Report on the Deliberation Results

December 4, 2018

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

Brand Name	Relumina Tablets 40 mg
Non-proprietary Name	Relugolix (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2018

Results of Deliberation

In its meeting held on December 3, 2018, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

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

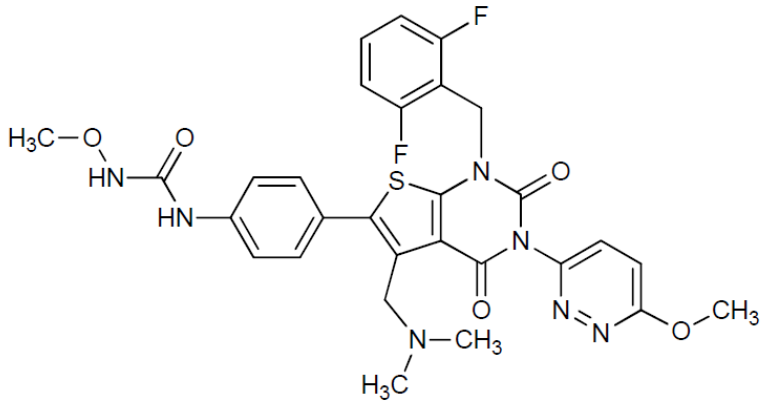
**Japanese Accepted Name (modified INN)*

Review Report

November 14, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name Relumina Tablets 40 mg
Non-proprietary Name Relugolix
Applicant Takeda Pharmaceutical Company Limited
Date of Application February 28, 2018
Dosage Form/Strength A tablet containing 40 mg of relugolix
Application Classification Prescription drug, (1) Drug with a new active ingredient
Chemical Structure



Molecular formula: $C_{29}H_{27}F_2N_7O_5S$
Molecular weight: 623.63
Chemical name: 1-(4-{1-(2,6-Difluorobenzyl)-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea

Items Warranting Special Mention None
Reviewing Office Office of New Drug II

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in relief of symptoms of menorrhagia, lower abdominal pain, lumbar pain, and anemia associated with uterine fibroids and that the product has acceptable safety in view of its benefits.

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

Indication	Relief of the following symptoms associated with uterine fibroids: menorrhagia, lower abdominal pain, lumbar pain, and anemia.
Dosage and Administration	The usual adult dosage is 40 mg of relugolix administered orally once daily before a meal. The initial dose should be administered on a day between Days 1 and 5 of a menstrual cycle.

Approval Conditions

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

Attachment

Review Report (1)

October 2, 2018

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

Product Submitted for Approval

Brand Name	Relumina Tablets 40 mg
Non-proprietary Name	Relugolix
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2018
Dosage Form/Strength	A tablet containing 40 mg of relugolix
Proposed Indication	Relief of the following symptoms associated with uterine fibroids: menorrhagia, lower abdominal pain, lumbar pain, and anemia.
Proposed Dosage and Administration	The usual adult dosage is 40 mg of relugolix administered orally once daily before a meal. The initial dose should be administered on a day between Days 1 and 5 of a menstrual cycle.

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List of Abbreviations

See Appendix.

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

Relugolix is a non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist developed by Takeda Pharmaceutical Company Limited. Relugolix competitively binds to GnRH receptors expressed in basophilic cells in the anterior pituitary, prevents GnRH binding to the GnRH receptor, and inhibits the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which are released from the basophilic cells in response to stimulation by GnRH, leading to reduction in blood levels of sex hormones (e.g., estrogen) controlled by LH and FSH.

A uterine fibroid is a benign tumor that originates from the smooth muscle of the myometrium, and its growth depends on sex hormones. The clinical symptoms associated with uterine fibroids include menorrhagia and accompanying anemia and pain. Currently, GnRH agonists are widely used for the pharmaceutical treatment of clinical symptoms associated with uterine fibroids. They desensitize the pituitary gland via continuous stimulation of GnRH receptors and in turn inhibit the secretion of LH and FSH. Early in the treatment, therefore, GnRH agonist therapy increases the secretion of LH and FSH via the stimulation of GnRH receptors and thereby causes a transient increase (flare-up) in blood levels of sex hormones.

Relugolix, a GnRH antagonist, lowers the blood levels of sex hormones without causing a flare-up and is thus expected to relieve clinical symptoms associated with uterine fibroids. In 20[redacted], the applicant started the clinical development of relugolix in Japan. On the basis of results of Japanese clinical studies and other data, the applicant has filed the marketing application of relugolix for the proposed indication of "relief of the following symptoms associated with uterine fibroids: menorrhagia, lower abdominal pain, lumbar pain, and anemia." As of September 2018, relugolix has not been approved in any country or region.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is white to yellowish white powder. The properties of the drug substance include description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, crystalline form (X-ray powder diffraction), thermal analysis (differential scanning calorimetry and thermogravimetric/differential thermal analysis), and crystalline polymorphism. Three [redacted] crystalline forms (Forms [redacted], [redacted], and [redacted]), one [redacted] crystalline form (Form [redacted]), 6 [redacted] (Forms [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]), and [redacted] have been identified for the drug substance. Only Form [redacted], however, has been confirmed to be produced during the manufacturing process at commercial scale.

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet and visible absorption spectrometry (UV/VIS), infrared spectrophotometry (IR), hydrogen (^{1}H-) and carbon (^{13}C-) nuclear magnetic resonance spectrometry (NMR), mass spectrometry (MS), and X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized from [redacted] and [redacted] as the starting materials in the [redacted] process steps.

The quality control strategy has been formulated by doing the following using a quality by design (QbD) approach (Table 1).

- Identification of [redacted] and [redacted] as critical quality attributes (CQAs)
- Evaluation of the manufacturing process risk based on a failure mode and effects analysis (FMEA)
- Identification of critical process parameters (CPPs) based on the design of experiments

Table 1. Outline of the quality control strategy for the drug substance

CQA	Control methods
[redacted]	Manufacturing process and specifications
[redacted]	Specifications

The [redacted] process, [redacted] process and [redacted] process have been specified as critical steps. [redacted] has been controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV/VIS, IR, and X-ray powder diffraction method), purity (related substances [high performance liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)]), water content, residue on ignition, [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The main stability studies performed for the drug substance are shown in Table 2. The photostability testing showed that the drug substance was photolabile.

Table 2. Main stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at pilot scale	25°C	60% RH	Polyethylene bag (double-layer) + aluminum-laminated bag [a]	18 months
Accelerated testing	3 batches at pilot scale	40°C	75% RH		6 months

a: [redacted]

Based on the above and in compliance with the ICH Q1E Guideline, a re-test period of 30 months has been proposed for the drug substance when stored in a double-layer polyethylene bag (double-layer) packed in an aluminum-laminated bag [redacted] at room temperature. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 40 mg of relugolix. It contains the following excipients: D-mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium oxide, carnauba wax, yellow ferric oxide, and red ferric oxide.

2.2.2 Manufacturing process

The drug product is manufactured in a process consisting of the following steps: [redacted], film coating[redacted]. [redacted] and [redacted] have been defined as critical steps, and the process controls and action limits have been established for [redacted] and [redacted].

The quality control strategy has been formulated by doing the following using a quality by design (QbD) approach (Table 3).

- Identification of [redacted] and [redacted] as CQAs
- Evaluation of the manufacturing process risk based on [redacted] and [redacted]

Table 3. Outline of control strategy for the drug product

CQA	Control methods
[redacted]	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications
[redacted]	Specifications
[redacted]	Specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (UV/VIS), purity (related substance [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies performed for the drug product are shown in Table 4. The photostability testing showed that the drug product was photostable.

Table 4. Main stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at pilot scale	25°C	60% RH	Blister pack [a] ＋ aluminum-laminated bag [b]	18 months
Accelerated testing	3 batches at pilot scale	40°C	75% RH		6 months

a: [redacted]
b: [redacted]

Based on the above and in compliance with the ICH Q1E Guideline, a shelf-life of 30 months has been proposed for the drug product when stored in a blister pack ([redacted]), packaged in an aluminum-laminated bag ([redacted]) at room temperature. The long-term testing will be continued for up to 36 months.

2.R Outline of the review conducted by PMDA

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

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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding effects of relugolix on GnRH receptor (CTD 4.2.1.1-1)

Cell membranes were prepared from Chinese hamster ovary (CHO) cells expressing rat, monkey, or human GnRH receptors. With the use of the cell membranes, relugolix (0.003-10 nmol/L), GnRH (0.03-100 nmol/L), a GnRH agonist leuprorelin (0.003-10 nmol/L), or a GnRH antagonist cetrorelix (0.003-10 nmol/L) was incubated with ^{125}I-labeled leuprorelin at room temperature for 1 hour in the presence or absence of inactivated fetal bovine serum to evaluate the binding affinity of individual medications to the GnRH receptors. The obtained 50% inhibitory concentration (IC_{50}) values are shown in Table 5.

Table 5. Binding affinity of relugolix to rat, monkey, or human GnRH receptors

	Fetal bovine serum concentration (%)	IC_{50} (nmol/L)			
		Relugolix	GnRH	Leuprorelin	Cetrorelix
Rat	0	2900	26	0.36	0.25
	40	9800	24	0.48	0.38
Monkey	0	0.15	17	2	0.28
	40	0.32	7.5	2.3	0.53
Human	0	0.12	31	2.9	0.85
	40	0.33	17	3	1.2

3.1.1.2 Effects of relugolix on GnRH-induced arachidonate release (CTD 4.2.1.1-2, 3)

CHO cells expressing monkey or human GnRH receptors were incubated with ^{3}H-labelled arachidonate overnight in the presence or absence of inactivated monkey or human plasma. After being washed, the CHO cells were spiked with relugolix (monkey, 3-10000 nmol/L; human, 0.03-300 nmol/L) or cetrorelix (monkey, 0.1-300 nmol/L; human, 0.1-300 nmol/L) and, 15 min later, stimulated with GnRH (1 nmol/L). Arachidonate levels in the cultures were determined 45 min after the cell stimulation. The results showed that relugolix and cetrorelix inhibited the GnRH-induced arachidonate release in a concentration-dependent manner. The IC_{50} and IC_{90} values are shown in Table 6.

Table 6. Inhibition of arachidonate release in CHO cells expressing monkey or human GnRH receptors

	Plasma concentration (%)	Relugolix		Cetrorelix	
		IC_{50} (nmol/L)	IC_{90} (nmol/L)	IC_{50} (nmol/L)	IC_{90} (nmol/L)
Monkey	0	16	77	0.78	3.0

	40	230	1700	12	49
Human	0	0.32	2.6	0.67	4.6
	40	1.6	18	4.5	75

3.1.2 *In vivo* studies

3.1.2.1 Effects of relugolix on the hypothalamic-pituitary axis in cynomolgus monkeys (CTD 4.2.1.1-4)

A single dose of relugolix (0.1, 0.3, 1, or 3 mg/kg) or vehicle was administered to castrated cynomolgus monkeys, and plasma LH levels were measured at 1, 2, 4, 8, 24, and 48 hours after the administration(3 animals per group). In the relugolix 1 mg/kg and 3 mg/kg groups, plasma LH levels decreased after administration compared with those before administration, and the extent of decrease reached the maximum at 8 hours after administration. Plasma LH levels remained low until 24 hours after administration in the relugolix 1 mg/kg group and 48 hours after administration in the relugolix 3 mg/kg group. No remarkable effects on the plasma LH levels were seen in the relugolix 0.1 mg/kg and 0.3 mg/kg groups.

3.1.2.2 Effects of relugolix on the hypothalamic-pituitary-gonadal axis in human GnRH receptor knock-in female mice (CTD 4.2.1.1-5, 4.2.1.1-7 [reference data])

Relugolix (30, 100, or 200 mg/kg) or vehicle (2 groups: non-ovariectomized and ovariectomized animals) was orally administered twice daily for 4 weeks to human GnRH receptor knock-in mice, to evaluate the level of expression of mRNA for GnRH receptor in the pituitary gland, the estrous cycle, the ovarian weight and uterine weight, and the density of the cancellous bones and cortical bones (8 animals per group). The administration of relugolix induced persistent diestrus in the relugolix ≥100 mg/kg groups. As compared with the vehicle (non-ovariectomized) group, the ovarian weight was significantly lower in the relugolix ≥30 mg/kg groups, and the uterine weight was significantly lower in the relugolix ≥100 mg/kg groups. The level of expression of mRNA for the GnRH receptor in the pituitary gland was significantly lower in the relugolix ≥100 mg/kg groups than in the vehicle (non-ovariectomized) group. Meanwhile, the density of the cancellous bones and cortical bones did not differ between the vehicle group (the non-ovariectomized and ovariectomized animals) and the relugolix group. The duration of persistent diestrus seen in the relugolix ≥100 mg/kg groups gradually started to be shortened approximately 5 days after treatment discontinuation, and the estrous cycle in the groups became similar to that in the vehicle (non-ovariectomized) group by 28 days after treatment discontinuation. The ovarian weight and uterine weight which decreased with administration of relugolix were restored to the previous levels by 14 days after treatment discontinuation.

3.2 Secondary pharmacodynamics

3.2.1 Effects of relugolix on receptors other than GnRH receptor, channels, and transporters (CTD 4.2.1.2-1 [reference data])

Effects of relugolix (10 μmol/L) on 134 types of receptors, channels, and transporters were evaluated with an enzyme and radiolabeled ligand binding assay. Inhibition of ≥50% of the radiolabeled ligand by relugolix was observed only for tachykinin NK_2 receptors (inhibition of 55%).

3.3 Safety pharmacology

Results of safety pharmacology studies are shown in Table 7.

Table 7. Outline of results of safety pharmacology studies

Item	Test system	Evaluated parameters, methods, etc.	Doses	Route of administration	Findings	CTD
Central nervous system	SD rats (6 males per group)	FOB method (under no anesthesia)	0, 200, 600, 2000 mg/kg Single dose	Oral	None	4.2.1.3-3
Cardiovascular system	HEK293 cells stably expressing hERG channel	hERG current	0, 0.3, 3, 30 μg/mL	*in vitro*	Significant inhibition with ≥3 μg/mL compared with vehicle (20.5% inhibition with 3 μg/mL, 78.5% inhibition with 30 μg/mL). IC_{50} of 9.7 μg/mL (15.6 μmol/L).	4.2.1.3-1
	Cynomolgus monkeys (4 males)	Blood pressure, heart rate, electrocardiography (under no anesthesia)	0, 30, 100, 300 mg/kg Escalating single dose	Oral	Prolonged QT and QTc interval with 100 and 300 mg/kg.	4.2.1.3-2
Respiratory system	SD rats (8 males per group)	Respiratory rate, tidal volume, minute ventilation, enhanced pause (under no anesthesia)	0, 200, 600, 2000 mg/kg Single dose	Oral	None	4.2.1.3-4

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about the effects of relugolix on clinical symptoms associated with uterine fibroids:

In *in vitro* studies, the IC_{50} value of relugolix for inhibition of human GnRH receptors was lower than those of GnRH, leuprorelin, and cetrorelix, and relugolix inhibited the GnRH-induced arachidonate release in CHO cells expressing monkey or human GnRH receptors. In *in vivo* studies, oral administration of relugolix led to decreases in plasma LH levels in castrated cynomolgus monkeys and decreases in ovarian and uterine weights in human GnRH receptor knock-in female mice. GnRH binds to the GnRH receptors in the pituitary gland and thereby induces the secretion of LH and FSH, which control the secretion of estrogen or other hormones from the ovary, and the resulting increase in estrogen aggravates clinical symptoms associated with uterine fibroids (*Am Fam Physician.* 2007;75(10): 1503-8). The efficacy of relugolix administered to humans at the clinical dose cannot be fully estimated from the results of the *in vivo* studies in castrated cynomolgus monkeys and human GnRH receptor knock-in mice, for the following reasons:

(a) Castrated or uncastrated status affected the blood LH-lowering effects of GnRH receptor inhibitors (*J Med Chem.* 2003;46: 113-24; *J Clin Endocrinol Metab.* 2003;88: 1697-704).

(b) The inhibitory effects of relugolix on GnRH-induced arachidonate release differed between monkeys and humans [see Section 3.1.1.2].

(c) Downstream molecules of GnRH receptors and GnRH secretion volume may differ between mice and humans.

However, the applicant considers that relugolix is expected to relieve clinical symptoms associated with uterine fibroids by decreasing blood estrogen levels through competitive inhibition of GnRH receptors.

PMDA's view:

As described by the applicant, the clinical dosage of relugolix should be adequately evaluated in clinical studies. However, the *in vitro* and *in vivo* studies have demonstrated that relugolix inhibits GnRH receptors and lowers plasma levels of LH, which involves in the control of blood estrogen levels. Therefore, PMDA considers that relugolix has shown pharmacological effects that can contribute to the relief of clinical symptoms associated with uterine fibroids.

3.R.2 Safety pharmacology

The applicant's explanation about the findings obtained during the investigation of the cardiovascular effects of relugolix:

The hERG current was inhibited at a relugolix concentration of ≥3 μg/mL. However, the IC_{50} value was 9.7 μg/mL (15.6 μmol/L), which is approximately 462 times higher than the exposure in humans (C_{max}: 21.0 ng/mL) treated with relugolix at the clinical dose (40 mg) [see Section 6.2.2.1]. In monkeys, QT and QTc intervals were prolonged after a single dose of relugolix at ≥100 mg/kg, whereas no effects were observed with a single oral dose of relugolix at 30 mg/kg. In a 4-week repeated oral dose toxicity study in monkeys, the mean C_{max} after the initial dose of relugolix at 20 mg/kg to male monkeys was 816.8 ng/mL. Based on the C_{max}, the mean C_{max} after administration of relugolix at 30 mg/kg was estimated to be 1225.2 ng/mL, which is approximately 58 times higher than the C_{max} in Japanese premenopausal women who received relugolix 40 mg once daily before a meal for 14 days. Based on the above, relugolix is considered unlikely to prolong the ventricular repolarization in its clinical use.

PMDA's view:

There is a sufficient gap between the relugolix exposure that induced cardiovascular effects and the expected clinical exposure. PMDA thus considers that the data from the safety pharmacology studies have not suggested a possibility that the cardiovascular effects of relugolix will be a significant issue in its clinical use. Meanwhile, the investigation of inhibitory effects of relugolix on GnRH-induced arachidonate release [see Section 3.1.1.2] suggests that species difference between monkeys and humans may exist in a relationship between relugolix exposure and its pharmacological effects. Therefore, the cardiovascular effects (including prolongation of QT/QTc interval) of relugolix administered at the clinical dose in humans should be evaluated based on data available from thorough QT/QTc studies and the occurrence of adverse events in clinical studies [see Sections 6.2.7 and 7.R.2.6]. PMDA has concluded that no data have been found in safety pharmacology studies that suggest any issues in the clinical use of relugolix.

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

The plasma relugolix levels were determined with liquid chromatography/tandem mass spectrometry (LC/MS/MS), with a limit of quantification of 0.5 ng/mL in rats and monkeys. The radioactivity in samples obtained from animals given ^{14}C-labeled relugolix was determined with a liquid scintillation counter.

The pharmacokinetic parameters are shown in mean ± standard deviation unless otherwise specified.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 to -4, -9, -10)

Table 8 shows the pharmacokinetic parameters of relugolix after a single oral or intravenous dose of relugolix in male rats or male monkeys.

Table 8. Pharmacokinetic parameters of relugolix after single dose of relugolix

Animal species	Route of administration	Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{0-48} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Rat	Oral	5	3	30.5 ± 30.7	2.0	107.4 ± 60.5	2.4 ± 0.8	−	−
		12	3	46.1 ± 7.5	4.0	297.9 ± 42.7	6.0 ± 1.9	−	−
		30	3	429.2 ± 94.0	4.0	1681 ± 283	5.0 ± 0.5	−	−
	Intravenous	0.5	3	57.3 ± 4.9 [b]	−	58.3 ± 4.1	3.7 ± 0.1	9335.4 ± 678.2	38453.4 ± 2148.7
		2	3	362.2 ± 55.2 [b]	−	322.8 ± 23.5	5.0 ± 0.5	6204.0 ± 421.3	24630.0 ± 2138.2
		10	3	2287 ± 44 [b]	−	2236 ± 205	6.4 ± 0.3	4472.5 ± 414.9	16425.3 ± 2443.2
Monkey	Oral	1	4	44.8 ± 23.7	0.75	180.6 ± 53.2	5.5 ± 0.5	−	−
		5	4	367.2 ± 159.7	2.0	2092.8 ± 849.7	6.7 ± 0.5	−	−
		20	4	2080.6 ± 129.4	2.0	14931.7 ± 1159.0	5.4 ± 0.2	−	−

a: Median
b: Value at 5 min postdose
−: Not calculated

A single oral dose of relugolix 5 mg and a single intravenous dose of relugolix 1 mg were administered to male rats (3 animals each) under fasting conditions. The bioavailability (BA) was 9.0%. (BA was calculated as a dose-adjusted ratio of oral AUC_{0-48} to intravenous AUC_{0-48}; the same applies hereinafter.)

A single oral dose of relugolix 1 mg under fasting or fed conditions and a single intravenous dose of relugolix 0.2 mg under fasting conditions were administered to male monkeys (4 animals each), and effects of foods on the pharmacokinetics of relugolix and BA of relugolix were evaluated. C_{max} and AUC_{0-48} after oral administration of relugolix was 3.7 ± 2.2 ng/mL and 25.0 ± 10.3 ng·h/mL, respectively, under fasting conditions and 0.7 ± 0.5 ng/mL and 1.2 ± 0.9 ng·h/mL, respectively, under fed conditions, showing lower values under fed conditions than those under fasting conditions. The median T_{max} of relugolix was shorter under fed conditions (0.25 h) than fasting conditions (1.5 h). The BA of relugolix was 6.9%.

A single oral dose of ^{14}C-labeled relugolix was administered to male rats (3 animals) at 30 mg/kg and to male monkeys (2 animals) at 20 mg/kg, and plasma radioactivity levels were determined. The plasma radioactivity levels peaked at 2.0 h postdose in rats and 2.5 h postdose in monkeys (0.596 and 2.574 μg eq/mL, respectively). Afterward, plasma radioactivity levels immediately decreased to 0.011 μg eq/mL in rats and 0.096 μg eq/mL in monkeys at 24 h postdose.

4.1.2 Repeated-dose studies (CTD 4.2.3.2-2, -6, -9)

Table 9 shows the pharmacokinetic parameters of relugolix after repeated oral doses of relugolix in male and female mice, male and female rats, and male and female monkeys.

Table 9. Pharmacokinetic parameters of relugolix after repeated oral doses of relugolix

Animal species	Duration of administration	Dose (mg/kg/day)	Time point (Day)	N	C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)	
					Males	Females	Males	Females
Mouse	13 weeks	200	1	3	8817.8	8383.1	41233	32918
			91	3	12327.3	14302.6	45162	44665
		600	1	3	12183.6	19109.5	62678	105011
			91	3	22062.4	25492.5	108063	127638
		2000	1	3	17258.1	23502.4	121198	187525
			91	3	39174.4	35663.1	317603	375128
Rat	26 weeks	10	1	3	2.3 ± 0.7	6.9 ± 8.7	13 ± 4	23 ± 21
			177	3	38.0 ± 15.1	62.1 ± 27.0	212 ± 70	249 ± 80
		30	1	3	65.4 ± 73.9	94.3 ± 72.6	350 ± 345	296 ± 156
			177	3	246.7 ± 41.2	257.1 ± 86.8	1653 ± 474	1534 ± 39
		100	1	3	630.7 ± 116.7	621.7 ± 199.8	2937 ± 860	2771 ± 990
			177	3	875.0 ± 518.1	1199.7 ± 189.7	7152 ± 4589	6109 ± 870
		300	1	3	1129.1 ± 301.8	1127.6 ± 107.4	6155 ± 1609	6754 ± 1359
			177	3	2911.2 ± 523.5	2541.1 ± 603.7	34077 ± 12262	26951 ± 1000
Monkey	39 weeks	1.5	1	4	20.2 ± 10.4	26.0 ± 21.0	103 ± 44	91 ± 58
			273	4	55.7 ± 13.0	50.2 ± 37.5	264 ± 72	190 ± 71
		5	1	4	181.1 ± 215.1	212.9 ± 59.5	717 ± 638	932 ± 201
			273	4	230.1 ± 129.0	333.9 ± 56.7	1087 ± 334	1554 ± 353
		15	1	4	1002.4 ± 485.0	608.4 ± 376.7	4173 ± 1471	3021 ± 1216
			273	4	989.8 ± 34.5	895.0 ± 95.9	5046 ± 409	5349 ± 213
		50	1	4	2815.9 ± 910.0	2810.2 ± 1195.6	16813 ± 8835	16251 ± 6278
			273	4	3048.5 ± 838.5	2472.7 ± 1345.4	19906 ± 6692	19369 ± 9372

4.1.3 Absorption sites (CTD 4.2.2.2-5)

A single dose of ^{14}C-labeled relugolix 5 mg/mL was administered into the stomach, duodenum, jejunum, ileum, and large intestine loop of male rats (3 animals) under fasting conditions, and the AUC_{0-4} of relugolix was 0.009 ± 0.008, 2.109 ± 0.466, 0.411 ± 0.266, 1.392 ± 1.187, and 0.174 ± 0.086 μg·h/mL, respectively, showing that the absorption of relugolix was highest in the duodenum, followed in order by the ileum, jejunum, large intestine, and stomach.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1 to -5)

A single oral dose of ^{14}C-labeled relugolix 5 m

g/kg was administered to male and female albino rats, and the radioactivity levels in individual tissues were determined at 1, 4, 8, 24, 72, and 168 h postdose (3 animals per time point). In most of the tissues, the radioactivity levels peaked at 4 or 8 h postdose. As compared with the peak radioactivity levels in plasma (0.016 and 0.020 μg/mL in male and female animals, respectively), the peak radioactivity levels were markedly higher in the liver (4.708 and 3.399 μg/g), intestinal wall (4.871 and 6.746 μg/g), gastric wall (1.599 and 2.256 μg/g), kidney (0.866 and 1.257 μg/g), adrenals (0.881 and 1.094 μg/g), thyroid (1.130 and 1.072 μg/g), and pituitary gland (1.197 and 1.166 μg/g). The radioactivity levels decreased below the limit of quantification in most of the tissues at 168 h postdose in both males and females, showing no residual radioactivity.

A single oral dose of ^{14}C-labeled relugolix 5 mg/kg was administered to male pigmented rats, and the plasma and ocular radioactivity levels were determined at 4, 8, 24, 72, and 168 h postdose and 2, 6, and 12 weeks postdose (3 animals per time point). Changes over time in plasma radioactivity levels in pigmented rats were

similar to those observed in the albino rats, whereas the ocular radioactivity levels in pigmented rats were higher than those in the albino rats, and radioactivity was detected in the eyes of pigmented rats even at 12 weeks postdose.

A single oral dose of ^{14}C-labeled relugolix 5 mg/kg was administered to male and female albino rats, and the distribution of radioactivity was evaluated with whole-body autoradiography at 1, 4, 8, 24, and 72 h postdose (2 animals per time point). The radioactivity was diffusely distributed in tissues until 4 to 8 h postdose, and high levels of radioactivity were detected in the pituitary gland, thyroid, liver, spleen, and kidney. The radioactivity, however, was eliminated within 72 h postdose from all tissues.

4.2.2 Plasma protein binding (CTD 4.2.2.3-6)

Mouse, rat, and monkey plasma was spiked with ^{14}C-labeled relugolix at a final concentration of 0.05 to 5 μg/mL, and the protein binding rate of relugolix was determined to be 80.1% to 83.2%, 73.6% to 76.3%, and 56.6% to 59.1%, respectively, showing a constant protein binding rate of relugolix across all concentrations tested.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-1, -7, -8)

Rat and monkey blood was spiked with ^{14}C-labeled relugolix at a final concentration of 0.05 to 5 μg/mL, and the distribution of relugolix in blood cells was determined to be 45.3% to 48.7% and 57.4% to 58.5%, respectively, showing a constant distribution in blood cells across all concentrations tested.

A single oral dose of ^{14}C-labeled relugolix was administered at 5 mg/kg to 3 male rats and at 1 mg/kg to 2 male monkeys, to determine the distribution of relugolix in blood cells. The distribution of relugolix in blood cells at 1, 4, 8, and 24 h postdose was 41.8%, 61.3%, 51.3%, and 41.4%, respectively, in rats and 38.5%, 35.1%, 26.7%, and 23.4%, respectively, in monkeys.

4.2.4 Transplacental distribution (CTD 4.2.2.3-9)

A single oral dose of ^{14}C-labeled relugolix 30 mg/kg was administered to pregnant rats on gestation day 18, and the radioactivity levels in tissues were determined at 1, 4, 8, 24, and 48 h postdose (3 animals per time point). The maternal plasma and placental radioactivity levels reached the maximum (0.276 μg/mL and 1.932 μg/g, respectively) at 4 h postdose and decreased to 0.006 μg/mL and 0.278 μg/g, respectively, at 48 h postdose. The fetal plasma radioactivity levels and the fetal radioactivity levels reached the maximum (0.031 μg/mL and 0.105 μg/g, respectively) at 8 h postdose and decreased below the limit of quantification and 0.019 μg/g, respectively, at 48 h postdose.

4.3 Metabolism

4.3.1 *In vitro* metabolism

4.3.1.1 Metabolism of relugolix (CTD 4.2.2.4-7)

Mouse, rat, dog, and monkey liver microsomes were spiked with ^{14}C-labeled relugolix at a final concentration

of 10 μmol/L and were incubated for 1 h at 37°C. The identified main metabolites of relugolix were Metabolite B (hydroxylated difluorobenzene ring) in mice and rats and Metabolite-A (O-demethylated methoxypyridazine) in dogs and monkeys.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma (CTD 4.2.2.4-3, -4)

A single oral dose of ^{14}C-labeled relugolix 30 mg/kg was administered to 3 male rats and 20 mg/kg to 2 male monkeys. Unchanged relugolix was most commonly identified in plasma at any time point (2, 4, and 6 h postdose in rats and 1, 4, 8, and 24 h postdose in monkeys). The plasma concentrations of Metabolites A, B, and C (N-demethoxylated methoxyurea) were all <10% of the plasma radioactivity.

4.3.2.2 Metabolites in urine and feces (CTD 4.2.2.4-5, -6)

After a single oral dose of ^{14}C-labeled relugolix 5 mg/kg in male rats, unchanged relugolix was mainly excreted in the urine up to 24 h postdose (91.7%; expressed as a percentage of the total radioactivity in the sample). Metabolite C was mainly excreted in the feces up to 48 h postdose (61.6%), and the percentage of unchanged relugolix excreted in feces was 8.3%.

After a single oral dose of ^{14}C-labeled relugolix 1 mg/kg in male monkeys, unchanged relugolix was mainly excreted in the urine up to 24 h postdose (55.8%). Metabolite C was mainly excreted in the feces up to 72 h postdose (50.0%), and the percentage of unchanged relugolix excreted in feces was 2.5%.

4.3.2.3 Metabolites in bile (CTD 4.2.2.4-5)

After a single oral dose of ^{14}C-labeled relugolix 5 mg/kg in male rats with bile duct cannulation, Metabolite B was mainly excreted in the bile up to 24 h postdose (38.5%; expressed as a percentage of total radioactivity in bile), and the percentage of unchanged relugolix excreted in the bile was 8.8%.

4.4 Excretion

4.4.1 Excretion in urine, feces, and expired air (CTD 4.2.2.5-1, 4.2.2.3-8)

After a single oral dose of ^{14}C-labeled relugolix 5 mg/kg to male rats, the percentage of excreted radioactivity in the urine, feces, and expired air (relative to the dosed radioactivity) up to 48 h postdose was 1.3%, 96.0%, and 0.3%, respectively.

After a single oral dose of ^{14}C-labeled relugolix 1 mg/kg to male monkeys, the percentage of excreted radioactivity in the urine and feces up to 96 h postdose was 4.9% and 91.6%, respectively.

4.4.2 Excretion in bile (CTD 4.2.2.5-2)

After a single oral dose of ^{14}C-labeled relugolix 5 mg/kg in male rats with bile duct cannulation, the percentage of excreted radioactivity in the bile (relative to the dosed radioactivity) up to 24 h postdose was 37.4%.

4.4.3 Excretion in milk (CTD 4.2.2.5-3, -4)

A single oral dose of ^{14}C-labeled relugolix 30 mg/kg was administered to rats on postpartum day 14, and the radioactivity levels in plasma and milk peaked both at 2 h postdose. The peak radioactivity in milk (4.262 μg eq/mL) was higher than the peak radioactivity in plasma (0.441 μg eq/mL) but decreased to 0.057 μg eq/mL at 48 h postdose.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that non-clinical pharmacokinetics of relugolix were adequately evaluated.

4.R.1 Tissue distribution

PMDA asked the applicant to discuss the possibility that safety issues might arise in humans when relugolix or its metabolite would be accumulated in tissues that had a high accumulation of radioactivity or showed slow elimination of radioactivity in the tissue distribution studies in rats.

The applicant's response:

Tissue distribution studies in rats demonstrated that radioactivity was highly accumulated in the liver, intestine, thyroid, kidney, and pituitary gland and that relugolix and its metabolites had an affinity to melanin. In the repeated dose toxicity studies in rats and monkeys [see Section 5.2], finding suggestive of phospholipidosis (PLD), e.g., cellular vacuolation, infiltration of foam cells, or proliferation of tingible body macrophages, were seen in the liver, intestine, kidney and pituitary gland. Although the reversibility of these findings has not been investigated in rats, resolution or a tendency toward resolution was observed after the end of the relugolix treatment period in monkeys. Necrosis of tubular epithelium was observed in the repeated dose toxicity studies in mice and rats [see Section 5.2], and single-cell necrosis of the hepatic cells, bile thrombus, and pigmentation in Kupffer cells were found in the repeated dose toxicity studies in monkeys [see Section 5.2]. However, the $AUC_{0\text{-}24}$ of the relugolix dose at which these kidney- or liver-related findings were observed was approximately 108 times and 51 times higher, respectively, than the exposure in humans ($AUC_{0\text{-}24}$ of 101 ng·h/mL) treated with the clinical dose (40 mg) [see Section 6.2.2.1], indicating a sufficient safety margin for hepatic and renal effects of relugolix. In any animal species, relugolix-associated abnormalities were not found in the eye or skin (i.e., tissues containing melanin) or the thyroid up to the highest dose tested.

Table 10 shows the incidence of adverse events related to the individual tissues in a pooled analysis of the Japanese clinical studies (Studies CCT-001, CCT-002, 3008, and OCT-101). The incidence of adverse events related to the intestine and eye was similar between the placebo and relugolix groups. The incidence of adverse events related to the liver, kidney, and skin and that related to the thyroid and pituitary gland were higher in the relugolix group than in the placebo group and were similar between the relugolix group and leuprorelin group. In the relugolix groups, the adverse events related to the kidney and those related to the thyroid and pituitary gland were all mild in severity, and there were no adverse events leading to discontinuation of the study drug. In the relugolix group, the adverse events related to the liver were all mild or moderate in severity. Among the

hepatic adverse events in the relugolix group, the study drug was discontinued due to the events in a patient in the relugolix 20 mg group (liver function test increased) and 2 patients in the relugolix 40 mg group (liver function test increased and alanine aminotransferase increased), but these events resolved after the discontinuation of relugolix. In the relugolix group, adverse events related to skin were all in mild or moderate in severity. Among the skin adverse events in the relugolix group, the study drug was discontinued due to the event in a patient in the relugolix 40 mg group (drug eruption), but the event resolved after the discontinuation of relugolix.

Based on the above, the tissues where radioactivity was highly accumulated, or elimination of radioactivity was delayed in the tissue distribution studies in rats seem to be of less safety concern in the clinical use of relugolix.

Table 10. Incidence of adverse events related to individual tissues in the Japanese clinical studies (Safety analysis set)

Adverse events	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Adverse events related to the liver [a]	1.3 (2)	3.9 (6)	10.4 (34)	11.3 (25)	2.2 (4)
Adverse events related to the intestine [b]	16.6 (25)	12.3 (19)	15.9 (52)	23.0 (51)	16.7 (31)
Adverse events related to the thyroid and pituitary gland [c]	2.0 (3)	1.9 (3)	5.2 (17)	7.2 (16)	1.1 (2)
Adverse events related to the kidney [d]	0.7 (1)	2.6 (4)	2.1 (7)	2.7 (6)	0 (0)
Adverse events related to the eye [e]	2.0 (3)	0 (0)	2.4 (8)	3.2 (7)	2.2 (4)
Adverse events related to the skin [f]	11.3 (17)	14.2 (22)	17.4 (57)	20.7 (46)	9.7 (18)

% (n)
Studies CCT-001, CCT-002, 3008, and OCT-101 were pooled.
a: Broad search in the MedDRA SMQ "Drug related hepatic disorders"
b: MedDRA SOC "Gastrointestinal disorders" and HLGTs "Gastrointestinal neoplasms malignant and unspecified" and "Gastrointestinal neoplasms benign."
c: MedDRA SOCs "Endocrine disorders" and "Metabolism and nutrition disorders" and HLGTs "Endocrine neoplasms malignant and unspecified" and "Endocrine investigations (incl sex hormones)."
d: MedDRA SOC "Renal and urinary disorders" and HLGT "Renal and urinary tract investigations and urinalyses,"
e: MedDRA SOC "Eye disorders"
f: MedDRA SOC" Skin and subcutaneous tissue disorders"

PMDA's view:

The liver was one of the organs/tissues where radioactivity was highly accumulated or elimination of radioactivity was delayed in the tissue distribution studies in rats. In the toxicity studies, hepatic toxicity was found, although at an exposure very higher than the exposure in humans treated with relugolix at the clinical dose (40 mg). The incidence of hepatic adverse events tended to increase in a dose-dependent manner. The incidence of hepatic adverse events in the relugolix 40 mg group was similar to that with leuprorelin whose labeling includes precautions for hepatic dysfunction. In light of these, careful attention should be paid to the effects on the liver in the clinical use of relugolix, and the hepatic dysfunction in association with relugolix is discussed in detail in Section 7.R.2.5. For organs/tissues other than the liver, PMDA has concluded that no safety concern related to an accumulation of relugolix or its metabolites is suggested, in view of relevant findings observed in the non-clinical and clinical studies.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data from the following toxicity studies of relugolix: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other studies (phototoxicity studies, studies on genotoxic impurities, and a study of effects on estrous cycle).

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in rats and monkeys (Table 11) to evaluate the acute toxicity of relugolix.

Table 11. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female rats (SD)	Oral	0[a], 200, 600, 2000	2000: decrease in feces, cloudy urine	>2000	4.2.3.1-1
Male and female rats (SD)	Intravenous	0[b], 0[c], 9, 30, 90	Death: 90 (5 of 5 males, 4 of 5 females), tonic-clonic convulsions, bradypnea, discoloration of lungs to dark red. ≥30: prone position, decreased activity, tremor (females)	90	4.2.3.1-3
Male and female cynomolgus monkeys	Oral	0[d], 60→200→600→2000	Acute toxicity was evaluated in a 7-day interval, escalating, single-dose study. ≥200: increased ALT and CK ≥600: vomiting, increased neutrophils, increased AST, increased total bilirubin, increased BUN, increased creatinine, decreased lymphocytes, decreased potassium, and decreased chloride. 2000: weight loss, increased inorganic phosphate, decreased calcium	>2000	4.2.3.1-4

a: 0.5% (w/v) methylcellulose solution
b: physiological saline
c: physiological saline containing 25% (v/v) *N*,*N*-dimethylformamide and 35% (v/v) polyethylene glycol 400
d: 0.5% (w/v) methylcellulose solution containing 6 mg/mL citric acid.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice (4 and 13 weeks), rats (2, 4, 13, and 26 weeks), and monkeys (2, 4, and 39 weeks) (Table 12). Major toxicity findings included effects on the liver and kidney and PLD. In the repeated oral dose toxicity studies in mice (13 weeks), rats (26 weeks), and monkeys (39 weeks), the exposure ($AUC_{0\text{-}24}$) at the no-observed-adverse-effect level (NOAEL; 600 mg/kg/day in mice; 30 mg/kg/day in male rats and 100 mg/kg/day in female rats; 1.5 mg/kg/day in monkeys) was 117,851 ng·h/mL in mice, 1653 ng·h/mL in male rats, 6109 ng·h/mL in female rats, and 227 ng·h/mL in monkeys. These are 1170, 16, 60, and 2 times higher, respectively, than the exposure in humans ($AUC_{0\text{-}24}$, 101 ng·h/mL) treated with relugolix at the clinical dose (40 mg).

Table 12. Repeated-dose toxicity studies

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female mice (B6C3F1)	Oral	4 weeks (once daily)	0[a], 60, 200, 600, 2000	2000: necrosis of renal tubular epithelium/basophilic renal tubule in the kidneys	600	4.2.3.2-1 reference data
Male and female mice (B6C3F1)	Oral	13 weeks (once daily)	0[a], 200, 600, 2000	2000: decreased red blood cell count, hemoglobin levels, and hematocrit; increased spleen weight; decreased kidney weight; necrosis of renal tubular epithelium/basophilic renal tubule in the kidneys; increased extramedullary hematopoiesis in the spleen; increased granulocytic hematopoietic cells in the bone marrow of the femur and sternum; mucosal epithelial hyperplasia and inflammatory cell infiltration of the cecum and colon.	600	4.2.3.2-2
Male and female rats (SD)	Oral	2 weeks (once daily)	0[a], 30, 100, 300	≥100: infiltration of foam cells in the testis	30 (males) 300 (females)	4.2.3.2-3 reference data
Male and female rats (SD)	Oral	4 weeks (once daily)	0[a], 10, 30, 300, 2000	Death: 2000 (8 of 10 males, 5 of 10 females); decreased activity; red and white lesions of the glandular stomach mucosa; atrophy of the spleen; red lesions of the duodenal mucosa (males); enlarged adrenal gland (males); atrophy of the thymus, testis, prostate, and seminal vesicle (males); PLD-related findings (infiltration of foam cells, cellular vacuolation, and increased tingible body macrophages in organs including the liver, kidney, heart, lung, and spleen). ≥300: increased vacuolated lymphocytes; PLD-related findings (infiltration of foam cells in the lung and testis, cellular vacuolation of the renal tubule, and increased tingible body macrophages in the mesenteric lymph node). 2000: reduction in body weight gain (males); decreased food consumption; reduced feces; increased urine volume; cloudy urine; decreased urine pH (males); decreased activity; salivation; stained fur; fur loss (males); incisor whitening; increased AST/ALT; increased BUN (males); cloudy lungs; dilated cecum; white lesion of the kidney; increased lung weight; increased liver weight (males); decreased prostate weight (males); PLD-related findings (cellular vacuolation and infiltration of foam cells in organs including the liver, kidney, heart, lung, and spleen; increased tingible body macrophages in lymphoid tissues; myelin-like layer structure in myocardial/adrenocortical cytoplasm); necrosis of the renal tubule, myocardial fiber, and other tissues; atrophy of the spleen, thymus, and other organs; gastrointestinal erosion/ulcer; degeneration, dilatation, hyaline casts, deposition of hyaline droplet, infiltration of inflammatory cells of the renal tubule in the kidneys; mineral deposition of the myocardial fiber; pigmentation in the Harderian gland; infiltration of mononuclear cells in the heart and tongue.	30	4.2.3.2-4

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female rats (SD)	Oral	13 weeks (once daily)	0[a], 30, 100, 300, 1000	Death: 1000 (1 of 10 males); cloudy urine; decreased body weight/food consumption; decreased activity; slow respiration; PLD-related findings (infiltration of foam cells, cellular vacuolation, and increased tingible body macrophages in organs including the liver, kidney, heart, lung, and spleen). ≥100: PLD-related findings (infiltration of foam cells in the testis); deposition of eosinophilic crystals in the epithelial cells of the epididymis. ≥300: PLD-related findings (infiltration of foam cells in the lung, infiltration of foam cells in the submandibular lymph node [males]) 1000: cloudy urine; incisor whitening (males); increased vacuolated lymphocytes; white spots in the lung; necrosis of the renal tubule, skeletal muscles, enamel epithelium cells; atrophy of lymphoid tissues; degeneration of renal tubule in the kidneys; cellular casts; hypertrophy and infiltration of inflammatory cells of epithelium of the renal collecting tubule and transitional epithelia; PLD-related findings (cellular vacuolation, infiltration of foam cells, and increased tingible body macrophages in organs including the liver, kidney, lung, and spleen).	30 (males) 100 (females)	4.2.3.2-5
Male and female rats (SD)	Oral	26 weeks (once daily)	0[a], 10, 30, 100, 300	≥100: PLD-related findings (infiltration of foam cells in the testis); deposition of eosinophilic crystals in the epithelial cells of the epididymis. 300: cloudy urine.	30 (males) 100 (females)	4.2.3.2-6
Male and female cynomolgus monkeys	Oral	2 weeks (once daily)	0[b], 20, 40, 100	≥40: PLD-related findings (infiltration of foam cells in the duodenum and cecum, vacuolation of the gastric wall cells). 100: cloudy urine; increases in ALT, leucine aminopeptidase, and glutamate dehydrogenase; increased AST (males); discoloration of the liver to dark red; bile thrombus; pigmentation of hepatic cells and sinusoidal cells; single-cell necrosis of the hepatic cells; PLD-related findings (infiltration of foam cells in organs including the lung, spleen, jejunum, ileum, colon, and rectum).	20 (males) 40 (females)	4.2.3.2-7 reference data
Male and female cynomolgus monkeys	Oral	4 weeks (once daily)	0[b], 5, 10, 20, 100	≥10: PLD-related findings (increased tingible body macrophages in the bone marrow, jejunum, cecum, thymus, submandibular lymph node, and mesenteric lymph node; infiltration of foam cells in the submandibular lymph node and mesenteric lymph node). ≥20: cloudy urine; PLD-related findings (increased tingible body macrophages in the spleen, stomach, duodenum, ileum, colon, and rectum; vacuolation of the gastric wall cells). 100: increased AST/ALT; bile thrombus; single-cell necrosis of the hepatic cells; pigmentation in the hepatic cells and Kupffer cells; PLD-related findings (infiltration of foam cells in the lungs; vacuolation and decreased zymogen granules of the pancreatic acinar cells; increased lysosomes including myelin-like corpuscles in the bone marrow).	5	4.2.3.2-8

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female cynomolgus monkeys	Oral	39 weeks (once daily)	0[b], 1.5, 5, 15, 50	≥5: decreased ovarian weight/corpus luteum [c]; PLD-related findings (vacuolation and increased tingible body macrophages in the gastric wall cells; infiltration of foam cells in the submandibular lymph node and mesenteric lymph node [d]). ≥15: increased ALP; PLD-related findings (increased tingible body macrophages in the bone marrow, spleen, cecum, colon, submandibular lymph node, and mesenteric lymph node). 50: decreased menstrual frequency [c]; cloudy urine; increases in AST, ALT, total cholesterol, and phospholipid; discoloration of the liver to dark red; bile thrombus; pigmentation in the Kupffer cells; PLD-related findings (increased tingible body macrophages in the duodenum, ileum, and rectum). Reversibility: observed.	1.5	4.2.3.2-9

a: 0.5% (w/v) methylcellulose solution.
b: 0.5% (w/v) methylcellulose solution containing 6 mg/mL citric acid.
c: Considered to represent changes associated with the pharmacological effects.
d: In the 1.5 mg/kg/day group, infiltration of foam cells in the mesenteric lymph node was also observed, but it was assessed as toxicologically insignificant because it was a minor change without traumatic changes.

5.3 Genotoxicity

A bacterial reverse mutation assay and a chromosomal aberration assay with Chinese hamster lung (CHL) cells were conducted as *in vitro* studies, and a micronucleus study with rat bone marrow was conducted as an *in vivo* study. No genetic toxicity was demonstrated (Table 13).

Table 13. Genotoxicity studies

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) Dose (mg/kg)	Study results	CTD
in vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	S9 -/+	0[a], 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvrA*				
	Chromosomal aberration assay with CHL cells	CHL cells	S9 - (6 h)	0[a], 150, 200, 250	Negative	4.2.3.3.1-2
			S9 + (6 h)	0 [a], 300, 350, 400		
			S9 - (24 h)	0 [a], 26.2, 32.8, 41.0, 51.2, 64		
in vivo	Micronucleus study in rodents	Male rats (SD) bone marrow		0[b], 500, 1000, 2000	Negative	4.2.3.3.2-1

a: DMSO
b: 0.5% (w/v) methylcellulose solution

5.4 Carcinogenicity

No carcinogenicity was found in a 2-year carcinogenicity study in mice and rats (Table 14).

Table 14. Carcinogenicity studies

Test system	Route of administration	Duration of administration	Main lesions		Dose (mg/kg/day)				Noncarcinogenic level (mg/kg/day)	CTD
					0[a]	10	30	100		
				N	55 males and females	55 males and females	55 males and females	55 males and females		
Male and female mice (B6C3F1)	Oral	24 months	Neoplastic lesions						100	4.2.3.4.1-1
			Femoral bone marrow Hemangioma	M	0	0	0	2[b]		
				F	0	0	0	0		
			Femoral bone marrow Angiosarcoma	M	2	1	1	1		
				F	1	2	3	1		
			Various tissues Hemangioma	M	3	0	1	3		
				F	2	1	2	0		
			Various tissues Angiosarcoma	M	7	5	3	3		
				F	3	5	3	2		
			Non-neoplastic lesions	F M	None					

Test system	Route of administration	Duration of administration	Main lesions		Dose (mg/kg/day)					Noncarcinogenic level (mg/kg/day)	CTD
					0[a]	10	30	200	600		
				N	60 males and females	60 males and females	60 males and females	60 males and females	60 males and females		
Male and female rats (SD)	Oral	24 months	Neoplastic lesions							600	4.2.3.4.1-2
			Mammary gland Adenoma	M	0	0	0	0	0		
				F	0	0	1	1	1		
			Mammary gland Fibroadenoma	M	0	0	1	1	2		
				F	19	15	16	15	15		
			Mammary gland Fibroma	M	0	0	0	0	0		
				F	1	0	1	1	1		
			Mammary gland Adenolipoma	M	0	0	0	0	0		
				F	1	0	0	0	0		
			Mammary gland Adenocarcinoma in fibroadenoma	M	0	0	0	0	0		
				F	11	11	16	13	17		
			Mammary gland Adenocarcinoma	M	1	0	2	0	0		
				F	23	22	25	16	18		
			Mammary gland Malignant mixed tumor	M	0	0	0	0	0		
				F	0	7[c]	3	1	5		
			Non-neoplastic lesions	F M	PLD-related findings (enlarged macrophages and pigmentation of the bone marrow, submandibular lymph node, and testis), tigroid altered hepatocytes in the liver,[d] hypertrophy of the renal papillary epithelium and collecting tubule.[d]						

a: 0.5% (w/v) methylcellulose solution
b: This was not considered to be a change attributable to relugolix because this fell within the historical data for B6C3F1 mice in several institutions (Toxicologic Histopathology, Nishimura Co., Ltd., 2017).
c: Although this is a statistically significant increase, no dose correlation was found, and there was no increase in other mammary tumors. Therefore, the finding was not considered to be a change attributable to relugolix.
d: Since this was a minor change, this finding was considered to be toxicologically less significant.

5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a study of fertility and early embryonic development to implantation in male and female rats, studies on effects on embryo-fetal development in rats and rabbits, and a study on effects on pre- and postnatal development, including the maternal function in rats (Table 15). In the study of fertility and early embryonic development to implantation

in male and female rats, no effects on fertility were shown. In the study on effects on embryo-fetal development in rabbits, all fetuses in a litter died, and this was considered to be attributable to the pharmacological effects of relugolix. In the study on pre- and postnatal development, including the maternal function in rats, no effects on fertility or neonatal development were observed. The exposure (AUC_{0-24}) at the NOAEL for embryo-fetal development (1000 mg/kg/day in rats, 3 mg/kg/day in rabbits) in rats and rabbits was 79,209 and 25 ng·h/mL, respectively, and was 784 times and 0.2 times higher, respectively, than the exposure in humans (AUC_{0-24}, 101 ng·h/mL) treated with the clinical dose (40 mg).

Table 15. Reproductive and developmental toxicity studies

Study type	Test system	Route of admini-stration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development	Male and female rats (SD)	Oral	14 days before mating to the previous day of necropsy (males) or Day 6 of gestation (females) (once daily)	0[a], 40, 200, 1000	Parent animals: 1000: decreased food consumption; reduction in body weight gain (males); incisor absent (males).	Parental animals (general toxicity): 200 (reproductive toxicity): 1000	4.2.3.5.1-2
Embryo-fetal development	Female rats (SD)	Oral	Days 6 to 17 of gestation (once daily)	0[a], 40, 200, 1000	Maternal animals: 1000: reduction in body weight gain; decreased food consumption.	Maternal animals (general toxicity): 200 Embryo-fetal developmental toxicity:1000	4.2.3.5.2-2
	Female rabbits (JW)	Oral	Days 6 to 18 of gestation (once daily)	0[a], 0.3, 1, 3, 9	Maternal animals: No findings. Fetuses: 9: death of all fetuses in a litter; increased fetal mortality; decreased number of live births; increased incidence of gross external abnormalities.[b]	Maternal animals (general toxicity): 9 Embryo-fetal developmental toxicity: 3	4.2.3.5.2-2
Effects on pre- and postnatal development, including maternal function	Female rats (SD)	Oral	Maternal animals: Day 6 of gestation to Day 20 of postpartum (once daily)	0[a], 20, 100, 1000	Maternal animals: 1000: reduction in body weight gain; decreased food consumption. F1 offspring: No findings.	Maternal animals (general toxicity): 100 (reproductive toxicity): 1000 Development of F1 offspring: 1000	4.2.3.5.3-1

a: 0.5% (w/v) methylcellulose solution
b: Cerebral membrane mass and open eyelid were observed in one fetus and nail absent in another fetus, but there was no increased incidence of any specific gross external abnormality. Therefore, these findings were not considered to be attributable to relugolix.

5.6 Other toxicity studies

5.6.1 Phototoxicity

Phototoxicity studies with mouse fibroblasts and in hairless mice were conducted, and based on the results, the phototoxicity of relugolix was considered unlikely to be clinically significant (Table 16).

Table 16. Phototoxicity studies

Study type	Test system	Test method	Main findings	CTD
Phototoxicity studies	Mouse fibroblasts Balb/c 3T3	0, 1.563, 3.125, 6.25, 12.5, 25, 50, 100, 200 μg/mL UV-A irradiation	Phototoxic (photostimulation factor 15.5)	4.2.3.7.7-2
	Male hairless mice (SKH1)	Single oral dose of 0, 200, 600, or 2000 mg/kg and ultraviolet irradiation at 0.5 MED.	No findings	4.2.3.7.7-3

5.6.2 Impurities

With reference to the ICH M7 Guideline, an *in silico* analysis was conducted with DEREK and MultiCASE for genotoxicity evaluation of related substances of relugolix. Since mutagenicity potential of Impurity U-2 was demonstrated, genotoxicity studies of Impurity U-2 were conducted (Table 17). Based on the results of these studies, the genotoxicity risk of Impurity U-2 in humans was considered to be low, and Impurity U-2 was classified as Class 5.

Table 17. Genotoxicity studies of Impurity U-2

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Study results	CTD
in vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	Rat S9 -/+	0, 39.1-5000	Positive in TA98 line of ≥625 μg/plate (rat S9 +)	4.2.3.7.6-3
			Human S9 -/+	0, 19.5-625 (TA100, TA1537) 0, 39.1-2500 (TA98, TA1535) 0, 156-5000 (WP2*uvrA*)	Negative	4.2.3.7.6-6
	Chromosomal aberration assay with CHL cells	CHL cells	Rat S9 - (6 h)	0,[a] 10-300	Negative	4.2.3.7.6-8
			Rat S9 + (6 h)	0,[a] 120-600		
			Rat S9 - (24 h)	0,[a] 5-80		
in vivo	Gene mutation test in rodents	Male mice (Muta) liver/bone marrow		0,[b] 20-300	Negative	4.2.3.7.6-10
	Unscheduled DNA synthesis (UDS) study	Male rats (SD) liver		0,[b] 500-2000	Negative	4.2.3.7.6-13
	Micronucleus study in rodents	Male rats (SD) bone marrow		0,[b] 125-1000	Negative	4.2.3.7.6-14

a: DMSO
b: 0.5% (w/v) methylcellulose solution

5.6.3 Effects of relugolix on estrous cycle

A study on effects of relugolix on estrous cycle (Table 18) showed no effects of relugolix on estrous cycle.

Table 18. Study on effects of relugolix on estrous cycle

Study type	Test system	Study methods	Main findings	CTD
Study on effects on estrous cycle	Female rats (SD)	Relugolix 0,[a] 40, 200, and 1000 mg/kg/day was orally administered for 14 days.	No effects on estrous cycle.	Reference data 4.2.3.5.1-1

a: 0.5% (w/v) methylcellulose solution

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that the non-clinical toxicity

evaluation showed no issues, except for effects on the liver, for clinical use of relugolix.

5.R.1 Effects of relugolix on the liver and kidneys

The applicant explained the effects on the liver observed in the repeated oral dose toxicity studies in rats and monkeys and the effects on the kidneys observed in the repeated oral dose toxicity studies in mice and rats.

The applicant's explanation:

The exposure ($AUC_{0\text{-}24}$) at the NOAEL for hepatic effects (300 mg/kg/day in rats, 15 mg/kg/day in monkeys) observed in the repeated oral dose toxicity studies in rats and monkeys was 30,514 ng·h/ml in rats and 5198 ng·h/mL in monkeys, which were 302 times and 51 times higher, respectively, than the exposure in humans ($AUC_{0\text{-}24}$, 101 ng·h/mL) treated with relugolix at the clinical dose (40 mg). The exposure ($AUC_{0\text{-}24}$) at the NOAEL for renal effects (600 mg/kg/day in mice, 300 mg/kg/day in rats) observed in the repeated oral dose toxicity studies in mice and rats was 117,851 ng·h/ml in mice and 23,915 ng·h/mL in rats, which were 1170 times and 237 times higher, respectively, than the exposure in humans ($AUC_{0\text{-}24}$, 101 ng·h/mL) treated with relugolix at the clinical dose (40 mg). Therefore, the safety margin was sufficient for the hepatic and renal effects of relugolix observed in mice, rats, and monkeys, and the findings were not considered to be relevant to humans.

PMDA's view:

As described by the applicant, the hepatic and renal toxicity in the toxicity studies was observed only at the exposures very higher than the exposure in humans treated with relugolix at the clinical dose (40 mg). However, in light of the occurrence of adverse events associated with hepatic dysfunction, careful attention should be paid to the effects on the liver in the clinical use of relugolix. The hepatic dysfunction associated with the clinical use of relugolix is discussed in detail in Section 7.R.2.5.

5.R.2 PLD

PLD-related findings were observed in animal organs in the repeated oral dose toxicity studies in rats and monkeys. The applicant explained the relationship between PLD and relugolix and the risk of PLD associated with the clinical use of relugolix.

The applicant's explanation:

PLD is reported as an adaptive response which is frequently observed after administration of a drug containing a cationic amphiphilic structure (*Expert Opin Drug Saf.* 2006;5:567-83). In general, PLD may occur even in humans when highly exposed to a drug with a cationic amphiphilic structure. The exposure at the NOAEL for PLD-related findings in male rats (NOAEL, 30 mg/kg/day), female rats (100 mg/kg/day), and monkeys (1.5 mg/kg/day) was 16 times, 60 times, and 2 times higher, respectively, than the exposure in humans ($AUC_{0\text{-}24}$, 101 ng·h/mL) treated with relugolix at the clinical dose (40 mg). In the 4-week and 13-week repeated oral dose toxicity studies in rats, dead rats (in the 2000 and 1000 mg/kg/day groups, respectively) had vacuolation of cardiomyocytes associated with PLD, and their death was suspected to be caused by decreased cardiac function

related to PLD, However, no other serious organ disorders associated with PLD were observed in the repeated oral dose toxicity studies in rats or monkeys. The exposure (AUC_{0-24}) in the 1000 mg/kg/day group (in which rats died) was 93,767 ng·h/mL, which was 930 times higher than the exposure in humans (AUC_{0-24}, 101 ng·h/mL) treated with relugolix at the clinical dose (40 mg). In the 39-week repeated oral dose toxicity study in monkeys, all PLD-related findings were reversible or tended to be reversible after the completion of the administration of relugolix, although the reversibility was not evaluated in rats. A pooled analysis of clinical studies revealed no occurrence of PLD-related adverse events.[1)] Based on the above, the risk of PLD is considered to be low in the clinical use of relugolix.

PMDA considers that the applicant's explanation is plausible. PMDA has concluded that the risk of PLD is low in the clinical use of relugolix.

5.R.3 Effects of relugolix on embryo-fetal development

The applicant's explanation about the cause of fetal toxicity observed in the embryo-fetal development study in rabbits [see Section 5.5]:

In the embryo-fetal development study, fetal toxicity including death of all fetuses in a litter was observed, and an implantation trace suggestive of early embryonic death was also observed in all dams in which all fetuses in a litter died. These findings suggest that administration of relugolix affected the implantation or the early embryo development after implantation. As plasma LH levels decrease after administration of relugolix with an inhibitory effect on the GnRH receptors [see Section 3.1.2.1], it is presumed that pregnancy could not be maintained because of decreased progesterone levels secondary to decreased LH levels (*Encyclopedia of REPRODUCTION Vol. 3*. Academic Press, 1998), which in turn led to the outcomes including fetal deaths. In light of these results, relugolix should be contraindicated in pregnant or potentially pregnant women.

PMDA considers that the applicant's explanation is plausible. PMDA has concluded that relugolix should be contraindicated in pregnant or potentially pregnant women and that information on the fetal toxicity observed in the study should be appropriately disseminated through its package insert etc.

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

The pharmacokinetic parameters are shown in mean ± standard deviation, unless otherwise specified.

6.1 Summary of biopharmaceutic studies and associated analytical methods

In a Japanese phase II study in patients with uterine fibroids (Study CCT-001), the used products (10, 20, and 40 mg tablets) were the proposed commercial product and the T2 product, which differed from the proposed commercial product only in the colorant contained in the film layer. The proposed commercial product (40 mg tablets) was used in Japanese phase III studies in patients with uterine fibroids (Studies CCT-002 and 3008)

[1)] MedDRA PT of phospholipidosis.

and a clinical study evaluating the effects of foods on the pharmacokinetics of relugolix (Study 1011). Bioequivalence between the T2 product 20 mg tablets and the proposed commercial product was demonstrated by dissolution testing in compliance with the guidelines for bioequivalence for different dosage-strengths and formulation changes.

The plasma relugolix concentrations were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS) with a lower limit of quantification of 0.01 ng/mL.

6.1.1 Effects of food (Study 1011, CTD 5.3.4.1-1)

A 6-arm, 3-period, crossover study (with a washout period of ≥14 days) was conducted in 12 Japanese healthy premenopausal women to evaluate food effects on the pharmacokinetics of relugolix. In the study, a single dose of relugolix 40 mg (a 40 mg tablet of the proposed commercial product) was orally administered in a fasting state (after ≥10-hour fasting beginning the previous evening of the administration; the same applies hereinafter), before a meal (30 min before a meal; the same applies hereinafter), or after a meal (30 min after a meal; the same applies hereinafter).

The geometric mean ratio (90% confidence interval [CI]) of C_{max} and $AUC_{0-\infty}$ of relugolix (after a meal/fasting state) was 0.45 (0.28, 0.74) and 0.53 (0.41, 0.68), respectively. The geometric mean ratio (90% CI) of C_{max} and $AUC_{0-\infty}$ of relugolix (before a meal/fasting state) was 1.13 (0.70, 1.82) and 0.84 (0.66, 1.07), respectively.

6.1.2 Absolute bioavailability study (Study 1009, CTD 5.3.3.1-3)

A single oral dose of relugolix 80 mg and a single intravenous dose of ^{14}C-labeled relugolix 80 μg were administered to 6 non-Japanese healthy men. AUC_{0-168} of relugolix was 233.1 ± 106.3 ng·h/mL after oral dosing and 2.2 ± 0.4 ng·h/mL after intravenous dosing, and the absolute bioavailability (calculated as a ratio of dose-adjusted AUC_{0-168} after oral dosing to that after intravenous dosing) was 11.6%.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies with human biological samples

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-6, -7)

After human plasma was spiked with ^{14}C-labeled relugolix at a final concentration of 0.05 to 5 μg/mL, the percentage of protein binding of relugolix was determined to be 68.2% to 70.8%, showing a constant protein binding at the tested concentrations.

After human blood was spiked with ^{14}C-labeled relugolix at a final concentration of 0.05 to 5 μg/mL, the percentage of distribution of relugolix in blood cells was determined to be 45.9% to 50.8%, showing a constant distribution in blood cells at the tested concentrations.

6.2.1.2 *In vitro* metabolism

6.2.1.2.1 Metabolism of relugolix (CTD 4.2.2.4-7, -8)

After human liver microsomes were spiked with ^{14}C-labeled relugolix at a final concentration of 10 μmol/L and were incubated for 1 hour at 37°C, Metabolites A and B were identified as the main metabolites of relugolix.

6.2.1.2.2 Identification of cytochrome P450 isoforms involved in metabolism of relugolix (CTD 4.2.2.4-8 to -10)

A series of the expression system of cytochrome P450 (CYP) isoforms were spiked with ^{14}C-labeled relugolix at a final concentration of 10 μmol/L and were incubated for 30 min at 37°C: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Relugolix was eliminated the fastest with the CYP3A4 expression system (66.1 pmol/h/pmol P450), followed in order by the CYP2C8 expression system (12.8 pmol/h/pmol P450) and the CYP2C19 expression system (4.8 pmol/h/pmol P450). The main metabolites identified was Metabolite A for the CYP3A4 expression system and Metabolite B for the CYP2C8 and CYP2C19 expression systems.

Human liver microsomes were spiked with ^{14}C-labeled relugolix at a final concentration of 10 μmol/L, and a correlation was evaluated between the elimination rate of relugolix and the elimination rate of substrates of individual CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11). The elimination rate of relugolix was most strongly correlated with that of CYP3A4/5 and was also correlated with that of CYP2C8.

Based on the above results, the applicant considered that CYP3A4 and CYP2C8 were the main CYP isoforms involved in the metabolism of relugolix.

6.2.1.3 Enzyme inhibition (CTD 4.2.2.4-11, -12)

Human liver microsomes and substrates of individual CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) were used to investigate the inhibitory effects of relugolix (at a final concentration of 3 to 100 μmol/L) on the metabolism of the substrates of the individual CYP isoforms. Relugolix inhibited CYP2C8, CYP2D6, and CYP3A4/5 with an IC_{50} of 52, 73, and 16 μmol/L, respectively. The IC_{50} of relugolix for other CYP isoforms was >100 μmol/L. Relugolix had no time-dependent inhibitory effects on any of the CYP isoforms.

The expression systems of human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were used to investigate the inhibitory effects of relugolix (at a final concentration of 1 to 30 μmol/L) on the metabolism of the substrates of the individual CYP isoforms. Relugolix inhibited the CYP2C8 isoform, and the CYP2C8 activity was inhibited by 64.1% in the presence of relugolix 30 μmol/L compared with that in the absence of relugolix.

6.2.1.4 Enzyme induction (CTD 4.2.2.4-13, -14)

Human primary hepatocytes were spiked with relugolix at a final concentration of 1 to 30 μmol/L and were incubated for 48 hours at 37°C, to evaluate the induction of CYP1A2, CYP2B6, and CYP3A4 by relugolix.

Relugolix increased the mRNA expression of CYP2B6 and CYP3A4 in a dose-dependent manner. If the percent increase in mRNA expression of CYP2B6 and CYP3A4 induced by a positive control (phenobarbital 1000 μmol/L for CYP2B6, rifampicin 10 μmol/L for CYP3A4) is defined as 100%, relugolix increased the mRNA expression of CYP2B6 by 33.4% (maximum) and that of CYP3A4 by 77.7% (maximum). Relugolix had almost no impact on the mRNA expression of CYP1A2 even at the highest concentration tested.

After human primary hepatocytes were spiked with relugolix at a final concentration of 1 to 30 μmol/L, relugolix increased the CYP3A4 activity in a concentration-dependent manner. If the percent increase in the CYP3A4 activity induced by rifampicin 10 μmol/L is defined as 100%, relugolix (at the highest concentration tested) increased CYP3A4 activity by 63.4% to 67.3%.

6.2.1.5 Study on transporters (CTD 4.2.2.2-11, 4.2.2.6-2 to -4)

Caco-2 cells were spiked with ^{14}C-labeled relugolix at a final concentration of 3 μmol/L. The apical-to-basal P_{app} ($P_{app\ A\ to\ B}$) of relugolix was $0.513 \pm 0.120 \times 10^{-6}$ cm/s, and the basal-to-apical P_{app} ($P_{app\ B\ to\ A}$) of relugolix was $8.43 \pm 0.75 \times 10^{-6}$ cm/s, with an excretion ratio ($P_{app\ B\ to\ A}/P_{app\ A\ to\ B}$) of 16.4. The excretion ratio of relugolix after addition of quinidine (an inhibitor of P-glycoprotein [P-gp]), Ko143 (an inhibitor of breast cancer resistance protein [BCRP]), and GF120918 (an inhibitor of P-gp and BCRP) was 2.2, 15.1, and 0.7, respectively, showing decreases in the excretion ratio of relugolix after addition of quinidine or GF120918.

HEK293 cells expressing OATP1B1 or OATP1B3 were spiked with ^{14}C-labeled relugolix at a final concentration of 1 or 10 μmol/L, and the uptake of relugolix in the cells was similar to that in control cells.

Caco-2 cells were used to investigate the inhibitory effects of relugolix at a final concentration of 10 to 1000 μmol/L on the P-gp-mediated transportation of ^{3}H-labeled digoxin, and the IC_{50} was determined to be 61.2 μmol/L.

LLC-PK1 cells expressing BCRP were used to investigate the inhibitory effects of relugolix at a final concentration of 1 to 100 μmol/L on the BCRP-mediated transportation of ^{3}H-labeled prazosin, and the IC_{50} was determined to be 24.9 μmol/L.

HEK293 cells expressing OATP1B1, OATP1B3, OCT2, MATE1, or MATE2-K or S2 cells expressing OAT1 or OAT3 were used to investigate the inhibitory effects of relugolix at a final concentration of 0.3 to 30 μmol/L on the transportation of substrates of individual transporters. Relugolix inhibited the MATE1 and MATE2-K, with an IC_{50} of 10.9 and 3.75 μmol/L, respectively. Relugolix had almost no inhibitory effects on other transporters even at the highest concentration tested.

6.2.1.6 Interactions mediated by protein binding (CTD 4.2.2.6-1)

Human plasma was spiked with relugolix at a final concentration of 0.1 μg/mL and warfarin, ibuprofen, digoxin, or propranolol. The addition of relugolix caused no changes to the plasma protein binding of these drugs.

6.2.2 Investigation in healthy adults

6.2.2.1 Single-dose and repeated-dose study in Japanese subjects (Study CPH-001, CTD 5.3.3.1-1)

A single oral dose of relugolix 1, 5, 10, 20, 40, or 80 mg was administered to 60 Japanese healthy premenopausal women in a fasting state. The pharmacokinetic parameters of relugolix are shown in Table 19.

Table 19. Pharmacokinetic parameters of relugolix after a single oral dose

Dose (mg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
1	10	0.09082 ± 0.031561	1.50	0.7674 ± 0.38652	7.096 ± 2.8350
5	10	0.6269 ± 0.42411	0.50	6.270 ± 3.7706	15.99 ± 2.0491
10	10	1.351 ± 0.35838	0.75	13.67 ± 4.5695	17.93 ± 1.8000
20	10	5.144 ± 3.1715	1.25	47.22 ± 25.260	19.83 ± 1.9322
40	10	13.53 ± 7.0915	4.00	117.1 ± 55.054	18.54 ± 1.7174
80	10	59.26 ± 37.425	4.00	396.2 ± 170.88	18.31 ± 1.7898

a: Median

A single oral dose of relugolix 40 mg was administered in a fasting state or after a meal and another single oral dose of relugolix 40 mg was administered in a fasting state or before a meal to 24 Japanese healthy premenopausal women. Effects of foods on the pharmacokinetics of relugolix were evaluated with a design of a 2-arm, 2-period, crossover method. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of relugolix (after a meal/fasting state) was 0.315 [0.192, 0.516] and 0.442 [0.351, 0.556], respectively. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of relugolix (before a meal/fasting state) was 1.545 [1.000, 2.387] and 0.770 [0.628, 0.945], respectively.

In total, 34 Japanese healthy premenopausal women received 14-day once-daily oral administration of relugolix 10, 20, or 40 mg after a meal, or relugolix 40 mg before a meal. The pharmacokinetics of relugolix are shown in Table 20. On both Days 1 and 14, the C_{max} and AUC_{τ} of relugolix 40 mg administered before a meal were higher than those after a meal. Serum E_2 levels after administration of relugolix were evaluated. The mean serum E_2 level decreased to a level below the baseline within 24 hours after relugolix administration in all relugolix groups, except for the relugolix 20 mg group, and then remained below the baseline during the subsequent study period. The serum E_2 level after the repeated dose of relugolix 40 mg before and after a meal was maintained at the menopausal levels (≤20 pg/mL, according to the Practice Guidelines for Obstetrics and Gynecology).

Table 20. Pharmacokinetic parameters of relugolix after repeated oral doses

Dose (mg)	Meal	N	Time point (Day)	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{τ} (ng·h/mL)	$t_{1/2}$ (h)
10	Postmeal	9	1	1.037 ± 0.57784	1.50	8.772 ± 3.7015	12.50 ± 3.0084
		9	14	1.546 ± 1.0987	1.50	14.99 ± 4.6917	21.60 ± 8.9571
20		9	1	1.836 ± 0.62790	1.50	17.17 ± 3.0261	18.05 ± 8.6700
		9	14	3.811 ± 1.8778	1.50	35.76 ± 10.775	23.70 ± 10.942
40		8	1	3.775 ± 0.95137	1.00	36.98 ± 5.4722	12.92 ± 2.9092
		8	14	7.996 ± 3.5102	1.25	82.60 ± 27.852	19.24 ± 2.6490
	Premeal	8	1	13.90 ± 10.564	0.50	52.18 ± 41.773	16.01 ± 5.1135
		8	14	20.95 ± 15.447	1.00	100.5 ± 44.178	24.60 ± 7.4014

a: Median

6.2.2.2 Single-dose and repeated-dose study in non-Japanese subjects (Study 101, CTD 5.3.3.1-4)

A single oral dose of relugolix 1, 5, 10, 20, 40, or 80 mg was administered to 60 non-Japanese healthy premenopausal women in a fasting state. The pharmacokinetic parameters of relugolix are shown in Table 21.

Table 21. Pharmacokinetic parameters of relugolix after a single oral dose

Dose (mg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
1	10	0.1424 ± 0.06242	0.78	1.072 ± 0.3395	6.3215 ± 1.52713
5	10	0.6132 ± 0.21943	0.99	8.046 ± 2.7729	14.5419 ± 1.42534
10	10	1.9032 ± 1.13706	1.02	16.956 ± 3.9843	15.5803 ± 2.51796
20	10	4.4462 ± 2.81666	1.75	45.162 ± 23.0727	16.1307 ± 0.84847
40	10	11.4330 ± 7.73259	1.50	103.684 ± 47.8892	16.0930 ± 2.67703
80	10	51.4120 ± 66.66872	4.00	348.096 ± 238.0285	15.8132 ± 1.75965

a: Median

Relugolix 10, 20, or 40 mg was repeatedly administered orally once daily in a fasting state for 14 days to 27 non-Japanese healthy premenopausal women. The pharmacokinetic parameters of relugolix are shown in Table 22.

Table 22. Pharmacokinetic parameters of relugolix after repeated oral doses

Dose (mg)	N	Time point (Day)	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{τ} (ng·h/mL)
10	9	1	1.3902 ± 0.43020	1.00	9.001 ± 3.1805
	9	14	2.3456 ± 1.06976	0.98	20.626 ± 7.7049
20	9	1	8.0944 ± 7.36850	1.00	30.368 ± 22.3518
	9	14	10.8400 ± 9.40906	1.48	57.102 ± 27.5719
40	9	1	17.8356 ± 8.45057	1.48	68.591 ± 29.0593
	9	14	19.3289 ± 8.71450	1.00	114.497 ± 30.4617

a: Median

6.2.2.3 Mass balance study (Study 1009, CTD 5.3.3.1-3)

A single oral dose of ^{14}C-labeled relugolix 80 mg was administered to 6 non-Japanese healthy men. Then, 4.4% ± 0.8% and 82.7% ± 6.4% of the administered radioactivity was excreted in urine and feces, respectively, by 288 hours postdose, showing that the radioactivity was excreted mainly in feces. Metabolite C was mainly excreted in feces (40.6% ± 4.9% of the total radioactivity in feces; the same applies hereinafter), and the percentage of unchanged relugolix of the total radioactivity excreted in feces was 4.2% ± 2.9%.

6.2.3 Studies in patients

6.2.3.1 A Japanese phase II study in patients with uterine fibroids and menorrhagia (Study CCT-001, CTD 5.3.5.1-1)

Relugolix 10, 20, or 40 mg was repeatedly administered orally once daily before a meal to Japanese patients with uterine fibroids. The C_{trough} of relugolix are shown in table 23, and the results suggest that plasma relugolix concentrations reach the steady state by 2 weeks after administration for all the tested doses.

Table 23. C_{trough} of relugolix (ng/mL)

Dose (mg)	Time point		
	Week 2	Week 4	Week 8
10	0.3014 ± 0.14726 (47)	0.3137 ± 0.16146 (48)	0.3588 ± 0.23052 (47)
20	0.6759 ± 0.30270 (55)	0.7570 ± 0.32646 (54)	0.7488 ± 0.38867 (52)
40	1.828 ± 1.6257 (54)	1.908 ± 1.4775 (53)	1.661 ± 0.82268 (54)

Mean ± standard deviation (n)

Changes over time in serum levels of E_2, LH, FSH, and progesterone after relugolix administration are shown in Tables 24 to 27. In the relugolix 40 mg group, the mean serum E_2 level began to decrease closely to the menopausal level at Week 2, and the lowering effects continued until Week 12. In the relugolix 10 and 20 mg groups, the serum E_2 levels varied widely among the subjects, and the mean serum E_2 level did not reach the menopausal level. The mean serum levels of LH and FSH tended to decrease dose-dependently throughout the administration period. The mean serum progesterone did not elevate during the administration period in the relugolix 20 and 40 mg groups.

Table 24. Changes in serum E_2 levels (pg/mL) (FAS)

Dose (mg)	Time point					
	Baseline	Week 2	Week 4	Week 8	Week 12	Follow-up [a]
10	65.3 ± 54.56 (48)	121.9 ± 136.59 (48)	94.7 ± 173.48 (48)	94.9 ± 122.88 (47)	77.5 ± 78.01 (47)	220.4 ± 630.74 (48)
20	75.2 ± 119.12 (55)	81.9 ± 136.28 (55)	46.1 ± 65.99 (55)	47.3 ± 62.07 (53)	41.0 ± 93.65 (53)	144.0 ± 129.70 (55)
40	55.1 ± 51.43 (54)	20.8 ± 59.95 (54)	11.6 ± 37.71 (54)	14.1 ± 60.08 (54)	9.0 ± 25.58 (54)	189.4 ± 153.87 (54)

Mean ± standard deviation (n)
a: 28 days after the completion of study treatment

Table 25. Changes in serum LH levels (mIU/mL) (FAS)

Dose (mg)	Time point					
	Baseline	Week 2	Week 4	Week 8	Week 12	Follow-up [a]
10	4.139 ± 2.8170 (48)	5.897 ± 6.1026 (48)	3.808 ± 3.8253 (48)	5.953 ± 8.6143 (47)	5.054 ± 5.9127 (47)	5.837 ± 5.7110 (48)
20	4.563 ± 2.9435 (55)	3.077 ± 2.8810 (55)	3.257 ± 8.7064 (55)	3.138 ± 2.9479 (53)	3.760 ± 5.5700 (53)	6.565 ± 8.6281 (55)
40	3.781 ± 2.1849 (54)	1.469 ± 1.7776 (54)	1.279 ± 1.7214 (54)	1.576 ± 3.4273 (54)	1.779 ± 3.4962 (54)	6.881 ± 10.0041 (54)

Mean ± standard deviation (n)
a: 28 days after the completion of study treatment

Table 26. Changes in serum FSH levels (mIU/mL) (FAS)

Dose (mg)	Time point					
	Baseline	Week 2	Week 4	Week 8	Week 12	Follow-up [a]
10	8.086 ± 5.7335 (48)	6.426 ± 3.4331 (48)	5.613 ± 3.1100 (48)	6.241 ± 3.0392 (47)	6.065 ± 3.1520 (47)	6.940 ± 6.8303 (48)
20	8.479 ± 7.1975 (55)	6.306 ± 2.8502 (55)	5.151 ± 3.3327 (55)	5.143 ± 2.2136 (53)	5.578 ± 2.0662 (53)	6.828 ± 7.9337 (55)
40	7.829 ± 4.8846 (54)	4.953 ± 2.7921 (54)	3.869 ± 2.1540 (54)	3.652 ± 2.1943 (54)	3.996 ± 3.0266 (54)	5.747 ± 6.4427 (54)

Mean ± standard deviation (n)
a: 28 days after the completion of study treatment

Table 27. Changes in serum progesterone levels (ng/mL) (FAS)

Dose (mg)	Time point					
	Baseline	Week 2	Week 4	Week 8	Week 12	Follow-up [a]
10	0.335 ± 0.5285 (48)	2.796 ± 5.5397 (48)	3.449 ± 4.9653 (48)	2.277 ± 4.5311 (47)	3.430 ± 5.7878 (47)	4.971 ± 8.1503 (48)
20	0.650 ± 1.2778 (55)	0.607 ± 2.6951 (55)	2.333 ± 4.2118 (55)	1.326 ± 2.5201 (53)	0.877 ± 2.3288 (53)	5.334 ± 7.2682 (55)
40	0.574 ± 1.8310 (54)	0.288 ± 0.2588 (54)	0.320 ± 0.3175 (54)	0.241 ± 0.1397 (54)	0.432 ± 1.1163 (54)	9.112 ± 8.2192 (54)

Mean ± standard deviation (n)
a: 28 days after the completion of study treatment

6.2.3.2 A Japanese Phase III study in patients with uterine fibroids and menorrhagia (Study CCT-002, CTD 5.3.5.1-2)

Japanese patients with uterine fibroids received oral relugolix 40 mg once daily before a meal or subcutaneous leuprorelin 1.88 or 3.75 mg once every 4 weeks. Changes over time in serum levels of E_2, LH, FSH, and progesterone are shown in Table 28 to 31.

The mean serum E_2 level increased from the baseline at Week 2 in the leuprorelin group, whereas the mean serum E_2 level began to decrease closely to the menopausal level at Week 2 in the relugolix group. Changes in the mean serum E_2 levels after Week 4 were comparable between the relugolix and leuprorelin groups and were maintained below the menopausal levels. The mean serum LH and FSH levels decreased from the baseline throughout the administration period in both groups, whereas no obvious changes were observed in the mean serum progesterone levels.

Table 28. Changes in serum E_2 levels (pg/mL) (FAS)

Group	Time point					
	Baseline	Week 2	Week 4	Week 12	Week 24	Follow-up [a]
Relugolix	69.6 ± 119.01 (138)	27.7 ± 63.92 (136)	11.8 ± 18.60 (137)	17.9 ± 42.01 (129)	15.8 ± 56.57 (122)	118.5 ± 99.45 (136)
Leuprorelin	57.0 ± 77.44 (142)	152.7 ± 298.59 (142)	16.2 ± 44.98 (142)	10.3 ± 11.33 (140)	10.9 ± 12.03 (131)	38.1 ± 56.99 (141)

Mean ± standard deviation
a: 28 days after the completion of study treatment

Table 29. Changes in serum LH levels (mIU/mL) (FAS)

Group	Time point					
	Baseline	Week 2	Week 4	Week 12	Week 24	Follow-up [a]
Relugolix	4.132 ± 3.1886 (138)	1.555 ± 3.4093 (136)	1.222 ± 2.8822 (137)	1.363 ± 1.7835 (129)	1.958 ± 3.5740 (122)	7.653 ± 10.2235 (136)
Leuprorelin	3.975 ± 3.4869 (142)	2.499 ± 1.4949 (142)	0.848 ± 0.6581 (142)	0.273 ± 0.1630 (140)	0.328 ± 0.4801 (131)	1.316 ± 1.4633 (141)

Mean ± standard deviation
a: 28 days after the completion of study treatment

Table 30. Changes in serum FSH levels (mIU/mL) (FAS)

Group	Time point					
	Baseline	Week 2	Week 4	Week 12	Week 24	Follow-up [a]
Relugolix	8.898 ± 6.7635 (138)	5.023 ± 5.4342 (136)	3.942 ± 3.2732 (137)	3.302 ± 2.1866 (129)	3.922 ± 3.9499 (122)	8.178 ± 9.7750 (136)
Leuprorelin	8.386 ± 7.4036	3.076 ± 2.3648	2.798 ± 1.3266	4.156 ± 1.5787	4.414 ± 2.0117	5.711 ± 3.0015

	(142)	(142)	(142)	(140)	(131)	(141)

Mean ± standard deviation
a: 28 days after the completion of study treatment

Table 31. Changes in serum progesterone levels (ng/mL) (FAS)

Group	Time point					
	Baseline	Week 2	Week 4	Week 12	Week 24	Follow-up [a]
Relugolix	0.32 ± 0.349 (138)	0.28 ± 0.918 (136)	0.39 ± 1.407 (137)	0.22 ± 0.510 (129)	0.24 ± 0.426 (122)	5.72 ± 7.385 (136)
Leuprorelin	0.35 ± 0.667 (142)	0.63 ± 1.619 (142)	0.40 ± 2.061 (142)	0.13 ± 0.083 (140)	0.16 ± 0.074 (131)	0.91 ± 3.683 (141)

Mean ± standard deviation
a: 28 days after the completion of study treatment

6.2.4 Population pharmacokinetic analysis (CTD 5.3.5.1-1)

A population pharmacokinetic analysis was conducted using data on plasma relugolix concentrations obtained from 157 patients (1200 time points) in the Japanese phase II study in Japanese patients with uterine fibroids (Study CCT-001). The base model used in this analysis was a 2-compartment model with first-order absorption and first-order elimination developed based on data on plasma relugolix concentrations following postmeal administration in the Japanese phase I studies (Studies CPH-001 and 101) in healthy women. For V_p/F and Q/F, values estimated from the base model were used (4670 L for V_p/F, 548 h^{-1} for Q/F).

Candidate covariates for ka and F_{rel} of relugolix were age, body weight, body mass index (BMI), lean body mass, glomerular filtration rate, albumin, total bilirubin, total cholesterol, blood glucose, urea nitrogen, total protein, uric acid, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase, gamma-glutamyl transpeptidase (γ-GTP), creatine kinase (CK), and triglyceride. However, none of them was selected as a covariate. The population pharmacokinetic parameters of relugolix in the final model (coefficient of variation [%]) were 198 L/h (7.88%) for CL/F, 328 L (33.2%) for V_c/F, 0.428 h^{-1} (23.3%) for ka, and 0.351 (12.1%) for F_{rel}.

Table 32 shows the estimated pharmacokinetic parameters of relugolix in the steady state after repeated oral dosing of relugolix 10, 20, or 40 mg once daily in Japanese patients with uterine fibroids by using the final model.

Table 32. Pharmacokinetic parameters (estimated) in steady state after repeated oral dosing of relugolix in patients with uterine fibroids

Dose (mg)	N	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_τ (ng·h/mL)
10	48	1.40 ± 0.839	0.305 ± 0.123	13.0 ± 5.17
20	54	3.28 ± 1.52	0.721 ± 0.269	30.7 ± 11.3
40	53	8.73 ± 5.02	1.85 ± 0.963	78.6 ± 41.1

6.2.5 Intrinsic factors

6.2.5.1 Study in patients with hepatic impairment (Study MVT-601-1002, CTD 5.3.3.3-1)

Table 33 shows the pharmacokinetic parameters of relugolix after single oral dosing of relugolix 40 mg in a

fasting state in 8 non-Japanese subjects with normal hepatic function (5 men and 3 women), 8 non-Japanese patients with mild hepatic impairment (with a Child-Pugh score of 5 to 6; 8 men), and 8 non-Japanese patients with moderate hepatic impairment (with a Child-Pugh score of 7 to 9; 5 men and 3 women).

Table 33. Pharmacokinetic parameters of relugolix after single oral dosing

	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Subjects with normal hepatic function	19.0 ± 16.1	3.00	149 ± 86.8[b]	48.7 ± 11.2[b]	430 ± 405[b]	24900 ± 12800[b]
Patients with mild hepatic impairment	12.8 ± 7.42	2.00	97.8 ± 43.4	51.7 ± 17.6	635 ± 691	38800 ± 24200
Patients with moderate hepatic impairment	28.5 ± 36.3	1.50	152 ± 111	50.6 ± 12.1	460 ± 360	29800 ± 20400

a: Median
b: 7 subjects

6.2.5.2 Study in patients with renal impairment (Study MVT-601-1003, CTD 5.3.3.3-2)

Table 34 shows the pharmacokinetic parameters of relugolix after single oral dosing of relugolix 40 mg in a fasting state in 8 non-Japanese subjects with normal renal function (with a creatinine clearance of ≥90 mL/min according to the Cockcroft-Gault equation; 6 men and 2 women) and 8 non-Japanese patients with severe renal impairment (with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disorder [MDRD] equation; 6 men and 2 women).

Table 34. Pharmacokinetic parameters of relugolix after single oral dosing

	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Subjects with normal renal function	16.5 ± 10.5	0.76	129 ± 90.3[b]	74.6 ± 31.1[b]	414 ± 193[b]	45300 ± 32000[b]
Patients with severe renal impairment	17.1 ± 8.28	3.13	172 ± 62.4	60.2 ± 14.1	258 ± 83.1	22400 ± 8070

a: Median
b: 7 subjects

6.2.6 Drug interactions

6.2.6.1 Caffeine, tolbutamide, dextromethorphan, and midazolam (Study 102, CTD 5.3.3.4-4)

In 16 non-Japanese healthy adults (6 men and 10 women), a single oral dose of substrates for CYP isoforms (caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, and midazolam 4 mg) were simultaneously administered on Days 1 and 10, and relugolix 20 mg was repeatedly administered orally once daily in a fasting state on Days 4 to 10. Table 35 shows the geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of individual substrates and their metabolites (substrates + relugolix [Day 10] / substrates alone [Day 1]).

Table 35. Effects of coadministration of relugolix on pharmacokinetics of substrates and their metabolites

Substrates and their metabolites	C_{max}	$AUC_{0-\infty}$
Caffeine (CYP1A2 substrate)		
Caffeine	0.92 [0.87, 0.97]	0.97 [0.89, 1.05]
1,7-paraxanthine	0.97 [0.93, 1.01]	0.99 [0.94, 1.06]
Tolbutamide (CYP2C9 substrate)		
Tolbutamide	1.02 [0.98, 1.06]	0.99 [0.93, 1.05]
4-hydroxytolbutamide	1.01 [0.95, 1.08]	0.98 [0.95, 1.02]
Carboxytolbutamide	0.99 [0.94, 1.05]	0.98 [0.95, 1.00]
Dextromethorphan (CYP2D6 substrate)		

Dextromethorphan	0.81 [0.69, 0.94]	0.82 [0.68, 1.00]
Dextrorphan	1.08 [1.01, 1.15]	1.09 [1.04, 1.13]
Midazolam (CYP3A substrate)		
Midazolam	1.06 [0.91, 1.24]	1.11 [1.00, 1.23]
1-hydroxymidazolam	0.96 [0.81, 1.15]	0.96 [0.87, 1.06]

Geometric mean ratio [90% CI] (substrates + relugolix / substrates alone).

6.2.6.2 Fluconazole and atorvastatin (Study C27005, CTD 5.3.3.4-2)

In 40 non-Japanese healthy adults (20 subjects [10 men and 10 women] per group), a single dose of relugolix 40 mg was orally administered before a meal on Days 1 and 10. Fluconazole was repeatedly administered orally once daily at 400 mg on Day 6 and at 200 mg on Days 7 to 14, or atorvastatin 80 mg was repeatedly administered orally once daily on Days 6 to 14. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of relugolix, respectively, was 1.44 [1.13, 1.83] and 1.19 [1.06, 1.33] (relugolix + fluconazole [Day 10] / relugolix alone [Day 1]), and 0.78 [0.51, 1.18] and 0.95 [0.77, 1.17] (relugolix + atorvastatin [Day 10] / relugolix alone [Day 1]).

6.2.6.3 Erythromycin (Study CPH-010, CTD 5.3.3.4-1)

In 20 Japanese healthy adults (10 men and 10 women), a single dose of relugolix 20 mg was administered orally before a meal on Days 1 and 15, and erythromycin 300 mg was repeatedly administered orally 4 times daily on Days 10 to 19. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of relugolix (relugolix + erythromycin [Day 15] / relugolix alone [Day 1]) was 6.18 [4.75, 8.04] and 6.25 [5.31, 7.35], respectively.

6.2.6.4 Rifampicin (Study MVT-601-1004, CTD 5.3.3.4-3)

In 18 non-Japanese healthy adults (13 men and 5 women), a single dose of relugolix 40 mg was orally administered in a fasting state on Days 1 and 13, and rifampicin 600 mg was repeatedly administered orally once daily on Days 6 to 17. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of relugolix (relugolix + rifampicin [Day 13] /relugolix alone [Day 1]) was 0.77 [0.56, 1.06] and 0.45 [0.33, 0.62], respectively.

6.2.7 Thorough QT study (Study 106, CTD 5.3.3.1-2)

A single oral dose of relugolix 60 or 360 mg, moxifloxacin 400 mg, or placebo was administered in a fasting state to 280 non-Japanese healthy adults (144 men and 136 women), and effects on QT interval were evaluated.

After a single oral dose of relugolix 60 or 360 mg, the t_{max} (median) of relugolix was 3.04 h and 3.02 h, respectively, C_{max} was 11.5 ± 7.83 ng/mL and 253 ± 200 ng/mL, respectively, and $AUC_{0-\infty}$ was 115 ± 55.5 ng·h/mL and 1762 ± 1003 ng·h/mL, respectively.

The upper limit of 95% CI of the difference from placebo in mean changes in QTcF (QT interval corrected by the Fridericia formula) from baseline (ΔΔQTcF) was below 10 msec at all time points in the relugolix 60 and 360 mg groups. The lower limit of 95% CI of ΔΔQTcF in the moxifloxacin group exceeded 5 msec at all time points.

6.R Outline of the review conducted by PMDA

6.R.1 Special dosing recommendations regarding timing of meals

The applicant's explanation about the special dosing recommendations regarding timing of meals for relugolix:
In the Japanese phase I study (Study CPH-001) in premenopausal healthy women, the effects of foods on the pharmacokinetics of relugolix were demonstrated, and the C_{max} and AUC of relugolix were both higher after premeal dosing than those after postmeal dosing. Serum E_2 levels after repeated dosing of relugolix 40 mg did not markedly differ between premeal dosing and postmeal dosing. As for safety, among adverse events for which causal relationship to the study drug could not be ruled out, the following events occurred at a higher incidence in subjects receiving relugolix 40 mg before a meal than in subjects receiving relugolix 40 mg after a meal: metrorrhagia (4 subjects for premeal dosing and 3 subjects for postmeal dosing); menorrhagia (2 subjects and 1 subject); somnolence (2 subjects and none); headache (1 subject and none); breast pain (1 subject and none); and feeling hot (1 subject and none). However, the events were all mild in severity and had resolved without treatment, suggesting that the effect of differences in administration method was negligible.

Based on the above, the applicant selected premeal administration of relugolix for the Japanese phase II study in Japanese patients with uterine fibroids (Study CCT-001), because blood relugolix concentrations could remain higher with premeal dosing than with postmeal dosing.

PMDA's view:
From a pharmacokinetic and pharmacodynamic point of view, PMDA considers it appropriate that Study CCT-001 used premeal dosing of relugolix based on the results of Study CPH-001. However, the appropriateness of the proposed timing of dosing of relugolix in relation to food intake should be evaluated also based on the results of Study CCT-001 conducted in Japanese patients with uterine fibroids and the Japanese phase III studies (Studies CCT-002 and 3008) [see Section 7.R.5].

6.R.2 Pharmacokinetic interaction with erythromycin

The applicant's explanation about the pharmacokinetic interaction between relugolix and erythromycin:
In Study CPH-010, the C_{max} and AUC of relugolix administered concomitantly with erythromycin were approximately 6 times higher than those of relugolix administered alone. Meanwhile, in a foreign phase I study (Study C27001) in non-Japanese healthy men, the tolerability and safety of relugolix 180 mg administered once daily for 14 days have been demonstrated, and the C_{max} and AUC at steady state of relugolix administered at the dosing regimen (168 ng/mL and 704 ng·h/mL, respectively) were higher than the estimated C_{max} and AUC of relugolix administered at the proposed dosing regimen in combination with erythromycin (126 ng/mL and 603 ng·h/mL, respectively). Study C27001 was conducted in non-Japanese men, and no clear differences in the pharmacokinetics or safety of relugolix have been observed between sexes or non-Japanese and Japanese patients. Accordingly, the applicant considers that the safety of relugolix administered concomitantly with erythromycin can be estimated based on data from Study C27001. Based on the above, although the exposure to relugolix has been shown to increase when the drug is administered concomitantly with erythromycin, the exposure to relugolix administered at the proposed dosing regimen in combination with erythromycin is

presumed to fall within the range where the tolerability of relugolix has been confirmed. Relugolix thus seems to be unlikely to raise a safety concern when administered concomitantly with erythromycin. Therefore, the applicant has proposed to include precautionary advice about concomitant use with erythromycin in the package insert.

Furthermore, relugolix has been shown to serve as a substrate of P-gp and be metabolized mainly by CYP3A, whereas, in Study C27005, co-administration of relugolix and drugs that inhibit CYP3A (i.e., fluconazole and atorvastatin) had almost no impact on the exposure to relugolix. In light of the findings, the increased exposure to relugolix after coadministration with erythromycin is attributable mainly to the inhibition of P-gp by erythromycin. Therefore, precautionary advice about concomitant use with P-gp inhibitors including erythromycin should be included in the package insert.

PMDA's view:
The submitted data do not suggest any significant safety concerns regarding the coadministration of relugolix at the proposed dosing regimen and erythromycin, and the applicant's explanation (i.e., the pharmacokinetic interaction between relugolix and erythromycin is mediated by the inhibition of P-gp by erythromycin) is considered to be acceptable. Based on the above, PMDA has concluded that it is acceptable that precautionary advice about the concomitant use with P-gp inhibitors including erythromycin should be included in the package insert.

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

A total of 4 studies, shown in Table 36, have been submitted as the main evaluation data for the efficacy and safety of relugolix [for pharmacokinetics and pharmacodynamics, see Section 6.2].

Table 36. List of clinical studies for the efficacy and safety

Data category	Area	Study ID	Phase	Study population	Number of enrolled subjects	Outline of dosing regimen	Main endpoints
Evaluation data	Japan	CPH-001	I	Healthy women	Single dose: 72 Crossover: 24 Repeated dose: 48	Single dose part: A single dose of relugolix 1, 5, 10, 20, 40, or 80 mg or placebo was administered orally in a fasting state without breakfast. Crossover part: Relugolix 40 mg was orally administered in a fasting state without breakfast or after breakfast. Relugolix 40 mg was orally administered in a fasting state without breakfast or before breakfast. Repeated dose part: Relugolix 10, 20, or 40 mg or placebo was administered orally once daily after breakfast. Relugolix 40 mg or placebo was administered orally once daily before breakfast.	Safety Pharmacokinetics Pharmacodynamics
		CCT-001	II	Patients with uterine fibroids and menorrhagia	216	Relugolix 10, 20, or 40 mg or placebo was repeatedly administered orally once daily before breakfast.	Efficacy Safety
		CCT-002	III	Patients with uterine fibroids and menorrhagia	280	Relugolix 40 mg was repeatedly administered orally once daily before breakfast, or leuprorelin 1.88 or 3.75 mg was repeatedly administered subcutaneously once every 4 weeks.	Efficacy Safety
		3008	III	Patients with uterine fibroids and pain symptoms	65	Relugolix 40 mg or placebo was repeatedly administered orally once daily before breakfast.	Efficacy Safety

7.1 Phase I study

7.1.1 A single- and repeated-dose study in Japanese healthy adults (Study CPH-001, CTD 5.3.3.1-1, [redacted] 20[redacted] to [redacted] 20[redacted])

A clinical study was conducted at one site in Japan to evaluate the safety, pharmacokinetics, and pharmacodynamics of relugolix and the effects of food on the safety and pharmacokinetics of relugolix after a single dose and repeated doses of relugolix in Japanese healthy premenopausal women.

The study consisted of a single-dose part (Steps 1 to 6), a crossover part (Steps 7a to 7d), and a repeated-dose part (Steps 8 to 11). The single-dose and repeated-dose parts were conducted as randomized, double-blind, placebo-controlled studies, and the crossover part was conducted as a 2-arm, 2-period, crossover study. The dosing regimens in the individual steps are shown in Table 37.

Table 37. Dosing regimens in individual steps

Part	Step	Number of subjects	Dosing regimen	Administration conditions
Single dosing	1 to 6	12 subjects per step (10 for relugolix, 2 for placebo)	A single oral dose of relugolix 1, 5, 10, 20, 40, or 80 mg or placebo	In a fasting state without breakfast
Crossover	7a, 7b	12 subjects	A single oral dose of relugolix 40 mg	7a: Day 1 (in a fasting state without breakfast), Day 8 (after breakfast) 7b: Day 1 (after breakfast), Day 8 (in

				a fasting state without breakfast)
	7c, 7d	12 subjects	A single oral dose of relugolix 40 mg	7c: Day 1 (in a fasting state without breakfast), Day 8 (before breakfast) 7d: Day 1 (before breakfast), Day 8 (in a fasting state without breakfast)
Repeated dosing	8 to 10	12 subjects per step (9 for relugolix, 2 for placebo)	Repeated oral doses of relugolix 10, 20, or 40 mg or placebo once daily for 14 days	After breakfast
	11		Repeated oral doses of relugolix 40 mg or placebo once daily for 14 days	Before breakfast

All 144 randomized subjects received the study drug and were included in the safety analysis set.

The incidence of adverse events during the single dose part was 75.0% (9 of 12) of subjects in the placebo group, 40.0% (4 of 10) of subjects in the relugolix 1 mg group, 50.0% (5 of 10) of subjects in the relugolix 5 mg group, 50.0% (5 of 10) of subjects in the relugolix 10 mg group, 80.0% (8 of 10) of subjects in the relugolix 20 mg group, 80.0% (8 of 10) of subjects in the relugolix 40 mg group, and 40.0% (4 of 10) of subjects in the relugolix 80 mg group. The following adverse events occurred in ≥2 subjects: Nasopharyngitis in 15 subjects (4 in the placebo group, 1 in the relugolix 1 mg group, 2 in the relugolix 5 mg group, 2 in the relugolix 10 mg group, 2 in the relugolix 20 mg group, 3 in the relugolix 40 mg group, 1 in the relugolix 80 mg group); menstruation irregular in 13 subjects (3 in the placebo group, 1 in the relugolix 1 mg group, 1 in the relugolix 10 mg group, 2 in the relugolix 20 mg group, 4 in the relugolix 40 mg group, and 2 in the relugolix 80 mg group); abdominal pain in 3 subjects (1 in the placebo group, 1 in the relugolix 1 mg group, and 1 in the relugolix 80 mg group); diarrhea in 3 subjects (2 in the placebo group and 1 in the relugolix 80 mg group); rhinitis in 3 subjects (1 in the placebo group, 1 in the relugolix 5 mg group, and 1 in the relugolix 20 mg group); headache in 2 subjects (1 in the relugolix 20 mg group and 1 in the relugolix 80 mg group); pharyngolaryngeal pain in 2 subjects (1 in the relugolix 5 mg group and 1 in the relugolix 10 mg group); and dysmenorrhea in 2 subjects (1 in the relugolix 5 mg group and 1 in the relugolix 20 mg group). No deaths or serious adverse events occurred.

In the crossover part, the incidence of adverse events in Steps 7a and 7b was 25.0% (3 of 12) of subjects receiving relugolix in a fasting state and 8.3% (1 of 12) of subjects receiving relugolix after a meal. An adverse event occurring in ≥2 subjects was headache in 2 subjects (1 subject receiving relugolix in a fasting state and 1 receiving relugolix after a meal). The incidence of adverse events in Steps 7c and 7d was 25.0% (3 of 12) of subjects receiving relugolix in a fasting state and 25.0% (3 of 12) of subjects receiving relugolix before a meal. An adverse event occurring in ≥2 subjects was menstruation irregular in 5 subjects (3 subjects receiving relugolix in a fasting state and 2 subjects receiving relugolix before a meal). No deaths, serious adverse events, or adverse events leasing to treatment discontinuation occurred.

In the repeated dosing part, the incidence of adverse events was 91.7% (11 of 12) of subjects in the placebo group, 100.0% (9 of 9) of subjects receiving relugolix 10 mg after a meal, 100.0% (9 of 9) of subjects receiving relugolix 20 mg after a meal, 100.0% (9 of 9) of subjects receiving relugolix 40 mg after a meal, and 100.0% (9 of 9) subjects receiving relugolix 40 mg before a meal. Adverse events occurring in ≥2 subjects are shown

in Table 38. An adverse event (blood potassium increased) led to discontinuation of the study drug in 1 subject receiving relugolix 40 mg after a meal, and a causal relationship between the event and the study drug could not be ruled out. No deaths or serious adverse events occurred.

Table 38. Incidence of adverse events occurring in ≥2 subjects (safety analysis set)

	Placebo (N = 12)	Relugolix 10 mg after meal (N = 9)	Relugolix 20 mg after meal (N = 9)	Relugolix 40 mg after meal (N = 9)	Relugolix 40 mg before meal (N = 9)
Menstruation irregular	16.7 (2)	66.7 (6)	88.9 (8)	88.9 (8)	88.9 (8)
Metrorrhagia	8.3 (1)	0 (0)	11.1 (1)	33.3 (3)	44.4 (4)
Headache	16.7 (2)	22.2 (2)	0 (0)	11.1 (1)	44.4 (4)
Somnolence	8.3 (1)	0 (0)	0 (0)	0 (0)	22.2 (2)
Pharyngolaryngeal pain	8.3 (1)	0 (0)	0 (0)	0 (0)	22.2 (2)
Menorrhagia	0 (0)	0 (0)	22.2 (2)	11.1 (1)	22.2 (2)
Rash	0 (0)	0 (0)	0 (0)	11.1 (1)	11.1 (1)
Abdominal pain upper	8.3 (1)	0 (0)	0 (0)	0 (0)	11.1 (1)
Feeling hot	8.3 (1)	0 (0)	0 (0)	0 (0)	11.1 (1)
Diarrhoea	8.3 (1)	33.3 (3)	22.2 (2)	44.4 (4)	0 (0)
Nasopharyngitis	8.3 (1)	0 (0)	0 (0)	44.4 (4)	0 (0)
Nausea	0 (0)	11.1 (1)	0 (0)	11.1 (1)	0 (0)
Constipation	16.7 (2)	0 (0)	0 (0)	11.1 (1)	0 (0)
Myalgia	16.7 (2)	0 (0)	0 (0)	11.1 (1)	0 (0)
Abdominal pain	8.3 (1)	0 (0)	11.1 (1)	0 (0)	0 (0)
Gastroenteritis	0 (0)	22.2 (2)	11.1 (1)	0 (0)	0 (0)
Blood triglycerides increased	0 (0)	11.1 (1)	11.1 (1)	0 (0)	0 (0)
Blood creatine phosphokinase increased	16.7 (2)	0 (0)	11.1 (1)	0 (0)	0 (0)
Blood urine present	8.3 (1)	0 (0)	11.1 (1)	0 (0)	0 (0)
Hordeolum	8.3 (1)	11.1 (1)	0 (0)	0 (0)	0 (0)

% (n)

7.2 Phase II studies

7.2.1 Japanese phase II study in patients with uterine fibroids and menorrhagia (Study CCT-001, CTD 5.3.5.1-1, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 36 sites in Japan to find the optimal dose of relugolix in Japanese patients with uterine fibroids and menorrhagia (target sample size, 55 patients per group, 220 patients in total)

Placebo was administered in a single-blind manner from the day of Visit 2 (between Days 1 and 5 of the first menstruation cycle after Visit 1) to the previous day of Visit 3 (between Days 1 and 5 of the second menstruation cycle after Visit 1). Relugolix 10, 20, or 40 mg or placebo was orally administered, in a double-blind manner, once daily before breakfast for 12 weeks beginning the day of Visit 3.

The main inclusion criteria included the following: Patients with uterine fibroids; age of ≥20 years; a diagnosis of menorrhagia; having regular menstruation with a cycle of 25 to 38 days (menstruation is defined as bleeding lasting for at least 3 consecutive days); and a total pictorial blood assessment chart (PBAC) score (Table 39) of ≥120 for the last menstruation before Visit 3.

Table 39. PBAC scores

Parameter	Extent	Score
Menstrual blood on sanitary items (pads or tampons)	Light	1
	Medium	5
	Heavy	20
Blood clot size	<1 cm in diameter (longest diameter)	1
	≥1 cm in diameter (longest diameter)	5

Five points are added when blood overflows from the sanitary item (flooding).

All 216 randomized patients (57 in the placebo group, 48 in the relugolix 10 mg group, 56 in the relugolix 20 mg group, and 55 in the relugolix 40 mg group) received the study drug. Of the 216 patients, 2 patients judged as GCP noncompliant were excluded (1 subject in the relugolix 20 mg group and 1 subject in the relugolix 40 mg group). The remaining 214 patients were included in the safety analysis set and the full analysis set (FAS). The FAS was used for the primary efficacy analyses.

The primary efficacy endpoint was "the percentage of patients with a total PBAC score of <10 between Weeks 6 and 12." Results of the primary efficacy endpoint are shown in Table 40, and significant differences existed between any of the relugolix group and the placebo group. Data on the blood Hb content, as a secondary endpoint, are shown in Table 41.

Table 40. Percentage of patients with a total PBAC score of <10 between Weeks 6 and 12 (FAS)

	Placebo (N = 57)	Relugolix 10 mg (N = 48)	Relugolix 20 mg (N = 54[b])	Relugolix 40 mg (N = 54)
Percentage of patients (%) (n)	0 (0)	20.8 (10)	42.6 (23)	83.3 (45)
Difference from placebo (%) [95%CI]	—	20.8 [9.344, 32.322]	42.6 [29.404, 55.781]	83.3 [73.393, 93.273]
p value [a]	—	0.0003	<0.0001	<0.0001

a: χ^2 test
Multiplicity was adjusted by a closed testing procedure testing the comparison between the relugolix 40 mg group and the placebo group, between the relugolix 20 mg group and the placebo group, and then between the relugolix 10 mg group and the placebo group, in this order.
b: A subject with missing data for the PBCA score between Weeks 6 and 12 was excluded.

Table 41. Changes in blood Hb contents (g/dL) (FAS)

	Placebo	Relugolix 10 mg	Relugolix 20 mg	Relugolix 40 mg
Baseline [a]	12.11 ± 1.504 (57)	12.18 ± 1.159 (48)	12.19 ± 1.389 (55)	11.95 ± 1.694 (54)
Week 12	12.42 ± 1.353 (55)	12.55 ± 1.350 (47)	12.98 ± 1.204 (53)	12.88 ± 1.382 (54)
Change from baseline	0.20 ± 1.003	0.35 ± 1.055	0.83 ± 1.172	0.93 ± 1.191

Mean ± standard deviation (n)
a: At Visit 3.

With regard to safety, the incidence of adverse events was 70.2% (40 of 57) of patients in the placebo group, 85.4% (41 of 48) of patients in the relugolix 10 mg group, 96.4% (53 of 55) of patients in the relugolix 20 mg group, and 88.9% (48 of 54) of patients in the relugolix 40 mg group. Adverse events with an incidence of ≥5% in any group are shown in Table 42.

Table 42. Incidence of adverse events occurring with an incidence of ≥5% in any group (safety analysis set)

	Placebo (N = 57)	Relugolix 10 mg (N = 48)	Relugolix 20 mg (N = 55)	Relugolix 40 mg (N = 54)
Hot flush	3.5 (2)	4.2 (2)	29.1 (16)	38.9 (21)
Metrorrhagia	17.5 (10)	27.1 (13)	30.9 (17)	27.8 (15)
Menorrhagia	7.0 (4)	12.5 (6)	23.6 (13)	22.2 (12)
Headache	1.8 (1)	2.1 (1)	14.5 (8)	13.0 (7)
Nasopharyngitis	28.1 (16)	18.8 (9)	7.3 (4)	13.0 (7)
Genital haemorrhage	3.5 (2)	4.2 (2)	10.9 (6)	11.1 (6)
Menstruation irregular	0 (0)	25.0 (12)	14.5 (8)	5.6 (3)
Arthralgia	5.3 (3)	2.1 (1)	1.8 (1)	5.6 (3)
Nausea	3.5 (2)	0 (0)	0 (0)	5.6 (3)
Oligomenorrhoea	0 (0)	6.3 (3)	7.3 (4)	3.7 (2)
Seasonal allergy	5.3 (3)	4.2 (2)	5.5 (3)	3.7 (2)
Hyperhidrosis	1.8 (1)	2.1 (1)	5.5 (3)	3.7 (2)

% (n)

No deaths occurred. Serious adverse events occurred in 1 patient in the placebo group (deafness neurosensory), 1 patient in the relugolix 20 mg group (dysphonia), and 1 patient in the relugolix 40 mg group (VIIth nerve palsy). A relationship to the study drug was ruled out for all of the serious adverse events. Adverse events led to discontinuation of the study drug in 1 patient in the placebo group (hemoglobin decreased) and 1 patient in the relugolix 20 mg group (tinnitus, libido decreased, menopausal depression, and hyperhidrosis). A relationship to the study drug could not be ruled out for all these events.

7.3 Phase III studies

7.3.1 Japanese phase III study in patients with uterine fibroids and menorrhagia (Study CCT-002, CTD 5.3.5.1-2, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, active-controlled, parallel-group study was conducted at 34 sites in Japan to evaluate the efficacy and safety of relugolix in Japanese patients with uterine fibroids and menorrhagia (target sample size, 144 patients in the relugolix group and 144 patients in the leuprorelin group).

Placebo was administered in a single-blind manner from the day of Visit 2 (between Days 1 and 5 of the first menstruation cycle after Visit 1) to the previous day of Visit 3 (between Days 1 and 5 of the second menstruation cycle after Visit 1). In a double-blind manner, beginning the day of Visit 3, relugolix 40 mg was repeatedly administered orally once daily before breakfast for 24 weeks, or leuprorelin 1.88 or 3.75 mg was repeatedly administered subcutaneously once every 4 weeks for 24 weeks.

The main inclusion criteria: Patients with uterine fibroids; age of ≥20 years; a diagnosis of menorrhagia; having regular menstruation with a cycle of 25 to 38 days (menstruation is defined as bleeding lasting for at least 3 consecutive days); and a PBAC score of ≥120 for the last menstruation before Visit 3.

Of 281 randomized patients (139 in the relugolix group and 142 in the leuprorelin group), a patient with protocol deviation in the relugolix group was excluded. The remaining 280 patients (138 in the relugolix group

and 142 in the leuprorelin group) received relugolix or leuprorelin and were included in the safety analysis set and the FAS. The FAS was used for the primary efficacy analyses.

The primary efficacy endpoint was "the percentage of patients with a total PBAC score of <10 between Weeks 6 and 12." Results of the primary efficacy endpoint are shown in Table 43, and the lower limit of two-sided 95% CI for differences between the relugolix and leuprorelin groups was above the predefined non-inferiority margin (-15%), demonstrating the non-inferiority of relugolix to leuprorelin. Data on the blood Hb content, a secondary endpoint, are shown in Table 44.

Table 43. Percentage of patients with a total PBAC score of <10 between Weeks 6 and 12 (FAS)

	Relugolix 40 mg (N = 135[a])	Leuprorelin (N = 142)
Percentage of subjects (%) (n)	82.2 (111)	83.1 (118)
Difference from leuprorelin (%) [95%CI]	−0.9 [−10.098, 8.346]	−

a: Three (3) patients with missing data for the PBCA score between Weeks 6 and 12 were excluded.

Table 44. Changes in blood Hb contents (g/dL) (FAS)

	Relugolix 40 mg	Leuprorelin
Baseline [a]	11.49 ± 1.368 (138)	11.62 ± 1.377 (142)
Week 12	12.84 ± 1.193 (129)	12.94 ± 1.155 (140)
Changes from baseline	1.38 ± 1.134	1.31 ± 1.000
Week 24	13.06 ± 1.025 (122)	13.26 ± 1.007 (131)
Changes from baseline	1.56 ± 1.281	1.65 ± 1.116

Mean ± standard deviation (n)
a: At Visit 3

With regard to safety, the incidence of adverse events was 94.9% (131 of 138) of patients in the relugolix group and 97.9% (139 of 142) of patients in the leuprorelin group. Adverse events with an incidence of ≥5% in either group are shown in Table 45.

Table 45. Incidence of adverse events occurring with an incidence of ≥5% in either group (safety analysis set)

	Relugolix 40 mg (N = 138)	Leuprorelin (N = 142)
Metrorrhagia	49.3 (68)	65.5 (93)
Hot flush	42.8 (59)	52.8 (75)
Viral upper respiratory tract infection	28.3 (39)	32.4 (46)
Menorrhagia	24.6 (34)	15.5 (22)
Headache	15.2 (21)	9.9 (14)
Hyperhidrosis	9.4 (13)	10.6 (15)
Dizziness	6.5 (9)	4.9 (7)
Arthralgia	5.8 (8)	6.3 (9)
Malaise	5.8 (8)	3.5 (5)
γ-GTP increased	5.1 (7)	6.3 (9)
Resorption bone increased	5.1 (7)	5.6 (8)
Bone resorption test abnormal	5.1 (7)	4.9 (7)
Genital haemorrhage	5.1 (7)	4.9 (7)
Somnolence	5.1 (7)	4.2 (6)
Bone density decreased	4.3 (6)	5.6 (8)

% (n)

No deaths occurred. Serious adverse events occurred in 2 patients in the leuprorelin group (large intestine polyp, ulna fracture). A relationship to the study drug was ruled out for the serious adverse events in both patients. Adverse events led to discontinuation of the study drug in 9 patients in the relugolix group (hot flush in 3 patients; malaise in 1 patient; fatigue and liver function test increased in 1 patient; arthralgia in 1 patient; tenosynovitis and tenosynovitis stenosans in 1 patient; hot flush and headache in 1 patient, and depression in 1 patient) and 7 patients in the leuprorelin group (abdominal pain, nausea, malaise, pyrexia, and liver function test increased in 1 patient; blood pressure increased in 1 patient; liver function test abnormal in 1 patient; arthralgia and back pain in 1 patient; drug eruption in 1 patient; hot flush in 1 patient; and hypertension in 1 patient). A causal relationship to the study drug could not be ruled out for all these events, except for fatigue in the relugolix group and abdominal pain, nausea, malaise, and pyrexia in the leuprorelin group.

7.3.2 Japanese phase III study in patients with uterine fibroids with pain symptoms (Study 3008, CTD 5.3.5.1-3, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 15 sites in Japan to evaluate the efficacy and safety of relugolix in patients with uterine fibroids with pain symptoms (target sample size, 32 patients in the relugolix group and 32 patients in the placebo group).

Placebo was administered in a single-blind manner from the day of Visit 2 (between Days 1 and 5 of the first menstruation cycle after Visit 1) to the previous day of Visit 3 (between Days 1 and 5 of the second menstruation cycle after Visit 1). Relugolix 40 mg or placebo was orally administered, in a double-blind manner, once daily before breakfast for 12 weeks beginning the day of Visit 3.

The main inclusion criteria: Patients with uterine fibroids; age of ≥20 years; having regular menstruation with a cycle of 25 to 38 days (menstruation is defined as bleeding lasting for at least 3 consecutive days); and a maximum numeric rating scale (NRS) score of ≥4 for the last menstruation before Visit 3.

All 65 randomized patients (33 in the relugolix group and 32 in the placebo group) received relugolix or placebo and were included in the safety analysis set and the FAS. The FAS was used for the primary efficacy analyses.

The primary efficacy endpoint was “the percentage of patients with a maximum NRS score of ≤1 during 28 days before the final dose of the study drug.” Results of the primary efficacy endpoint are shown in Table 46, demonstrating significant differences between the relugolix group and the placebo group.

Table 46. Percentage of patients with a maximum NRS score of ≤1 during 28 days before the final dose of the study drug (FAS)

	Relugolix 40 mg (N = 33)	Placebo (N = 32)
Percentage of subjects (%) (n)	57.6 (19)	3.1 (1)
Odds ratio [95%CI]	42.071 [5.113, 346.181]	−
p value [a]	<0.0001	−

a: Fisher’s exact test

With regard to safety, the incidence of adverse events was 87.9% (29 of 33) of patients in the relugolix group and 56.3% (18 of 32) of patients in the placebo group. Adverse events with an incidence of ≥5% in either group are shown in Table 47.

Table 47. Adverse events occurring with an incidence of ≥5% in any group (safety analysis set)

	Relugolix 40 mg (N = 33)	Placebo (N = 32)
Hot flush	45.5 (15)	0 (0)
Metrorrhagia	39.4 (13)	9.4 (3)
Viral upper respiratory tract infection	21.2 (7)	28.1 (9)
Hyperhidrosis	15.2 (5)	0 (0)
Menorrhagia	12.1 (4)	9.4 (3)
Insomnia	9.1 (3)	0 (0)
ALT increased	6.1 (2)	0 (0)
AST increased	6.1 (2)	0 (0)
Genital haemorrhage	6.1 (2)	0 (0)
Oropharyngeal pain	6.1 (2)	0 (0)
Menstruation irregular	3.0 (1)	9.4 (3)
Headache	0 (0)	6.3 (2)
Cough	0 (0)	6.3 (2)

% (n)

No deaths or serious adverse events occurred. Adverse events led to discontinuation of the study drug in 1 patient in the relugolix group (depression, insomnia, and hot flush) and 1 patient in the placebo group (palpitations). A causal relationship to the study drug could not be ruled out for all these events.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Menorrhagia

7.R.1.1.1 Design of the Japanese phase III study (Study CCT-002)

7.R.1.1.1.1 Rationale for selecting the evaluation index for menstrual blood loss

PMDA asked the applicant to explain the rationale for the use of the PBAC score to evaluate the menstrual blood loss in Study CCT-002, because the PBAC score has not been used often for evaluation of menstrual blood loss in clinical studies conducted in Japanese subjects.

The applicant's explanation:

An alkaline hematin method is an established method to assess menstrual blood loss quantitatively, in which Hb content is determined from used sanitary items. A PBAC score is a combined score for the extent of menstrual blood in sanitary items, the number of sanitary items used, the size and number of blood clots, and the frequency of flooding of blood. With the PBAC score, menstrual blood loss is assessed on the basis of the total score recorded by the subjects themselves for the appearance and number of used sanitary items. A study suggests a relationship between the assessment of menstrual blood loss with the PBAC score and the measurement of menstrual blood loss with the alkaline hematin method (*Br J Obstet Gynecol*. 1990;97:734-49). The assessment of menstrual blood loss with the PBAC score can be done without a collection of sanitary items from test subjects. The PBAC score is simple to use compared with the alkaline hematin method, and

menstrual blood loss can be assessed in detail with the PBAC score compared with history taking by interview at their visits. Therefore, the guidelines in the U.K., in the section of menorrhagia, describes the PBAC as the best practical tool for the assessment of menstrual blood loss (*Haemophilia*. 2006; 12: 301-36), and menstrual blood loss has been assessed with the PBAC score in many clinical trials (*N Eng J Med*. 2012;366:421-32; *Eur J Obstet Gynecol Reprod Biol*. 2011;157:212-6; *Med J Armed Forces India*. 2017;73:267-73). These facts suggest that the PBAC score has been well established as a tool for the assessment of menstrual blood loss outside Japan. In Japan, conversely, the use of the PBAC score is limited. Therefore, the feasibility of assessment of menstrual blood loss with the PBAC score in Japanese women was investigated in patients with uterine fibroids with menorrhagia. The investigation showed that how to describe for the PBAC score was understood well, and the PBAC score in most of the cases was ≥100, which is a score reflecting the blood loss (>80 mL) meeting the criterion for the diagnosis of menorrhagia. Based on these findings, it was considered that menstrual blood loss could be assessed adequately with the PBAC score in Japanese women.

PMDA's view:

The assessment of menstrual blood loss with the PBAC score has been reported to correlate with the measurement of menstrual blood loss with the alkaline hematin method, which is an established method for quantification of menstrual blood loss. Outside Japan, the PBAC score has been used as a practical tool to assess the menstrual blood loss with a certain accuracy without collection of used sanitary items. Meanwhile, care should be taken because the PBAC method is not a tool to quantify menstrual blood loss precisely. However, in light of the fact that results of the assessment of menstrual blood loss with the PBAC score reflected the blood loss per menstruation cycle which met the criterion for the diagnosis of menorrhagia, PMDA considers it appropriate that the PBAC score was used for the assessment of menstrual blood loss in Study CCT-002, which was conducted to evaluate the effectiveness of relugolix for menorrhagia.

7.R.1.1.1.2 Appropriateness of subjects assessed

In Study CCT-002, patients with a diagnosis of menorrhagia and a total PBAC score of ≥120 were considered eligible for participation in the study. PMDA asked the applicant to provide a justification for this inclusion criterion.

The applicant's justification:

Generally, menorrhagia is diagnosed when menstrual blood loss per menstruation cycle exceeds 80 mL (*Acta Obstet Gynecol Scand*. 1966;45:320-51), and a menstrual blood loss of 80 mL corresponds to a total PBAC score of 100 (*Br J Obstet Gynaecol*. 1990;97:734-9). Anemia (blood Hb content of <12 g/dL) was more frequently diagnosed in patients with menstrual blood loss per cycle of >100 mL (corresponding to a total PBAC of 120) than those with menstrual blood loss per cycle of ≤100 mL (J *Reprod Med*. 1987;32:822-6). Since Study CCT-002 was a study designed to evaluate the efficacy of relugolix for anemia, as well as menorrhagia, in Japanese patients with uterine fibroids, the inclusion criteria required patients to have a diagnosis of menorrhagia and a total PBAC score of ≥120 in order to evaluate both menorrhagia and anemia. In clinical practice in Japan, menorrhagia is diagnosed on the basis of complaints from a patient, and menstrual

blood loss is not measured strictly (Glossary of Obstetrics and Gynecology, 4th Edition, edited by the Japan Society of Obstetrics and Gynecology), suggesting that a diagnosis is unlikely to be made on the basis of menstrual blood loss confirmed by a PBAC score or other tools. In light of the practice of making a diagnosis of menorrhagia in Japan, the efficacy of relugolix on menorrhagia can be evaluated by conducting a study in patients with a diagnosis of menorrhagia and a PBAC score of ≥120.

PMDA's view:
As per the applicant, a diagnosis of menorrhagia is not made uniformly on the basis of the extent of menstrual blood loss in clinical practice in Japan, and patients with a diagnosis of menorrhagia are likely to have anemia concomitantly (Glossary of Obstetrics and Gynecology, 4th Edition, edited by the Japan Society of Obstetrics and Gynecology). In view of the applicant's explanation, PMDA recognizes that the diagnosis of menorrhagia is made on the basis of the manifestation of anemia symptoms or therapeutic intervention for anemia. In consideration of the circumstances for the diagnosis of menorrhagia in clinical practice, it is reasonable to administer relugolix to patients with a diagnosis of menorrhagia and menstrual blood loss suggestive of a high probability of medically significant anemia as a clinical symptom associated with menorrhagia. PMDA has thus concluded it appropriate to include a PBAC score of ≥120 in the inclusion criteria for menorrhagia in Study CCT-002 taking into account a possible increased risk of comorbidity with anemia.

7.R.1.1.1.3 Appropriateness of the cutoff value for the primary efficacy endpoint

PMDA asked the applicant to provide a justification for the cutoff value of 10 for a total PBAC score as the primary endpoint in Study CCT-002.

The applicant's explanation:
A total PBAC score of <10 corresponds to, for instance, a situation with one or less occurrence of moderate bleeding (5 points) with more than one occurrence of mild bleeding (1 point) during an evaluation period (Table 39). Accordingly, when a total PBAC score of <10 is achieved by a patient eligible for Study CCT-002 who has uterine fibroids and menorrhagia with a total PBAC score of 120, it means that her genital hemorrhage is marginal and her bleeding profile has improved considerably.

PMDA's view:
In light of the applicant's explanation about bleeding status in patients with a total PBCA score of <10, it can be concluded that bleeding profile has improved considerably from the status of menorrhagia when the patients achieve a total PBAC score of <10 for 6 weeks including at least a regular menstruation cycle (a cycle of 25 to 38 days) [see Section 7.R.1.1.1.4]. PMDA thus has concluded that the cutoff value of 10 for the total PBAC score as the primary endpoint in Study CCT-002 was appropriate.

7.R.1.1.1.4 Appropriateness of the assessment period

In Study CCT-002, the assessment period of the primary endpoint was from Week 6 to Week 12. PMDA asked the applicant to provide a justification for the duration.

The applicant's justification:

The assessment period for the primary endpoint in Study CCT-002 was determined on the basis of the data from clinical studies of leuprorelin which were available at the time of planning of Study CCT-002. In a foreign phase III study (the PEARL II study) to evaluate the improvement effects of ulipristal acetate on menorrhagia associated with uterine fibroids in which leuprorelin (3.75 mg, subcutaneously administered, once every 4 weeks) was used as an active comparator, the total 28-day PBAC score began to decline below 2 within 40 days in many patients in the leuprorelin group, with a median of 21 days after the start of treatment (*N ENgl J Med*. 2012;366:421-32). In the Japanese phase III study of leuprorelin (3.75 mg, subcutaneously administered, once every 4 weeks) in patients with uterine fibroids, the percentage of patients with their treatment assessed as "useful or very useful"[2)] at Week 16 of study treatment, the primary efficacy endpoint, was 85% (85 of 100 of patients) in the leuprorelin group, and the percentage of patients showing "improvement" or greater in menorrhagia at Weeks 4, 8, 12, and 16 was 79% (68 of 86), 100% (86 of 86), 95% (82 of 86), and 92% (79 of 86), respectively, of patients in the leuprorelin group (*Obstetrics and Gynecology.* 1995;62(5):741-69). The above data suggest that the efficacy of leuprorelin for menorrhagia reaches its peak and becomes stable before Week 6 of treatment. Since at least one regular menstruation cycle (a cycle of 25 to 38 days) should be included in the assessment period to evaluate the efficacy for menorrhagia, the assessment period for the primary efficacy endpoint was defined as a period from Week 6 to Week 12 of study treatment.

In the leuprorelin group in Study CCT-002, the percentage of patients with a total PBAC score of <10 between Weeks 18 and 24 was 94.7% (126 of 133) of patients, which was higher than that between Weeks 6 and 12 (118 of 142 patients, 83.1%). Of the 126 patients, 18 achieved a total PBAC score of <10 for the first time between Weeks 18 and 24, whereas the remaining 108 achieved a total PBAC score of <10 between Weeks 6 and 12 as well as between Weeks 18 and 24. However, changes in serum E_2 levels were similar in both patient groups, and no differences were found between the patient groups in baseline characteristics (e.g., childbirth history, type of myoma, treatment history of myoma, baseline total PBAC score, and leuprorelin dose) that might have affected the time to onset of the effect of leuprorelin. Therefore, the reasons for the difference in the time to onset of the effect between the patient groups could not be identified, and the difference was thus considered to be coincidental.

Based on the above, it was considered reasonable that the period from Week 6 to Week 12 was chosen as the assessment period for the primary endpoint in Study CCT-002 based on data from the leuprorelin clinical studies available at the time of planning of Study CCT-002.

PMDA's view:

Since a comparison of efficacy between relugolix and a comparator should be performed under conditions where the maximum and stable effects of both drugs are exerted, it is appropriate that the assessment period

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[2)] Percentage of patients with an assessment of "useful" or higher with a 5-grade assessment scale for the usefulness in comprehensive evaluation of general improvement and general safety: very useful, useful, slightly useful, not useful, and unfavorable.

for the primary endpoint in Study CCT-002 was determined in light of the time to onset of the effect of leuprorelin, the comparator used in Study CCT-002. Based on data from the clinical studies which were available at the time of the planning of Study CCT-002 and in which leuprorelin was administered to patients with uterine fibroids who were the target population of relugolix, the applicant assumed that the effects of leuprorelin reached the peak and became stable by Week 6 of treatment. The applicant's assumption is reasonable. In the leuprorelin group in Study CCT-002, the percentage of patients with a total PBAC score of <10 between Weeks 18 and 24 was higher than that between Weeks 6 and 12. However, even in patients who achieved a total PBAC score of <10 for the first time between Week 18 and Week 24, the mean serum E_2 level after administration of leuprorelin decreased to the menopausal level at Week 4 and was maintained at the level subsequently throughout the treatment period [see Section 6.2.3.2]. Therefore, the time to the maximum effect of leuprorelin which was estimated based on clinical study data available at the time of planning of Study CCT-002 could be used as the basis for it. Also, in Study CCT-001, the mean E_2 level after administration of relugolix 40 mg decreased to the menopausal level by Week 2 and was maintained at the level subsequently throughout the treatment period including the period from Week 6 and Week 12 [see Section 6.2.3.1]. In addition to the above, it is considered appropriate that the assessment period for the primary endpoint in Study CCT-002 was defined as the period between Weeks 6 and 12 of study treatment in order to include at least one regular menstruation cycle in the assessment period.

7.R.1.1.1.5 Appropriateness of non-inferiority margin

PMDA asked the applicant to provide a justification for the non-inferiority margin of −15% used in Study CCT-002.

The applicant's justification:

The non-inferiority margin in Study CCT-002 was investigated with reference to findings on similar medicines available at the time of planning of the study. In the above-mentioned PEARL II study [see Section 7.R.1.1.1.4], the non-inferiority margin was set at −20% for the primary endpoint, the percentage of patients with a total PBAC score of <75 for 28 days before Week 13 (*N ENgl J Med.* 2012;366:421-32). Ulipristal acetate was approved in Europe based on the results of the PEARL II study and is widely used as a standard therapeutic agent for uterine fibroids. The inclusion criteria and primary endpoints for menorrhagia were similar between Study CCT-002 and the PEARL II study. In the leuprorelin group in the PEARL II study, the percentage of patients with a total PBAC score of <75 for 28 days before Week 13 was 89.1% (82 of 92) of patients, and the percentage of patients with a total PBAC score of ≤2 for that period was 80.4% (74 of 92) of patients. As for the primary endpoint in Study CCT-001, the percentage of patients with a total PBAC score of <10 between Weeks 6 and 12 was 83.3% (45 of 54) of patients in the relugolix 40 mg group. These findings suggest that the effect size on menorrhagia was similar between leuprorelin and relugolix 40 mg, and the smallest effect size that leuprorelin would be reliably expected to have can be estimated to be 83.3% (two-sided 95% CI: [73.4%, 93.3%]).

Based on the above, it is considered appropriate that the non-inferiority margin in Study CCT-002 was set at

−15%, which was substantially lower than the smallest effect size that leuprorelin would be reliably expected to have and was lower than the non-inferiority margin (−20%) specified in the PEARL II study, a confirmatory study for a similar drug which is widely used as a standard therapeutic agent for uterine fibroids in Europe.

PMDA's view:
The PEARL II study and Study CCT-002 were both conducted in patients with uterine fibroids with a diagnosis of menorrhagia based on their PBAC scores and were designed to evaluate a total PBAC score for a specified period to confirm the non-inferiority to leuprorelin for the percentage of subjects with the total PBAC score lower than the prespecified cutoff value. The specified cutoff value for total PBAC scores for the primary endpoints differed between the studies but could serve as a threshold for the judgment of clinical improvement of menorrhagia, and the used endpoints were considered to be similar between the studies. In addition, at the time of planning of Study CCT-002, there were very limited clinical study data which could be used to determine a non-inferiority margin with leuprorelin as an active comparator. Given the above circumstance, PMDA considers the applicant's decision acceptable that the non-inferiority margin was determined with reference to the data on the efficacy in the leuprorelin group in the PEARL II study and data on the primary endpoints in the relugolix 40 mg group in Study CCT-001 because there seems no other choice. Based on the above, PMDA considers it appropriate that the non-inferiority margin was set at −15% to evaluate the non-inferiority of relugolix to leuprorelin in Study CCT-002.

7.R.1.1.2 Efficacy on menorrhagia associated with uterine fibroids

The applicant's explanation about the efficacy of relugolix on menorrhagia associated with uterine fibroids:
The percentage of patients with a total PBAC score of <10 between Weeks 6 and 12, the primary efficacy endpoint in Study CCT-002, is shown in Table 43, and the non-inferiority of relugolix 40 mg to leuprorelin has been demonstrated. The results of the primary endpoint in Study CCT-002 were evaluated according to patient characteristics (i.e., age, baseline total PBAC score, childbirth history, baseline uterine volume, baseline BMI, and uterine fibroid type), showing no marked differences across strata of each patient characteristic.

Based on the above, it was considered that the results of Study CCT-002 demonstrated the efficacy of relugolix 40 mg for menorrhagia associated with uterine fibroids.

PMDA's view:
The non-inferiority of relugolix 40 mg to leuprorelin has been demonstrated for the percentage of patients with a total PBAC score of <10 between Weeks 6 and 12 as the primary efficacy endpoint in Study CCT-002. Therefore, PMDA has concluded that the non-inferiority of the efficacy of relugolix 40 mg for menorrhagia associated with uterine fibroids to leuprorelin has been demonstrated.

7.R.1.2 Anemia

The applicant's explanation about the efficacy of relugolix for anemia:
Anemia in patients with uterine fibroids is induced by menorrhagia, and menstrual blood loss and increased

bleeding period lead to iron deficiency anemia (*Clinical Treatment of Uterine Fibroids*, first edition, Medical View Co., Ltd., 2008. p28-9). In clinical studies of leuprorelin, anemia was ameliorated with the resolution of menorrhagia (*Obstetrics and Gynecology* 1995;62:569-96; *Obstetrics and Gynecology* 1995;62:741-69). In Study CCT-001, which evaluated relugolix in patients with uterine fibroids and menorrhagia, anemia was ameliorated with the resolution of menorrhagia (Table 41). Based on the above, anemia was considered to be related to menorrhagia in uterine fibroids, and improvement in menorrhagia in patients with uterine fibroids would lead to improvement in relief of anemia. Study CCT-002 was thus designed to primarily evaluate the therapeutic effect of relugolix on menorrhagia causing anemia and to secondarily evaluate the therapeutic effect of relugolix on anemia by using blood Hb content as the secondary endpoint and blood hematocrit, serum iron, and serum ferritin as other endpoints. Changes from baseline in blood Hb contents in Study CCT-002 are summarized in Table 44 and were similar between the relugolix 40 mg and leuprorelin groups. Results on blood hematocrit, serum iron, and serum ferritin also supported those on blood Hb contents. Therefore, the applicant considers that the efficacy of relugolix for anemia has been demonstrated.

In Study CCT-002, no inclusion criteria were specified for anemia, and the use of iron preparations was permitted during the study period. PMDA therefore asked the applicant to provide results on endpoints related to anemia (blood Hb content, blood hematocrit, serum iron, and serum ferritin) with and without the use of iron preparations during the study period in patients having anemia at the time of enrollment and, based on the results, to discuss the efficacy of relugolix for anemia.

The applicant's response:

In Study CCT-002, the percentage of patients with anemia (blood Hb content <12.0 g/dL) at baseline was 59.3% (166 of 280) of patients. Table 48 shows the results for endpoints related to anemia at Weeks 12 and 24 in these patients with and without the use of iron preparations. Blood Hb content increased after administration of relugolix or leuprorelin, regardless of the use of iron preparations, and the results on blood hematocrit, serum iron, and serum ferritin also supported those on blood Hb contents. Based on these data, the applicant considers that the efficacy of relugolix for anemia has been demonstrated.

Table 48. Changes in anemia-related parameters in patients with blood Hb content of <12 g/dL (Study CCT-002: FAS)

	With iron treatment		Without iron treatment	
	Relugolix 40 mg	Leuprorelin	Relugolix 40 mg	Leuprorelin
Blood Hb content (g/dL)				
Baseline [a]	10.58 ± 1.287 (26)	10.69 ± 0.974 (24)	10.64 ± 0.862 (56)	10.71 ± 0.887 (60)
Week 12	13.16 ± 1.199 (25)	13.09 ± 1.217 (23)	12.08 ± 0.943 (53)	12.18 ± 0.906 (60)
Changes from baseline	2.47 ± 1.195	2.37 ± 1.165	1.48 ± 0.922	1.47 ± 0.699
Week 24	13.26 ± 1.175 (22)	13.20 ± 1.058 (22)	12.59 ± 0.829 (50)	12.77 ± 0.860 (56)
Changes from baseline	2.54 ± 1.308	2.46 ± 1.004	1.97 ± 1.087	2.05 ± 0.937
Blood hematocrit (%)				
Baseline [a]	32.64 ± 3.762 (26)	32.99 ± 2.858 (24)	32.55 ± 2.233 (56)	32.70 ± 2.307 (60)
Week 12	39.16 ± 3.047 (25)	38.88 ± 3.542 (23)	36.55 ± 2.473 (53)	36.74 ± 2.357 (60)
Week 24	39.27 ± 2.779 (22)	38.60 ± 3.068 (22)	37.49 ± 2.246 (50)	37.73 ± 2.490 (56)
Serum iron (μg/dL)				
Baseline [a]	61.8 ± 44.86 (26)	52.1 ± 49.01 (24)	33.3 ± 18.83 (56)	38.3 ± 25.41 (60)

Week 12	95.0 ± 53.23 (24)	92.5 ± 49.66 (22)	64.2 ± 36.59 (53)	67.2 ± 32.08 (60)
Week 24	93.3 ± 54.21 (22)	93.7 ± 33.41 (22)	69.9 ± 36.77 (50)	81.6 ± 35.73 (55)
Serum ferritin (ng/mL)				
Baseline [a]	22.64 ± 12.787 (26)	19.62 ± 9.979 (24)	8.63 ± 14.612 (56)	8.97 ± 6.848 (60)
Week 12	35.00 ± 26.392 (25)	32.60 ± 19.901 (23)	10.41 ± 7.599 (53)	13.67 ± 11.001 (60)
Week 24	36.49 ± 31.125 (22)	43.50 ± 33.008 (22)	15.22 ± 14.908 (50)	17.81 ± 11.814 (56)

Mean ± standard deviation (n)
a: At Visit 3

PMDA's view:

The applicant considered that anemia in patients with uterine fibroids was caused by menorrhagia, and therefore assessed anemia-related endpoints in clinical studies conducted to evaluate the efficacy of relugolix for menorrhagia. In this way, the applicant evaluated the efficacy of relugolix for anemia associated with uterine fibroids. This applicant's approach for evaluation of efficacy for anemia is considered appropriate because, in clinical practice, patients diagnosed with menorrhagia often also have anemia (Glossary of Obstetrics and Gynecology, 4th edition, edited by the Japan Society of Obstetrics and Gynecology). As a result of the approach, a certain number of patients with uterine fibroids accompanied by anemia were enrolled in Study CCT-002, and PMDA considers that this situation made it possible to evaluate the efficacy of relugolix for anemia on the basis of results of Study CCT-002. PMDA has concluded that the efficacy of relugolix for anemia associated with uterine fibroids has been demonstrated by the following findings in Study CCT-002:

(1) In addition to reduction of menorrhagia, increases from baseline in blood Hb content, an anemia index, were observed.
(2) The changes in blood hematocrit, serum iron, serum ferritin supported the results of blood Hb content.
(3) Improvement in anemia-related endpoints was observed in the subgroup of patients with anemia (blood Hb content <12.0 g/dL) at baseline, regardless of the use of iron preparations during relugolix therapy.

7.R.1.3 Lower abdominal pain and lumbar pain associated with uterine fibroids

7.R.1.3.1 Design of the Japanese phase III study (Study 3008)

7.R.1.3.1.1 Control

In Japan, drugs approved for relief of lower abdominal pain and lumbar pain associated with uterine fibroids are available and used in clinical practice. PMDA asked the applicant to explain the reason why placebo was used as a control in Study 3008 in such a circumstance.

The applicant's explanation:

There were drugs already approved for relief of lower abdominal pain and lumbar pain associated with uterine fibroids. However, none of the drugs had been evaluated in a clinical study for the efficacy for pain with the parameter used in Study 3008 (NRS score) in the population eligible for Study 3008. Accordingly, Study 3008 was not designed to evaluate the non-inferiority of relugolix to approved drugs, and placebo was chosen as a control to evaluate the efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids.

PMDA's view:

Drugs with an indication for the relief of lower abdominal pain and lumbar pain associated with uterine fibroids were approved in the 1990s, and the endpoint (overall improvement) used in clinical studies conducted at that time is not in use currently as an endpoint for evaluation of pain under the current scientific level. Currently, the NRS score has been established as the endpoint for pain. However, at the time of planning of Study 3008, there were no clinical studies in which the NRS scores of the approved drugs were compared with those of placebo in the patient population used in Study 3008. Given the above-mentioned circumstances, PMDA thinks that there was no choice other than using placebo as a control in Study 3008, and PMDA considers it appropriate that the efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids was determined by the evaluation of superiority of relugolix over placebo.

7.R.1.3.1.2 Appropriateness of primary endpoint

The applicant's explanation about the rationale and appropriateness of the primary endpoint of Study 3008:

The primary endpoint of Study 3008 was the "percentage of patients with a maximum NRS score of ≤1 during the 28 days before the final dose of the study drug." Since lower abdominal pain and lumbar pain associated with uterine fibroids were observed in both menstrual and non-menstrual periods, a 28-day period, which is the average menstrual duration in Japanese women, was chosen for the evaluation to include both menstrual and non-menstrual periods. Pain symptoms associated with uterine fibroids are known to significantly affect the quality of life (QOL) of patients (*Clinical Manual for Treatment of Uterine Myoma, Endometriosis, and Adenomyosis Uteri, Diagnosis and Treatment*. 2013; *Curr Med Res Opin.* 2017;33:1971-8), and relugolix was developed as a drug to eliminate pains associated with uterine fibroids. Therefore, the applicant decided not to evaluate the extent of reduction in pain symptoms in individual subjects by using the "changes or percent change" in the maximum NRS scores, but to evaluate the percentage of patients achieving disappearance of pain symptoms, which is the goal of pain treatment with relugolix, by using the maximum NRS score as an endpoint. Of note, however, treatment with relugolix is not intended to radically treat uterine fibroids, and uterine fibroid itself continues to exist after treatment with relugolix. In such a situation, even very mild strange sensation might have been regarded as pain due to a uterine fibroid. In light of them, it was considered appropriate to evaluate the percentage of patients with a maximum NRS score of ≤1, not the percentage of patients achieving the maximum NRS score of 0. With regard to the clinical significance of improvement of pain scores, it has been reported that improvement in pain from baseline by 10% to 20%, ≥30%, and ≥50% can be regarded as minimally important changes, moderate clinically important differences, substantial improvements, respectively, based on investigation of a relationship between the changes in pain scales (e.g., NRS scores) and changes in QOL scores in clinical studies (*J Pain.* 2008;9:105-21). Since Study 3008 enrolled patients with moderate or severe pain symptoms requiring pharmacotherapies (a maximum NRS score of ≥4 for the last menstrual cycle before Visit 3), improvement to the maximum NRS score of ≤1 is considered to represent a clinically significant change in these patients.

PMDA's view:

It was appropriate that the study was designed to evaluate pain during a period with an average menstrual cycle in consideration that lower abdominal pain and lumbar pain associated with uterine fibroids can occur in both

menstrual and non-menstrual periods. Also, it was appropriate that relugolix was intended to be developed as a drug to eliminate pains associated with uterine fibroids and that the percentage of patients achieving the maximum NRS score consistent with the disappearance of pain was to be evaluated. Based on the applicant's explanation about the extent of improvement in NRS scores, it could be considered that clinically significant improvement in pain was achieved, regardless of menstrual or non-menstrual status, when the maximum NRS score for 28 days was ≤1. Based on these findings, PMDA has concluded that it was appropriate that the percentage of patients achieving the maximum NRS score of ≤1 for 28 days before the last dose of the study drug was evaluated as the primary endpoint in Study 3008.

7.R.1.3.2 Efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids

The applicant's explanation about the efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids:

The results of the primary endpoint in Study 3008 are shown in Table 46, and the superiority of relugolix over placebo for reduction of pain has been demonstrated. The percentage of patients with a maximum NRS score of ≤1 for individual evaluation periods between Day 1 and Day 28, Day 29 and Day 56, and Day 57 and Day 84 was 24.2% (8 of 33) of patients, 45.5% (15 of 33) of patients, and 59.4% (19 of 32) of patients, respectively, in the relugolix 40 mg group and 0% (0 of 32) of patients, 12.9% (4 of 31) of patients, and 12.9% (4 of 31) of patients, respectively, in the placebo group. The percentage of patients with a maximum NRS score of ≤1 was higher in the relugolix 40 mg group than in the placebo group in all the evaluation periods and increased in a duration-dependent manner in the relugolix 40 mg group. These results demonstrated the efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids.

PMDA's view:

Achieving the maximum NRS score of ≤1 is clinically significant in patients with uterine fibroids accompanied by pain symptoms enrolled in Study 3008 [see Section 7.R.1.3.1.2], and the superiority of relugolix over placebo has been demonstrated for the primary endpoint "the percentage of patients with a maximum NRS score of ≤1 during 28 days before the final dose of the study drug" in Study 3008. Based on the above findings, PMDA has concluded that the efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids has been demonstrated.

7.R.2 Safety

7.R.2.1 Adverse events occurring in Studies CCT-001, CCT-002, and 3008

The applicant's explanation about adverse events occurring in Studies CCT-001, CCT-002, and 3008:

In Study CCT-001, the incidence of adverse events was 70.2% (40 of 57) of patients in the placebo group, 85.4% (41 of 48) of patients in the relugolix 10 mg group, 96.4% (53 of 55) of patients in the relugolix 20 mg group, and 88.9% (48 of 54) of patients in the relugolix 40 mg group. Adverse events with an incidence of ≥5% in any group are shown in Table 42. With regard to the severity of the adverse events, a severe adverse event occurred in 1 patient in the relugolix 40 mg group (VIIth nerve palsy) but was assessed as unrelated to the study drug, and other adverse events were mild or moderate. Serious adverse events occurred in 3 patients and

were all assessed as unrelated to the study drug.

In Study CCT-002, the incidence of adverse events was 94.9% (131 of 138) of patients in the relugolix 40 mg group and 97.9% (139 of 142) of patients in the leuprorelin group. Adverse events with an incidence of ≥5% in either group are shown in Table 45. With regard to the severity of the adverse events, severe adverse events occurred in 2 patients in the relugolix 40 mg group (musculoskeletal stiffness in 1 patient and depression in 1 patient) and 1 patient in the leuprorelin group (ulna fracture), and other adverse events were mild or moderate. Serious adverse events occurred in 2 patients in the leuprorelin group and were all assessed as unrelated to the study drug.

In Study 3008, the incidence of adverse events was 87.9% (29 of 33) of patients in the relugolix 40 mg group and 56.3% (18 of 32) of patients in the placebo group. Adverse events with an incidence of ≥5% in either group are shown in Table 47. With regard to the severity of the adverse events, severe adverse events occurred in 1 patient in the relugolix 40 mg group (insomnia, depression, and hot flush), and other adverse events were mild or moderate. No serious adverse events occurred.

As shown the above, major adverse events observed in Studies CCT-001, CCT-002, and 3008 were adverse events associated with uterine hemorrhage, those associated with decreased bone density, those associated with climacteric-like symptoms, and those associated with hepatic dysfunction. Further, the pharmacological action and the nonclinical study results of relugolix suggest that attention should be paid also to effects on QTc interval, ovarian function, and metabolism and the cardiovascular system. These effects are discussed in detail in the sections below, based on the results of a pooled analysis of 4 studies: Studies CCT-001, CCT-002, and 3008 and a Japanese clinical study (Study OCT-101) conducted in patients with endometriosis, a benign sex hormone-dependent disease as uterine fibroids, who had similar patient characteristics to those in patients with uterine fibroids. Among other adverse events, serious or severe ones were assessed as unrelated to the study drug, and the remaining adverse events were mild or moderate in severity. In light of these findings, treatment with relugolix is not associated with adverse events requiring special attention.

PMDA's view:
In Studies CCT-001 and 3008 with a placebo-controlled design, adverse events associated with uterine hemorrhage, decreased bone density, climacteric-like symptoms, or hepatic dysfunction, occurred more frequently in the relugolix group than in the placebo group. These adverse events are discussed in detail in the sections below [see Sections 7.R.2.2, 7.R.2.3, 7.R.2.4, and 7.R.2.5]. In light of the applicant's explanation, it is considered reasonable that the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101 was used to investigate these adverse events. Among adverse events other than the above, nausea occurred more frequently in the relugolix 40 mg group than in the placebo group but was mild in severity in all cases, and the adverse event nausea is thus considered to be manageable in the clinical use of relugolix. Major adverse events observed in the relugolix and placebo groups in Study CCT-002 were adverse events associated with uterine hemorrhage, decreased bone density, climacteric-like symptoms, or hepatic dysfunction. Among other adverse

events, viral upper respiratory tract inflammation occurred frequently in the relugolix 40 mg group (39 of 138 patients, 28.3%) and the leuprorelin group (46 of 142 patients, 32.4%), but was assessed as unrelated to the study drug in all of the cases, and viral upper respiratory tract inflammation is not considered to be a specific adverse event requiring caution in the use of relugolix.

As shown above, among adverse events occurring in Studies CCT-001, CCT-002, or 3008, there were no events requiring special caution for treatment with relugolix, except for adverse events discussed in detail in the sections below. PMDA has thus concluded that the adverse events observed in Studies CCT-001, CCT-002, or 3008 will raise no significant safety issues, except for the events discussed below.

7.R.2.2 Uterine hemorrhage

The applicant's explanation about adverse events associated with uterine hemorrhage with the use of relugolix: Uterine hemorrhage is caused by endometrial deciduation, inhibition of endometrial growth, and atrophic endometrial changes in association with inhibition of estrogen and progesterone secretion (*Japanese Journal of Clinical Medicine.* 2009;67:116-9; *Standard Obstetrics and Gynecology.* 4th Edition. Igaku-Shoin Ltd. 2011. p62-5). In light of the pharmacological action of relugolix, adverse events associated with uterine hemorrhage occurring with the use of relugolix is attributable to the above mechanism of action. As shown in Table 49, the incidence of adverse events associated with uterine hemorrhage[3)] in the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101 was higher in the relugolix group than in the placebo group but was lower in the relugolix group than in the leuprorelin group. In addition, the majority of the adverse events were mild in severity, and no severe adverse events were reported. In the relugolix 10 and 20 mg groups and the placebo group, the incidence of adverse events associated with uterine hemorrhage was highest after Day 29 (48.3% [73 of 151 patients] in the relugolix 10 mg; 44.7% [68 of 152 patients] in the relugolix 20 mg; 19.6% [36 of 184 patients] in the placebo group). In the relugolix 40 mg and leuprorelin groups, the incidence was highest between Days 1 and 14 (40.9% [134 of 328 patients] in the relugolix 40 mg group; 44.6% [99 of 222 patients] in the leuprorelin group). The occurrence of adverse events associated with uterine hemorrhage was examined for each uterine fibroid site, which showed no consistent tendency for the affected sites. Based on the above, uterine hemorrhage occurring with the use of relugolix is considered to be clinically tolerable.

Table 49. Adverse events related to uterine hemorrhage (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	54.3 (82)	70.3 (109)	57.6 (189)	75.2 (167)	22.6 (42)
Metrorrhagia	27.2 (41)	34.2 (53)	38.4 (126)	56.3 (125)	11.3 (21)
Menorrhagia	11.3 (17)	18.7 (29)	19.8 (65)	14.0 (31)	6.5 (12)
Genital haemorrhage	3.3 (5)	7.1 (11)	6.7 (22)	6.8 (15)	2.2 (4)
Menstruation irregular	21.9 (33)	18.7 (29)	3.4 (11)	4.5 (10)	4.3 (8)
Oligomenorrhoea	9.9 (15)	10.3 (16)	1.2 (4)	0.0 (0)	1.1 (2)
Polymenorrhoea	0.0 (0)	0.6 (1)	0.3 (1)	1.8 (4)	1.6 (3)
Menometrorrhagia	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.5 (1)

3) MedDRA PTs "Bleeding anovulatory," "Menometrorrhagia," "Menorrhagia," "Menstrual disorder," "Menstruation irregular," "Oligomenorrhoea," "Polymenorrhoea," "Vaginal haemorrhage," "Genital haemorrhage," and "Metrorrhagia."

Menstrual disorder	0.7 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)
Bleeding anovulatory	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)	0.0 (0)

% (n)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

The pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101 showed that menorrhagia, as an adverse event, occurred more frequently in the relugolix group than in the leuprorelin group. PMDA asked the applicant to discuss the possibility that this finding may indicate worsening of menorrhagia associated with uterine fibroids, based on data obtained from clinical studies conducted in patients with uterine fibroids.

The applicant's explanation:

Among cases of the adverse event of menorrhagia (PT) occurring in individual studies, the event was diagnosed as menostaxis (LLT) in 34 of 35 patients in Study CCT-001, 47 of 56 patients in Study CCT-002, 6 of 7 patients in Study 3008, and 54 of 56 patients in Study OCT-101. In Studies CCT-001 and CCT-002, which enrolled patients with a total PBAC score of ≥120 for a menstrual cycle, almost all patients receiving relugolix 40 mg had a total PBAC score of <100 (equivalent to menstrual blood loss of 80 mL) during the adverse event; this blood loss volume was lower than the diagnostic threshold for menorrhagia. A total of 13 patients had a PBAC score of ≥100 during the adverse event (3 patients in Study CCT-001 and 10 patients in Study CCT-002). However, the total PBAC score during the adverse event was higher than the baseline score only in 3 of the 13 patients. In 2 of the 3 patients, the adverse event developed on Day 1 of relugolix treatment and persisted for more than 30 days. In all but one of the 13 patients, the event was diagnosed as menostaxis and mild in severity and resolved during relugolix therapy. In Study 3008, since the PBAC scores were not evaluated, the blood loss during the adverse event was undetermined in patients experiencing menorrhagia; in all of these patients, however, the observed adverse events of menorrhagia were mild and resolved during relugolix therapy. Based on the above, none of the events of menorrhagia developing after treatment with relugolix suggest a worsening of menorrhagia associated with uterine fibroids.

PMDA's view:

In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with uterine hemorrhage other than menorrhagia did not markedly differ between the relugolix 40 mg group and the leuprorelin group, and most of the observed events were mild in severity. In clinical practice in Japan, leuprorelin is used for various symptoms associated with uterine fibroids. Study CCT-002 demonstrated the non-inferiority of relugolix to leuprorelin. In light of the above findings, PMDA has concluded that adverse events of uterine hemorrhage other than menorrhagia are clinically tolerable. According to the applicant's explanation about menorrhagia, most of the adverse events occurring during the treatment with relugolix were menostaxis, which means a prolonged bleeding period, and there were almost no patients having greater blood loss than that before the administration of relugolix. Menorrhagia also resolved during relugolix therapy even in patients whose total PBAC score during the adverse event was higher than baseline total PBAC score. In light of these findings, PMDA has concluded that menorrhagia is not a significant issue in the clinical use of relugolix. Based on the above, PMDA has concluded that adverse events associated with uterine hemorrhage occur with a high incidence but are manageable in the clinical use of relugolix.

7.R.2.3 Effects of relugolix on bone

The applicant's explanation about the effects of relugolix on bone:

Effects on bone are observed with GnRH agonists having the estrogen-lowering effects, as with relugolix, and relugolix is expected to have effects on bone based on its pharmacological action. Bone density was measured in Studies CCT-002 and OCT-101, and the results are shown in Tables 50 and 51. The absolute percent change from baseline in bone density increased with the increase in the relugolix dose and was similar between the relugolix 40 mg group and the leuprorelin group. The absolute percent change from baseline in bone density increased over time and was higher at Week 24 than at Week 12 within each relugolix group and the leuprorelin group.

Table 50. Percent change in bone density in Study CCT-002 (safety analysis set)

	Relugolix 40 mg	Leuprorelin
Baseline (g/cm^2)	1.0800 ± 0.15038 (138)	1.0854 ± 0.14730 (142)
Week 12 (g/cm^2)	1.0627 ± 0.15106 (138)	1.0629 ± 0.14810 (141)
Percent changes from baseline (%)	−1.62 ± 2.314	−2.12 ± 2.374
Week 24 (g/cm^2)	1.0385 ± 0.14859 (124)	1.0368 ± 0.13934 (133)
Percent changes from baseline (%)	−4.24 ± 3.011	−4.28 ± 2.923

Mean ± standard deviation (n)

Table 51. Percent change in bone density in Study OCT-101 (safety analysis set)

	Relugolix 10 mg	Relugolix 20 mg	Relugolix 40 mg	Leuprorelin	Placebo
Baseline (g/cm^2)	1.0459 ± 0.12503 (103)	1.0257 ± 0.13670 (100)	1.0593 ± 0.14940 (103)	1.0593 ± 0.14556 (80)	1.0519 ± 0.14157 (97)
Week 12 (g/cm^2)	1.0364 ± 0.12955 (103)	1.0147 ± 0.13105 (95)	1.0366 ± 0.14413 (103)	1.0372 ± 0.14549 (79)	1.0490 ± 0.13912 (93)
Percent changes from baseline (%)	−0.95 ± 1.875	−1.34 ± 2.087	−2.10 ± 2.218	−2.16 ± 1.671	−0.07 ± 1.727
Week 24 (g/cm^2)	1.0305 ± 0.12859 (81)	0.9977 ± 0.12752 (77)	0.9979 ± 0.14045 (88)	1.0091 ± 0.14771 (64)	1.0483 ± 0.13204 (75)
Percent changes from baseline (%)	−1.61 ± 2.338	−2.58 ± 2.936	−4.90 ± 2.912	−4.43 ± 2.157	−0.23 ± 1.986

Mean ± standard deviation (n)

The incidence of adverse events associated with decreased bone density[4)] in the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101 is shown in Table 52, and no marked difference was observed in the incidence between the relugolix 40 mg group and the leuprorelin group. In addition, all adverse events were mild in severity, except for an adverse event observed in a patient in the leuprorelin group (moderate bone density decreased). In addition, all events resolved or were resolving after the completion of study treatment, except for those occurring in a patient in the relugolix 20 mg group (bone density decreased) and 4 patients in the leuprorelin group (bone density decreased in 2 patients and bone resorption test abnormal in 2 patients).

In light of the risk of decreased bone density shown in the above clinical studies, the duration of treatment with relugolix is determined to be up to 6 months in principle. When relugolix is used for a period of <6 months (which is the duration confirmed in clinical studies), the risk of the development of clinically significant bone

[4)] MedDRA SMQ "Osteoporosis/osteopenia" broad search.

density decreased during the treatment period is small and bone density is expected to be restored to the baseline after the completion of treatment. Accordingly, the effects of relugolix on bone is considered to be clinically tolerable.

Table 52. Adverse events related to decreased bone density (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	0.7 (1)	1.9 (3)	8.5 (28)	11.7 (26)	0.5 (1)
Bone density decreased	0.7 (1)	1.9 (3)	4.0 (13)	5.4 (12)	0.5 (1)
Bone resorption test abnormal	0 (0)	0 (0)	2.4 (8)	3.2 (7)	0 (0)
Resorption bone increased	0 (0)	0 (0)	2.1 (7)	3.6 (8)	0 (0)

% (n)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

PMDA's view:

Relugolix has been developed with a concept of a drug that exerts its efficacy by decreasing serum E_2 levels to the menopausal level as leuprorelin does. It can be easily anticipated that bone density decreases when the serum E_2 level is reduced to the menopausal level. Actually, in Studies CCT-002 and OCT-101, bone density decreased after treatment with relugolix, and the degree of decreased bone density became greater as the duration of relugolix treatment became longer. The degree of decreased bone density at Week 24 was similar between the relugolix 40 mg group and the leuprorelin group in clinical studies in which the study drug was administered for 24 weeks (Studies CCT-002 and OCT-101), and the incidence of adverse events associated with decreased bone density was also similar between the relugolix 40 mg group and the leuprorelin group in the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101. Time to recovery of serum E_2 levels after completion of treatment in the relugolix group did not tend to be longer than that in the leuprorelin group [see Section 6.2.3.2]. Given these findings, PMDA has concluded that the effects of relugolix on the bone is clinically tolerable when relugolix is administered for 6 months or less, in principle, which is the same treatment period for leuprorelin.

7.R.2.4 Climacteric-like symptoms including depression

The applicant's explanation about the occurrence of climacteric-like symptoms with the use of relugolix:

Climacteric-like symptoms occur with the use of GnRH agonists having estrogen-lowering effects, as with relugolix, and are expected to occur based on the pharmacological action of relugolix. In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with climacteric-like symptoms[5)] was 25.2% (38 of 151) of patients in the relugolix 10 mg group, 45.2% (70 of 155)

[5)] MedDRA PTs "Alopecia," "Alopecia areata," "Anxiety," "Apathy," "Arthralgia," "Atrophic vulvovaginitis," "Autonomic nervous system imbalance," "Breast pain," "Breast swelling," "Depressed mood," "Depression," "Disturbance in attention," "Dizziness," "Dizziness postural," "Dysphoria," "Fatigue," "Feeling abnormal," "Feeling cold," "Feeling hot," "Feeling jittery," "Head discomfort," "Headache," "Hyperhidrosis," "Increased appetite," "Initial insomnia," "Insomnia," "Irritability," "Joint stiffness," "Libido decreased," "Listless," "Malaise," "Menopausal symptoms," "Mental impairment," "Middle insomnia," "Migraine," "Muscular weakness," "Musculoskeletal pain," "Myalgia," "Night sweats," "Oedema," "Oedema peripheral," "Oestrogen deficiency," "Pain in extremity," "Palpitations," "Paraesthesia," "Sleep disorder," "Somnolence," "Vertigo," "Vision blurred," "Weight decreased," "Weight increased," "Premenstrual dysphoric disorder," "Musculoskeletal stiffness," "Affect lability," "Anxiety disorder," "Hot flush," "Decreased appetite,"

of patients in the relugolix 20 mg group, 61.3% (201 of 328) of patients in the relugolix 40 mg group, 67.6% (150 of 222) of patients in the leuprorelin group, and 23.7% (44 of 186) of patients in the placebo group. Adverse events associated with climacteric-like symptoms occurring with an incidence of ≥5% in any group are shown in Table 53; these adverse events occurred more frequently in the relugolix 20 mg group, the relugolix 40 mg group, and the leuprorelin group than in the placebo group, but no marked difference in the incidence was observed between the relugolix 40 mg group and the leuprorelin group. Among adverse events associated with climacteric-like symptoms, the incidence of adverse events associated with depression[6)] is shown in Table 54, showing no marked difference among the groups.

Table 53. Adverse events related to climacteric-like symptoms with an incidence of ≥5% in any group (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Hot flush	9.3 (14)	25.2 (39)	45.7 (150)	50.5 (112)	5.4 (10)
Headache	4.0 (6)	12.9 (20)	11.9 (39)	11.3 (25)	7.0 (13)
Hyperhidrosis	3.3 (5)	9.0 (14)	9.1 (30)	11.3 (25)	1.1 (2)
Arthralgia	1.3 (2)	2.6 (4)	5.5 (18)	5.4 (12)	2.7 (5)
Malaise	2.0 (3)	1.9 (3)	4.6 (15)	3.2 (7)	5.4 (10)
Dizziness	1.3 (2)	0.6 (1)	4.3 (14)	6.3 (14)	2.7 (5)

% (n)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

Table 54. Adverse events related to depression (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	0.7 (1)	1.3 (2)	2.4 (8)	1.8 (4)	1.1 (2)
Depressed mood	0 (0)	0 (0)	0.9 (3)	0 (0)	0 (0)
Depression	0.7 (1)	0.6 (1)	0.6 (2)	0.5 (1)	1.1 (2)
Listless	0 (0)	0 (0)	0.3 (1)	0.9 (2)	0 (0)
Initial insomnia	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Middle insomnia	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Menopausal depression	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)
Apathy	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)

% (n)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

While most of the adverse events associated with climacteric-like symptoms were mild in severity, severe or moderate adverse events occurred: severe adverse events of depression in 2 patients, musculoskeletal stiffness in 1 patient, insomnia in 1 patient, and hot flush in 1 patient (all in the relugolix 40 mg group) and moderate adverse events of headache in 3 patients (1 patient in the relugolix 20 mg group and 2 patients in the relugolix 40 mg group), oedema peripheral in 1 patient (the relugolix 40 mg group), and hot flush in 1 patient (the relugolix 40 mg group). Among patients with severe adverse events, the patient experiencing depression discontinued relugolix but recovered without receiving pharmacotherapy; this suggests that the event fell within the range of mood fluctuations observed in general menopausal symptoms. Depression was reported in

and "Menopausal depression."
6) MedDRA SMQs "Depression (excl suicide and self injury)" broad search and "Suicide/self-injury" narrow search.

another patient, who concurrently presented with severe insomnia and hot flush. In the patient, hot flush resolved after discontinuation of relugolix, and insomnia resolved with pharmacotherapy. However, depression persisted, and pharmacotherapy was started for depression more than 4 months after the relugolix treatment; this suggests that the event was related to the subject's underlying disease or condition. In the case of musculoskeletal stiffness, the patient presented with fingers stiffness and recovered from the event during study treatment. A causal relationship to the study drug could not be ruled out for all moderate or severe adverse events, except for moderate headache in a patient.

Among adverse events associated with climacteric-like symptoms, the time of onset of headache, hyperhidrosis, and hot flush (Days 1 to 28, Days 29 to 56, Days 57 to 84, Days 85 to 112, and Day 113 or later) was examined on the basis of data from Study CCT-002, which used leuprorelin as an active comparator. The results showed that headache tended to occur earlier in the relugolix 40 mg group than in the leuprorelin group, but the time of onset of hyperhidrosis or hot flush did not clearly differ between the relugolix 40 mg group and the leuprorelin group. No clear tendency was observed also for the time of onset of adverse events associated with depression.

As discussed above, the incidence, severity, and time of onset of adverse events associated with climacteric-like symptoms including depression with the use of relugolix were similar to those observed with the use of leuprorelin and are not considered to represent any clinically significant issues.

PMDA's view:
In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with climacteric-like symptoms increased in proportion to the dose of relugolix in the relugolix groups but was similar between the relugolix 40 mg group and the leuprorelin group. Furthermore, most of the observed adverse events were mild in severity and resolved after discontinuation of the study drug or during treatment with the study drug. Based on these findings, PMDA has concluded that the risk of development of climacteric-like symptoms with the use of relugolix 40 mg is similar to that observed with the use of leuprorelin. Among adverse events associated with climacteric-like symptoms, a depressed state is an event that may result in a medically significant outcome, and the incidence of a depressed state was not high but similar between the relugolix 40 mg group and the leuprorelin group. In addition, there was severe depression for which a causal relationship to relugolix could not be ruled out. Based on the above findings, a depressed state is considered to be an event requiring caution and close monitoring of patient conditions with the use of relugolix, as with other approved GnRH agonists including leuprorelin. In patients receiving relugolix, climacteric-like symptoms tended to occur at the same or earlier time than in those receiving leuprorelin. Serum E_2 levels in patients receiving relugolix tended to decrease faster (i.e., decreased to the menopausal level by Week 2 of treatment) than in patients receiving leuprorelin [see Section 6.2.3.2]. This difference in the profile of action may have contributed to the modest difference in time to onset of climacteric-like symptoms between the relugolix and leuprorelin groups. Particularly, the time of onset of depressed state is clinically important information, but the investigation of currently available data is limited. Therefore, PMDA has concluded that post-marketing

information should be collected on the occurrence of climacteric-like symptoms including depressed state (e.g., information on the time of onset). New information should be communicated appropriately to healthcare professionals when it becomes available.

7.R.2.5 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction with the use of relugolix:

Hepatic dysfunction with the use of relugolix was investigated because hepatotoxicity was observed in non-clinical studies and because precautionary statements for hepatic dysfunction are included in the package inserts of approved GnRH agonists. As shown in Table 55, in the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with hepatic dysfunction[7)] was higher in the relugolix 40 mg group and leuprorelin group, but no marked difference in the incidence was observed between the relugolix 40 mg group and the leuprorelin group. Adverse events associated with hepatic dysfunction led to treatment discontinuation in 3 patients in the relugolix group and in 2 patients in the leuprorelin group. Among patients experiencing the adverse events, a causal relationship to the study drug could not be ruled out in a patient in the relugolix 40 mg group (ALT increased) in Study OCT-101 and in a patient in the relugolix 40 mg group (liver function test increased). However, these events were non-serious and resolved after discontinuation of relugolix treatment. The event of liver function test increased in a patient receiving relugolix 20 mg in Study OCT-101 was serious and its causal relationship to the study drug could not be ruled out. However, the patient was using drugs known to cause hepatic dysfunction (celecoxib and acetaminophen) concomitantly, and her hepatic function test data returned to the baseline after discontinuation of relugolix and the concomitant drugs. The concomitant drugs might have contributed to the event of liver function test increased.

As shown above, the incidence of adverse events associated with hepatic dysfunction was similar between the relugolix 40 mg group and the leuprorelin group. However, most of the adverse events in the relugolix 40 mg group were mild in severity, and there were no serious adverse events associated with hepatic dysfunction strongly suggesting a causal relationship to relugolix. Therefore, the effects of relugolix on hepatic function are considered to be clinically tolerable.

[7)] MedDRA SMQ "Drug related hepatic disorders" broad search

Table 55. Adverse events related to hepatic dysfunction (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	1.3 (2)	3.9 (6)	10.4 (34)	11.3 (25)	2.2 (4)
ALT increased	0 (0)	0.6 (1)	3.4 (11)	2.3 (5)	0.5 (1)
γ-GTP increase	0 (0)	1.3 (2)	2.7 (9)	5.0 (11)	1.1 (2)
Liver function test increased	0 (0)	2.6 (4)	2.1 (7)	1.4 (3)	0 (0)
Blood ALP increased	0 (0)	0 (0)	1.8 (6)	1.8 (4)	0.5 (1)
Hepatic function abnormal	0 (0)	0.6 (1)	1.5 (5)	0.9 (2)	0 (0)
AST increased	0.7 (1)	0 (0)	1.5 (5)	1.8 (4)	1.1 (2)
Blood bilirubin increased	0 (0)	0 (0)	0.9 (3)	0.9 (2)	0 (0)
Hepatic steatosis	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Hepatic enzyme increased	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Liver function test abnormal	0.7 (1)	0 (0)	0 (0)	0.5 (1)	0 (0)
Total bile acids increased	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)

n (%)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

PMDA's view:

In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with hepatic dysfunction tended to increase in proportion to the relugolix dose, and the incidence and the severity of these adverse events in the relugolix 40 mg group were similar to those observed in the leuprorelin group. These findings warrant cautions for the occurrence of hepatic dysfunction with the use of relugolix, as with leuprorelin. The applicant stated that concomitant drugs might have contributed to the development of serious event of liver function test increased (AST and ALT increased), but the investigator assessed that a causal relationship between the event and relugolix could not be ruled out. PMDA thus has concluded that precautionary statements should be included in the package insert, stating that hepatic dysfunction, even serious ones, may develop with the use of relugolix, as with leuprorelin.

7.R.2.6 Effects of relugolix on QTc intervals

The applicant's explanation about the effects of relugolix on QTc intervals:

Since inhibition of the hERG current and prolonged QT and QTc intervals were observed in the safety pharmacology studies of relugolix [see Section 3.3], the effects of relugolix on QTc intervals were examined. A thorough QT study was conducted in healthy adults (Study 106). No prolonged QT intervals were observed in association with the use of relugolix after single dosing of relugolix at 60 and 360 mg [see Section 6.2.7], and no electrocardiographic adverse events occurred. In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, as shown in Table 56, no marked difference in the incidence of adverse events associated with prolonged QTc intervals[8)] was observed among the groups. In the relugolix groups, syncope (in 1 patient in the relugolix 20 mg group) and electrocardiogram QT prolonged (in 1 patient in the relugolix 40 mg group) were reported but were both mild in severity. Although a causal relationship to the study drug could not be ruled out for the event of electrocardiogram QT prolonged, the event occurred after completion of the relugolix treatment (on the day of the final dose of relugolix), and the outcome of the event was reported as resolved.

8) MedDRA SMQ "Torsade de pointes/QT prolongation" broad search.

Based on the above, the effects of relugolix on QTc intervals are considered to be unlikely to be clinically significant.

Table 56. Incidence of adverse events related to prolonged QTc interval (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	0 (0)	0.6 (1)	0.3 (1)	0 (0)	0 (0)
Electrocardiogram QT prolonged	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Syncope	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)

% (n)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

PMDA's view:

No adverse events associated with prolonged QT interval or electrocardiography occurred with the use of relugolix in Study 106. In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, the incidence of adverse events associated with prolonged QTc intervals did not markedly differ among the groups. There were no specific adverse events associated with prolonged electrocardiogram QT that tended to occur more frequently with the use of relugolix. The adverse events for which a causal relationship to the study drug could not be ruled out, were mild in severity and all resolved. Based on these findings and the submitted data, although nonclinical data raise concerns for adverse events associated with prolonged QTc intervals, PMDA has concluded that adverse events associated with prolonged QTc intervals are unlikely to be clinically significant in the clinical use of relugolix.

7.R.2.7 Effects of relugolix on metabolic and cardiovascular systems

The applicant's explanation about the effects of relugolix on the metabolic and cardiovascular systems:

A study reports that treatment with relugolix may decrease blood estrogen levels and may be associated with metabolic changes (*J Clin Endocrinol Metab.* 2003;88:2404-11). Long-term treatment with GnRH agonists has effects on the metabolic and cardiovascular systems (insulin resistance, dyslipidemia, and weight increased), increasing the risks of diabetes and cardiovascular diseases (*J Clin Oncol.* 2006;24:4448-56; *J Androl.* 2008;29:534-9). Based on the findings, the effects of relugolix on the metabolic and cardiovascular systems were investigated. The incidence of metabolic or cardiovascular adverse events[9)] in the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101 is shown in Table 57, and most of the adverse events observed in the relugolix groups were mild in severity. In light of the status of occurrence of adverse events in these clinical studies and the maximum treatment duration of 6 months for relugolix, the effects of relugolix on the metabolic and cardiovascular systems are unlikely to be clinically significant.

9) MedDRA SMQs "Dyslipidaemia" narrow search, "Embolic and thrombotic events" broad search, "Central nervous system vascular disorders" broad search, "Cardiac failure" broad search, "Ischaemic heart disease" broad search, "Hyperglycaemia/new onset diabetes mellitus" broad search, and "Hypertension" broad search.

Table 57. Metabolic or cardiovascular adverse events (safety analysis set)

	Relugolix 10 mg (N = 151)	Relugolix 20 mg (N = 155)	Relugolix 40 mg (N = 328)	Leuprorelin (N = 222)	Placebo (N = 186)
Overall	8.6 (13)	8.4 (13)	11.0 (36)	16.2 (36)	6.5 (12)
Blood cholesterol increased	0.7 (1)	0 (0)	1.8 (6)	2.7 (6)	0.5 (1)
Hyperlipidaemia	0.7 (1)	1.3 (2)	1.5 (5)	1.8 (4)	0.5 (1)
Blood creatine phosphokinase increased	2.0 (3)	0.6 (1)	1.5 (5)	1.8 (4)	1.6 (3)
Oedema	0.7 (1)	0.6 (1)	1.5 (5)	0.5 (1)	0.5 (1)
Dyslipidaemia	0.7 (1)	0 (0)	1.2 (4)	1.4 (3)	0.5 (1)
Low density lipoprotein increased	0 (0)	0.6 (1)	0.9 (3)	2.3 (5)	0.5 (1)
Hypertension	0 (0)	0.6 (1)	0.9 (3)	2.3 (5)	0 (0)
Oedema peripheral	0 (0)	1.9 (3)	0.6 (2)	0.5 (1)	0.5 (1)
Weight increased	0.7 (1)	1.3 (2)	0.6 (2)	0.9 (2)	0 (0)
Blood pressure increased	0 (0)	0 (0)	0.6 (2)	0.9 (2)	0 (0)
Weight decreased	1.3 (2)	0.6 (1)	0.3 (1)	0.9 (2)	0 (0)
Increased appetite	0.7 (1)	0.6 (1)	0.3 (1)	0 (0)	0 (0)
Blood triglycerides increased	0.7 (1)	0 (0)	0.3 (1)	1.8 (4)	1.1 (2)
Hypercholesterolaemia	0.7 (1)	0 (0)	0.3 (1)	0.5 (1)	0 (0)
Blood glucose increased	0.7 (1)	0.6 (1)	0 (0)	0 (0)	0 (0)
Glucose urine present	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	0 (0)	0 (0)	0.3 (1)	0.5 (1)	0 (0)
Dehydration	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Hyperglycaemia	0 (0)	0 (0)	0 (0)	0.9 (2)	0 (0)
Thirst	0 (0)	0 (0)	0.3 (1)	0 (0)	0.5 (1)
Peripheral swelling	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)
Glycosylated haemoglobin increased	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)
Lipids increased	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)
Lacunar infarction	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (1)

n (%)
Data combined from Studies CCT-001, CCT-002, 3008, and OCT-101.

PMDA's view:

In the pooled analysis of Studies CCT-001, CCT-002, 3008, and OCT-101, almost no incidence of metabolic and cardiovascular adverse events was higher in the relugolix group than in the leuprorelin group, and there was no tendency showing a more frequent occurrence of specific adverse events with the use of relugolix. Given the submitted data, PMDA has concluded that the risk of these events associated with the use of relugolix is not higher than that associated with leuprorelin, which is an approved drug, and that the effects of relugolix on the metabolic and cardiovascular systems are unlikely to be clinically significant. Meanwhile, there is a report suggesting that decreased blood estrogen levels due to the pharmacological effects of relugolix are related to the effects of relugolix on the metabolic and cardiovascular systems. The package inserts of GnRH agonists include precautionary statements for these adverse events. (Both GnRH agonists and relugolix are used for a similar period and reduce blood estrogen to similar levels during treatment.) In view of the above, the size of clinical studies submitted might not be enough to provide adequate data to evaluate the risk of these events. Therefore, PMDA has concluded that information on the occurrence of these adverse events should be collected in the postmarketing routine pharmacovigilance activities.

7.R.2.8 Effects of relugolix on ovarian function

The applicant's explanation about the recovery of ovarian function after completion (or discontinuation) of treatment with relugolix:

Table 58 shows the duration in days between the completion (or discontinuation) of the study drug and the subsequent resumption of menstruation in Studies CCT-001, CCT-002, 3008, and OCT-101.

Table 58. Days between the completion (or discontinuation) of study treatment and resumption of menstruation (safety analysis set)

Study ID	Treatment	Patients evaluated	Patients with resumption of menstruation	Days to resumption of menstruation [a] (Days)	Days to resumption of menstruation [b] (Days)
Study CCT-001	Relugolix 10 mg	48	47	22.0 (3, 40)	19.8 ± 9.26
	Relugolix 20 mg	55	54	28.0 (5, 113)	30.8 ± 17.72
	Relugolix 40 mg	54	51	37.0 (6, 54)	36.4 ± 7.71
	Placebo	57	57	19.0 (1, 52)	18.6 ± 8.75
Study CCT-002	Relugolix 40 mg	138	131	37.0 (5, 133)	40.8 ± 17.23
	Leuprorelin	142	133	65.0 (10, 105)	64.7 ± 18.50
Study 3008	Relugolix 40 mg	33	33	35.0 (19, 49)	35.6 ± 6.08
	Placebo	32	32	17.5 (2, 54)	17.0 ± 11.54
Study OCT-101	Relugolix 10 mg	103	103	23.0 (1, 98)	21.0 ± 12.32
	Relugolix 20 mg	100	95	28.0 (2, 84)	26.0 ± 12.97
	Relugolix 40 mg	103	97	37.0 (8, 79)	36.9 ± 9.49
	Leuprorelin	80	71	72.0 (32, 159)	73.3 ± 21.11
	Placebo	97	93	18.0 (1, 39)	17.3 ± 8.49

a: Median (minimum, maximum)
b: Mean ± standard deviation

In Studies CCT-001, CCT-002, 3008, and OCT-101, the resumption of menstruation after completion (or discontinuation) of study treatment was not confirmed in 45 patients (23 in the relugolix group, 18 in the leuprorelin group, and 4 in the placebo group), consisting of 29 patients who received other hormone drugs before the resumption of menstruation, 6 patients who underwent surgery, 3 patients who were switched to other therapy (unspecified), 3 patients who experienced menopause, 2 patients who got pregnant, 1 patient who was lost to follow up, and 1 patient who was judged by the investigator as unnecessary to follow up. Among them, relugolix had been administered to 16 patients receiving other hormone drugs before the resumption of menstruation, 3 patients undergoing surgery, 2 patients becoming pregnant, 1 patient switched to another therapy (unspecified), and 1 patient experiencing menopause. In 3 patients undergoing surgery, no safety issues were identified at the completion of treatment with relugolix, and they were considered to be eligible for surgery. Therefore, serum E_2 levels were not measured 28 days after the completion of the study drug in them (the follow-up period was 28 days after treatment completion). Of 16 patients receiving other hormone drugs, 2 patients received hormone drugs (estrogen preparations) during their follow-up period. The remaining 14 patients received hormone drugs after determination of serum E2 levels after the follow-up period, which were higher than those at the completion of study treatment in all, except for 1 patient who prematurely discontinued study treatment because she had been given leuprorelin wrongly by mistake. Also in the patient switching to another therapy (unspecified), the serum E_2 levels after follow-up were higher than those at the completion of study treatment. The patient who was judged to be menopausal was a 49-year-old woman, and her menopause was considered natural for her age. As discussed above, no irreversible effects of relugolix on the ovarian function were identified in the clinical studies.

PMDA's view:

In the clinical studies, the resumption of menstruation was confirmed in most patients after a certain period of time from the completion (or discontinuation) of study treatment (Table 58). In light of the findings, together with the applicant's explanation about patients without the resumption of menstruation, it is unlikely that relugolix might have irreversibly affected the ovarian function. Therefore, PMDA has concluded that the effects of relugolix on the ovarian function is clinically tolerable in clinical practice.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of relugolix:

In Japan, surgery and pharmacotherapy are the mainstream treatment of uterine fibroids. Radical treatment with hysterectomy is performed for patients with symptoms such as menorrhagia who do not wish or need to preserve their fertility. Meanwhile, for patients who want to preserve their fertility, the necessity of uterine myomectomy is considered, and pharmacotherapy is performed for menorrhagia, anemia, and pain; GnRH agonists are widely used for pharmacotherapy (Practice Guidelines For Obstetrics And Gynecology, Obstet Gynecol. 2004;104:393-406). According to the Practice Guidelines, GnRH agonists for the treatment of uterine fibroids are administered to relieve anemia due to menorrhagia; to reduce the size of uterine fibroids before hysterectomy or uterine myomectomy to shorten the surgery time or reduce intraoperative blood loss; and to induce natural menopause in women just before menopause. The Practice Guidelines also state that pharmacotherapy with drugs including GnRH agonists can be intermittently performed in patients who wish or need to preserve their fertility but do not want to have a child soon so as to reduce the size of uterine fibroids or to relieve symptoms until they develop a desire to bear a child (Practice Guidelines For Obstetrics And Gynecology).

With regard to efficacy, leuprorelin, a GnRH agonist approved for the treatment of symptoms associated with uterine fibroids, was used as an active comparator in Study CCT-002 conducted in patients with uterine fibroids and menorrhagia. In the study, the non-inferiority of relugolix 40 mg to leuprorelin was demonstrated for reduction of menorrhagia, and the efficacy of relugolix for anemia was also shown. Also, in Study 3008 conducted in patients with lower abdominal pain or lumbar pain associated with uterine fibroids, the superiority of relugolix 40 mg to placebo was demonstrated for the relief of pain [see Section 7.R.1]. Regarding safety, while the incidence of uterine hemorrhage or climacteric-like symptoms was higher with the use of relugolix, these events were manageable by monitoring the patients without any active treatment or by discontinuing relugolix, and adverse events associated with decreased bone density are expected to be clinically insignificant when relugolix is administered for 6 months or less in principle, as with leuprorelin, and patients are monitored with tests conducted appropriately [see Section 7.R.2]. Furthermore, relugolix is a GnRH antagonist, and serum E_2 levels reached the menopausal level immediately after administration of relugolix [see Section 6.2.3.2]. Accordingly, relugolix is characterized by the features that relugolix is not associated with a concern of flare up in contrast to approved GnRH agonists, and that relugolix can be administered orally while approved GnRH agonists are administered subcutaneously or intranasally. Based on the above findings, as with approved GnRH agonists, relugolix can be positioned as a pharmacotherapeutic option to be administered for ≤6 months, in principle, to relieve menorrhagia, anemia, lower abdominal pain, and lumbar pain in the following situations:

(a) administered to patients just before menopause until natural menopause; (b) administered preoperatively to patients who are scheduled to undergo surgery for uterine fibroids; and (c) administered on an intermittent basis to relieve the symptoms in patients who want to preserve their fertility but do not want to bear a child soon.

PMDA's view:
The results of Study CCT-002 showed that the efficacy of relugolix was not inferior to that of leuprorelin for menorrhagia and anemia associated with uterine fibroids [see Sections 7.R.1.1 and 7.R.1.2]. Although the strict positional relationship with approved GnRH agonists is unclear, the results of Study 3008 conducted as a placebo-controlled study demonstrated the clinically meaningful efficacy of relugolix for lower abdominal pain and lumbar pain associated with uterine fibroids [see Section 7.R.1.3]. In view of the observed benefits, the safety profile of relugolix is tolerable when relugolix is administered for 6 months or less in principle, as with leuprorelin [see Section 7.R.2]. Based on these findings, relugolix is positioned as a drug which is not intended to radically treat uterine fibroids, as with approved GnRH agonists, but as a drug administered for no longer than 6 months, in principle, to relieve menorrhagia, anemia, lower abdominal pain, and lumbar pain associated with uterine fibroids. The description about the use of approved GnRH agonists in the Practice Guidelines For Obstetrics And Gynecology can lead to the conclusion that relugolix should be administered for no longer than 6 months just before menopause or before surgery to relieve menorrhagia, anemia, and lower abdominal pain and lumbar pain associated with uterine fibroids. In patients who want to preserve their fertility but do not want to bear a child soon, relugolix can be used for no longer than 6 months, in principle, to relieve menorrhagia, anemia, and lower abdominal pain and lumbar pain associated with uterine fibroids. However, the submitted clinical trial data are not enough to determine the appropriate duration of interval between treatments that would ensure safe intermittent treatment with relugolix (e.g., safety in terms of the effects on bone density) in such patients. Therefore, at present, PMDA does not consider that intermittent treatment with relugolix can be performed safely.

Based on the above, and in consideration of the facts that relugolix is not indicated for regression of myoma for which approved GnRH agonists are indicated [see Section 7.R.4] and that the mechanism of action and route of administration of relugolix differ from those of approved GnRH agonists, PMDA has concluded that relugolix is positioned as a therapeutic option among products including approved GnRH agonists for relief of menorrhagia, anemia, and lower abdominal pain and lumbar pain associated with uterine fibroids

7.R.4 Indication

The submitted clinical data demonstrated the efficacy of relugolix for menorrhagia, anemia, lower abdominal pain, and lumbar pain associated with uterine fibroids [see Section 7.R.1], and the safety profile of relugolix is considered to be tolerable in view of its observed benefits [see Section 7.R.2]. PMDA thus has concluded that the proposed indication, "Relief of the following symptoms associated with uterine fibroids: menorrhagia, lower abdominal pain, lumbar pain, and anemia," is appropriate.

7.R.5 Dosage and administration

The applicant's explanation about the dosage and administration of relugolix:

The data from the Japanese phase I study (Study CPH-001) in healthy premenopausal women suggest that relugolix should be administered before a meal [see Section 6.R.1]. Further, the initial dose of relugolix should be administered on a day between "Days 1 and 5 of a menstrual cycle," for the following reasons:

(1) Relugolix is contraindicated in pregnant women based on data from the reproductive and developmental toxicity studies [see Section 5.5].
(2) Relugolix should be started in women who are not pregnant confirmed by the menstruation before pregnancy becomes possible because in humans, the proliferative phase usually starts on Day 6 of a menstrual cycle, and pregnancy can occur after that.
(3) Since estrogen decreases during the menstrual phase and increases during the proliferation phase (*Medical Disease: An Illustrated Reference Guide, Vol. 9, Gynecology and Breast Surgery, 3rd Edition.* Institute for Health Care Information Sciences (Ed.). MEDIC MEDIA Co., Ltd. 2017. p23), relugolix is expected to exert its effects rapidly when the treatment is started before the proliferative phase.

In the Japanese phase II study (Study CCT-001) conducted in patients with uterine fibroids and menorrhagia, relugolix 10, 20, and 40 mg was started a day between Days 1 and 5 of a menstrual cycle and was administered orally once daily before a meal, and the efficacy and safety of relugolix were compared with those of placebo. In all relugolix groups, menorrhagia was reduced as compared with the placebo group, and the percentage of patients with improvement increased with an increase in the relugolix dose and was highest in the relugolix 40 mg group. Similar improvement was observed for blood Hb content and pain symptoms, and serum E_2 levels were maintained at a menopausal level during the treatment period only in the relugolix 40 mg group [see Section 6.2.3.1]. No significant safety issues were identified, and relugolix was well tolerated at the doses investigated in Study CCT-001.

Based on the above, it was considered appropriate to evaluate the dosing regimen of relugolix 40 mg administered orally once daily before a meal, with the initial dose starting between Days 1 and 5 of a menstrual cycle. Relugolix was administered with the dosing regimen in Studies CCT-002 and 3008, and the data from these studies demonstrated the efficacy of relugolix for menorrhagia, anemia, lower abdominal pain, and lumbar pain associated with uterine fibroids [see Section 7.R.1] and the clinically tolerable safety of relugolix [see Section 7.R.2].

Accordingly, it was considered appropriate that the dosage and administration of relugolix should be specified as "The usual adult dosage is 40 mg of relugolix administered orally once daily before a meal. The initial dose should be administered on a day between Days 1 and 5 of a menstrual cycle."

PMDA considers the following applicant's explanation to be appropriate: that pre-prandial administration was chosen based on the pharmacokinetics of relugolix: that the timing of initial dose was specified as a day

between Days 1 and 5 of a menstrual period because the patient in the period is surely assumed to be in pre-pregnant state based on the mechanism of action of relugolix and the menstrual cycle; that the recommended dose of relugolix was determined to be 40 mg based on data from Study CCT-001. In light of the results for the efficacy and safety of relugolix obtained from Studies CCT-002 and 3008 conducted with the dosing regimen, PMDA has concluded that the proposed dosage and administration of relugolix is appropriate.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing investigations for relugolix:

A general drug use-results survey (with a survey period of 2 years) is scheduled to be conducted in patients with uterine fibroids to collect data on adverse events associated with bone density decreased, hepatic dysfunction, climacteric-like symptoms, depression, or uterine hemorrhage, which are adverse events of special interest for relugolix, in order to investigate the safety profiles of the drug when used in a broader range of patient populations in routine clinical practice as compared with the patient population examined in the clinical studies. The observation period was set at a maximum of 12 months after the start of relugolix therapy (a treatment period of 6 months and a follow-up period of up to 6 months until the resumption of menstruation), for the following reasons: (1) The treatment period of relugolix is 6 months in principle because of the risk of decreased bone density; (2) the resumption of menstruation can probably be confirmed during a 6-month follow-up period in almost all patients because the maximum duration from the completion of relugolix therapy to the resumption of menstruation was 133 days in the relugolix 40 mg group of Study CCT-002. Further, among adverse events associated with bone density decreased, hepatic dysfunction, climacteric-like symptoms, depression, and uterine hemorrhage, depressed state had the lowest incidence (4 of 226 patients, 0.9%) in the Japanese clinical studies (Studies CCT-001, CCT-002, and 3008). Therefore the target sample size of this survey was set at 340 patients because this number would allow estimating the incidence of depressed state with a certain level of accuracy

PMDA considers that the outline of the post-marketing surveillance presented by the applicant is generally appropriate. A final decision on the details of the post-marketing surveillance will be made, taking account of comments from the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3, 5.3.5.4-1, and 5.3.5.4-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, non-compliance with GCP was found in a study site. PMDA concluded that the review should be conducted after appropriate measures were taken, including the exclusion of data of cases noncompliant with GCP from the submitted application dossier. The inspection also revealed the following finding requiring corrective action at a study site, although the finding had no significant impact on the overall assessment of the studies. The head of the relevant medical institution was notified of the finding requiring corrective action.

Non-compliance with GCP

Medical institution

・Inappropriate archiving of some raw materials (medical records)

Finding requiring corrective action

Medical institution

・Incomplete description in a contract document for partial outsourcing of trial-related duties
・Inappropriate archiving of some raw materials (new written consent from subjects by using a revised informed consent document)

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

On the basis of the data submitted, PMDA has concluded that relugolix has efficacy in relief of symptoms of menorrhagia, anemia, lower abdominal pain, and lumbar pain associated with uterine fibroids and that relugolix has acceptable safety in view of its benefits. PMDA considers it clinically meaningful to make relugolix available in clinical practice because the product offers a new treatment option for patients with uterine fibroids.

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

Review Report (2)

November 12, 2018

Product Submitted for Approval

Brand Name	Relumina Tablets 40 mg
Non-proprietary Name	Relugolix
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the efficacy, indication, and dosage and administration for relugolix as described in the Review Report (1).

1.1 Safety

The following comments were raised from the expert advisors:

- The post-marketing surveillance should be conducted taking into account that patients older than those enrolled in the clinical studies will receive relugolix in clinical practice.
- As for climacteric-like symptoms including depression, the package insert of relugolix should include precautionary statements similar to those currently provided for the approved GnRH agonists.
- Physicians should use relugolix while keeping in mind that the pattern of changes in serum E_2 levels during the therapy differs from that observed with approved GnRH agonists.

PMDA explained its conclusion:

The safety profile of relugolix in routine clinical practice to be collected in post-marketing surveillance should be examined in terms of differences in age between patients in the clinical studies and patients in clinical practice. As for adverse events associated with depression, healthcare professionals should be provided with information on the pharmacological effects of relugolix and leuprorelin, changes in serum E_2 levels with these drugs, and the occurrence of adverse events associated with climacteric-like symptoms or depression observed in the clinical studies. As with approved GnRH agonists, the package insert for relugolix

should include precautionary statements to the effect that patients treated with relugolix should closely be monitored.

The above conclusion made by PMDA was supported by the expert advisors. The expert advisors also supported all PMDA's conclusions on the safety of relugolix described in Section "7.R.2 Safety" in the Review Report (1).

PMDA asked the applicant to provide precautions to healthcare professionals in clinical practice and to develop a post-marketing surveillance plan taking into account the above considerations. The applicant responded appropriately.

1.2 Clinical positioning

PMDA concluded that relugolix is not a drug intended to radically treat uterine fibroids and is anticipated to be used to mainly treat symptoms associated with uterine fibroids just before menopause or before surgery with a maximum treatment duration of 6 months in principle (see Section 7.R.3 in the Review Report (1)). This PMDA's conclusion was supported by the expert advisors. No study has been conducted to provide evidence that relugolix can be administered for longer than 6 months or can be intermittently administered (e.g., resumed with an interval after 6-month administration). Therefore the expert advisors commented that a cautious stance should be taken for such use at present. Given the comments from the expert advisors, PMDA has concluded that healthcare professionals should be informed about the fact that the safety profile of long-term (>6 months) or intermittent treatment with relugolix, as described above, has not been studied and remains unestablished.

PMDA asked the applicant to appropriately provide information to healthcare professionals in clinical practice taking into account the above considerations. The applicant responded appropriately.

1.3 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) should include the safety specification presented in Table 59, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 60 and a general drug use-results survey shown in Table 61.

Table 59. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Bone density decreased ・Hepatic dysfunction ・Climacteric-like symptoms including depression	・Diabetes mellitus ・Cardiovascular disease-related events (e.g. myocardial infarction, cerebral infarction)	・None
Efficacy specification		
・None		

Table 60. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・General drug use-results survey	・Dissemination of data collected during the early post-marketing phase vigilance ・Preparation and provision of materials for healthcare professionals

Table 61. Outline of the use-results survey (draft)

Objectives	To evaluate the safety etc. of relugolix in patients with uterine fibroids in clinical practice
Survey method	Central registration
Population	Patients with uterine fibroids
Observation period	12 months
Planned sample size	340 patients
Main survey items	・Patient characteristics (e.g., age, disease duration, comorbidities) ・Status of treatment with relugolix ・Adverse events (e.g., bone density decreased, hepatic dysfunction, climacteric-like symptoms, depression, and events related to uterine hemorrhage)

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following condition. Since this product is classified as a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Relief of the following symptoms associated with uterine fibroids: menorrhagia, lower abdominal pain, lumbar pain, and anemia.

Dosage and Administration

The usual adult dosage is 40 mg of relugolix administered orally once daily before a meal. The initial dose should be administered on a day between Days 1 and 5 of a menstrual cycle.

Approval Conditions

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

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve of the analyte
AUC_{τ}	AUC during a dosing interval
$AUC_{0\text{-}24}$	AUC from 0 to 24 hours
$AUC_{0\text{-}\infty}$	AUC from 0 to infinity
BA	Bioavailability
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CL/F	Apparent total clearance
CK	Creatine Kinase
C_{max}	Maximum concentration of analyte in plasma
CPP	Critical process parameter
CQA	Critical quality attribute
C_{trough}	Trough concentration of analyte in plasma
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
E_2	Estradiol
FAS	Full analysis set
FMEA	Failure Mode and Effect Analysis
FOB	Functional observation battery
F_{rel}	Relative BA
FSH	Follicle-stimulating hormone
γ-GTP	γ-glutamyl transpeptidase
GC	Gas chromatography
GnRH	Gonadotropin-releasing hormone
Guidelines for bioequivalence of different dosage-strengths	Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms, Attachment 2 of the Partially Revised Guidelines for Bioequivalence Studies of Generic Products (PFSB/ELD Notification No. 0229-10, dated February 29, 2012, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare)
Guidelines for bioequivalence of formulation changes	Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms, Attachment 3 of the Partially Revised Guidelines for Bioequivalence Studies of Generic Products (PFSB/ELD Notification No. 0229-10, dated February 29, 2012, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare)
Hb	Hemoglobin
hERG	Human ether-a-go-go-related gene
HPLC	High performance liquid chromatography
ICH M7 Guideline	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
ICH Q1E Guideline	Evaluation of Stability Data
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
IR	Infrared absorption spectrum
JW	Japanese white

ka	Absorption rate constant
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
leuprorelin	Leuprorelin acetate
LH	Luteinizing hormone
LLT	Lowest level term
MATE	Multidrug and toxin extrusion
MedDRA	Medical dictionary for regulatory activities
mRNA	Messenger ribonucleic acid
MS	Mass spectrum
[redacted]	[redacted]
NMR	Nuclear magnetic resonance spectrum
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app}	Apparent permeability coefficient
PBAC	pictorial blood loss assessment chart
P-gp	P-glycoprotein
PLD	Phospholipidosis
PMDA	Pharmaceuticals and Medical Devices Agency
Practice Guidelines for Obstetrics and Gynecology	The Japan Society of Obstetrics and Gynecology and the Japan Association of Obstetricians and Gynecologists eds. Practice Guidelines for Obstetrics and Gynecology: Outpatient Gynecology 2017.
PT	Preferred term
QbD	Quality by Design
Q/F	Apparent intercompartmental clearance
SD rat	Sprague-Dawley rat
SMQ	Standardised MedDRA queries
SOC	System organ class
t_{max}	Time to reach the maximum concentration
$t_{1/2}$	Half-life
UDS	Unscheduled DNA synthesis
UV/VIS	Ultraviolet and visible absorption spectrometry
V_c/F	Apparent distribution volume of the central compartment
V_p/F	Apparent distribution volume of the peripheral compartment
V_z/F	Apparent distribution volume during terminal phase