Report on the Deliberation Results

December 6, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour, and Welfare

Brand Name	Goofice Tablets 5 mg
Non-proprietary Name	Elobixibat Hydrate (JAN*)
Applicant	EA Pharma Co., Ltd.
Date of Application	February 1, 2017

Results of Deliberation

In its meeting held on December 4, 2017, 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. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

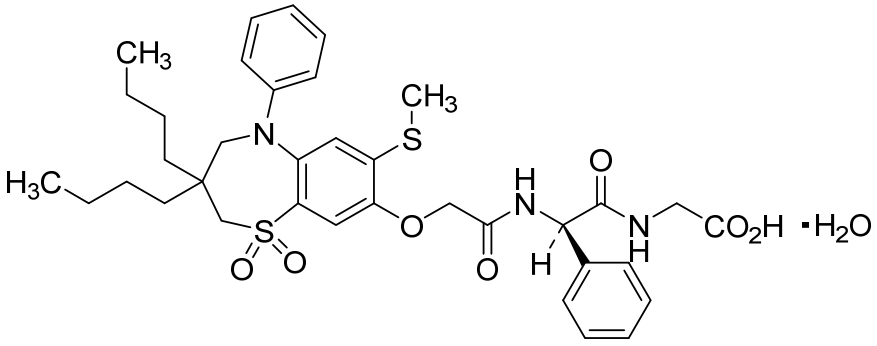
Review Report

November 16, 2017
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	Goofice Tablets 5 mg
Non-proprietary Name	Elobixibat Hydrate
Applicant	EA Pharma Co., Ltd.
Date of Application	February 1, 2017
Dosage Form/Strength	Tablet containing 5 mg of elobixibat (5.13 mg as elobixibat hydrate)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula:	$C_{36}H_{45}N_3O_7S_2 \cdot H_2O$
Molecular weight:	713.90
Chemical name:	[(2*R*)-2-(2-{[3,3-Dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzothiazepin-8-yl]oxy}acetamido)-2-phenylacetamido]acetic acid monohydrate

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

Results of Review

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

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

Indication

Chronic constipation (excluding constipation caused by organic disease)

Dosage and Administration

The usual adult dosage is 10 mg of elobixibat administered orally once daily before a meal. The dose may be adjusted according to the patient's symptoms, not exceeding a maximum dose of 15 mg per day.

Conditions of Approval

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

Attachment

Review Report (1)

October 24, 2017

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	Goofice Tablets 5 mg
Non-proprietary Name	Elobixibat Hydrate
Applicant	EA Pharma Co., Ltd.
Date of Application	February 1, 2017
Dosage Form/Strength	Tablet containing 5 mg of elobixibat (5.13 mg as elobixibat hydrate).
Proposed Indication	Chronic constipation (excluding constipation caused by organic disease)
Proposed Dosage and Administration	The usual adult dosage is 10 mg of elobixibat administered orally once daily before a meal. The dose may be adjusted according to the patient's symptoms.

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List of Abbreviations

See Appendix.

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

Constipation refers to a condition characterized by accumulation of feces in the colon and difficulty in passing stools. The diagnosis is made based on a decreased bowel movement frequency, stool consistency, difficulty in defecation, and a sense of incomplete evacuation. The main symptoms of constipation include abdominal pain, sensation of incomplete rectal evacuation, and abdominal distension. In Japan, constipation is roughly classified into acute constipation and chronic constipation based on its onset and course, and is further classified into functional, organic, and other types of constipation based on its cause, clinical condition, and other factors ("Clinical Practice Guidelines for Chronic Constipation 2017" compiled by the Research Group on the Diagnosis and Treatment of Chronic Constipation, a research group of the Japanese Society of Gastroenterology).

While constipation is treated with drugs such as irritant laxatives (eg, sennoside, sodium picosulfate hydrate), saline laxatives (eg, magnesium oxide), and drugs that alter intestinal epithelial function (eg, lubiprostone), as a single agent or in combination with other drugs, the long-term use of these drugs carries the risk of developing resistance or habituation, electrolyte abnormalities including hypermagnesemia, and nausea, respectively.

Elobixibat hydrate (hereinafter referred to as "elobixibat") is an inhibitor of the ileal bile acid transporter (IBAT) involved in the reabsorption of bile acids in the ileum. Elobixibat suppresses the reabsorption of bile acids in the ileum by inhibiting the IBAT, and thereby increases the amount of bile acids in the colon. As a result, secretion of fluid and electrolytes in the intestinal tract and gastrointestinal motility are enhanced. In the expectation that the drug would improve constipation, development of elobixibat was initiated.

The applicant conducted Japanese clinical studies, which demonstrated the efficacy and safety of the drug. Based on the results, a marketing application has now been filed.

As of September 2017, elobixibat has not been approved in any countries.

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 a white powder, and its description, solubility, hygroscopicity, sorption-desorption isotherm, melting point, dissociation constant (pKa), distribution coefficient (logP), optical rotation, and crystalline polymorphism have been determined. At least 4 crystal forms of the drug substance ([redacted], [redacted], [redacted], and [redacted]) have been identified. Only [redacted] ([redacted]), which is stable at room temperature, has been identified in the commercial manufacturing process.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), ultraviolet spectroscopy (UV), infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrometry (^{13}C-NMR), optical rotation, and

single crystal X ray crystallography. Elobixibat hydrate has a single asymmetric carbon, and the drug substance is an *R*-enantiomer.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as the starting materials.

[redacted], [redacted], and [redacted] are identified as critical process steps. [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The drug substance specifications have been set for strength, description (visual), identification (UV, IR), purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC]), water content, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

The main stability studies on the drug substance are shown in Table 1. The results of the photostability studies showed that the drug substance is unstable when exposed to light.

Table 1. Stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	[redacted] polyethylene bag/ [redacted] polyethylene drum	18 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when placed in a [redacted] polyethylene bag and stored in a [redacted] polyethylene drum at room temperature, in accordance with the ICH Q1E Guideline. Long-term testing of the drug substance will be conducted 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 5.13 mg of the drug substance (5 mg as elobixibat) per tablet. The drug product comprises a core tablet and a film coating layer. The core tablet contains crystalline cellulose, D-mannitol, hypromellose, croscarmellose sodium, light anhydrous silicic acid, and magnesium stearate, and the film coating layer contains hypromellose, macrogol 6000, titanium oxide, yellow ferric oxide, and carnauba wax as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through processes comprising [redacted], [redacted], [redacted], [redacted], [redacted]. The [redacted] process and [redacted] process are identified as critical processes, for which in-process controls and limits are established.

2.2.3 Control of drug product

The drug product specifications have been set for strength, description (visual), identification (UV), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [UV]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies on the drug product are shown in Table 2. The results of the photostability studies showed that the drug product is photostable.

Table 2. Stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	PTP/aluminum laminated film/white box	18 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a shelf life of [redacted] months has been proposed for the drug product when placed in a press through packaging (PTP) (polypropylene film/aluminum foil) and aluminum laminated film and stored at room temperature, in accordance with the ICH Q1E Guideline. Long-term testing of the drug product will be conducted for up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

In primary pharmacodynamic studies, inhibitory effect on bile acid transporters, suppressive effect on bile acid reabsorption, and improving effect of constipation were investigated. In secondary pharmacodynamic studies, selectivity of receptors, etc., other than bile acid transporters was investigated. In safety pharmacology studies, the effects on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and renal/urinary system were investigated.

3.1 Primary pharmacodynamics

3.1.1 Inhibitory effect on bile acid transporters (CTD 4.2.1.1-1, Study [redacted])

Using human embryonic kidney cell line HEK 293 (HEK293 cells) expressing the IBAT or human liver bile acid transporter (LBAT), the inhibitory effect of elobixibat against the IBAT and LBAT was investigated.

Elobixibat inhibited human IBAT and LBAT with a mean half maximal inhibitory concentration (IC_{50}) value of 0.53 and 240 nmol/L, respectively.

3.1.2 Suppressive effect on bile acid reabsorption (CTD 4.2.1.1-2 and 4.2.1.1-3, Studies [redacted] and [redacted])

Female apolipoprotein E (ApoE) knockout mice received tauro-23-[^{75}-Se]selena-25-homocholic acid (^{75}SeHCAT), an analogue of taurocholate, orally as a bile acid tracer 0.5 hours after receiving a single oral dose of elobixibat at 0.109, 0.435, or 1.7 mg/kg or vehicle (a mixture of 70% polyethylene glycol [PEG] and 10% ethanol). The percent inhibition of ^{75}SeHCAT absorption in each dose group of elobixibat relative to the vehicle control group 24 hours after administration of ^{75}SeHCAT was calculated. The percent inhibition of absorption in the elobixibat 0.109, 0.435, and 1.7 mg/kg groups was 36%, 59%, and 70%, respectively, showing a dose-dependent increase in the suppressive effect of elobixibat. The 50% effective dose (ED_{50}) of elobixibat was 0.274 mg/kg.

Female ApoE knockout mice received ^{75}SeHCAT orally 0.5, 3, or 8 hours after receiving a single oral dose of elobixibat at 1.7 mg/kg or vehicle (a mixture of 70% PEG and 10% ethanol). The percent inhibition of ^{75}SeHCAT absorption in the elobixibat 1.7 mg/kg group relative to the vehicle control group 24 hours after administration of ^{75}SeHCAT was calculated. The percent inhibition of absorption at 0.5, 3, and 8 hours post-dose in the elobixibat 1.7 mg/kg groups was 70%, 71%, and 31%, respectively, showing that the suppressive effect of elobixibat on bile acid reabsorption in the mouse ileum continues for at least 3 hours after administration and decreases 8 hours after administration.

3.1.3 Improvement of loperamide hydrochloride-induced constipation (CTD 4.2.1.1-4, Study [redacted])

Male rats received loperamide hydrochloride (5 mg/kg as loperamide) orally 1 hour after receiving a single oral dose of elobixibat at 3, 10, or 30 mg/kg or vehicle (water for injection). Fecal wet weights up to 8 hours after administration of loperamide hydrochloride are shown in Table 3. A dose-dependent increase in fecal wet weight was observed in the elobixibat groups. A significant increase in fecal wet weight was detected in the elobixibat 30 mg/kg group compared to the vehicle control group.

Table 3. Fecal wet weight up to 8 hours post-dose in rats with loperamide hydrochloride-induced constipation

Treatment group		Fecal wet weight (g)
Vehicle control		0.95±0.57
Elobixibat (mg/kg)	3	0.95±0.65
	10	1.13±0.71
	30	1.45±0.71*

Mean ± standard deviation; n = 20
*: $P < 0.05$ (relative to the vehicle control group; Dunnett's test)

3.2 Secondary pharmacodynamics

3.2.1 Selectivity (CTD 4.2.1.2-1, Study [redacted] [reference data])

Effects of elobixibat on 23 types of enzymes, receptors, and transporters other than bile acid transporters and 11 types of tissue specimens were investigated. Elobixibat exhibited agonistic activity against somatostatin receptor type 2 (sst_2 receptor) of 99% when administered at 30 μmol/L and of −1% and 28% when administered at 0.3 and 3 μmol/L, respectively. Elobixibat exerted an activating effect on cyclooxygenase-1 (COX-1) of 112% when administered at 10 μmol/L and an inhibitory effect on COX-1 of 1% and 21% when administered at 0.1 and 1 μmol/L, respectively. Furthermore, elobixibat exerted an inhibitory effect on the binding of ligands to tachykinin NK_2 receptors of 134% when administered at 10 μmol/L and of 10% and 95% when administered at 0.1 and 1 μmol/L, respectively.

Based on the above, even in the target molecules on which elobixibat exhibited a relatively potent effect when administered at 10 or 30 μmol/L, there was barely any effect when elobixibat was administered at 0.1 or 0.3 μmol/L. Considering that the maximum concentration (C_{max}) of elobixibat after administration at 15 mg, the maximum clinical dose, is 0.63 nmol/L, elobixibat is unlikely to affect any molecular targets other than IBAT when used in clinical practice.

3.3 Safety pharmacology

The applicant submitted data from safety pharmacology studies as summarized in Table 4. The vehicle used was 0.3% dimethyl sulfoxide (DMSO)-containing 2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffer saline in *in vitro* studies and 20% PEG 400 aqueous solution in *in vivo* studies.

Table 4. Summary of safety pharmacology studies

Organ system	Study sample	Endpoint, assessment method	Dose	Route of administration	Findings	CTD (Study number)
Central nervous	Rats (8 males per group)	Irwin method	0, 3.5, 35, or 350 mg/kg	Oral	No effects of elobixibat were observed at any time point in the 3.5, 35, and 350 mg/kg groups, except that a significant decrease was observed in the amount of feces 6 hours post-dose in the 3.5 mg/kg group. The results suggest that elobixibat has no toxic effects.	4.2.1.3-1 ([redacted])
	Rats (8 males per group)	Locomotor activity, etc.	0, 3.5, 35, or 350 mg/kg	Oral	Although locomotor activity significantly increased at 0.5 hours post-dose in the 35 mg/kg group and significantly decreased at 2 hours post-dose in the 350 mg/kg group, both changes were minor.	4.2.1.3-2 ([redacted])
	Rats (10 males per group)	Coordinated motion (rotor rod test)	0, 3.5, 35, or 350 mg/kg	Oral	Elobixibat had no effects when administered at a dose of up to 350 mg/kg.	4.2.1.3-3 ([redacted])
Cardiovascular	HEK293 cells (vehicle control group, 3 samples; elobixibat group, 6 samples)	hERG current	0 or 0.65 μmol/L	*in vitro*	The percent inhibition of hERG current in the 0.65 μmol/L group was 6.0%, which was a minor change.	4.2.1.3-4 ([redacted])
	Dogs (n = 3 per sex per group)	Arterial pressure, heart rate, pulmonary arterial pressure, ECG, blood gas, etc. (under anesthesia)	0, 0.0035, 0.035, 0.35, or 3.5 mg/kg	IV	A significant decrease in coronary blood flow in ≥0.35 mg/kg groups and a significant increase in coronary vascular resistance in the 3.5 mg/kg group were observed. The level of HCO_3^- in the arterial blood significantly decreased at 29.5 minutes post-dose in the 3.5 mg/kg group.	4.2.1.3-5 ([redacted])
	Rats (8 males per group)	Blood pressure, heart rate	0, 3.5, 35, or 350 mg/kg	Oral	Elobixibat had no effects when administered at a dose of up to 350 mg/kg.	4.2.1.3-6 ([redacted])
Respiratory	Rats (8 males per group)	WBP (respiratory rate, tidal volume, minute ventilation, etc.)	0, 3.5, 35, or 350 mg/kg	Oral	Elobixibat had no effects when administered at a dose of up to 350 mg/kg.	4.2.1.3-7 ([redacted])
Gastrointestinal	Rats (8 males per group)	Gastrointestinal propulsion	0, 3.5, 35, or 350 mg/kg	Oral	A significant decrease in the small intestinal propulsion of a charcoal meal was observed in the 350 mg/kg group (decreased by approximately 30% compared to the vehicle control group).	4.2.1.3-8 ([redacted])
Renal/urinary	Rats (8 males per group)	Urinary output, urinary/plasma parameters (Na^+ level, K^+ level, etc.), creatinine clearance	0, 3.5, 35, or 350 mg/kg	Oral	In the 350 mg/kg group, a significant decrease (26%) in urinary excretion of Na^+ was observed at 0 to 24 hours post-dose, and a significant increase (82%) in urinary urea concentration was observed at 6 to 24 hours post-dose.	4.2.1.3-9 ([redacted])

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

The applicant's explanation about the pharmacological effects of elobixibat:

Bile acids biosynthesized in the liver are secreted into the duodenal lumen and then reabsorbed via the IBAT, a bile acid transporter localized in luminal epithelial cells in the terminal ileum (*Scand J Gastroenterol.* 2010;45:645-664). Elobixibat suppresses the reabsorption of bile acids by inhibiting the IBAT from the luminal surface and thereby increases the flow of bile acids into the colon. A resulting increase in bile acids in the colonic lumen enhances the secretion of fluid and electrolytes to the colonic luminal surface and promotes gastrointestinal motility, improving colonic propulsion. With this mechanism of action, elobixibat is assumed to have a therapeutic effect on constipation (*Ther Adv Gastroenterol.* 2014;7:167-175, *Gut.* 1975;16:894-902, etc.).

The submitted data from studies demonstrated that elobixibat has inhibitory effects on the IBAT and suppresses bile acid reabsorption in the ileum. Moreover, elobixibat improved constipation in a rat model with constipation induced by oral administration of loperamide hydrochloride. Based on the above results, elobixibat is assumed to inhibit the IBAT and suppress bile acid reabsorption in the colon and thereby improve constipation.

Based on the submitted data from primary pharmacodynamic studies, PMDA considers that elobixibat has a suppressive effect on bile acid reabsorption by inhibiting the IBAT and thereby improves constipation.

3.R.2 Safety pharmacology

The applicant's explanation about the findings from each safety pharmacology study:

Following a single intravenous dose of elobixibat at 0.0035 to 3.5 mg/kg to dogs, a significant decrease in coronary blood flow was observed in ≥0.35 mg/kg groups. Based on this result, the non-observed effect level was assumed to be 0.035 mg/kg. The plasma concentrations of elobixibat in dogs following an intravenous dose of 0.35 mg/kg, at which effects were observed on the coronary artery, were 959 to 999 nmol/L, which was approximately 1500-fold the C_{max} (0.63 nmol/L) after administration of elobixibat at the maximum clinical dose, 15 mg. Therefore, elobixibat is unlikely to have any adverse effects when used in clinical practice. While a decrease in the level of bicarbonate ion (HCO_3^-) in the arterial blood was observed in the 3.5 mg/kg group, this was a minor, transient change unaccompanied by changes in arterial blood pH or pCO_2 and was considered to be of little toxicological significance.

Following oral administration of elobixibat at 350 mg/kg to rats, small intestinal propulsion was decreased by approximately 30% as compared with the vehicle control group, though its mechanism is unknown. However, based on the assumption that the human body weight is 60 kg, the dose of 350 mg/kg in rats is equivalent to approximately 1400-fold the maximum clinical dose of 15 mg (0.25 mg/kg) in humans. Therefore, elobixibat is unlikely to reduce small intestinal propulsion when used in clinical practice.

Following oral administration of elobixibat at 350 mg/kg to rats, a decrease in urinary excretion of sodium ion (Na^+) and an increase in urinary urea concentration were observed. However, since no findings of particular concern were found in the kidney in the 350 mg/kg group in a rat repeated-dose toxicity study [see Section 5.2.4], these changes were unlikely to indicate renal dysfunction. In a comparison of the area under concentration-time curve (AUC) and C_{max} in rats after administration at 350 mg/kg with those after administration at 15 mg, the maximum clinical dose, the safety margin was 271- to 502-fold for males and 346- to 465-fold for females. Therefore, elobixibat is unlikely to cause the above changes when used in clinical practice.

PMDA's view:
Based on the submitted data from safety pharmacology studies and the applicant's discussion, elobixibat is unlikely to have significant pharmacological effects on the central nervous, cardiovascular, respiratory, gastrointestinal, or renal/urinary system when used in clinical practice.

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

Pharmacokinetics in rats or dogs following oral or intravenous administration of elobixibat or ^{14}C-elobixibat were investigated. Plasma concentrations of unchanged elobixibat in rats were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS) with the lower limit of quantitation of 1 nmol/L (CTD 4.2.3.2-5). Plasma concentrations of unchanged elobixibat in dogs were measured by liquid chromatography with mass spectrometry (LC/MS; CTD 4.2.2.2-2) or LC/MS/MS (CTD 4.2.3.2-9) with the lower limit of quantitation of 20 and 1 nmol/L, respectively.

Radioactivity levels after administration of ^{14}C-elobixibat were measured by liquid scintillation counter, quantitative whole-body autoradiography, or radio-HPLC.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Oral single-dose study in dogs (CTD 4.2.2.2-2 [reference data], Study [redacted])

After administration of a single oral or intravenous dose of elobixibat to fasted male and female dogs, the pharmacokinetic parameters of unchanged elobixibat in plasma were as shown in Table 5. The results suggested the low systemic distribution of elobixibat after oral administration.

Table 5. Pharmacokinetic parameters of unchanged elobixibat in plasma after a single oral or intravenous administration of elobixibat in dogs

Route of administration	Dose of elobixibat (mg/kg)	C_{max} (nmol/L)	t_{max}[a)] (h)	$AUC_{0-\infty}$ (nmol·h/L)	$t_{1/2}$ (h)	Bioavailability[b)] (%)
Oral	7.0	146 (82, 233)	1 (0.5, 1)	314 (231, 445)	0.5 (0.3, 0.9)	2.0 (1.5, 2.9)
	35	256 (199, 322)	2 (0.5, 3)	943 (797, 1190)	1.5 (0.8, 2.6)	1.2 (0.9, 1.5)
Intravenous	1.7	-	-	3,960 (3,300, 4,900)	0.3 (0.2, 0.4)	-

Geometric mean (minimum, maximum); n = 3
a) Median (minimum, maximum)
b) Calculated using $AUC_{0-\infty}$ after intravenous administration at 1.7 mg/kg.

4.1.2 Repeated-dose studies

4.1.2.1 Repeated oral dose studies in rats and dogs (CTD 4.2.3.2-5 and 4.2.3.2-9, Studies [redacted] and [redacted])

In toxicity studies, elobixibat was administered orally once daily for 12 or 13 weeks to rats or dogs of both sexes to evaluate its toxicokinetics. Table 6 shows the pharmacokinetic parameters of unchanged elobixibat in plasma after repeated oral administration of elobixibat once daily for 12 weeks to male and female rats. No sex-related differences in pharmacokinetics were observed.

Table 6. Pharmacokinetic parameters of unchanged elobixibat in plasma in rats after repeated oral administration for 12 weeks

Dose of elobixibat (mg/kg/day)	Sex	Measurement time point	C_{max} (nmol/L)	t_{max} (h)	AUC_{0-t} (nmol·h/L)
3.5	Male	Day 1	4	2	12
		Week 12	4	1	5
	Female	Day 1	3	1	8
		Week 12	4	2	5
35	Male	Day 1	47	1	141
		Week 12	40	1	99
	Female	Day 1	37	1	115
		Week 12	27	1	66
350	Male	Day 1	302	1	3400
		Week 12	523	2	2900
	Female	Day 1	451	1	3220
		Week 12	302	1	2200

Each parameter was estimated based on the mean of plasma concentrations in 3 rats for each measurement time point.

Table 7 shows the pharmacokinetic parameters of unchanged elobixibat in plasma after repeated oral administration of elobixibat once daily for 13 weeks to male and female dogs. No sex-related differences in pharmacokinetics were observed.

Table 7. Pharmacokinetic parameters of unchanged elobixibat in plasma in dogs after repeated oral administration for 13 weeks

Dose of elobixibat (mg/kg/day)	Sex	Measurement time point	C_{max} (nmol/L)	t_{max}[a)] (h)	AUC_{0-t} (nmol·h/L)
3.5	Male	Day 1	8±5	(1, 2)	16±12
		Week 13	8±4	(1, 2)	24±8
	Female	Day 1	12±4	1[b)]	26±15
		Week 13	10±3	(1, 2)	28±5
17.5	Male	Day 1	61±30	(1, 2)	139±55
		Week 13	44±20	(1, 1)	106±44
	Female	Day 1	56±28	(1, 2)	134±92
		Week 13	34±9	1[b)]	118±41
140	Male	Day 1	114±46	(1, 2)	361±144
		Week 13	113±41	(1, 2)	520±200
	Female	Day 1	130±52	(1, 2)	436±104
		Week 13	101±60	(1, 2)	385±198

Mean ± standard deviation; n = 4
a) (minimum, maximum), b) The t_{max} in all the animals was 1 hour post-dose.

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-1, Study [redacted])

The radioactivity levels in tissues in male pigmented rats during the 7 days following a single dose of ^{14}C-elobixibat administered orally at 2.5 mg/kg or intravenously at 1.3 mg/kg were investigated.[1)]

Following oral dose of 2.5 mg/kg ^{14}C-elobixibat, most of the radioactivity administered was found in the gastric mucosa and small intestinal contents. Radioactivity was detected also in the liver, bile, renal cortex, prostate gland, urine, skin, and intestinal wall by 4 hours post-dose, only in intestinal contents at 24 hours post-dose, and was not detected in any tissues at 2 days post-dose.

Following intravenous dose of 1.3 mg/kg ^{14}C-elobixibat, the radioactivity level reached its peak in most tissues by 1 hour post-dose and then decreased over time. At 5 minutes post-dose, the radioactivity level in the liver, bile, renal cortex, and lung was higher than that in the blood. The radioactivity level in intestinal contents reached its peak at 1 hour post-dose in the small intestine and 4 hours post-dose in the cecum and colon. At 24 hours post-dose, radioactivity was detected only in the liver, cecum contents, and colonic contents. At 7 days post-dose, no radioactivity was detected in the body. No affinity for melanin was identified. Radioactivity was not detected in the central nervous system at any measurement time point.

[1] Radioactivity levels were determined after oral administration in the following tissues: brain, cardiac blood, cardiac muscle, lung, liver, bile, spleen, renal cortex, renal medulla (inside), renal medulla (outside), adrenal gland, testis, epididymis, prostate gland, urine, skeletal muscle, skin, gastric mucosa, intestinal wall, small intestinal contents, cecal contents, and colonic contents.
Radioactivity levels were determined after intravenous administration in the following tissues: brain, pineal gland, pituitary gland, lens, uveal/retinal pigment epithelium, vitreous body, exorbital lacrimal gland, Harderian gland, sublingual salivary gland, submandibular salivary gland, parotid salivary gland, thyroid gland, cardiac blood, cardiac muscle, thymus gland, lung, liver, bile, spleen, renal cortex, renal medulla (inside), renal medulla (outside), adrenal gland, testis, epididymis, prostate gland, vesicular gland, urine, bone, bone marrow, spinal cord, skeletal muscle, brown fat, skin, pigmented skin, gastric mucosa, pancreas, intestinal wall, lymph node, small intestinal contents, cecal contents, and colonic contents.

4.2.2 Placental transfer in rats (CTD 4.2.2.3-1, Study [redacted])

Radioactivity levels in maternal and fetal tissues were determined after administration of a single intravenous dose of 1.3 mg/kg ^{14}C-elobixibat to pregnant rats on gestation days 18 and 19. The radioactivity level in most maternal tissues reached its peak within 15 minutes of administration and then decreased over time. Radioactivity was detected in the liver and amnion also at 4 hours post-dose, but was not detected in any tissues at 24 hours post-dose. The radioactivity level in the fetus was below the lower limit of quantitation at any measurement time point.

4.3 Metabolism

4.3.1 *In vitro* study of metabolites (CTD 4.2.2.4-1, Study [redacted])

Metabolism of ^{14}C-elobixibate was evaluated using rat, mouse, and dog liver microsomes. In all of these animal species, 2 types of monohydroxides (M2 and M3) were identified as the major metabolites. The ratios of the monohydroxides (sum of M2 and M3) and unchanged elobixibat to the total radioactivity in the sample after reaction for 120 minutes were 23.0% and 65.4%, respectively, in the rat, 16.6% and 63.0% in the mouse, and 40.3% and 35.0% in the dog.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.3-1 and 4.2.2.5-1, Studies [redacted] and [redacted])

After a single oral dose of 2.5 mg/kg ^{14}C-elobixibat to male rats, a low level of radioactivity was detected in urine 15 to 60 minutes post-dose. The radioactivity level in the bile and intestinal contents reached its peak at 1 to 4 hours post-dose and then decreased over time. At 24 hours post-dose, radioactivity was detected only in intestinal contents.

After administration of a single dose of ^{14}C-elobixibat orally at 50 mg/kg or intravenously at 3 mg/kg to male rats with biliary cannulation, the urinary, fecal, and biliary excretion rates at 48 hours post-dose were as presented in Table 8.

Table 8. Excretion rate after a single dose of ^{14}C-elobixibat in rats with biliary cannulation

Route of administration	Dose of elobixibat (mg/kg)	Urinary excretion (%)	Fecal excretion (%)	Biliary excretion (%)
Oral	50	0.6±0.1	81.0±5.1	7.6±4.0
Intravenous	3	1.2±0.1	0.4±0.1	94.6±1.3

Mean ± standard deviation, n = 3

The results showed that elobixibat, after oral administration to rats, was hardly absorbed and was excreted in the feces and that most of elobixibat absorbed was excreted in the feces via bile.

4.4.2 Excretion into milk in rats (CTD 4.2.2.5-2, Study [redacted])

After a single oral dose of 50 mg/kg ^{14}C-elobixibat to lactating rats, the radioactivity levels in plasma and milk were determined. The radioactivity level in plasma and milk reached its peak at 2 and 8 hours post-dose,

respectively, and then decreased over time. At 8 hours post dose, the radioactivity level in milk was 1.3-fold that in plasma. After oral administration, the radioactivity level in milk did not markedly exceed that in plasma, and its elimination time course was similar to that in plasma. In rats, it was confirmed that elobixibat is excreted in milk after oral administration.

4.R Outline of the review conducted by PMDA

PMDA concluded there are no particular problems with the nonclinical pharmacokinetics of elobixibat.

5. Toxicity and Outline of the Review Conducted by PMDA

As toxicity studies of elobixibat, the following studies were conducted: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, and reproductive toxicity studies. In each study, doses of elobixibat are expressed as free base. For vehicle, 1% methylcellulose aqueous solution containing 0.5% Tween 80 was used unless otherwise noted.

5.1 Single-dose toxicity

5.1.1 Single oral dose toxicity study in mice (CTD 4.2.3.1-1, Study [redacted])

A single oral dose of elobixibat 2000 mg/kg was administered to male mice using 20% PEG 400 aqueous solution as vehicle. No deaths occurred. Staining around the anus, tail, and genital organs and loose stools were observed. Based on the above, the approximate lethal dose was determined to be >2000 mg/kg.

5.1.2 Single oral dose toxicity study in rats (CTD 4.2.3.1-2, Study [redacted])

A single oral dose of elobixibat 2000 mg/kg was administered to male and female rats using 20% PEG 400 aqueous solution as vehicle. No deaths occurred. Staining around the anus, tail, and genital organs and loose stools were observed. Based on the above, the approximate lethal dose was determined to be >2000 mg/kg.

5.1.3 Single oral dose toxicity study in dogs (CTD 4.2.3.1-3 [reference data], Study [redacted])

A single oral dose of elobixibat 8.4, 17, 35, 70, or 140 mg/kg or vehicle (1.0% polyvinyl pyrrolidone, 0.2% sodium dodecylsulphate, and 5% mannitol aqueous solution) was administered to male and female dogs in this study with a dose-escalation design. No deaths occurred. Loose stools or diarrhea was observed after administration at 8.4 to 70 mg/kg and vomiting was observed after administration at a dose of ≥35 mg/kg. Based on the above, the approximate lethal dose was determined to be >140 mg/kg.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in mice (for 13 weeks), rats (for 4, 13, or 26 weeks), and dogs (for 4, 13, or 52 weeks). The major findings were hepatocellular vacuolation in mice, suppressed body weight gain and low food consumption in rats, and vomiting, changes in fecal properties, and demodicosis-related changes in dogs. The no-observed-adverse-effect levels (NOAEL) in the 13-week study in mice, the 26-week study in rats, and the 52-week study in dogs was determined to be 200 mg/kg/day, 350 mg/kg/day, and 140 (male) and 17.5 (female) mg/kg/day, respectively. The exposure (AUC) at the NOAEL in male and

female mice, rats, and dogs was 721- and 588-fold, 502- and 465-fold, and 116- and 69-fold the exposure (AUC) at the proposed clinical dose (15 mg/day), respectively.

5.2.1 Thirteen-week repeated oral dose toxicity study in mice (CTD 4.2.3.2-1, Study [redacted])

Elobixibat at 200, 500, or 1500 mg/kg/day (80 mg/kg/day at Days 1 and 2) or vehicle was administered orally once daily for 13 weeks to male and female mice. One of 12 males and 1 of 12 females in the 500 mg/kg/day group and 3 of 12 males and 1 of 12 females in the 1500 mg/kg/day group were sacrificed moribund due to deteriorated clinical signs. The findings observed in these sacrificed animals included piloerection, abdominal distension, loose stools, staining of the urogenital organ, pallor, decreased body temperature, and decreased locomotor activity. In 1 of the 12 males in the 1500 mg/kg/day group among the sacrificed animals, severe elobixibat-related hepatocellular vacuolation was observed. Rhinitis attributed to the regurgitation of the administered solution was observed in 1 of 12 males and 1 of 12 females in the 500 mg/kg/day group and 2 of 12 males in the 1500 mg/kg/day group. In animals in ≥200 mg/kg/day groups, suppressed body weight gain, high blood aspartate aminotransferase (AST) level, and high blood alanine aminotransferase (ALT) level were observed. The applicant explained that the high blood AST and ALT levels observed in ≥200 mg/kg/day groups were of little toxicological significance because their incidences or changes were not dose-dependent and because there were no related hepatic histopathological changes. The NOAEL was determined to be 200 mg/kg/day for both sexes.

5.2.2 Four-week repeated oral dose toxicity study and 5-week reversibility study in rats (CTD 4.2.3.2-4, Study [redacted])

Elobixibat at 3.48, 34.8, or 348 mg/kg/day or vehicle (20% PEG 400 aqueous solution [pH 7.5]) was administered orally once daily for 4 weeks to male and female rats, and reversibility was evaluated after a 5-week recovery period in the 348 mg/kg/day group and the vehicle control group. While low urinary output and high urinary specific gravity were observed in males and females in the 348 mg/kg/day group, there were no changes in kidney weight or histopathological examination results. In the 348 mg/kg/day group, shortening of activated partial thromboplastin time (APTT) was observed in females but in none of the males, and there was no change in prothrombin time (PT) in either sex. Therefore, the applicant explained that the shortening of APTT was an incidental change. Changes were reversed after the recovery period. The NOAEL was determined to be 348 mg/kg/day for both sexes.

5.2.3 Thirteen-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-5, Study [redacted])

Elobixibat at 3.5, 35, or 350 mg/kg/day or vehicle was administered orally once daily for 13 weeks to male and female rats. In the 350 mg/kg/day group, suppressed body weight gain, low food consumption, high urinary specific gravity, low urinary output and pH, high incidence of phosphoric acid crystals in the urine, and high incidence of urinary occult blood were observed; however, there were no changes in kidney weight or renal histopathological findings. The NOAEL was determined to be 350 mg/kg/day for both sexes.

5.2.4 Twenty-six-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-6, Study [redacted])

Elobixibat at 3.5, 35, or 350 mg/kg/day or vehicle was administered orally once daily for 26 weeks to male and female rats. The following findings were observed: high blood AST and ALT levels in females in ≥3.5 mg/kg/day groups; suppressed body weight gain and low food consumption in males in the 350 mg/kg/day group; and high blood inorganic phosphorus level in males and females in the 350 mg/kg/day group. The applicant explained that the high blood AST and ALT levels were of little toxicological significance because these events were not accompanied by any histopathological changes. The NOAEL was determined to be 350 mg/kg/day for both sexes.

5.2.5 Four-week repeated oral dose toxicity study and a 4-week reversibility study in dogs (CTD 4.2.3.2-8, Study [redacted])

Elobixibat at 3.48, 17.4, or 139.2 mg/kg/day or vehicle (20% PEG 400 aqueous solution [pH 7.0]) was administered orally once daily for 4 weeks to male and female dogs, and reversibility was evaluated after a 4-week recovery period in the 139.2 mg/kg/day group and the vehicle control group. Loose or liquid stools and decreased blood triglycerides were observed in ≥17.4 mg/kg/day groups, and vomiting was observed in the 139.2 mg/kg/day group. The applicant explained that the loose or liquid stools were attributed to the pharmacological action of elobixibat and the decreased blood triglycerides reflected the effect of an elobixibat-related increase in bile acids on the lipid metabolism. Changes were reversed after the recovery period. The NOAEL was determined to be 17.4 mg/kg/day for both sexes.

5.2.6 Thirteen-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-9, Study [redacted])

Elobixibat at 3.5, 17.5, or 140 mg/kg/day or vehicle was administered orally once daily for 13 weeks to male and female dogs. Liquid stools were observed in ≥3.5 mg/kg/day groups and vomiting (in females only) and decreased blood total cholesterol were observed in the 140 mg/kg/day group. Based on the above, the NOAEL was determined to be 140 mg/kg/day for males and 17.5 mg/kg/day for females.

5.2.7 Fifty-two-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-10, Study [redacted])

Elobixibat at 3.5, 17.5, or 140 mg/kg/day or vehicle was administered orally once daily for 52 weeks to male and female dogs. The dose for females in the 140 mg/kg/day group was reduced to 70 mg/kg/day from Week 29 due to deteriorated clinical condition. Loose or liquid stools were observed in ≥17.5 mg/kg/day groups and demodicosis was observed in females in the 140 mg/kg/day group, in which the following demodicosis-related findings were also observed: reddening of skin, erosion, traumatic injury, thinning of hair, decreased red blood cell count, decreased hematocrit, and decreased hemoglobin. Because no effects were observed on the thymus or lymphoid tissue and there were no changes suggesting immunosuppression other than demodicosis in females in the 140 mg/kg/day group, the applicant explained that the mechanism of onset of demodicosis after administration of elobixibat is unknown. Based on the above, the NOAEL was determined to be 140 mg/kg/day for males and 17.5 mg/kg/day for females.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, and 4.2.3.3.2-1, Studies [redacted], [redacted], and [redacted])

Genotoxicity was evaluated in a bacterial reverse mutation assay, a gene mutation assay using the mouse lymphoma L5178Y cell line (L5178Y cells), and a rat bone-marrow micronucleus assay, in none of which elobixibat showed genotoxicity.

5.4 Carcinogenicity

Carcinogenicity was evaluated in studies in mice and rats, in none of which elobixibat showed carcinogenicity. The exposure (AUC) at the non-carcinogenic doses in mice and rats (125 and 200 mg/kg/day, respectively, for male and female mice, and 285 mg/kg/day for male and female rats) was 395- (male mice), 415-fold (female mice), 831- (male rats), and 621-fold (female rats) the exposure (AUC) at the proposed clinical dose (15 mg/day), respectively.

5.4.1 Two-year oral carcinogenicity study in mice (CTD 4.2.3.4.1-1, Study [redacted])

Elobixibat at 25, 75, or 200 mg/kg/day or vehicle was administered orally once daily to male for 104 weeks and female mice for 92 weeks. The dose in males in the 75 and 200 mg/kg/day groups was reduced to 50 and 125 mg/kg/day, respectively, in and after Week 25, because many males in these dose groups died. Rhinitis and intestinal distension were observed in fatal cases. According to the applicant's explanation, rhinitis caused by the regurgitation of the test drug was likely to cause airway obstruction and intestinal distension, and the regurgitation of the test drug may have been attributable to the viscosity of the solution administered or administration procedure.

No elobixibat-related neoplastic lesions were observed in the study, and no evidence of carcinogenicity was found in mice receiving elobixibat.

5.4.2 Two-year oral carcinogenicity study in rats (CTD 4.2.3.4.1-2, Study [redacted])

Elobixibat at 35, 100, or 285 mg/kg/day or vehicle was administered orally once daily to male and female rats for 104 weeks. Although the number of deaths from pituitary tumor was slightly higher in males in the 285 mg/kg/day group than in the vehicle control group, there was no increase in the incidence of pituitary tumors nor was a dose-dependent tendency observed in relation to the event. No elobixibat-related neoplastic lesions were identified in the study, and no carcinogenicity was observed in rats receiving elobixibat. As non-neoplastic lesions, an increase in the incidence or severity of biliary hyperplasia and basophilic cell nests in the liver was observed in each dose group. The applicant explained that these findings were of little toxicological significance because they were considered spontaneous age-related changes (*Toxicologic histopathology, first edition.* Nishimura Shoten, 2017;238-251) and because no neoplastic lesions were observed in the liver or the bile duct.

5.5 Reproductive and developmental toxicity

A rat study of fertility and embryo-fetal development, a rabbit embryo-fetal development study, and a rat study for effects on pre- and postnatal development, including maternal function were conducted. The exposure

(AUC) at the NOAEL for embryo-fetal development in rats and rabbits (1000 mg/kg/day for rats and 150 mg/kg/day for rabbits) was 648-fold and 81-fold, respectively, the human exposure (AUC) at the proposed clinical dose (15 mg/day). It was suggested that hardly any elobixibat crosses the placenta but is excreted in milk [see Sections 4.2.2 and 4.4.2].

5.5.1 Fertility and embryo-fetal development in rats (CTD 4.2.3.5.2-2, Study [redacted])

Elobixibat at 175, 350, or 1000 mg/kg/day or vehicle was administered orally once daily to male and female rats for 2 weeks prior to mating and throughout the mating period until the day before necropsy for males and until gestation day 17 for females. No effects were observed on parent animals or embryo-fetal development. Based on the above, the NOAEL was determined to be 1000 mg/kg/day for general toxicity and fertility in parent animals and embryo-fetal development.

5.5.2 Embryo-fetal development in rabbits (CTD 4.2.3.5.2-5, Study [redacted])

Elobixibat at 20, 55, or 150 mg/kg/day or vehicle was administered orally once daily to pregnant rabbits from gestation day 7 to 19. One of 21 dams in the 55 mg/kg/day group was sacrificed moribund on gestation day 17 due to emaciation. The applicant explained that the emaciation was not related to the administration of elobixibat because a marked decrease in food consumption had been observed in this animal from before the start of administration. Abortion occurred in 2 of 19 dams in the 150 mg/kg/day group on gestation days 19 and 27, respectively. Concerning the dam in which abortion occurred on gestation day 19, the cause of the abortion was unknown because no changes were observed in clinical condition or body weight and necropsy revealed no abnormalities. Considering that no effects were observed on embryo-fetuses when the uterus was examined, the applicant explained that the abortion was not related to administration but was an incidental event. The applicant attributed the abortion that occurred in the other dam at gestation day 27 to deteriorated clinical condition associated with a decrease in food consumption. There were no effects on maternal animals or embryo-fetuses. Based on the above, the NOAEL was determined to be 150 mg/kg/day for the general toxicity and fertility in maternal animals and the embryo-fetus development.

5.5.3 Effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3-1, Study [redacted])

Elobixibat at 100, 350, or 1000 mg/kg/day or vehicle was administered orally once daily to pregnant rats from gestation day 6 to lactation day 20. Eleven of 22 dams in the 1000 mg/kg/day group were sacrificed moribund during the period from lactation day 0 to 5. Ten of these 11 dams were sacrificed moribund because of the death of the entire litter, and most of them exhibited hunched posture, fecal abnormalities, piloerection, and decreased lactation. In addition, suppressed body weight gain and decreased body weight were observed during the final several days before delivery. In the other dam, decreased locomotor activity and partially closed eyes were observed besides the above findings. Gastrointestinal abnormalities (distension and abnormal discoloration of contents) were found in all these dams. In the 1000 mg/kg group, suppressed body weight gain and decreased food consumption were observed. In litters in the 1000 mg/kg group, sensation of cold, bradypnea, and poor milk intake were observed, and many of them died within 5 days after birth (death of the entire litter occurred in 10 dams). The applicant attributed decreased 7-day survival and lactation rates to

decreased lactation behavior in dams. Suppressed body weight gain was observed in ≥350 mg/kg/day groups and delayed differentiation (pinna unfolding and eyelid opening) and a decreased success rate of static righting reflex were observed in the 1000 mg/kg/day group. Based on the above, the NOAEL was determined to be 350 mg/kg/day for general toxicity and fertility in dams and 100 mg/kg/day for litters.

5.R Outline of the review conducted by PMDA

The applicant's explanation about the maternal toxicity of elobixibat:

In the 1000 mg/kg/day group, elobixibat was well tolerated in maternal animals until a few days before delivery, and maternal toxicity began to be observed at the end of pregnancy [see Section 5.5.3]. Bile production has been reported to be increased in female rats during late pregnancy and early lactation compared to non-pregnant rats or male rats (*Drug Metab Dispos.* 1978;6:120-124; *Hepatology.* 1984;4:633-638). Gastrointestinal disorder may have been induced by the bile acid increasing effect of elobixibat in addition to a physiological increase in bile production during late pregnancy and early lactation, affecting the lactation behavior and milk production in maternal animals.

PMDA's view:

The applicant's discussion about maternal toxicity is understood. Furthermore, the exposure (AUC) in maternal animals at 100 mg/kg/day, at which elobixibat has no effects on litters, is 207-fold the exposure (AUC) at the proposed clinical dose (15 mg/day). However, considering that there is no clinical experience with the use of elobixibat in pregnant or possibly pregnant women, the following caution statement should be provided in the "Use during Pregnancy, Delivery or Lactation" section of the package insert: "Use of the product in pregnant or possibly pregnant women is recommended only when expected therapeutic benefits outweigh potential risks."

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

In clinical studies for which data have been submitted for this application as evaluation data, the formulations shown in Table 9 were used. A change from Formulation B to Formulation C (proposed formulation) is ranked as Level [redacted] in terms of the level of formulation changes according to the "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000; partially revised based on PFSB/ELD Notification No. 0229-10 dated February 29, 2012) because the 2 formulations are different in the composition and content of [redacted]. Therefore, a dissolution test was conducted, and the bioequivalence between the formulations was demonstrated.

Table 9. Formulations used in clinical studies (evaluation data)

Clinical study	Formulation
Japanese phase I study (Study AJG533/CP1) Foreign drug interaction study (Study 000132)	Formulation A Film-coated tablets (each tablet contains 2.5, 5, 10, or 15 mg of elobixibat) In the foreign drug interaction study, only 5-mg tablets were used.
Japanese phase II study (Study AJG533/ET1)	Formulation B Film-coated tablets (each tablet contains 5 mg of elobixibat)
Japanese phase III study (Study AJG533/CT1) Long-term study (Study AJG533/LT1)	Formulation C (proposed formulation) Film-coated tablets (each tablet contains 5 mg of elobixibat)

Concentrations of unchanged elobixibat in plasma or urine were measured by LC/MS/MS. The lower limit of quantitation for plasma concentration of unchanged elobixibat was 10.0 pg/mL in the Japanese phase I study and 0.1 nmol/L in the foreign drug interaction study. The lower limit of quantitation for urinary concentration of unchanged elobixibat was 10.0 pg/mL. C4, an intermediate during the synthesis of bile acids from cholesterol, was used as the pharmacodynamic index. Plasma concentrations of C4 were measured by LC/MS/MS, and its lower limit of quantitation was 2.0 ng/mL.

Plasma concentrations of dabigatran and midazolam were measured by LC/MS/MS, and the lower limit of quantitation was 1.0 and 0.1 ng/mL, respectively.

6.1.1 Studies in human biomaterials

6.1.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-2, Study [redacted])

The percent plasma protein binding of ^{14}C-elobixibat 400 nmol/L in human plasma was 99.5% ± 0.0%. The distribution in blood cells of ^{14}C-elobixibat 100 and 400 nmol/L in human blood was both <5%.

6.1.1.2 *In vitro* study of metabolites (CTD 4.2.2.4-1, Study [redacted])

The metabolism of ^{14}C-elobixibat was evaluated using human liver microsomes. Two types of monohydroxides (M2 and M3) were identified as the major metabolites. The M2, M3, and unchanged elobixibat accounted for 4.3%, 11.6%, and 75.2%, respectively, of the total radioactivity in the sample after reaction for 120 minutes, showing that most of the administered elobixibat remained unchanged.

6.1.1.3 Inhibitory effects of elobixibat on human liver drug-metabolizing enzymes (CTD 5.3.2.2-1, Study [redacted])

The inhibitory effects of elobixibat (0.2-200 nmol/L; 0.12-120 μmol/L for CYP3A4/5 only) on CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) were investigated using human liver microsomes.[2)] The results showed that elobixibat exhibited an inhibitory effect on CYP3A4/5, and the inhibition constant (Ki) values for testosterone and midazolam, typical substrates of CYP3A4/5, were 25 and 7.7 μmol/L, respectively. Elobixibat also exhibited a pre-incubation time-dependent inhibitory effect on CYP3A4/5, and the maximal inactivation rate concentration (k_{inact}) and the half-maximal inactivation rate

[2] The following subtrates were used as reference materials:
CYP1A2, phenacetin; CYP2B6, efavirenz; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, S-mephenytoin; CYP2D6, dextromethorphan; CYP3A4/5, testosterone and midazolam

concentration (K_I) was 0.057 min^{-1} and 7.3 μmol/L, respectively, for the metabolism of testosterone and 0.037 min^{-1} and 3.1 μmol/L for the metabolism of midazolam. The enzymatic activity of CYP3A4/5 was not fully recovered by re-isolation of microsomes incubated with elobixibat or re-isolation after treatment with potassium ferricyanide, demonstrating that the inhibitory effect of elobixibat on CYP3A4/5 is irreversible. Inhibitory effects of elobixibat on other CYP enzymes were not identified.

6.1.1.4 Induction effects of elobixibat on human liver drug-metabolizing enzymes (CTD 5.3.2.2-2, Study [redacted])

Induction effects of elobixibat (0.0005-15 μmol/L) on CYP1A2, CYP2B6, and CYP3A4/5 were investigated using frozen human hepatocytes. Within the concentration range investigated, elobixibat did not exhibit any induction effects on any of the CYP enzymes examined.

6.1.1.5 P-gp- or BCRP-mediated transportation (CTD 5.3.2.2-3, Study [redacted])

P-gp-mediated transportation of elobixibat (0.625-10 μmol/L) was investigated using human colon carcinoma cell line Caco-2 (Caco-2 cells) and P-glycoprotein (P-gp) knockdown Caco-2 (CPT-P1 cells). The results suggested that elobixibat is unlikely to be a P-gp substrate.

The inhibitory effects of elobixibat (0.0412-10 μmol/L) on P-gp were investigated using Caco-2 cells. The results showed that elobixibat inhibited the transportation of digoxin, a P-gp substrate, with a half maximal inhibitory concentration (IC_{50}) value of 2.65 μmol/L.

Breast cancer resistance protein (BCRP)-mediated transportation of elobixibat (2.5 μmol/L) was investigated using Caco-2 cells. The results suggested that elobixibat is unlikely to be a BCRP substrate.

Inhibitory effects of elobixibat (0.0412-10 μmol/L) on BCRP were investigated using Caco-2 cells. As a result, the IC_{50} value of elobixibat against the transportation of cladribine, a BCRP substrate, was estimated to be approximately 6 μmol/L. Taking into account that the expected maximum concentration of elobixibat in the gastrointestinal tract after administration at the maximum clinical dose of 15 mg is 50.7 to 67.0 μmol/L, which is approximately 10-fold the IC_{50} value, the applicant explained that elobixibat is unlikely to have any inhibitory effect on BCRP when used in clinical practice.

6.1.1.6 Transportation of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K (CTD 5.3.2.2-4, Study [redacted])

Concerning the inhibitory effects of elobixibat on OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K, the effects of elobixibat (60-600 nmol/L [3, 10, 30, 100, 300, 600, and 1000 nmol/L for OATP1B1 only]) on reference materials were investigated using cells expressing these transporters.[3)] The IC_{50} value of elobixibat was 258 nmol/L against the transportation of the reference material for OATP1B1 and was estimated

[3] The following subtrates were used as reference materials:
OATP1B1 and OATP1B3, estradiol-17β-glucuronide; OAT1, p-aminohippuric acid; OAT3, estrone-3-sulfate; OCT2, metformin; MATE1 and MATE2-K, metformin

to exceed 600 nmol/L against the transportation of the reference material for the other transporters. Considering that the C_{max} of unchanged elobixibat after administration at the proposed maximum clinical dose (15 mg/day) in the fed state and fasted state was 0.39 and 2.19 ng/mL, respectively [see Section 6.2.1], the applicant explained that elobixibat is unlikely to have inhibitory effect on these transporters when used in clinical practice.

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose and multiple-dose study (food effect) (CTD 5.3.3.2-1, Study AJG533/CP1 [April 2013 to October 2013])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study (a crossover study for the investigation of food effects) was conducted in Japanese patients with chronic constipation aged ≥20 to <65 years (target sample size, 120 subjects [60 subjects to be included in both the single-dose part and the multiple-dose part]; 10 for placebo and 10 for each dose group of elobixibat) at 1 study site in Japan to investigate the pharmacokinetics, food effects on the pharmacokinetics, and safety of elobixibat.

(a) Single oral dose administration

A single dose of placebo or elobixibat at 2.5, 5, 10, 15, or 20 mg was administered orally under the fasted condition and before breakfast.

All 60 randomized subjects (10 for placebo and 10 for each dose group of elobixibat) were included in the safety analysis set, and all 50 subjects who received elobixibat were included in the pharmacokinetic and pharmacodynamic analysis sets.

The pharmacokinetic parameters of unchanged elobixibat are shown in Table 10. Plasma concentrations of unchanged elobixibat increased after administration under the fasted condition compared to administration before breakfast.

The mean urinary excretion rate of unchanged elobixibat was <0.01% in any dose group after administration under the fasted condition or before breakfast.

Table 10. Pharmacokinetic parameters of unchanged elobixibat in plasma after administration of a single oral dose of elobixibat under fasted condition or before breakfast

Dose of elobixibat	Food	n	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-t} (pg·h/mL)	$t_{1/2}$ (h)
2.5 mg	Fasted	10	490±325	2.5±0.7	1861±989	2.3±0.9
	Before breakfast	10	140±127	1.1±0.7[a)]	264±158	2.0±1.4
5 mg	Fasted	10	643±262	2.6±0.7	2982±992	4.6±2.7
	Before breakfast	10	187±87	1.8±1.6	745±460	3.3±3.1
10 mg	Fasted	10	1611±1048	2.0±0.7	6265±3769	6.6±4.1
	Before breakfast	10	386±215	1.9±1.6	1217±644	2.5±1.5
15 mg	Fasted	10	2194±1002	2.5±1.5	8871±3731	13.7±13.0
	Before breakfast	10	390±104	1.8±0.6	1565±458	3.2±1.5
20 mg	Fasted	9	3767±2038	2.3±0.8	14,194±5808	13.4±6.0
	Before breakfast	10	890±682	1.3±0.6	3569±2551	5.8±5.6

Mean ± standard deviation; a) n = 8

Plasma concentrations of C4, an intermediate during the synthesis of bile acids, were measured as the pharmacodynamic parameter. The AUC_{0-t} of plasma C4 concentrations after administration of placebo or elobixibat under the fasted condition or before breakfast is shown in Table 11. The AUC_{0-t} of plasma C4 concentrations in the elobixibat groups increased after administration before breakfast compared to administration under the fasted condition.

Table 11. AUC_{0-t} (ng·h/mL) of plasma C4 concentrations after administration of a single oral dose of elobixibat under fasted condition or before breakfast

Dose of elobixibat	Food	n	AUC_{0-t} (ng·h/mL)	
			Day −1	Day 1
Placebo	Fasted	10	416±295	377±285
	Before breakfast	10	484±494	490±466
2.5 mg	Fasted	10	361±183	392±233
	Before breakfast	10	402±293	684±652
5 mg	Fasted	10	432±221	485±324
	Before breakfast	10	395±203	713±311
10 mg	Fasted	10	497±268	544±312
	Before breakfast	10	415±276	705±390
15 mg	Fasted	10	599±516	724±671
	Before breakfast	10	586±593	1286±1184
20 mg	Fasted	9	500±229	620±287
	Before breakfast	10	474±229	1217±544

Mean ± standard deviation

After administration under the fasted condition, adverse events occurred in 40.0% (4 of 10) of subjects in the placebo group, 40.0% (4 of 10) of subjects in the elobixibat 2.5 mg group, 50.0% (5 of 10) of subjects in the 5 mg group, 30.0% (3 of 10) of subjects in the 10 mg group, 100.0% (10 of 10) of subjects in the 15 mg group, and 44.4% (4 of 9) of subjects in the 20 mg group. After administration before breakfast, adverse events occurred in 70.0% (7 of 10) of subjects in the placebo group, 40.0% (4 of 10) of subjects in the elobixibat 2.5 mg group, 80.0% (8 of 10) of subjects in the 5 mg group, 20.0% (2 of 10) of subjects in the 10 mg group, 60.0% (6 of 10) of subjects in the 15 mg group, and 40.0% (4 of 10) of subjects in the 20 mg group. After

administration under the fasted condition, adverse drug reactions occurred in 20.0% (2 of 10) of subjects in the placebo group, 30.0% (3 of 10) of subjects in the elobixibat 2.5 mg group, 50.0% (5 of 10) of subjects in the 5 mg group, 30.0% (3 of 10) of subjects in the 10 mg group, 100.0% (10 of 10) of subjects in the 15 mg group, and 33.3% (3 of 9) of subjects in the 20 mg group. After administration before breakfast, adverse drug reactions occurred in 50.0% (5 of 10) of subjects in the placebo group, 40.0% (4 of 10) of subjects in the elobixibat 2.5 mg group, 80.0% (8 of 10) of subjects in the 5 mg group, 20.0% (2 of 10) of subjects in the 10 mg group, 60.0% (6 of 10) of subjects in the 15 mg group, and 30.0% (3 of 10) of subjects in the 20 mg group. The adverse events that occurred in ≥2 subjects in any group are shown in Table 12 and Table 13. All these adverse events, except for abdominal pain lower reported in 1 subject in the 5 mg group after administration under the fasted condition, were assessed as adverse drug reactions. The adverse event leading to treatment discontinuation was headache, which was observed in 10.0% (1 of 10) of subjects in the 20 mg group after administration before breakfast. The event was assessed as an adverse drug reaction; however, it was mild in severity and resolved after discontinuation of study treatment. There were no deaths or serious adverse events. No marked difference was detected in the incidence of adverse events or adverse drug reactions between administration under the fasted condition and administration before breakfast.

Table 12. Adverse events that occurred in ≥2 subjects in any group after administration under the fasted condition

	Placebo (n = 10)	Elobixibat 2.5 mg (n = 10)	Elobixibat 5 mg (n = 10)	Elobixibat 10 mg (n = 10)	Elobixibat 15 mg (n = 10)	Elobixibat 20 mg (n = 9)
Overall	40.0 (4)	40.0 (4)	50.0 (5)	30.0 (3)	100.0 (10)	44.4 (4)
Abdominal distension	10.0 (1)	0 (0)	20.0 (2)	0 (0)	20.0 (2)	11.1 (1)
Diarrhoea	0 (0)	0 (0)	30.0 (3)	0 (0)	70.0 (7)	0 (0)
Abdominal pain lower	10.0 (1)	10.0 (1)	20.0 (2)	10.0 (1)	30.0 (3)	0 (0)

MedDRA/J ver.16.0; % incidence (number of subjects)

Table 13. Adverse events that occurred in ≥2 subjects in any group after administration before breakfast

	Placebo (n = 10)	Elobixibat 2.5 mg (n = 10)	Elobixibat 5 mg (n = 10)	Elobixibat 10 mg (n = 10)	Elobixibat 15 mg (n = 10)	Elobixibat 20 mg (n = 10)
Overall	70.0 (7)	40.0 (4)	80.0 (8)	20.0 (2)	60.0 (6)	40.0 (4)
Abdominal distension	20.0 (2)	20.0 (2)	0 (0)	0 (0)	10.0 (1)	20.0 (2)
Abdominal pain lower	30.0 (3)	20.0 (2)	40.0 (4)	10.0 (1)	10.0 (1)	10.0 (1)
Diarrhoea	10.0 (1)	0 (0)	40.0 (4)	0 (0)	50.0 (5)	0 (0)

MedDRA/J ver.16.0; % incidence (number of subjects)

(b) Multiple oral dose administration

Placebo or elobixibat at 2.5, 5, 10, 15, or 20 mg was administered orally once daily before breakfast for 14 days. Of 60 randomized subjects, 59 subjects were included in the safety analysis set,[4)] and all 49 subjects treated with elobixibat were included in the pharmacokinetic analysis set. Adverse events occurred in 60.0% (6 of 10) of subjects in the placebo group, 80.0% (8 of 10) of subjects in the elobixibat 2.5 mg group, 90.0% (9 of 10) of subjects in the 5 mg group, 100.0% (9 of 9) of subjects in the 10 mg group, 90.0% (9 of 10) of

4 One subject was excluded from the analysis population because of non-compliance with GCP (use of a false name).

subjects in the 15 mg group, and 90.0% (9 of 10) of subjects in the 20 mg group. Adverse drug reactions occurred in 50.0% (5 of 10) of subjects in the placebo group, 80.0% (8 of 10) of subjects in the elobixibat 2.5 mg group, 80.0% (8 of 10) of subjects in the 5 mg group, 88.9% (8 of 9) of subjects in the 10 mg group, 80.0% (8 of 10) of subjects in the 15 mg group, and 90.0% (9 of 10) of subjects in the 20 mg group. The adverse events that occurred in ≥2 subjects in any group are shown in Table 14. All these adverse events, except for nasopharyngitis in 2 subjects in the 10 mg group and diarrhoea in 1 subject in the 20 mg group, were assessed as adverse drug reactions. The adverse event leading to treatment discontinuation was urticaria, which was observed in 11.1% (1 of 9) of subjects in the 10 mg group. The event was assessed as an adverse drug reaction; however, it was mild in severity and resolved after discontinuation of study treatment. There were no deaths or serious adverse events.

Table 14. Adverse events that occurred in ≥2 subjects in any group

	Placebo (n = 10)	Elobixibat 2.5 mg (n = 10)	Elobixibat 5 mg (n = 10)	Elobixibat 10 mg (n = 9)	Elobixibat 15 mg (n = 10)	Elobixibat 20 mg (n = 10)
Overall	60.0 (6)	80.0 (8)	90.0 (9)	100 (9)	90.0 (9)	90.0 (9)
Diarrhoea	0 (0)	10.0 (1)	40.0 (4)	44.4 (4)	40.0 (4)	80.0 (8)
Abdominal distension	30.0 (3)	30.0 (3)	30.0 (3)	22.2 (2)	40.0 (4)	60.0 (6)
Abdominal pain lower	20.0 (2)	40.0 (4)	30.0 (3)	33.3 (3)	40.0 (4)	50.0 (5)
Abdominal pain upper	0 (0)	0 (0)	20.0 (2)	22.2 (2)	0 (0)	20.0 (2)
ALT increased	0 (0)	10.0 (1)	10.0 (1)	0 (0)	30.0 (3)	10.0 (1)
AST increased	0 (0)	0 (0)	10.0 (1)	0 (0)	20.0 (2)	10.0 (1)
Nasopharyngitis	0 (0)	0 (0)	0 (0)	22.2 (2)	0 (0)	0 (0)

MedDRA/J ver.16.0; % incidence (number of subjects)

The pharmacokinetic parameters are shown in Table 15. Multiple dose administration caused no notable accumulation of elobixibat.

The mean urinary excretion rate of unchanged elobixibat at Day 1 and Day 14 was <0.01% in any dose group of elobixibat.

Table 15. Pharmacokinetic parameters of unchanged elobixibat in plasma after multiple oral doses of elobixibat administered once daily before breakfast for 14 days

Dose of elobixibat	Measurement time point	n	C_{max} (pg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (pg·h/mL)	$t_{1/2}$ (h)
2.5 mg	Day 1	10	112.5±64.0	1.8±1.6	386.1±89.0[a)]	2.1±0.8[a)]
	Day 14	10	90.6±45.7	1.3±0.8	314.4±66.9[a)]	2.7±1.3[a)]
5 mg	Day 1	10	192.7±105.4	1.2±0.5	675.1±247.5	2.5±0.8
	Day 14	10	178.1±62.3	1.3±0.5	867.6±240.1	4.1±2.5
10 mg	Day 1	9	307.1±121.6	1.2±0.5	1254.2±265.3	2.8±0.9
	Day 14	8	250.5±86.3	1.7±0.8	1667.3±679.1	10.5±15.4
15 mg	Day 1	10	531.2±338.2	1.2±0.5	2047.9±1021.9	3.9±3.0
	Day 14	10	449.9±330.7	1.4±0.5	2305.8±1025.4	7.4±5.5
20 mg	Day 1	10	1139.4±868.9	1.1±0.6	3423.1±1696.2	3.7±2.3
	Day 14	10	1100.3±590.1	1.0±0.6	3785.8±1131.1	7.8±2.9

Mean ± standard deviation; a) n = 9

6.2.2 Foreign phase I study (mass balance study) (CTD 5.3.3.1-2 [reference data], Study A3309-004 [February 2010 to March 2010])

An open-label study was conducted in non-Japanese healthy adult male subjects aged ≥30 to ≤60 years (target sample size, 6 subjects) at 1 foreign study site to evaluate mass balance after a single oral dose of ^{14}C-elobixibat.

A single dose of ^{14}C-elobixibat 5 mg was administered orally before a meal.

All 6 subjects enrolled in the study were included in the safety and pharmacokinetic analysis sets. Whole blood and plasma concentrations were slightly higher than the lower limit of quantitation, suggesting the low systemic distribution of elobixibat after oral administration. No metabolites of elobixibat were identified in plasma.

Table 16. Plasma pharmacokinetic parameters after a single dose of ^{14}C-elobixibat

Dose of elobixibat	n	C_{max} (nmol/L)	t_{max} (h)[a)]	$AUC_{0\text{-}t}$ (nmol·h/L)	$t_{1/2}$ (h)[b)]
5 mg	6	0.5±0.3	0.8 (0.5, 2.0)	0.7±0.5	0.8±0.2

Mean ± standard deviation; a) Median (minimum, maximum); b) n = 3

By 72 hours after administration of ^{14}C-elobixibat, 99.2% of administered radioactivity was excreted in feces. Four types of isomers of monohydroxides of elobixibat were identified as metabolites in feces, a total of which accounted for 3.1% of radioactivity in feces. No other metabolites accounted for more than 1% of radioactivity in feces. In urine, 0.02% of radioactivity administered was excreted.

Adverse events occurred in 83.3% (5 of 6) of subjects, and all these events were assessed as adverse drug reactions. The adverse events that occurred in ≥2 subjects were abdominal discomfort and diarrhoea, each of which was reported in 50.0% (3 of 6) of subjects. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.3 Foreign phase I study (drug interaction with a CYP3A4 substrate or a P-gp substrate) (CTD 5.3.3.4-1, Study 000132 [February 2014 to April 2014])

An open-label study was conducted in healthy adult non-Japanese subjects aged ≥18 to <45 years (target sample size, 25 subjects) at 1 foreign study site to evaluate the effects of elobixibat on the pharmacokinetics of midazolam (a CYP3A4 substrate) and dabigatran (a P-gp substrate).

Elobixibat 10 mg was administered orally once daily from Day 5 to Day 9; midazolam 2 mg was administered orally once daily on Days 1, 5, and 9; and dabigatran etexilate 150 mg was administered orally once daily on Days 1 and 5 under the fasted condition.

All 25 subjects enrolled in the study received the study drugs and were included in the pharmacokinetic analysis set.

The geometric mean ratios (concomitant use versus non-concomitant use) of C_{max} and AUC_{0-t} for midazolam and dabigatran are shown in Table 17 at a single dose of midazolam or dabigatran etexilate in combination with elobixibat 10 mg (Day 5) and midazolam with 5-day multiple doses of elobixibat 10 mg (Day 9) versus a single dose of midazolam alone or dabigatran etexilate alone (without concomitant use of elobixibat) (Day 1). After administration of elobixibat in combination with dabigatran etexilate, the geometric mean ratios (90% confidence intervals [CIs]) of AUC_{0-t} and C_{max} of dabigatran did not fall within the pre-defined limits of 0.80 to 1.25. The above results indicated that elobixibat interacts with dabigatran.

Table17. Geometric mean ratios of plasma pharmacokinetic parameters of midazolam and dabigatran etexilate

Administration condition	Test drug (Oral administration)	Item measured	Geometric mean ratio [90% CI][a)]	
			C_{max}	AUC_{0-t}
Coadministration of a single dose of elobixibat[b)]	A single dose of midazolam 2 mg	Unchanged midazolam	1.09 [1.01, 1.18]	1.08 [1.01, 1.16]
Coadministration of multiple 5-day doses of elobixibat[c)]	A single dose of midazolam 2 mg	Unchanged midazolam	0.94 [0.87, 1.01]	0.78 [0.73, 0.83]
Coadministration of a single dose of elobixibat[d)]	Dabigatran etexilate 150 mg	Dabigatran	1.13 [0.96, 1.33]	1.17 [1.00, 1.36]

n = 25

a) C_{max} or AUC_{0-t} after administration with elobixibat 10 mg versus C_{max} or AUC_{0-t} after administration without elobixibat
b) Single administration of midazolam 2 mg on Day 1, and single administration of midazolam 2 mg in combination with elobixibat 10 mg on Day 5.
c) Single administration of midazolam 2 mg on Day 1, multiple once daily administration of elobixibat 10 mg from Day 5 to Day 9, and single coadministration with midazolam 2 mg on Days 5 and 9
d) Single administration of dabigatran etexilate 150 mg on Day 1, and single administration of dabigatran etexilate 150 mg in combination with elobixibat 10 mg on Day 5

6.R Outline of the review conducted by PMDA

6.R.1 Interactions with midazolam

The applicant's explanation about the interactions between elobixibat and midazolam:

In an *in vitro* study using human liver microsomes [see Section 6.1.1.3], the irreversible inhibitory effect of elobixibat on CYP3A4 was confirmed, and the k_{inact} and K_I values were 0.057 min^{-1} and 7.3 μmol/L, respectively, for the metabolism of testosterone and 0.037 min^{-1} and 3.1 μmol/L for the metabolism of midazolam. Given that the C_{max} of unchanged elobixibat in blood after administration at the proposed maximum clinical dose (15 mg/day given before a meal) is 0.63 nmol/L [see Section 6.2.1], elobixibat is unlikely to have any inhibitory effect on CYP3A4 when used in clinical practice.

Meanwhile, in the foreign drug interaction study [see Section 6.2.3], the AUC_{0-t} of midazolam after administration of midazolam in combination with elobixibat decreased to 0.78-fold (90% CI, 0.73-0.83) compared with that after administration of midazolam alone. Unlike the results of the *in vitro* study using human liver microsomes, the reason why the blood concentration of midazolam after administration with elobixibat became lower than that after administration without elobixibat in the foreign drug interaction study is unclear. However, it is considered unnecessary to provide any caution statements in the package insert warning against the concomitant use of elobixibat and CYP3A4 substrates on the basis of the following considerations: the blood concentration of midazolam would have increased after administration of midazolam in combination with elobixibat if elobixibat had interacted with midazolam via CYP3A4, but the blood

concentration decreased; and the incidence of adverse events did not tend to increase when elobixibat was administered in combination with a CYP3A4 substrate in the Japanese phase II, phase III, or long-term study.

PMDA's view:
Currently, it is not clear why the blood concentration of midazolam after administration with elobixibat became lower than that after administration without elobixibat in a clinical study. However, taking into account that the $AUC_{0\text{-}t}$ of midazolam after administration of midazolam in combination with elobixibat decreased to 0.78-fold (90% CI, 0.73-0.83) compared with that after administration of midazolam alone, a caution statement on the concomitant use of elobixibat and midazolam should be provided in the package insert.

6.R.2 Interactions with P-gp substrates

The applicant's explanation about the interactions between elobixibat and P-gp substrates:
Considering that an *in vitro* study using Caco-2 cells demonstrated the inhibitory effect of elobixibat on the transportation of digoxin, a P-gp substrate [see Section 6.1.1.5], and that a foreign drug interaction study using dabigatran etexilate, a P-gp substrate, showed the inhibitory effect of elobixibat on P-gp [see Section 6.2.3], a caution statement on the potential effects of concomitant use of elobixibat and digoxin will be provided in the package insert.

Concerning the safety of the concomitant use of elobixibat and a P-gp substrate, effects of the concomitant use of a P-gp substrate on the safety of elobixibat were studied in Japanese phase II, phase III, and long-term studies (Table 18). Those who received at least 1 dose of a P-gp substrate during treatment with the study drugs were defined as subjects treated with concomitant P-gp substrates.

Table 18. Incidence of adverse events by the concomitant use status of P-gp substrates

	Treatment with concomitant P-gp substrates	Treatment without concomitant P-gp substrates
Japanese phase II study	35.3% (6 of 17 subjects) (Placebo group, 25.0% [1 of 4 subjects])	30.2% (32 of 106 subjects) (Placebo group, 13.9% [5 of 36 subjects])
Japanese phase III study	55.6% (5 of 9 subjects) (Placebo group, 40.0% [2 of 5 subjects])	36.7% (22 of 60 subjects) (Placebo group, 15.5% [9 of 58 subjects])
Japanese long-term study	97.1% (68 of 70 subjects)	72.6% (196 of 270 subjects)

In the Japanese phase II study, there was no marked difference in the incidence of adverse events between subjects who did and did not receive concomitant P-gp substrates. In the Japanese phase III study, although the incidence of adverse events in subjects who received concomitant P-gp substrates was higher than that in subjects who did not receive concomitant P-gp substrates in the elobixibat group, the same tendency was also observed in the placebo group. Therefore, the higher incidence of adverse events in those who received concomitant P-gp substrates was unlikely to be attributable to any interaction between elobixibat and P-gp substrates. In the Japanese long-term study, the incidence of adverse events in subjects who received concomitant P-gp substrates was higher than that in subjects who did not receive concomitant P-gp substrates. However, out of a total of 68 subjects who received concomitant P-gp substrates and who experienced adverse events, 36 subjects used elobixibat and P-gp substrates concomitantly and 32 subjects received P-gp substrates

to treat adverse events that developed during treatment with elobixibat alone. The incidence of adverse events that occurred during the concomitant use of elobixibat and P-gp substrates was 51.4% (36 of 70 subjects), which was not higher than that in subjects who did not receive concomitant P-gp substrates. Therefore, the incidence of adverse events did not tend to increase when P-gp substrates were used concomitantly with elobixibat. Concomitant use of digoxin with elobixibat was reported in 2 subjects in the Japanese long-term study, and the incidence of adverse events in these subjects was 100% (2 of 2 subjects). Based on the above, it is considered unnecessary to include a caution statement on interactions between elobixibat and P-gp substrates other than digoxin in the package insert at this stage.

PMDA's view:

Considering that the concomitant use of elobixibat and dabigatran etexilate were observed to have effects on the blood concentrations of dabigatran in the foreign drug interaction study conducted using dabigatran etexilate, a caution statement on the use of elobixibat in combination with dabigatran etexilate should be included in the package insert. Since currently available data on interactions of elobixibat are limited, it is necessary to continue to collect relevant information via post-marketing surveillance.

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

As evaluation data, the results from a Japanese phase II study and 2 Japanese phase III studies were submitted (Table 19). The main inclusion and exclusion criteria, definitions of efficacy endpoints, and the Bristol stool scale (BSS) are shown in Table 20, Table 21, and Table 22, respectively.

Table 19. Summary of evaluation data on efficacy and safety (Japanese studies)

Phase	Study No.	Study population	Study design	Duration of treatment	Group (number of subjects treated)	Main endpoints
Phase II	AJG533/ ET1	Patients with chronic constipation	Double-blind, parallel-group, comparative study	2 weeks	Placebo (n = 40) Elobixibat 5 mg (n = 43) Elobixibat 10 mg (n = 39) Elobixibat 15 mg (n = 41)	Change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (mean ± standard deviation) Placebo, 2.60 ± 2.89 Elobixibat 5 mg, 3.50 ± 2.96 Elobixibat 10 mg, 5.66 ± 4.15 Elobixibat 15 mg, 5.59 ± 3.51
Phase III	AJG533/ CT1	Patients with chronic constipation	Double-blind, parallel-group, comparative study	2 weeks	Placebo (n = 63) Elobixibat 10 mg (n = 69)	Change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (mean ± standard deviation) Placebo, 1.73 ± 1.88 Elobixibat 10 mg, 6.40 ± 4.73
Phase III	AJG533/ LT1	Patients with chronic constipation	Open-label, uncontrolled study	52 weeks	Elobixibat (n = 340) Starting dose, 10 mg Range of dose adjustment, 5-15 mg	Safety evaluation Change in SBM frequency in the treatment period Week 52 from the screening period Week 2 (mean ± standard deviation) Elobixibat, 3.12 ± 2.40

Table 20. Main inclusion and exclusion criteria

Inclusion criteria • Patients with SBM frequency <6 during the 2-week screening period • Patients with at least 1 of the following symptoms related to SBM (a) Straining during ≥25% of defecations; (b) Lumpy or hard stools in ≥25% of defecations; (c) Sensation of incomplete evacuation for ≥25% of defecations. • Patients confirmed to have no organic lesions in the large intestine by colonoscopy or radiographic contrast enema in 5 years prior to enrollment **Exclusion criteria** • Patients with mushy or watery stool (BSS 6 or 7) in SBM during the 2-week screening period • Patients with confirmed or are suspected to have symptomatic or drug-induced constipation

Table 21. Main efficacy endpoints and evaluation methods

SBM	Defecation without laxative, enema, or digital evacuation (defecation within 24 hours after the use of a laxative or rescue medication will not be deemed as SBM)
Weekly SBM frequency	7 × (Total number of SBM during the screening period)/(Number of days of observation)
SBM responder rate	Proportion of patients with weekly SBM frequency of ≥3 and weekly SBM frequency improved by ≥1 from screening period Week 2
CSBM	SBM without sensation of incomplete evacuation
CSBM responder rate	Proportion of patients with weekly CSBM frequency of ≥3 and weekly CSBM frequency improved by ≥1 from baseline

Table 22. BSS

1	Separate hard lumps, like nuts (hard to pass)
2	Sausage-shaped, but lumpy
3	Like a sausage, but with cracks on the surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges (passed easily)
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces

7.1 Japanese phase II study (CTD 5.3.5.1-1, Study AJG533/ET1 [July 2014 to December 2014])

A multicenter, randomized, double-blind, parallel-group, comparative study was conducted in patients with chronic constipation aged ≥20 to <75 years (Table 20) (target sample size, 176 subjects [44 per group]) to investigate the efficacy and safety of elobixibat at 16 study sites in Japan.

Placebo or elobixibat 5, 10, or 15 mg was administered orally once daily before breakfast for 14 days.

All 163 randomized subjects (40 in the placebo group, 43 in the elobixibat 5 mg group, 39 in the 10 mg group, and 41 in the 15 mg group) received the study drug and were included in the full analysis set (FAS) and the safety analysis set. The FAS was regarded as the primary efficacy analysis set. Study treatment was discontinued in 9 subjects comprising 1 subject in the placebo group (due to “lack of efficacy” in 1 subject), 4 subjects in the elobixibat 5 mg group (due to “adverse events” in 4 subjects), 1 subject in the 10 mg group (due to “adverse events” in 1 subject), and 3 subjects in the 15 mg group (due to “adverse event” in 2 subjects and “request from subject” in 1 subject).

The primary efficacy endpoint was "change in spontaneous bowel movement (SBM) frequency in treatment period Week 1 from screening period Week 2," and the efficacy results are shown in Table 23. A statistically significant difference was observed in the elobixibat 10 and 15 mg groups compared with the placebo group (10 mg group, $P = 0.0005$; 15 mg group, $P = 0.0001$; analysis of covariance; two-sided significance level of 5%; multiplicity adjusted by a closed testing procedure).

Table 23. Change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (FAS)

	Placebo (n = 40)	Elobixibat 5 mg (n = 43)	Elobixibat 10 mg (n = 39)	Elobixibat 15 mg (n = 41)
SBM frequency in the screening period Week 2	1.80±1.07	1.81±0.82	1.62±0.96	1.78±0.82
SBM frequency in the treatment period Week 1	4.40±2.94	5.33±2.98[c)]	7.24±4.26[c)]	7.31±3.81[c)]
Change in SBM frequency from the screening period	2.60±2.89	3.50±2.96	5.66±4.15	5.59±3.51
Between-group difference in least squares mean for changes in SBM frequency (Elobixibat group – Placebo group) [95% CI][a)]		0.91 [-0.38, 2.20]	3.00 [1.36, 4.64]	3.00 [1.54, 4.45]
P-value[a) b)]		0.1629	0.0005	0.0001

Mean ± standard deviation

a) Analysis of covariance (ANCOVA) using SBM frequency in screening period Week 2 as the covariate; multiplicity was adjusted by a closed testing procedure from high to low dose.
b) Two-sided significance level of 5%
c) 41 subjects in the 5 mg group, 38 subjects in the 10 mg group, 39 subjects in the 15 mg group. Five subjects who discontinued the study <5 days after the start of study treatment were excluded from the analysis due to missing data (2 subjects in the 5 mg group, 1 subject in the 10 mg group, and 2 subjects in the 15 mg group).

Adverse events occurred in 15.0% (6 of 40) of subjects in the placebo group, 41.9% (18 of 43) of subjects in the elobixibat 5 mg group, 30.8% (12 of 39) of subjects in the 10 mg group, and 19.5% (8 of 41) of subjects in the 15 mg group. Adverse drug reactions occurred in 5.0% (2 of 40) of subjects in the placebo group, 32.6% (14 of 43) of subjects in the elobixibat 5 mg group, 28.2% (11 of 39) of subjects in the 10 mg group, and 17.1% (7 of 41) of subjects in the 15 mg group. The adverse events and adverse drug reactions that occurred in ≥2 subjects in any group are shown in Table 24 and Table 25, respectively.

Table 24. Adverse events that occurred in ≥2 subjects in any group

	Placebo (n = 40)	Elobixibat 5 mg (n = 43)	Elobixibat 10 mg (n = 39)	Elobixibat 15 mg (n = 41)
Overall	15.0 (6)	41.9 (18)	30.8 (12)	19.5 (8)
Abdominal pain	0 (0)	23.3 (10)	25.6 (10)	12.2 (5)
Diarrhoea	0 (0)	9.3 (4)	5.1 (2)	7.3 (3)
Abdominal distension	0 (0)	7.0 (3)	0 (0)	2.4 (1)
Headache	0 (0)	0 (0)	5.1 (2)	0 (0)
Nasopharyngitis	2.5 (1)	9.3 (4)	0 (0)	0 (0)

MedDRA/J ver.17.0; % incidence (number of subjects)

Table 25. Adverse drug reactions that occurred in ≥2 subjects in any group

	Placebo (n = 40)	Elobixibat 5 mg (n = 43)	Elobixibat 10 mg (n = 39)	Elobixibat 15 mg (n = 41)
Overall	5.0 (2)	32.6 (14)	28.2 (11)	17.1 (7)
Abdominal pain	0 (0)	23.3 (10)	25.6 (10)	12.2 (5)
Diarrhoea	0 (0)	9.3 (4)	5.1 (2)	7.3 (3)
Abdominal distension	0 (0)	7.0 (3)	0 (0)	2.4 (1)

MedDRA/J ver.17.0; % incidence (number of subjects)

Neither deaths nor serious adverse events occurred in any group. None of the patients in the placebo group experienced adverse events leading to treatment discontinuation; however, adverse events leading to treatment discontinuation occurred in 9.3% (4 of 43) of subjects in the elobixibat 5 mg group (diarrhoea, abdominal pain, and nausea; defaecation urgency and abdominal pain; dizziness, feeling abnormal, yawning, and loss of consciousness; and diarrhoea and abdominal pain in 1 subject each), 2.6% (1 of 39) of subjects in the 10 mg group (headache, nausea, abdominal pain lower, and malaise in 1 subject), and 4.9% (2 of 41) of subjects in the 15 mg group (diarrhoea and abdominal pain in 2 subjects). All these events were assessed as adverse drug reactions; however, they were all mild or moderate in severity and their outcomes were assessed as resolved.

7.2 Japanese phase III study (CTD 5.3.5.1-3, Study AJG533/CT1 [November 2015 to June 2016])

A multicenter, randomized, double-blind, parallel-group, comparative study was conducted in patients with chronic constipation aged ≥20 years (Table 20) (target sample size, 120 subjects [60 per group]) to investigate the efficacy and safety of elobixibat at 16 study sites in Japan.

Placebo or elobixibat 10 mg was administered orally once daily before breakfast for 14 days.

Of 133 randomized subjects (63 in the placebo group and 70 in the elobixibat group), 132 subjects (63 in the placebo group and 69 in the elobixibat group) excluding 1 subject in the elobixibat group with no visits after enrollment, received the study drug and were included in the FAS and the safety analysis set. The FAS was regarded as the primary efficacy analysis set. Study treatment was discontinued in 4 subjects, all of whom were in the elobixibat group (due to “adverse events” in 4 subjects).

The primary efficacy endpoint was “change in SBM frequency in the treatment period Week 1 from the screening period Week 2” and the efficacy results are shown in Table 26. The difference between the elobixibat group and the placebo group [95% CI] was 4.69 [3.45, 5.93], showing a statistically significant difference ($P < 0.0001$, analysis of covariance, two-sided significance level of 5%).

Table 26. Change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (FAS)

	Placebo (n = 63)	Elobixibat 10 mg (n = 69)
SBM frequency in the screening period Week 2	1.70±0.96	1.77±0.93
SBM frequency in the treatment period Week 1	3.43±2.00	8.19±4.82[c)]
Change in SBM frequency from the screening period	1.73±1.88	6.40±4.73
Between-group difference in least squares mean for changes in SBM frequency (Elobixibat group – Placebo group) [95% CI][a)]	4.69 [3.45, 5.93]	
P-value[a) b)]	$P < 0.0001$	

Mean ± standard deviation
a) Analysis of covariance (ANCOVA) using SBM frequency in screening period Week 2 as the covariate
b) Two-sided significance level of 5%
c) n = 67. Two subjects who discontinued the study <5 days after the start of study treatment were excluded from the analysis due to missing data.

Adverse events occurred in 17.5% (11 of 63) of subjects in the placebo group and 39.1% (27 of 69) of subjects in the elobixibat group, and adverse drug reactions occurred in 7.9% (5 of 63) of subjects in the placebo group and 30.4% (21 of 69) of subjects in the elobixibat group. The adverse events and adverse drug reactions that occurred in ≥2 subjects in either group are shown in Table 27 and Table 28, respectively.

Table 27. Adverse events that occurred in ≥2 subjects in either group

	Placebo (n = 63)	Elobixibat 10 mg (n = 69)
Overall	17.5 (11)	39.1 (27)
Abdominal pain	1.6 (1)	18.8 (13)
Diarrhoea	0 (0)	13.0 (9)
Abdominal pain lower	0 (0)	4.3 (3)
Nausea	0 (0)	2.9 (2)
Liver function test abnormal	3.2 (2)	1.4 (1)
Nasopharyngitis	4.8 (3)	0 (0)

MedDRA/J ver.18.0; % incidence (number of subjects)

Table 28. Adverse drug reactions that occurred in ≥2 subjects in either group

	Placebo (n = 63)	Elobixibat 10 mg (n = 69)
Overall	7.9 (5)	30.4 (21)
Abdominal pain	1.6 (1)	18.8 (13)
Diarrhoea	0 (0)	13.0 (9)
Abdominal pain lower	0 (0)	4.3 (3)
Nausea	0 (0)	2.9 (2)
Liver function test abnormal	3.2 (2)	1.4 (1)

MedDRA/J ver.18.0; % incidence (number of subjects)

Neither deaths nor serious adverse events occurred in either group. None of the subjects in the placebo group experienced adverse events leading to treatment discontinuation; however, 5.8% (4 of 69) of subjects in the elobixibat group (diarrhoea and abdominal pain in 3 subjects, and diarrhoea, abdominal pain, and nausea in 1 subject) experienced adverse events leading to treatment discontinuation. All these events were assessed as

adverse drug reactions; however, they were mild or moderate in severity and their outcomes were assessed as resolved.

7.3 Japanese long-term study (CTD 5.3.5.2-2, Study AJG533/LT1 [October 2015 to March 2017])

A multicenter, open-label, uncontrolled study was conducted in patients with chronic constipation aged ≥20 years (Table 20) (target sample size, 360 subjects) to investigate the long-term safety and efficacy of elobixibat at 36 study sites in Japan.

Elobixibat was administered orally once daily for 52 weeks in accordance with Table 29.

Table 29. Dosage and administration

Starting dose	10 mg
Range of dose adjustment	5-15 mg
Dose adjustment methods	**Dose increase** The dose increase is allowed when both of the following conditions are met. However, the dose increase of 5 mg to 15 mg is not allowed. • The subject took the study drug for ≥6 days during the 7 days before the planned day for dose increase. • The CSBM frequency during the 7 days before the planned day for dose increase is <3. **Dose reduction** The dose reduction is allowed based on the investigator's instruction or at the discretion of the subject when the subject has an excessive response to the treatment or experiences discomfort. **Interruption or resumption of treatment** Treatment is allowed to be interrupted based on the investigator's instruction or at the discretion of the subject when adverse events occur or before the conduct of gastrointestinal examination. Treatment may be resumed at or below the last dose level before the interruption.

Of 341 subjects enrolled in this study, 340 subjects, excluding 1 subject who did not receive any dose of elobixibat,[5)] were included in the FAS and the safety analysis set. The FAS was regarded as the primary efficacy analysis set. Study treatment was discontinued in 49 subjects. The reasons for discontinuation were "adverse events" in 23 subjects, "request from subject" in 14 subjects, "lack of efficacy" in 9 subjects, and "ineligible based on the inclusion or exclusion criteria," "no visits," and "pregnancy" in 1 subject each.

The primary efficacy endpoint was "change in SBM frequency in treatment period Week 52 from the screening period Week 2," and the SBM frequency was 3.12 ± 2.40 (Table 30).

5 The subject was suspected of having used prohibited rescue medication during the screening period and was discontinued from the study before the initiation of study treatment.

Table 30. Change in SBM frequency in treatment period Week 52 from the screening period Week 2 (FAS)

	Elobixibat (n = 340)
SBM frequency in screening period Week 2	1.47±0.97
SBM frequency in treatment period Week 52	4.59±2.43
Change in SBM frequency from the screening period	3.12±2.40

Mean ± standard deviation

Adverse events occurred in 77.6% (264 of 340) of subjects, and adverse drug reactions occurred in 47.9% (163 of 340) of subjects. The adverse events and adverse drug reactions that occurred in ≥2.0% of subjects are shown in Table 31 and Table 32, respectively.

Table 31. Adverse events that occurred in ≥2.0% of subjects

	Elobixibat group (n = 340)		Elobixibat group (n = 340)
Overall	77.6 (264)	Pharyngitis	2.9 (10)
Nasopharyngitis	25.6 (87)	Bronchitis	2.6 (9)
Abdominal pain	25.0 (85)	Gastroenteritis	2.6 (9)
Diarrhoea	15.9 (54)	Abdominal pain upper	2.6 (9)
Abdominal pain lower	5.0 (17)	Back pain	2.6 (9)
Nausea	5.0 (17)	Eczema	2.4 (8)
Upper respiratory tract inflammation	3.8 (13)	Dental caries	2.1 (7)
Influenza	3.5 (12)	Gastritis	2.1 (7)
Abdominal distension	3.5 (12)	Faeces soft	2.1 (7)
Liver function test abnormal	3.5 (12)	Blood creatine phosphokinase increased	2.1 (7)
Abdominal discomfort	3.2 (11)		

MedDRA/J ver.19.0; % incidence (number of subjects)

Table 32. Adverse drug reactions that occurred in ≥2.0% of subjects

	Elobixibat group (n = 340)		Elobixibat group (n = 340)
Overall	47.9 (163)	Abdominal distension	3.2 (11)
Abdominal pain	24.1 (82)	Nausea	2.9 (10)
Diarrhoea	14.7 (50)	Liver function test abnormal	2.9 (10)
Abdominal pain lower	5.0 (17)	Abdominal discomfort	2.1 (7)

MedDRA/J ver.19.0; % incidence (number of subjects)

There were no deaths. Serious adverse events occurred in 1.5% (5 of 340) of subjects (subarachnoid haemorrhage, subdural haematoma, skull fracture, and subdural hygroma; pneumonia mycoplasmal; carpal tunnel syndrome; retinal detachment; and inguinal hernia in 1 subject each). Of these events, inguinal hernia was assessed as an adverse drug reaction, and its outcome was assessed as resolved. Adverse events leading to treatment discontinuation occurred in 6.8% (23 of 340) of subjects (abdominal pain and diarrhoea in 4 subjects; diarrhoea and liver function test abnormal in 2 subjects each; and rash; abdominal pain; abdominal pain and abdominal pain upper; abdominal distension; abdominal distension, abdominal discomfort, and flatulence; hepatic function abnormal; urticaria and abdominal pain; menopausal symptoms; depressed mood; faeces soft; inguinal hernia; pneumonia mycoplasmal; subarachnoid haemorrhage, subdural haematoma, skull fracture, and subdural hygroma; facial paralysis; and oedema peripheral and vascular pain in 1 subject each). All these events,

except for hepatic function abnormal; menopausal symptoms; depressed mood; pneumonia mycoplasmal; subarachnoid haemorrhage, subdural haematoma, skull fracture, and subdural hygroma; and vascular pain, were assessed as adverse drug reactions and their outcomes were assessed as resolved or resolving.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the review and the results of confirmation presented in Sections 7.R.1.1 through 7.R.1.4, PMDA considers that the efficacy of elobixibat in patients with chronic constipation has been demonstrated.

A final decision on the efficacy of elobixibat will be made, taking account of comments raised in the Expert Discussion.

7.R.1.1 Primary endpoint

The applicant's explanation about the rationale for the primary endpoint in the Japanese phase III study:
Taking into account that frequency of weekly bowel movement is specified as a diagnostic criterion for functional constipation in the Rome diagnostic criteria[6)] used worldwide and that it is considered inappropriate to include bowel movements resulting from the use of rescue medication in the assessment of efficacy endpoints, SBM frequency was selected as an endpoint. Because elobixibat is expected to act quickly, "change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (1 week immediately before the start of study treatment)" was set as the primary endpoint in the Japanese phase II and phase III studies.

In the Japanese phase III study, the "change in SBM frequency in the treatment period Week 1 from the screening period Week 2 (mean ± standard deviation)" was 1.73 ± 1.88 in the placebo group and 6.40 ± 4.73 in the elobixibat group, demonstrating the superiority of the elobixibat group over the placebo group ($P < 0.0001$, analysis of covariance, two-sided significance level of 5%).

The above results indicated that the efficacy of elobixibat has been demonstrated in patients with chronic constipation.

PMDA's view:
There is no particular problem with setting the primary endpoint of the Japanese phase III study as "change in SBM frequency in the treatment period Week 1 from the screening period Week 2." Since the superiority of the elobixibat group over the placebo group was verified in the Japanese phase III study, the efficacy of elobixibat in treating chronic constipation was demonstrated.

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6 The Rome III criteria (*Gastroenterology.* 2006;130:1480-1491), which were available as published criteria at the time of planning the study, were used. While the Rome IV criteria (*Bowel Dis Gastroenterol.* 2016;150:1393-1407) were published in May 2016, the diagnostic criteria for functional constipation were similar to those of the Rome III criteria.

7.R.1.2 Main secondary endpoints

"Change in complete spontaneous bowel movement (CSBM) frequency in treatment period Week 1 from screening period Week 2," "SBM responder rate in treatment period Week 1," "CSBM responder rate in treatment period Week 1," and "median weekly BSS-based stool consistency in treatment period Week 1" in the Japanese phase III study are as presented in Table 33. The elobixibat group tended to show higher effect in all SBM or CSBM-related endpoints than that in the placebo group. In addition, BSS-based stool consistency tended to change after treatment with elobixibat.

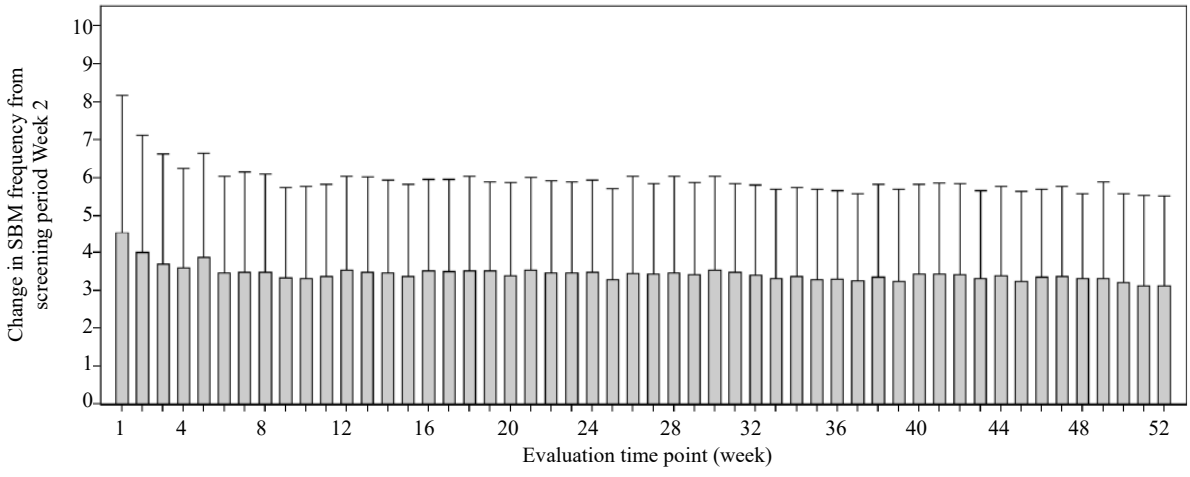
Table 33. Results of main secondary endpoints (Japanese phase III study; FAS)

	Placebo (n = 63)	Elobixibat 10 mg (n = 69)
Change in CSBM frequency in the treatment period Week 1 from the screening period Week 2 (mean ± standard deviation)	0.62±1.44 (n = 63)	3.39±3.86 (n = 67)
Between-group difference in least squares mean for changes in CSBM frequency(Elobixibat group – Placebo group) [95% CI]	2.77 [1.76, 3.78]	
SBM responder rate in treatment period Week 1 [95% CI]	60.3% (n = 38/63) [48.0, 71.5]	94.0% (n = 63/67) [85.6, 97.7]
CSBM responder rate in the treatment period Week 1 [95% CI]	17.5% (n = 11/63) [10.0, 28.6]	52.2% (n = 35/67) [40.5, 63.8]
Median weekly BSS-based stool consistency in the treatment period Week 1 (mean ± standard deviation)	2.5±1.2 (n = 61)	4.4±1.3 (n = 66)

Figures in the parentheses indicate the number of subjects evaluated (subjects who discontinued the study <5 days after the start of study treatment were excluded from the analysis due to missing data)

7.R.1.3 Long-term efficacy

Figure 1 presents the time course of the "change in SBM frequency at each week of the treatment period from screening period Week 2" in the long-term study. The time course shows that a certain level of therapeutic effect was maintained also in and after treatment period Week 2.



Evaluation time point (week)	1	4	8	12	16	20	24	28	32	36	40	44	48	52
Number pf subjects	339	333	321	319	314	312	309	306	303	300	295	292	291	186

Figure 1. Time course of the change in SBM frequency from screening period Week 2 (Japanese long-term study)

7.R.1.4 Efficacy by patient characteristics

In the Japanese phase III study, the "change in SBM frequency in the treatment period Week 1 from the screening period Week 2" by main patient characteristics was as shown in Table 34. The change in the elobixibat group tended to be greater than that in the placebo group. Concerning "subjects with no SBM in screening period Week 2" and "subjects with constipation, for which severity was assessed as 'none' (absence of constipation symptoms) in screening period Week 2 ," there were no clear differences between the 2 groups. However, because of a limited number of applicable subjects, it was difficult to compare these results between the groups.

Table 34. Change in SBM frequency in the treatment period Week 1 from the screening period Week 2 by patient characteristics (Japanese phase III study; FAS)

Stratification factor	Category	Placebo (n = 63)	Elobixibat 10 mg (n = 67)	Between-group difference (Elobixibat group – placebo group) [95% CI]
Sex	Male	1.3 (11)	5.3 (12)	4.1 [1.4, 6.7]
	Female	1.8 (52)	6.6 (55)	4.8 [3.4, 6.2]
Age	<65 years	1.6 (58)	6.2 (61)	4.5 [3.2, 5.8]
	≥65 years	3.0 (5)	8.8 (6)	5.8 [0.0, 11.6]
BMI	<25 kg/m^2	1.8 (55)	6.5 (62)	4.6 [3.3, 6.0]
	≥25 kg/m^2	1.1 (8)	5.8 (5)	4.7 [1.4, 7.9]
Complications	Yes	1.9 (36)	7.3 (43)	5.4 [3.7, 7.2]
	No	1.6 (27)	4.8 (24)	3.3 [1.6, 4.9]
Past history	Yes	1.7 (11)	5.7 (10)	4.0 [2.2, 5.8]
	No	1.7 (52)	6.5 (57)	4.8 [3.3, 6.3]
IBS-C[a)]	Criteria met	1.2 (13)	6.4 (22)	5.2 [2.9, 7.5]
	Criteria not met	1.9 (50)	6.4 (45)	4.5 [3.0, 6.1]
SBM frequency in Week2 of the screening period	0	1.6 (8)	3.3 (6)	1.7 [-0.6, 4.0]
	1	2.6 (15)	7.4 (18)	4.8 [2.3, 7.3]
	2	1.5 (30)	7.1 (27)	5.7 [3.4, 7.9]
	3	1.0 (8)	5.2 (16)	4.2 [1.6, 6.9]
	4	2.5 (2)	– (0)	–
Severity of constipation in Week2 of the screening period[b)]	None	6.0 (2)	1.0 (1)	−5.0 [−71.0, 61.0]
	Mild	– (0)	3.0 (2)	–
	Moderate	1.0 (18)	6.2 (23)	5.2 [3.6, 6.9]
	Severe	1.8 (33)	6.9 (30)	5.0 [3.0, 7.1]
	Very severe	1.6 (9)	6.5 (11)	5.0 [1.2, 8.8]
BSS-based stool consistency	1-2	1.9 (40)	6.4 (37)	4.5 [2.7, 6.4]
	3-5	1.4 (15)	7.1 (24)	5.7 [3.7, 7.8]

Change (number of subjects; subjects who discontinued the study <5 days after the start of study treatment were excluded from the analysis due to missing data)

a) Assessed according to the Rome III diagnostic criteria

b) None = having no constipation symptoms; Mild = having slight constipation symptoms; Moderate = experiencing constipation without severe constipation symptoms; Severe = experiencing severe constipation with difficulty in defecation or sensation of incomplete evacuation; Very severe = having persistent constipation with little defecation or strong sensation of incomplete evacuation

PMDA's view:

It is necessary to continue collecting information by patient characteristics via post-marketing surveillance and to further investigate factors that may affect the efficacy of elobixibat.

7.R.2 Safety

Based on the review and the results of confirmation presented in Sections 7.R.2.1 through 7.R.2.6, PMDA considers that the safety of elobixibat in patients with chronic constipation is acceptable.

A final decision on the safety of elobixibat will be made, taking account of comments raised in the Expert Discussion.

7.R.2.1 Comparison with placebo

The applicant's explanation about the safety of elobixibat relative to placebo based on data from the pooled analysis of the Japanese phase II and phase III studies:

The incidences of adverse events and adverse drug reactions in data from the pooled analysis of the Japanese phase II and phase III studies are shown in Table 35 and Table 36, respectively. The incidences of adverse events and adverse drug reactions were higher in the elobixibat combined group than the placebo group, and the most common events were abdominal pain and diarrhoea.

Table 35. Summary of adverse events that occurred in ≥2.0% of the subjects in the elobixibat combined group (Pooled analysis of the Japanese phase II and phase III studies)

	Placebo (n = 103)	Elobixibat 5 mg (n = 43)	Elobixibat 10mg (n = 108)	Elobixibat 15 mg (n = 41)	Elobixibat combined group (n = 192)
Overall	16.5 (17)	41.9 (18)	36.1 (39)	19.5 (8)	33.9 (65)
Abdominal pain	1.0 (1)	23.3 (10)	21.3 (23)	12.2 (5)	19.8 (38)
Diarrhoea	0 (0)	9.3 (4)	10.2 (11)	7.3 (3)	9.4 (18)
Abdominal pain lower	1.0 (1)	0 (0)	3.7 (4)	2.4 (1)	2.6 (5)
Abdominal distension	1.0 (1)	7.0 (3)	0 (0)	2.4 (1)	2.1 (4)
Nausea	0 (0)	2.3 (1)	2.8 (3)	0 (0)	2.1 (4)
Nasopharyngitis	3.9 (4)	9.3 (4)	0 (0)	0 (0)	2.1 (4)

MedDRA/J ver.19.0; % incidence (number of subjects)

Table 36. Summary of adverse drug reactions that occurred in ≥2.0% of the subjects in the elobixibat combined group (Pooled analysis of the Japanese phase II and phase III studies)

	Placebo (n = 103)	Elobixibat 5 mg (n = 43)	Elobixibat 10 mg (n = 108)	Elobixibat 15 mg (n = 41)	Elobixibat combined group (n = 192)
Overall	6.8 (7)	32.6 (14)	29.6 (32)	17.1 (7)	27.6 (53)
Abdominal pain	1.0 (1)	23.3 (10)	21.3 (23)	12.2 (5)	19.8 (38)
Diarrhoea	0 (0)	9.3 (4)	10.2 (11)	7.3 (3)	9.4 (18)
Abdominal pain lower	1.0 (1)	0 (0)	3.7 (4)	2.4 (1)	2.6 (5)
Abdominal distension	0 (0)	7.0 (3)	0 (0)	2.4 (1)	2.1 (4)
Nausea	0 (0)	2.3 (1)	2.8 (3)	0 (0)	2.1 (4)

MedDRA/J ver.19.0; % incidence (number of subjects)

Neither deaths nor serious adverse events were observed in any group. The adverse events leading to treatment discontinuation are shown in Table 37. All these events observed in elobixibat groups were assessed as adverse drug reactions; however, they were mild or moderate in severity and their outcomes were assessed as resolved.

Table 37. Adverse events leading to treatment discontinuation
(Data from the pooled analysis of the Japanese phase II and phase III studies)

Treatment group	Incidence (Number of subjects)	Name of event
Placebo	0% (0/103)	None
Elobixibat 5 mg	9.3% (4/43)	Diarrhoea, abdominal pain, and nausea; defaecation urgency and abdominal pain; dizziness, feeling abnormal, yawning, and loss of consciousness; and diarrhoea and abdominal pain in 1 subject each
Elobixibat 10 mg	4.6% (5/108)	Diarrhoea and abdominal pain in 3 subjects; and diarrhoea, abdominal pain, and nausea; and headache, nausea, abdominal pain lower, and malaise in 1 subject each
Elobixibat 15 mg	4.9% (2/41)	Diarrhoea and abdominal pain in 2 subjects each

PMDA confirmed that there were no clinically marked differences in the incidence of adverse events except for abdominal pain and diarrhoea between the elobixibat combined group and the placebo group in data from the pooled analysis of the Japanese phase II and phase III studies. Gastrointestinal disorders including abdominal pain and diarrhoea, which occurred with a higher incidence in the elobixibat combined group, will be reviewed in Section 7.R.2.3.

7.R.2.2 Long-term safety

The applicant's explanation about the long-term safety of elobixibat:

The incidence of adverse events by time period in the Japanese long-term study is shown in Table 38. There was no tendency towards an increase in the incidence of adverse events with longer administration period. High incidence of abdominal pain and diarrhoea were noted within 28 days of the initiation of treatment, but there was no tendency towards an increase thereafter.

Table 38. Incidence of adverse events by time period (Japanese long-term study)

	1-28 days (n = 340)	29-56 days (n = 330)	57-84 days (n = 320)	85-112 days (n = 319)	113-140 days (n = 314)	141-168 days (n = 309)	169-196 days (n = 308)
Overall	36.2 (123)	15.5 (51)	16.3 (52)	14.7 (47)	15.9 (50)	13.3 (41)	13.0 (40)
Abdominal pain	15.9 (54)	2.4 (8)	1.9 (6)	0.6 (2)	1.3 (4)	1.0 (3)	1.3 (4)
Diarrhoea	8.2 (28)	1.5 (5)	1.6 (5)	1.3 (4)	1.6 (5)	0.3 (1)	0.3 (1)
	197-224 days (n = 305)	225-252 days (n = 302)	253-280 days (n = 298)	281-308 days (n = 294)	309-336 days (n = 292)	≥337 days (n = 291)	Overall period (n = 340)
Overall	11.8 (36)	12.3 (37)	14.1 (42)	10.9 (32)	15.4 (45)	10.3 (30)	77.6 (264)
Abdominal pain	0.3 (1)	0 (0)	0.3 (1)	0 (0)	0.7 (2)	0 (0)	25.0 (85)
Diarrhoea	0 (0)	0.3 (1)	0 (0)	0.7 (2)	0.3 (1)	0.3 (1)	15.9 (54)

MedDRA/J ver.19.0; % incidence (number of subjects)

7.R.2.3 Gastrointestinal disorders

In data from the pooled analysis of the Japanese phase II and phase III studies, the incidence of abdominal pain and diarrhoea in the elobixibat group was higher than that in the placebo group [see Section 7.R.2.1]. The applicant's explanation about the occurrences of abdominal pain and diarrhoea in subjects treated with elobixibat:

In data from the pooled analysis of the Japanese phase II and phase III studies, all the adverse events that occurred in ≥2.0% of the subjects in the elobixibat combined group (Table 35) were gastrointestinal disorder-related events except for nasopharyngitis. The gastrointestinal disorder-related events with a high incidence were abdominal pain and diarrhoea.

The incidence and severity of abdominal pain and diarrhoea reported in the Japanese phase II and phase III studies are shown in Table 39 and Table 40, respectively. The incidence of these events did not increase with the dose increase, and all the events were mild or moderate in severity.

Table 39. Incidence of abdominal pain
(Data from the pooled analysis of the Japanese phase II and phase III studies)

	Placebo group (n = 103)	Elobixibat 5 mg group (n = 43)	Elobixibat 10 mg group (n = 108)	Elobixibat 15 mg group (n = 41)	Elobixibat combined group (n = 192)
Overall	1.0 (1)	23.3 (10)	21.3 (23)	12.2 (5)	19.8 (38)
Mild	1.0 (1)	23.3 (10)	19.4 (21)	7.3 (3)	17.7 (34)
Moderate	0 (0)	0 (0)	1.9 (2)	4.9 (2)	2.1 (4)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain leading to treatment discontinuation	0 (0)	7.0 (3)	3.7 (4)	4.9 (2)	4.7 (9)

MedDRA/J ver.19.0; % incidence (number of subjects)

Table 40. Incidence of diarrhoea
(Data from the pooled analysis of the Japanese phase II and phase III studies)

	Placebo group (n = 103)	Elobixibat 5 mg group (n = 43)	Elobixibat 10 mg group (n = 108)	Elobixibat 15 mg group (n = 41)	Elobixibat combined group (n = 192)
Overall	0 (0)	9.3 (4)	10.2 (11)	7.3 (3)	9.4 (18)
Mild	0 (0)	9.3 (4)	10.2 (11)	4.9 (2)	8.9 (17)
Moderate	0 (0)	0 (0)	0 (0)	2.4 (1)	0.5 (1)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea leading to treatment discontinuation	0 (0)	4.7 (2)	3.7 (4)	4.9 (2)	4.2 (8)

MedDRA/J ver.19.0; % incidence (number of subjects)

In the Japanese long-term study, abdominal pain occurred in 25.0% (85 of 340) of subjects (126 events) and diarrhoea occurred in 15.9% (54 of 340) of subjects (92 events) (Table 38). All these events were mild or moderate in severity. Many of the subjects who developed abdominal pain or diarrhoea recovered from these events without changing or reducing the dose of elobixibat. Subjects in whom the study treatment was interrupted or discontinued also recovered from these events. Therefore, abdominal pain or diarrhoea would not be of clinically significant problem if treated appropriately.

PMDA's view:
Although abdominal pain and diarrhoea occurred with a certain incidence according to the data from the pooled analysis of the Japanese phase II and phase III studies and in the Japanese long-term study, all these events were mild or moderate in severity and resolved after appropriate measures, such as dose reduction and the

interruption of treatment, were taken. Therefore, these events are not regarded as clinically significant problems. However, the following caution statement should be included in the package insert: “If abdominal pain or diarrhoea occurs during treatment with elobixibat, appropriate measures, such as dose reduction or the interruption of treatment, should be taken.”

7.R.2.4 Effects on lipid-related parameters

The applicant’s explanation about the effects of elobixibat on lipid-related parameters:
Since elobixibat inhibits the reabsorption of bile acids in the ileum, synthesis of bile acids from low-density lipoprotein (LDL)-cholesterol is enhanced to replace excreted bile acids and, as a result, the LDL-cholesterol level in the blood is expected to decrease. Therefore, the effects of elobixibat on lipid-related parameters (i.e., LDL-cholesterol, high-density lipoprotein [HDL]-cholesterol, and total cholesterol) were evaluated in Japanese clinical studies.

The lipid-related parameters in the Japanese phase III study are shown in Table 41. While a decrease in the serum LDL-cholesterol level and total cholesterol level was observed in the elobixibat group in treatment period Week 2, there was no change in the serum HDL-cholesterol level.

Table 41. Changes in lipid-related parameters (Japanese phase III study)

	Treatment period	Placebo (n = 63)	Elobixibat 10 mg (n = 69)
Serum LDL-cholesterol level (mg/dL)	At enrollment	113.4±31.5	117.9±29.9
	Treatment period Week 2	114.9±31.4	104.5±25.9
Serum HDL-cholesterol level (mg/dL)	At enrollment	67.1±15.9	69.0±12.2
	Treatment period Week 2	69.6±17.2	68.8±12.7
Serum total cholesterol level (mg/dL)	At enrollment	191.0±34.7	197.3±32.8
	Treatment period Week 2	195.9±35.0	185.2±29.8

Mean ± standard deviation

The lipid-related parameters in the long-term study are shown in Table 42. The serum LDL-cholesterol level decreased by approximately 10% after initiation of treatment and then remained unchanged thereafter. Elobixibat did not decrease the serum LDL-cholesterol level over time. There was no marked change in the serum HDL-cholesterol level. While the total cholesterol level decreased by approximately 5%, the level was similar to that at enrollment in Week 52.

Table 42. Changes in lipid-related parameters (Japanese long-term study)

	At enrollment (n = 339)	Week 4 (n = 339)	Week 12 (n = 332)	Week 24 (n = 314)	Week 36 (n = 302)	Week 52 (n = 289)
Serum LDL-cholesterol level (mg/dL)	117.4±31.2	107.8±29.4	108.3±30.5	108.1±30.0	109.9±30.5	111.2±29.5
Serum HDL-cholesterol level (mg/dL)	69.4±15.7	71.8±16.6	70.2±15.8	68.1±16.1	69.1±16.1	72.3±17.2
Serum total cholesterol level (mg/dL)	199.0±35.4	191.9±33.9	191.5±33.8	189.8±34.0	192.7±34.7	197.6±34.8

Mean ± standard deviation

As shown above, the LDL-cholesterol level decreased by approximately 10% in both the Japanese phase III study and the long-term study and did not decrease over time during the long-term administration of elobixibat. In both studies, there was no abnormal decrease in the LDL-cholesterol level. Therefore, elobixibat is unlikely to cause a clinically significant decrease in LDL-cholesterol levels.

PMDA's view:
Changes in lipid-related parameters such as LDL-cholesterol after administration of elobixibat in the Japanese phase III study and long-term study are unlikely to become clinically significant problems.

7.R.2.5 Effects on fat-soluble vitamins

The applicant's explanation about the effects of elobixibat on fat-soluble vitamins:
Since elobixibat inhibits the reabsorption of bile acids in the ileum, the resulting decrease in the amount of circulating bile acids could affect the absorption of fat-soluble vitamins during the long-term use of elobixibat. Therefore, changes in fat-soluble vitamins including vitamin A, vitamin D, and vitamin E and coagulation indexes including PT and APTT in which vitamin K is involved were investigated in the Japanese long-term study.

The results showed that long-term use of elobixibat caused no clinically significant changes in fat-soluble vitamins (vitamin A, vitamin D, and vitamin E) and coagulation indexes (PT and APTT) in which vitamin K is involved (Table 43).

Table 43. Changes in fat-soluble vitamins (Japanese long-term study)

	At enrollment (n = 339)	Week 4 (n = 339)	Week 12 (n = 322)	Week 24 (n = 314)	Week 36 (n = 303)	Week 52 (n = 289)
Serum vitamin A level (IU/dL)	138.1±37.4	143.9±38.4	140.7±39.6	135.0±36.6	134.1±36.6	135.8±36.0
Serum vitamin D level (ng/mL)	18.7±6.8	18.9±6.3	19.6±6.6	18.7±5.9	17.2±4.6[b)]	15.6±4.1[e)]
Serum vitamin E level (mg/dL)	1.13±0.26	1.18±0.26	1.20±0.26	1.18±0.27[a)]	1.18±0.25[b)]	1.19±0.28
PT (sec)	12.2±0.7	12.2±0.7 [c)]	12.5±0.7	12.5±0.7	12.5±0.7[d)]	12.6±0.7[e)]
APTT (sec)	29.4±2.2	29.4±2.4 [c)]	29.9±2.4	29.6±2.4	28.9±2.5[d)]	27.9±2.1[e)]

Mean ± standard deviation
a) n = 313, b) n = 302, c) n = 338, d) n = 299, and e) n = 288

7.R 2.6 Safety by patient characteristics

Based on the data from the pooled analysis of the Japanese phase II and phase III studies, the incidence of adverse events by main patient characteristics was as shown in Table 44.

Table 44. Incidence of adverse events by patient characteristics (data from the pooled analysis of the Japanese phase II and phase III studies)

Stratification factor	Category	Placebo group (n = 103)	Elobixibat combined group (n = 192)
Sex	Male	7.7 (1/13)	16.7 (5/30)
	Female	17.8 (16/90)	37.0 (60/162)
Age	<65 years	14.7 (14/95)	33.1 (59/178)
	≥65 years	37.5 (3/8)	42.9 (6/14)
BMI	<25 kg/m^2	13.2 (12/91)	33.7 (57/169)
	≥25 kg/m^2	41.7 (5/12)	34.8 (8/23)
Complications	Yes	21.2 (14/66)	34.6 (44/127)
	No	8.1 (3/37)	32.3 (21/65)
Past history	Yes	11.8 (2/17)	40.5 (15/37)
	No	17.4 (15/86)	32.3 (50/155)
IBS-C [a)]	Criteria met	8.0 (2/25)	26.7 (16/60)
	Criteria not met	19.2 (15/78)	37.1 (49/132)
SBM frequency in the screening period Week 2	0	13.3 (2/15)	22.2 (4/18)
	1	10.0 (2/20)	31.4 (16/51)
	2	20.8 (10/48)	34.5 (29/84)
	3	17.6 (3/17)	41.0 (16/39)
	4	100 (3/3)	–
Severity of constipation in the screening period Week 2[b)]	None	0 (0/3)	33.3 (1/3)
	Mild	–	25.0 (1/4)
	Moderate	21.9 (7/32)	29.7 (19/64)
	Severe	17.0 (9/53)	35.3 (30/85)
	Very severe	7.1 (1/14)	38.9 (14/36)
BSS-based stool consistency	1-2	15.6 (10/64)	38.0 (41/108)
	3-5	20.8 (5/24)	30.3 (20/66)
Liver function test abnormality[c)]	Yes	14.3 (1/7)	35.7 (5/14)
	No	16.7 (16/96)	33.7 (60/178)
eGFR	<60 mL/min/1.73m^2	0 (0/2)	14.3 (1/7)
	60-90 mL/min/1.73m^2	13.8 (8/58)	35.2 (37/105)
	≥90 mL/min/1.73m^2	20.9 (9/43)	33.8 (27/80)

% incidence (number of subjects)

a) Assessed according to the Rome III diagnostic criteria

b) None = having no constipation symptoms; Mild = having slight constipation symptoms of constipation; Moderate = experiencing constipation without severe symptoms; Severe = experiencing severe constipation with difficulty in defecation or sensation of incomplete evacuation; Very severe = having persistent constipation with little defecation or strong sensation of incomplete evacuation

c) AST, ALT, or total bilirubin exceeding the reference value at the final registration day

The applicant's explanation about the tolerance of elobixibat in female patients:

In data from the pooled analysis of the Japanese phase II and phase III studies, the incidence of adverse events in female subjects tended to be higher than that in male subjects; however, the number of male subjects was limited. Taking into account that the incidence of adverse events in male subjects was 77.2% (44 of 57 subjects), which was not markedly different from that in female subjects, 77.7% (220 of 283 subjects), in the long-term study and that there were no specific adverse events that occurred with a higher incidence in female subjects compared with male subjects in any Japanese clinical study, there would appear to be no tolerance-related problems in female patients associated with the use of elobixibat.

PMDA's view:

The incidence of adverse events tended to be higher in female subjects than in male subjects based on the data from the pooled analysis of the Japanese phase II and phase III studies. However, there were no specific adverse events that occurred with a higher incidence in female subjects compared with male subjects, and no severe or serious adverse events were reported in either male or female subjects. In addition, there was no marked difference in the incidence of adverse events between male and female subjects in the long-term study. Based on the above, at present, there would appear to be no tolerance-related problems in female patients associated with the use of elobixibat.

7.R.3 Clinical positioning

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

As drug therapy for constipation, the physician currently prescribes several types of drugs with different mechanisms of action based on his/her experience and in consideration of the condition of individual patients. In Japan, saline laxatives and stimulant laxatives have been the main agents used for years. However, magnesium oxide, the representative saline laxative, requires careful administration particularly in elderly patients because of the risk of hypermagnesemia. Stimulant laxatives are known to develop resistance or habituation and to cause melanosis coli and other clinical conditions. Lubiprostone, a drug that alters intestinal epithelial function, has been reported to cause nausea as an adverse drug reaction (*Neurogastroenterol Motil.* 2011;23:544-e205; *Clin Gastroenterol Hepatol.* 2015;13:294-301). As shown above, existing laxatives are known to have safety issues or cause problems when used for a long time. Elobixibat inhibits the IBAT expressed in the terminal ileum and thereby allows bile acids to flow into the colon. Bile acids increased in the colonic lumen promote bowel motility and induce the secretion of fluid and electrolytes into the colonic lumen (*Am J Physiol Gastrointest Liver Physiol.* 2002;282:G443-449; *J Clin Invest.* 1971;50:1569-1577). Therefore, it can be said that elobixibat is a drug that has the pharmacological actions of both stimulant laxatives and saline laxatives; that is, the prokinetic effect of stimulant laxatives and the effect of saline laxatives to increase water content in the feces (*Ther Adv Gastroenterol.* 2014;7:167-175). Moreover, the results of Japanese clinical studies demonstrated that elobixibat not only increases SBM frequency in patients with chronic constipation but also increases CSBM frequency, improves stool consistency, and remains effective over a long period of time. Its main adverse drug reactions are abdominal pain and diarrhoea, which are attributable to the pharmacological action of the drug. No other safety issues have been identified. Based on the above, elobixibat is assumed to be a novel treatment option for patients with chronic constipation.

PMDA's view:

Given that Japanese clinical studies in patients with chronic constipation demonstrated the efficacy of elobixibat [see Section 7.R.1] and acceptable safety [see Section 7.R.2], the effectiveness of elobixibat for treating chronic constipation is considered confirmed. Elobixibat is different from existing drugs in terms of mechanism of action and is likely to be a treatment option for patients with chronic constipation.

7.R.4 Indication

The applicant's explanation about the indication of elobixibat:

Elobixibat is expected to be used for treating chronic constipation. In general, laxatives are not indicated for treating patients whose chronic constipation has an organic cause. Therefore, patients with organic constipation were regarded ineligible for treatment with elobixibat and were excluded from the Japanese phase III study.

Patients with symptomatic or drug-induced constipation were also excluded from the Japanese phase III study, because of the diversity of causative disorders and because drugs used for treating such causative disorders could greatly affect the assessment of the efficacy and safety of elobixibat. However, symptomatic or drug-induced constipation is not different from functional constipation in terms of clinical condition, though different in terms of the cause of decreased bowel motility. Considering that elobixibat inhibits the IBAT in the terminal ileum and suppresses the reabsorption of bile acids and thereby increases the amount of bile acids flowing into the colon and promotes bowel movements, the drug is expected to be also effective in treating symptomatic or drug-induced constipation, although there is no clinical experience in these patient populations. Based on the above, symptomatic or drug-induced constipation can also be included in the indications for elobixibat.

PMDA's view:

Taking into account that the Japanese phase III study demonstrated the efficacy of elobixibat [see Section 7.R.1] and acceptable safety [see Section 7.R.2] in patients with chronic constipation, no problem is found in defining the indication of elobixibat as "chronic constipation (excluding constipation caused by organic disease)." Taking into account the mechanism of action of elobixibat and the safety data and other information from relevant clinical studies conducted, there is no need to restrict the use of elobixibat in patients with symptomatic or drug-induced constipation. However, as the applicant explained, the efficacy and safety of elobixibat are expected to vary depending on the diversity of causative disorders and the type of drugs used to treat such causative disorders; therefore, a caution statement that there is no clinical experience with the use of elobixibat in patients with symptomatic or drug-induced constipation should be included in the package insert.

A final decision on the indication of elobixibat will be made, taking account of comments raised in the Expert Discussion.

7.R.5 Dosage and administration

(a) Timing of administration of elobixibat

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

Elobixibat exerts its therapeutic effect by inhibiting the reabsorption of bile acids in the terminal ileum. In order to obtain efficient effect, it is desirable for elobixibat to be administered before bile acids are released into the duodenum by stimulation such as food intake. In the Japanese phase I study in patients with chronic constipation (AJG533/CP1), the blood concentration of C4, an intermediate during the synthesis of bile acids, was higher when elobixibat was administered before breakfast than that under the fasted condition [see Section 6.2.1]. In addition, the C_{max} and AUC of elobixibat were higher when elobixibat was administered under the

fasted condition than that before breakfast [see Section 6.2.1]; elobixibat acts directly in the gastrointestinal tract, and blood elobixibat concentration has no effects on the efficacy of the drug [see Section 3.R.1]. Thus it was decided to administer elobixibat before breakfast in Japanese clinical studies from a safety point of view, when the amount of the drug distributed in the blood is smaller.

Although elobixibat was administered before breakfast in Japanese clinical studies, the therapeutic effect of the drug when elobixibat is administered before lunch or dinner is likely to be similar to that before breakfast, because bile acids are secreted also after lunch or dinner. Therefore, it was decided to administer elobixibat before a meal, including but not be limited to breakfast.

(b) Dosage and administration of elobixibat

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

In the Japanese phase II study, placebo or elobixibat 5, 10, or 15 mg was administered orally once daily before breakfast for 14 days. The primary endpoint of "change in SBM frequency in the treatment period Week 1 from the screening period Week 2" was 2.60 ± 2.89 in the placebo group, 3.50 ± 2.96 in the elobixibat 5 mg group, 5.66 ± 4.15 in the 10 mg group, and 5.59 ± 3.51 in the 15 mg group, showing that the changes in the elobixibat 10 mg and 15 mg groups were similar with a statistically significant difference relative to the placebo group (Table 23). The secondary endpoint of "BSS-based stool consistency (mean ± standard deviation)" in the elobixibat 10 mg group was 2.25 ± 1.11 in screening period Week 2, 4.00 ± 0.94 in treatment period Week 1, and 4.25 ± 1.03 in treatment period Week 2, which was close to 4, the most desirable stool consistency.

Serious or severe adverse events were not observed in any group. The incidence of adverse events was 15.0% (6 of 40 subjects) in the placebo group, 41.9% (18 of 43 subjects) in the elobixibat 5 mg group, 30.8% (12 of 39 subjects) in the 10 mg group, and 19.5% (8 of 41 subjects) in the 15 mg group. The incidence of adverse drug reactions was 5.0% (2 of 40 subjects) in the placebo group, 32.6% (14 of 43 subjects) in the elobixibat 5 mg group, 28.2% (11 of 39 subjects) in the 10 mg group, and 17.1% (7 of 41 subjects) in the 15 mg group. The results showed no dose-dependency in the incidence of adverse events or adverse drug reactions (Table 24 and Table 25). The adverse drug reactions that occurred in ≥2 subjects in any group were abdominal pain, diarrhoea, and abdominal distension. The incidence of any of these reactions was not dose dependent (Table 25).

Based on the above, it was decided to administer elobixibat 10 mg orally once daily before breakfast for 14 days in the Japanese phase III study.

Since the results of the Japanese phase III study demonstrated the superiority of the elobixibat group over the placebo group with acceptable safety, it is considered appropriate to set the dosage and administration of elobixibat as 10 mg for the usual dose, which is administered once daily, similarly to the regimen used in the Japanese phase III study.

The applicant's explanation about the dose adjustment of elobixibat:
In the Japanese long-term study, elobixibat was started at a dose of 10 mg administered once daily. The dose was allowed to be adjusted within a range of 5 to 15 mg according to the patient's symptoms in and after Week 2 [see Section 7.3].

In the last 4 weeks (treatment period Weeks 49 to 52) of the Japanese long-term study, 29.9% (87 of 291) of subjects were in the 5 mg group, 32.6% (95 of 291) of subjects were in the 10 mg group, 36.1% (105 of 291) of subjects were in the 15 mg group, 0.7% (2 of 291) of subjects were in the 5 or 10 mg group, and 0.7% (2 of 291) of subjects were in the 10 or 15 mg group.

During the 52 weeks of the Japanese long-term study, 18.8% (64 of 340) of subjects received elobixibat 10 mg only, 35.0% (119 of 340) of subjects received 5 or 10 mg, 38.5% (131 of 340) of subjects received 10 or 15 mg, and 7.6% (26 of 340) of subjects received 5 to 15 mg, showing that the dose was adjusted in many subjects.

Elobixibat was administered at 5 mg to 145 subjects and at 15 mg to 157 subjects. The number of days of treatment (mean ± standard deviation) was 201.8 ± 137.7 days for 5 mg, 132.9 ± 142.0 days for 10 mg, and 209.8 ± 136.4 days for 15 mg. The number of days of treatment at 5 or 15 mg was greater than that at 10 mg.

In subjects who experienced no dose change in the last 4 weeks (Weeks 49 to 52) of the study, the change in SBM frequency in treatment period Week 52 from screening period Week 2 by dose was as shown in Table 45. There was no marked dose-related difference in the change in SBM frequency, and roughly the same favorable improvement in SBM frequency was observed in the 5 mg group and the 15 mg group as in the 10 mg group.

Table 45. Change in SBM frequency in the treatment period Week 52 from the screening period Week 2 by dose (FAS)

	Elobixibat 5 mg (n = 87)	Elobixibat 10 mg (n = 95)	Elobixibat 15 mg (n = 105)
SBM frequency in the screening period Week 2	1.79±0.78	1.58±0.88	1.06±1.00
SBM frequency in the treatment period Week 52	5.06±2.06[a)]	4.67±2.19[b)]	4.04±2.72[c)]
Change in SBM frequency from the screening period	3.28±2.26[a)]	3.08±2.12[b)]	3.00±2.61[c)]

Mean ± standard deviation (number of subjects)
a) 56 subjects, b) 61 subjects, c) 67 subjects

Abdominal pain and diarrhoea, the main adverse events of elobixibat, resulted in dose reduction in 48 cases and 21 cases, respectively. However, study treatment in these cases was able to be continued at a reduced dose [see Section 7.R.2.3]. The incidence of adverse events before and after the first dose increase to 15 mg was 7.6% (12 of 157 subjects) and 8.9% (14 of 157 subjects), respectively, showing that there was no tendency towards an increase in the incidence of adverse events related to a dose increase to 15 mg.

The above results supported the appropriateness of adjusting the dose of elobixibat according to symptoms.

PMDA's view:
There is no objection to the administration of elobixibat before a meal and to the usual dose of 10 mg administered orally once daily similarly to the regimen used in the Japanese phase III study. It is also acceptable to adjust the dose according to the patient's symptoms within a range of 5 to 15 mg as in the Japanese long-term study. However, taking into account that abdominal pain and diarrhoea occurred at a certain incidence in patients treated with elobixibat and that these events were resolved by taking appropriate measures such as dose reduction or the interruption of treatment, the following caution statement should be provided in the package insert: "If abdominal pain or diarrhoea occurs during treatment with elobixibat, appropriate measures, such as dose reduction or the interruption of treatment, should be taken. Meanwhile, treatment with elobixibat should not be continued without careful consideration to prevent needless exposure to the drug."

A final decision on the dosage and administration of elobixibat will be made, taking account of comments raised in the Expert Discussion.

7.R.6 Concomitant use with existing laxatives

Considering that elobixibat is expected to be used in combination with existing laxatives, PMDA asked the applicant to explain the efficacy and safety of elobixibat when used concomitantly with existing laxatives.

The applicant's response:
As laxatives that are expected to be used concomitantly with elobixibat, magnesium oxide and lubiprostone, which soften stools, may be used at a relatively high frequency. When sufficient bowel movements are not achieved even after administration of elobixibat in combination with these drugs, it is expected that stimulant laxatives including bisacodyl suppository, sennoside, and sodium picosulfate will be coadministered.

In Japanese clinical studies, use of bisacodyl suppository was allowed as rescue medication when bowel movements were not achieved in 72 consecutive hours. The proportion of subjects who used rescue medication at least once during treatment with elobixibat was 5.7% (7 of 123 subjects) in the Japanese phase II study, 2.9% (2 of 69 subjects) in the Japanese phase III study, and 40.6% (138 of 340 subjects) in the Japanese long-term study. Based on the above, a certain percentage of patients are likely to require the use of existing laxatives in combination with elobixibat in the post-marketing setting.

Elobixibat has different mechanism of action from the existing laxatives, and the efficacy of elobixibat, is unlikely to be affected when elobixibat is used in combination with existing laxatives. In the Japanese long-term study, the "change in SBM frequency in treatment period Week 52 from screening period Week 2" was 3.02 ± 2.47 in subjects who used rescue medication for constipation at least once during treatment with elobixibat and 3.21 ± 2.34 in those who did not use any rescue medication, indicating that the effect of elobixibat was maintained also in those who used rescue medication.

In Japanese clinical studies, there were no events that could be a safety concern, except for abdominal pain and diarrhoea that were attributable to the pharmacological action of elobixibat. Therefore, combination use of

elobixibat and existing laxatives is unlikely to cause any safety problems. The incidence of adverse events in subjects who used rescue medication at least once during treatment with elobixibat and in those who did not use it was 28.6% (2 of 7 subjects) and 31.0% (36 of 116 subjects), respectively, in the Japanese phase II study, 0% (0 of 2 subjects) and 40.3% (27 of 67 subjects) in the Japanese phase III study, and 77.5% (107 of 138 subjects) and 77.7% (157 of 202 subjects) in the Japanese long-term study. As shown, there was no increase in the incidence of adverse events associated with the use of rescue medication.

Based on the above, the use of elobixibat in combination with existing laxatives is unlikely to cause any clinically significant problems at present, while the dose of elobixibat or existing laxatives should be adjusted as needed according to the symptoms of abdominal pain or diarrhoea.

PMDA's view:
PMDA confirmed that, at present, there are no particular problems with the efficacy and safety of elobixibat administered in combination with other laxatives. However, considering that bisacodyl suppository was the only rescue medication allowed to be used concomitantly with elobixibat in Japanese clinical studies and that various drugs for the treatment of constipation may be used concomitantly with elobixibat in clinical practice, it is necessary to continue to collect information on the safety and efficacy of elobixibat administered in combination with other laxatives via post-marketing surveillance.

7.R.7 Post-marketing investigations

The applicant plans to conduct a post-marketing use-results survey as shown in Table 46.

Table 46. Outline of use-results survey plan (draft)

Objectives	To evaluate the safety, efficacy, and other properties of elobixibat in patients with chronic constipation in clinical practice
Survey method	Central registration method
Population	Patients with chronic constipation
Planned sample size	3000 patients
Survey period	3 years and 6 months (registration period, 3 years)
Observation period	4 weeks
Main survey items	• Patient characteristics (age, sex, duration of disease, complications, medical history, etc.) • Use status of elobixibat (duration of administration, daily dose, time of day of dosing, reasons for discontinuation) • Use status of prior and/or concomitant drugs for treating constipation (presence or absence of prior and/or concomitant drugs, names of drugs, route of administration, daily dose, duration of administration) • Efficacy (SBM frequency, CSBM frequency, BSS-based stool consistency, etc.) • Adverse events (date of onset, seriousness, outcome, continuation or discontinuation of treatment with elobixibat, causal relationship with elobixibat, etc.) • Laboratory test values

PMDA's view:
Considering that elobixibat is expected to be administered repeatedly over a long period of time, it is necessary to collect information on the duration of administration, status of intermittent use (eg, mean time to retreatment, retreatment status), and the safety and efficacy when administered repeatedly over a long period of time. In

addition, it is also necessary to collect information on the following issues. A final decision will be detailed, taking account of comments raised in the Expert Discussion.

- Safety and efficacy of elobixibat when used in combination with existing laxatives
- Interactions with elobixibat (concomitant drugs other than existing laxatives, complications)

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, 5.3.5.1-3, and 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that elobixibat hydrate has efficacy in the treatment of chronic constipation, and that elobixibat hydrate has acceptable safety in view of its benefits. The product, a tablet containing elobixibat hydrate as the active ingredient, is clinically meaningful because it offers a new treatment option for patients with chronic constipation. The efficacy, safety, indication, dosage and administration, and post-marketing investigations of the product need further evaluation.

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

Review Report (2)

November 15, 2017

Product Submitted for Approval

Brand Name	Goofice Tablets 5mg
Non-proprietary Name	Elobixibat Hydrate
Applicant	EA Pharma Co., Ltd.
Date of Application	February 1, 2017

1. Content of the Review

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

1.1 Efficacy, safety, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration" in the Review Report (1). In addition, the expert advisors made the following comments:

- It is necessary to provide a caution statement that elobixibat, which improves constipation by suppressing the reabsorption of bile acids, may be ineffective in patients with serious hepatic impairment (eg, biliary obstruction, decreased bile acid secretion).

Taking account of the above comments from the expert advisors, PMDA instructed the applicant to include a caution statement in the package insert to the effect that elobixibat may not be effective in patients with reduced or no bile acid excretion into the small intestine due to serious hepatic impairment. The applicant responded accordingly, and PMDA accepted the applicant's response.

Based on comments from the Expert Discussion, PMDA accepted the proposed indication of elobixibat shown below. PMDA asked the applicant to modify the proposed dosage and administration as follows and provide the following statements in the "Precautions for Indication" section and the "Precautions for Dosage and Administration" section. The applicant responded accordingly, and PMDA accepted the applicant's response.

Indication

Chronic constipation (excluding constipation caused by organic disease)

[Precautions for Indication]
There is no clinical experience with the use of the product in patients with drug-induced or symptomatic constipation.

Dosage and administration
The usual adult dosage is 10 mg of elobixibat administered orally once daily before a meal. The dose may be adjusted according to the patient's symptoms, not exceeding a maximum dose of 15 mg per day.

[Precautions for Dosage and Administration]
The product may cause abdominal pain or diarrhoea. It is necessary to consider dose reduction, interruption, or discontinuation of treatment according to the patient's symptoms and to periodically review the need for continuation of treatment so that treatment with elobixibat will not be continued without careful consideration.

1.2 Risk management plan (draft)

The expert advisors supported PMDA's conclusion on issues presented in "7.R.5 Post-marketing investigations" in the Review Report (1).

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for elobixibat hydrate should include the safety and efficacy specifications presented in Table 47, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 48 as well as the specified use-results survey presented in Table 49.

Table 47. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• None	• None	• None
Efficacy specification		
• Efficacy in routine clinical practice		

Table 48. 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 • Specified use-results survey	• Disseminate data gathered during early post-marketing phase vigilance

Table 49. Outline of specified use-results survey (draft)

Objective	To evaluate the safety, efficacy, and other properties of elobixibat in patients with chronic constipation in clinical practice
Survey method	Central registration method
Population	Patients with chronic constipation
Planned sample size	3000 patients (at least 300 patients who continue receiving elobixibat at 4 weeks will be observed for 52 weeks)
Survey period	4 years and 7 months (registration period, 3 years)
Observation period	4 weeks (at least 300 patients who continue receiving elobixibat at 4 weeks will be observed for 52 weeks)
Main survey items	• Patient characteristics (age, sex, duration of disease, complications, medical history, etc.) • Use status of elobixibat (duration of administration, daily dose, time of day of dosing, reasons for discontinuation) • Use status of prior drugs for treating constipation (presence or absence of prior drugs, names of drugs, route of administration, daily dose, duration of administration) • Use status of concomitant drugs (presence or absence of concomitant drugs, names of drugs, route of administration, daily dose, duration of administration) • Efficacy (SBM frequency, CSBM frequency, BSS-based stool consistency, etc.) • Adverse events (date of onset, seriousness, outcome, continuation or discontinuation of treatment with elobixibat, causal relationship with elobixibat, etc.) • Laboratory test values

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration statements as shown below, with the following conditions. As the application falls under the category of drugs with new active ingredients, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Chronic constipation (excluding constipation caused by organic disease)

Dosage and Administration

The usual adult dosage is 10 mg of elobixibat administered orally once daily before a meal. The dose may be adjusted according to the patient's symptoms, not exceeding a maximum dose of 15 mg per day.

Conditions of Approval

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

List of Abbreviations

Adverse drug reaction	An adverse event for which a causal relationship to the study drug cannot be ruled out
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoE	Apolipoprotein E
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSS	Bristol stool scale
C4	7α-hydroxy-4-cholesten-3-one
Caco-2 cells	Human colon carcinoma cell line Caco-2
COX-1	Cyclooxygenase-1
CPT-P1 cells	P-glycoprotein knockdown Caco-2
CTD	Common technical document
C_{max}	Maximum concentration
CPK	Creatine phosphokinase
CSBM	Complete spontaneous bowel movement
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
ED_{50}	50% effective dose
eGFR	estimate glomerular filtration rate
Elobixibat	Elobixibat hydrate
FAS	Full analysis set
GCP	Good clinical practice
HDL	High-density lipoprotein
HEK293 cells	Human embryonic kidney cell line HEK293
HEPES	2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid
hERG	Human ether-à-go-go related gene
HPLC	High performance liquid chromatography
IBAT	Ileal bile acid transporter
IBS-C	Irritable bowel syndrome with constipation
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E Guideline	Guideline on Evaluation of Stability Data (PFSB/ELD notification No. 0603004 dated June 3, 2003)
IR	Infrared absorption spectrum
K_I	Half-maximal inactivation rate concentration
K_i	Inhibition constant
k_{inact}	Maximal inactivation rate concentration
L5178Y cells	The mouse lymphoma L5178Y cell line
LBAT	Liver bile acid transporter
LC/MS	Liquid chromatography with mass spectrometry
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
logP	Partition coefficient
M2	Metabolite 2 (a monohydroxide of elobixibat with the hydroxylated tert-butyl side chain; monohydroxy elobixibat; a main metabolite)
M3	Metabolite 3 (a monohydroxide of elobixibat with the hydroxylated tert-butyl side chain; monohydroxy elobixibat; a main metabolite)

MATE	Multidrug and toxic extrusion transporter
MedDRA/J	Medical dictionary for regulatory activities Japanese version
MS	Mass spectrum
NMR	Nuclear magnetic resonance spectrum
NK_2	Neurokinin(Tachykinin) 2 receptor
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PKa	Acid dissociation constant
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
PTP	Press through packaging
RH	Relative humidity
Rome III	Diagnostic criteria established by the Rome Committee, an international working group for functional gastrointestinal disorder (*Gastroenterology.* 2006;130:1480-1491)
Rome IV	Diagnostic criteria established by the Rome Committee, an international working group for functional gastrointestinal disorder (*Bowel Dis Gastroenterol.* 2016;150:1393-1407)
SBM	Spontaneous bowel movement (excluding a bowel movement that occurs within 24 hours of rescue laxative use)
^{75}SeHCAT	Tauro-23-[^{75}-Se]selena-25-homocholic acid
sst_2	Somatostatin receptor type 2
$t_{1/2}$	Elimination half life
t_{max}	Time to reach maximum concentration
UV	Ultraviolet
WBP	Whole body plethysmography