	29.1 ± 10.8	25.2 ± 12.2	37.9 ± 13.0	24.3 ± 17.3	13.7 ± 8.16	50.1 ± 30.0
$AUC_{0\text{-}12\ h}$ (ng·h/mL)	420 ± 74.4	224 ± 106	178 ± 82.8	247 ± 109	146 ± 97.2	49.9 ± 28.5	215 ± 121

Mean ± standard deviation; BID, twice daily.
C_{max}, maximum concentration of unchanged eliglustat in plasma; $AUC_{0\text{-}12h}$, area under the plasma unchanged eliglustat concentration-time curve to 12 hours postdose; PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; URM, ultra-rapid metabolizer

Table 11 shows the pharmacokinetic parameters of unchanged eliglustat in plasma of Japanese and non-Japanese EM subjects following twice daily repeated oral administration of 100 or 150 mg eliglustat (at Week 13).

Table 11. Pharmacokinetic parameters of unchanged eliglustat in plasma of Japanese and non-Japanese subjects (CYP2D6 EM phenotype, Week 13)

	Japanese		Non-Japanese	
Dose	100 mg BID[a)]	150 mg BID	100 mg BID	150 mg BID
Number of subjects	1	4	111	5
C_{max} (ng/mL)	36.8	66.2 ± 55.1	26.3 ± 18.3	55.9 ± 27.2
t_{max} (h)	1.00	1.98 (0.50, 3.00)	2.00 (0.00, 4.28)	1.03 (1.00, 2.08)
$AUC_{0\text{-}12h}$ (ng·h/mL)	277	310 ± 258	157 ± 106	265 ± 150

Mean ± standard deviation except for t_{max} (median [minimum, maximum]); BID, twice daily;
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma; $AUC_{0\text{-}12h}$, area under the plasma unchanged eliglustat concentration-time curve to 12 hours postdose; EM, extensive metabolizer
a) Value for 1 subject

Pharmacodynamic evaluation revealed the percent reduction in glucosylceramide from baseline (100%) to Weeks 26, 52, and 78 (mean ± standard deviation) was 57.8% ± 20.9% (9 subjects), 49.1% ± 23.0% (6 subjects), and 39.4% and 16.7% (2 subjects, individual values), respectively, in the Japanese subjects and 34.3% ± 21.6% (118 subjects), 37.7% ± 22.3% (35 subjects), and 33.6% ± 33.8% (12 subjects), respectively, in the non-Japanese subjects.

4.(ii).A.(3).3) Phase III study in treatment-naïve patients with Gaucher disease type 1 (5.3.5.1-1: Study GZGD02507 [ENGAGE] [November 2009 to [redacted] data cutoff])

A placebo-controlled, double-blind, parallel-group, comparative study was conducted to evaluate the efficacy, safety, and pharmacokinetics of eliglustat in non-Japanese patients with Gaucher disease type 1 [for more

[68] Pharmacokinetic analysis of unchanged eliglustat in plasma was performed in the non-Japanese population by determining trough and peak levels at 1 day postdose and at Weeks 2, 6, 13, 26, 39, 52, 65, and 78 and with full pharmacokinetic analysis at Week 13. Analysis in the Japanese population was performed by determining trough levels at 1 day postdose and at Weeks 2, 4, 6, 8, 13, 26, 39, 52, 65, and 78 and peak levels at 1 day postdose and at Weeks 2, 6, 13, 26, 39, 52, 65, and 78 and with full pharmacokinetic analysis at 1 day postdose and at Weeks 2, 6, and 13.

information on the study design and efficacy and safety data, see "4.(iii).A.(2).2) Phase III study in treatment-naïve patients with Gaucher disease type 1"].

The pharmacokinetic parameters[69] of unchanged eliglustat in plasma following repeated oral doses of eliglustat are shown in Table 12.

Table 12. Pharmacokinetic parameters of unchanged eliglustat in plasma following repeated oral doses of eliglustat

Time points	Day 1		Week 4		Week 39	
Dose	50 mg QD		50 mg BID	100 mg BID	50 mg BID	100 mg BID
Number of subjects	20		4	15	3	16
C_{max} (ng/mL)	6.45 ± 6.03		24.3 ± 13.7	20.8 ± 15.4	18.1 ± 4.89	22.4 ± 18.1[b)]
C_{trough} (ng/mL)	-		5.94 ± 3.49	2.57 ± 2.37[b)]	5.45 ± 2.35	4.88 ± 4.66
t_{max} (h)	1.74 (0.92, 4.00)		1.51 (1.00, 2.08)	1.58 (1.00, 4.00)	2.08 (2.00, 2.17)	1.75[b)] (1.00, 4.00)
$AUC_{0\text{-}12h}$ (ng·h/mL)	16.8 ± 14.1[a)]		135 ± 78.2	96.7 ± 77.3[c)]	124 ± 33.2	120 ± 109[b)]
Pharmacokinetic parameters by CYP2D6 phenotype						
Time points	Day 1		Week 4		Week 39	
Dose	50 mg QD		50 mg BID	100 mg BID	50 mg BID	100 mg BID
Phenotype (number of subjects)	EM (18)		EM (3)	EM (14)	EM (2)	EM (13)
C_{max} (ng/mL)	6.40 ± 6.15		23.0 ± 16.5	21.7 ± 15.6	18.4, 22.8	23.7 ± 18.1
$AUC_{0\text{-}12h}$ (ng·h/mL)	16.4 ± 13.7		128 ± 94.0	102 ± 77.7	136, 216	128 ± 110
Phenotype (number of subjects)	IM (1)	URM (1)	IM (1)	URM (1)	IM (1)	URM (1)
C_{max} (ng/mL)	11.7	2.00	28.0	7.62	13.1	5.39
$AUC_{0\text{-}12h}$ (ng·h/mL)	36.7	4.41	157	27.7	87.1	18.8

Mean ± standard deviation except for IM and URM (values for 1 subject) and t_{max} (median [minimum, maximum]); -, not evaluated.
QD, once daily; BID, twice daily; IM, intermediate metabolizer; EM, extensive metabolizer; URM, ultra-rapid metabolizer;
C_{max}, maximum concentration of unchanged eliglustat in plasma; C_{trough}, trough concentration of unchanged eliglustat following repeated dosing; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
$AUC_{0\text{-}12h}$, area under the plasma unchanged eliglustat concentration-time curve to 12 hours postdose ($AUC_{0\text{-}4h}$ on Day 1).
a) n = 19, b) n = 14, c) n = 13

Pharmacodynamic evaluation revealed the percent reduction in glucosylceramide from baseline (100%) to Weeks 4, 13, 26, and 39 (mean ± standard deviation) was 6.39% ± 20.1%, 4.91% ± 22.5%, 14.5% ± 26.5%, and 3.88% ± 20.6%, respectively, in the placebo group and 60.7% ± 17.2%, 72.4% ± 9.18%, 69.5% ± 25.2%, and 72.7% ± 10.9%, respectively, in the eliglustat group.

4.(ii).A.(3).4) Phase III study in patients switching from ERT (5.3.5.1-2: Study GZGD02607 [ENCORE] [September 2009 to [redacted] data cutoff])

An active-controlled, randomized, open-label, comparative study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in non-Japanese patients with Gaucher disease type 1 [for more information on the study design and efficacy and safety data, see "4.(iii).A.(2).3) Phase III study in patients with a history of ERT"].

The pharmacokinetic parameters[70] of unchanged eliglustat in plasma following repeated oral doses of eliglustat are shown by CYP2D6 phenotype in Table 13.

[69] Pharmacokinetic parameters of unchanged eliglustat in plasma were determined with trough levels at Weeks 2, 4, 13, 26, and 39 and peak levels at 1 day postdose and at Weeks 4 and 39.

[70] Pharmacokinetic parameters of unchanged eliglustat in plasma were determined with trough levels at Weeks 2, 6, 13, 26, 39, and 52 and peak levels at 1 day postdose and at Weeks 13, 39, and 52.

Table 13 Pharmacokinetic parameters of unchanged eliglustat in plasma following repeated oral doses of eliglustat by CYP2D6 phenotype

CYP2D6 phenotype	Time points	Day 1	Week 13			Week 52		
EM	Dose	50 mg BID	50 mg BID	100 mg BID	150 mg BID	50 mg BID	100 mg BID	150 mg BID
	Number of subjects	84	11	31	42	9	30	41
	C_{max} (ng/mL)	6.03 ± 6.32	27.4 ± 19.0	37.2 ± 26.6	39.9 ± 27.2	26.8 ± 20.0	35.1 ± 21.3	38.1 ± 30.8
	t_{max} (h)	1.99 (0.70, 4.58)	1.48 (0.95, 4.05)	1.83 (0.00, 4.03)	1.94 (0.97, 7.50)	2.50 (1.00, 4.07)	2.02 (1.00, 4.08)	1.98 (0.98, 4.00)
	$AUC_{0\text{-}12h}$ (ng·h/mL)	15.4 ± 16.3	201 ± 170	195 ± 103	228 ± 157	214 ± 196	201 ± 118[a)]	195 ± 125[b)]
IM	Dose	50 mg BID	50 mg BID	100 mg BID	150 mg BID	50 mg BID	100 mg BID	150 mg BID
	Number of subjects	12	7	4	1	5	4	1
	C_{max} (ng/mL)	13.7 ± 9.60	30.1 ± 10.9	52.8 ± 22.2	8.02	34.9 ± 8.11	58.7 ± 32.7	2.94
	t_{max} (h)	2.00 (1.00, 4.48)	2.00 (0.83, 4.00)	1.01 (1.00, 3.00)	1.08	2.00 (1.00, 4.05)	1.51 (1.02, 2.02)	3.00
	$AUC_{0\text{-}12h}$ (ng·h/mL)	35.4 ± 28.4	199 ± 65.9	323 ± 130	33.2	200 ± 54.3	400 ± 286	3.00
PM	Dose	50 mg BID	50 mg BID			50 mg BID		
	Number of subjects	4	4			4		
	C_{max} (ng/mL)	40.1 ± 13.4	76.9 ± 34.1			78.5 ± 38.4		
	t_{max} (h)	3.51 (2.00, 4.00)	3.50 (1.67, 4.10)			3.00 (1.83, 4.18)		
	$AUC_{0\text{-}12h}$ (ng·h/mL)	102 ± 58.0	718 ± 316			648 ± 231		
URM	Dose	50 mg BID	50 mg BID			50 mg BID		
	Number of subjects	4	4			4		
	C_{max} (ng/mL)	3.31 ± 3.57	16.5 ± 8.4			16.6 ± 9.90		
	t_{max} (h)	1.12 (1.00, 2.00)	1.12 (1.00, 2.15)			2.02 (1.00, 2.12)		
	$AUC_{0\text{-}12h}$ (ng·h/mL)	6.21 ± 4.71	107 ± 67.2			88.5 ± 52.0		

Mean ± standard deviation except for t_{max} (median [minimum, maximum]); BID, twice daily;
PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; URM, ultra-rapid metabolizer;
C_{max}, maximum concentration of unchanged eliglustat in plasma; t_{max}, time to maximum concentration of unchanged eliglustat in plasma;
$AUC_{0\text{-}12h}$, area under the plasma unchanged eliglustat concentration-time curve to 12 hours postdose ($AUC_{0\text{-}4h}$ on Day 1).
a) n = 29, b) n = 40

Pharmacodynamic evaluation revealed the percent reduction in glucosylceramide from baseline (100%) to Weeks 13, 26, 39, and 52 (mean ± standard deviation) was 9.47% ± 20.7%, 6.74% ± 21.1%, 3.72% ± 27.2%, and 9.31% ± 23.2%, respectively, in the imiglucerase group and 58.5% ± 14.2%, 58.3% ± 12.9%, 57.0% ± 18.7%, and 58.2% ± 13.5%, respectively, in the eliglustat group.

4.(ii).A.(4) Drug-drug interactions

4.(ii).A.(4).1) Drug interaction study with paroxetine hydrochloride (5.3.3.4-1: Study GZGD02007 [to], reference data)

An open-label study was conducted to evaluate the effects of paroxetine hydrochloride (hereinafter referred to as paroxetine), a strong CYP2D6 inhibitor, on the pharmacokinetics of eliglustat in healthy non-Japanese adults (target sample size, 36).

The subjects orally received a single dose of 100 mg eliglustat once daily on Day 1 (single-dosing period of eliglustat), repeated oral doses of 100 mg eliglustat twice daily from the evening of Day 2 to the morning of Day 18 (Day 2 to Day 8, repeated-dosing period of eliglustat), and oral doses of 30 mg of paroxetine once daily from Day 9 to Day 18 (paroxetine co-administration period).

All 36 treated subjects (33 EMs, 1 IM, and 2 URMs) were included in the pharmacokinetics and safety analysis populations.

The geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of unchanged eliglustat (eliglustat plus paroxetine vs. eliglustat alone) with their 90% confidence intervals were 7.31 [5.85, 9.13] and 8.93 [7.15, 11.10], respectively.

Safety evaluation revealed adverse events in 4 of 36 subjects in the single-dosing period of eliglustat, 15 of 36 subjects in the repeated-dosing period of eliglustat, and 32 of 35 subjects in the paroxetine co-administration period. Of these, events identified as adverse drug reactions[71] occurred in 2 of 36 subjects[72] in the single-dosing period of eliglustat, 10 of 36 subjects[73] in the repeated-dosing period of eliglustat, and 25 of 35 subjects[74] in the paroxetine co-administration period. No deaths or serious adverse events were reported. The adverse events leading to treatment discontinuation were 1 event (gastritis) in 1 of 36 subjects in the repeated-dosing period of eliglustat and 4 events (dizziness/nausea, panic attack/nausea) in 2 of 35 subjects in the paroxetine co-administration period, and all of the events were classified as adverse drug reactions.

4.(ii).A.(4).2) Drug interaction study with ketoconazole (5.3.3.4-2: Study GZGD01807 [to], reference data)

An open-label study was conducted to evaluate the effects of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of eliglustat in healthy non-Japanese adults (target sample size, 36).

The subjects orally received a single dose of 100 mg eliglustat once daily on Day 1 (single-dosing period of eliglustat), repeated oral doses of 100 mg eliglustat twice daily from the evening of Day 2 to the morning of Day 15 (Days 2 to 8: repeated-dosing period of eliglustat), and oral doses of 400 mg of ketoconazole once daily from Days 9 to 15 (ketoconazole co-administration period).

All 36 treated subjects (34 EMs and 2 URMs) were included in the pharmacokinetics and safety analysis population.

The geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of unchanged eliglustat (eliglustat plus ketoconazole vs. eliglustat alone) with their 90% confidence intervals were 3.84 [3.41, 4.33] and 4.27 [3.87, 4.71], respectively.

Safety evaluation revealed adverse events in 4 of 36 subjects in the single-dosing period of eliglustat, 11 of 34 subjects in the repeated-dosing period of eliglustat, and 16 of 33 subjects in the ketoconazole co-administration

71 The number of adverse drug reactions was not counted and is therefore unknown.

72 Nausea, headache, and dizziness.

73 Nausea, abdominal pain lower, constipation, gastritis, inappetence, musculoskeletal pain, musculoskeletal stiffness, headache, somnolence, affect lability.

74 Palpitations, sinus tachycardia, vision blurred, visual disturbance, nausea, abdominal discomfort, abdominal distension, abdominal pain lower, abdominal pain upper, constipation, diarrhoea, dyspepsia, oesophagitis, stomach discomfort, vomiting, feeling cold, asthenia, chest discomfort, chest pain, feeling abnormal, feeling jittery, hunger, irritability, thirst, blood pressure increased, decreased appetite, inappetence, back pain, pain in extremity, headache, dizziness, dysgeusia, hypoaesthesia, lethargy, paraesthesia, restless legs syndrome, somnolence, tremor, anxiety, euphoric mood, insomnia, nervousness, panic attack, urine flow decreased, dyspnoea, tachypnoea, cold sweat, flushing, hot flush

period. Of these, events identified as adverse drug reactions[71] occurred in 2 of 36 subjects[75] in the single-dosing period of eliglustat, 8 of 34 subjects[76] in the repeated-dosing period of eliglustat, and 12 of 33 subjects[77] in the ketoconazole co-administration period. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

4.(ii).A.(4).3) Other drug interaction studies (5.3.3.4-3, Study GZGD02707 [to], reference data; 5.3.3.4-4, Study GZGD01907 [to], reference data; 5.3.3.4-5, Study GZGD02407 [to], reference data; 5.3.3.4-6, Study GZGD03610 [August to November 2011], reference data; 5.3.3.4-7: Study GZGD04112 [to], reference data)

The results of the other drug interaction studies are shown in Table 14.

Table 14. Results of drug interaction studies

Study no.	Dosage of eliglustat	Co-administered drug and dose	Analyte in plasma (number of subjects: monotherapy/co-administration)	Comparison of plasma pharmacokinetic parameters (co-administration/monotherapy)	
				C_{max}	AUC[g)]
GZGD 01907[h)]	100 mg QD	Antacid[c)] (aluminum hydroxide 1600 mg, magnesium hydroxide 1600 mg, simethicone 160 mg)	Unchanged eliglustat (24/23)	1.15 [0.99, 1.32]	1.14 [0.99, 1.30]
		Antacid[c)] (calcium carbonate 1000 mg)	Unchanged eliglustat (24/21)	1.12 [0.96, 1.30]	1.09 [0.94, 1.26]
		Pantoprazole [c)] 40 mg	Unchanged eliglustat (24/21)	1.08 [0.91, 1.27]	1.09 [0.92, 1.28]
GZGD 02407[i)]	100 mg QD[a)]	Rifampicin[d)] 600 mg i.v.	Unchanged eliglustat (6/6)	0.97 [0.86, 1.10]	0.95 [0.88, 1.03]
	150 mg QD[b)]		Unchanged eliglustat (19/19)	1.19 [0.98, 1.44]	1.19 [0.98, 1.45]
	100 mg BID[a)]	Rifampicin[d)] 600 mg p.o.	Unchanged eliglustat (6/5)	0.05 [0.04, 0.06]	0.04 [0.03, 0.05]
	150 mg BID[b)]		Unchanged eliglustat (19/16)	0.16 [0.11, 0.22]	0.15 [0.11, 0.21]
GZGD 03610[j)]	100 mg BID[a)]	Digoxin[e)] 0.25 mg	Unchanged digoxin (28/27)	1.70 [1.56, 1.84]	1.49 [1.33, 1.66]
	150 mg BID[b)]				
GZGD 04112[k)]	150 mg BID	Metoprolol tartrate[f)] 50 mg	Unchanged metoprolol (14/14)	1.53 [1.31, 1.79]	2.08 [1.82, 2.38]
GZGD 02707[l)]	100 mg BID	Oral contraceptive (ethinylestradiol 0.035 mg, norethindrone 1.0 mg)	Unchanged ethinylestradiol (29/29)	1.04 [1.00, 1.08]	1.02 [0.99, 1.06]
			Unchanged norethindrone (29/29)	1.03 [0.96, 1.11]	0.99 [0.96, 1.03]

Geometric mean ratio with 90% confidence interval for plasma pharmacokinetic parameters of unchanged eliglustat or co-administered drug (administered in combination/administered alone)
QD, once daily; BID, twice daily
a) Phenotype, PM. b) Phenotype; EM, IM, URM. c) Drug not approved in Japan
d) Inducer of CYP and transporters including CYP3A and P-gp. e) P-gp substrate. f) CYP2D6 substrate.
g) $AUC_{0-\infty}$, Studies GZGD01907, GZGD02407 (i.v.), GZGD04112; AUC_{0-last}, Study GZGD03610; AUC_{0-12h}, Studies GZGD02407 (p.o.); AUC_{0-24h}, Study GZGD02707
h) CYP2D6 phenotype, 22 EMs and 2 IMs. i) CYP2D6 phenotype; 12 EMs, 2 IMs, 6 PMs, and 5 URMs
j) CYP2D6 phenotype; 19 EMs, 1 IM, 4 PMs, and 4 URMs, k) CYP2D6 phenotype; 8 EMs, 5 IMs, and 1 URM
l) CYP2D6 phenotype; 24 EMs, 3 PMs, and 2 URMs

75 Abdominal pain, headache

76 Dyspepsia, abdominal pain, abdominal pain lower, nausea, sensation of foreign body, feeling hot, headache, pharyngolaryngeal pain

77 Dyspepsia, abdominal pain, abdominal pain upper, dry mouth, nausea, sensation of foreign body, headache, dizziness

4.(ii).A.(5) Pharmacodynamics

QT/QTc study (5.3.4.1-1: Study GZGD01707 [to])

A randomized, double-blind, 4-period, crossover study was conducted to evaluate the effects of a single dose of eliglustat on QT/QTc intervals in healthy non-Japanese men and women (target sample size, 48).

The subjects received a single oral dose of placebo, 200 or 800 mg eliglustat, or 400 mg moxifloxacin (positive control) under fasted conditions. A washout period of 5 to 7 days was between the period s.

All 47 treated subjects (32 EMs, 13 IMs, and 2 PMs) were included in the pharmacodynamics and safety analysis populations. Forty-five subjects were included in the pharmacokinetic analysis population. Excluded were 2 subjects who used a prohibited concomitant drug (antimicrobial agent) after developing adverse events (urinary tract infection and prostatitis) following placebo treatment.

Pharmacokinetic evaluation showed that C_{max} (mean ± standard deviation) of unchanged eliglustat in plasma following a single oral dose of 200 and 800 mg eliglustat was 26.5 ± 30.3 ng/mL and 299 ± 184 ng/mL, respectively, $AUC_{0\text{-last}}$ (mean ± standard deviation) was 247 ± 404 and 2464 ± 1822 ng·h/mL, respectively, and median t_{max} (minimum, maximum) was 2.60 (0.60, 4.60) and 3.60 (0.60, 5.10) hours, respectively.

In electrocardiography, the adjusted mean with 2-sided 90% confidence interval of the difference in the change from baseline in the $QTcF^{27}$ interval (ΔΔQTcF) between eliglustat and placebo reached a maximum of 0.7 [-2.0, 3.5] ms at 10 hours after administration of 200 mg eliglustat and 6.5 [3.6, 9.3] ms at 7 hours after administration of 800 mg eliglustat. The upper bound of the confidence interval was below 10 ms at both doses. The adjusted mean and 2-sided 90% confidence interval of ΔΔQTcF for moxifloxacin, however, reached a maximum of 12.1 [8.1, 16.1] ms at 4 hours postdose, and the lower bound of the confidence interval exceeded 5 ms from 1.5 to 6 hours postdose.

Safety evaluation revealed adverse events in 5 of 45 subjects following placebo administration, 4 of 44 subjects following administration of 200 mg eliglustat, 8 of 45 subjects following administration of 800 mg eliglustat, and 7 of 42 subjects following moxifloxacin administration. Of these adverse events, adverse drug reactions occurred in 1 of 45 subjects following placebo administration (musculoskeletal pain), 3 of 44 subjects following administration of 200 mg eliglustat (nausea, vomiting, feeling hot, dizziness, headache), 8 of 45 subjects following administration of 800 mg eliglustat (vision blurred, abdominal pain, abdominal pain lower, constipation, nausea, vomiting, myalgia, dizziness, hypoaesthesia), and 6 of 42 subjects following moxifloxacin administration (nausea, vomiting, hunger, dizziness, hypoaesthesia, throat irritation). No death, serious adverse event, or adverse event leading to treatment discontinuation was reported.

4.(ii).A.(6) Other investigations

Population pharmacokinetic analysis (5.3.3.5-1)

With plasma concentration data of unchanged eliglustat obtained at 14,073 time points from 516 subjects in 13 clinical studies,[78] population pharmacokinetics (PPK) analysis was conducted with a non-linear mixed effects model (software: NONMEM [version 7.2.0]) using a 2-compartment model with a stepwise, zero- and first-order absorption process as the basic model. The PPK analysis population included 516 subjects (305 men and 211 women) with the mean age (minimum-maximum) of 30.6 (18-71) years and the mean weight of 72.4 (40.7-136) kg. Subjects' CYP2D6 phenotypes were classified into 20 PMs, 76 IMs, 46 IMs/EMs,[79] 221 EMs, 50 EMs/URMs [79], 14 URMs, and 89 unknown types. The following potential covariates were examined in a stepwise manner: age, sex, body weight, body surface area, lean body mass, race, subject type (healthy adult or patient), CYP2D6 phenotype, meal type (fasting, normal meals, high-fat meals), concomitant drugs (oral contraceptive, paroxetine, ketoconazole, rifampicin, antacid/proton pump inhibitor), eliglustat dose, repeated dosing status, renal function (creatinine clearance), and hepatic function (bilirubin, albumin, ALT, aspartate aminotransferase [AST], alkaline phosphatase).

According to the results of above examination, the following parameters were incorporated into the final model as covariates: CYP2D6 phenotype, repeated dosing, eliglustat dose (800 mg, exceeding the recommended dose), and concomitant drugs (paroxetine, ketoconazole, rifampicin) as covariates for absolute bioavailability (F); CYP2D6 phenotype and eliglustat dose (800 mg dose exceeding the recommended dose) as covariates for the zero-order absorption process; subject type (healthy adult or patient) and body weight as covariates for central compartment volume of distribution; and concomitant drug (paroxetine), CYP2D6 phenotype (PM), and subject type (healthy adult or patient) as covariates for clearance (CL). Evaluation of the covariates obtained with the final model indicated that CYP2D6 phenotype was the major intrinsic factor affecting variability, and F of eliglustat was estimated to be 0.0417 in CYP2D6 EMs and to be approximately 20-fold higher in PMs than in EMs. The CL estimate in PMs was calculated to be slightly lower (0.703-fold) than those in patients with other CYP2D6 phenotypes. F of eliglustat in URMs was estimated to be approximately half that in EMs.

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

4.(ii).B.(1) Pharmacokinetics and drug interactions by CYP2D6 phenotype

4.(ii).B.(1).1) Pharmacokinetics by CYP2D6 phenotype

The applicant explained as follows:

Eliglustat is metabolized mainly by CYP2D6 and partially by CYP3A. PPK analysis indicates that CYP2D6 phenotype is the most important determinant of pharmacokinetics. The pharmacokinetics of eliglustat in patients with Gaucher disease type 1 was estimated using pharmacokinetic data classified according to CYP2D6 phenotype obtained with the final model. With twice daily (BID) repeated dosing of 100 mg, C_{max} and $AUC_{0\text{-}12h}$ were approximately 9.3-fold and 11.2-fold higher in PMs than in EMs, respectively, and

[78] Phase I studies (Studies GZGD00103, GZGD00204, GZGD02107, GZGD01807, GZGD02007, GZGD02407, GZGD01907, GZGD00404, GZGD01707, and GZGD02707), phase II study (Study GZGD00304), and phase III studies (Studies GZGD03109 and GZGD02607)

[79] May be classified as EM depending on the analytical procedure.

approximately 2.7-fold and 2.8-fold higher in IMs than in EMs, respectively. C_{max} and $AUC_{0\text{-}12h}$ in URMs were approximately 47% of those in EMs. Half-life values were similar among IMs, EMs, and URMs and approximately 1.2-fold greater in PMs than in the other phenotypes (Table 15).

Table 15. Pharmacokinetic parameters by CYP2D6 phenotype as estimated with the final model

Dosage of eliglustat	CYP2D6 phenotype	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	$t_{1/2}$ (h)
50 mg BID	PM	149 ± 40.5	1170 ± 357	10.1 ± 2.39
	IM	43 ± 27.5	282 ± 187	7.86 ± 1.41
	EM	16.7 ± 14.7	110 ± 99.0	8.06 ± 1.66
	URM	7.27 ± 7.41	46.4 ± 46.5	7.91 ± 1.48
100 mg BID	PM	294 ± 79.5	2300 ± 673	9.94 ± 2.15
	IM	86.5 ± 55.8	576 ± 382	8.05 ± 1.60
	EM	31.6 ± 27.6	206 ± 182	7.98 ± 1.47
	URM	14.9 ± 15.7	97.8 ± 107	7.97 ± 1.58
150 mg BID	PM	448 ± 127	3510 ± 1110	9.97 ± 2.24
	IM	133 ± 87.4	887 ± 597	8.00 ± 1.49
	EM	47.5 ± 41.6	311 ± 280	8.01 ± 1.57
	URM	22.6 ± 24.3	146 ± 161	8.01 ± 1.50

Mean ± standard deviation
C_{max}, maximum concentration in plasma; $AUC_{0\text{-}12h}$, area under the plasma concentration-time curve to 12 hours postdose; $t_{1/2}$, elimination half-life;
PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; URM, ultra-rapid metabolizer.

4.(ii).B.(1).2) Ethnic differences in pharmacokinetics

The applicant provided the following discussion about the similarity of the pharmacokinetics of eliglustat in Japanese and non-Japanese patients:

The evaluation was based on the data of Japanese and non-Japanese subjects obtained in a global phase III study (Study EDGE) that included Japanese patients with Gaucher disease type 1. As shown in Table 11, C_{max} and $AUC_{0\text{-}12h}$ (mean ± standard deviation) in the EM subjects at Week 13 of eliglustat treatment were 66.2 ± 55.1 ng/mL and 310 ± 258 ng·h/mL, respectively, in Japanese subjects at 150 mg BID (4 subjects) and 55.9 ± 27.2 ng/mL and 265 ± 150 ng·h/mL, respectively, in non-Japanese subjects at this dosage (5 subjects). C_{max} of 140 ng/mL and $AUC_{0\text{-}12h}$ of 659 ng·h/mL in one Japanese subject at 150 mg BID indicated high exposure, but investigation of subject background and other characteristics revealed no factors that influenced exposure. The trough levels for this subject were within the range of trough levels of the other Japanese subjects, and the exposure at Week 13 in this subject was thought to be within the range of individual variability. Although only one Japanese subject in Study EDGE received 100 mg BID, and data from only small number of subjects at 150 mg BID were available as shown above, thus allowing a comparison to a limited extent, pharmacokinetics in the Japanese and non-Japanese data did not differ substantially.

4.(ii).B.(1).3) Drug-drug interactions

The applicant explained as follows:

In vitro studies indicated that eliglustat is metabolized primarily by CYP2D6 and, to a lesser extent, by CYP3A4 [see "4.(ii).A.(1) Studies using human biomaterials"]. In a clinical study, eliglustat was administered at 100 mg BID with paroxetine, a strong CYP2D6 inhibitor, at 30 mg for 10 days or ketoconazole, a strong CYP3A inhibitor, at 400 mg for 7 days to healthy adults with non-PM phenotypes. As a result, C_{max} of unchanged eliglustat in plasma upon coadministration with paroxetine and ketoconazole was 7.31-fold and 3.84-fold higher, respectively, and $AUC_{0\text{-}12h}$ was 8.93-fold and 4.27-fold higher, respectively, than those when

eliglustat was administered alone, indicating substantially higher exposure in agreement with the *in vitro* study findings [see "4.(ii).A.(4) Drug-drug interactions"]. In the paroxetine coadministration study, the incidences of adverse events following administration of eliglustat with and without paroxetine were 91.4% (32 of 35 subjects) and 41.7% (15 of 36 subjects), respectively. In the ketoconazole co-administration study, the incidences of adverse events following administration of eliglustat with and without ketoconazole were 48.5% (16 of 33 subjects) and 32.4% (11 of 34 subjects), respectively. Adverse event incidences were higher following co-administration. The applicant decided to include precautionary statement about co-administration with a strong CYP2D6 inhibitor or a strong CYP3A inhibitor in the Precautions for coadministration section of the package insert.

Simulations were performed with physiologically-based pharmacokinetics (PBPK) modeling using SimCyp on drug-drug interactions associated with eliglustat co-administered with a moderate or strong CYP2D6 inhibitor (terbinafine, paroxetine) or a moderate or strong CYP3A inhibitor (fluconazole, ketoconazole) alone or with combinations of multiple drugs. Plasma concentration-time profiles were simulated to characterize exposure ratios in the presence and absence of concomitant drugs (following co-administration/administration of eliglustat alone). Estimated C_{max} and AUC values of unchanged eliglustat in plasma are shown in Table 16.

Table 16 Simulation results of drug-drug interactions

CYP2D6 phenotype	Dosage of eliglustat	Co-administered drug and dose	Comparison of plasma pharmacokinetic parameters (co-administration/monotherapy	
			C_{max}	$AUC_{0\text{-}12\ h}$
EM	100 mg BID	Terbinafine 250 mg (moderate CYP2D6 inhibitor)	3.30 (2.15, 3.82)	3.85 (2.26, 4.95)
EM	100 mg BID	Fluconazole 400 mg[a)] + 200 mg (moderate CYP3A inhibitor)	2.40 (2.20, 2.68)	2.75 (2.46, 3.01)
EM	100 mg BID	Terbinafine 250 mg + fluconazole (400 mg[a)] + 200 mg) (moderate CYP2D6 inhibitor + moderate CYP3A inhibitor)	8.85 (6.27, 10.4)	11.7 (7.22, 15.7)
EM/URM	100 mg BID	Paroxetine 30 mg + ketoconazole 400 mg (strong CYP2D6 inhibitor + strong CYP3A inhibitor)	17.1 (14.5, 21.4)	24.5 (20.6, 32.3)

Ratio (co-administration/monotherapy) of pharmacokinetic parameters (minimum, maximum) of unchanged eliglustat or co-administered drug
Software, SimCYP (EM, EMs and IMs cannot be distinguished in SimCYP. The proportions for EM/URM were assumed to be 91.7% and 8.3%)
Degree of inhibition is based on categories in the US Food and Drug Administration's draft guidance, "Drug Interaction Studies."
a) Loading dose

Based on the observed exposure to unchanged eliglustat in plasma in these studies, the applicant decided to contraindicate co-administration of eliglustat simultaneously with a moderate or strong CYP2D6 inhibitor and a moderate or strong CYP3A inhibitor and to list co-administration of eliglustat with a moderate CYP2D6 inhibitor or a moderate CYP3A inhibitor in the Precautions for Coadministration section of the package insert.

C_{max} and $AUC_{0\text{-}12h}$ of unchanged eliglustat in plasma were markedly reduced to 0.16-fold and 0.15-fold, respectively, in a study in which healthy subjects with non-PM phenotypes received eliglustat at 150 mg BID with 600 mg of rifampicin (p.o.), a strong inducer of CYP3A, 2B6, 2C8, 2C9, 2C19, UGT1A1, GST-A, and P-gp. Also in healthy subjects with PM phenotypes who received eliglustat at 100 mg BID with 600 mg of rifampicin (p.o.), C_{max} and $AUC_{0\text{-}12h}$ of unchanged eliglustat in plasma were markedly reduced to 0.05-fold and 0.04-fold, respectively. These decreases in exposure were attributed to induction by rifampicin of CYP3A overexpression in the intestines and liver with consequent enhancement of first-pass metabolism. The effects

of rifampicin are thought to have been stronger in the healthy subjects with PM phenotype, and the contribution of CYP3A to eliglustat metabolism is thought to have been greater in the PMs. The applicant decided to include precautionary statement about co-administration with a strong CYP3A inducer in the precautions for co-administration section of the package insert because co-administration with a strong CYP3A inducer may reduce the efficacy of eliglustat.

PMDA considers as follows:
PMDA finds acceptable the applicant's statement about the data on pharmacokinetics of eliglustat in and out of Japan that there are no major differences although comparisons were done with limited data for Japanese subjects. The target population for eliglustat will be further discussed in the following section in terms of efficacy and safety [see "4.(iii).B.(5) Dosage and administration"].

The applicant must urge careful administration by issuing appropriate statements cautioning about co-administration because eliglustat is metabolized primarily by CYP2D6 and CYP3A4, inhibitors of which could increase exposure when co-administered with eliglustat. The applicant must collect information on safety and efficacy in association with co-administration with drugs that could have drug interactions with eliglustat (e.g., CYP2D6 inhibitors and CYP3A inhibitors) through post-marketing surveillance. PMDA will provide a final decision on this matter after taking account of comments raised in the Expert Discussion.

4.(ii).B.(2) QT/QTc prolongation and proarrhythmic risk
The applicant explained as follows:
The adjusted mean ΔΔQTcF following a single dose of the high dose (800 mg) in a study to evaluate QT/QTc in healthy non-Japanese men and women was 6.5 ms, and the upper bound of the one-sided 95% confidence interval was 9.3 ms, which constitute a negative result according to "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (PFSB/ELD Notification No. 1023-1, dated October 23, 2009; ICH E14 guidelines). However, drug concentration-response modeling in the thorough QT/QTc study revealed that the plasma concentrations of unchanged eliglustat were positively correlated with placebo-adjusted mean changes from baseline in QTcF, PR, and QRS intervals. (The mean slopes of the QTcF interval, PR interval, and QRS interval with 90% confidence intervals were 0.025 [0.0220, 0.0284], 0.036 [0.0334, 0.0387], and 0.012 [0.0112, 0.0134] ms·mL/ng, respectively).

Placebo-adjusted predicted changes from baseline in electrocardiographic parameters for various plasma concentrations of unchanged eliglustat as predicted by drug concentration-response modeling are shown in Table 17.

Table 17. Placebo-adjusted predicted changes from baseline in electrocardiographic parameters for various plasma concentrations of unchanged eliglustat (drug concentration-response model, thorough QT/QTc study)

Concentration of unchanged eliglustat in plasma (ng/mL)	ΔΔQTcF	ΔΔPR	ΔΔQRS
50	1.0 ± 0.81 (2.3)	2.5 ± 0.71 (3.7)	0.7 ± 0.43 (1.4)
100	2.3 ± 0.81 (3.6)	4.3 ± 0.71 (5.5)	1.3 ± 0.43 (2.0)
150	3.5 ± 0.82 (4.9)	6.1 ± 0.72 (7.3)	1.9 ±0.43 (2.6)
200	4.8 ±0.84 (6.2)	7.9 ±0.73 (9.2)	2.5 ±0.44 (3.2)
250	6.1 ± 0.87 (7.5)	9.8 ± 0.76 (11.0)	3.1 ± 0.44 (3.9)
300	7.3 ± 0.91 (8.8)	11.6 ± 0.79 (12.9)	3.8 ± 0.45 (4.5)
350	8.6 ± 0.95 (10.1)	13.4 ± 0.83 (14.7)	4.4 ± 0.46 (5.1)
400	9.8 ± 1.01 (11.5)	15.2 ± 0.87 (16.6)	5.0 ± 0.48 (5.8)
450	11.1 ± 1.07 (12.8)	17.0 ± 0.92 (18.5)	5.6 ± 0.49 (6.4)
500	12.3 ± 1.13 (14.2)	18.8 ± 0.97 (20.4)	6.2 ± 0.51 (7.1)
550	13.6 ± 1.20 (15.6)	20.6 ± 1.03 (22.3)	6.8 ± 0.53 (7.7)
600	14.9 ± 1.27 (17.0)	22.4 ± 1.09 (24.2)	7.4 ± 0.55 (8.4)

Mean effect ± standard error (upper bound of one-sided 95% confidence interval)

Certain drug interactions could increase exposure to eliglustat because eliglustat is extensively metabolized by CYP2D6 and partially by CYP3A, and QTcF, PR, and QRS interval prolongation could occur under conditions in which marked drug interactions occur.

With regard to plasma concentrations of unchanged eliglustat observed in the clinical studies, the mean C_{max} (minimum, maximum) at steady state (ng/mL) in the phase II and III studies was 62.6 [40.1, 136] in PMs (n = 8), 32.1 [13.1, 67.2] in IMs (n = 17), and 23.2 [2.13, 62.8] in EMs (n = 21) at 50 mg BID; 45.6 [22.5, 108] in IMs (n = 11), 27.0 [3.23, 111] in EMs (n = 172), and 11.6 [5.24, 21.5] in URMs (n = 4) at 100 mg BID; and 2.94 in an IM (n = 1), 42.1 [5.95, 169] in EMs (n = 50), and 16.6 [5.43, 27.6] in URMs (n = 4) at 150 mg BID. Maximum C_{max} at steady state in the phase II and III studies was 111 ng/mL in CYP2D6 IMs and EMs at the recommended dose of 100 mg BID and 169 ng/mL[80] in all CYP2D6 phenotypes at 50, 100, and 150 mg BID, which was lower than the mean C_{max} (minimum-maximum) at 800 mg in the QT/QTc study of 299 (27.0-761) ng/mL.

Regarding exposure under conditions with drug interactions, except when eliglustat was co-administered with strong CYP2D6 and CYP3A inhibitors, a mean C_{max} was estimated to be 200 ng/mL at 100 mg BID in CYP2D6 IMs and EMs. This was lower than C_{max} following a single dose of the high dose of 800 mg in the QT/QTc study, for which the result was negative.

PMDA asked the applicant to discuss, in the context of CYP2D6 EMs and IMs, exposure following co-administration of 100 mg BID of eliglustat with a CYP2D6 inhibitor and/or CYP3A inhibitor, exposure

[80] The data of 1 patient reaching a concentration of 261 ng/mL due to accidental overdose were excluded from the combined data of the phase II studies (to Week 52), Study ENGAGE (to Week 39), Study ENCORE (to Week 52), and Study EDGE (to Week 13).

following once daily (QD) administration of 100 mg of eliglustat under these conditions of co-administration, and the appropriateness of administration in this population.

The applicant responded as follows:

A PBPK-based simulation[81] was conducted to predict C_{max} of unchanged eliglustat in plasma at steady state in IMs and EMs taking eliglustat with a CYP2D6 inhibitor and/or CYP3A inhibitor, and the results are shown in Table 18.

Table. 18 Predicted C_{max} of unchanged eliglustat in plasma following co-administration with CYP inhibitors in IMs and EMs

	IM			EM		
	100 mg BID	100 mg BID	100 mg QD	100 mg BID	100 mg BID	100 mg QD
	Eliglustat alone	With CYP inhibitor	With CYP inhibitor	Eliglustat alone	With CYP inhibitor	With CYP inhibitor
With a strong CYP2D6 inhibitor and a strong CYP3A inhibitor	62.7 [14.1, 174]	470 [197, 892]	313 [164, 500]	24.6 [4.83, 76.9]	412 [182, 781]	281 [147, 468]
With a strong CYP2D6 inhibitor and a moderate CYP3A inhibitor	59.5 [13.4, 149]	288 [87.2, 616]	189 [66.4, 384]	28.3 [5.20, 91.5]	260 [83.5, 530]	175 [60.5, 348]
With a moderate CYP2D6 inhibitor and a strong CYP3A inhibitor	59.7 [14.0, 150]	467 [187, 929]	314 [160, 551]	28.4 [5.53, 88.4]	447 [185, 910]	300 [155, 531]
With a moderate CYP2D6 inhibitor and a moderate CYP3A inhibitor	59.5 [13.5, 149]	261 [77.7, 577]	172 [59.2, 353]	28.4 [5.20, 91.5]	251 [75.7, 541]	165 [57.0, 333]
With a strong CYP2D6 inhibitor alone	62.8 [14.2, 174]	133 [29.9, 343]	94.9 [24.8, 223]	24.7 [4.64, 76.9]	124 [28.9, 319]	90.1 [23.7, 205]
With a moderate CYP2D6 inhibitor alone	59.8 [14.0, 150]	97.2 [21.1, 223]	70.5 [16.8, 153]	28.5 [5.57, 88.4]	93.9 [20.4, 218]	68.5 [16.4, 148]
With a strong CYP3A inhibitor alone	62.9 [13.7, 176]	274 [46.6, 615]	147 [27.2, 342]	24.6 [5.01, 79.9]	98.9 [8.07, 353]	38.1 [5.90, 126]
With a moderate CYP3A inhibitor alone	59.8 [14.0, 150]	159 [34.7, 352]	88.0 [21.9, 202]	28.5 [5.57, 88.4]	68.5 [8.20, 211]	31.4 [6.05, 109]

Unit, ng/mL; geometric mean [90% confidence interval]

Paroxetine as a strong CYP2D6 inhibitor, ketoconazole as a strong CYP3A inhibitor, terbinafine as a moderate CYP2D6 inhibitor, and fluconazole as a moderate CYP3A inhibitor were simulated. (Degree of inhibition is based on categories in the US Food and Drug Administration's draft guidance, "Drug Interaction Studies.")

C_{max} (geometric mean) following dose of 800 mg eliglustat, which had a negative result in the thorough QT/QTc study, was 237 ng/mL.

Overlap of metabolic activity has been reported in IMs and EMs,[82] and the range of exposure in IMs and EMs in the phase II and III studies indeed overlapped. Thus, combining IM and EM patients into a single population, the applicant used PPK modeling to predict C_{max} at steady state following administration at 100 mg BID in IM/EM patients.[83] Predicted C_{max} (mean ± standard deviation) was 36.0 ± 35.1 ng/mL, which is in the

81 Virtual trials were conducted for each PBPK model simulation. (Degree of inhibition is based on categories in the US Food and Drug Administration's draft guidance, "Drug Interaction Studies.") For co-administration with ketoconazole (a strong CYP3A inhibitor) or paroxetine (a strong CYP2D6 inhibitor), a simulation was conducted in which 36 subjects (50% women) aged 18 to 45 years received eliglustat (100 mg BID or 100 mg QD) alone (Days 1 to 8) and with paroxetine (30 mg QD) or ketoconazole (400 mg QD) co-administered (Days 9 to 18). For concomitant drugs not studied in the clinical studies (simulations of fluconazole [a moderate CYP3A inhibitor], terbinafine [a moderate CYP2D6 inhibitor], and fluvoxamine [a weak CYP3A inhibitor]), 10 subjects (50% women) aged 18 to 40 years received eliglustat (100 mg BID or 100 mg QD) alone (Period 1: Days 1 to 18) and with fluconazole (Day 8 or 9 [when terbinafine was co-administered] at 400 mg QD and Days 9 or 10 to 18 at 200 mg QD), terbinafine (Days 9 to 18 at 250 mg QD), or fluvoxamine (Days 9 to 18 at 300 mg QD) (Period 2: Days 9 to 18). The demographic characteristics of the simulation populations were matched with those of the subjects actually enrolled in the studies when necessary. PBPK model simulations were conducted with the SimCyp Population Based Simulator V11.1 (SimCyp Ltd, part of Certera, Sheffield, UK) for CYP2D6 PMs receiving eliglustat at 100 mg BID or 100 mg QD.

82 Chou WH, et al., *Clin Chem*, 2003; 49: 542-51

83 A simulation of exposure to unchanged eliglustat in patients with Gaucher disease type 1 was performed with a final PPK model incorporating phenotype distribution and numbers of patients in the general population (Hicks JK, et al., *Clin Pharmacol Ther*, 2013; 93(5):402-8). The simulation was conducted at 50 mg BID for CYP2D6 PMs, 100 mg BID for IMs, 100 mg BID for EMs, and 150 mg BID for URMs. A simulation was also conducted at 50 mg BID in 1 IM patient and 150 mg BID in 1 EM patient. With the data of these simulations factoring in inter-subject variability, individual exposure (C_{max} and $AUC_{0\text{-}12h}$) at steady state were calculated, and data were tabulated for the overall population.

acceptable range for effects on electrocardiographic parameters in light of values shown in Table 17. The predicted C_{max} with PBPK modeling in IM/EM patients taking eliglustat 100 mg BID with a strong CYP3A inhibitor and a strong CYP2D6 inhibitor under P-gp inhibition was 406 ng/mL (range, 362-459 ng/mL), which is in a range predicted to cause mild to moderate increases in ECG intervals according to the data in Table 17.

In conclusion, patient safety can be assured by contraindicating eliglustat in patients on a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor.

PMDA asked the applicant to discuss exposure following co-administration of 100 mg BID or 100 mg QD of eliglustat with a CYP3A inhibitor in PMs and the appropriateness of administration in this population.

The applicant responded as follows:
A PBPK-based simulation was conducted to predict C_{max} of unchanged eliglustat in plasma at steady state in PMs receiving eliglustat with a CYP3A inhibitor, and the results are shown in Table 19.

Table 19. Predicted Cmax of the unchanged eliglustat in plasma following co-administration with CYP inhibitors in PMs

	PM (100 mg BID)		PM (100 mg QD)	
	Eliglustat alone	With a CYP inhibitor	Eliglustat alone	With a CYP inhibitor
With a strong CYP3A inhibitor alone	105 [25.7, 273]	478 [201, 914]	75.2 [22.0, 180]	321 [168, 546]
With a moderate CYP3A inhibitor alone	98.8 [21.4, 229]	272 [73.7, 628]	71.5 [17.0, 157]	179 [56.8, 365]
With a weak CYP3A inhibitor alone	-	-	72.3 [18.4, 174]	81.7 [25.2, 198]

Unit, ng/mL; geometric mean [90% confidence interval]; -, not calculated
Ketoconazole as a strong CYP3A inhibitor, fluconazole as a moderate CYP3A inhibitor, and fluvoxamine as a weak CYP3A inhibitor were simulated.
C_{max} (geometric mean) following dose of 800 mg eliglustat, which had a negative result in the QT/QTc study, was 237 ng/mL.

Since few PM patients were treated in the clinical studies, only 20 PMs (9 patients with Gaucher disease type 1 and 11 healthy subjects) were included in the PPK modeling. Moreover, no PMs have continued to receive treatment at a dose exceeding 50 mg BID in the clinical studies. Thus, exposure predictions in this population must be carefully interpreted because of the small amount of data in PMs and the large variability among subjects while exposure can be predicted in PMs. In addition, the range of exposure in PMs cannot be accurately predicted in the post-marketing phase, in which patients may take eliglustat more frequently with other medications including over-the-counter drugs and take eliglustat with grapefruit-containing beverages, which inhibit CYP3A. The risk of exposure far exceeding the range found clinically safe and effective must therefore be considered.

It is therefore appropriate to exclude PMs from the population eligible for treatment.

PMDA considers as follows:
Although QTcF interval prolongation at the high dose in the QT/QTc study was negative according to the ICH E14 guidelines, changes from baseline in QTcF, PR, and QRS intervals determined with drug concentration-response modeling showed a positive correlation. Since eliglustat is metabolized primarily by CYP2D6 and CYP3A, the risk cannot be ruled out that arrhythmias and conduction block may occur due to QTcF, PR, and

QRS interval prolongation in excess of the thresholds in the ICH E14 guidelines when interactions cause eliglustat exposure higher than that associated with the high dose in the QT/QTc study. Although the data were inferred based on modelling, they indicate that the degrees of QTcF, PR, and QRS interval prolongation could differ individually according to the degree of drug interactions associated with co-administration. From the standpoint of proarrhythmic risk associated with QTcF interval prolongation, it is appropriate to maintain eliglustat exposure in plasma to a level expected to produce QTcF interval prolongation below the threshold specified in the ICH E14 guidelines.

The applicant states, with regard to CYP2D6 phenotypes, that safety can be ensured by excluding PMs from the population eligible for treatment due to concerns about QTcF, PR, and QRS interval prolongation associated with CYP3A inhibitor co-administration and by contraindicating eliglustat in EMs and IMs on a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor. But in the absence of drug interactions, the range of exposure in PMs at 100 mg QD is comparable to the range in IMs at 100 mg BID. Moreover, the range of exposure at 100 mg BID in an IM taking a strong CYP3A inhibitor would be comparable to the range under conditions for which the applicant proposes contraindication (i.e., co-administration with a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor). As exposure is expected to increase in the co-administration regimens above, the applicant must provide precise information on whether or not each type of concomitant drugs can be used. It is considered necessary to provide precautions and select appropriate dosage in accordance with the population for treatment and the degree of drug interactions involved. PMDA will decide on this matter taking account of comments from the Expert Discussion [see “4.(iii).B.(3).1) Proarrhythmic risk” for proarrhythmic risk and “4.(iii).B.(5) Dosage and administration” for more information on dosage].

4.(iii) Summary of clinical efficacy and safety

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

The results from the global phase III study in Japanese and non-Japanese patients with Gaucher disease (Study GZGD03109) and foreign studies in non-Japanese patients with Gaucher disease (Studies GZGD00304, GZGD02507, and GZGD02607) were submitted as the evaluation data. The main results from the studies are described below.

4.(iii).A.(1) Global phase III study in Japanese and non-Japanese patients with Gaucher disease (5.3.5.1-3: Study GZGD03109 [EDGE] [June 2010 to [redacted] data cutoff])

An open-label study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in Japanese and non-Japanese[84] patients with Gaucher disease type 1[85] (target sample size, 170)[86] [for more information on pharmacokinetics, see "4.(ii).A.(3).2) Global phase III study in Japanese and non-Japanese patients with Gaucher disease"].

Oral dose of eliglustat 50 mg BID was administered at Weeks 0 to 4 (or, in Japanese patients, 50 mg QD on Day 1 and 50 mg BID from Day 2 to Week 4). The dosage at Weeks 4 to 8 was adjusted as shown in Table 20 according to the plasma concentration of unchanged eliglustat at Week 2, and the dosage from Week 8 onward was adjusted according to the concentration at Week 6[87] (treatment period, 6 to 18 months). For patients with their dose reduced to 50 mg QD or 50 mg once every other day (QOD) during the dose adjustment period, the dose could be adjusted to 50 mg BID by changing concomitant drugs or other conditions according to the criteria for the trough and peak concentrations of unchanged eliglustat (C_{trough} <5 ng/mL and C_{max} <50 ng/mL).

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84 Their nationalities are the United States of America, Canada, Brazil, Austria, the Netherlands, Greece, Croatia, Sweden, Serbia, France, Portugal, Romania, India, Russian Federation, Australia, and the People's Republic of China.

85 Main inclusion criteria: patients ≥18 years of age with a diagnosis of Gaucher disease type 1 confirmed by decreased glucocerebrosidase activity in white blood cells or cultured skin fibroblasts who meet all of the following conditions at screening with or without prior ERT
- hemoglobin level ≥9 g/dL,
- platelet count ≥70 × 10^3/μL,
- spleen volume ≤25 multiples of normal (MN),
- liver volume ≤2 MN

Main exclusion criteria: patients who meet one or more of the following conditions
- A CYP2D6 non-PM or an indeterminate metabolizer with one allele identified as active who has been chronically receiving both a strong inhibitor of CYP2D6 and a strong inhibitor of CYP3A for which no reasonable alternative medications exist.
- A CYP2D6 PM or an indeterminate metabolizer with neither allele known to be active who has been chronically receiving a strong inhibitor of CYP3A for which no reasonable alternative medications exist.
- Patients who have received miglustat within 6 months of study drug administration.

86 The study is planned as a double-blind, parallel-group, comparative study (with a 52-week primary analysis period) in which subjects remained stable and met the randomization criteria following the open-label lead-in period are randomized to the doses used in the double-blind period at QD dosing (the daily dose is the same as that used in the open-label lead-in period) or BID dosing (identical dosing to lead-in period), but the results shown are only for the lead-in period because the double-blind period is now underway. Compliance with the randomization criteria was evaluated at Weeks 26, 52, and 78 of the open-label lead-in period. Subjects not meeting the randomization criteria by Month 18 were to enter an open-label extended treatment period at the dose used in the open-label lead-in period. Subjects completing the double-blind primary analysis period were to enter a long-term treatment period.

The randomization criteria were as follows: (1) hemoglobin level ≥11 g/dL if female and ≥12 g/dL if male; (2) platelet count ≥100,000/μL; (3) spleen volume (spleen volume [MN] = spleen volume in cc/[weight in kg × 2]) measured by magnetic resonance imaging (MRI) ≤10 MN; (4) liver volume (liver volume [MN] = liver volume in cc/[weight in kg × 25]) measured by MRI ≤1.5 MN; (5) no more than 1 bone crisis and free of other clinically symptomatic bone disease; (6) on treatment at 50 mg BID or 100 mg BID for at least 4 months; and (7) peak concentration of unchanged eliglustat in plasma <50 ng/mL

87 Initially, dose escalation to 150 mg BID was allowed at Week 8, but the upper limit was changed to 100 mg BID in version 3 of the protocol. The dose for the subjects who were at 150 mg BID before the revision were reduced to 100 mg BID. As an exception, if subjects had been receiving 150 mg BID for at least 65 weeks since the start of study drug administration when the institutional review board/ethics committee approved the amended protocol, the subjects were allowed to continue at 150 mg BID. Subjects continuing at 150 mg BID were to continue in the open-label lead-in period to Month 18 and then enter the extended-treatment period at the same dosage. These subjects were not randomized to the double-blind primary assessment period.

Table 20. Dose adjustment procedures in the eliglustat group in open-label lead-in period (Study EDGE)

Timing	Adjustment criteria	Dosage
Weeks 4 to 8	C_{trough} <5 ng/mL and C_{max} <50 ng/mL at Week 2	100 mg BID (200 mg/day)
	C_{trough} ≥5 ng/mL and C_{max} <50 ng/mL at Week 2	50 mg BID (100 mg/day)
	C_{max} ≥50 ng/mL at Week 2, and the patient is a CYP2D6 non-PM or an indeterminate metabolizer with 1 allele identified as active	Investigate concomitant drug usage while administering eliglustat 50 mg BID. Continue 50 mg BID (100 mg/day) if C_{max} is <50 ng/mL at Week 6.
		Investigate concomitant drug usage while administering eliglustat 50 mg BID. Reduce the dosage to 50 mg QD (50 mg/day) if C_{max} is ≥50 ng/mL at Week 6 and if concomitant drug usage or other causative factors cannot be changed.
	C_{max} ≥50 ng/mL at Week 2, and the patient is a CYP2D6 PM or an indeterminate metabolizer with neither allele known to be active	Suspend eliglustat treatment and investigate concomitant drug. Maintain eliglustat dosage at 50 mg BID (100 mg/day) if concomitant drug usage or other causative factors can be changed.
		Suspend eliglustat treatment and investigate concomitant drug. Reduce the dosage to 50 mg QD (50 mg/day) if concomitant drug usage or other causative factors cannot be changed.
After Week 8	C_{trough} <5 ng/mL and C_{max} <50 ng/mL at Week 6	a) Maintain dosage (200 mg/day) if the patient is on 100 mg BID [a)] b) Increase dosage to 100 mg BID (200 mg/day) if the patient is on 50 mg BID c) Maintain dosage (50 mg/day) if the patient is on 50 mg QD unless concomitant drug usage are changed.
	C_{trough} ≥5 ng/mL and C_{max} <50 ng/mL at Week 6	Maintain dosage
	C_{max} ≥50 ng/mL at Week 6, and the patient is a CYP2D6 non-PM or an indeterminate metabolizer with 1 allele identified as active	Investigate concomitant drug usage while maintaining eliglustat dose. Maintain dosage if C_{max} is <50 ng/mL at Week 10.
		Investigate concomitant drug usage while maintaining eliglustat dose. Reduce the dose by 1 level as shown below if C_{max} is ≥50 ng/mL at Week 10 and if concomitant drug usage or other causative factor cannot be changed. a) Reduce dosage to 50 mg BID (100 mg/day) if the patient is on 100 mg BID b) Reduce dosage to 50 mg QD (50 mg/day) if the patient is on 50 mg BID c) Reduce dosage to 50 mg QOD (25 mg/day) if the patient is on 50 mg QD
	C_{max} ≥50 ng/mL at Week 6, and the patient is a CYP2D6 PM or an indeterminate metabolizer with neither allele known to be active	Suspend eliglustat treatment and investigate concomitant drug. Maintain dosage if concomitant drug usage or other causative factor can be changed.
		Suspend eliglustat treatment and investigate concomitant drug. Reduce the dosage by 1 level as shown below if concomitant drug usage or other causative factor cannot be changed. a) Reduce dosage to 50 mg BID (100 mg/day) if the patient is on 100 mg BID b) Reduce dosage to 50 mg QD (50 mg/day) if the patient is on 50 mg BID c) Reduce dosage to 50 mg QOD (25 mg/day) if the patient is on 50 mg QD

a) Before version 3, the protocol allowed dose adjustment up to 150 mg BID at Week 8, but in version 3 and thereafter, the dosage was allowed to be increased up to 100 mg BID. (See footnote 87.)

Treatment with eliglustat was temporarily suspended in patients with a peak plasma concentration of unchanged eliglustat of ≥150 ng/mL. These patients were allowed to resume treatment at a reduced dose or the dose used before suspension according to peak plasma concentrations of unchanged eliglustat, safety findings, and whether concomitant drug usage could be adjusted.

All 170 treated subjects (including 10 Japanese) were included in the safety analysis population and efficacy analysis population. The subjects who discontinued the study in the open-label lead-in period were as follows: 1 Japanese subject (for withdrawal of consent) and 11 non-Japanese subjects (2 for adverse events, 4 for withdrawal of consent, 1 due to protocol noncompliance, and 4 for other reasons). A total of 131 subjects (including 9 Japanese) completed the open-label lead-in period.[88]

Twenty subjects (including 2 Japanese) received 50 mg BID, 115 subjects (including 3 Japanese) received 100 mg BID, 7 subjects (including 4 Japanese) received 150 mg BID/100 mg BID, and 28 subjects (including 1 Japanese) received other dosages.

88 Twenty-seven subjects (including no Japanese subjects) remained in the open-label lead-in period, 115 subjects (including 8 Japanese) were randomized, and 16 subjects (including 1 Japanese) entered the open-label extension period.

Distribution of CYP2D6 phenotypes in the subjects were 4% (7 of 170 subjects) PMs, 14% (23 of 170 including 3 Japanese) IMs, 77% (131 of 170, 6 Japanese) EMs, 2% (3 of 170) URMs, and 4% (6 of 170, 1 Japanese) were unknown CYP2D6 metabolizer phenotypes.

The percentage of subjects who had reached the therapeutic goals in the treatment of Gaucher disease[89] in the open-label lead-in period, which was the primary endpoint, was 83.0% (137 of 165 subjects) overall and 100% (10 of 10 subjects) among the Japanese subjects (Table 21). Changes in the parameters studied were evaluated as major secondary endpoints and are shown in Table 22.

Table 21. Primary endpoint data (Study EDGE, open-label lead-in period)

Endpoint	Overall population				Japanese population			
	Week 26 (n = 165)	Week 52 (n = 60)	Week 78 (n = 21)	Overall study (n = 165)	Week 26 (n = 10)	Week 52 (n = 8)	Week 78 (n = 2)	Overall study (n = 10)
Achieving all the therapeutic goals below	78.2 (129)	73.3 (44)	47.6 (10)	83.0 (137)	80.0 (8)	100 (8)	100 (2)	100 (10)
Hemoglobin	92.7 (153)	90.0 (54)	85.7 (18)	93.9 (155)	90.0 (9)	100 (8)	100 (2)	100 (10)
Platelet count	86.7 (143)	83.3 (50)	76.2 (16)	91.5 (151)	80.0 (8)	100 (8)	100 (2)	100 (10)
Liver volume	93.3 (154)	93.3 (56)	81.0 (17)	94.5 (156)	90.0 (9)	100 (8)	100 (2)	100 (10)
Spleen volume	99.4 (164)	98.3 (59)	95.2 (20)	98.8 (163)	100 (10)	100 (8)	100 (2)	100 (10)
Bone crises	98.8 (163)	100 (60)	100(21)	100 (165)	90.0 (9)	100 (8)	100 (2)	100 (10)

Percentage (number of subjects)
Numbers of subjects observed to time point in question in the open-label lead-in period
Figures differ from the number of subjects in the efficacy analysis population because some patients entered the double-blind primary analysis period, discontinued the study, or were not observed to the respective evaluation point because of data cut-off.

89 Achievement of the therapeutic goals in the treatment of Gaucher disease in Study EDGE was evaluated based on the numbers of subjects achieving the individual criteria and all 5 criteria in terms of the following parameters. (1) Hemoglobin level ≥11 g/dL if female and ≥12 g/dL if male, (2) platelet count ≥100 × 10^3/μL, (3) liver volume ≤1.5 MN, (4) spleen volume ≤10 MN, and (5) no more than 1 bone crisis and no other clinically symptomatic bone diseases over the past 6 months.

Table 22. Major secondary endpoint data (Study EDGE, open-label lead-in period)

Endpoint		Overall population				Japanese population			
		Baseline	Week 26	Week 52	Week 78	Baseline	Week 26	Week 52	Week 78
Hemoglobin concentration[a] (g/dL)	Number of subjects	170	163	56	22	10	9	6	3
	Value at evaluation point	13.433 ± 1.560	13.443 ± 1.382	13.467 ± 1.465	13.127 ± 1.669	13.640 ±1.319	13.472 ±1.286	13.592 ± 1.636	12.600 ± 0.755
	Change[b]	-	-0.032 ± 0.802 (-0.100)	0.079 ± 0.927 (-0.050)	0.009 ± 0.738 (0.100)	-	-0.333 ± 0.781 (-0.100)	-0.292 ± 1.169 (0.000)	0.117 ± 0.548 (0.300)
Platelet count[a] ($10^3/\mu L$)	Number of subjects	170	163	56	22	10	9	6	3
	Value at evaluation point	178.67 ± 92.72	180.02 ± 85.43	167.57 ± 76.66	159.59 ± 79.64	182.15 ± 77.93	168.94 ± 50.16	167.33 ± 64.82	195.17 ± 102.34
	Percent change[b] (%)	-	5.864 ± 18.971 (4.000)	14.021 ± 21.798 (11.126)	9.488 ± 30.398 (6.485)	-	4.137 ± 14.227 (8.462)	9.010 ± 11.874 (10.108)	-9.999 ± 4.586 (-12.287)
Liver volume (MN[c])	Number of subjects	170	156	54	19	10	9	6	2
	Value at evaluation point	1.044 ± 0.243	1.043 ± 0.229	1.053 ± 0.248	1.100 ± 0.240	0.873 ± 0.148	0.855 ± 0.148	0.901 ± 0.135	0.858 ± 0.030
	Percent change[b] (%)	-	0.736 ± 8.794 (0.116)	1.549 ± 11.322 (0.051)	1.688 ± 11.523 (1.607)	-	-1.775 ± 7.471 (-3.022)	5.092 ± 11.122 (5.898)	-0.144 ± 1.406 (-0.144)
Spleen volume (MN[c])	Number of subjects	124	116	41	13	5	5	4	-
	Value at evaluation point	4.269 ± 2.429	3.816 ± 1.968	4.278 ± 1.781	5.613 ± 1.873	3.660 ± 1.954	3.422 ± 1.255	3.825 ± 1.319	-
	Percent change[b] (%)	-	-3.120 ± 42.771 (-8.112)	-12.158 ± 18.648 (-16.173)	-8.547 ± 15.432 (-14.020)	-	-0.073 ± 16.482 (2.612)	1.814 ± 20.538 (-2.032)	-

Mean ± standard deviation (median); -, Not applicable.
a) Mean of 2 measurements (1 day apart) for each evaluation point
b) Change from baseline
c) Calculated with the following formulas using volume measured by MRI: spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

The baseline characteristics of and the dosage employed in individual subjects in the Japanese population are shown in Table 23. The primary and secondary endpoint data for individual subjects are shown in Table 24.

Table 23. Individual baseline characteristics and dosages (Study EDGE, open-label lead-in period, Japanese population)

	Subject number									
	Subject A	Subject B	Subject C	Subject D	Subject E	Subject F	Subject G	Subject H	Subject I	Subject J
Sex	Male	Male	Male	Male	Female	Female	Female	Male	Male	Male
Age (years)[a)]	5[redacted]	5[redacted]	6[redacted]	2[redacted]	3[redacted]	2[redacted]	3[redacted]	2[redacted]	4[redacted]	2[redacted]
Body weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYP2D6 phenotype	EM	EM	EM	EM	EM	EM	IM	IM	IM	Unknown
Presence/absence of spleen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eliglustat dosage	100 mg BID	100 mg BID	150 mg BID/100 mg BID	150 mg BID/100 mg BID	150 mg BID/100 mg BID	Other	100 mg BID	50 mg BID	50 mg BID	150 mg BID/100 mg BID
Eliglustat dosage in different treatment periods	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD	Day 1 50 mg QD
	Days 2-29 50 mg BID	Days 2-56 50 mg BID	Days 2-34 50 mg BID	Days 2-30 50 mg BID	Days 2-35 50 mg BID	Days 2-28 50 mg BID	Days 2-34 50 mg BID	Days 2-329 50 mg BID	Days 2-401 50 mg BID	Days 2-35 50 mg BID
	Days 30-215 100 mg BID		Days 35-57 100 mg BID	Days 31-62 100 mg BID	Days 36-63 100 mg BID	Days 29-58 100 mg BID	Days 35-202 100 mg BID			Days 36-63 100 mg BID
		Days 57-303 100 mg BID	Days 58-219 150 mg BID	Days 63-371 150 mg BID	Days 64-293 150 mg BID	Days 59-148 150 mg BID				Days 64-83 150 mg BID
			Days219-393 100 mg BID	Days 372-562 100 mg BID	Days 294-553 100 mg BID	Days 149-252 50 mg BID				Days 84-413 100 mg BID
						Days 253-469 100 mg BID				

a) Age on Day 1 of treatment

Table 24. Primary and secondary endpoint data for individual subjects (Study EDGE, open-label lead-in period, Japanese population)

		Subject number									
		Subject A	Subject B	Subject C	Subject D	Subject E	Subject F	Subject G	Subject H	Subject I	Subject J
Presence/absence of spleen		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYP2D6 phenotype		EM	EM	EM	EM	EM	EM	IM	IM	IM	Unknown
Eliglustat dosage		100 mg BID	100 mg BID	150 mg BID/100 mg BID	150 mg BID/100 mg BID	150 mg BID/100 mg BID	Other	100 mg BID	50 mg BID	50 mg BID	150 mg BID/100 mg BID
Mean trough level		≥5 ng/mL	≥5 ng/mL	≥5 ng/mL	<5 ng/mL	<5 ng/mL	≥5 ng/mL	≥5 ng/mL	≥5 ng/mL	≥5 ng/mL	<5 ng/mL
All parameters	Week 26	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	Not satisfied	Satisfied	Satisfied	Not satisfied	Satisfied
	Week 52	-	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	-	Satisfied	Satisfied	Satisfied
	Week 78	-	-	-	Satisfied	-	Satisfied	-	-	-	-
Hemoglobin concentration[a)] (g/dL)	Baseline	13.35	12.40	15.75	13.00	12.30	12.15	14.15	13.20	15.65	14.45
	Week 26	13.20	12.65	15.65	13.80	11.15	-	12.70	13.35	14.35	14.40
	Week 52	-	-	16.00	13.95	11.80	11.90	-	-	13.20	14.70
	Week 78	-	-	-	13.30	11.80	12.70	-	-	-	-
Platelet count[a)] ($10^3/\mu L$)	Baseline	176.5	181.0	93.0	146.5	165.5	328.5	197.5	301.5	101.5	130.0
	Week 26	181.0	214.0	112.5	162.0	192.0	-	180.0	250.5	87.5	141.0
	Week 52	-	-	104.5	158.0	177.0	289.0	-	-	125.0	150.5
	Week 78	-	-	-	128.5	144.0	313.0	-	-	-	-
Liver volume (MN[b)])	Baseline	0.77	0.79	0.73	0.85	0.67	0.87	1.00	0.97	0.92	1.17
	Week 26	0.71	0.73	0.71	0.93	0.71	-	1.02	0.86	0.94	1.09
	Week 52	-	-	0.75	0.84	0.75	1.04	-	-	1.00	1.02
	Week 78	-	-	-	0.84	-	0.88	-	-	-	-
Spleen volume (MN[b)])	Baseline			6.54		2.12		2.15		2.68	4.82
	Week 26			5.10		2.23		2.63		2.75	4.41
	Week 52			5.59		2.68		-		2.96	4.07
	Week 78			-		-		-		-	-

-, Not applicable.

a) Mean of 2 measurements (1 day apart) for each evaluation point. (Subject E underwent only 1 measurement at Week 78)

b) Calculated with the following formulas using volume measured by MRI: spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

Based on bone mineral density assessments made with dual energy X-ray absorptiometry (DXA) in Study EDGE, lumbar Z-scores (mean ± standard deviation)[90] were -0.614 ± 1.290 in the overall population (n = 122) and -1.000 ± 0.899 in the Japanese population (n = 9), left femur Z-scores were -0.023 ± 1.344 in the overall population (n = 116) and -1.000 ± 1.083 in the Japanese population (n = 7), and right femur Z-scores were -0.069 ± 1.332 in the overall population (n = 113) and -1.360 ± 0.503 in the Japanese population (n = 5). The mean Z-score in each population remained within the normal range, never falling below -2. Throughout the open-label lead-in period, evaluations of mobility, bone pain, and bone crises showed no change from baseline in these measures in most patients.

The incidences of the adverse events and adverse drug reactions occurring in at least 3% of the overall population are shown in Table 25. The incidences of the adverse events and adverse drug reactions reported in the Japanese population are shown in Table 26.

Table 25. Incidences of adverse events (including laboratory test abnormalities) and adverse drug reactions occurring in at least 3% of subjects (Study EDGE, overall population)

	Overall population (n = 170)		Japanese population (n = 10)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	141 (82.9)	63 (37.1)	8 (80.0)	2 (20.0)
Nasopharyngitis	24 (14.1)	0 (0.0)	2 (20.0)	0 (0.0)
Headache	21 (12.4)	8 (4.7)	1 (10.0)	0 (0.0)
Dizziness	20 (11.8)	11 (6.5)	2 (20.0)	0 (0.0)
Abdominal pain upper	12 (7.1)	5 (2.9)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	11 (6.5)	0 (0.0)	1 (10.0)	0 (0.0)
Diarrhoea	11 (6.5)	5 (2.9)	1 (10.0)	0 (0.0)
Constipation	10 (5.9)	6 (3.5)	1 (10.0)	0 (0.0)
Dyspepsia	9 (5.3)	6 (3.5)	0 (0.0)	0 (0.0)
Back pain	9 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	9 (5.3)	3 (1.8)	0 (0.0)	0 (0.0)
Abdominal pain	8 (4.7)	1 (0.6)	0 (0.0)	0 (0.0)
Nausea	8 (4.7)	5 (2.9)	2 (20.0)	1 (10.0)
Arthralgia	8 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	8 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	7 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	7 (4.1)	2 (1.2)	1 (10.0)	1 (10.0)
Fatigue	7 (4.1)	2 (1.2)	0 (0.0)	0 (0.0)
Oropharyngeal pain	7 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	6 (3.5)	2 (1.2)	1 (10.0)	0 (0.0)
Pain in extremity	6 (3.5)	2 (1.2)	0 (0.0)	0 (0.0)
Epistaxis	6 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)

Number of subjects with event (incidence %); MedDRA/J version 15.1

[90] Z-scores are differences from the mean bone mineral density of healthy subjects matched for age, sex, ethnicity, and body weight, divided by standard deviation (SD). A Z-score of zero corresponds to the 50th percentile for that age and sex.

Table 26. Incidences of adverse events and adverse drug reactions (Study EDGE, Japanese population)

	Adverse event	Adverse drug reaction
All events	8 (80.0)	2 (20.0)
Nausea	2 (20.0)	1 (10.0)
Nasopharyngitis	2 (20.0)	0 (0.0)
Dizziness	2 (20.0)	0 (0.0)
Rhinitis allergic	2 (20.0)	0 (0.0)
Vomiting	1 (10.0)	1 (10.0)
Syncope	1 (10.0)	1 (10.0)
Olfactory nerve disorder	1 (10.0)	1 (10.0)
Dermatitis	1 (10.0)	1 (10.0)
Upper respiratory tract infection	1 (10.0)	0 (0.0)
Urinary tract infection	1 (10.0)	0 (0.0)
Tonsillitis	1 (10.0)	0 (0.0)
Otitis externa	1 (10.0)	0 (0.0)
Periodontitis	1 (10.0)	0 (0.0)
Diarrhoea	1 (10.0)	0 (0.0)
Constipation	1 (10.0)	0 (0.0)
Headache	1 (10.0)	0 (0.0)
Hypoaesthesia	1 (10.0)	0 (0.0)
Musculoskeletal stiffness	1 (10.0)	0 (0.0)
Blood creatine phosphokinase increased	1 (10.0)	0 (0.0)
Alanine aminotransferase increased	1 (10.0)	0 (0.0)
Angiotensin converting enzyme increased	1 (10.0)	0 (0.0)
Blood acid phosphatase increased	1 (10.0)	0 (0.0)
Blood uric acid increased	1 (10.0)	0 (0.0)
White blood cell count increased	1 (10.0)	0 (0.0)
Dry skin	1 (10.0)	0 (0.0)
Onychogryphosis	1 (10.0)	0 (0.0)
Depression	1 (10.0)	0 (0.0)
Middle insomnia	1 (10.0)	0 (0.0)
Neurosis	1 (10.0)	0 (0.0)
Age-related macular degeneration	1 (10.0)	0 (0.0)
Diabetic retinopathy	1 (10.0)	0 (0.0)
Vitreous floaters	1 (10.0)	0 (0.0)

Number of subjects with event (incidence %); MedDRA/J version 15.1

No deaths were reported. Serious adverse events were observed in 9 EMs (syncope [Japanese subject at 150 mg BID]; syncope/hepatitis A, syncope, dizziness/fall, convulsions, cholecystitis, myocardial infarction [100 mg BID]; and hepatic enzyme increased and femur fracture [50 mg BID]), 2 IMs (aortic aneurysm and medical device pain [50 mg BID]), and 1 PM (ischaemic stroke [100 mg BID]). The event syncope in 3 EMs (including 1 Japanese subject) was considered to be an adverse drug reaction.

Adverse events leading to treatment discontinuation were reported in 1 IM (chills/headache/nausea/asthenia/anaemia, 50 mg BID) and 1 EM (erectile dysfunction, 50 mg BID), and the events of headache, nausea, and anaemia were considered to be adverse drug reactions.

There were no clinically significant changes in vital signs or physical findings.

4.(iii).A.(2) Foreign clinical studies

4.(iii).A.(2).1) Phase II study in treatment-naïve patients with Gaucher disease type 1 (5.3.5.2-1: Study GZGD00304 [June 2006 to [redacted] data cutoff][91])

An open-label study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in non-Japanese patients with Gaucher disease type 1[92] (target sample size, 25) [for more information on pharmacokinetics, see "4.(ii).A.(3).1) Phase II study in treatment-naïve patients with Gaucher disease type 1"].

In the primary analysis period of the study (to Week 52), subjects orally received eliglustat 50 mg QD on Day 1 and eliglustat 50 mg BID on Days 2 to 19. On Day 20, the dose was increased to 100 mg BID in subjects whose trough concentration of unchanged eliglustat in plasma was <5 ng/mL on Day 10. The dose was maintained at 50 mg BID in subjects whose trough concentration was ≥5 ng/mL (Table 27). Subjects completing the primary analysis period were to enter the long-term treatment period (after Week 52) and to receive the dosage given at the end of the primary analysis period. Beyond Month 24, subjects treated for at least 24 months with 100 mg BID who did not achieve the therapeutic goals of Gaucher disease[93] were allowed to receive 150 mg BID, but no subjects received 150 mg BID.

Table 27. Dose adjustment procedures through Week 52 (Study GZGD00304)

Treatment duration	Adjustment criteria	Dosage
Day 20 to Week 52	Plasma trough concentration of unchanged eliglustat <5 ng/mL on Day 10	100 mg BID (200 mg/day)
	Plasma trough concentration of unchanged eliglustat ≥5 ng/mL on Day 10	50 mg BID (100 mg/day)

All 26 treated subjects were included in the full analysis set (FAS) and safety analysis population. The FAS was used as the efficacy analysis population. Four subjects discontinued the study by Week 52 (2 for adverse events and 2 for other reasons) and 3 by Month 48 (1 for an adverse event, 1 for withdrawal of consent, and 1 for another reason). A total of 22 subjects completed the study through Week 52 (85%) and 19 completed the study through Month 48 (73%). Of the subjects completing through Week 52, 17 continuously received 100 mg BID and 5 continuously received 50 mg BID. Of the subjects completing through Month 48, 15 continuously received 100 mg BID and 4 continuously received 50 mg BID.

Twenty-five subjects were CYP2D6 EMs, and 1 was a PM.

The composite endpoint[94] and individual endpoints (hemoglobin concentration, platelet count, and spleen volume) are shown in Table 28.

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91 As of the present, the subjects have participated for at least 5 years.

92 Main inclusion/exclusion criteria: the following patients were included in the study.
Patients ≥18 years of age with a diagnosis of Gaucher disease type 1 confirmed by decreased glucocerebrosidase activity in white blood cells or cultured skin fibroblasts who had not received substrate reduction therapy or ERT within 12 months of enrollment, who had not undergone splenectomy (partial or total), and who met the following conditions
• Hemoglobin level of 8-10 g/dL if female and 8-11 g/dL if male or platelet count of 45-100 × 10^3/μL and spleen volume ≥10 MN at screening
• Not receiving a CYP2D6 inducer or inhibitor or a drug that could prolong QT intervals within 30 days of enrollment

93 In study GZGD00304, the therapeutic goals for Gaucher disease were based on those reported for imiglucerase data that follow.
(1) Hemoglobin level of ≥11 g/dL if female and ≥12 g/dL if male; (2) in non-splenectomized patients, (a) a platelet count above the lower limit of normal within 2 years if baseline platelet count was 60-120 × 10^3/μL, or (b) >2 times baseline within 2 years and even higher within 3 to 5 years if baseline platelet count was <60 × 10^3/μL; (3) spleen volume reduced by 50% to 60% in 2 to 5 years; (4) liver volume reduced by 20% to 30% within 2 years and 30% to 40% within 3 to 5 years and 1.0 to 1.5 MN with further treatment; and (5) fewer bone crises and less osteonecrosis

94 Defined as improvement in ≥2 of the 3 parameters (hemoglobin concentration, platelet count, and spleen volume). When an abnormality was present at baseline, improvement was judged to have occurred when the hemoglobin concentration increased by ≥0.5 g/dL from baseline, the platelet count increased by ≥15% from baseline, or the spleen volume relative to the normal value decreased by ≥15% from baseline.

Table 28. Primary endpoint data at Week 52 (Study GZGD00304)

	Composite endpoint	Hemoglobin concentration improved	Platelet count improved	Spleen volume improved
Number of subjects meeting endpoint	76.9 (20/26)	90.0 (9/10)	68.0 (17/25)	84.6 (22/26)

Percentage of subjects (subjects with improvement/subjects evaluated)
When an abnormality was present at baseline, improvement was judged to have occurred when the hemoglobin concentration increased by ≥0.5 g/dL from baseline, the platelet count increased by ≥15% from baseline, or the spleen volume relative to the normal value decreased by ≥15% from baseline.

As the secondary endpoints, changes over time in the endpoints (hemoglobin concentration, platelet count, liver volume, spleen volume) were evaluated. The results are shown in Figure 1, and the major secondary endpoints at Week 52 and Month 48 are shown in Table 29.

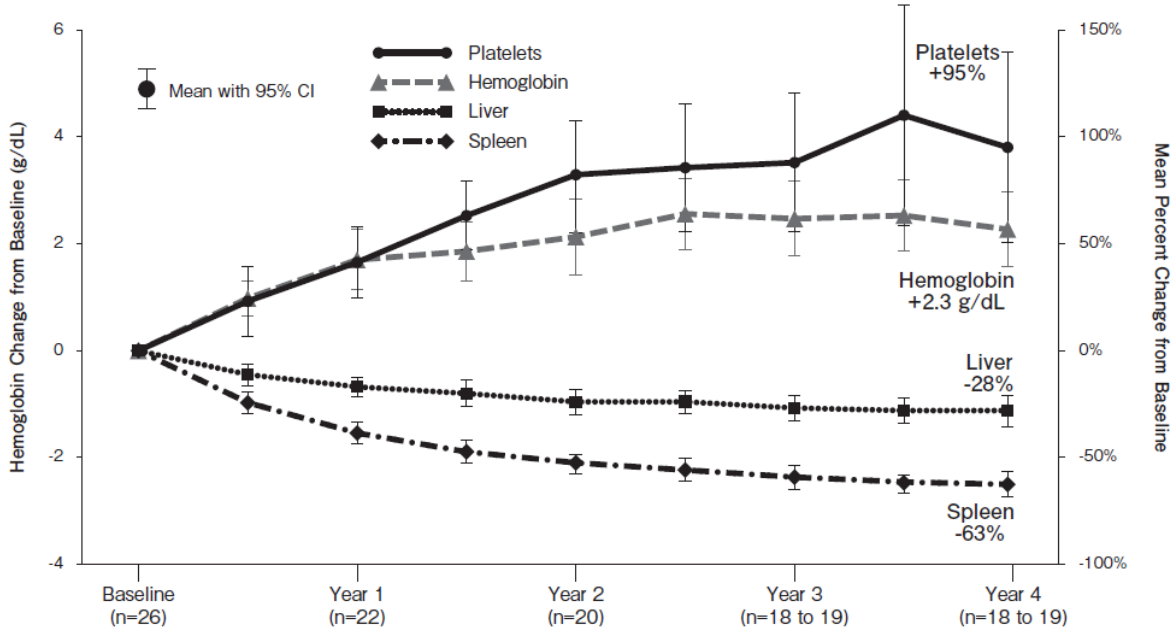

Figure 1. Changes over time in endpoints (hemoglobin concentration, platelet count, liver volume, spleen volume) (Study GZGD00304)

Table 29. Major secondary endpoint data (Study GZGD00304)

Endpoint		Subjects treated for 52 weeks		Subjects treated for 48 months		LOCF[c)]	
		Baseline	Week 52	Baseline	Month 48	Baseline	Month 48
Hemoglobin concentration[a)] (g/dL)	No. of subjects	n = 22	n = 22	n = 19	n = 19	n = 25	n = 25
	Value at each time point	10.99 ± 1.691 (11.33)	12.70 ± 1.626 (12.98)	11.30 ± 1.543 (11.75)	13.57 ± 1.227 (13.50)	11.02 ± 1.652 (11.20)	12.92 ± 1.732 (13.40)
	Change[b)]	-	1.70 [1.14, 2.27]	-	2.27 [1.57, 2.97]	-	1.91 [1.23, 2.58]
Platelet count[a)] ($10^3/\mu L$)	No. of subjects	n = 22	n = 22	n = 19	n = 19	n = 25	n =2 5
	Value at each time point	67.46 ± 20.081 (63.75)	93.91 ± 32.253 (93.75)	68.68 ± 21.165 (66.50)	125.40 ± 51.077 (112.00)	66.82 ± 20.453 (61.00)	112.24 ± 50.997 (103.00)
	Percent change[b)] (%)	-	41.3 [24.9, 57.7]	-	95.0 [50.7, 139.4]	-	77.1 [40.9, 113.3]
Liver volume (MN[d)])	No. of subjects	n = 22	n = 22	n = 18	n = 18	n = 23	n = 23
	Value at each time point	1.73 ± 0.465 (1.74)	1.41 ± 0.345 (1.42)	1.70 ± 0.422 (1.59)	1.19 ± 0.279 (1.13)	1.82 ± 0.636 (1.88)	1.28 ± 0.378 (1.16)
	Percent change[b)] (%)	-	-16.9 [-21.6, -12.3]	-	-28.0 [-34.9, -21.2]	-	-27.0 [-33.3, -20.8]
Spleen volume (MN[d)])	No. of subjects	n = 22	n = 22	n = 18	n = 18	n = 23	n = 23
	Value at each time point	20.03 ± 13.375 (14.28)	12.66 ± 10.491 (9.19)	17.32 ± 9.531 (13.52)	6.08 ± 3.401 (5.58)	20.03 ± 13.067 (14.55)	9.26 ± 9.926 (5.71)
	Percent change[b)] (%)	-	-38.5 [-43.6, -33.5]	-	-62.5 [-68.3, -56.7]	-	-56.2 [-63.9, -48.5]

Mean ± standard deviation (median), mean [95% confidence interval]; -, Not applicable
a) Mean of 2 measurements (1 day apart) for each time point
b) Change from baseline
c) Missing values were imputed with last observation carried forward (LOCF).
d) Calculated with the following formulas using volume measured by MRI:
spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

Bone mineral density evaluation[95] was performed in this phase II study. The lumbar Z-score (mean ± standard deviation) was -1.17 ± 0.918 at baseline and -0.48 ± 1.073 at Month 48. The change from baseline and 95% confidence interval were 0.69 [0.25, 1.13]. The Z-score for the femur (mean ± standard deviation) was 0.27 ± 0.704 at baseline and 0.48 ± 0.773 at Month 48. The change from baseline and 95% confidence interval were 0.21 [-0.13, 0.54]. Most of the subjects (92% to 100%) had few mobility restrictions and no bone crises at baseline. Evaluations of these measures did not show clinically significant changes from baseline.

The incidences of the adverse events and adverse drug reactions occurring in ≥10% of the eliglustat groups are shown in Table 30.

Table 30. Incidences of adverse events (including laboratory test abnormalities) and adverse drug reactions occurring in ≥10% of subjects treated with eliglustat (Study GZGD00304, Month 48)

	Overall eliglustat group (n = 26)		Eliglustat 50 mg BID group (n = 6)		Eliglustat 100 mg BID group (n = 18)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	23 (88.5)	8 (30.8)	6 (100.0)	2 (33.3)	15 (83.3)	5 (27.8)
Viral infection	6 (23.1)	0 (0.0)	2 (33.3)	0 (0.0)	4 (22.2)	0 (0.0)
Upper respiratory tract infection	4 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)
Urinary tract infection	4 (15.4)	0 (0.0)	1 (16.7)	0 (0.0)	3 (16.7)	0 (0.0)
Nasopharyngitis	3 (11.5)	0 (0.0)	1 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)
Sinusitis	3 (11.5)	0 (0.0)	1 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)
Arthralgia	3 (11.5)	0 (0.0)	1 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)
Pain in extremity	3 (11.5)	0 (0.0)	1 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)
Blood pressure increased	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)
Nerve conduction studies abnormal	3 (11.5)	2 (7.7)	1 (16.7)	1 (16.7)	2 (11.1)	1 (5.6)
Diarrhoea	3 (11.5)	2 (7.7)	2 (33.3)	1 (16.7)	1 (5.6)	1 (5.6)
Headache	3 (11.5)	1 (3.8)	0 (0.0)	0 (0.0)	3 (16.7)	1 (5.6)

Number of subjects with event (incidence %); MedDRA/J version 14.1

95 Subjects with data at baseline and Month 48 were evaluated (lumbar bone mineral density, 15 subjects; femur bone mineral density, 13 subjects).

No deaths were reported.[96] Serious adverse events were reported in 3 EMs (ventricular tachycardia [50 mg QD], 1 episode of spontaneous abortion/2 episodes of maternal exposure during pregnancy, and 1 episode of maternal exposure during pregnancy [100 mg BID]). Ventricular tachycardia was classified as an adverse drug reaction and led to treatment discontinuation.

Adverse events leading to treatment discontinuation were reported in 3 EMs (ventricular tachycardia in 2 subjects [50 mg QD] and osteonecrosis in 1 subject [100 mg BID]). Ventricular tachycardia in 1 subject was classified as an adverse drug reaction.

There were no clinically significant changes in vital signs or physical findings.

4.(iii).A.(2).2) Phase III study in treatment-naïve patients with Gaucher disease type 1 (5.3.5.1-1: Study GZGD02507 [ENGAGE] [November 2009 to [redacted] data cutoff])

A placebo-controlled, double-blind, parallel-group, comparative study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in non-Japanese treatment-naïve patients with Gaucher disease type 1[97] (target sample size, 36) [for more information on pharmacokinetics, see "4.(ii).A.(3).3) Phase III study in treatment-naïve patients with Gaucher disease type 1"].

Subjects orally received eliglustat or placebo for 39 weeks during the primary analysis period (to Week 39), with the dosage adjusted as in Table 31. Treatment was temporarily suspended in subjects in whom the peak plasma concentration of unchanged eliglustat reached ≥150 ng/mL during the primary analysis period, and the primary analysis period was terminated for those subjects. When safety findings or a change in concomitant drugs allowed study continuation, the treatment was resumed at the dose reduced in the open-label period or at the dosage used before treatment suspension.[98]

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96 One subject died of postoperative complications of laparoscopic cholecystectomy performed approximately 6.5 months after treatment discontinuation, but a causal relationship with eliglustat was ruled out.

97 Main inclusion criteria: Patients ≥16 years of age with a diagnosis of Gaucher disease type 1 confirmed by decreased glucocerebrosidase activity in white blood cells or cultured skin fibroblasts who had not received substrate reduction therapy within 6 months of randomization or ERT within 9 months of randomization, who had not undergone splenectomy (partial or total), and who meet the following conditions:
- Symptoms of Gaucher disease at screening, including:
  a) Hemoglobin level of 8 to 11 g/dL (females) or 8 to 12 g/dL (males) or platelet count of 50-130 × 10^3/μL;
  b) Spleen volume of 6 to 30 MN; and
  c) If hepatomegaly present, liver volume <2.5 MN.
- No treatment with a drug that could cause QTc interval prolongation or on a CYP3A4 inhibitor within 30 days of randomization.
- No treatment with a strong CYP3A inhibitor within 30 days of randomization if the patient was a CYP2D6 PM or an indeterminate metabolizer with neither allele known to be active.
- No treatment with a strong inhibitor of CYP3A or CYP2D6, if the patient was not a CYP2D6 PM or indeterminate metabolizer with one allele identified as active, except where the patient had chronically received either of the inhibitors (but not both) for at least 30 days prior to randomization and could continue the same dosage during the primary analysis period of this study.

98 After the days of approval of the 5th version of the protocols ([redacted] for Study ENGAGE and [redacted] for Study ENCORE), treatment was temporarily suspended in subjects with a peak level ≥150 ng/mL and, when applicable, the primary analysis period was terminated for those subjects. Resumption of study drug treatment in an open-label manner was allowed at a reduced dose or the BID dose received before treatment suspension according to patient peak levels, the period in the study in which the peak levels were reported, concurrently identified safety findings, and any adjustments made to concomitant drugs. Subsequent dose reductions and increases were determined according to ongoing evaluations of patient data in consultation with the sponsor. As dose reduction was allowed in the long-term period even when eliglustat was poorly tolerated, dose reduction was controlled in consultation with the sponsor and, as necessary, the data monitoring committee. The minimum and maximum permitted doses in the study were 50 mg QD and 150 mg BID.

Table 31. Dose adjustment procedures through Week 39 in the eliglustat group (Study GZGD02507 [ENGAGE])

	Timing	Adjustment criteria	Dosage in eliglustat group
Primary analysis period	Day 1	-	50 mg QD (50 mg/day)
	Day 2 to Week 4	-	50 mg BID (100 mg/day)
	Weeks 4 to 39	Plasma trough concentration of unchanged eliglustat <5 ng/mL at Week 2	100 mg BID (200 mg/day)
		Plasma trough concentration of unchanged eliglustat ≥5 ng/mL at Week 2	50 mg BID (100 mg/day)

Subjects completing the primary analysis period were to enter the long-term treatment period (after Week 39).[99]

All 40 treated subjects (20 in the eliglustat group and 20 in the placebo group) were included in the FAS and safety analysis population. The FAS was used as the efficacy analysis population. One subject (for withdrawal of consent) discontinued the study.

Seventeen subjects in the eliglustat group underwent dose escalation to 100 mg BID at Week 4, and the other 3 subjects were maintained at 50 mg BID throughout the 39-week double-blind period.

One IM, 18 EMs, and 1 URM were in the eliglustat group and 2 IMs and 18 EMs in the placebo group.

Percent change in spleen volume from baseline to Week 39 in the FAS, the primary endpoint, is shown in Table 32. The values demonstrated superiority of eliglustat over placebo ($p<0.0001$, with a 2-sided significance level of 5%, in an analysis of covariance [ANCOVA] model).

Table 32. Percent change in spleen volume (MN[b)]) from baseline to Week 39 (Study ENGAGE, primary analysis period, FAS)

Treatment group	Baseline	Week 39	Percent change from baseline (%)	Between-group difference[a)] (%)	*p* value[a)]
Placebo group (n = 20)	12.50 ± 5.959	12.84 ± 6.395	2.07 ± 8.777	-30.03 [-36.82, -23.24]	<0.0001
Eliglustat group (n = 20)	13.89 ± 5.929	10.17 ± 5.065	-27.58 ± 12.591		

Mean ± standard deviation except for between-group difference (expressed as adjusted mean [2-sided 95% confidence interval]), LOCF
a) 2-sided level of significance of 5%, ANCOVA model with treatment group and spleen severity at baseline as explanatory variables.
b) Calculated with the following formulas using volume measured by MRI: spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2.

[99] Only the primary analysis period results are shown for this study because the long-term period is now underway. In the long-term period, all subjects (all of those assigned to eliglustat or placebo group in the primary analysis period) were to receive eliglustat 50 mg BID orally in Weeks 39 to 43. For Weeks 43 to 47, the dose was to be elevated to 100 mg BID (200 mg/day) in subjects with a trough level <5 ng/mL at Week 41 or was to be maintained at 50 mg BID (100 mg/day) in subjects with a trough level ≥5 ng/mL at Week 41. After week 47, the dose was to be elevated by 1 level in subjects with a trough <5 ng/mL at Week 45 (subjects at 100 mg BID were to be given 150 mg BID [300 mg/day], subjects at 50 mg BID were to be given 100 mg BID [200 mg/day]). The current dosage was to be maintained in subjects with a trough level ≥ 5 ng/mL at Week 45.

The results for the major secondary endpoints are shown in Table 33.

Table 33. Major secondary endpoint data (Study ENGAGE, primary analysis period)

Endpoint		Placebo group (n = 20)	Eliglustat group (n = 20)
Hemoglobin concentration[a] (g/dL)	Baseline	12.75 ± 1.629	12.05 ± 1.816
	Week 39	12.17 ± 2.010	12.78 ± 1.561
	Change from baseline	-0.54 [-1.00, -0.08]	0.69 [0.23, 1.14]
	Between-group difference	-	1.22 [0.57, 1.88]
Platelet count[a] (10^3/μL)	Baseline	78.48 ± 22.611	75.05 ± 14.095
	Week 39	71.50 ± 25.157	98.95 ± 28.372
	Percent change from baseline (%)	-9.06 [-21.12, 3.00]	32.00 [19.94, 44.06]
	Between-group difference	-	41.06 [23.95, 58.17]
Liver volume (MN[b])	Baseline	1.36 ± 0.280	1.44 ± 0.354
	Week 39	1.39 ± 0.309	1.35 ± 0.280
	Percent change from baseline (%)	1.44 [-1.89, 4.78]	-5.20 [-8.53, -1.87]
	Between-group difference (%)	-	-6.64 [-11.37, -1.91]

Mean ± standard deviation except for changes (or percent changes) and between-group differences (expressed as adjusted means [2-sided 95% confidence interval]), LOCF; -, Not applicable.
a) Mean of 2 measurements (1 day apart) for each time point.
b) Calculated with the following formula using volume measured by MRI:
liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

Lumbar Z-scores for bone mineral density measured by DXA were - 1.17 ± 1.175 in the placebo group and -1.15 ± 0.938 in the eliglustat group at baseline, and the changes from baseline to Week 39 (adjusted mean and 95% confidence interval) were -0.1 [-0.23, 0.02] and 0.1 [-0.06, 0.20] in the respective groups. No change from baseline was observed. Evaluations of mobility and bone crises revealed few mobility restrictions and no bone crises in most of the subjects (93% to 100%). These measures did not show clinically significant changes from baseline. MRI was used to score the severity of bone marrow infiltration as bone marrow burden (BMB scores).[100] Total BMB scores (mean ± standard deviation) were 9.8 ± 2.75 in the placebo group and 10.9 ± 2.62 in the eliglustat group at baseline, and the changes from baseline to Week 39 were 0.0 ± 0.71 and -1.1 ± 1.29 in the respective groups.

The incidences of the adverse events occurring in ≥10% of the subjects in either group and adverse drug reactions are shown in Table 34.

[100] Scored with MRI of lumbar vertebrae (the site of initial infiltration) and femur (the site of the limb usually more affected by disease progression) (Maas M, et al., *Radiol,* 2003; 229(2): 554-61, Robertson PL, et al., *Am J Roentgenol*, 2007; 188(6): 1521-8), followed by calculation of total score (0 [no abnormalities] to 16). Bone marrow burden (BMB) scores correlate well with the fractional fat signal of bone marrow determined through quantitative chemical shift imaging (QCSI), and QCSI data are closely related to clinical bone symptoms (Maas M, et al., *Am J Roentgenol*, 2002:179:961-5) and spleen volume (Rosenthal DI, et al., *Pediatrics*, 1995;96:629-37).

Table 34. Adverse events occurring in ≥10% of subjects in either group and adverse drug reactions
(Study GZGD02507 [ENGAGE], primary analysis period)

	Placebo group (n = 20)		Eliglustat group (n = 20)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	14 (70.0)	9 (45.0)	18 (90.0)	8 (40.0)
Arthralgia	2 (10.0)	0 (0.0)	9 (45.0)	1 (5.0)
Headache	6 (30.0)	3 (15.0)	8 (40.0)	1 (5.0)
Diarrhoea	4 (20.0)	4 (20.0)	3 (15.0)	2 (10.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)
Flatulence	1 (5.0)	1 (5.0)	2 (10.0)	2 (10.0)
Nausea	1 (5.0)	0 (0.0)	2 (10.0)	1 (5.0)
Sinusitis	1 (5.0)	0 (0.0)	2 (10.0)	0 (0.0)
Migraine	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Oropharyngeal pain	1 (5.0)	0 (0.0)	2 (10.0)	0 (0.0)
Nasal obstruction	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Contusion	3 (15.0)	0 (0.0)	2 (10.0)	0 (0.0)
Abdominal pain	2 (10.0)	2 (10.0)	1 (5.0)	1 (5.0)
Vomiting	2 (10.0)	0 (0.0)	1 (5.0)	1 (5.0)
Upper respiratory tract infection	4 (20.0)	0 (0.0)	1 (5.0)	0 (0.0)
Toothache	3 (15.0)	0 (0.0)	1 (5.0)	0 (0.0)
Dizziness	2 (10.0)	2 (10.0)	1 (5.0)	0 (0.0)
Fatigue	2 (10.0)	0 (0.0)	1 (5.0)	0 (0.0)
Influenza	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)

Number of subjects with event (incidence %). MedDRA/J version 15.0

No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported. There were no clinically significant changes in vital signs or physical findings.

4.(iii).A.(2).3) Phase III study in patients with a history of ERT (5.3.5.1-2: Study GZGD02607 [ENCORE] [September 2009 to [redacted] data cutoff])

An open-label, imiglucerase-controlled, parallel-group, comparative study was conducted to evaluate the safety, efficacy, and pharmacokinetics of eliglustat in non-Japanese patients with Gaucher disease type 1[101] (target sample size, 150) [for more information on pharmacokinetics, see "4.(ii).A.(3).4) Phase III study in patients switching from ERT"].

Subjects received eliglustat or imiglucerase in the primary analysis period (to Week 52) of the study. The subjects in the eliglustat group continued receiving imiglucerase every other week until 1 day before treatment assignment, and then orally received eliglustat 50 mg BID from Day 1 to Week 4, and underwent dose

[101] Main inclusion/exclusion criteria: the following patients were included in the study.
Patients ≥18 years of age with a diagnosis of Gaucher disease type 1 confirmed by decreased glucocerebrosidase activity in white blood cells or cultured skin fibroblasts who meet the following conditions
- Having been on ERT for ≥3 years and having received an ERT (total monthly dose of 30 to 130 U/kg), approved as of treatment assignment in the country where the subject lived, for ≥6 months within 9 months of treatment assignment
- Spleen volume <10 MN and liver volume <1.5 MN
- Having achieved the following Gaucher disease therapeutic goals before randomization:
  a) No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures during the past year
  b) Hemoglobin level ≥11 g/dL if female and ≥12 g/dL if male at the time of screening
  c) Platelet count ≥100 $\times 10^3/\mu L$ at the time of screening
- No treatment with a drug that could cause QTc interval prolongation or with a CYP3A4 inhibitor within 30 days of randomization (unless the drug was used as pretreatment for ERT).
- No treatment with a strong CYP3A inhibitor within 30 days of randomization if patient was a CYP2D6 PM or an indeterminate metabolizer with neither allele known to be active.
- No treatment with a strong inhibitor of CYP3A or CYP2D6, if the patient was not a CYP2D6 PM or indeterminate metabolizer with one allele identified as active, except where the patient had chronically received either of the inhibitors (but not both) for ≥30 days before randomization and could continue the same dosage during the primary analysis period of this study.

adjustment according to plasma concentrations of unchanged eliglustat as shown in Table 35. Subjects in the imiglucerase group were maintained on the same dosage as before enrollment. Treatment was temporarily suspended in the subjects in whom the peak plasma concentration of unchanged eliglustat was ≥150 ng/mL in the primary analysis period and the primary analysis period was terminated for those subjects. When safety findings or a change in concomitant drugs allowed study continuation, the treatment was resumed at the dose reduced in the open-label period or the dosage used before treatment suspension.[98]

Table 35. Dose adjustment procedures through Week 52 in the eliglustat group (Study ENCORE)

Time	Adjustment criteria	Dosage in the eliglustat group
To Week 4	-	50 mg BID (100 mg/day)
Weeks 4 to 8	C_{trough} <5 ng/mL at Week 2	100 mg BID (200 mg/day)
	C_{trough} ≥5 ng/mL at Week 2	50 mg BID (100 mg/day)
Weeks 8 to 52	C_{trough} <5 ng/mL at Week 6	Dose escalated by 1 level as follows: a) Increase dosage to 150 mg BID (300 mg/day) if patient is at 100 mg BID b) Increase dosage to 100 mg BID (200 mg/day) if patient is at 50 mg BID
	C_{trough} ≥5 ng/mL at Week 6	Current dosage maintained

Subjects completing the primary analysis period were to enter the long-term treatment period (after Week 52). Subjects in the eliglustat group continued to receive eliglustat, and subjects in the imiglucerase group were switched to eliglustat treatment.[102]

All 159 treated subjects (106 in the eliglustat group and 53 in the imiglucerase group) were included in the FAS and safety analysis population. The per protocol set (PPS) consisted of 146 subjects (99 in the eliglustat group and 47 in the imiglucerase group), that is, all FAS subjects other than 13 subjects[103] who were excluded due to protocol non-compliance. The PPS was used as the primary efficacy analysis population. Three subjects discontinued the study (for adverse events).

In the eliglustat group, 20% (21 of 106) of the subjects received 50 mg BID, 32% (34 of 106) of the subjects received 100 mg BID, and 48% (51 of 106) of the subjects received 150 mg BID.

CYP2D6 phenotype distribution in the FAS was 79% (84 of 106 subjects) EM, 11% (12 of 106) IM, 4% (4 of 106) PM, 4% (4 of 106) URM, and 2% (2 of 106) unknown phenotype in the eliglustat group; and was 72% (38 of 53 subjects) EM, 17% (9 of 53) IM, 4% (2 of 53) PM, 2% (1 of 53) URM, 6% (3 of 53) unknown phenotype in the imiglucerase group. The phenotype distribution in the PPS was 80% (79 of 99 subjects) EM, 10% (10 of 99) IM, 4% (4 of 99) PM, 4% (4 of 99) URM, 2% (2 of 99) unknown phenotype in the eliglustat group; and was 70% (33 of 47 subjects) EM, 17% (8 of 47) IM, 4% (2 of 47) PM, 2% (1 of 47) URM, 6% (3 of 47) unknown phenotype in the imiglucerase group.

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102 Only the primary analysis period results are shown because the long-term period is now underway. In the long-term period, subjects switched from imiglucerase to eliglustat in or after week 52 were orally given eliglustat at 50 mg BID from Weeks 52 to 56 and then, from Weeks 56 to 60, elevated to 100 mg BID if the trough level at Week 54 was <5 ng/mL or maintained at 50 mg BID if the trough level at Week 54 was ≥5 ng/mL. Dosage in Week 60 and beyond was determined according to the trough plasma concentrations at Week 58. (Subjects at 50 mg BID with a trough level <5 ng/mL were elevated to 100 mg BID, subjects at 100 mg BID with a trough level <5 ng/mL were elevated to 150 mg BID, and subjects at 50 mg BID or 100 mg BID with a trough level ≥5 ng/mL continued to receive eliglustat at 50 mg BID or 100 mg BID.)

103 Three subjects discontinued the study before Week 52 (2 in the eliglustat group and 1 in the imiglucerase group), 5 subjects with <80% compliance (2 in the eliglustat group and 3 in the imiglucerase group), 4 with stratification factor error at randomization (2 in the eliglustat group and 2 in the imiglucerase group), and 1 with missing data for platelet count or hemoglobin at baseline or Week 52 (1 subject in the eliglustat group).

The percentage of subjects in the PPS in whom efficacy was sustained at Week 52,[104] which was the primary endpoint, is shown in Table 36. Non-inferiority of the eliglustat group to the imiglucerase group was demonstrated because the lower bound of the 2-sided 95% confidence interval of the between-group difference (eliglustat group – imiglucerase group) of -18.6% exceeded the predefined non-inferiority margin (-25%[105]). Secondary analysis of the primary endpoint in the FAS revealed a stability rate of 82.1% (87 of 106 subjects) in the eliglustat group and 90.6% (48 of 53 subjects) in the imiglucerase group. The between-group difference and the 2-sided 95% confidence interval were -8.5% [-18.1, 4.3].

Table 36. Sustained efficacy rate in patients with Gaucher disease at Week 52 (Study ENCORE, PPS)

		Overall		Pre-treatment dose of ERT			
				<35 U/kg		≥35 U/kg	
		Eliglustat group (n = 99)	Imiglucerase group (n = 47)	Eliglustat group (n = 38)	Imiglucerase group (n = 18)	Eliglustat group (n = 61)	Imiglucerase group (n = 29)
Composite endpoint	Success rate	83/99 (83.8)	44/47 (93.6)	32/38 (84.2)	17/18 (94.4)	51/61 (83.6)	27/29 (93.1)
	Between-group difference[a)] (%)	-9.8 [-18.6, 3.3]	-	-10.2 [-25.2, 10.2]	-	-9.5 [-21.8, 6.2]	-
Hemoglobin concentration	Success rate	94/99 (94.9)	47/47 (100)	35/38 (92.1)	18/18 (100)	59/61 (96.7)	29/29 (100)
Platelet count	Success rate	92/99 (92.9)	47/47 (100)	36/38 (94.7)	18/18 (100)	56/61 (91.8)	29/29 (100)
Liver volume	Success rate	95/99 (96.0)	44/47 (93.6)	38/38 (100)	17/18 (94.4)	57/61 (93.4)	27/29 (93.1)
Spleen volume	Success rate	67/71 (94.4)	39/39 (100)	25/27 (92.6)	14/14 (100)	42/44 (95.5)	25/25 (100)

Number of applicable subjects/subjects evaluated (%) except for between-group differences (expressed as adjusted means [2-sided 95% confidence interval].

a) 95% confidence interval adjusted by pre-treatment ERT dose as a stratification factor (Agresti and Caffo, *American Statistician*, 2000; 54(4):280-8)

Secondary endpoint values in the PPS are shown in Table 37. Non-inferiority of the eliglustat group to the imiglucerase group was demonstrated because the upper bound of the 2-sided 95% confidence interval of the between-group difference (eliglustat group – imiglucerase group) in the percent change in spleen volume from baseline to Week 52 in the PPS[106] (2.62%) was below the predefined non-inferiority margin (15%).

104 The predefined sustained efficacy in patients with Gaucher disease was as follows: (a) decrement in hemoglobin concentration from baseline ≤1.5 g/dL and decrement in platelet count from baseline ≤25% (b) increment in spleen volume (MN) from baseline ≤25% and increment in liver volume (MN) from baseline ≤20%

105 In the International Collaborative Gaucher Group (ICGG) Gaucher Registry, 51% of patients who discontinued imiglucerase treatment for 1 year after achieving the therapeutic goals with imiglucerase met the sustained efficacy criteria, and 95% of the patients treated with imiglucerase were estimated to have met the criteria. The noninferiority margin was set at 25% which was approximately half of the expected difference between the imiglucerase group and placebo group.

106 Efficacy endpoint recommended by the United States Food and Drug Administration (FDA)

Table 37. Major secondary endpoint data (Study ENCORE, PPS, primary analysis period)

Endpoint		Eliglustat group	Imiglucerase group
Hemoglobin concentration[a] (g/dL)	Baseline	13.592 ± 1.2467	13.797 ± 1.2234
	Week 52	13.380 ± 1.2840	13.835 ± 1.2932
	Change (g/dL)[b), c)]	-0.22 [-0.36, -0.08]	0.05 [-0.14, 0.25]
	Between-group difference	-0.28 [-0.52, -0.03]	-
Platelet count[a] ($10^3/\mu L$)	Baseline	206.750 ± 80.7371	192.298 ± 57.3367
	Week 52	216.281 ± 83.9567	198.340 ± 61.1593
	Percent change (%)[b), c)]	3.93 [0.55, 7.31]	2.63 [-2.25, 7.52]
	Between-group difference	1.30 [-4.65, 7.24]	-
Liver volume (MN[d])	Baseline	0.948 ± 0.1911	0.911 ± 0.1622
	Week 52	0.963 ± 0.1856	0.944 ± 0.1670
	Percent change (%)[b), c)]	1.99 [0.13, 3.86]	3.13 [0.43, 5.83]
	Between-group difference	-1.14 [-4.42, 2.15]	-
Spleen volume (MN[d])	Baseline (%)	3.23 ± 1.37	2.62 ± 1.08
	Week 52	3.07 ± 1.39	2.53 ± 0.99
	Percent change (%)[b), c)]	-5.96 [-9.12, -2.80]	-3.21 [-7.47, 1.06]
	Between-group difference	-2.75 [-8.12, 2.62]	-

Mean ± standard deviation; adjusted mean [2-sided 95% confidence interval]; -, Not applicable
a) Mean of 2 measurements (1 day apart) for each time point
b) Change from baseline
c) ANCOVA model with treatment group, baseline value, and pre-treatment ERT dose as explanatory variables
d) Calculated with the following formulas using volume measured by MRI:
spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

Lumbar Z-scores for bone mineral density measured by DXA (mean ± standard deviation) were -0.35 ± 1.260 in the eliglustat group and -0.14 ± 1.108 in the imiglucerase group at baseline, and the changes from baseline to Week 52 (adjusted mean and 95% confidence interval) were 0.06 [0.00, 0.12] in the eliglustat group and 0.06 [-0.02, 0.15] in the imiglucerase group. Femur Z-scores for bone mineral density (mean ± standard deviation) were 0.09 ± 1.020 in the eliglustat group and -0.18 ± 1.122 in the imiglucerase group at baseline, and the changes from baseline (adjusted mean and 95% confidence interval) were 0.03 [0.00, 0.07] in the eliglustat group and 0.02 [-0.03, 0.06] in the imiglucerase group. Sustained efficacy was observed in both groups.

The incidences of the adverse events occurring in ≥5% of the subjects in either group and adverse drug reactions are shown in Table 38.

Table 38. Incidences of adverse events (including laboratory test abnormalities) occurring in ≥5% of subjects in either group and adverse drug reactions (Study ENCORE, primary analysis period)

	Eliglustat group (n = 106)		Imiglucerase group (n = 53)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
All events	97 (91.5)	40 (37.7)	42 (79.2)	6 (11.3)
Arthralgia	16 (15.1)	4 (3.8)	9 (17.0)	0 (0.0)
Fatigue	15 (14.2)	4 (3.8)	1 (1.9)	0 (0.0)
Headache	14 (13.2)	4 (3.8)	1 (1.9)	0 (0.0)
Diarrhoea	13 (12.3)	5 (4.7)	2 (3.8)	0 (0.0)
Nausea	13 (12.3)	3 (2.8)	0 (0.0)	0 (0.0)
Back pain	13 (12.3)	1 (0.9)	3 (5.7)	1 (1.9)
Pain in extremity	12 (11.3)	2 (1.9)	1 (1.9)	0 (0.0)
Abdominal pain upper	11 (10.4)	2 (1.9)	0 (0.0)	0 (0.0)
Nasopharyngitis	11 (10.4)	0 (0.0)	5 (9.4)	0 (0.0)
Upper respiratory tract infection	11 (10.4)	0 (0.0)	3 (5.7)	0 (0.0)
Sinusitis	11 (10.4)	0 (0.0)	1 (1.9)	0 (0.0)
Dizziness	9 (8.5)	2 (1.9)	0 (0.0)	0 (0.0)
Asthenia	9 (8.5)	2 (1.9)	0 (0.0)	0 (0.0)
Dyspepsia	7 (6.6)	3 (2.8)	1 (1.9)	1 (1.9)
Gastrooesophageal reflux disease	7 (6.6)	3 (2.8)	0 (0.0)	0 (0.0)
Cough	7 (6.6)	1 (0.9)	2 (3.8)	0 (0.0)
Blood creatine phosphokinase increased	7 (6.6)	0 (0.0)	1 (1.9)	0 (0.0)
Bone pain	6 (5.7)	1 (0.9)	1 (1.9)	0 (0.0)
Influenza	6 (5.7)	0 (0.0)	2 (3.8)	0 (0.0)
Urinary tract infection	5 (4.7)	0 (0.0)	5 (9.4)	0 (0.0)
Toothache	2 (1.9)	0 (0.0)	3 (5.7)	0 (0.0)
Hepatomegaly	1 (0.9)	1 (0.9)	3 (5.7)	0 (0.0)

Number of subjects with event (incidence %), MedDRA/J version 15.1

No deaths were reported. There were no serious adverse events in the imiglucerase group. In the eliglustat group, serious adverse events were reported in 8 EMs (syncope [2 subjects] and cholecystitis at 150 mg BID; colitis ischaemic, joint dislocation, and appendicitis at 100 mg BID; hepatic neoplasm malignant and mammoplasty at 50 mg BID) and in 3 IMs (uterine leiomyoma at 100 mg BID; myocardial infarction and diverticulitis at 50 mg BID). Hepatic neoplasm malignant was classified as an adverse drug reaction.[107] Adverse events leading to treatment discontinuation were reported in 2 IMs in the eliglustat group (myocardial infarction and palpitations at 50 mg BID) and 1 EM in the imiglucerase group (psychotic disorder). The event palpitations was classified as an adverse drug reaction.

There were no clinically significant changes in vital signs or physical findings.

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

4.(iii).B.(1) Clinical positioning of eliglustat

The applicant explained as follows:

Gaucher disease is an autosomal recessive disorder in which a mutation in the gene for glucocerebrosidase, a lysosome enzyme responsible for breaking down glucosylceramide into glucose and ceramide, results in reduced glucocerebrosidase activity. Low glucocerebrosidase activity leads to the accumulation of glucosylceramide in lysosomes and hepatosplenomegaly, anemia, thrombocytopenia, and bone manifestations (e.g., low bone mineral density, bone crises, bone pain) as a consequence.[2]

[107] The causality assessment was changed from "possibly related" to "probably unrelated" after database lock because retrospective review of previous MRI revealed the presence of lesions.

In Japan, imiglucerase and velaglucerase alfa are approved as glucosylceramide-reducing therapies for the indication of "the alleviation of the symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, bone symptoms)." These enzyme replacement therapies supplement deficient enzymes in the body to catabolize and break down glucosylceramide accumulating in the lysosomes, thus alleviating hepatosplenomegaly, anemia, and thrombocytopenia.[108] Long-term replacement therapy additionally alleviates bone pain, bone crises, and other bone manifestations.[109] The ERT, however, requires an intravenous infusion once every 2 weeks and is associated with the adverse events of hypersensitivity and infusion-related reactions. Furthermore, antibody and, albeit less frequently, neutralizing antibody may be produced.[110] Eliglustat is a small-molecule drug that works by suppressing substrate synthesis and is therefore expected to be effective in cells deficient in the mannose receptors.[31]

The above highlights the need for an oral drug, but no oral drug is available in Japan for patients with Gaucher disease. Unlike enzyme replacement therapies for supplementing a deficient enzyme, eliglustat is a new glucosylceramide synthase inhibitor that suppresses the synthesis of glucosylceramide.[32] As eliglustat is taken orally, there is no need for patients to receive intravenous infusions every other week. Eliglustat therefore represents a new therapeutic option for patients with Gaucher disease type 1.

PMDA considers as follows:
Gaucher disease type 1 is a very rare and serious condition. Enzyme replacement therapies are available for treatment of Gaucher disease but require the patient to visit a medical institution for an intravenous infusion every other week. Eliglustat is an oral capsule, and the substrate reduction therapy with eliglustat differs from existing enzyme replacement therapies in the mechanism of action and administration route. If eliglustat is approved, physicians can provide therapy suitable for their patient conditions. Making eliglustat available in clinical settings will be significant, adding a treatment option for alleviation of symptoms in patients with Gaucher disease.

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

In light of the rare nature and seriousness of Gaucher disease, PMDA evaluated the efficacy of eliglustat with data including those from non-Japanese clinical studies. PMDA evaluated the efficacy also in the individual Japanese subjects because the number of Japanese patients were as small as 10 in the global phase III study (Study EDGE)[111] in which Japanese subjects participated.

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108 Weinreb NJ, et al., *Am J Med*, 2002; 113:112-9, Pastores GM, et al., *Semin Hematol*, 2004; 41(S5):4-14, Masek BJ, et al., *Qual Life Res*, 1999; 8(3):263-8

109 Wenstrup RJ, et al., *J Bone Mineral Res*, 2007; 22(1):119-26

110 Cerezyme Package Insert in the US and Cerezyme Summary of Product Characteristics in EU

111 "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007) proposes a reference range of around 15% to 20% for the Japanese sample size in global clinical studies, but recruiting patients was difficult due to the rare nature of the disease. Japanese patients were enrolled in the global phase III study (Study EDGE) at a feasible level, and no Japanese sample size was set for ensuring consistency between the results of the overall and Japanese patient populations.

4.(iii).B.(2).1) Efficacy in patients with a history of ERT

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

The applicant responded as follows:

There is no difference in diagnostic procedures in and outside Japan, and manifestations differ greatly from patient to patient. Pharmacokinetics did not differ substantially between Japanese and non-Japanese patients with CYP2D6 EM [see "4.(ii).B.(1) Pharmacokinetics and drug interactions by CYP2D6 phenotype"]. Because ERT status was not specified in Study EDGE and patients with a wide range of disease severities were able to participate, patients with diverse treatment histories and characteristics were actually enrolled. The baseline ages (mean ± standard deviation) of the overall population (37.4 ± 15.0 years [n = 170]) and Japanese population (38.7 ± 14.3 years [n = 10]) were similar. As all 10 Japanese patients had undergone ERT, subject characteristics were verified in patients with a history of ERT, specifically in those patients who had received the therapy within 9 months of the study treatment, and efficacy was then evaluated in the Japanese and non-Japanese populations. All 10 Japanese patients and 107 of the 160 non-Japanese patients[112] (67%) were classified as having a history of ERT. Among those with a history of ERT, the baseline ages (mean ± standard deviation) of the overall population (38.1 ± 15.4 years [n = 117]) and Japanese population (38.7 ± 14.3 years [n = 10]) were similar. The percentage of subjects meeting the therapeutic goals at baseline was 73.5% (86 of 117 patients) in the overall population, 90.0% (9 of 10 patients) in the Japanese population, and 72.0% (77 of 107) in the non-Japanese population. Five of 10 Japanese patients and 29 of 107 non-Japanese patients had undergone total splenectomy. Efficacy results in the patients with a history of ERT are shown in Table 39. A total of 100% (10 of 10 subjects) of the Japanese population and 83% (94 of 113 subjects) of the overall population achieved all 5 therapeutic goals (hemoglobin concentration, platelet count, spleen volume, liver volume, bone symptoms) at the end of the open-label lead-in period. Since most subjects in both populations achieved the therapeutic goals, the 2 populations did not differ substantially.

Table 39. Efficacy results in patients with a history of ERT (Study EDGE, open-label lead-in period)

Endpoint	Treatment history with ERT		
	Overall population (n = 117)	Japanese population (n = 10)	Non-Japanese population (n = 107)
No. of subjects with a history of ERT evaluated	113	10	103
Meeting all 5 criteria	83.2 (94)	100 (10)	81.6 (84)
Meeting bone crisis criterion	100 (113)	100 (10)	100 (103)
Meeting hemoglobin criterion	92.9 (105)	100 (10)	92.2 (95)
Meeting platelet count criterion	91.2 (103)	100 (10)	90.3 (93)
Meeting spleen volume criterion	99.1 (112)	100 (10)	99.0 (102)
Meeting liver volume criterion	96.5 (109)	100 (10)	96.1 (99)

Percentage (number of subjects)

[112] Eighteen of the 107 non-Japanese subjects were in the open-label lead-in period.

Endpoint results in the patients with a history of ERT are shown in Table 40.[113] The changes in each endpoint from baseline to the respective time points were generally stable, with no major differences between the Japanese and overall populations.

Table 40. Endpoint results in patients with a history of ERT (Study GZGD03109 [EDGE], open-label lead-in period)

Endpoint	Time point	Overall population	Japanese population	Non-Japanese population
Hemoglobin concentration (g/dL)	Baseline	13.68 ± 1.53 (n = 117)	13.64 ± 1.32 (n = 10)	13.68 ± 1.55 (n = 107)
	Change (Week 26)	-0.21 ± 0.74 (n = 112)	-0.33 ± 0.78 (n = 9)	-0.20 ± 0.74 (n = 103)
	Change (Week 52)	-0.22 ± 0.84 (n = 36)	-0.29 ± 1.17 (n = 6)	-0.20 ± 0.79 (n = 30)
	Change (Week 78)	-0.17 ± 0.67 (n = 18)	0.12 ± 0.55 (n = 3)	-0.23 ± 0.69 (n = 15)
Platelet count (10^3/μL)	Baseline	190.96 ± 94.37 (n = 117)	182.15 ± 77.93 (n = 10)	191.79 ± 96.03 (n = 107)
	Percent change (Week 26) (%)	3.32 ± 18.20 (n = 112)	4.14 ± 14.23 (n = 9)	3.25 ± 18.56 (n = 103)
	Percent change (Week 52) (%)	9.13 ± 21.09 (n = 36)	9.01 ± 11.87 (n = 6)	9.15 ± 22.64 (n = 30)
	Percent change (Week 78) (%)	7.56 ± 32.44 (n = 18)	-10.00 ± 4.59 (n = 3)	11.07 ± 34.57 (n = 15)
Liver volume (MN[a])	Baseline	1.012 ± 0.236 (n = 117)	0.873 ± 0.148 (n = 10)	1.025 ± 0.239 (n = 107)
	Percent change (Week 26) (%)	0.59 ± 8.86 (n = 107)	-1.77 ± 7.47 (n = 9)	0.81 ± 8.98 (n = 98)
	Percent change (Week 52) (%)	1.05 ± 8.93 (n = 34)	5.09 ± 11.12 (n = 6)	0.18 ± 8.37 (n = 28)
	Percent change (Week 78) (%)	-0.17 ± 9.32 (n = 15)	-0.14 ± 1.41 (n = 2)	-0.17 ± 10.06 (n = 13)
Spleen volume (MN[a])	Baseline	4.045 ± 2.378 (n = 83)	3.660 ± 1.954 (n = 5)	4.070 ± 2.411 (n = 78)
	Percent change (Week 26) (%)	-4.06 ± 12.47 (n = 77)	-0.07 ± 16.48 (n = 5)	-4.34 ± 12.25 (n = 72)
	Percent change (Week 52) (%)	-6.32 ± 16.47 (n = 27)	1.81 ± 20.54 (n = 4)	-7.73 ± 15.77 (n = 23)
	Percent change (Week 78) (%)	-9.05 ± 16.33 (n = 11)	-	-9.05 ± 16.33 (n = 11)

Mean ± standard deviation; -, Not applicable
a) Calculated with the following formulas using volume measured by MRI:
spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

As shown in Table 24, all Japanese subjects achieved all 5 therapeutic goals at the final evaluation point in the open-label lead-in period and sustained efficacy was observed in every endpoint.

The percentage of subjects who remained stable[104] at Week 52 in Study ENCORE, a foreign study, in patients with a history of ERT showed the noninferiority of eliglustat to imiglucerase (Table 36). The percentages of subjects meeting the stability criteria at Week 52 were 94.4% (67 of 71 patients) in the eliglustat group and 100% (39 of 39 patients) in the imiglucerase group for spleen volume, 94.9% (94 of 99 subjects) in the eliglustat group and 100% (47 of 47 subjects) in the imiglucerase group for hemoglobin concentration, 92.9% (92 of 99 subjects) in the eliglustat group and 100% (47 of 47 subjects) in the imiglucerase group for platelet count, and 96.0% (95 of 99 subjects) in the eliglustat group and 93.6% (44 of 47 subjects) in the imiglucerase group for liver volume.

4.(iii).B.(2).2) Efficacy in treatment-naïve patients (with no history of ERT)

The applicant explained as follows:

Treatment-naïve patients were included in Study ENGAGE, a foreign study, and the foreign phase II study. Evaluation of the percent change in spleen volume from baseline to Week 39, the primary endpoint in Study ENGAGE, demonstrated the superiority of eliglustat over placebo (Table 32). The subjects in the phase II study maintained these improvements through Month 48 (Figure 1).

PMDA's view on the efficacy of eliglustat based on 1) and 2) above:

[113] If patients met the therapeutic goals and additional randomization criteria at evaluation points in the open-label lead-in period, they were randomized and transitioned to the primary analysis period. Therefore, the numbers of patients and baseline values at the respective time points differ as a result.

In Study ENGAGE, a foreign study, in treatment-naïve patients, the superiority of eliglustat over placebo has been demonstrated in the primary endpoint of percent change in spleen volume at Week 39. In Study ENCORE, a foreign study, in patients with a history of ERT, the noninferiority of eliglustat to imiglucerase has been demonstrated in the primary endpoint of the percentage of subjects in whom efficacy was sustained at Week 52. In patients with a history of ERT in the global phase III study, which included Japanese patients, the subjects in both the overall and Japanese populations remained stable.

It may be interpreted from the above findings that the efficacy of eliglustat in patients with Gaucher disease type 1 has been generally shown. The applicant must continue to collect information on the efficacy of eliglustat in post-marketing surveillance because only small number of Japanese subjects have been evaluated. PMDA will provide a final decision on this matter after taking account of comments raised in the Expert Discussion.

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

The applicant explained as follows:

The incidences of adverse events in Study EDGE, the global study, are shown in Table 41. Adverse events were not more frequent in the Japanese population than the in non-Japanese population. Common adverse events (with an incidence of ≥5%) in the overall population were nasopharyngitis, headache, dizziness, abdominal pain upper, upper respiratory tract infection, diarrhoea, constipation, dyspepsia, back pain, and palpitations. The events reported by at least 2 subjects in the Japanese population (n = 10) were nasopharyngitis, nausea, dizziness, and allergic rhinitis, each of which occurred in 2 subjects. There were no notable safety findings in the Japanese subjects as compared with the non-Japanese subjects through Week 78 of Study EDGE.

Table 41. Incidences of adverse events in Study EDGE

	Overall study			Treatment history with ERT		
	Overall population (n = 170)	Japanese population (n = 10)	Non-Japanese population (n = 160)	Overall population (n = 117)	Japanese population (n = 10)	Non-Japanese population (n = 107)
Adverse event	141 (82.9) 412	8 (80.0) 409	133 (83.1) 412	98 (83.8) 419	8 (80.0) 409	90 (84.1) 420
Adverse drug reaction	63 (37.1) 99	2 (20.0) 48	61 (38.1) 103	44 (37.6) 92	2 (20.0) 48	42 (39.3) 97
Serious adverse event	12 (7.1) 10	1 (10.0) 10	11 (6.9) 10	5 (4.3) 6	1 (10.0) 10	4 (3.7) 6
Serious adverse drug reaction	3 (1.8) 2	1 (10.0) 10	2 (1.3) 1	2 (1.7) 2	1 (10.0) 10	1 (0.9) 1
Adverse event leading to treatment discontinuation	2 (1.2) 4	0 (0.0) 0	2 (1.3) 4	1 (0.9) 1	0 (0.0) 0	1 (0.9) 1
Mild adverse event	132 (77.6) 303	8 (80.0) 333	124 (77.5) 301	93 (79.5) 309	8 (80.0) 333	85 (79.4) 307
Moderate adverse event	65 (38.2) 92	4 (40.0) 67	61 (38.1) 94	45 (38.5) 95	4 (40.0) 67	41 (38.3) 98
Severe adverse event	17 (10.0) 16	1 (10.0) 10	16 (10.0) 16	11 (9.4) 15	1 (10.0) 10	10 (9.3) 15

Number of subjects with event (incidence %) number of events per 100 patient-years

In the pooled analysis of the phase II/III studies,[114] the incidences of adverse events and adverse drug reactions were 85.0% (334 of 393 subjects) and 40.5% (159 of 393 subjects), respectively. The incidence of serious adverse events was 8.9% (35 of 393 subjects), and that of adverse events leading to treatment discontinuation was 3.3% (13 of 393 subjects). The serious adverse events reported by at least 2 subjects were syncope (5 subjects), myocardial infarction (3 subjects), maternal exposure during pregnancy (2 subjects), and cholecystitis (2 subjects). Of these, syncope in 3 subjects was assessed as an adverse drug reaction.

[114] Pooled data for 393 patients with Gaucher disease type 1 receiving eliglustat in the phase II and III studies as of the [redacted] data cutoff. (Data of Study EDGE includes only data in the lead-in period.)

The incidences of adverse events occurring in ≥5% of the subjects in the pooled analysis of the phase II/III studies are shown in Table 42. Most events were mild in severity.

Table 42. Incidences of adverse events in ≥5% of subjects in the pooled analysis of phase II/III studies

	Overall eliglustat group (n = 393)				
	All adverse events	All adverse drug reactions	Mild adverse events	Moderate adverse events	Severe adverse events
All adverse events	334 (85.0)	159 (40.5)	153 (38.9)	136 (34.6)	45 (11.5)
Headache	66 (16.8)	21 (5.3)	49 (12.5)	13 (3.3)	4 (1.0)
Arthralgia	55 (14.0)	7 (1.8)	32 (8.1)	18 (4.6)	5 (1.3)
Nasopharyngitis	53 (13.5)	0 (0.0)	44 (11.2)	9 (2.3)	0 (0.0)
Upper respiratory tract infection	43 (10.9)	0 (0.0)	35 (8.9)	8 (2.0)	0 (0.0)
Diarrhoea	39 (9.9)	17 (4.3)	34 (8.7)	5 (1.3)	0 (0.0)
Dizziness	38 (9.7)	18 (4.6)	31 (7.9)	7 (1.8)	0 (0.0)
Back pain	35 (8.9)	1 (0.3)	16 (4.1)	17 (4.3)	2 (0.5)
Abdominal pain upper	33 (8.4)	12 (3.1)	26 (6.6)	5 (1.3)	2 (0.5)
Nausea	33 (8.4)	13 (3.3)	22 (5.6)	11 (2.8)	0 (0.0)
Pain in extremity	31 (7.9)	5 (1.3)	21 (5.3)	9 (2.3)	1 (0.3)
Fatigue	29 (7.4)	8 (2.0)	18 (4.6)	9 (2.3)	2 (0.5)
Dyspepsia	28 (7.1)	16 (4.1)	17 (4.3)	9 (2.3)	2 (0.5)
Abdominal pain	25 (6.4)	10 (2.5)	17 (4.3)	7 (1.8)	1 (0.3)
Influenza	23 (5.9)	0 (0.0)	14 (3.6)	9 (2.3)	0 (0.0)
Sinusitis	23 (5.9)	2 (0.5)	12 (3.1)	11 (2.8)	0 (0.0)
Urinary tract infection	23 (5.9)	2 (0.5)	14 (3.6)	9 (2.3)	0 (0.0)
Constipation	23 (5.9)	13 (3.3)	18 (4.6)	5 (1.3)	0 (0.0)
Cough	23 (5.9)	1 (0.3)	20 (5.1)	3 (0.8)	0 (0.0)
Gastrooesophageal reflux disease	20 (5.1)	10 (2.5)	13 (3.3)	7 (1.8)	0 (0.0)
Palpitations	20 (5.1)	7 (1.8)	18 (4.6)	2 (0.5)	0 (0.0)

Number of subjects with event (incidence %); MedDRA/J version 15.1

The incidences of adverse events by dose at onset were as shown in Table 43. Although adverse event incidences increased with increasing dose, the number of events per 100 patient-years did not tend to increase as the dose increased.

Table 43. Incidence of adverse events by dose at onset in the pooled analysis of phase II/III studies

	50 mg BID (n = 391)	100 mg BID (n = 319)	150 mg BID (n = 98)	Overall (n = 393)
Adverse event	181 (46.3) 547	225 (70.5) 364	78 (79.6) 413	334 (85.0) 437
Adverse drug reaction	77 (19.7) 149	86 (27.0) 55	34 (34.7) 71	159 (40.5) 83
Serious adverse event	11 (2.8) 9	12 (3.8) 5	9 (9.2) 10	35 (8.9) 8
Mild	157 (40.2) 420	203 (63.6) 267	68 (69.4) 300	308 (78.4) 325
Moderate	67 (17.1) 108	103 (32.3) 91	35 (35.7) 95	171 (43.5) 99
Severe	18 (4.6) 19	14 (4.4) 7	14 (14.3) 18	45 (11.5) 13

Number of subjects with event (incidence %) number of events per 100 patient-years

The incidences of adverse events by duration of treatment were as shown in Table 44. The incidences and number of events per 100 patient-years did not increase with increasing duration of treatment.

Table 44. Incidence of adverse events by duration of treatment in the pooled analysis of phase II/III studies

	≤6 months (n = 393)	>6 to ≤12 months (n = 348)	>12 to ≤18 months (n = 204)	>18 to ≤24 months (n = 114)	>24 to ≤30 months (n = 62)	>30 to ≤36 months (n = 32)	>36 to ≤42 months (n = 20)	>42 to ≤48 months (n = 19)
Adverse event	298 (75.8) 210	186 (53.4) 99	101 (49.5) 46	49 (43.0) 29	22 (35.5) 12	8 (25.0) 3	7 (35.0) 3	7 (36.8) 3
Adverse drug reaction	121 (30.8) 53	52 (14.9) 16	17 (8.3) 6	11 (9.6) 3	3 (4.8) 1	0 (0) 0	1 (5.0) 0	0 (0) 0
Serious adverse event	16 (4.1) 3	12 (3.4) 3	5 (2.5) 1	1 (0.9) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

Number of subjects with event (incidence %) number of events per 100 patient-years

The incidence of adverse events was 85% (219 of 259 subjects) in the subjects with a history of ERT[115] and 86% (115 of 134 subjects) in the subjects without a history of ERT. Incidences did not differ substantially according to prior treatment status.

PMDA asked the applicant why the incidences of adverse events tended to be higher in the eliglustat group than in the imiglucerase group in Study ENCORE as shown in Table 38.

The applicant responded as follows:
The incidences of adverse events in Study ENCORE were 91.5% (97 of 106 subjects) in the eliglustat group and 79.2% (42 of 53 subjects) in the imiglucerase group. Study ENCORE was open-label because eliglustat is an oral dosage form and the comparator imiglucerase is an intravenous infusion. ERT has been the standard of care for patients with Gaucher disease for over 20 years, and imiglucerase, approved in 1998, has long been in use. The patients enrolled in Study ENCORE were likely tolerable of long-term ERT because the inclusion criteria of the study required at least 3 years of previous ERT. Infusion associated reactions, a common reaction to ERT, occur less frequently with continued treatment and by adjusting the infusion rate.[116] Thus, the inclusion of patients already treated with imiglucerase and the open-label nature of the study may have affected the incidence of adverse events.

Given that the applicant provides appropriate precautionary statement, PMDA has concluded that the safety of eliglustat is acceptable with respect to the incidences of adverse events in the global phase III study (Study EDGE) and foreign clinical studies and in light of the discussion about individual events described in 1) to 5) below.

4.(iii).B.(3).1) Proarrhythmic risk

The applicant explained as follows:
The upper bound of the one-sided 95% confidence interval of ΔΔQTcF at the high dose of 800 mg in the thorough QT/QTc study was 9.3 ms, which is negative according to the ICH E14 guidelines. However, drug concentration-response modeling demonstrated a positive correlation between the plasma concentrations of unchanged eliglustat and the mean changes in placebo-adjusted QTcF, PR, and QRS intervals from baseline. These findings suggested that QTcF, PR, and QRS interval prolongation occurred under conditions of marked drug interactions because eliglustat is extensively metabolized by CYP2D6 and partially metabolized by CYP3A [see "4.(ii).B.(2) QT/QTc prolongation and proarrhythmic risk"].

115 Patients who had not undergone ERT within 12 months of study entry (phase II study) or 9 months of study entry (Studies ENGAGE and EDGE) were considered to be without a history of ERT. (The durations without ERT prior to study entry for the phase II study and Study ENGAGE agree with their inclusion criteria.) The patients enrolled in Study ENCORE and patients in Study EDGE who were not found to be "without a history of ERT" were considered to be "with a history of ERT."

116 Starzyk K, et al., *Mol Gen Metab*, 2007; 90:157-63

No sudden cardiac death or torsade de pointes (TdP) was found as an adverse event in the pooled analysis of phase II/III studies.[114] The incidence of proarrhythmic events[117] in the eliglustat group in the pooled analysis of phase II/III studies was 3.8% (15 of 393 subjects) (2 [phase II study], 3 [Study ENGAGE], 6 [Study ENCORE], and 4 [Study EDGE]). These events included atrioventricular block second degree/atrioventricular block in 1 subject (Study ENGAGE); atrioventricular block second degree in 3 subjects (1 [Study ENGAGE] and 2 [Study ENCORE]); ventricular tachycardia in 3 subjects (2 [phase II study] and 1 [Study ENCORE]); supraventricular tachycardia in 2 subjects (Study EDGE); atrioventricular block first degree in 1 subject (Study ENCORE); sinoatrial block in 1 subject (Study ENCORE); arrhythmia supraventricular in 1 subject (Study EDGE); atrial tachycardia in 1 subject (Study EDGE); ventricular extrasystoles in 1 subject (Study ENCORE); and tachycardia in 1 subject (Study ENGAGE). All events other than atrioventricular block second degree in 1 subject and ventricular tachycardia in 1 subject were classified as adverse drug reactions.

The subjects experiencing a proarrhythmic event who concomitantly used a CYP2D6 inhibitor, CYP3A inhibitor, or QT-interval prolonging drug at the time of onset were an EM in Study ENCORE with atrioventricular block second degree (a strong CYP2D6 inhibitor), an IM in Study ENCORE with ventricular tachycardia (a weak CYP3A inhibitor and a weak CYP2D6/weak CYP3A inhibitor), an EM in the phase II study with ventricular tachycardia (a weak CYP3A inhibitor), and an EM in Study EDGE with supraventricular tachycardia (a strong CYP3A inhibitor/QT-interval prolonging drug). Among them, the subject with atrioventricular block second degree had an abnormal electrocardiogram (abnormal PR interval).

Serious proarrhythmic events occurred in 2 subjects (atrioventricular block/atrioventricular block second degree, ventricular tachycardia). Both were subjects with CYP2D6 EM phenotype.

The subject with atrioventricular block/atrioventricular block second degree was a 23-year-old non-Japanese woman in Study ENGAGE on 150 mg BID in the long-term treatment period. She experienced dizziness upon standing from Days 413 to 416, and atrioventricular block/atrioventricular block second degree was identified in Holter monitoring performed on Day 421. Each event was mild in severity and classified as an adverse drug reaction. Treatment with eliglustat was suspended from Days 434 to 442 but later was resumed at the reduced dose of 50 mg BID and then increased to 100 mg BID. No events occurred subsequently. The subject received no concomitant drugs and had no QTcF, PR, or QRS interval abnormality at event onset. A cardiologist concluded that these episodes of early morning atrioventricular block/atrioventricular block second degree were likely to be physiological phenomena related to nocturnal vagotonia. In the subject, atrioventricular block first degree was diagnosed at screening, and atrioventricular block second degree was found by Holter monitoring at Week 13 visit, but these events were not considered to be clinically significant.

The subject with ventricular tachycardia was a 60-year-old non-Japanese man in the phase II study. Consecutive asymptomatic monomorphic ventricular tachycardia (3 couplets, 155 bpm) was identified in Holter monitoring 12 hours after the subject received 50 mg QD on Day 1. The subject then discontinued

[117] All events listed under the 4 High Level Terms “Cardiac conduction disorders,” “Rate and rhythm disorders,” “Supraventricular arrhythmias,” and “Ventricular arrhythmias and cardiac arrest” in the relevant High-Level Group Term.

treatment. The event was mild in severity and classified as an adverse drug reaction. Atrioventricular block first degree (PR interval, 210-220 ms) was identified in electrocardiography performed after event occurrence but was found to be clinically insignificant. No other changes in electrocardiograms were identified as compared with those taken before the event onset. An independent ventricular extrasystole was only identified in Holter monitoring 24 hours postdose. The subject had a history of mild aortic valve thickening identified in echocardiography. Slight atrial extrasystoles and ventricular extrasystoles were seen approximately 1 hour before the first dose. The subject received no concomitant drugs and had no QTcF, PR, or QRS interval abnormality at event onset.

Proarrhythmic events leading to treatment discontinuation were ventricular tachycardia occurring in 2 subjects. Both were EMs in the phase II study and discontinued treatment after the first dose of 50 mg eliglustat.

Of these, one subject, a 56-year-old non-Japanese woman, was found to have mitral valve prolapse in echocardiography performed approximately 4 months before study enrollment. The subject discontinued treatment because of 2 episodes of non-sustained asymptomatic ventricular tachycardia occurring after the first dose of 50 mg eliglustat. The first episode was a non-sustained 4-beat run of asymptomatic ventricular tachycardia (heart rate, 158 bpm) 6 hours postdose. The second episode occurred as slow ventricular tachycardia with aberrant conduction (non-sustained ventricular tachycardia with right bundle branch block morphology; heart rate, 120 bpm) 13 hours postdose. Both episodes were mild and non-serious, and a causal relationship with the study drug was ruled out. The longest, fastest run was a 13-beat run (heart rate, 203 bpm).

The other subject was the previously mentioned subject with serious ventricular tachycardia. For each subject, electrocardiography performed after eliglustat administration revealed no clinically significant changes as compared with previous electrocardiographic findings, and no tendency toward QTcF interval prolongation was observed in association with changes in plasma concentrations of unchanged eliglustat.

PMDA asked the applicant to present details about subjects with abnormal electrocardiogram (ECG) found in the clinical studies in patients, and occurrence of any arrhythmia-related adverse events in these subjects.

The applicant responded as follows:
Holter monitoring and 12-lead electrocardiography at C_{max} were performed in the phase II study,[118] Study ENGAGE,[119] and Study ENCORE.[120] Electrocardiograms were read centrally. Holter monitoring and 12-lead

[118] In the phase II study, 12-lead electrocardiographic assessment was performed at the following time points: at screening; 0 (predose), 1, 2, 3, 4, 6, 12, and 24 hours postdose on Day 1; 0 (predose), 1, 2, 3, and 6 hours postdose on Days 10 and 20 and at Weeks 13, 39, and 52; 0 (predose), 1, 2, 3, 4, 6, and 12 hours postdose on Day 30 and at Week 26; and 0 (predose), 1, 2, 3, and 4 hours postdose at Weeks 65, 78, 91, and 104. Twenty-four-hour Holter electrocardiography was performed at Week 52.

[119] In Study ENGAGE, 12-lead electrocardiographic assessment was performed at screening, 0 (predose), 1, 2, 3, and 4 hours postdose on Day 1 and Week 39, and 1, 2, 3, and 4 hours postdose at Weeks 4, 13, 26, 41, 43, 45, 47, 52, 65, 78, 91, 104, 117, and 130. Twenty-four-hour Holter electrocardiography was performed at screening and Weeks 13 and 52.

[120] In Study ENCORE, 12-lead electrocardiographic assessment was performed at screening, 0 (predose), 1, 2, 3, and 4 hours postdose on Day 1 and Weeks 13, 26, 39, 52, 65, 78, 91, and 104. Twenty-four-hour Holter electrocardiography was performed at screening and Weeks 13 and 65.

electrocardiography were also performed in Study EDGE,[121] but electrocardiograms were read by a machine. Of the 389 subjects who received eliglustat and underwent electrocardiographic evaluation in the phase II and III clinical studies, 28 (7.2%) had findings considered to be electrocardiographic parameter abnormalities.[122] No subject in the control groups (the placebo group in Study ENGAGE and the imiglucerase group in Study ENCORE) had abnormal findings in any parameters.

Findings indicating QTcF interval abnormalities are given in Table 45. Of the subjects with the abnormalities, a 2[redacted]-year-old Japanese woman with EM in Study EDGE experienced dizziness, syncope, and an adverse event corresponding to the Standardized MedDRA Query (SMQ) term of "cardiac arrhythmia." The subject experienced dizziness (Day 29 at 100 mg BID) and syncope (Day 113 at 150 mg BID). Syncope was classified as a serious adverse drug reaction [see "4.(iii).B.(3).2) Syncope" for more information on syncope]. No tendency toward an increase in QTc interval related to study drug administration or plasma concentrations of unchanged eliglustat was noted on the day of onset of dizziness or at the Day 99 visit (150 mg BID, before syncope occurrence).

Table 45. Findings indicating QTcF interval abnormalities in phase II and III studies (12-lead electrocardiography)

Study name	Age	Race	Sex	CYP2D6 phenotype	Dosage at onset	Time of onset	Time after dose (h)	Baseline (ms)	Measurement at maximum change (ms)	Maximum change (ms)	C_{max} at maximum change (ng/mL)
EDGE[a)]	51	Non-Japanese	F	EM	100 mg BID	Week 26	1	462	502	40	10.2[d)]
	65	Non-Japanese	F	EM	50 mg BID	Day 1	2	463	483	19	50.5[d)]
	2[redacted]	Japanese[b)]	M	IM	50 mg BID	Week 2	1	340	451	111	21.9
	2[redacted]	Japanese[b)]	F	EM	150 mg BID	Week 8	pre	354	415	61	6.66
	35	Non-Japanese[b)]	M	EM	100 mg BID	Week 26	2	363	435	72	13.8
	30	Non-Japanese[b)]	M	EM	50 mg BID	Week 2	3	363	432	69	10.5[d)]
	24	Non-Japanese	M	EM	50 mg BID	Week 2[c)]	4	351	427	77	33.3[d)]
	26	Non-Japanese	F	EM	100 mg BID	Week 78	3	379	441	62	18.9[d)]

a) Electrocardiograms were read by an analyzer.
b) PR and QRS interval abnormalities were also noted.
c) Abnormal ECG was also found at other times.
d) Plasma concentrations of unchanged eliglustat were not concurrently obtained. The maximum plasma concentrations of unchanged eliglustat recorded in the study are listed instead.

Findings indicating PR interval abnormalities are given in Table 46. Of the subjects with PR interval abnormalities, 2 in Study ENCORE experienced dizziness, syncope, and SMQ cardiac arrhythmia.

One of the 2 subjects was a 69-year-old non-Japanese man with EM in Study ENCORE who experienced atrioventricular block second degree (Day 92 at 50 mg BID) on the day of the PR interval abnormality. The subject exhibited PR interval prolongation throughout the study and had Mobitz type 1 and 2:1 atrioventricular

[121] In Study EDGE, 12-lead electrocardiographic assessment was performed for the Japanese subjects at 0 (predose) hours postdose on Days 1 and 2 and at 0 (before), 1, 2, 3, and 4 hours postdose at Weeks 2, 4, 8, 13, 26, 52, and 78 or on transition to the double-blind period. Twelve-lead electrocardiographic assessment was performed for the non-Japanese subjects at 0 (before), 1, 2, 3, and 4 hours postdose on Day 1 and Weeks 2, 13, 26, 52, and 78 or on transition to the double-blind period. Twenty-four hour Holter monitoring was performed at screening and Week 78 or on transition to the double-blind period.

[122] The predefined criteria for abnormal findings were QRS interval of ≥120 ms for QRS interval abnormality, PR interval increase of >200 ms and ≥25% from baseline for PR interval abnormality, and QTcF interval change from ≤480 ms at baseline to >480 ms after treatment or increase of >60 ms from baseline for QTcF interval abnormality.

block on the Week 13 Holter monitoring. The central reader considered this subject to have severe pre-existing atrioventricular conduction system disease, as evidenced by the extremely prolonged PR interval at baseline, and judged it was unclear whether or not eliglustat treatment contributed to further prolongation of the PR interval and episodes of atrioventricular block. The subject was on a strong CYP2D6 inhibitor at event onset. The other subject was a 35-year-old non-Japanese woman with EM who experienced syncope on Day 105 at 150 mg BID. No tendency toward an increase in PR interval was observed at the visit following syncope onset (Day 114 at 150 mg BID).

Table 46. Findings indicating PR interval abnormalities in phase II and III studies (12-lead electrocardiography)

Study name	Age	Race	Sex	CYP2D6 phenotype	Dosage at onset	Time of onset	Time after dose (h)	Baseline (ms)	Measurement at maximum change (ms)	Maximum change (ms)	C_{max} at maximum change (ng/mL)
ENCORE[a)]	69	Non-Japanese	M	EM	50 mg BID	Week 13	4	398	568	170	32.6
	35	Non-Japanese	F	EM	150 mg BID	Week 52	1	154	208	54	29.9
	20	Non-Japanese	F	EM	150 mg BID	Week 13	Pre	137	206	69	23.7
	42	Non-Japanese	F	IM	100 mg BID	Week 52[c)]	2	155	205	50	40.4
EDGE[a)]	2[redacted]	Japanese[b)]	M	IM	50 mg QD	Day 1	3	207	260	53	5.61
	33	Non-Japanese	F	EM	100 mg BID	Week 13[c)]	1, 2	120	220	100	20.8
	44	Non-Japanese	M	EM	50 mg BID	Week 2	1	160	240	80	28.5[d)]

a) Electrocardiograms were read by a specialist at the center in Study ENCORE and by an analyzer in Study EDGE study.
b) QTcF and QRS interval abnormalities were also noted.
c) Abnormal ECG was also found at other times.
d) Plasma concentrations of unchanged eliglustat were not concurrently obtained. The maximum plasma concentrations of unchanged eliglustat recorded in the study are listed instead.

Findings indicating QRS interval abnormalities are given in Table 47. Among all subjects other than 2 subjects whose data were judged by a cardiologist to have been misread, dizziness, syncope, and SMQ cardiac arrhythmia were reported in one 2[redacted]-year-old Japanese woman with EM in Study EDGE (same subject with QTcF interval abnormality noted previously) and one 46-year-old non-Japanese man with EM in Study EDGE. The 46-year-old non-Japanese man with EM developed a QRS interval abnormality before taking 100 mg BID at Week 13 and experienced dizziness when taking 50 mg BID on Day 2, but no abnormal ECG findings were observed at the visits (Days 1 and 15 at 50 mg BID) around the dizziness episode.

Table 47. Findings indicating QRS interval abnormalities in phase II and III studies (12-lead electrocardiography)

Study name	Age	Race	Sex	CYP2D6 phenotype	Dosage at onset	Time of onset	Time after dose (h)	Baseline (ms)	Measurement at maximum change (ms)	Maximum change (ms)	C_{max} at maximum change (ng/mL)
ENGAGE[a)]	31	Non-Japanese	M	EM	150 mg BID	Week 143	3	104	120	16	24.7[e)]
	24	Non-Japanese	M	EM	100 mg BID	Week 4[c)]	2	106	127	21	21.7
ENCORE[a)]	54	Non-Japanese	M	EM	50 mg BID	Day 1[c)]	4	105	122	17	4.82
EDGE[a)]	2[redacted]	Japanese[b)]	M	IM	50 mg BID	Week 2[c)]	Pre	67	240	173	6.42
	2[redacted]	Japanese[b)]	F	EM	50 mg QD	Day 1	1	120	120	0	7.84
					50 mg BID	Week 2	Pre, 1, 2, 3, 4				
	35	Non-Japanese[b)]	M	EM	50 mg BID	Day 1	1, 2, 3, 4	113	120	7	2.64
	30	Non-Japanese[b)]	M	EM	50 mg BID	Day 1	4	100	120	20	10.5[e)]
	33	Non-Japanese	M	EM	100 mg BID	Week 52[c)]	1	113	129	16	29.1[e)]
	33	Non-Japanese	M	EM	100 mg BID	Weeks 13 and 26[c)]	1	113	126	13	6.43
	46	Non-Japanese	M	EM	100 mg BID	Week 13	pre	101	122	21	2.03
	34	Non-Japanese	M	EM	100 mg BID	Week 26[c)]	1	106	134	28	28.8[e)]
	49	Non-Japanese	F	EM	50 mg BID	Week 2	2	80	120	40	11.6
					100 mg BID	Week 26	1		120	40	59.6[e)]
	64	Non-Japanese	M	EM	100 mg BID	Week 26	pre	100	120	20	16.8[e)]
	44	Non-Japanese	F	EM	100 mg BID	Week 26[c)]	1	103	134	31	34.7[e)]
	45	Non-Japanese	M	EM	50 mg BID	Week 2[c)]	3	133	141	8	18.0[e)]
	54	Non-Japanese	M	EM	100 mg BID	Week 13	pre, 1	117	120	3	12.1
	19	Non-Japanese	M	EM	100 mg BID	Week 6	pre	100	100[d)]	0	6.32
	22	Non-Japanese	M	EM	50 mg BID	Week 2	4	106	112[d)]	6	37.9[e)]

a) Electrocardiograms were read by a specialist at the center in Studies ENGAGE and ENCORE and by an analyzer in Study EDGE.
b) QTcF and PR interval abnormalities were also noted.
c) Abnormal ECG was also found at other times.
d) Reassessed values after initially judged by a cardiologist to have been misread (initial values were 124 mg for the 19-year-old man and 122 ms for the 22-year-old man)
e) Plasma concentrations of unchanged eliglustat were not concurrently obtained. The maximum plasma concentrations of unchanged eliglustat recorded in the study are listed instead.

In summary, many of the subjects with abnormal ECG did not experience dizziness, syncope, or SMQ cardiac arrhythmia, and adverse events were unrelated to the abnormal ECG. Therefore, calling attention to use with concomitant drugs according to the results of drug concentration-response modeling conducted in the thorough QT/QTc study as well as PBPK modeling will be sufficient to maintain the eliglustat exposure within the range found safe and effective in the clinical studies. It was thus decided to include precautionary statements in the package insert on drug interactions that possibly increase substantially plasma concentrations of unchanged eliglustat (e.g., interaction with multiple drugs). Precautionary statements on concomitant use with drugs that potentially prolong QT intervals were also to be included in the package insert.

PMDA asked the applicant to discuss the need for an electrocardiographic examination at the start of and regular examinations during eliglustat treatment and the need for electrocardiographic examinations upon any changes in concomitant drug regimen that possibly affect the pharmacokinetics of eliglustat.

The applicant responded as follows:
Patients with structural heart disease, myocardial infarction, congestive cardiac failure, or arrhythmia were not evaluated in the clinical studies. Use of eliglustat should thus be avoided in patients with cardiac disease (congestive cardiac failure, acute myocardial infarction, bradycardia, cardiac block, ventricular arrhythmia), patients with QT prolongation syndrome, or patients on a class IA (e.g., quinidine) or class III (e.g., amiodarone,

sotalol) antiarrhythmic. Moreover, eliglustat should be used with care in patients with mild cardiac findings or symptoms. Drug interactions with drugs that potentially affect significantly the pharmacokinetics of eliglustat can be appropriately addressed by including precautionary statements in the package insert given that QT prolongation was not detected at the 800 mg dose in the thorough QT/QTc study and that treatment with eliglustat is to be recommended only in patients with CYP2D6 IM and EM. Electrocardiographic monitoring is therefore considered unnecessary during treatment with eliglustat or upon any changes in a concomitant drug regimen that possibly affect pharmacokinetics of eliglustat.

PMDA considers as follows:
Although QT prolongation was not detected after a single dose of 800 mg eliglustat according to the ICH E14 guidelines, but it was suggested that QTcF, PR, and QRS intervals possibly increase with increasing plasma concentrations of unchanged eliglustat. In the phase II and III studies, thorough electrocardiographic examinations were performed regularly and revealed proarrhythmic events (e.g., atrioventricular block) and abnormal ECG in the eliglustat groups, even among the patients with CYP2D6 EM. After the market launch, eliglustat will be used in a wider patient population than that studied in the clinical studies, and many various drugs are likely to be used concomitantly with eliglustat. Accordingly, exposure in some patients may be higher than that achieved at the high dose in the thorough QT/QTc study, which in turn may result in marked QTcF interval prolongation and occurrence of atrioventricular block. The applicant must therefore appropriately provide precautionary advice not only about the intended population and drug interactions with concomitant drugs but also about implementation of electrocardiography during treatment with eliglustat. The applicant must also continue to collect information on proarrhythmic risk (including that associated with concomitant drugs) in the post-marketing phase. PMDA will make a final decision on the wording of the precautionary statements about proarrhythmic risk in the package insert based on comments from the Expert Discussion.

4.(iii).B.(3).2) Syncope
The applicant explained as follows:
The incidence of adverse event syncope in the eliglustat group in the pooled analysis of the phase II/III studies[114] was 2.0% (8 of 393 subjects) (4 subjects in Study ENCORE, 4 subjects in Study EDGE). Syncope occurred in 1 subject with CYP2D6 PM (at 50 mg QD [mild]) and 7 subjects with EM (4 at 100 mg BID [mild, 1; moderate, 2; severe, 1] and 3 at 150 mg BID [severe]). All cases of syncope occurred in women. The events were classified as serious adverse events in 5 subjects and as adverse drug reactions in 3 subjects.

Of the subjects who experienced syncope, subjects who were concomitantly using a CYP2D6 inhibitor, CYP3A inhibitor, or QT-interval prolonging drug at the time of onset were 3 EMs in Study ENCORE (a weak CYP2D6/weak CYP3A inhibitor, a weak CYP3A inhibitor, a weak CYP2D6 inhibitor), 1 PM in Study EDGE (a weak CYP2D6/weak CYP3A inhibitors), and 1 EM in Study EDGE (a weak CYP2D6 inhibitor/QT-interval prolonging drug). Abnormal ECG (abnormal PR interval) was found in the subject who received eliglustat concomitantly with weak CYP2D6/weak CYP3A inhibitors in Study ENCORE.

One of the 4 subjects in the eliglustat group of Study EDGE who experienced syncope was Japanese, and the event was classified as a serious adverse event. The subject, a 2[redacted]-year-old woman with EM, experienced strong abdominal discomfort and shortness of breath when standing and suddenly lost consciousness on Day 113 of treatment with eliglustat 150 mg BID but regained consciousness 2 minutes later without treatment. An electrocardiogram on ambulance arrival was normal, blood pressure was 132/83 mmHg, and heart rate was 98 bpm. The event was severe in intensity and was classified as an adverse drug reaction. Thereafter, she was asymptomatic and had a normal electrocardiogram 6 days after the event occurrence. After syncope occurrence, the eliglustat dose was reduced from 150 mg BID to 50 mg BID on Day 149 but was later increased to 100 mg BID. For the patient, Holter monitoring at screening was normal while QRS interval abnormalities were observed on Day 1 and at Week 2, and QTcF interval abnormalities were seen at Week 8. These abnormal ECG findings were not considered clinically significant [see "4.(iii).B.(3).1) Proarrhythmic risk"].

One of the other 3 subjects was a CYP2D6 PM. Syncope in all the 3 subjects was vasovagal in nature, and was associated with other risk factors (empty stomach, antihypertensive use, untreated hypotension, dehydration). None of the 3 subjects had an abnormal ECG. No factors that could have caused syncope were revealed in electrocardiography, computed tomography (CT) scans, or radiography performed after event onset in these 4 subjects with syncope in Study EDGE.

In the primary analysis period of Study ENCORE, syncope occurred in 3 of 106 subjects (3%) in the eliglustat group but in none of the 53 subjects in the imiglucerase group. All of the 3 subjects experiencing syncope were CYP2D6 EMs. The 3 subjects with syncope in the eliglustat group had risk factors (hunger, blood sampling, pain), and syncope in these subjects were judged by the investigator to be vasovagal syncope. A cardiologist found no evidence supporting cardiogenic syncope and likewise classified these events as vasovagal syncope. In 1 of the 3 subjects (a 35-year-old Caucasian woman), syncope occurred on Day 105, and PR interval abnormalities (PR interval was 32.5% to 35.1% higher than that at baseline and 204 to 208 ms in duration) were observed 1 and 2 hours postdose at Week 52.

In the 8 subjects with syncope, the number of days from the start of eliglustat treatment and the time from the most recent administration to the occurrence show no clear patterns, and no adverse events related to cardiac conduction or rhythm disorders developed. No subjects discontinued study treatment because of syncope occurrence. Data of echocardiographic examinations performed after administration were collected in Studies ENGAGE and ENCORE and revealed no adverse drug reactions of concern.

Except for 1 occurrence of syncope for which the cause is not reported (the first subject described above in Study EDGE), the syncope in the clinical studies was vasovagal in nature and had associated risk factors (blood sampling, empty stomach, pain). Electrocardiography performed as part of the post-event diagnostic tests revealed no arrhythmias that could have caused syncope. The electrocardiographic findings are therefore considered unrelated to syncope.

PMDA considers that the applicant must continue to collect information on syncope in the post-marketing phase because serious syncope has occurred, eliglustat has a QTcF interval prolonging effect, and a limited number of subjects were evaluated in the clinical studies.

4.(iii).B.(3).3) Gastrointestinal symptoms

The applicant explained as follows:

The incidences of adverse events in the SOC "gastrointestinal disorders" by dose at onset in the pooled analysis of the phase II/III studies[114] were as shown in Table 48. Although adverse event incidences increased with increases in dose, the number of events per 100 patient-years did not tend to increase as the dose increased.

Table 48. Incidence of gastrointestinal disorder adverse events by dose at onset in the pooled analysis of phase II/III studies

SOC Gastrointestinal disorders	50 mg BID (n = 391)	100 mg BID (n = 319)	150 mg BID (n = 98)	All doses (n = 393)
Adverse events	67 (17.1) 89	93 (29.2) 59	35 (35.7) 74	163 (41.5) 72
Mild	56 (14.3) 68	76 (23.8) 44	30 (30.6) 54	143 (36.4) 53
Moderate	18 (4.6) 20	28 (8.8) 14	16 (16.3) 19	52 (13.2) 17
Severe	2 (0.5) 2	5 (1.6) 2	2 (2.0) 2	10 (2.5) 2

Number of subjects with event (incidence %) number of events per 100 patient-years

Major events were diarrhoea, abdominal pain upper, nausea, dyspepsia, abdominal pain, constipation, and reflux gastroenteritis. Most events were mild in severity and occurred within 6 months of the start of eliglustat treatment. Most episodes of diarrhoea were transient (median duration, 3 days).

PMDA accepts the applicant's explanation but considers that the applicant must continue to collect information on gastrointestinal disorders in the post-marketing phase because only a limited number of subjects were evaluated in the clinical studies.

4.(iii).B.(3).4) Neurological symptoms

The applicant explained as follows:

The incidences of adverse events in the SOC "nervous system disorders" in the pooled analysis of the phase II/III studies[114] by dose at onset were as shown in Table 49. Although incidences increased with increases in dose, the number of events per 100 patient-years did not tend to increase as the dose increased. Most events were headache or dizziness, and both of them were mostly mild in severity.

Table 49. Incidence of nervous system disorder adverse events by dose at onset in pooled analysis of phase II/III studies

SOC Nervous system disorders	50 mg BID (n = 391)	100 mg BID (n = 319)	150 mg BID (n = 98)	All doses (n = 393)
Adverse events	61 (15.6) 76	66 (20.7) 43	33 (33.7) 48	126 (32.1) 54
Mild	56 (14.3) 66	51 (16.0) 30	26 (26.5) 35	111 (28.2) 42
Moderate	9 (2.3) 8	22 (6.9) 11	6 (6.1) 7	35 (8.9) 10
Severe	2 (0.5) 2	3 (0.9) 1	6 (6.1) 5	10 (2.5) 2

Number of subjects with event (incidence %) number of events per 100 patient-years

These events were mostly reported within the first 6 months of treatment. The incidence of headache did not increase over time. Dizziness was not cardiogenic in nature and occurred within the first month of treatment in approximately half of the subjects and within the first week of treatment in 14 of 38 subjects. Dizziness occurred in the other subjects 46 to 812 days after initial treatment. Electrocardiographic findings of potential clinical significance were noted in 2 subjects who experienced adverse events of dizziness, but neither subject

experienced an adverse event related to a cardiac conduction or rhythm disorder. The events lasted less than 1 week in many of the 38 subjects. The durations of the events with known starting and ending dates ranged from 1 to 112 days.

PMDA accepts the applicant's explanation but considers that the applicant must continue to collect information on nervous system disorders in the post-marketing phase because only a limited number of subjects were evaluated in the clinical studies.

4.(iii).B.(3).5) Safety by CYP2D6 phenotype

The incidences of adverse events in the pooled analysis of the phase II/III studies[114] by CYP2D6 phenotype are shown in Table 50. Incidences of adverse events were 87.7% (272 of 310 subjects) in the EMs, 73.5% (36 of 49 subjects) in the IMs, and 78.6% (11 of 14 subjects) in the PMs, showing no increasing trend in the PMs. The PMs were treated with a dose of 50 mg BID or lower, while many URMs were treated with elevated dose of 150 mg BID. The incidences of adverse events in the IMs were 67.3% (33 of 49 subjects) at 50 mg BID and 63.2% (12 of 19 subjects) at 100 mg BID, showing no increasing trend at 100 mg BID. The incidences of adverse events in the EMs were 41.2% (127 of 308 subjects) at 50 mg BID and 73.4% (207 of 282 subjects) at 100 mg BID. Although incidences were higher at 100 mg BID, the number of events per 100 patient-years was 520 events at 50 mg BID and 362 events at 100 mg BID and was not higher at 100 mg BID. There were few URMs and indeterminate metabolizers.

Table 50. Incidence of adverse events by CYP2D6 phenotype and dose at onset in pooled analysis of phase II/III studies

		PM	IM	EM	URM	Unknown[a)]	Overall
All dosages	No. of subjects	n = 14	n = 49	n = 310	n = 9	n = 5	n = 393
	Adverse events	11 (78.6) 571	36 (73.5) 526	272 (87.7) 418	9 (100) 715	4 (80.0) 352	334 (85.0) 437
	Adverse drug reactions	5 (35.7) 187	13 (26.5) 86	134 (43.2) 74	5 (55.6) 246	2 (40.0) 117	159 (40.5) 83
	Serious adverse events	1 (7.1) 5	7 (14.3) 14	27 (8.7) 8	0 (0.0) 0	0 (0.0) 0	35 (8.9) 8
50 mg BID	No. of subjects	n = 14	n = 49	n = 308	n = 9	n = 5	n = 391
	Adverse events	11 (78.6) 573	33 (67.3) 571	127 (41.2) 520	5 (55.6) 1477	4 (80.0) 714	181 (46.3) 547
	Adverse drug reactions	5 (35.7) 194	12 (24.5) 117	56 (18.2) 144	3 (33.3) 682	1 (20.0) 204	77 (19.7) 149
	Serious adverse events	1 (7.1) 5	6 (12.2) 20	4 (1.3) 5	0 (0.0) 0	0 (0.0) 0	11 (2.8) 9
100 mg BID	No. of subjects	n = 0	n = 19	n = 282	n = 9	n = 3	n = 319
	Adverse events	0 (0.0) 0	12 (63.2) 413	207 (73.4) 362	6 (66.7) 810	0 (0.0) 0	225 (70.5) 364
	Adverse drug reactions	0 (0.0) 0	2 (10.5) 37	81 (28.7) 55	3 (33.3) 187	0 (0.0) 0	86 (27.0) 55
	Serious adverse events	0 (0.0) 0	1 (5.3) 6	11 (3.9) 5	0 (0.0) 0	0 (0.0) 0	12 (3.8) 5
150 mg BID	No. of subjects	n = 0	n = 1	n = 88	n = 6	n = 1	n = 98
	Adverse events	0 (0.0) 0	1 (100) 270	69 (78.4) 405	5 (83.3) 534	1 (100) 4000	78 (79.6) 413
	Adverse drug reactions	0 (0.0) 0	0 (0.0) 0	29 (33.0) 60	4 (66.7) 203	1 (100) 4000	34 (34.7) 71
	Serious adverse events	0 (0.0) 0	0 (0.0) 0	9 (10.2) 11	0 (0.0) 0	0 (0.0) 0	9 (9.2) 10

Number of subjects with event (incidence %) number of events per 100 patient-years
a) Patients with "indeterminate" result in CYP2D6 genetic testing

The incidences of adverse events in the pooled analysis of the phase II/III studies by CYP2D6 phenotype, dose at onset, and severity were as shown in Table 51. At any dose at onset, severe events did not occur more frequently in any of non-EM phenotype than in the EM phenotype.

Table 51. Incidence of adverse events by CYP2D6 phenotype, dose at onset, and severity in pooled analysis data of phase II/III studies

		PM	IM	EM	URM	Unknown[a)]	Overall
All doses	No. of subjects	n = 14	n = 49	n = 310	n = 9	n = 5	n = 393
	Mild	9 (64.3) 404	33 (67.3) 374	252 (81.3) 316	8 (88.9) 439	4 (80.0) 293	308 (78.4) 325
	Moderate	6 (42.9) 148	23 (46.9) 138	130 (41.9) 89	8 (88.9) 253	2 (40.0) 59	171 (43.5) 99
	Severe	3 (21.4) 20	7 (14.3) 14	34 (11.0) 12	1 (11.1) 22	0 (0.0) 0	45 (11.5) 13
50 mg BID	No. of subjects	n = 14	n = 49	n = 308	n = 9	n = 5	n = 391
	Mild	9 (64.3) 394	29 (59.2) 424	111 (36.0) 416	4 (44.4) 1023	3 (60.0) 612	157 (40.2) 420
	Moderate	6 (42.9) 158	17 (34.7) 123	40 (13.0) 86	3 (33.3) 455	1 (20.0) 102	67 (17.1) 108
	Severe	3 (21.4) 21	7 (14.3) 23	8 (2.6) 18	0 (0.0) 0	0 (0.0) 0	18 (4.6) 19
100 mg BID	No. of subjects	n = 0	n = 19	n = 282	n = 9	n = 3	n = 319
	Mild	0 (0.0) 0	11 (57.9) 265	187 (66.3) 269	5 (55.6) 436	0 (0.0) 0	203 (63.6) 267
	Moderate	0 (0.0) 0	6 (31.6) 148	92 (32.6) 86	5 (55.6) 312	0 (0.0) 0	103 (32.3) 91
	Severe	0 (0.0) 0	0 (0.0) 0	13 (4.6) 6	1 (11.1) 62	0 (0.0) 0	14 (4.4) 7
150 mg BID	No. of subjects	n = 0	n = 1	n = 88	n = 6	n = 1	n = 98
	Mild	0 (0.0) 0	1 (100) 270	61 (69.3) 300	3 (50.0) 331	1 (100) 2000	68 (69.4) 300
	Moderate	0 (0.0) 0	0 (0.0) 0	27 (30.7) 86	5 (83.3) 192	1 (100) 2000	35 (35.7) 95
	Severe	0 (0.0) 0	0 (0.0) 0	13 (14.8) 19	1 (16.7) 11	0 (0.0) 0	14 (14.3) 18

Number of subjects with event (incidence %) number of events per 100 patient-years
a) Patients with "indeterminate" result in CYP2D6 genetic testing

The incidences of adverse events in the 69 subjects with exposure (C_{max}, AUC_{τ}, or trough levels) in the top 10th percentile in the phase II and III studies are shown in Table 52. The SOCs of adverse events (event terms) occurring more frequently in these subjects than in the overall population included gastrointestinal disorders (nausea, diarrhoea, abdominal pain upper), skin and subcutaneous tissue disorders (acne), nervous system disorders (headache, dizziness, syncope), musculoskeletal and connective tissue disorders (arthralgia, joint stiffness, muscle spasms, bone pain), and general disorders and administration site conditions (fatigue). The incidences of the other events did not differ substantially from those in the overall population.

Table 52. Incidences of adverse events in subjects with exposure in the top 10th percentile[a)] in phase II/III studies

	C_{max}	AUC_{τ}	Trough level	Any[b)]	Overall
No. of subjects	n = 53	n = 3	n = 32	n = 69	n = 393
All adverse events	44 (83.0) 659	3 (100) 1128	28 (87.5) 661	57 (82.6) 588	334 (85.0) 437
Serious adverse events	7 (13.2) 9	0 (0.0) 0	5 (15.6) 10	11 (15.9) 11	35 (8.9) 8

Number of subjects with event (incidence %) number of events per 100 patient-years
a) Subjects with C_{max} in the top 10th percentile were those with C_{max} of >67.4 ng/mL; subjects with AUC_{τ} in the 10th percentile were those having AUC_{τ} of >459.1 ng·h/mL at least twice; and subjects with trough levels in the top 10th percentile were those having trough levels of >19.9 ng/mL at least twice.
b) Subjects meeting any of the criteria for C_{max}, AUC_{τ}, or trough level

PMDA considers as follows:

Evaluation of incidences of adverse events by dose at onset did not reveal an increasing number of events per 100 patient-years with increasing dose in subjects with EM or IM. But at all doses, the number of events per 100 patient-years increased in the descending order in subjects with PM, IM, and EM, which is consistent with the descending order of expected exposure levels for these populations. PMDA considers that the applicant must continue to collect information on safety by CYP2D6 phenotype in post-marketing surveillance because a limited number of subjects were evaluated in the clinical studies.

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

PMDA asked the applicant to discuss the development plan for other types of Gaucher disease and children and the appropriateness of the indication.

The applicant responded as follows:
Gaucher disease is classified as type 1, 2, or 3 according to the presence or absence and severity of neurological symptoms. Types 2 and 3 feature CNS involvement. Gaucher disease type 2 is the acute neuropathic form, occurring in infancy and resulting in death by age 3. Gaucher disease type 3 is the chronic neuropathic form and occurs in or after late childhood, and patients with Gaucher disease type 3 can survive into early adulthood.[2]

ERT is used to treat Gaucher disease in Japan. Imiglucerase (Genetical Recombination) was approved in March 1998, and Velaglucerase Alfa (Genetical Recombination) was approved in July 2014. Both can be used in all patients with Gaucher disease types 1, 2, and 3 including children.

The estimated incidence and prevalence of Gaucher disease type 1 varies widely in different regions and races.[123] More than 90% of the patients in the International Collaborative Gaucher Group (ICGG) Gaucher Registry consisting mostly North American, South American, or European Caucasians had Gaucher disease type 1.[124] In contrast, it was reported that 41.9% of Japanese patients with Gaucher disease had type 1, 24.0% had type 2, and 34.1% had type 3 disease.[125]

All clinical studies of eliglustat in and out of Japan were conducted in adult patients with Gaucher disease type 1, and eliglustat has therefore not been used in patients with other types or in pediatric patients. Being a substrate of the efflux transporter P-glycoprotein (P-gp), eliglustat is generally considered not to cross the blood-brain barrier, thus, eliglustat has not been shown to have efficacy on neurological symptoms in patients with Gaucher disease. The applicant does not currently plan to develop eliglustat for type 2 and 3 patients with neurological symptoms. Gaucher disease type 1 is therefore currently the only indication. The applicant is considering a post-marketing clinical study for pediatric development following approval for treatment in adult patients with Gaucher disease type 1 outside Japan and intends to consider pediatric development in Japan while monitoring the progress of this clinical study and while taking account of the medical need and the feasibility of a study in Japan. Given that 91% of patients with Gaucher disease type 1 treated with imiglucerase in Japan were adults,[126] there are estimated to be 49 adult patients with Gaucher disease type 1 there.

PMDA asked the applicant to discuss whether it envisions combination use of eliglustat with ERT and, if so, to discuss the need to provide precautions for safety and efficacy related to the combination use.

The applicant responded as follows:
The applicant has not evaluated the efficacy or safety of eliglustat in combination with ERT in the development phase, and eliglustat is not intended to be used in such combination in the post-marketing phase. Therefore, the

123 Grabowski GA, *Genet Test*, 1997; 1(1):5-12
124 Charrow J, et al., *Arch Intern Med*, 2000; 160:2835-43
125 Inoue H. *Lysosomal Storage Disease: Latest findings in pathology and progress in diagnosis and treatment.* In: Eto Y. eds. Tokyo, Japan: Shindan-to-Chiryo-Sha. 2011;144-8
126 Internal document of Genzyme Japan K.K.

package insert must contain a precautionary statement that eliglustat has not been used concomitantly with imiglucerase or other enzyme replacement therapies.

PMDA considers as follows:
PMDA sees no major problems with the indication as currently proposed by the applicant because eliglustat was clinically developed for Gaucher disease type 1 and has not been used in patients with type 2 and 3 disease. However, the percentage of Japanese patients with Gaucher disease type 2 or 3 is relatively high as compared with that of non-Japanese patients, and the existing enzyme replacement therapies have been approved for all disease types in Japan. The pharmacological mechanism of eliglustat suggests that it is effective against systemic symptoms, not neurological in nature. Therefore, the applicant should consider the need to develop eliglustat for the other disease types according to the need in clinical practice identified after the market launch. PMDA will provide a final decision on this matter after taking account of comments raised in the Expert Discussion.

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

4.(iii).B.(5).1) Effects of trough concentrations

Noting that eliglustat doses in the clinical studies in and out of Japan were determined according to trough plasma concentrations of unchanged eliglustat, PMDA asked the applicant to explain, in terms of efficacy and safety, why the applicant considered it unnecessary to adjust the dosage regimen according to trough concentrations.

The applicant responded as follows:
Five of the 8 subjects receiving eliglustat 350 mg BID in a phase I repeated-dose study (study GZGD00204) discontinued treatment due to gastrointestinal adverse events (nausea, vomiting) or adverse events related to neurological symptoms (dizziness, headache). The maximum tolerable dose in 12-day repeated dosing was therefore determined to be 200 mg BID.

An investigation of plasma trough concentrations of unchanged eliglustat on Day 12 in a 12-day repeated-dose study in healthy subjects (1.6 ng/mL at 50 mg BID, 24.8 ng/mL at 200 mg BID, and 33.8 ng/mL at 350 mg BID) indicated that the trough levels at 50 mg BID were assumed to be near the IC_{50} for glucosylceramide synthase (7.9 ng/mL: 4.2.1.1-2).

A starting dose of 50 mg BID and target trough level of 5 ng/mL were therefore selected in the phase II study and subsequent studies in patients.[127] In the placebo-controlled phase III study in treatment-naïve patients (Study ENGAGE), treatment was started at 50 mg BID and the dose was increased to 100 mg BID if the trough level was <5 ng/mL or was maintained at 50 mg BID if the level was ≥5 ng/mL.[128] In the imiglucerase-

[127] In the eliglustat group in the phase II study, 6 subjects continued to be treated with 50 mg BID (5 EMs and 1 PM) and 18 subjects continued to be treated with 100 mg BID (all EMs).

[128] In the eliglustat group in Study ENGAGE, 3 subjects continued to be treated with 50 mg BID (2 EMs and 1 IM) and 17 subjects continued to be treated with 100 mg BID (16 EMs and 1 URM).

controlled study in patients with a history of ERT (Study ENCORE), the dose was allowed to be escalated up to 150 mg BID when the trough level was <5 ng/mL.[129] Patients with and without a history of ERT were allowed to participate in the global phase III study (Study EDGE), in which eliglustat treatment was started at 50 mg BID (or 50 mg QD only on Day 1 for Japanese patients). Eliglustat dose was increased to 100 mg BID if the trough level was <5 ng/mL or was maintained at 50 mg BID if the level was ≥5 ng/mL, and dose adjustment was subsequently allowed according to trough levels.[130]

Eliglustat dosage was determined in the clinical studies according to trough levels, and the effect of trough levels on efficacy was investigated (Table 53). In Study ENGAGE (FAS) and Study ENCORE (PPS), the CYP2D6 EMs who remained on eliglustat 100 mg BID had similar baseline levels regardless of whether the trough level was <5 ng/mL or ≥5 ng/mL. Furthermore, the levels of parameters at each time point (Weeks 39 and 52) in the <5 ng/mL group were not clinically significantly different from those in the ≥5 ng/mL group in either study.

Table 53. Efficacy results by trough level in CYP2D6 EMs who remained on eliglustat 100 mg BID in phase III studies

			<5 ng/mL (n = 8)	≥5 ng/mL (n = 8)
Study ENGAGE	Hemoglobin (g/dL)	Baseline	11.594 ± 2.088	12.038 ± 1.598
		Week 39	12.056 ± 1.683	13.181 ± 1.388
		Change	0.463 ± 1.005	1.144 ± 0.929
	Platelets (10^3/μL)	Baseline	75.000 ± 14.059	72.750 ± 17.815
		Week 39	100.563 ± 34.764	94.500 ± 24.324
		Percent change (%)	32.629 ± 36.727	31.056 ± 30.072
	Spleen volume (MN[a)])	Baseline	14.084 ± 6.738	14.711 ± 5.545
		Week 39	10.308 ± 4.254	10.964 ± 5.591
		Percent change (%)	-24.504 ± 10.641	-27.584 ± 12.618
	Liver volume (MN[a)])	Baseline	1.478 ± 0.345	1.478 ± 0.349
		Week 39	1.371 ± 0.244	1.365 ± 0.270
		Percent change (%)	-6.025 ± 7.712	-6.896 ± 5.156
			<5 ng/mL (n = 8)	≥5 ng/mL (n = 21)
Study ENCORE	Hemoglobin (g/dL)	Baseline	12.850 ± 1.143	13.802 ± 1.317
		Week 52	12.725 ± 1.125	13.605 ± 1.194
		Change	-0.125 ± 0.876	-0.198 ± 0.710
	Platelets (10^3/μL)	Baseline	204.375 ± 69.573	247.405 ± 110.301
		Week 52	200.438 ± 60.868	259.929 ± 110.370
		Percent change (%)	1.700 ± 18.941	6.283 ± 15.445
	Spleen volume (MN[a)])	Baseline	3.774 ± 2.370	3.158 ± 1.477
		Week 52	3.530 ± 2.357	3.048 ± 1.521
		Percent change (%)	-4.988 ± 14.026	-5.202 ± 11.585
	Liver volume (MN[a)])	Baseline	0.928 ± 0.131	0.955 ± 0.209
		Week 52	1.019 ± 0.114	0.961 ± 0.219
		Percent change (%)	10.568 ± 10.896	0.699 ± 7.411

Mean ± standard deviation

a) Calculated with the following formulas using volume measured by MRI:
spleen volume (MN) = spleen volume (cc)/body weight (kg) × 2; liver volume (MN) = liver volume (cc)/body weight (kg) × 25.

In the overall population of Study EDGE, the percentage of subjects who achieved all 5 therapeutic goals for Gaucher disease in the open-label lead-in period were 84% (58 of 69 subjects) in the subjects with a trough

129 In the eliglustat group in Study ENCORE (PPS), 19 subjects continued to be treated with 50 mg BID (10 EMs, 5 IMs, and 4 PMs), 33 subjects continued to be treated with 100 mg BID (29 EMs and 4 IMs), and 47 subjects continued to be treated with 150 mg BID (40 EMs, 1 IM, 4 URMs, and 2 indeterminate metabolizers). In the eliglustat group in Study ENCORE (FAS), 21 subjects continued to be treated with 50 mg BID (10 EMs, 7 IMs, and 4 PMs), 35 subjects continued to be treated with 100 mg BID (31 EMs and 4 IMs), and 50 subjects continued to be treated with 150 mg BID (43 EMs, 1 IM, 4 URMs, and 2 indeterminate metabolizers).

130 In the eliglustat group in Study EDGE, 20 subjects continued to be treated with 50 mg BID (4 EMs, 12 IMs [including 2 Japanese subjects], 4 PMs), 115 subjects continued to be treated with 100 mg BID (100 EMs [including 2 Japanese subjects], 7 IMs [including 1 Japanese subject], 3 URMs, and 5 indeterminate metabolizers), 7 subjects were in the 150 mg BID/100 mg BID group (6 EMs [including 3 Japanese subjects] and 1 indeterminate metabolizer [a Japanese subject]), and 28 subjects were in other dosage groups (21 EMs [including 1 Japanese subject], 4 IMs, and 3 PMs). "Other dosage groups" refers to groups undergoing dosage adjustment other than the protocol-specified maintenance at 50 mg BID, elevation to 100 mg BID, or elevation to 150 mg BID followed by dose reduction to 100 mg BID.

concentration of <5 ng/mL, 82% (78 of 95 subjects) in the subjects with that of ≥5 ng/mL, and 1 of 1 subject with an unknown concentration. All subjects in the Japanese population (3 with a trough concentration of <5 ng/mL and 7 with that of ≥5 ng/mL) met all 5 treatment goals for Gaucher disease.

While the dose in the phase II/III studies was 50 mg BID at the start of treatment and then adjusted according to trough concentrations, there was no clinically significant difference in efficacy between patients with trough concentrations of <5 ng/mL and ≥5 ng/mL. Therefore, dose adjustment according to trough concentrations is considered unnecessary from the efficacy point of view.

Safety results by trough level were as shown in Table 54. The incidences of adverse events and adverse drug reactions in the CYP2D6 EMs remaining on 100 mg BID in Study ENGAGE were higher in the subjects with a trough concentration ≥5 ng/mL than in those with trough concentration <5 ng/mL, but no serious adverse events were reported. Incidences of adverse events under the SOC gastrointestinal disorders differed between subjects with trough concentrations of <5 ng/mL and ≥5 ng/mL, occurring at 25.0% (2 of 8 subjects) and 62.5% (5 of 8 subjects), respectively. The incidences of adverse events and adverse drug reactions in the CYP2D6 EMs maintained at 100 mg BID in Study ENCORE were higher in the subjects with trough concentration of ≥5 ng/mL than in those with trough concentration <5 ng/mL. No serious adverse drug reactions were reported in either study. The SOCs of adverse events with a difference in incidence were general disorders and administration site conditions (0% [0 of 8] and 33.3% [7 of 21] in subjects with trough concentrations <5 ng/mL and ≥5 ng/mL, respectively) and musculoskeletal and connective tissue disorders (12.5% [1 of 8] and 38.1% [8 of 21] in subjects with trough concentrations <5 ng/mL and ≥5 ng/mL, respectively). The incidence of adverse events under the SOC gastrointestinal disorders was 75.0% (6 of 8) and 66.7% (14 of 21) in subjects with trough concentrations <5 ng/mL and ≥5 ng/mL, respectively, showing no substantial difference. Thus, dose adjustment based on trough levels is considered unnecessary also from the safety point of view.

Table 54. Safety results by trough level in CYP2D6 EMs remaining on eliglustat 100 mg BID in phase III studies

		<5 ng/mL (n = 8)	≥5 ng/mL (n = 8)
Study ENGAGE	Adverse events	6 (75.0) 40	8 (100) 56
	Adverse drug reactions	1 (12.5) 1	5 (62.5) 25
	Serious adverse events	0 (0.0) 0	0 (0.0) 0
	Serious adverse drug reactions	0 (0.0) 0	0 (0.0) 0
	Adverse events leading to treatment discontinuation	0 (0.0) 0	0 (0.0) 0
	Mild adverse events	5 (62.5) 29	7 (87.5) 34
	Moderate adverse events	3 (37.5) 11	8 (100) 22
	Severe adverse events	0 (0.0) 0	0 (0.0) 0
		<5 ng/mL (n = 8)	≥5 ng/mL (n = 21)
Study ENCORE	Adverse events	7 (87.5) 26	21 (100) 133
	Adverse drug reactions	1 (12.5) 2	10 (47.6) 22
	Serious adverse events	0 (0.0) 0	3 (14.3) 3
	Serious adverse drug reactions	0 (0.0) 0	0 (0.0) 0
	Adverse events leading to treatment discontinuation	0 (0.0) 0	0 (0.0) 0
	Mild adverse events	7 (87.5) 26	20 (95.2) 99
	Moderate adverse events	0 (0.0) 0	12 (57.1) 31
	Severe adverse events	0 (0.0) 0	1 (4.8) 3

Number of subjects with event (incidence %) number of events

4.(iii).B.(5).2) Dosage and administration by CYP2D6 phenotype

The applicant explained as follows:

The final PPK model was used to estimate the exposure by CYP2D6 phenotype after multiple administration of eliglustat 100 mg BID in the subjects with Gaucher disease type 1. In comparison with the EMs, C_{max} and $AUC_{0\text{-}12\ h}$ were estimated to be approximately 9.3-fold and 11.2-fold higher, respectively, in the PMs, approximately 2.7-fold and 2.8 fold higher, respectively, in the IMs, and approximately 47% in the URMs [see "4.(ii).B.(1) Pharmacokinetics and drug interactions by CYP2D6 phenotype"].

Noting that patients with all CYP2D6 phenotypes were allowed to be enrolled in the clinical studies in Gaucher disease type 1 patients in and out of Japan and that in each study, eliglustat treatment was started at 50 mg QD or 50 mg BID, and some subjects were maintained at a dose other than 100 mg BID, PMDA asked the applicant to justify the intended patient population and dosage by CYP2D6 phenotype in consideration of efficacy, safety, and plasma unchanged eliglustat concentrations.

The applicant responded as follows:

(a) CYP2D6 EM and IM phenotypes

In the IM/EM subjects in the eliglustat group in Study ENGAGE who were maintained at a dose other than 100 mg BID, all 3 in the 50 mg BID group achieved the therapeutic goal for spleen volume (reduction of ≥30%). The incidences of adverse events and adverse drug reactions in the 50 mg BID group was 100% (3 of 3 subjects) and 33.3% (1 of 3 subjects), respectively. The incidences of adverse events and adverse drug reactions in the IM/EM subjects was 70.0% (14 of 20 subjects) and 45.0% (9 of 20 subjects), respectively, in the placebo group and 87.5% (14 of 16 subjects) and 37.5% (6 of 16 subjects), respectively, in the 100 mg BID group, showing no substantial differences among the placebo, 50 mg BID, and 100 mg BID groups.

Among the IM/EM subjects in the eliglustat group in Study ENCORE who were maintained at a dose other than 100 mg BID, the percentage of subjects (in the PPS) achieving the composite endpoint as the primary endpoint was 80.0% (12 of 15 subjects) in the 50 mg BID group and 85.4% (35 of 41 subjects) in the 150 mg BID group, which did not differ greatly from the percentage in the 100 mg BID group (84.8% [28 of 33 subjects]). The incidences of adverse events and adverse drug reactions in the IM/EM subjects in the safety analysis population were 82.4% (14 of 17 subjects) and 35.3% (6 of 17 subjects), respectively, in the 50 mg BID group and 88.6% (39 of 44 subjects) and 38.6% (17 of 44 subjects), respectively, in the 150 mg BID group. The incidences of adverse events and adverse drug reactions in the IM/EM subjects in the 100 mg BID group were 97.1% (34 of 35 subjects) and 37.1% (13 of 35 subjects), respectively, which did not differ substantially from those in the 50 mg BID or 150 mg BID groups.

Among the IM/EM subjects in the eliglustat group of Study EDGE who were maintained at a dose other than 100 mg BID, 73.3% (11 of 15 subjects) in the 50 mg BID group achieved all 5 therapeutic goals (and the 4 subjects who did not achieve the therapeutic goals remain in the lead-in period). Achievement of individual therapeutic goals ranged from 86.7% to 100% (13 to 15 of 15 subjects), which did not differ greatly from achievement in the 100 mg BID group (83.0% [88 of 106 subjects]). All 6 subjects in the 150 mg BID/100 mg

BID group achieved all 5 therapeutic goals. In the other dose groups, 80.0% (20 of 25 subjects) achieved all 5 therapeutic goals, and achievement of individual therapeutic goals ranged from 88.0% to 100% (22 to 25 of 25 subjects), which did not differ greatly from achievement in the 100 mg BID group. The incidences of adverse events and adverse drug reactions in the IM/EM subjects were 87.5% (14 of 16 subjects) and 18.8% (3 of 16 subjects), respectively, in the 50 mg BID group and 83.3% (5 of 6 subjects) and 16.7% (1 of 6 subjects), respectively, in the 150 mg BID/100 mg BID group. The incidences of adverse events and adverse drug reactions in the IM/EM subjects in the 100 mg BID group were 83.2% (89 of 107 subjects) and 38.3% (41 of 107 subjects), respectively, which did not differ substantially from those in the 50 mg BID or 150 mg BID/100 mg BID groups.

Of the IM/EM subjects in the eliglustat group in the phase II study who were maintained at a dose other than 100 mg BID, 5 subjects were maintained at 50 mg BID. One of the 5 subjects discontinued the study by Week 52, and 3 achieved the primary endpoint at Week 52. The remaining 1 subject did not achieve the primary endpoint by Week 52 and still had not achieved the therapeutic goals by Month 48 in the long-term period. The incidences of adverse events and adverse drug reactions in the 50 mg BID group were 100% (5 of 5subjects) and 40.0% (2 of 5 subjects), respectively, which did not differ substantially from those in the 100 mg BID group of 83.3% (15 of 18 subjects) and 27.8% (5 of 18 subjects).

In all dose groups in all studies, the exposure estimated at 100 mg BID generally fell into the ranges investigated in the clinical studies.

The above findings suggested that treatment with eliglustat at 100 mg BID is expected to achieve similar efficacy and safety in the subjects with CYP2D6 IM or EM phenotype who were maintained at 50 mg BID or 150 mg BID in Studies ENGAGE and ENCORE. Thus, administration of eliglustat at 100 mg BID to patients with the CYP2D6 IM or EM phenotype should have little impact on efficacy and safety and create no concerns.

This is why the applicant selected 100 mg BID as the recommended dosage for IM and EM patients.

(b) CYP2D6 PM phenotype

In the clinical studies, no PMs received eliglustat at 100 mg BID, 9 PMs received 50 mg BID, and 3 PMs received 50 mg QD. No PMs were enrolled in Study ENGAGE. One PM in the phase II study was maintained at 50 mg BID, achieving percent changes from baseline to Week 52 of -64.5% in spleen volume, -28.1% in liver volume, and 75.0% in platelet count, and change in hemoglobin concentration over the same period, of 2.45 g/dL. Four PM subjects were maintained at 50 mg BID in Study ENCORE.[131] Percent changes from baseline to Week 52 were -22.1% to -5.1% in spleen volume (3 subjects), -15.5% to 10.8% in liver volume (4 subjects), and -42.7% to 53.0% in platelet count (4 subjects), and changes over the same period in hemoglobin volume were -0.75 to 0.70 g/dL (4 subjects). In the PMs, the mean plasma trough concentrations of unchanged eliglustat at Week 13 and subsequent weeks ranged from 26.52 to 52.97 ng/mL. In Study EDGE, 7 PMs (all

[131] Data of the primary analysis period (data cutoff date: [redacted])

non-Japanese) received eliglustat. Four of the 7 subjects were maintained at 50 mg BID, and the other 3 were maintained at reduced dose of 50 mg QD. Of the 5 subjects (3 at 50 mg BID, 2 at 50 mg QD) with data for all 5 parameters (hemoglobin concentration, platelet count, spleen volume, liver volume, bone symptoms), 4 subjects (2 at 50 mg BID, 2 at 50 mg QD) achieved the therapeutic goals at the end of the open-label lead-in period. In the 50 mg QD group and 50 mg BID group, percent changes from baseline to the final observation were -15.5% to -14.8% (2 subjects) and -26.5% to 12.2% (3 subjects), respectively, in spleen volume, -9.3% to -7.1% (2 subjects) and -15.9% to 7.6% (3 subjects), respectively, in liver volume, -15.9% to 25.7% (3 subjects) and -22.7% to 9.3% (4 subjects), respectively, in platelet count, and the changes in hemoglobin concentrations over the same period were -0.85 to 0.4 g/dL (3 subjects) and -1.1 to 1.3 g/dL (4 subjects), respectively. The incidences of adverse events and adverse drug reactions were 66.7% (2 of 3 subjects) and 33.3% (1 of 3 subjects), respectively, in the 50 mg QD group and 50.0% (2 of 4 subjects) and 25.0% (1 of 4 subjects), respectively, in the 50 mg BID group. The mean trough levels in individual patients ranged from 9.40 to 42.64 ng/mL (6 subjects) at Week 13 and subsequent weeks. No serious adverse events, including deaths, were reported in PMs in any study.

Predicted C_{max} (mean ± standard deviation) in the PMs receiving 100 mg BID was 294 ± 79.5 ng/mL, which was approximately 10-fold that in the EMs receiving 100 mg BID. In PMs, the metabolic route of eliglustat may be completely inhibited when eliglustat is co-administered with a strong CYP3A inhibitor, and the predicted C_{max} (mean) was 448 ng/mL (range, 335-548 ng/mL). The applicant decided to exclude PMs from the intended patient population for eliglustat because recommending concomitant drugs to patients by CYP2D6 phenotype and managing such concomitant medications is complicated.

PMDA asked the applicant to explain the reasons for the inclusion of PMs in the intended patient population in the United States and whether PMs need to be included in the intended patient population.

The applicant responded as follows:
In the new drug application in the U.S., the proposed dosage was 100 mg BID in CYP2D6 IMs and EMs, and PMs and URMs were excluded from the intended patient population, as in the Japanese marketing application. As a result of the review, PMs were included in the intended patient population, and a dosage of 100 mg QD was proposed for PMs based on PBPK modeling. The dosage for PM patients was selected based on the simulations with PBPK modeling using SimCyp. Mean predicted C_{max} and $AUC_{0\text{-}24h}$ [5th and 95th percentiles] in PM patients receiving 100 mg QD were estimated to be 75.2 [22.0, 180] ng/ml and 956 [179, 2660] ng·h/mL, respectively. The predicted $AUC_{0\text{-}24h}$ in PM patients at 100 mg QD was similar to the predicted mean $AUC_{0\text{-}24h}$ [5th and 95th percentiles] in IM patients at 100 mg BID (1054 [204, 3180] ng·h/mL) based on PBPK modeling, and fell generally within the ranges of C_{max} (2.13-169 ng/mL) and AUC ($AUC_{0\text{-}12h}$, 2-fold 16.3 to 992 ng·h/mL) in the clinical studies. Based on the relationship between plasma concentrations of unchanged eliglustat and QT intervals determined in the thorough QT/QTc study, the C_{max} predicted from PBPK modeling in PM patients at 100 mg QD was found not to pose safety concerns in terms of QT intervals. The dosage of 100 mg QD was selected for PM patients for the above reason.

Whether PM patients need to be included in the intended patient population is discussed next. Only 9 PMs have participated in the clinical studies to present. No PMs continued to receive doses exceeding 50 mg BID, and several PMs in Study EDGE received 50 mg QD in the open-label lead-in period. The available efficacy and safety data are therefore insufficient for setting the recommended dosage for PM patients. The possibility of plasma exposure greatly exceeding the range observed in the clinical studies must be considered because concomitant drugs would likely be used more frequently in routine use after the market launch. While C_{max} and $AUC_{0\text{-}12h}$ in PMs at 50 mg BID are within values determined in IMs and EMs, more pharmacokinetic, safety, and efficacy data in PMs are needed before the recommended dosage for PMs can be set. The overall Japanese population was reported to consist of approximately 1% CYP2D6 PMs, 23% IMs, 74% EMs, and 2% URMs.[132]

(c) CYP2D6 URM phenotype

No URMs were enrolled in the phase II study. One URM in Study ENGAGE was maintained at 100 mg BID, achieving percent changes from baseline to Week 39 of -11.5% in spleen volume, and 0.0% in liver volume, -3.0% in platelet count, and change in hemoglobin concentration over the same period of 1.25 g/dL. Trough concentrations of unchanged eliglustat in plasma were 0.84 ng/mL from Week 13 onward. Four URMs were maintained at 150 mg BID in Study ENCORE. Percent changes from baseline to Week 52 were -5.9% to 3.5% in spleen volume (3 subjects), -7.9% to 13.6% in liver volume (4 subjects), and -21.5% to 11.7% in platelet count (4 subjects), and changes over the same period in hemoglobin volume were -0.85 to 1.10 g/dL (4 subjects). The mean trough concentrations of unchanged eliglustat in plasma ranged from 1.62 to 7.13 ng/mL from Week 13 onward. Three URMs (all non-Japanese) were maintained at 100 mg BID in Study EDGE. All 3 subjects had achieved the therapeutic goals (clinically symptomatic bone disease, hemoglobin concentration, platelet count, spleen volume, liver volume) at the final observation in the open-label lead-in period. Percent changes from baseline to the final observation were 4.3% to 6.4% in spleen volume (2 subjects), 5.6% to 19.6% in liver volume (2 subjects), and -18.3% to 20.7% in platelet count (3 subjects), and changes over the same period in hemoglobin concentration were -0.55 to 0.60 g/dL (3 subjects). The mean trough concentrations of unchanged eliglustat in plasma ranged from 0.62 to 1.16 ng/mL (3 subjects) from Week 13 onward. No serious adverse events, including deaths, were reported in any study.

Thus URMs were excluded from the intended patient population because exposure in URMs was approximately half that in EMs on the above basis, and selecting a recommended dosage for URMs unfeasible currently due to the very limited number of subjects evaluated in the clinical studies (8 in the phase II and III studies).

[132] Myrand SP, et al., *Clin Pharmacol Ther*, 2008; 84(3):347-61

(d) Indeterminate metabolizers

CYP2D6 indeterminate metabolizers are excluded from the intended patient population because metabolic activity is unknown and no consistent trends were seen in these patients, making it impossible to select a recommended dosage based on CYP2D6 phenotypes.

PMDA considers, in light of the information presented in items 1) and 2) above, as follows:

From an efficacy point of view, there are no specific problems with not adjusting the dosage based on trough concentrations because efficacy was demonstrated even at trough concentrations below levels specified in the studies although dose adjustment was performed according to the trough concentrations of unchanged eliglustat in plasma in the phase II and III studies in patients. From a safety point of view, there are also no specific problems with the applicant's statement that dosage will be considered based on CYP2D6 phenotypes because eliglustat is metabolized primarily by CYP2D6.

There are no specific problems with selecting 100 mg BID as the dosage for IMs and Ems because many EMs and IMs received 100 mg BID in the clinical studies, and no major efficacy or safety concerns are likely to occur if eliglustat 100 mg BID is given to those who were maintained at other doses in the eliglustat groups. There are no specific problems with excluding URMs from the intended patient population because selecting a recommended dosage for URMs are unfeasible at present due to their low exposure (approximately half the exposure that EMs have) and the small sample size evaluated in the clinical studies. Also, there are no specific problems with excluding CYP2D6 indeterminate metabolizers because the extent of increases in exposure cannot be predicted. Although the applicant responded that it did not intend to include PMs in the intended patient population because of the small number of subjects evaluated in the clinical studies and because controlling concomitant drugs by CYP2D6 phenotype using package insert would be complicated, PMDA notes that exposure in PMs receiving 100 mg QD is estimated to be comparable to that in IMs receiving 100 mg BID. Thus, there is room for the applicant to reconsider including PMs in the intended patient population.

Finally, dosage regimen must be selected appropriately according to particular patients and extent of drug interactions with concomitant drugs because proarrhythmic risk is expected to differ depending on the extent of interactions [see "4.(ii).B.(2) QT/QTc prolongation and proarrhythmic risk"]. PMDA will provide a final decision on this matter after taking account of comments raised in the Expert Discussion.

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

4.(iii).B.(6).1) Elderly patients

The incidences of adverse events in the pooled analysis of the phase II/III studies[114] by age were as shown in Table 55. Adverse events did not tend to occur more frequently in the younger or older subjects. No adverse events (SOCs or preferred terms [PTs]) occurred in a specific age group. Many of the adverse events reported in patients older than 65 years were in the SOCs of infections and infestations (4 subjects), nervous system disorders (4 subjects), and gastrointestinal disorders (3 subjects). Adverse events (PTs) frequently reported in this age group were similar to those reported most frequently in the overall population (nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhoea, nausea, headache, dizziness). The adverse events

occurring in the subjects older than 65 years were mild in severity with the exception of some moderate events (headache [2 subjects], dizziness [1], nausea [1], excoriation [1], fall [1]). No serious adverse events were reported in subjects older than 65 years.

Table 55. Incidences of adverse events in phase II/III studies by age

	≥16 to ≤30 years (n = 157)	>30 to ≤65 years (n = 226)	>65 years (n = 10)	Overall (n = 393)
Adverse events	124 (79.0) 343	202 (89.4) 512	8 (80.0) 400	334 (85.0) 437
Adverse drug reactions	55 (35.0) 66	99 (43.8) 95	5 (50.0) 155	159 (40.5) 83
Serious adverse events	12 (7.6) 8	23 (10.2) 8	0 (0) 0	35 (8.9) 8
Serious adverse drug reactions	3 (1.9) 2	2 (0.9) 1	0 (0) 0	5 (1.3) 1
Adverse events leading to treatment discontinuation	1 (0.6) 0	11 (4.9) 5	1 (10.0) 64	13 (3.3) 4
Mild	116 (73.9) 256	185 (81.9) 379	7 (70.0) 310	308 (78.4) 325
Moderate	61 (38.9) 78	107 (47.3) 116	3 (30.0) 90	171 (43.5) 99
Severe	12 (7.6) 9	33 (14.6) 16	0 (0) 0	45 (11.5) 13

Number of subjects with event (incidence %) number of events per 100 patient-years

The incidence of adverse events in the patients without a history of ERT was 81.8% (45 of 55 subjects) in the subjects ≥16 to ≤30 years of age, 89.5% (68 of 76 subjects) in the subjects >30 to ≤65 years of age, and 66.7% (2 of 3 subjects) in the subjects older than 65 years. The incidence of adverse events in the subjects with a history of ERT was 77.5% (79 of 102 subjects) in the subjects ≥16 to ≤30 years of age, 89.3% (134 of 150 subjects) in the subjects >30 to ≤65 years of age, and 85.7% (6 of 7 subjects) in the subjects older than 65 years. No substantial differences were observed among the age groups.

PMDA agrees with the applicant's explanation but considers that the applicant must continue to collect information on safety in elderly patients in post-marketing surveillance because of the small number of patients evaluated.

4.(iii).B.(6).2) Patients with renal or hepatic impairment

The applicant explained as follows:

Patients with moderate to severe renal or hepatic disease and patients with an ALT, AST, or total bilirubin level exceeding 2 times the upper limit of normal were excluded from the phase II and III studies. No efficacy or safety data are thus available for these patient populations. Moreover, the extent of increases in exposure is unknown in subjects with moderate to severe renal or hepatic impairment because no pharmacokinetic study was performed in these patient populations.

The pooled analysis set of phase II/III studies[114] included 13 subjects with an estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disorder formula of <60 mL/min/1.73 m^2 (43.4 to 59.7) and 4 subjects with hepatic impairment. Those patients experienced no events posing a safety concern as compared with the overall population.

In response to requests from the U.S. and the European Union regulatory authorities, the applicant plans to conduct a postmarketing study to evaluate the pharmacokinetics and safety in subjects with a hepatic or renal disorder. In Japan, use of eliglustat in patients with moderate to severe renal or hepatic impairment is basically not recommended. Accordingly, patients with moderate to severe renal or hepatic impairment should be

included in the careful administration section of the package insert to appropriately call attention to these patient populations.

PMDA considers as follows:
There are no specific problems with the applicant's position that use of eliglustat should not be basically recommended in patients with renal or hepatic impairment because pharmacokinetics and safety have not been evaluated in these patients. The applicant must continue to collect information on safety in patients with renal or hepatic impairment in post-marketing surveillance because of the small number of subjects evaluated in the clinical studies.

4.(iii).B.(6).3) Sex

The applicant explained as follows:
The incidences of adverse events by sex in the pooled analysis of the phase II/III studies[114] are shown in Table 56. The incidences of adverse events and serious adverse events did not differ according to sex. The adverse events occurring more frequently (≥5% difference) in women than in men were influenza (9% versus 3%), urinary tract infection (9% versus 2%), arthralgia (18% versus 10%), abdominal pain upper (11% versus 6%), nausea (12% versus 5%), headache (20% versus 13%), dizziness (13% versus 6%), back pain (12% versus 6%), pain in extremity (11% versus 5%), fatigue (11% versus 4%), bone pain (7% versus 2%), and cough (8% versus 3%). Syncope was reported only in women (4%). Electrocardiographic analysis revealed no sex-related differences. No adverse events occurred more frequently (≥5% difference) in men than in women.

Table 56. Incidences of adverse events by sex in pooled analysis of phase II/III studies

	Males (n = 191)	Females (n = 202)	Overall (n = 393)
Adverse events	161 (84.3) 342	173 (85.6) 525	334 (85.0) 437
Adverse drug reactions	76 (39.8) 70	83 (41.1) 96	159 (40.5) 83
Serious adverse events	14 (7.3) 6	21 (10.4) 9	35 (8.9) 8
Serious adverse drug reactions	1 (0.5) 0	4 (2.0) 2	5 (1.3) 1
Adverse events leading to treatment discontinuation	8 (4.2) 4	5 (2.5) 4	13 (3.3) 4
Mild	146 (76.4) 261	162 (80.2) 384	308 (78.4) 325
Moderate	79 (41.4) 70	92 (45.5) 127	171 (43.5) 99
Severe	22 (11.5) 11	23 (11.4) 14	45 (11.5) 13

Number of subjects with event (incidence %) number of events per 100 patient-years

Incidences of adverse events were 84.4% (54 of 64 subjects) in men and 87.1% (61 of 70 subjects) in women without a history of ERT; and 84.3% (107 of 127 subjects) in men and 84.8% (112 of 132 subjects) in women with a history of ERT. There were no large gender-related differences in the incidences of adverse events

PMDA agrees with the applicant's explanation but considers that the applicant must continue to collect information on the safety according to sex in post-marketing surveillance because syncope occurred only in women and a limited number of patients were evaluated in the clinical studies.

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

The applicant explained as follows:

A specified drug use-results survey (with 8-year survey period and observation period from registration to the end of follow-up) will be conducted in all patients who receive eliglustat. Hemoglobin concentration, platelet count, liver/spleen volume, bone density, etc., will be investigated as efficacy parameters. Adverse drug reactions will be collected as safety data without setting priority investigation items.

PMDA considers as follows:

There are no specific problems with conducting post-marketing surveillance in all patients who receive eliglustat, but PMDA considers that the applicant must collect information on the following safety concerns: proarrhythmic risk (including information of its relationship with concomitant drugs) and syncope; safety by CYP2D6 phenotype; safety in patients with renal or hepatic impairment; and safety by age and sex. PMDA will provide a final decision on the specifics of post-marketing surveillance after taking account of comments raised in the Expert Discussion.

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

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

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-3). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of eliglustat (Cerdelga) in patients with Gaucher disease type 1 has been demonstrated and its safety is acceptable in view of its observed benefits. The product is expected to be a therapeutic option in patients with Gaucher disease type 1 and has clinical significance. PMDA considers that proarrhythmic risk, safety by CYP2D6 phenotype, and other issues must be further evaluated through post-marketing surveillance.

This application may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 4, 2015

I. Product Submitted for Registration

[Brand name]	Cerdelga Capsules 100 mg
[Non-proprietary name]	Eliglustat tartrate
[Applicant]	Genzyme Japan K.K.
[Date of application]	June 30, 2014

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Pharmacokinetics and pharmacodynamics

1) Pharmacokinetics and drug interactions by CYP2D6 phenotype

PMDA's view on this matter is as follows:

PMDA agreed with the applicant's explanation that no substantial differences exist between Japanese and non-Japanese data on the pharmacokinetics of eliglustat tartrate (hereinafter referred to as "eliglustat"), although comparisons were done with limited data for Japanese subjects.

The applicant must urge careful administration by including appropriate precautionary statements in the package insert about concomitant drugs because eliglustat is metabolized primarily by CYP2D6 and CYP3A4 and evidence has been shown that an inhibitor of these enzymes could increase exposure to eliglustat when they are co-administered. The applicant must collect information in post-marketing surveillance on the safety and efficacy in association with concomitant use with drugs, such as CYP2D6 inhibitors and CYP3A inhibitors that could have drug interactions with eliglustat.

This conclusion by PMDA was supported by the expert advisors.

2) QT/QTc prolongation and proarrhythmic risk

PMDA's view on this matter is as follows:

Although QTcF interval prolongation at the high dose of eliglustat (800 mg) in the QT/QTc study was negative according to ICH E14 guidelines, changes from baseline in QTcF, PR, and QRS intervals showed a positive correlation in a drug concentration-response modeling. Since eliglustat is metabolized primarily by CYP2D6 and CYP3A4, there may be risks that arrhythmias and conduction block occur due to QTcF, PR, and QRS interval prolongation exceeding the thresholds in the ICH E14 guidelines when drug interactions cause

eliglustat exposure higher than that associated with the high dose in the QT/QTc study. Although it was inferred based on modelling, the data indicate that the degrees of increased exposure and the degrees of QTcF, PR, and QRS interval prolongation could differ individually according to the degree of drug interactions associated with co-administration. At least from the standpoint of proarrhythmic risk associated with QTcF interval prolongation, eliglustat exposure in plasma should be maintained within the range expected to produce QTcF interval prolongation below the threshold specified in the ICH E14 guidelines.

With regard to CYP2D6 phenotypes, the applicant states that safety can be ensured (i) by excluding PMs from the population intended for treatment due to concerns about QTcF, PR, and QRS interval prolongation associated with CYP3A inhibitor co-administration and (ii) by contraindicating eliglustat in EMs and IMs on a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor. However, in the absence of drug interactions, the range of exposure in PMs at 100 mg QD is comparable to the range in IMs at 100 mg BID. Moreover, the range of exposure at 100 mg BID in IMs taking a strong CYP3A inhibitor is comparable to the range under conditions for which the applicant proposes contraindication (co-administration with a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor). As exposure can be higher depending on co-administration regimens, the applicant must rigorously set restrictions by type of concomitant drugs. Precautions and dosages must therefore be appropriately selected according to the patient population to be treated and degree of drug interactions expected.

This conclusion by PMDA was supported by the expert advisors [see "(3) Safety" for more information on proarrhythmic risk and "(5) Dose and administration" for information on dosage regimens according to the patient population and degree of drug interactions].

(2) Efficacy

PMDA's view on this matter is as follows:

Superiority of Cerdelga Capsules (eliglustat) over placebo has been demonstrated in percent change in spleen volume from baseline to Week 39, the primary endpoint, in Study ENGAGE in treatment-naïve non-Japanese patients. Noninferiority of eliglustat to imiglucerase has been demonstrated in the percentage of subjects in whom efficacy is sustained at Week 52, the primary endpoint, in Study ENCORE in non-Japanese patients with a history of prior ERT. In patients with a history of prior ERT in the global phase III study which included Japanese patients, the subjects in both the overall and Japanese populations remained stable.

It may be interpreted from the above findings that efficacy of eliglustat in patients with Gaucher disease type 1 has been generally shown. The applicant must continue to collect information on the efficacy of eliglustat in post-marketing surveillance because only a small number of Japanese subjects have been evaluated.

This conclusion by PMDA was supported by the expert advisors.

(3) Safety

1) Proarrhythmic risk

PMDA's view on this matter is as follows:

Data for the single 800 mg dose of eliglustat did not indicate QTcF interval prolongation according to the ICH E14 guidelines but suggested that QTcF, PR, and QRS intervals increased with increasing plasma concentrations of unchanged eliglustat. Regular, detailed electrocardiographic examinations were performed in the phase II and III studies and revealed proarrhythmic events such as atrioventricular block and abnormal ECG in the eliglustat groups, even among the CYP2D6 EMs. After the market launch, eliglustat will be used in a wider patient population than that studied in the clinical studies, and many different concomitant drugs are likely to be used with eliglustat. Accordingly, exposure in some patients may be higher than those at the high dose used in the thorough QT/QTc study, which in turn could result in marked QTcF interval prolongation and occurrence of atrioventricular block. The applicant must therefore appropriately provide precautionary advice not only about the intended population and drug interactions with concomitant drugs but also about implementation of electrocardiography during treatment with eliglustat. The applicant must also continue to collect information on proarrhythmic risk (including that associated with concomitant drugs) in the post-marketing phase.

This conclusion by PMDA was supported by the expert advisors. The expert advisors also indicated that Holter monitoring, an effective means of detecting atrioventricular block, should be performed when necessary.

PMDA asked the applicant to include precautionary statement about this issue in the package insert and confirmed that the applicant had appropriately responded [see "(7) Risk management plan (draft)"].

(4) Indication

PMDA's view on this matter is as follows:

There are no substantial problems with the indication as currently proposed by the applicant because eliglustat was clinically developed in patients with Gaucher disease type 1 and has not been used in patients with Gaucher disease type 2 and 3. However, the percentage of Japanese patients with Gaucher disease type 2 or 3 is higher than that of non-Japanese patients, and the existing enzyme replacement therapies in Japan are approved for all disease types. The pharmacological mechanism of eliglustat indicates that it could be effective in general symptoms not neurological in nature. Therefore, the applicant should consider the need to develop eliglustat for the other disease types in light of the clinical need identified following the market launch.

The expert advisors commented on this conclusion by PMDA as follows:

- Although eliglustat has not been used in patients with Gaucher disease type 2 and 3, eliglustat is expected to be effective in patients with types 2 and 3 because the disease type classification is based on the clinical features.
- There have been patients in whom the disease was initially diagnosed as type 1 and was later as type 3 based on the subsequent appearance of neurological symptoms. Eliglustat is expected to be effective for non-neurological symptoms in such patients.

• Indicating eliglustat for all types of Gaucher disease (including type 2 and 3) is therefore appropriate.

In light of the above, PMDA determined that allowing treatment in patients with Gaucher disease type 2 and 3 would be appropriate if the following conditions are met: the applicant provides information that eliglustat was not used in this population in the clinical studies and eliglustat is not expected to be effective for the neurological symptoms of the disease; the benefits are found to outweigh the risks in individual patients.

PMDA asked the applicant to revise the indication and related statements as below and confirmed that the applicant properly addressed:

[Indication]
Alleviation of symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, and skeletal pathology)

[Precautions for indication]
(1) Eliglustat is to be used only in patients with a confirmed diagnosis of Gaucher disease.
(2) Eliglustat is to be used in patients with Gaucher disease type 2 or 3 only when the benefit is found to outweigh the risk and the patient has been fully informed that eliglustat has not been used in these patients.
(3) Eliglustat is not effective for the neurological symptoms of Gaucher disease.

(5) Dosage and administration
PMDA's view on this matter is as follows:
Although dose adjustment was performed according to the trough concentrations of unchanged eliglustat in plasma in the phase II and III studies in patients, efficacy was demonstrated even at lower trough concentrations than specified in the studies. Thus, from an efficacy point of view, there are no specific problems with not adjusting the dosage based on trough concentrations. From a safety point of view also, there are no specific problems with the applicant's statement that dosage will be considered based on CYP2D6 phenotypes because eliglustat is metabolized primarily by CYP2D6.

There are no special problems with the dosage of 100 mg BID for IMs and EMs because many of the EMs and IMs in the clinical studies received 100 mg BID. There are no specific problems with excluding URMs from the intended patient population because exposure in URMs is approximately half that in EMs and the small number of URMs evaluated in the clinical studies makes setting a recommended dosage currently unfeasible. There are no specific problems with excluding indeterminate CYP2D6 metabolizers at present because the extent of increases in exposure in this population cannot be predicted. Although the applicant stated that it does not intend to include PMs in the intended patient population because of the small number of PMs evaluated in the clinical studies and because controlling concomitant drugs for different CYP2D6 phenotypes according to the package insert would be complicated, PMDA notes that exposure in PMs receiving 100 mg QD is estimated to be comparable to that in IMs receiving 100 mg BID. Thus, there is room for the applicant to reconsider including PMs in the intended patient population.

Finally, dosage regimen must be selected appropriately according to particular patients and extent of drug interactions with concomitant drugs because proarrhythmic risk is expected to differ depending on the extent of interactions.

This conclusion by PMDA was supported by the expert advisors. The expert advisors expressed the following views:

- Use of eliglustat in CYP2D6 PMs should generally be avoided because of inter-patient variability in blood concentrations. However, it is important to include PMs in the intended patient population because these patients can be treated by careful administration of eliglustat in reference to the dosage approved outside Japan.
- Although exposure increases in association with drug interactions with moderate or stronger CYP2D6 and CYP3A inhibitors, it is unfeasible to comprehensively classify and list all drugs that could increase exposure because the extents of inhibition are not always certain.
- Since eliglustat is a drug for treatment of a rare disease, information in forms of information leaflet describing updated information on drugs with CYP2D6 or CYP3A inhibition should be provided to healthcare professionals in clinical settings to treat individual patients.

Based on the above, PMDA considered that the dosage and administration should be changed as indicated below.

PMDA asked the applicant to modify the proposed dosage and administration and related statements and confirmed that the applicant properly addressed:

[Dosage and administration]
The usual dosage for adults who are CYP2D6 extensive or intermediate metabolizers is 100 mg of eliglustat tartrate administered orally, twice daily. The dose should be reduced according to the condition of the patient.

[Precautions for dosage and administration]
(1) CYP2D6 phenotype of the patient should be determined before administration of eliglustat.
(2) Concomitant drugs should be checked whether any of them inhibits CYP2D6 or CYP3A,[133] and if so, the dosage should be adjusted in reference to the following table.

[133] A drug with a strong inhibitory effect: A drug thought to increase AUC of the victim drug ≥5-fold or reduce clearance to <1/5. A drug with a moderate inhibitory effect: A drug thought to increase AUC of the victim drug ≥2-fold to <5-fold or reduce clearance to ≥1/5 to <1/2.

	CYP2D6 EMs	CYP2D6 IMs
Coadministered with both a drug that inhibits CYP2D6 and a drug that inhibits CYP3A	Contraindicated	Contraindicated
Coadministered with only a drug that inhibits CYP2D6	100 mg QD	100 mg QD
Coadministered with only a drug that inhibits CYP3A	100 mg QD	Contraindicated

(3) Refer to the following if the patient is not a CYP2D6 EM or IM:

- Use of eliglustat should be avoided in CYP2D6 PMs because of higher blood eliglustat concentrations induced. If eliglustat is to be used in PMs, eliglustat is administered with care, basically at a dose of 100 mg once daily.
- Use of eliglustat should be avoided in CYP2D6 ultra rapid metabolizers (URMs) because low blood concentrations of eliglustat may result in reduced efficacy.
- Use of eliglustat should be avoided in patients with an indeterminate CYP2D6 phenotype in whom the metabolic capacity of CYP2D6 is undetermined.

(4) Patients should be instructed to take a dose at the next scheduled time when forgetting to take a dose and to never take 2 doses at once.

PMDA believes the applicant must provide information in the form of information leaflet regarding drugs that have an inhibitory effect on CYP2D6 or CYP3A and establish a system to address questions from healthcare providers regarding concomitant drugs. The extent of CYP2D6 or CYP3A inhibition may not be clearly determined for some concomitant drugs. For such drugs, the applicant should provide information to healthcare professionals in clinical settings to ensure the safety of the patient, recommending consideration of electrocardiographic evaluation, switching to an alternative drug, or, when necessary, discontinuation of use of eliglustat. PMDA asked the applicant to address these matters, and the applicant responded that it would. PMDA accepted this response of the applicant.

(6) Special patient populations

Patients with renal or hepatic impairment

PMDA's view on this matter is as follows:

There are no specific problems with the applicant's position that use of eliglustat should not be recommended in patients with renal or hepatic impairment because pharmacokinetics and safety have not been evaluated in these patients. The applicant must continue to collect information on safety in patients with renal or hepatic impairment in post-marketing surveillance because only a small number of subjects have been evaluated in the clinical studies.

This conclusion by PMDA was supported by the expert advisors [see "(7) Risk management plan (draft)" for more information about the post-marketing investigations].

(7) Risk management plan (draft)

PMDA considers that the following should be additionally considered in the risk management plan in light of the discussion in the section "II.4.(iii).B.(7) Post-marketing investigations" in the Review Report (1) and the comments raised by the expert advisors in the Expert Discussion:

- Safety of eliglustat in patients without a history of ERT
- Safety of eliglustat in patients with Gaucher disease type 3
- Effects of CYP2D6 phenotypes on safety of eliglustat
- Selecting pulmonary function as an efficacy measure

PMDA asked the applicant to address the above points. In response, the applicant submitted the following summary of the risk management plan (draft) (Tables 57 and 58) and outline of its plan for specified drug use-results surveillance (Table 59). PMDA found these plans acceptable.

Table 57. Safety specification and efficacy specification in risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
	• Effects of interactions with drugs that inhibit CYP2D6 or CYP3A • Conduction disorders and arrhythmias • Syncope	• Safety in patients without a history of ERT • Safety in patients with Gaucher disease type 3 • Effects by CYP2D6 phenotype on safety • Safety in patients with a history of cardiac disease or syncope • Safety in patients with hepatic impairment
Efficacy investigations		
• Efficacy in long-term use		

Table 58. Summary of additional pharmacovigilance and risk minimization activities in risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey (all-patient surveillance) • Study EDGE[a)]	• Creation and provision of information leaflets for healthcare providers • Creation and dissemination of information leaflets for patients • Information provision through early post-marketing phase vigilance

a) Now underway

Table 59. Outline of specified drug use-results survey (draft)

Objective	To evaluate long-term safety and efficacy in clinical settings.
Format	All-patient survey
Patients	All patients receiving eliglustat
Follow-up period	Maximum of 8 years for each patient
Proposed sample size	All patients receiving eliglustat
Main survey items	Patient demographics, information on administration of eliglustat, concomitant drugs, safety evaluation (e.g., conduction disorders/arrhythmias, syncope, gastrointestinal symptoms, neurological symptoms), efficacy evaluation (e.g., hemoglobin level, platelet count, liver/spleen volume, bone density, pulmonary arterial pressure)

III. Overall Evaluation

As a result of the above review, PMDA concludes that eliglustat may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. The re-examination period is 10 years because eliglustat is an orphan drug. The drug substance and the drug product are both classified as a powerful drug, and eliglustat is not classified as a biological product or a specified biological product.

[Indication]	Alleviation of symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, and skeletal pathology)
[Dosage and administration]	The usual dosage for adults who are CYP2D6 extensive or intermediate metabolizers is 100 mg as eliglustat tartrate administered orally, twice daily. The dose should be reduced according to the condition of the patient.

[Conditions for approval]

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Conduct a post-marketing drug use-results survey covering all patients treated with the product during the reexamination period to obtain characteristics of the patients since the number of subjects in the clinical study in Japan was very limited; and at the same time, ensure that safety and efficacy data on the product is collected without delay and that necessary measures are taken to facilitate the proper use of the product.