Report on the Deliberation Results

March 8, 2018

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

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet (JAN*)
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	April 27, 2017

Results of Deliberation

In its meeting held on March 1, 2018, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug substance and the drug product are classified as a poisonous drug and a powerful drug, respectively.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

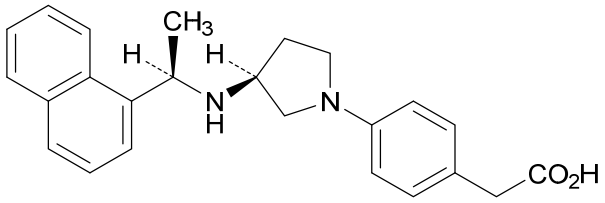
Review Report

February 19, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	April 27, 2017
Dosage Form/Strength	Tablets: Each tablet contains 1 or 2 mg of evocalcet.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{24}H_{26}N_2O_2$

Molecular weight: 374.48

Chemical name: 2-{4-[(3*S*)-3-{[(1*R*)-1-(Naphthalen-1-yl)ethyl]amino}pyrrolidin-1-yl]phenyl} acetic acid

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 secondary hyperparathyroidism in patients on maintenance dialysis, 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

Secondary hyperparathyroidism in patients on maintenance dialysis

Dosage and Administration

The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Condition of Approval

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

Attachment

Review Report (1)

January 19, 2018

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

Product Submitted for Approval

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	April 27, 2017
Dosage Form/Strength	Tablets: Each tablet contains 1 or 2 mg of Evocalcet.
Proposed Indication	Secondary hyperparathyroidism in patients on maintenance dialysis

Proposed Dosage and Administration

The usual starting dosage for adults is 1 or 2 mg of evocalcet administered orally once daily. The subsequent oral dose is adjusted within the range of 1 to 6 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily in patients whose PTH levels cannot be controlled by the previous dose.

Table of Contents

List of Abbreviations

See Appendix.

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

Secondary hyperparathyroidism (SHPT) is attributable to excessive secretion of parathyroid hormone (PTH) induced by decreased phosphate (P) excretion as well as to decreased blood calcium (Ca) associated with vitamin D deficiency in patients with advanced chronic kidney disease (CKD) (Clinical Practice Guideline for the Management of Chronic Kidney Disease-Mineral and Bone Disorder [Clinical Practice Guideline for CKD-MBD], edited by the Japanese Society for Dialysis Therapy, 2012 [hereinafter referred to as "Clinical Practice Guideline for CKD-MBD 2012"]). Excessive PTH secretion in patients with SHPT promotes bone resorption, which cause bone pain and fracture, leading to the release of excess Ca and P from bone into blood, thereby resulting in the calcification of heart and blood vessels. Consequently, these symptoms affect life prognosis. In addition, persistent excessive PTH secretion leads to parathyroid gland hyperplasia, resulting in further progression of SHPT. Under the circumstances, the Clinical Practice Guideline for CKD-MBD 2012 presents the target range for serum P, Ca, and PTH in patients on dialysis. The target range for serum intact parathyroid hormone (iPTH) levels is 60 to 240 pg/mL.

Drug therapies for the management of PTH levels in patients with SHPT include (1) cinacalcet hydrochloride, an oral calcium-sensing receptor (CaR) agonist; (2) etelcalcetide hydrochloride, an injection administered via the dialysis circuit; and (3) the activated vitamin D. The therapies are selected according to the patient's conditions.

Evocalcet is a novel CaR agonist with a naphthylalkylamine skeleton discovered by the applicant and Mitsubishi Tanabe Pharma Corporation. The clinical development of evocalcet was undertaken because evocalcet was expected to reduce the incidence of upper gastrointestinal disorder that is an adverse event associated with the use of cinacalcet hydrochloride.

Recently, the applicant submitted the marketing application for evocalcet with the claim that the efficacy and safety of evocalcet have been confirmed in Japanese clinical studies.

Evocalcet is not approved in any foreign country as of November 2017.

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

2.1 Drug substance

The drug substance evocalcet is registered in the Drug Master File (DMF) by Mitsubishi Tanabe Pharma Corporation (DMF number: 229MF10027).

2.1.1 Characterization

The drug substance is a white powder, and the determined general properties include description, solubility, hygroscopicity, melting point and thermal analysis, dissociation constant, partition coefficient, and optical rotation. The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet-visible spectrophotometry (UV), infrared absorption spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry (MS), tandem mass spectrometry (MS/MS), and single-crystal X-ray diffractometry. The drug

substance exists in 2 crystalline polymorphisms (A and B). The Form B is unstable thermodynamically, and batch analyses of the drug substance have confirmed that only Form A is produced.

2.1.2 Manufacturing process

See Annex.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [high performance liquid chromatography (HPLC)], optical isomers [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows the results of main stability studies of the drug substance. A photostability testing showed that the drug substance is photolabile.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial batches	25°C	60% RH	[redacted] polyethylene bag (double-layered)/fiber drum	18 months
Accelerated testing	3 commercial batches	40°C	75% RH		6 months

Based on the above, a retest period of 30 months has been proposed for the drug substance when stored at room temperature in a double-layered [redacted] polyethylene bag placed in a fiber drum, in accordance with the Guideline on the Evaluation of Stability Data (PFSB/ELD Notification No. 0603004 dated June 3 2003) (which is also known as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Q1E Guideline). The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 1 or 2 mg of evocalcet. Excipients contained in the drug product are D-mannitol, microcrystalline cellulose, [redacted], croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, [redacted], hypromellose, titanium oxide, macrogol 6000, lactose hydrate, yellow ferric oxide, and carnauba wax.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], packaging, and testing/storage. [redacted], [redacted], and [redacted] are identified as the critical steps.

The strategy for quality control was developed by the following investigations, etc., using a quality-by-design (QbD) approach:

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as critical quality attributes (CQAs)

- Identification of critical material attributes (CMAs) and critical process parameters (CPPs) based on quality risk assessment, etc.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (UV), purity (related substances [HPLC]), uniformity of dosage unit (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows the results of main stability studies of the drug product. A photostability testing showed that the drug product is photostable.

Table 2. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot batches	25°C	60% RH	Blister pack/[redacted]	18 months
Accelerated testing	3 pilot batches	40°C	75% RH	[redacted]	6 months

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

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled adequately. Data contained in the DMF of evocalcet were submitted separately by the DMF holder. Results of the review of DMF conducted by PMDA are shown in Supplement.

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

The primary pharmacodynamic studies were conducted to investigate CaR activation and mode of action, inhibition of PTH secretion, and suppression of parathyroid gland hyperplasia. The secondary pharmacology studies were conducted to investigate inhibitory effect on binding to receptors other than CaR, effects on urinary electrolytes, and effects of the metabolites of evocalcet. Effects on the central nervous system, cardiovascular system, and respiratory system were investigated in safety pharmacology studies. In *in vivo* studies, 0.5% methylcellulose solution was used as vehicle.

3.1 Primary pharmacodynamics

3.1.1 CaR activation

3.1.1.1 Human CaR activation (Common technical document [CTD] 4.2.1.1-1, Study [redacted])

Human embryonic kidney cell lines HEK293 (HEK293 cells) forced to express human CaR were incubated with evocalcet (0.003-30 μmol/L) or cinacalcet (0.003-30 μmol/L) in the presence of 1.0 mmol/L Ca^{2+}, to measure intracellular Ca^{2+} levels. Both evocalcet and cinacalcet increased intracellular Ca^{2+} in a concentration-dependent manner, with a geometric mean half maximal effective concentration (EC_{50}) [95% confidence interval (CI)] of 0.09 [0.03, 0.30] μmol/L and 0.18 [0.07, 0.43] μmol/L, respectively.

3.1.1.2 Mode of action on human CaR (CTD 4.2.1.1-2, Study [redacted])

HEK293 cells forced to express human CaR were incubated with evocalcet (0-60 nmol/L) or cinacalcet (0-60 nmol/L) in the presence of 0.25 to 3 mmol/L Ca^{2+}, to measure intracellular Ca^{2+}levels. Both evocalcet and cinacalcet increased intracellular Ca^{2+} in a concentration-dependent manner and, at the same time, shifted the extracellular Ca^{2+} concentration-response curve to the direction of lower extracellular Ca^{2+} levels.

3.1.2 Inhibition of PTH secretion

3.1.2.1 Effects on plasma PTH and Ca in mice (CTD 4.2.1.1-3, Study d-[redacted]-0838)

Evocalcet (0.3, 1, or 3 mg/kg) or vehicle was administered orally once daily to male and female mice for 2 weeks. Table 3 shows plasma PTH and Ca levels after 2 weeks of administration.

In both male and female mice, plasma PTH and Ca levels tended to decrease in mice treated with evocalcet at ≥0.3 mg/kg compared with vehicle-treated mice.

Table 3. Plasma PTH and Ca levels after 2 weeks of administration in mice

Treatment group		Plasma PTH levels (pg/mL)		Plasma Ca levels (mg/dL)	
		Baseline	Week 2[a)]	Baseline	Week 2[a)]
Male	Vehicle control	171.4 ± 22.8	150.9 ± 27.4	8.1 ± 0.2	7.3 ± 0.1
	Evocalcet 0.3 mg/kg	153.1 ± 32.8	102.7 ± 10.3	7.9 ± 0.3	7.0 ± 0.2
	Evocalcet 1 mg/kg	149.2 ± 15.9	76.0 ± 4.5	8.2 ± 0.3	6.2 ± 0.1
	Evocalcet 3 mg/kg	163.6 ± 38.9	72.3 ± 2.6	7.8 ± 0.1	5.5 ± 0.2
Female	Vehicle control	110.4 ± 6.9	112.3 ± 5.9	8.5 ± 0.2	7.6 ± 0.2
	Evocalcet 0.3 mg/kg	161.2 ± 31.9	99.4 ± 6.3	8.2 ± 0.3	7.0 ± 0.1
	Evocalcet 1 mg/kg	114.6 ± 7.4	82.8 ± 7.0	8.5 ± 0.2	6.2 ± 0.1
	Evocalcet 3 mg/kg	157.3 ± 22.4	67.0 ± 2.4	8.1 ± 0.2	5.3 ± 0.2

n = 6, Mean ± standard error (SE)
a) Blood was collected 4 hours after administration of evocalcet.

3.1.2.2 Effects on serum PTH, Ca, and IP in rats (CTD 4.2.1.1-4, Study d-[redacted]-926)

A single dose of evocalcet (0.03, 0.1, 0.3, or 1 mg/kg) or vehicle was administered orally to male rats. Table 4 shows serum PTH, Ca, and inorganic phosphorus (IP) levels 4 hours post-dose.

Evocalcet decreased serum PTH in a dose-dependent manner, showing a significant decrease at ≥0.3 mg/kg compared with vehicle control. Evocalcet decreased serum Ca as well in a dose-dependent

manner, showing a significant decrease at ≥0.1 mg/kg compared with vehicle control. Serum IP levels tended to be higher in all evocalcet groups than in the vehicle control group.

Table 4. Serum PTH, Ca, and IP levels 4 hours post-dose in rats

Treatment group	Serum PTH levels (pg/mL)		Serum Ca levels (mg/dL)		Serum IP levels (mg/dL)	
	Baseline	4 hours post-dose	Baseline	4 hours post-dose	Baseline	4 hours post-dose
Vehicle control	76.9 ± 15.7	157.3 ± 11.5	11.0 ± 0.1	10.7 ± 0.1	9.1 ± 0.1	9.9 ± 0.2
Evocalcet 0.03 mg/kg	117.3 ± 7.7	147.7 ± 16.0	10.9 ± 0.1	10.4 ±0.1	9.1 ± 0.1	10.7 ± 0.2
Evocalcet 0.1 mg/kg	100.3 ± 14.7	152.0 ± 18.8	10.9 ± 0.1	9.8 ± 0.1***	8.9 ± 0.1	10.7 ± 0.2
Evocalcet 0.3 mg/kg	133.2 ± 22.6	81.1 ± 8.7**	10.9 ± 0.1	9.2 ± 0.1***	8.9 ± 0.2	10.6 ± 0.2
Evocalcet 1 mg/kg	118.0 ± 16.6	21.6 ± 6.1***	11.2 ± 0.2	8.6 ± 0.1***	9.0 ± 0.1	10.8 ± 0.2

n = 10, Mean ± SE
** $P < 0.01$, *** $P < 0.001$ (vs. vehicle control group, Steel test)

3.1.2.3 Effects on serum PTH, Ca, and IP in partially-nephrectomized CKD rats (CTD 4.2.1.1-5, Study d-[redacted]-0633)

Evocalcet (0.03, 0.1, 0.3, or 1 mg/kg) or vehicle was administered orally once daily to 5/6 nephrectomized (Nx) CKD rats for 2 weeks. Table 5 shows serum PTH, Ca, and IP levels after 2 weeks of administration. The 5/6 Nx CKD rats were prepared according to the following procedure: Two-thirds of the left kidney was ectomized from each of the male rats, followed by right nephrectomy 1 week later. The 5/6 Nx rats were fed a high P diet (containing 0.6% Ca and 0.9% P) for 2 weeks starting at 1 week after the right nephrectomy to promote the progression of SHPT.

Serum PTH and Ca levels decreased significantly in rats at ≥0.1 mg compared with vehicle-treated rats. In contrast, there was no significant difference in serum IP levels between the evocalcet groups and the vehicle control group.

Table 5. Serum PTH, Ca, and IP levels in 5/6 Nx CKD rats after 2 weeks of administration

Treatment group	Serum PTH levels (pg/mL)		Serum Ca levels (mg/dL)		Serum IP levels (mg/dL)	
	Baseline	Week 2[a)]	Baseline	Week 2[a)]	baseline	Week 2[a)]
Vehicle control	2,764 ± 283	2,159 ± 396	7.8 ± 0.2	7.6 ± 0.3	12.1 ± 0.5	9.9 ± 0.7
Evocalcet 0.03 mg/kg	2,235 ± 252	1,350 ± 316	7.9 ± 0.2	7.9 ± 0.4	9.5 ± 0.5	8.6 ± 0.2
Evocalcet 0.1 mg/kg	3,006 ± 303	662 ± 79*	7.7 ± 0.2	6.9 ± 0.2*	10.7 ± 0.5	9.5 ± 0.4
Evocalcet 0.3 mg/kg	2,360 ± 261	244 ± 60***	7.2 ± 0.4	5.9 ± 0.1**	9.7 ± 0.5	9.6 ± 0.3
Evocalcet 1 mg/kg	2,488 ± 278	206 ± 69***	7.8 ± 0.2	4.8 ± 0.2***	9.7 ± 0.4	11.0 ± 0.3

n = 12, Mean ± SE
a) Blood was collected at 4 hours after administration of evocalcet.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (vs. vehicle control group, Steel test)

3.1.3 Suppression of parathyroid gland hyperplasia (CTD 4.2.1.1-6 [Reference], Study r-[redacted]-0196)

Evocalcet (0.1 or 0.3 mg/kg) or vehicle was administered orally once daily to 5/6 Nx CKD rats for 4 weeks. Table 6 shows serum PTH levels, number of proliferating parathyroid cells, and parathyroid gland weight. The 5/6 Nx CKD rats were prepared according to the following procedure: Two-thirds of the left kidney was ectomized from each of the male rats, followed by right nephrectomy 1 week later. The 5/6 Nx rats were fed a high P diet (containing 0.6% Ca and 0.9% P) for 2 weeks starting at 1 week after the right nephrectomy to promote the progression of parathyroid gland hyperplasia.

Serum PTH levels decreased significantly in all evocalcet groups compared with the vehicle control group. Parathyroid cell proliferation and parathyroid gland weight increase were both significantly suppressed in all evocalcet groups compared with the vehicle control group.

Table 6. Serum PTH levels, parathyroid cell proliferation, and parathyroid gland weight in 5/6 Nx CKD rats after 4 weeks of administration

Treatment group	Serum PTH levels (pg/mL)		Parathyroid gland	
	Baseline	Week 4[a)]	Percentage of proliferating cells (%)[b)]	Weight per body weight (mg/kg)
Vehicle control	3,212 ± 269	3,359 ± 619	23.3 ± 1.6	2.5 ± 0.3
Evocalcet 0.1 mg/kg	3,033 ± 248	1,072 ± 464*	12.9 ± 1.9†††	1.6 ± 0.1*
Evocalcet 0.3 mg/kg	3,278 ± 251	616 ± 181**	10.9 ± 1.3†††	1.1 ± 0.1**

n = 10 to 11, Mean ± SE
a) Blood was collected at 4 hours after administration of evocalcet.
b) Percentage of cells in growth phase = Percentage of BrdU-positive cells among the total cells in a single section of parathyroid gland
* $P < 0.05$, ** $P < 0.01$ (vs. vehicle control, steel test)
††† $P < 0.001$ (vs. vehicle control, Dunnett test)

3.2 Secondary pharmacodynamics

3.2.1 Study of selectivity (CTD 4.2.1.2-1, Study [redacted]137[redacted])

Binding-inhibitory activity of evocalcet at 10 μmol/L was investigated using a panel of 46 types of receptors, ion channels, and transporters. Evocalcet at 10 μmol/L showed ≥40% inhibition of binding to human adrenergic α2A receptor, human adrenergic α2B receptor, human adrenergic α2C receptor, and human dopamine D_3 receptor, whereas evocalcet at 1 μmol/L (24.6 times C_{max} following administration of evocalcet at the maximum clinical dose [12 mg]) did not show ≥40%inhibition of binding to these receptors.

3.2.2 Effect on urinary electrolytes (CTD 4.2.1.2-2, Study [redacted]170)

A single dose of evocalcet (0.3, 1, or 3 mg/kg) or vehicle was administered orally to male rats deprived of food and water. Urinary volume, urinary electrolyte concentrations, etc., were measured during the first 6 hours post-dose.

Increased Ca excretion and decreased IP excretion were observed at ≥0.3 mg/kg. Increased chloride (Cl) excretion was observed at ≥1 mg/kg, and decreased urine pH was observed at 3 mg/kg. Evocalcet did not affect urinary volume, Na^+ excretion, or K^+ excretion.

3.2.3 Study on the effect of metabolites (CTD 4.2.1.2-4, Study [redacted]6361[redacted])

A study was conducted to investigate the effect of the main metabolites of evocalcet in humans, M1 (taurine conjugate) and M2 (glycine conjugate of evocalcet). HEK293 cells forced to express human CaR were incubated with M1 (0.003-30 μmol/L) or M2 (0.003-30 μmol/L) in the presence of 1 mmol/L Ca^{2+} to measure intracellular Ca^{2+} levels. Both M1 and M2 increased intracellular Ca^{2+} in a concentration-dependent manner, with a geometric mean EC_{50} [95% CI] of 0.10 [0.04, 0.26] μmol/L and 0.20 [0.13, 0.31] μmol/L, respectively, showing that the pharmacological effects of the two metabolites are similar to that of unchanged evocalcet.

3.3 Safety pharmacology

The applicant submitted safety pharmacology data from studies shown in Table 7.

Table 7. Outline of safety pharmacology data

Organ	Test system	Evaluation items and methods	Dose of evocalcet	Route of administration	Findings	CTD (Study)
Central nervous system	Rats (6 males/group)	Modified Irwin method (clinical signs, behavior)	0, 1, 3, 10 mg/kg	p.o.	No effect was observed in all doses up to the maximum dose (10 mg/kg). The NOEL of evocalcet for the central nervous system of rats was determined to be >10 mg/kg (>32-forld safety margin).	4.2.1.3-1 ([redacted]275)
Cardiovascular system	HEK293 cells (4 samples/group)	hERG current	0, 3, 10, 30, 100 μmol/L	*In vitro*	Evocalcet (0, 3, 10, 30, and 100 μmol/L) inhibited hERG current by 3.6, 2.8, 3.4, 9.4, and 23.2%, respectively (IC_{50} >100 μmol/L)	4.2.1.3-2 ([redacted]037)
	CHO cells or HEK293 cells (4-5 samples/group)	hCav1.2 current (CHO cells) hKv1.5 current hKvLQT1/minK current hKv4.3 current hNav1.5 current (HEK293 cells)	10 μmol/L	*In vitro*	10 μmol/L evocalcet had no effect on hCav1.2, hKv1.5, hKvLQT1/minK, hKv4.3, or hNav1.5 current (>246-fold safety margin)	4.2.1.3-3 ([redacted]923[redacted])
	Papillary muscles isolated from male guinea pigs (5/group)	Action potentials (e.g., APA, APD)	10 μmol/L	*In vitro*	10 μmol/L evocalcet had no effect on active potentials tested (>246-fold safety margin).	4.2.1.3-5 ([redacted]271)
	Right atrium isolated from male rats (5/group)	Beating rate	10 μmol/L	*In vitro*	10 μmol/L evocalcet had no effect (>246- fold safety margin).	4.2.1.3-6 ([redacted]713)
	Rats (6 males/group)	Heart rate, blood pressure (systolic, diastolic, mean) (under unanesthetized and unrestrained conditions)	0, 1, 3, 10 mg/kg	p.o.	The heart rate increased at ≥3 mg/kg, diastolic pressure and mean blood pressure increased transiently at 10 mg/kg. The NOEL for the cardiovascular system in rats was determined to be 1 mg/kg (4-fold safety margin).	4.2.1.3-7 ([redacted]362[redacted])
	Cynomolgus monkeys (4 males/group)	Heart rate, blood pressure (systolic, diastolic, mean), ECG (under unanesthetized and unrestrained conditions)	0, 1, 3, 10 mg/kg	p.o.	The heart rate increased at ≥3 mg/kg and blood pressure increase and QTc prolongation were observed at 10 mg/kg. The NOEL for the cardiovascular system in monkeys was determined to be 1 mg/kg (0.4-fold safety margin).	4.2.1.3-8 ([redacted]167)
Respiratory system	Rats (8 males/group)	WBP (respiratory rate, tidal volume, minute ventilation)	0, 1, 3, 10 mg/kg	p.o.	Evocalcet at all doses up to the maximum dose (10 mg/kg) did not show any effect on tidal volume or minute ventilation. The NOEL for the respiratory system in rats was determined to be >10 mg/kg (>32-fold safety margin).	4.2.1.3-9 ([redacted]012)

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action

The applicant's explanation about the pharmacological action of evocalcet:

Excessive PTH secretion in patients with SHPT promotes increased bone turnover associated with enhanced bone resorption, leading to the release of excess Ca and P from bone into blood, thereby resulting in the calcification of blood vessels and soft tissues as well as osteitis fibrosa. In addition, persistent PTH elevation causes parathyroid gland hyperplasia, further exacerbating SHPT (Clinical Practice Guideline for CKD-MBD 2012).

Evocalcet is an agonist for CaR which regulates PTH secretion, parathyroid gland cell proliferation, etc. Similar to cinacalcet, evocalcet shifted the extracellular Ca^{2+} concentration-response curve to the direction of lower extracellular Ca^{2+} levels. The result suggests that evocalcet binds to the membrane-spanning region of CaR, thereby activating CaR allosterically [see Section 3.1.1]. Evocalcet inhibited PTH secretion in partially-nephrectomized (PNx) CKD rats [see Section 3.1.2.3] and suppressed parathyroid cell proliferation and progression of parathyroid gland hyperplasia [see Section 3.1.3]. These results suggest that evocalcet decreases serum PTH levels by inhibiting PTH secretion from parathyroid cells and by suppressing the proliferation of parathyroid cells.

The active metabolites of evocalcet, M1 and M2, showed a similar pharmacological effect to that of unchanged evocalcet [see Section 3.2.3]. However, the mean $AUC_{0\text{-}72h}$ of unchanged evocalcet, M1, and M2 in a mass balance study in humans was 1.70 μmol eq•h/L, 0.254 μmol eq•h/L, and 0.170 μmol eq•h/L, respectively [see Section 6.2.3], suggesting that M1 and M2 have only a limited effect on the efficacy of evocalcet in humans.

PMDA asked the applicant to explain the effect of evocalcet on heterotopic calcification and on abnormal bone metabolism.

The applicant's response:
The primary pharmacodynamic studies submitted for the application did not evaluate the effect of evocalcet on heterotopic calcification or on abnormal bone metabolism. However, evocalcet decreased serum PTH levels. In addition, some published articles reported that cinacalcet, a drug with a similar mechanism of action to that of evocalcet, decreased serum PTH levels, thereby suppressing heterotopic calcification in blood vessels, heart, etc., and osteitis fibrosa in PNx CKD rats (Review Report on "Regpara Tablets 25 mg, etc." [July 17, 2007], *Kidney Int*. 2008;74:1270-1277). In light of these findings, it is inferred that evocalcet also reduce serum PTH levels, thereby suppressing heterotopic calcification and abnormal bone metabolism.

Moreover, in normal rats, serum IP levels were higher in the evocalcet groups than in the vehicle control group [see Section 3.1.2.2], whereas in PNx rats, there were no significant difference in the serum IP levels between the evocalcet groups and the vehicle control group [see Section 3.1.2.3]. Taking account of these findings, PMDA asked the applicant to explain the effect of evocalcet on serum IP levels.

The applicant's response:
Pharmacological actions of PTH include inhibition of renal tubuler reabsorption of phosphate (*J Clin Invest*. 2008;118:3820-3828). It is inferred that in normal rats, evocalcet decreased serum PTH levels, resulting in attenuated effects of PTH on renal tubules, which in turn enhanced phosphate reabsorption from urine to blood, leading to increased serum IP levels. In contrast, the effect of PTH on renal tubules would be reduced in PNx CKD rats with decreased number of renal tubules due to the nephrectomy. Consequently, it is inferred that evocalcet-induced decrease in PTH levels leads to reduced renal tubular phosphate reabsorption, resulting in an attenuated increase in serum IP levels in PNx rats as compared with normal rats. In addition, decreased PTH levels led to the improvement of

bone turnover, decreasing the release of P from bones and thereby reducing serum P levels. Serum IP did not tend to be higher in evocalcet-treated PNx CKD rats than in vehicle-treated PNx CKD rats. These results suggest that evocalcet is unlikely to increase serum IP in SHPT patients with decreased renal function.

PMDA's view:
No study data on the effect of evocalcet on heterotopic calcification or abnormal bone metabolism have been submitted in the present application. However, in light of the reports that evocalcet decreased serum PTH levels and that cinacalcet, a drug with CaR-agonist activity as is the case with evocalcet, improved heterotopic calcification and abnormal bone metabolism by reducing serum PTH levels, PMDA accepts the applicant's above discussion that evocalcet is effective to treat these pathological conditions. Evocalcet is expected to be effective for the treatment of SHPT.

3.R.2 Safety pharmacology

The applicant's explanation about the effect of evocalcet on the central nervous, cardiovascular, and respiratory systems in humans, based on the safety pharmacology data submitted:
The no observed effect level (NOEL) of evocalcet for the central nervous and respiratory systems in rats was 10 mg/kg, with a ≥32-fold safety margin (ratio of C_{max} at the maximum clinical dose [12 mg] to that at the NOEL). This suggests that evocalcet is unlikely to affect the central nervous or respiratory system in humans.

On the other hand, safety pharmacology studies investigating the effect on the cardiovascular system, showed an increase in heart rate and a transient increase in blood pressure in rats and an increase in heart rate, an increase in blood pressure, and QTc prolongation in monkeys (Table 7), with 4.0- and 0.4-fold safety margins in rats and monkeys, respectively. Because (1) the timing of these changes was independent from t_{max} of plasma evocalcet concentration, but was mainly coincident with the timing of the decrease in serum Ca levels, and (2) these changes resolved or tended to resolve with the return of serum Ca levels to baseline, these results suggest that the changes were secondary to the decrease in serum Ca levels. As for QTc prolongation observed in monkeys, evocalcet is unlikely to inhibit myocardial ion channels, in light of the results of *in vitro* studies showing that evocalcet did not affect the current of various myocardial ion channel currents or the action potential of papillary muscles in male guinea pigs.

The above results suggest that the findings observed in the cardiovascular system were secondary to decreased serum Ca levels resulting from the pharmacological action of evocalcet. Evocalcet can be used safely if the patient's serum Ca is periodically monitored in clinical settings.

PMDA accepted the applicant's explanation.

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

Evocalcet or ^{14}C-labeled evocalcet was administered to mice, rats, and monkeys to investigate the pharmacokinetics of evocalcet. Plasma evocalcet concentrations were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was

2 ng/mL in mice and 0.1 ng/mL or 50 ng/mL in rats and monkeys. In studies using ^{14}C-labeled evocalcet, radioactivity was measured by the liquid scintillation counter method, high-performance chromatography-radioactivity detector (HPLC-RAD) method, or quantitative whole-body autoradiography method. Result of the main studies are described below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-3 and 4.2.2.2-4; Studies [redacted]877 and [redacted]878)

A single dose of evocalcet was administered orally or intravenously to male rats and male monkeys. Table 8 shows pharmacokinetic parameter values observed. Bioavailability tended to be lower in monkeys than in rats. The applicant explained that the higher susceptibility of evocalcet to metabolism in monkeys than in rats [see Section 4.3.1] is likely to contribute to the interspecies difference.

Table 8. Plasma pharmacokinetic parameters following oral or intravenous administration of evocalcet

Animal species	Route of administration	Dose of evocalcet (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	Bioavailability[b] (%)
Male rats	p.o.	0.1	222 ± 20	0.3 ± 0.0	819 ± 262	6.7 ± 1.9	81.6 ± 26.1
		0.3	600 ± 60	0.4 ± 0.1	2,578 ± 403	5.8 ± 0.3	85.6 ± 13.4
		1	2,188 ± 291	0.8 ± 0.4	8,445 ± 1,108	6.1 ± 0.6	84.2 ± 11.0
	i.v.	0.3	-	-	3,010 ± 131	7.3 ± 1.9	-
Male monkeys	p.o.	0.1	55 ± 31	1.5 ± 0.6	151 ± 62[a]	5.5 ± 1.9[a]	44.1 ± 22.4[a]
		0.3	179 ± 32	1.3 ± 0.5	443 ± 101	8.8 ± 4.5	45.7 ± 7.1
		1	746 ± 344	1.4 ± 0.8	1,660 ± 351	8.9 ± 1.7	55.8 ± 28.2
	i.v.	0.3	-	-	987 ± 267	10.2 ± 1.2	-

n = 4, Mean ± standard deviation (SD); -, Not calculated
a) n = 3
b) Calculated using $AUC_{0-\infty}$ observed following intravenous administration at 0.3 mg/kg.

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study in rats (CTD 4.2.3.2-2 and 4.2.3.2-4; Studies [redacted]949 and [redacted]153)

In a 4-week oral repeated-dose toxicity study, evocalcet was administered to male and female rats to investigate the toxicokinetics of evocalcet. Table 9 shows plasma pharmacokinetic parameters of evocalcet in rats receiving evocalcet once daily for 4 weeks. C_{max} and AUC_{0-24h} tended to be higher in females than in males at all doses investigated.

Table 9. Plasma pharmacokinetic parameters following 4-week repeated oral administration in rats

Dose of evocalcet (mg/kg/day)	Sampling point	Male			Female		
		C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg•h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg•h/mL)
0.1	Day 1	0.1 ± 0.0	1.3 ± 0.5	1.3 ± 0.5	0.2 ± 0.0	3.5 ± 3.0	3.0 ± 0.6
	Day 28	0.1 ± 0.0	1.0 ± 0.0	0.8 ± 0.3	0.3 ± 0.0	1.0 ± 0.0	3.7 ± 0.5
0.3	Day 1	0.4 ± 0.0	1.3 ± 0.5	3.8 ± 1.1	0.6 ± 0.1	4.0 ± 2.8	8.2 ± 1.0
	Day 28	0.3 ± 0.1	1.3 ± 0.5	2.3 ± 0.6	0.8 ± 0.1	1.5 ± 0.6	11.0 ± 1.9
1.5	Day 1	1.8 ± 0.4	1.3 ± 0.5	16.4 ± 6.9	3.3 ± 0.3	1.5 ± 0.6	40.1 ± 7.8
	Day 28	1.2 ± 0.1	2.8 ± 3.5	11.6 ± 5.0	3.9 ± 0.8	1.3 ± 0.5	54.7 ± 7.6
6	Day 1	6.6 ± 1.2	4.5 ± 2.5	89.7 ± 16.4	9.0 ± 1.8	6.3 ± 3.5	158.1 ± 40.2
	Day 28	6.5 ± 4.0	2.3 ± 1.3	75.4 ± 43.4	18.0 ± 2.0	3.3 ± 3.2	267.6 ± 34.1

Mean ± SD, n = 4

4.1.2.2 Repeated-dose study in monkeys (CTD 4.2.3.2-8, Study [redacted]163)

In a 39-week oral repeated-dose toxicity study, evocalcet was administered to male and female monkeys to investigate the toxicokinetics of evocalcet. Table 10 shows plasma pharmacokinetic parameters of evocalcet in male and female monkeys receiving evocalcet once daily for 39 weeks. At 0.3 and 1 mg/kg, C_{max} and $AUC_{0\text{-}24h}$ tended to be slightly higher in males than in females, whereas at 3 mg/kg, there was no clear difference in C_{max} and $AUC_{0\text{-}24h}$ between males and females. C_{max} and $AUC_{0\text{-}24h}$ showed no marked changes during the repeated administration in males or females.

Table 10. Plasma pharmacokinetic parameters following 39-week repeated oral administration in monkeys

Dose of evocalcet (mg/kg/day)	Sampling point	Male			Female		
		C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (μg•h/mL)	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (μg•h/mL)
0.3	Day 1	0.3 ± 0.1	2.8 ± 1.5	1.1 ± 0.6	0.1 ± 0.0	1.5 ± 0.6	0.3 ± 0.1
	Day 273	0.2 ± 0.1	2.1 ± 1.4	0.9 ± 0.4	0.0 ± 0.0	1.3 ± 0.9	0.2 ± 0.0
1	Day 1	1.1 ± 0.2	2.0 ± 0.0	4.0 ± 1.0	0.4 ± 0.1	1.8 ± 0.5	1.5 ± 0.3
	Day 273	1.0 ± 0.3	1.6 ± 0.8	4.2 ± 1.0	0.3 ± 0.2	1.8 ± 0.5	1.0 ± 0.4
3	Day 1	2.3 ± 1.5	2.0 ± 0.0	8.2 ± 4.4	2.6 ± 1.6	2.0 ± 0.0	7.7 ± 4.8
	Day 273	2.1 ± 0.6	1.8 ± 0.5	6.5 ± 1.9	2.0 ± 1.3	1.6 ± 0.8	7.2 ± 3.6

Mean ± SD, n = 4

4.1.2.3 Repeated-dose study in partially-nephrectomized CKD rats (CTD 4.2.2.7-1, Study [redacted]651)

Evocalcet (0.03, 0.1, 0.3, or 1 mg/kg) was administered once daily for 2 weeks to male 5/6 Nx CKD rats. Table 11 shows plasma evocalcet concentrations at 0.5 and 24 hours post-dose on Day 1 and Day 14. The plasma evocalcet concentration on Day 14 was similar to that on Day 1.

Table 11. Plasma evocalcet concentrations following 14-day repeated oral administration to male 5/6 Nx CKD rats

Dose of evocalcet (mg/kg/day)	Day 1		Day 14	
	0.5 hours post-dose (ng/mL)	24 hours post-dose (ng/mL)	0.5 hours post-dose (ng/mL)	24 hours post-dose (ng/mL)
0.03	65 ± 15	5 ± 3	51 ± 24	9 ± 7
0.1	204 ± 64	22 ± 16	134 ± 71	29 ± 30
0.3	546 ± 155	90 ± 65	687 ± 310	102 ± 97
1	1,635 ± 733	286 ± 197	1,769 ± 1,109	491 ± 402

Mean ± SD, n = 12

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.2-1, Study [redacted]795[redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male albino rats to investigate radioactivity concentrations in individual tissues[1)] at 1, 8, 12, 24, 48, and 96 hours post-dose. The radioactivity concentration reached the maximum level within 1 hour post-dose in most of the tissues investigated. The radioactivity concentration was high in the Harderian gland and liver during the first 1 hour post-dose, being 1.7 and 1.5 times, respectively, the plasma radioactivity level, whereas radioactivity in other tissues was 0.06 to 1.1 times the plasma radioactivity level. Tissue

1) Radioactivity concentration was measured in the following tissues: Adrenal gland, blood, bone marrow, brain, brown fat, epididymis, eyeball, white fat, Harderian gland, heart, kidney, large intestine, liver, lung, submandibular gland, mesenteric lymph node, pancreas, pituitary gland, prostate gland, vesicular gland, skeletal muscle, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, bladder, gastric content, small intestinal content, large intestinal content, and intravesical urine.

radioactivity levels decreased over time, becoming undetectable in most of the tissues at 96 hours post-dose.

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male pigmented rats to investigate radioactivity levels.[2)] The radioactivity concentration in the eyeballs was higher in male pigmented rats than in male albino rats. The radioactivity was eliminated only gradually from the eyeballs, pigmented skin, and uvea of male pigmented rats. These results suggested that evocalcet has an affinity for melanin.

4.2.2 Protein binding (CTD 4.2.2.3-1, Study [redacted]738)

Protein binding of ^{14}C-labeled evocalcet (0.1-10 μg eq./mL) was investigated using plasma samples of mice, rats, rabbits, and monkeys. The mean protein binding rate was 88.7% to 89.6% in mice, 95.2% to 95.8% in rats, 95.6% to 96.2% in rabbits, and 95.1% to 96.2% in monkeys. The protein binding rate was not concentration-dependent within the concentration range investigated.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-3, Study [redacted]739)

Distribution of ^{14}C-labeled evocalcet (0.1-10 μg eq./mL) in blood cells was investigated using blood samples of rats and monkeys. The mean rate of distribution in blood cells was 7.6% to 9.0% in rats and 27.1% to 27.9% in monkeys. The distribution of the drug in blood cells was not concentration-dependent within the concentration range investigated.

4.2.4 Placental transfer in rats (CTD 4.2.2.3-4, Study [redacted]472[redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to pregnant rats on gestation day 18. Tissue radioactivity concentrations were measured in dams and fetuses. In all tissues except for fetal intestinal content, the radioactivity concentration reached the maximum level at 1 hour post-dose, then decreased over time. The radioactivity concentration in fetal intestinal content was higher at 48 hours post-dose than at 1 and 10 hours post-dose, showing it was 29.7-fold that in the plasma of dams. These results demonstrated that evocalcet crossed the placenta and was distributed in fetuses.

4.3 Metabolism

4.3.1 *In vitro* study of metabolism (CTD 4.2.2.4-1, Study [redacted]860[redacted])

Metabolism of ^{14}C-labeled evocalcet was investigated using rat and monkey hepatocytes. The main metabolites detected were M1 and M5 (naphthylethylamine). M1 and M5 accounted for 1.6% to 3.4% and 6.7% to 11.6%, respectively, of the radioactivity in the sample (total peak radioactivity) in rats and 23.4% to 24.3% and 17.0% to 33.0%, respectively, in monkeys. The residual rate of unchanged evocalcet after 4 hours of incubation was 58.9% to 70.8% in rats and 5.1% to 30.6% in monkeys.

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2) Radioactivity concentration was measured in the following tissues: Adrenal gland, blood, bone marrow, brain, brown fat, epididymis, eyeball, white fat, Harderian gland, heart, kidney, large intestine, lens, liver, lung, submandibular gland, mesenteric lymph node, pancreas, pituitary gland, prostate gland, vesicular gland, skeletal muscle, skin (pigmented), skin (non-pigmented), small intestine, spleen, stomach, testis, thymus, thyroid gland, bladder, uvea, gastric content, small intestinal content, large intestinal content, and intravesical urine.

4.3.2 Metabolites in plasma and urine (CTD 4.2.2.4-2 and 4.2.2.4-3; Studies [redacted] and [redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male rats to investigate metabolites in plasma. Unchanged evocalcet was the predominant compound in plasma, and the main metabolites, M1 and M5, were detected in minimal amounts. Unchanged evocalcet was not detected in urine during the first 48 hours post-dose, but M9 (dihydrodiol form of M5) was detected mainly. Unchanged evocalcet and M1 were mainly detected in feces during the first 48 hours post-dose, and M1 in the bile.

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male monkeys to investigate metabolites in plasma. Unchanged evocalcet was detected in a large amount in plasma, and the main metabolites detected were M1, M2, M5, and M6 (dihydrodiol form of evocalcet). M5 and M7 (naphthyl acetate) were mainly detected in urine during the first 72 hours post-dose.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.2-1, Study [redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male rats to investigate urinary, fecal, and biliary excretion in rats. The radioactivity excretion rate in urine, feces, and expired air up to 168 hours post-dose was 21.3%, 79.1%, and 0.7%, respectively. Following single intravenous administration of ^{14}C-labeled evocalcet (1 mg/kg) to male rats, the radioactivity excretion rate in urine, feces, and expired air up to 168 hours post-dose was 25.0%, 71.9%, and 0.9%, respectively.

Following single oral administration of ^{14}C-labeled evocalcet (1 mg/kg) to bile duct-cannulated male rats, the radioactivity excretion rate in bile, urine, and feces was 94.7%, 4.9%, and 0.7%, respectively. These results showed that, in rats, radioactivity absorbed after oral administration was excreted mainly in feces via bile.

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered to bile duct-cannulated male rats, and 2 mL of radioactive bile collected from the rats over 24 hours was administered intraduodenally to a separate set of bile duct-cannulated rats. The results showed that the biliary and urinary excretion rate of radioactivity up to 48 hours post-dose was 60.8% and 11.8%, respectively, indicating that approximately 70% of radioactivity was excreted into bile was re-absorbed.

4.4.2 Urinary and fecal excretion in monkeys (CTD 4.2.2.2-2, Study [redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to male rats to investigate the urinary and fecal excretion in monkeys. The urinary and fecal excretion rate of radioactivity up to 336 hours post-dose was 57.3% and 30.2%, respectively. Following a single intravenous administration of ^{14}C-labeled evocalcet (0.3 mg/kg), the urinary and fecal excretion rate of radioactivity up to 336 hours post-dose was 58.6% and 27.3%, respectively. These results suggested that, in monkeys, both unchanged evocalcet and metabolites are excreted in urine and feces.

4.4.3 Excretion into milk in rats (CTD 4.2.2.5-1, Study [redacted])

A single dose of ^{14}C-labeled evocalcet (1 mg/kg) was administered orally to female rats on postpartum day 11 to investigate the excretion of evocalcet into milk at 2, 8, 24, and 48 hours post-dose. The radioactivity in milk reached the maximum level (1,239 ng eq./mL which was 0.99 times the plasma radioactivity concentration) at 8 hours post-dose, after which the concentration decreased over time. The ratio of radioactivity concentration in milk to that in plasma at 24 hours post-dose was 3.7. These results demonstrated that evocalcet is excreted into milk.

4.R Outline of the review conducted by PMDA

4.R.1 Sex difference of pharmacokinetics observed in rats

In the 4-week repeated-dose study in rats, plasma evocalcet concentrations tended to be higher in female rats than in male rats [see Section 4.1.2.1]. Based on the results, the applicant explained the possibility that sex differences affect the pharmacokinetics of evocalcet in humans.

The applicant's explanation:
Although $AUC_{0\text{-}24h}$ tended to be higher in females than in males in the 4-week repeated-dose study in rats, no clear sex difference was noted in the 39-week repeated-dose study in monkeys [see Section 4.1.2.2].

In a Japanese phase I/II study in Japanese patients with SHPT on hemodialysis (HD) (Study 7580-003), C_{max} and $AUC_{0\text{-}t}$ in patients receiving evocalcet (1 mg) were 61 ± 23 ng/mL and 1,151 ± 694 ng•h/mL, respectively, in women and 65 ± 17 ng/mL and 1,191 ± 1,112 ng•h/mL, respectively, in men, showing no marked difference between men and women. On basis of the above findings, it is unlikely that there are sex differences in the pharmacokinetics of evocalcet in humans.

PMDA accepted the applicant's explanation.

4.R.2 Melanin affinity

A study using pigmented rats suggests that evocalcet has an affinity for melanin [see Section 4.2.1]. PMDA asked the applicant to explain the possibility of safety concerns associated with accumulation of evocalcet in melanin-containing tissues in humans.

The applicant's response:
Evocalcet may possibly accumulate in melanin-containing tissues, e.g., eyeballs (uvea among others) and skin. However, no effect of evocalcet on the eye or the skin was observed in the repeated-dose toxicity studies in monkeys or in the phototoxicity study in pigmented rats [see Sections 5.2.4-5.2.6 and 5.6.2.2]. Also, no clinically relevant adverse events associated with eye disorders or with skin and subcutaneous tissue disorders occurred in patients with SHPT on HD (the Japanese phase III comparative study and the Japanese long-term treatment study) or in patients with SHPT on peritoneal dialysis (PD) (the Japanese open-label clinical study).

These results suggest that evocalcet is unlikely to cause safety problems associated with its melanin affinity in humans.

PMDA accepted the applicant's explanation. However, the information on the study results suggesting the melanin affinity of evocalcet in pigmented rats should be communicated to health professionals via the package insert.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of evocalcet were conducted: Repeated-dose toxicity studies, a genotoxicity study, a carcinogenicity study, reproductive and developmental toxicity studies, and other toxicity studies (a study on the effect on the lens and a phototoxicity study). In *in vivo* studies, 0.5% methylcellulose solution was used as vehicle.

5.1 Single-dose toxicity (CTD 4.2.3.2-1 and 4.2.3.2-5 [Reference]; Studies [redacted]220 and [redacted]391)

No single-dose toxicity study was conducted. Instead, acute toxicity of evocalcet was evaluated in a 2-week oral dose toxicity study in rats and a 2-week oral dose toxicity in monkeys.

In a 2-week oral dose toxicity study in rats, evocalcet (0.3, 1, 3, or 10 mg/kg) was administered orally once daily to male and female rats for 2 weeks. One female in the 10 mg/kg group started having muscle twitching before the second dose, which persisted immediately after and 2 hours after the second dose, resulting in death. In a 2-week repeated oral dose toxicity study in monkeys, evocalcet (1, 3, or 10 mg/kg) was administered orally once daily to male and female monkeys. Neither death nor change in clinical signs was observed after the first dose.

Based on the above, the approximate oral lethal dose was determined to be 10 mg/kg in rats and >10 mg/kg in monkeys. The exposure (C_{max}) at these approximate lethal doses was 27.6/30.4 times (male/female rats) and 7.0/10.1 times (male/female monkeys) the human exposure (C_{max}) at the maximum clinical dose (12 mg/day).

5.2 Repeated-dose toxicity

Oral dose toxicity studies were conducted in male and female rats (4, 13, and 26 weeks) and in male and female monkeys (4, 13, and 39 weeks). Main findings in rats were atrophy of parathyroid gland, decreased serum PTH and Ca levels, increased serum IP levels, bone findings associated with decreased serum PTH levels (hyperostosis of outer circumferential lamellae, hypertrophy of trabecular bones, etc.), muscle twitching associated with decreased serum Ca levels, ocular findings (lenticular opacities, fiber swelling, etc.), dental findings (missing incisors, etc.), mineral deposition in blood vessels, etc., due to increased serum IP levels, cardiac findings (degeneration and fibrosis), bile duct epithelial cell hypertrophy, and decreases in body weight and food consumption. Main findings in monkeys were decreased serum PTH and Ca levels, increased serum IP levels, QTc prolongation associated with decreased serum Ca levels, mineral deposition and interstitial edema in kidney associated with increased serum IP levels, and hypertrophy of collecting duct epithelial cells in kidney. These findings in rats and monkeys were considered to be the direct or secondary effects of the pharmacological action of evocalcet. The exposure (AUC) at the no observed adverse effect level (NOAEL) in rats (26 weeks) and monkeys (39 weeks) (<0.3 mg/kg/day [male rats], <0.1 mg/kg/day

[female rats], and 0.3 mg/kg/day [male and female monkeys]) was <0.32/<0.91 times (male/female rats) and 0.15/0.027 times (male/female monkeys) the human exposure (AUC) at the maximum clinical dose (12 mg/day).

5.2.1 Four-week oral dose toxicity study in rats with a 4-week recovery period (CTD 4.2.3.2-2, Study [redacted]949)

Evocalcet (0.1, 0.3, 1.5, or 6 mg/kg/day) or vehicle was administered orally once daily for 4 weeks to male and female rats, and reversibility after a 4-week recovery period was investigated in the 6 mg/kg/day group and in the vehicle control group. Findings observed at ≥0.1 mg/kg/day were opacity of anterior crystalline lens cortex, decreased serum Ca levels, and increased IP levels. Findings at ≥0.3 mg/kg/day were increased urinary Ca excretion and lenticular fiber swelling. Findings at 1.5 mg/kg/day were decreased food consumption, increases in white blood cell count and neutrophil count, increases in serum alanine aminotransferase (ALT) and creatine kinase (CK) levels, myocardial fiber degeneration/necrosis, and bile duct epithelial cell hypertrophy. Findings at 6 mg/kg/day were muscle twitching, decreased body weight, decreased urine specific gravity, increased urine volume, duodenal erosion, and mineral deposition in the heart. Changes other than opacity of anterior crystalline lens cortex were reversible or tended to be reversible after the recovery period. The NOAEL was determined to be <0.1 mg/kg/day in both male and female rats.

5.2.2 Thirteen-week oral dose toxicity study in rats (CTD 4.2.3.2-3, Study [redacted]163)

Evocalcet (0.3/0.1, 1.5/0.6, or 6/3 mg/kg/day [male/female]) or vehicle was administered orally once daily for 13 weeks to male and female rats.[3)] Findings observed at ≥0.3/0.1 mg/kg/day (male/female) were opacity of anterior crystalline lens cortex, increased urinary Ca excretion, decreased serum Ca levels, increased serum IP levels, and hyperostosis of outer circumferential lamellae of femur. Findings at ≥1.5/0.6 mg/kg/day (male/female) were myocardial degeneration and fibrosis, inflammatory cell infiltration in heart, lenticular fiber swelling, and bile duct epithelial cell hypertrophy. Findings at 6/3 mg/kg/day (male/female) were muscle twitching; lower body weight; decreased food consumption; decreased urine specific gravity; increased urine volume; increases in lymphocyte, neutrophil, and monocyte counts; mineral deposition in renal pelvis; subendocardial hemorrhage; duodenal erosion; and atrophy of adrenocortical zona glomerulosa cells. Increased urinary Ca excretion, decreased serum Ca levels, and increased serum IP levels were attributable to the pharmacological action of evocalcet and not considered to be toxicity findings. The NOAEL was determined to be <0.3 mg/kg/day in male rats and 0.1 mg/kg/day in female rats.

5.2.3 Twenty-six-week oral dose toxicity study in rats (CTD 4.2.3.2-4, Study [redacted]153)

Evocalcet (0.3/0.1, 1.5/0.6, or 6/3 mg/kg/day [male/female]) or vehicle was administered orally once daily for 26 weeks to male and female rats.[3)] One male in the 0.3 mg/kg/day group died on Day 91. The death was considered to be accidental because there were no findings suggestive of the cause of death. Findings observed at ≥0.3/0.1 mg/kg/day (male/female) were opacity of anterior crystalline lens cortex, increased urinary Ca excretion, decreased serum Ca levels, increased serum IP levels, atrophy of parathyroid gland, localized mineral deposition in pulmonary artery wall, hyperostosis of outer

3) The doses in males and females were determined by referring to the difference in the exposure between males and females observed in the 4-week oral dose toxicity study in rats [see Section 5.2.1].

circumferential lamellae of femur, remnant cartilage in femoral cortical and trabecular bones, remnant cartilage in sternal trabecular bone, expanded dentinal tubules and incomplete calcification of maxillary incisors. Findings at ≥1.5/0.6 mg/kg/day (male/female) were hypertrophy of trabecular bones of femur and sternum, myocardial degeneration and fibrosis, inflammatory cell infiltration in heart, interstitially localized mineral deposition in epididymis, lenticular fiber swelling, irregular ameloblast layer of maxillary incisors, inflammatory cell infiltration in periodontal tissue, localized bile duct epithelial cell hypertrophy, and mineral deposition in renal pelvis. Findings at 6/3 mg/kg/day (male/female) were muscle twitching; missing maxillary and mandibular incisors, decreased body weight; decreased food consumption; decreased urine specific gravity; increased urine volume; increased urinary IP excretion; increases in lymphocyte, neutrophil, monocyte, and white blood cell counts; atrophy of adrenocortical zona glomerulosa cells; incomplete enamel calcification of maxillary incisors; single-cell/localized necrosis of ameloblasts and pulp necrosis; and centrilobular hepatocyte hypertrophy. The NOAEL was determined to be <0.3 mg/kg/day in male rats and <0.1 mg/kg/day in female rats.

5.2.4 Four-week oral dose toxicity study in monkeys with a 4-week recovery period (CTD 4.2.3.2-6, Study [redacted]973)

Evocalcet (0.1, 0.3, 1, or 3 mg/kg/day) or vehicle was administered orally once daily for 4 weeks to male and female monkeys, and reversibility after a 4-week recovery period was investigated in the 3 mg/kg group and in the vehicle control group. Findings observed at ≥1 mg/kg/day were QTc prolongation, increased urinary IP excretion, decreased blood Ca, increased serum IP, myocardial fiber degeneration and necrosis, and hypertrophy of collecting duct epithelial cells of kidney. Findings at 3 mg/kg/day were interstitial edema of kidney and papillary mineral deposition. These changes were reversible after the recovery period. The NOAEL was determined to be 0.3 mg/kg/day in both male and female monkeys.

5.2.5 Thirteen-week oral dose toxicity study in monkeys (CTD 4.2.3.2-7, Study [redacted]228)

Evocalcet (0.3, 1, or 3 mg/kg/day) or vehicle was administered orally once daily for 13 weeks to male and female monkeys. Findings observed at ≥1 mg/kg/day were QTc prolongation, increased urinary IP excretion, decreased serum Ca levels, increased serum IP levels, and hypertrophy of collecting duct epithelial cells of kidney. Findings at3 mg/kg/day were increased or decreased heart rate, ventricular extrasystoles, and subepicardial inflammatory cell infiltration and fibrosis. The NOAEL was determined to be 0.3 mg/kg/day in male monkeys and 1 mg/kg/day in female monkeys.

5.2.6 Thirty-nine-week oral dose toxicity study in monkeys (CTD 4.2.3.2-8, Study [redacted]163)

Evocalcet (0.3, 1, or 3 mg/kg/day) or vehicle was administered orally once daily for 39 weeks to male and female monkeys. A finding observed at ≥0.3 mg/kg/day was decreased serum Ca. Findings at ≥1 mg/kg/day were QTc prolongation, increased urinary IP secretion, and increased serum IP. Findings at 3 mg/kg/day were increased heart rate, increased kidney weight, hypertrophy of collecting duct epithelial cells of kidney, mineral deposition in renomedullary interstitium, inflammatory cell infiltration in renomedullary interstitium, edema of renomedullary interstitium, and mineral deposition in renal pelvis. Decreased serum Ca was attributable to the pharmacological action of evocalcet and

not considered to be a toxicity finding. The NOAEL was determined to be 0.3 mg/kg/day in both male and female monkeys.

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]964, [redacted]0965, and [redacted]967)

A bacterial reverse mutation assay, a chromosomal aberration assay using Chinese hamster lung-derived fibroblast CHL/IU cell line, and a bone marrow micronucleus assay in rats were conducted. Evocalcet did not show genotoxicity in any of these assays.

5.4 Carcinogenicity

Carcinogenicity studies were conducted using male and female mice and male and female rats. No carcinogenicity was observed in any of the studies. The exposure (AUC) at the highest non-tumorigenic dose in mice (30 mg/kg/day in male, 20 mg/kg/day in female) or rats (6 mg/kg/day in male, 3 mg/kg/day in female) was 66.5/59.6 times (male/female mice) and 3.6/19.8 times (male/female rats) the human exposure at the maximum clinical dose (12 mg/day).

5.4.1 Oral dose carcinogenicity study in rasH2 mice (CTD 4.2.3.4.2-3, Study [redacted]851)

Evocalcet (3/2, 10/6, or 30/20 [male/female] mg/kg/day) or vehicle was administered orally once daily to male and female mice for 26 weeks. Evocalcet had no impact on the incidence of tumorigenic changes, showing no carcinogenicity. Non-tumorigenic changes observed included hyperplasia of squamous epithelial cells in the anterior stomach. Based on the publication reporting that the anterior stomach of rasH2 mice is highly sensitive to stimuli and that chemical substances induce hyperplasia of squamous epithelial cells in the anterior stomach (New Toxicologic Histopathology, edited by the Japanese Society of Toxicologic Pathology, 2017), the applicant explained that the hyperplasia of squamous epithelial cells was a change caused by physical or chemical stimuli associated with the administration of evocalcet.

5.4.2 Two-year oral dose carcinogenicity study in rats (CTD 4.2.3.4.1-1, Study [redacted]920)

Evocalcet (0.3/0.1, 1.5/0.6, or 6/3 [male/female] mg/kg/day) or vehicle was administered orally once daily to male and female rats for 104 weeks. Because females in the 3 mg/kg/day group showed reduced body weight gain and missing incisors, the dose was decreased to 2 mg/kg/day from Week 47 onward, and the administration was continued. Tumorigenic changes observed were endometrial stromal sarcoma and breast adenocarcinoma, and their incidence significantly increased in females at 3 mg/kg/day compared with vehicle control. However, evocalcet is considered to be non-carcinogenic for the following reasons: (1) Neither tumor was correlated with dose levels, (2) the incidence of endometrial stromal sarcoma was very low and considered to be within the range of spontaneous development, and (3), as for breast adenocarcinoma, the incidence of the total of mammary gland tumor (sum of adenocarcinoma, adenoma, and fibroadenoma) and breast hyperplasia did not differ among treatment groups. Non-tumorigenic changes observed were mineral deposition in various arteries, hyperplasia of thyroid C cells, parathyroid gland atrophy, sperm congestion in testis and epididymis, atrophy of seminiferous tubule in testis, mineral deposition in epididymis and sperm granuloma, cardiomyopathy, mineral deposition in kidney and urothelial hyperplasia, trabecular bone proliferation in femur and sternum, mineral deposition in muscle layer of forestomach and glandular

stomach, and ocular cataract and retinal atrophy. The applicant explained that these non-tumorigenic changes are the direct or secondary effects of the pharmacological action of evocalcet.

5.5 Reproductive and developmental toxicity

The following studies were conducted: A study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function in rats. The exposure (AUC) at the NOAEL (0.3 mg/kg/day in rats, 0.6 mg/kg/day in rabbits) for embryo-fetal development was 1.3 times (rats) and 1.4 times (rabbits) the human exposure at the maximum clinical dose (12 mg/day). Evocalcet has been shown to cross the placenta and to be excreted into milk [see Section 4.2.4].

5.5.1 Study of fertility and early embryonic development to implantation in rats (CTD 4.2.3.5.1-1, Study [redacted]702)

Evocalcet (0.3/0.1, 1.5/0.6, or 6/3 [male/female] mg/kg/day) or vehicle was administered orally once daily to male rats from 2 weeks pre-mating through the mating period until the day before necropsy and to female rats from 2 weeks pre-mating, through the mating period until gestation day 7. Findings in male rats at 6 mg/kg/day were lower or decreased body weight and decreased food consumption. Findings in female rats at 3 mg/kg/day were lower or decreased body weight, decreased food consumption, tendency of decreased frequency of estrus, tendency of prolonged estrus cycle, and decreases in corpora lutea count, implantation, and live conceptuses. According to the applicant's explanation, changes in female rats at 3 mg/kg/day (tendency of decreased frequency of estrus, tendency of prolonged estrus cycle, and decreased corpora lutea count) were the effects secondary to decreases in body weight and food consumption, and the decreased implantation and decreased number of live conceptuses were due to the decreased corpora lutea count, judging from the lack of difference between pre- and post-implantation loss. The NOAEL was determined to be 1.5 mg/kg/day (males) and 0.6 mg/kg/day (females) for general toxicity in parent animals, and 6 mg/kg/day (males) and 0.6 mg/kg/day (females) for fertility of parent animals and for embryo-fetal development.

5.5.2 Embryo-fetal development study in rats (CTD 4.2.3.5.2-2, Study [redacted]119)

Evocalcet (0.3, 1, or 3 mg/kg/day) or vehicle was administered orally once daily to pregnant rats from gestation day 6 through gestation day 17. Findings in dams at ≥1 mg/kg/day were decreased body weight or reduced body weight gain, and decreased food consumption. Findings fetuses at ≥1 mg/kg/day were lower body weight, and findings in fetuses at 3 mg/kg/day were skeletal variations (increased frequency of 14 short extra ribs and bifid ossification of sternebrae, lower number of ossified metatarsal bones) and visceral variations (lung discoloration). The skeletal variations were considered to be changes secondary to the maternal toxicity. The lung discoloration was considered to be an effect of anesthesia during the cesarean section or a transient change, judging from the observation that newborns at 3 mg/kg/day did not show any pulmonary abnormality or respiratory function disorder in the study for effects on pre- and postnatal development, including maternal function in rats [see Section 5.5.4]. Thus, there were no abnormalities suggestive of teratogenicity. The NOAEL was determined to be 0.3 mg/kg/day for general toxicity and reproductive functions in dams and for embryo-fetal development.

5.5.3 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2-4, Study [redacted]120)

Evocalcet (0.1, 0.25, or 0.6 mg/kg/day) or vehicle was administered orally once daily to pregnant rabbits from gestation day 6 through gestation day 18. Findings in dams at 0.6 mg/kg/day were decreased feces, reduced body weight gain, and lower food consumption. There was no effect on embryos or fetuses. The NOAEL was determined to be 0.25 mg/kg/day for the general toxicity in maternal animals and 0.6 mg/kg/day for the reproductive functions of dams and for embryo-fetal development.

5.5.4 Study for effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3-1, Study [redacted]172)

Evocalcet (0.3, 1, or 3 mg/kg/day) or vehicle was administered orally once daily to pregnant rats from gestation day 6 through lactation day 20. Findings observed in dams were as follows: At ≥1 mg/kg/day, death of all pups including stillbirth of all pups, reduced body weight gain during gestation period, lower body weight during the first half of the lactation period, and lower food consumption during the gestation period and the lactation period; and at 3 mg/kg/day, lower body weight during the gestation period, prolonged gestation period, lower delivery rate, and intrauterine conceptuses (all pups died on lactation day 1 in 2 of 6 dams). Findings observed in pre-weaning pups were as follows: At ≥1 mg/kg/day, higher stillbirth rate, lower survival rate on Day 4 after birth, lower body weight, opacity of eyeball, prolonged righting reflex time, and loss of free fall reflex and of pupillary reflex; and at 3 mg/kg/day, lower birth rate and lower survival rate on Day 21 after birth. The measurement of plasma Ca and necropsy were conducted on Day 4 after birth in the 1 mg/kg/day group (not in the 0.3 and 3 mg/kg/day groups). Results showed lower plasma Ca concentration, dark red foci in lung, ascites, dilated renal pelvis and renal tubule, and intestinal adhesion. Findings observed in post-weaning pups were as follows: At ≥0.3 mg/kg/day, lower body weight, lenticular opacities, delayed cleavage of the balanopreputial gland, and increased total running distance and increased rearing times in the open filed test; at ≥1 mg/kg/day, opacity of eyeballs and persistent pupillary membrane of the iris; and at 3 mg/kg/day, fracture of incisors and delayed vaginal opening. The NOAEL was determined to be 0.3 mg/kg/day for general toxicity and reproductive functions in dams and <0.3 mg/kg/day for the development of embryos, fetuses, and pups.

5.6 Other toxicity studies

5.6.1 Effect on lens

5.6.1.1 Calcium supplementation study (CTD 4.2.3.7.3-1 [Reference], Study [redacted]099)

A study was conducted to elucidate the mechanism of opacity of anterior crystalline lens cortex observed in the repeated-dose toxicity studies in rats [see Sections 5.2.1-5.2.3]. Evocalcet (10 mg/kg/day) was administered orally once daily for 1 week to male rats while Ca gluconate solution (150 mg/kg/h for Ca supplementation) or physiological saline was continuously administered intravenously to the rats. Findings in physiological saline-treated rats were lower plasma Ca, opacity of anterior crystalline lens cortex (disseminated opacity in 5 of 12 rats, diffuse opacity in 7 of 12 rats) and lenticular fiber swelling (in 5 of 12 rats), whereas neither decreased plasma Ca nor lenticular fiber swelling was observed in Ca gluconate-treated rats, revealing opacity of anterior crystalline lens cortex (disseminated opacity) in only 1 out of 10 rats. Thus, opacity of anterior crystalline lens cortex and lenticular fiber swelling were observed less frequently in the Ca gluconate group than in the

physiological saline group, from which the applicant considered that opacity of anterior crystalline lens cortex observed in rats was considered to be an effect secondary to decreased blood Ca.

5.6.1.2 Study for measurement of evocalcet concentration in aqueous humor (CTD 4.2.3.7.3-2 and 4.2.3.7.3-3; Studies [redacted]891 and [redacted]892)

The repeated-dose toxicity studies revealed the development of opacity of anterior crystalline lens cortex in rats but not in monkeys [see Section 5.2]. A study was conducted to investigate the exposure of lens to evocalcet. Evocalcet (6 mg/kg/day) was administered orally once daily to male rats and monkeys for 7 days. Ophthalmological examination was conducted before the last dose and evocalcet concentrations in plasma and in aqueous humor was measured at 2 hours after the last dose. In rats, fine-grained opacity of lens and decreased serum Ca were observed. Evocalcet concentrations in aqueous humor and in plasma were 0.196 μg/mL and 7.244 μg/mL, respectively, with the distribution rate in lens being approximately 2.7%. In monkeys, no effect on the eye was observed, while decreased serum Ca was observed, and evocalcet concentrations in aqueous humor and in plasma ranged from 0.014 to 0.052 μg/mL and from 1.190 to 4.028 μg/mL, respectively, indicating that the distribution rate of evocalcet in lens ranged from 1.2% to 1.5%. Thus, lenticular opacity was observed only in rats, but evocalcet was detected in the aqueous humor of both rats and monkeys, and there were no significant differences in the distribution in lens between these animal species.

5.6.2 Phototoxicity

An *in vitro* phototoxicity study and a phototoxicity study in pigmented rats were conducted. The phototoxicity potential of evocalcet could not be ruled out in the *in vitro* phototoxicity study. In contrast, the phototoxicity study in pigmented rats did not show any adverse skin reaction, and ophthalmological examination and histopathological examination of the eyeballs did not reveal any effect of evocalcet. On the basis of these results, the applicant considered that evocalcet is not phototoxic.

5.6.2.1 *In vitro* phototoxicity study (CTD 4.2.3.7.7-1, Study [redacted]001)

A phototoxicity study was conducted using murine fetal fibroblast-derived BALB/3T3 clone A31 cell line. Evocalcet was not cytotoxic in the concentration range of 3.9 to 500 μg/mL without UV irradiation but cytotoxic under UV irradiation with the half maximal inhibitory concentration (IC_{50}) being 130 μg/mL. Because the IC_{50} of evocalcet without UV irradiation could not be calculated, photo-irritation factor (PIF) was calculated on the assumption that IC_{50} was 500 μg/mL (the maximum concentration investigated). The resulting PIF was 3.8. Thus, the phototoxicity potential could not be excluded.

5.6.2.2 Phototoxicity study in pigmented rats (CTD 4.2.3.7.7-2, Study [redacted]690)

A single dose of evocalcet (1, 3, or 6 mg/kg/day) or vehicle was administered orally to female pigmented rats to evaluate the phototoxicity of evocalcet. In the study for evaluation of skin reaction, no adverse skin reaction was observed either in light or dark skin areas. Also, ophthalmological examination and histopathological examination of the eyeball did not reveal any effect of evocalcet. On the basis of the above results, the applicant considered that evocalcet does not induce phototoxicity in the skin or eyes of rats.

5.R Outline of the review conducted by PMDA

5.R.1 Findings caused by the pharmacological action of evocalcet

The applicant's explanation about the findings attributable to the pharmacological action of evocalcet:
The following findings were observed in the repeated oral dose toxicity studies in rats and monkeys, etc., submitted in the present application: Decreased serum PTH and associated bone findings (e.g., hyperostosis of outer circumferential lamellae of femur, hypertrophy of trabecular bones), decreased serum Ca and associated muscle twitching, QTc prolongation, and dental findings (e.g., missing incisors). All of these findings were reported also in the results of nonclinical toxicity studies using cinacalcet hydrochloride, a CaR agonist similar to evocalcet (Review Report on Regpara Tablets 25 mg, etc. [dated on July 17, 2007]). This suggests that these changes were attributable to decreases in blood PTH and Ca levels due to CaR activation induced by evocalcet. Thus, evocalcet may be used safely in clinical settings if the patient's serum PTH and Ca are periodically monitored.

Also, increased blood IP and associated mineral deposition in various organs were observed in several studies. Increased blood IP resulting from the administration of evocalcet was observed in animals with remaining renal function and is unlikely to occur in patients with SHPT [see Section 3.R.1]. Monkeys were shown to have interstitial edema and inflammatory cell infiltration in interstitium, but they also had mineral deposition, suggesting the possibility that these findings are effects secondary to mineral deposition.

PMDA's view:
Findings attributable to decreases in serum PTH and Ca levels will pose no particular problem, provided that serum PTH and Ca levels are periodically monitored in clinical settings. Findings caused by increased blood IP are unlikely to occur in patients with SHPT.

5.R.2 Myocardial effects

The applicant's explanation about the effect of evocalcet on the heart in humans, based on myocardial degeneration and fibrosis observed in the repeated oral dose toxicity studies in rats and monkeys:
Whereas PTH induces cardiac hypertrophy and is involved in the progression of cardiovascular diseases, it also protects myocardium (e.g., *Am J Physiol Heart Circ Physiol*. 2003;284:H49-55, *Horm Res*. 2004;61:234-241). These reports suggest that the myocardial degeneration and fibrosis observed in rats were due to the clinical conditions of the animals apt to develop myocardial disorder because of the chronic decrease in blood PTH levels. Myocardial degeneration and fibrosis were observed in monkeys in the 4- and 13-week repeated oral dose toxicity studies, but only a small number of monkeys had these abnormalities (1 of 8 monkeys in the 1 mg/kg group and 1 of 12 monkeys in the 3 mg/kg group in the 4-week study, 1 of 8 monkeys in the 3 mg/kg group in the 13-week study). No clear correlation was observed between myocardial degeneration or fibrosis and serum Ca. In addition, neither myocardial degeneration nor fibrosis was observed in the longer-term (39 weeks) repeated oral dose toxicity study. Based on these results, the applicant considered that the cardiac findings observed in the 4- and 13-week toxicity studies in monkeys were not caused by evocalcet.

Although myocardial effects attributable to the pharmacological action of evocalcet were observed in rats, there was little or no change in the levels of markers for myocardial disorders in the Japanese clinical studies (Studies 7580-001, 7580-002, and 7580-009). On the basis of these results, the applicant considered that myocardial degeneration and fibrosis observed in rats are unlikely to be relevant to humans.

PMDA's view:
The applicant's explanation is acceptable. Myocardial degeneration and fibrosis are unlikely to develop as far as blood PTH levels are monitored periodically in patients with SHPT on treatment with evocalcet.

5.R.3 Lenticular opacities and cataract

The applicant's explanation about the lenticular opacities in rats and about the possibility of development of cataract in humans:
Cataract develops according to the following mechanism: Increased intralenticular Ca promotes activation of Ca-dependent protease, which cleaves soluble crystallins into insoluble fragments, resulting in lenticular opacities (*Dokkyo J Med Sci*. 1999;26:369-376, *Invest Ophtalmol Vis Sci*. 2000;41:2255-2261). In a rabbit model of hypocalcemic cataract, sustained hypocalcemia causes an increase in Ca levels in the lens, leading to cataract (*Metab Pediatr Ophthalmol*. 1981;5:77-82). On the other hand, CaR activation induces an increase in intracellular Ca via phosphoinositide 3-kinase (PI3K) pathway (*Folia pharmacologica Japonica*. 2008;132:301-308). Since evocalcet was detected in the aqueous humor of rats [see Section 5.6.1.2], it was also inferred that evocalcet activated the CaR of the lens, leading to an increase in intralenticular Ca levels. However, when Ca supplementation prevented the development of hypocalcemia in rats in a Ca supplementation study, the incidence of lenticular opacities caused by evocalcet was reduced [see Section 5.6.1.1]. These results suggest that the lenticular opacities observed in rats receiving evocalcet were effects secondary to decreased blood Ca levels and associated increase in Ca levels in lenticular cells.

In the repeated-dose toxicity studies, opacity of anterior crystalline lens cortex was observed in rats but not in monkeys [see Section 5.2]. Despite the decreased serum Ca both in rats and monkeys, lenticular opacity was observed only in rats and not in monkeys [see Section 5.6.1.2]. In transgenic mice engineered to constitutively activate CaR, cataract develops at 4 to 6 weeks of age (*Proc Natl Acad Sci USA*. 2004;101:13566-13571), whereas cataract developed in patients with hypocalcemia with serum Ca levels <6 mg/dL persisting for approximately 6 to 12 months (*Lancet*. 1972;1:509-511). These results suggest there are species differences in the development of lenticular opacities, with rats and mice being highly prone to develop lenticular opacities.

Although the possibility cannot be excluded that lenticular opacities develop also in patients with chronic hypocalcemia, it is unlikely that hypocalcemia persists for a long period of time in clinical settings. Thus, lenticular opacities and cataract are unlikely to develop in patients receiving evocalcet, and the development of lenticular opacities and cataract can be prevented if the patient's serum Ca levels are appropriately monitored to prevent hypocalcemia during treatment with evocalcet.

Information on the incidences of lens disorder-related events will be continuously collected in the post-marketing surveillance, etc.

PMDA's view:
The applicant's explanation is acceptable. The package insert should include a precautionary statement advising that blood Ca levels should be periodically monitored to avoid the risk of hypocalcemia in clinical practice. The incidence of lenticular opacities and cataract in clinical studies is discussed separately in Section 7.R.3.4.2.

5.R.4 Effect on pregnant, parturient, and nursing women

The applicant's explanation about the high stillbirth rate, low birth rate, and abnormalities observed in the tests of sensation and reflex and of behavioral development in the study for effects on pre- and postnatal development, including maternal function in rats:
In the study for effects on pre- and postnatal development, including maternal function in rats, evocalcet-induced teratogenicity was not observed, whereas animals showed a high stillbirth rate, low birth rate, low survival rate on Day 4 and 21 after birth, lower body weight, and abnormalities in the sensation/reflex test (e.g., prolonged righting reflex time, loss of free fall reflex and pupillary reflex). CaR activation contributed to increased number of fetal deaths, decreased birth rate, decreased survival rate of newborns, and lower body weight associated with decreased food consumption (*J Bone Miner Res*. 2015;30:1980-1993). Evocalcet crosses the placenta and is excreted into milk. Because dams received evocalcet, their fetuses and offspring were exposed to evocalcet from the embryonic stage until weaning, leading to CaR activation, which may have resulted in increased stillbirth rate, decreased birth rate, decreased survival rate, and lower body weight. Abnormalities in sensation/reflex test are likely to be due to growth retardation, taking account of the lower body weight observed.

Thus, evocalcet significantly affects the development of the offspring. The applicant therefore considered that evocalcet should be contraindicated in pregnant women or women who may possibly be pregnant. Also, since evocalcet is excreted into milk, women during lactation period should avoid breast-feeding while receiving evocalcet.

PMDA's view:
Although teratogenicity was not observed in nonclinical studies, a high stillbirth rate, low birth rate, and lower body weight of the offspring were observed. Therefore, the contraindication of evocalcet for pregnant women or women who may possibly be pregnant is appropriate. In addition, because (1) evocalcet is excreted into milk and (2) evocalcet in milk may possibly retard the development of suckling infants, lactating women should avoid breast-feeding while receiving evocalcet. This precaution should be included in the package insert of evocalcet.

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

The formulations listed in Table 12 were used in the clinical studies submitted as the evaluation data for the present application. Since the change from the Formulation B to Formulation C corresponds to Level [redacted] in the formulation change 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 by PFSB/ELD Notification No. 0229-10 dated February 29, 2012]), a dissolution test was conducted to demonstrate the bioequivalence of the two formulations. Also, since the change from the Formulation C to Formulation D, which consists of changes in [redacted] and [redacted], corresponds to Level [redacted] in the formulation change 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 by PFSB/ELD Notification No. 0229-10 dated February 29, 2012]), a dissolution test was conducted to demonstrate the bioequivalence of the two formulations.

Table 12. Formulations used in clinical studies (evaluation data)

Clinical studies	Formulation
Japanese phase I single-dose study (Study 7580-001), Japanese phase I multiple-dose study (Study 7580-002), Japanese phase I/II study (Study 7580-003), Japanese phase I study (Study 7580-004), foreign phase I study (mass-balance study, Study 7580-006)	Formulation A: Capsules (each capsule contains 0.1, 1, or 10 mg of evocalcet)
Japanese phase I study (effect of hepatic impairment, Study 7580-008), Japanese phase II study (Study 7580-005), Japanese phase I study (drug-drug interactions, Study 7580-009)	Formulation B: Film-coated tablets (each tablet contains 0.5, 1, or 2 mg of evocalcet)
Japanese phase III comparative study (Study 7580-010), Japanese long-term treatment study (Study 7580-011), Japanese open-label clinical study (Study 7580-012)	Formulation C: Film-coated tablets (each tablet contains 1 or 2 mg of evocalcet)
Japanese phase I study (food effect, Study 7580-013)	Formulation D (commercial formulation): Film-coated tablets (each tablet contains 2 mg of evocalcet)

The concentrations of unchanged evocalcet in plasma, urine, and peritoneal dialysate were measured by LC/MS/MS. The lower limit of quantitation of evocalcet was 0.05 ng/mL in plasma, 0.1 ng/mL in urine, and 1.0 ng/mL in peritoneal dialysate.

6.1.1 Japanese phase I study (food effect) (CTD 5.3.1.1-1, Study 7580-013 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, two-treatment, two-period crossover study was conducted in healthy adult Japanese men aged ≥20 and <40 years (target sample size, 16 subjects) at a single study site in Japan to investigate the effect of food on the pharmacokinetics of evocalcet following a single oral dose of evocalcet (2 mg).

A single dose of evocalcet (2 mg) was administered orally under fasted conditions or after breakfast (within 10 minutes after intake of a high-fat diet), with a washout period of ≥9 days between the two periods.

All of 16 randomized subjects were included in the pharmacokinetics and safety analysis sets. Table 13 shows the pharmacokinetics obtained.

Table 13. Pharmacokinetic parameters of unchanged evocalcet in plasma following administration of evocalcet (2 mg) under fasted and fed conditions

	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng•h/mL)	$t_{1/2}$ (h)
Fasted	16	168 (24.9)	0.9 (69.0)	1,618 (26.9)	13.7 (22.1)
Fed	16	137 (19.4)	1.4 (45.4)	1,560 (31.0)	13.9 (35.3)

Geometric mean (geometric coefficient of variation [%])

The geometric mean ratios of C_{max} and AUC_{0-t} in the fed state to those in the fasted state (fed/fasted) [90% CI] were 0.81 [0.73, 0.91] and 0.96 [0.84, 1.11], respectively. According to the applicant's explanation, a slight decrease in C_{max} in the fed state compared with the fasted state is unlikely to cause any problems in humans, because (1) AUC_{0-t} in the fasted state did not differ from that in the fed state, and (2) evocalcet is administered at the dose adjusted appropriately through close monitoring of serum PTH and Ca of each patient.

No adverse event occurred in subjects in the fed state, but one (6.3% [1 of 16 subjects], pharyngitis) in subjects in the fasted state. A causal relationship of the adverse event to evocalcet was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.1.2 Studies using human biomaterials

6.1.2.1 Plasma protein binding (CTD 4.2.2.3-1 and 4.2.2.3-3; Studies [redacted]738 and [redacted]739)

Following the incubation of human plasma with ^{14}C-labeled evocalcet (0.1-10 μg eq./mL), the mean plasma protein binding rate ranged from 97.8% to 98.4%, showing no concentration dependency within the concentration range investigated. Following the incubation of human serum albumin solution (40 mg/mL), α1-acid glycoprotein solution (1 mg/mL), and γ-globulin solution (15 mg/mL) with ^{14}C-labeled evocalcet (0.1-10 μg eq./mL), the mean serum protein binding ranged from 96.9% to 97.3%, from 54.1% to 98.2%, and from 18.4% to 22.0%, respectively. This suggested that evocalcet is mainly bound to serum albumin and to α1-acid glycoprotein in human plasma.

6.1.2.2 Distribution in blood cells (CTD 4.2.2.3-3, Study [redacted]739)

Following the incubation of human blood with ^{14}C-labeled evocalcet (0.1-10 μg eq./mL), the mean distribution in blood cells ranged from 5.2% to 9.2%, showing no concentration dependency within the concentration range investigated.

6.1.2.3 *In vitro* studies for identification of metabolites (CTD 4.2.2.4-1, 4.2.2.4-4, and 4.2.2.4-5; Studies [redacted]860[redacted], [redacted]01, and [redacted]02)

Metabolites of ^{14}C-labeled evocalcet were investigated using human hepatocytes. Main metabolites detected were M1, M2, M3, M4, and M5. No human-specific metabolites were observed. The residual rate of unchanged evocalcet after 4-hour reaction was 78.0% to 78.8%.

A study was conducted using recombinant human cytochrome P450 (CYP) isoform-expressing systems and human uridine diphosphate-glucuronosyltransferase (UGT) isoform-expressing systems.

Results suggested that evocalcet is metabolized to M3 by UGT1A1 and UGT1A3 and to M4 by CYP2D6 and CYP3A4.

Metabolism of ^{14}C-labeled evocalcet was investigated using human hepatocyte microsomes. Main metabolites were M3, M4, and M5, all of which were detected at an extremely small amount (each metabolite accounted for <4% of the total radioactivity in the test sample).

On the basis of the above findings, the applicant explained that the contribution of CYP and UGT isoforms to evocalcet metabolism is limited and therefore that CYP inhibitors and UGT inhibitors are unlikely to affect the pharmacokinetics of evocalcet in humans.

6.1.2.4 Induction of hepatic drug-metabolizing enzymes by evocalcet (CTD 4.2.2.4-6, Study [redacted]03)

Human hepatocytes were incubated with evocalcet to investigate the activity of evocalcet to induce CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4). The expression level of messenger ribonucleic acid (mRNA) for CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4 increased in a concentration-dependent manner, with the maximum induction rate (at the concentration of 50 μmol/L evocalcet) being 1.1 to 29.1, 3.4 to 8.7, 3.4 to 9.5, 1.6 to 2.8, and 3.2 to 13.8 fold, respectively [see Section 6.2.7].

6.1.2.5 Inhibition of human hepatocyte drug-metabolizing enzymes by evocalcet (CTD 4.2.2.4-7 and 4.2.2.4-8; Studies [redacted]432 and [redacted]944)

Human microsomes were incubated with evocalcet to investigate the potential of evocalcet to inhibit the enzymatic activity of CYP isoforms[4)] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A). The potential of evocalcet to inhibit CYP2D6 metabolism was weak, with IC_{50} being higher than the maximum concentration of evocalcet tested (50 μmol/L [18.7 μg/mL]). The time-dependent inhibition of CYP3A metabolism by evocalcet was also weak, with IC_{50} being higher than the maximum concentration of evocalcet tested (50 μmol/L [18.7 μg/mL]). Evocalcet did not decrease the enzymatic activity of any of the other CYP isoforms up to the maximum evocalcet concentration tested (50 μmol/L).

The estimated median C_{max} at steady state following the administration of evocalcet at the maximum clinical dose (12 mg) was 843 ng/mL which was far below the IC_{50} value above. On the basis of this finding, the applicant explained that evocalcet is unlikely to inhibit CYP isoforms in humans.

6.1.2.6 Evaluation of evocalcet as a substrate or inhibitor of transporters (CTD 4.2.2.6-1, 4.2.2.6-2, and 4.2.2.6-3; Studies [redacted]144[redacted], [redacted]204[redacted], and [redacted]405[redacted])

Human colon carcinoma cell lines Caco-2 (Caco-2 cells) were incubated with ^{14}C-labeled evocalcet (0.5 and 5 μmol/L). Results showed that evocalcet does not serve as a substrate for P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). The potential of evocalcet[5)] to inhibit P-gp and

4) The inhibitory effect of evocalcet was evaluated using the following substrates: Phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, midazolam and testosterone for CYP3A4/5.

5) The following substrates were used in the evaluation: ^{3}H-digoxin for P-gp and ^{3}H-estrone-3-sulfate for BCRP.

BCRP-mediated substrate transport was investigated. IC_{50} values of evocalcet were >50 μmol/L (18.7 μg/mL) for both transporters, which was sufficiently higher than the median C_{max} (843 ng/mL) following the administration of evocalcet at the maximum clinical dose (12 mg), indicating that evocalcet is unlikely to inhibit P-gp or BCRP in humans.

HEK293 cells expressing organic anion transporting polypeptide (OATP)1B1 or OATP1B3 were incubated with ^{14}C-labeled evocalcet (0.5 and 5 μmol/L). Results showed that evocalcet does not serve as a substrate for OATP1B1 or OATP1B3. The potential of evocalcet[6] to inhibit OATP1B1- and OATP1B3-mediated transport was investigated. The uptake of a substrate of OATP1B1 decreased in an evocalcet concentration-dependent manner. However, IC_{50} values of evocalcet against OATP1B1 were >10 μmol/L (3.7 μg/mL), which was sufficiently higher than the median C_{max} (843 ng/mL) observed following the administration of evocalcet at the maximum clinical dose (12 mg), indicating that evocalcet is unlikely to inhibit OATP1B1 in humans. Evocalcet did not inhibit OATP1B3.

HEK293 cells expressing organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxic extrusion transporter (MATE)1, and MATE2-K[7] were incubated with evocalcet (0.1-10 μmol/L). IC_{50} values of evocalcet against all of these transporters were >10 μmol/L (3.7 μg/mL), which was sufficiently higher than the median C_{max} (843 ng/mL) observed following the administration of evocalcet at the maximum clinical dose (12 mg), indicating that evocalcet is unlikely to inhibit these transporters.

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose study (CTD 5.3.3.1-1, Study 7580-001 [[redacted] 20[redacted] to [redacted] 20[redacted]]

A randomized, single-blind, placebo-controlled study was conducted in healthy adult Japanese men aged ≥20 and <40 years (target sample size 56 subjects; 14 in the placebo group, 6 in each evocalcet group) at a single study site in Japan to investigate the pharmacokinetics and safety of evocalcet after a single oral dose.

A single dose of placebo or evocalcet (0.3 mg, 1 mg, 3 mg, 6 mg, 12 mg, or 20 mg) was administered orally to subjects under fasted conditions, or a single dose of evocalcet (6 mg) was administered orally to subjects under fed conditions.

All of the 56 randomized subjects (14 in the placebo group, 6 in each evocalcet group) were included in the safety analysis set, and all of the 42 subjects receiving evocalcet were included in the pharmacokinetics analysis population.

Table 14 shows the plasma pharmacokinetic parameters of unchanged evocalcet following the administration of evocalcet under fasted conditions. C_{max} and AUC_{0-t} increased in proportion to dose.

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6) The following substrates were used in the evaluation: ^{3}H-estradiol-17β-D-glucuronide for OATP1B1 and OATP1B3.

7) The following substrates were used in the evaluation: ^{3}H-p-aminohippuric acid for OAT1, ^{3}H-estrone-3-sulfate for OAT3, metformin for OCT2, ^{14}C-metformin for MATE1 and MATE2-K.

The cumulative urinary excretion rate of unchanged evocalcet up to 72 hours post-dose was 0.041% to 0.073% of the dose in the fasted state and 0.084% in the fed state.

Table 14. Plasma pharmacokinetic parameters of unchanged evocalcet following single oral administration of evocalcet under fasted conditions

Dose of evocalcet	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-t} (ng•h/mL)	$t_{1/2}$ (h)
0.3 mg[b)]	18 ± 4	1.5 (1.0, 3.0)	195 ± 46	15.7 ± 11.3
1 mg	59 ± 13	1.5 (1.0, 3.0)	567 ± 127	19.8 ± 13.8
3 mg	217 ± 24	1.5 (1.0, 3.0)	2,179 ± 294	17.3 ± 6.7
6 mg	376 ± 54	1.5 (1.0, 2.0)	3,979 ± 1,131	14.8 ± 2.7
12 mg	867 ± 109	2.0 (1.0, 3.0)	8,641 ± 975	13.0 ± 4.9
20 mg	1,400 ± 240	2.0 (1.0, 3.0)	14,502 ± 3,487	18.9 ± 9.0

n = 6, Mean ± SD
a) Median (maximum, minimum)
b) The 0.1 mg capsules used in the 0.3 mg group met the study drug specification of the release test but the dissolution rate did not meet the specification.

The safety of evocalcet evaluated for administration under fasted conditions. Adverse events were observed in 16.7% (1 of 6) of subjects in the 0.3 mg group (tonsillitis) and in 33.3% (2 of 6) of subjects in the 20 mg group (abdominal discomfort/vomiting and nausea in 1 subject each). Abdominal discomfort/vomiting and nausea in the 20 mg group were considered to be adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reaction). No adverse events were observed in the fed state. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation in any of the treatment groups.

6.2.2 Japanese phase I multiple-dose study (CTD 5.3.3.1-2, Study 7580-002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, single-blind, placebo-controlled study in healthy adult Japanese men aged ≥20 and <40 years (target sample size 18 subjects; 6 per group) was conducted at a single study site in Japan to investigate the pharmacokinetics and efficacy of evocalcet after multiple oral administration.

Placebo or evocalcet (6 or 12 mg) was administered orally once daily to subjects for 8 days under fasted conditions.

All of the 18 randomized subjects (6 per group) were included in the safety analysis set. Of 12 subjects receiving evocalcet, 11 subjects were included in the pharmacokinetics analysis set and the remaining 1 subject in the evocalcet 12 mg group was excluded from analysis because the subject discontinued the study due to an adverse event.

Table 15 shows the plasma pharmacokinetic parameters of unchanged evocalcet. Plasma concentration of unchanged evocalcet on Day 1 were similar to that on Day 8, showing no accumulation after multiple administration.

Table 15. Plasma pharmacokinetic parameters of unchanged evocalcet after multiple oral administration of evocalcet

Dose of evocalcet	Measuring time point	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng•h/mL)	$t_{1/2}$ (h)
6 mg	Day 1	393 ± 118	3.8 ± 0.4	3,447 ± 721	-[a)]
	Day 8	394 ± 97	3.5 ± 0.8	3,861 ± 643	18.5 ± 3.8
12 mg	Day 1	898 ± 182	3.6 ± 0.9	8,518 ± 2,600	-[a)]
	Day 8	1,050 ± 250	4.0 ± 2.4	10,836 ± 4,691	16.3 ± 5.2

n = 5 to 6, Mean ± SD
a) $t_{1/2}$ was not calculated on Day 1.

No adverse events were observed in the placebo or evocalcet 6 mg groups. An adverse event was observed in 16.7% (1 of 6) of subjects in the evocalcet 12 mg group (tetany). The tetany in 1 subject in the evocalcet 12 mg group was considered to be an adverse drug reaction, leading to the discontinuation of evocalcet. The symptom resolved after the discontinuation. There were no deaths or serious adverse events. Except for tetany in 1 patient in the evocalcet 12 mg group, there were no adverse events leading to treatment discontinuation.

6.2.3 Foreign phase I study (mass balance study) (CTD 5.3.3.1-3, Study 7580-006 [[redacted] to [redacted]])

An open-label study in healthy adult non-Japanese men aged ≥18 and ≤45 years (target sample size, 11 subjects [6 in Part 1, 5 in Part 2]) was conducted at a single study site in a foreign country to investigate the mass balance following administration of a single oral dose of ^{14}C-labeled evocalcet.

In Part 1, a single dose of ^{14}C-labeled evocalcet (1 mg solution) was administered orally to subjects under fasted conditions. In Part 2, a single dose of evocalcet (1 mg capsule) was administered orally to subjects under fasted conditions and, 2 hours later, ^{14}C-labeled evocalcet (4 μg) was administered intravenously over 15 minutes.

All of the 11 subjects enrolled in the study were included in the pharmacokinetics and safety analysis sets.

Table 16 shows the pharmacokinetic parameters of unchanged evocalcet and metabolites in Part 1. Unchanged evocalcet, M1, and M2 accounted for 80.0%, 11.2%, and 8.5%, respectively, of the total plasma radioactivity (based on AUC_{0-72h}), showing that unchanged evocalcet was predominant in plasma. The bioavailability of evocalcet, calculated using $AUC_{0-\infty}$ in Part 1 and Part 2, was 62.7% ± 5.6%.

In Part 1, 61.2% and 32.7% of the administered radioactivity were excreted in urine and feces, respectively, within 264 hours post-dose. In Part 2, 51.2% and 23.9% of the administered radioactivity were excreted in urine and feces, respectively, within 96 hours post-dose. Unchanged evocalcet was not detected in urine.

Table 16. Plasma pharmacokinetic parameters following single oral administration of ^{14}C-labeled evocalcet (Part 1)

dose of evocalcet	Analyte	C_{max} (μmol eq./L)	t_{max}[a)] (h)	$AUC_{0\text{-}72h}$ (μmol eq.•h/L)
1 mg	Unchanged evocalcet	0.15 ± 0.04	2.0 (2.0, 2.0)	1.70 ± 0.55
	M1	0.01 ± 0.01	8.0 (4.0, 8.0)	0.26 ± 0.16
	M2	0.00 ± 0.00	8.0 (8.0, 72.0)	0.17 ± 0.05

n = 6, Mean ± SD
a) Median (minimum, maximum)

Adverse events were observed in 50.0% (3 of 6) of subjects in Part 1 (nausea/oropharyngeal pain in 1 subject, rhinitis/headache in 1 subject, and ocular hyperaemia/nausea/myalgia/dizziness/headache/skin irritation in 1 subject). An adverse events was observed in 20% (1 of 5) of subjects in Part 2 (presyncope). Nausea (33.3% [2 of 6] of subjects) observed in Part 1 was considered to be an adverse drug reaction. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.4 Japanese phase I/II study in patients with SHPT on HD (CTD 5.3.3.2-1, Study 7580-003 [August 2013 to March 2014])

An open-label, individual dose titration study in Japanese patients with SHPT on HD aged ≥20 and <75 years (target sample size, 20 subjects) was conducted at 20 study sites in Japan to investigate the safety and pharmacokinetics of evocalcet following single and multiple oral administration. In this study, each of the patients underwent Steps 1 through 7. All of the 29 patients enrolled in the study were included in the pharmacokinetics and safety analysis sets.

6.2.4.1 Single oral administration

The treatment started with a single oral dose of 1 mg of evocalcet (Step 1), followed by a single oral dose of 4 mg (Step 2) and then 12 mg (Step 3) according to the step transition criteria.[8)] A 3-week treatment-free period was allowed between the adjacent steps.

Study treatment was discontinued in 2 patients: 1 patient at 1 mg (at the discretion of the investigator, etc.) and 1 patient at 12 mg (adverse event).

Table 17 shows plasma pharmacokinetic parameters of evocalcet. C_{max} and $AUC_{0\text{-}t}$ increased in a dose-dependent manner.

8) A patient who met any of the following criteria was to withdraw from the study. A patient who met the following criteria after a single dose of 4 mg (Step 2) was allowed to receive multiple doses of 1 mg (Step 4) and withdraw from the study after Step 4 without receiving multiple doses of 4 mg (Step 5). Even if a patient did not meet any of the following criteria after multiple administration of 4 mg (Step 5), the investigator or subinvestigator was allowed to decide on the patient's withdrawal from the study for the safety of the patient.
- Occurrence of a serious adverse event for which a causal relationship to the study drug could not be ruled out
- Decrease of adjusted serum Ca levels to <7.5 mg/dL
- When the investigator, etc., concluded that the patient should not proceed to the next step, because of the onset of an adverse event for which a causal relationship to the study drug could not be ruled out

Table 17. Pharmacokinetic parameters of plasma unchanged evocalcet in patients with SHPT on HD receiving single oral dose of evocalcet

Dose of evocalcet	N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-t} (ng•h/mL)	$t_{1/2}$ (h)
1 mg	29	62 ± 22	4.0 (2.0, 11.9)	1,162 ± 809	20.9 ± 13.1
4 mg	28	210 ± 98	4.1 (2.0, 12.1)	4,542 ± 4,217	22.4 ± 16.9
12 mg	26	706 ± 208	4.0 (0.9, 11.9)	13,064 ± 7,236	22.5 ± 12.2

Mean ± SD
a) Median (minimum, maximum)

Adverse events were observed in 31.0% (9 of 29) of patients at 1 mg, in 28.6% (8 of 28) of patients at 4 mg, and in 38.5% (10 of 26) of patients at 12 mg. Adverse events reported in ≥2 patients in any step were contact dermatitis (13.8% [4 of 29] of patients at 1 mg, 3.6% [1 of 28] of patients at 4 mg, 0% [0 of 26] of patients at 12 mg) and anaemia (6.9% [2 of 29] of patients at 1 mg, 3.6% [1 of 28] of patients at 4 mg, 0% [0 of 26] of patients at 12 mg). Adverse drug reactions were observed in 3.6% [1 of 28] of patients at 4 mg and in 3.8% [1 of 26] of patients at 12 mg. No death occurred. A serious adverse event (shunt occlusion) occurred in 3.4% (1 of 29) of patients at 1 mg, and an adverse event leading to treatment discontinuation (breast mass) was observed in 3.8% (1 of 26) of patients at 12 mg. Their causal relationship to evocalcet was ruled out.

6.2.4.2 Multiple oral administration

Patients who completed Step 2 or 3 in the single administration part were enrolled in the study. The treatment was started with multiple oral administration of evocalcet 1 mg once daily (Step 4), followed by multiple oral administration of 4 mg (Step 5), 8 mg (Step 6), and then 12 mg (Step 7) once daily in a stepwise manner according to the step transition criteria.[8)] The duration of administration was 14 days each in Step 4 and Step 5, and 7 days each in Step 6 and Step 7. A 7- to 14-day treatment-free period was allowed between adjacent steps.

Study treatment was discontinued in 6 patients (1 patient at 1 mg, 5 patients at 4 mg). The reasons for the discontinuation were adverse events in 5 patients (1 patient at 1 mg, 4 patients at 4 mg) and decision of the investigator, etc., in 1 subject (at 4 mg). Two patients who completed the 1-mg administration, 14 patients who completed the 4-mg administration, and 1 patient who completed the 8-mg administration withdrew from the study without entering the next step, according to the step transition criteria.

Table 18 shows changes in plasma trough evocalcet concentrations over time. Dialysis clearance was low both at 1 mg and at 4 mg, suggesting that the pharmacokinetics of evocalcet is not affected by HD.

Table 18. Plasma trough evocalcet concentration before hemodialysis in patients with SHPT on HD receiving multiple administration of evocalcet

Dose of evocalcet		Plasma trough evocalcet concentration before dialysis				
		Day 3	Day 5	Day 8	Day 12	Day 15
1 mg	Number of patients	27	27	27	25	26
	Evocalcet concentration in plasma (ng/mL)	26 ± 23	31 ± 29	36 ± 39	35 ± 35	33 ± 27
4 mg	Number of patients	24	24	23	18	19
	Evocalcet concentration in plasma (ng/mL)	97 ± 96	125 ± 135	140 ± 120	174 ± 166	152 ± 106
8 mg[a)]	Number of patients	5	5	5	-	-
	Evocalcet concentration in plasma (ng/mL)	139 ± 133	234 ± 275	201 ± 247	-	-
12 mg[a)]	Number of patients	4	4	4	-	-
	Evocalcet concentration in plasma (ng/mL)	165 ± 202	171 ± 185	208 ± 245	-	-

Mean ± SD

a) Both doses of evocalcet, 8 mg and 12 mg, were administered for 7 days.

Adverse events were observed in none of patients at 8 mg, in 29.6% (8 of 27) of patients at 1 mg, in 62.5% (15 of 24) of patients at 4 mg, and in 25.0% (1 of 4) of patients at 12 mg. Adverse drug reactions were not observed at 1, 8, or 12 mg, but observed in 37.5% (9 of 24) of patients at 4 mg. Adverse events reported in ≥2 patients in any group were nasopharyngitis (7.4% [2 of 27] of patients at 1 mg, 12.5% [3 of 24] of patients at 4 mg, 0% [0 of 5] of patients at 8 mg, 25.0% [1 of 4] of patients at 12 mg) and blood calcium decreased (0% [0 of 27] of patients at 1 mg, 33.3% [8 of 24] of patients at 4 mg, 0% [0 of 5] of patients at 8 mg, 0% [0 of 4] of patients at 12 mg). Blood calcium decreased were all considered to be adverse drug reactions. There were no deaths or serious adverse events. Adverse events leading to treatment discontinuation were observed in 3.7% (1 of 27) of patients at 1 mg (liver function test abnormal) and in 16.7% (4 of 24) of patients at 4 mg (blood calcium decreased in 3 patients, vitreous detachment in 1 patient). Blood calcium decreased in 3 patients at 4 mg were all considered to be adverse drug reactions, and resolved after treatment discontinuation.

6.2.5 Japanese phase I study in patients with SHPT on PD (CTD 5.3.3.2-2, Study 7580-004 [[redacted] to [redacted]])

A multicenter, open-label, uncontrolled study in Japanese patients with SHPT on PD aged ≥20 and <75 years (target sample size, 8 subjects) was conducted at 8 study sites in Japan to investigate the safety and pharmacokinetics of evocalcet following single oral administration of evocalcet.

A single dose of evocalcet (1 mg) was administered orally to subjects after breakfast.

All of the 9 patients enrolled in the study were included in the pharmacokinetics and safety analysis sets.

Table 19 shows plasma pharmacokinetic parameters of evocalcet. The concentration of unchanged evocalcet in dialysis effluent was below the lower limit of quantitation (1 ng/mL) at a majority of sampling points. Little excretion of evocalcet in dialysis effluent suggests that the pharmacokinetics of evocalcet is not affected by PD.

Table 19. Pharmacokinetic parameters of unchanged evocalcet in plasma in patients with SHPT on PD after single oral administration of evocalcet

Dose of evocalcet	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-t} (ng•h/mL)	$t_{1/2}$[b)] (h)
1 mg	104 ± 49	4.0 (0.9, 24.1)	2,378 ± 1,862	33.6 ± 11.6

n = 9, mean ± SD
a) Median (minimum, maximum)
b) n = 7 (2 patients without sufficient data of the final elimination phase were excluded.)

Adverse events were observed in 11.1% (1 of 9) of patients. No adverse drug reaction was observed. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.6 Japanese phase I study (effect of hepatic impairment) (CTD 5.3.3.3-1, Study 7580-008 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, open-label, parallel-group study was conducted at 3 study sites in Japan to investigate the effect of hepatic impairment on the pharmacokinetics of evocalcet following a single oral administration of evocalcet in Japanese subjects aged ≥20 and <80 years with normal hepatic function,[9)] mild hepatic impairment (Child-Pugh score A), or moderate hepatic impairment (Child-Pugh score B) (target sample size, 24 subjects; 6 per group).

A single dose of evocalcet (1 mg) was administered orally to subjects within 30 minutes after a meal.

All of the 24 subjects (6 per group) enrolled in the study were included in the pharmacokinetics and safety analysis sets.

Table 20 shows the plasma pharmacokinetic parameters of evocalcet. The ratios of mean C_{max} and AUC_{0-inf} in subjects with mild hepatic impairment group to those in subjects with normal hepatic function were 1.10 and 2.18, respectively. The ratios of mean C_{max} and AUC_{0-inf} in subjects with moderate hepatic impairment to those in subjects with normal hepatic function were 0.91 and 1.28, respectively. The results showed increased AUC_{0-inf} in the mild and moderate impairment groups.

The mean plasma protein binding rates of evocalcet were 98.0% to 98.1% in subjects with mild impairment and from 97.9% to 98.1% in subjects with moderate impairment. The binding rates in control subjects with normal hepatic function, matched patients with mild and moderate hepatic impairment, were 98.0% to 98.1% and 97.9% to 98.2%, respectively. There was no difference in the plasma protein binding rate of evocalcet between the normal hepatic function group and hepatic impairment groups.

9) Subjects with normal hepatic function were matched with patients with mild or moderate hepatic impairment for age (±10 years), sex, and body weight (±20%).

Table 20. Pharmacokinetic parameters of unchanged evocalcet in plasma in healthy adults and patients with renal impairment

	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$t_{1/2}$ (h)
Patients with mild hepatic impairment	83.7 ± 36.7	4.0 (1.0, 8.0)	1,861.4 ± 1,265.1	13.8 ± 4.2
Subjects with normal hepatic function[c)]	75.8 ± 17.3	3.0 (2.0, 4.0)	853.0 ± 231.3	13.7 ± 6.5
Patients with moderate hepatic impairment	67.6 ± 25.2	4.0 (2.0, 8.0)	1,129.8 ± 409.4	12.7 ± 3.0
Subjects with normal hepatic function[d)]	74.4 ± 34.4	3.5 (3.0, 12.0)	884.5 ± 312.8[b)]	10.5 ± 2.2[b)]

n = 6, Mean ± SD
a) Median (minimum, maximum)
b) n = 5
c) Subjects with normal hepatic function, matched with patients with mild hepatic impairment
d) Subjects with normal hepatic function, matched with patients with moderate hepatic impairment

Adverse events were not observed in the normal hepatic function group, but observed in 33.3% (2 of 6) of subjects in the mild impairment group and in 16.7% (1 of 6) of subjects in the moderate impairment group. There were no adverse events reported in ≥2 subjects in any group. Adverse drug reactions were observed in 16.7% (1 of 6) of subjects in the mild impairment group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.7 Japanese phase I study (drug interaction with CYP substrate drugs) (CTD 5.3.3.4-1, Study 7580-009 [[redacted] to [redacted]])

In vitro studies using human hepatocytes suggested that evocalcet induces CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A) [see Section 6.1.2.4]. A Japanese phase I study in healthy Japanese adults (target sample size, 40 subjects) was conducted at a single study site in Japan to investigate the effect of evocalcet on drugs (theophylline, efavirenz, repaglinide, diclofenac sodium, and tadalafil) which serve as substrates of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A).

Subjects received a cocktail of CYP substrate drugs (theophylline 100 mg, efavirenz 200 mg, repaglinide 0.25 mg, diclofenac sodium 25 mg, and tadalafil 5 mg) orally on Day 1 and Day 18, and evocalcet (6 mg) orally once daily from Day 4 to Day 20.

All of the 40 subjects enrolled in the study were included in the pharmacokinetics and safety analysis sets.

Table 21 shows the geometric mean ratio of C_{max} and $AUC_{0\text{-}t}$ of CYP substrate drugs in combination with evocalcet to those of CYP substrate drugs alone. Concomitant evocalcet tended to increase $AUC_{0\text{-}t}$ of theophylline.

Table 21. Geometric mean ratio of plasma pharmacokinetic parameters of CYP substrate drugs in combination with evocalcet

CYP substrate drug (p.o.)	Geometric mean ratio[a] [90% CI]	
	C_{max}	AUC_{0-t}
Theophylline 100 mg	1.15 [1.10, 1.20]	1.26 [1.19, 1.33]
Efavirenz 200 mg	0.96 [0.89, 1.04]	1.11 [1.07, 1.15]
Repaglinide 0.25 mg	0.97 [0.86, 1.10]	1.11 [1.04, 1.18]
Diclofenac sodium 25 mg	0.91 [0.75, 1.10]	1.09 [1.02, 1.17]
Tadalafil 5 mg	0.99 [0.93, 1.05]	1.05 [1.01, 1.10]

n = 40

a) "C_{max} or AUC_{0-t} of CYP substrate drugs in combination with evocalcet"/"C_{max} or AUC_{0-t} of CYP substrate drugs alone"

Adverse events were observed in 5.0% (2 of 40) of subjects. There were no adverse events reported in ≥2 subjects. Adverse drug reactions were observed in 2.5% (1 of 40) of subjects. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.R Outline of the review conducted by PMDA

6.R.1 Drug-drug interactions

The applicant's explanation about the effect of evocalcet on the pharmacokinetics of concomitant drugs that serve as substrates of CYP2C9 or CYP1A2:

An *in vitro* study using human hepatocytes [see Section 6.1.2.4] suggested that evocalcet induces CYP2C9. However, in the Japanese phase I study in healthy Japanese adults [drug-drug interaction study, see Section 6.2.7], concomitant evocalcet did not affect the C_{max} or AUC_{0-t} of diclofenac sodium, a substrate of CYP2C9. Therefore, it is not necessary that the package insert provides advice about the interaction of evocalcet with CYP2C9 substrate drugs.

A study evaluated the drug-drug interaction of evocalcet with CYP1A2 substrate drugs. In the Japanese phase I study in healthy Japanese adults [drug-drug interaction study, see Section 6.2.7], the geometric mean ratio [90% CI] of AUC_{0-t} of theophylline, a CYP1A2 substrate drug, in combination with evocalcet to that of theophylline alone was 1.26 [1.19, 1.33], with the upper limit of the 90% CI exceeding 1.25. It is unclear why blood theophylline concentrations increased after administration of theophylline in combination with evocalcet compared with theophylline alone in the Japanese phase I study (drug-drug interaction study). This result was inconsistent with the results of the *in vitro* study using human hepatocytes [see Section 6.1.2.4]. However, given that the extent of increase in AUC_{0-t} of theophylline is only limited (1.26 fold), the effect of evocalcet on CYP1A2 substrate drugs is minimal. On the basis of the above, the applicant considers it not necessary currently that the package insert provides advice about the interaction of evocalcet with CYP1A2 substrate drugs.

PMDA's view:

It is unclear why theophylline concentrations in blood increased after administration of theophylline in combination with evocalcet compared with theophylline alone in the Japanese phase I study (drug-drug interaction study). However, because of the narrow effective blood concentration range of theophylline, variations in blood theophylline concentrations may result in adverse drug reactions. Therefore, the package insert of evocalcet should provide advice about the interaction of evocalcet with theophylline.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 4 Japanese clinical studies listed in Table 22.

Table 22. Outline of efficacy and safety evaluation data

Phase	Study identifier	Study population	Study design	Study period	Group (No. of patients receiving study drug)	Efficacy endpoint
Phase II	7580-005	Patients with SHPT on HD	Randomized, double-blind, parallel-group, placebo-controlled study (patients in the cinacalcet group were unblinded)	3 weeks	Placebo: 30 Evocalcet 0.5 mg: 31 Evocalcet 1 mg: 30 Evocalcet 2 mg: 30 Cinacalcet 25 mg: 30	Mean percent change [95% CI] in iPTH levels at the end of study treatment Placebo: 5.4% [−4.8, 15.7] Evocalcet 0.5 mg: −8.4% [−18.3, 1.5] Evocalcet 1 mg: −10.6% [−20.5, −0.7] Evocalcet 2 mg: −20.2% [−30.4, −9.9] Cinacalcet: −25.9% [−36.1, −15.6]
Phase III	7580-010	Patients with SHPT on HD	Randomized, double-blind, parallel-group, active drug-controlled study	30 weeks	Evocalcet (1-8 mg): 317 Cinacalcet (12.5-100 mg): 317	Percentage [95% CI] of patients who achieved mean iPTH levels ≥60 and ≤240 pg/mL during the evaluation period (Weeks 28-30) Evocalcet: 72.7% [66.8, 78.1] Cinacalcet: 76.7% [71.1, 81.6]
Phase III	7580-011	Patients with SHPT on HD	Open-label, uncontrolled study	52 weeks	Evocalcet (1-12 mg): 137	Percentage [95% CI] of patients who achieved mean iPTH levels ≥60 and ≤240 pg/mL at Week 52 Evocalcet: 72.3% [64.0, 79.6]
Phase III	7580-012	Patients with SHPT on PD	Open-label, uncontrolled study	52 weeks	Evocalcet (1-12 mg): 39	Percentage [95% CI] of patients who achieved mean iPTH levels ≥60 and ≤240 pg/mL during the evaluation period (Weeks 30 and 32) Evocalcet: 71.8% [55.1, 85.0]

7.1 Phase II study

7.1.1 Japanese phase II study in patients on HD (CTD 5.3.5.1-1, Study 7580-005 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients with SHPT on HD aged ≥20 and <75 years (Table 23) (target sample size, 150 subjects; 30 per group) was conducted at 40 study sites in Japan to investigate the efficacy, safety, and dose-response of evocalcet.

Table 23. Key inclusion/exclusion criteria

Key inclusion criteria • Patients with iPTH levels ≥240 pg/mL at the screening test • Patients with adjusted serum Ca levels ≥8.4 mg/dL at the screening test • Patients with stable chronic renal failure who were receiving HD 3 times a week and had a hemodialysis history of ≥12 weeks before the screening test Key exclusion criteria • Patients who used cinacalcet within 2 weeks before the screening test • Patients who received the modified regimen of activated vitamin D or its derivative, P adsorbent, or Ca preparation, or patients who newly received any of these drugs, within 2 weeks before the screening test. • Patients who underwent any change in the dialyzing conditions within 2 weeks before the screening test.

Subjects received placebo, evocalcet (0.5 mg, 1 mg, or 2 mg), or cinacalcet (25 mg)[10] orally once daily for 3 weeks.

Of 152 randomized patients, 151 patients (30 in the placebo group, 31 in the evocalcet 0.5 mg group, 30 in the evocalcet 1 mg group, 30 in the evocalcet 2 mg group, 30 in the cinacalcet 25 mg group) received study drug and were included in the safety analysis set, and the remaining 1 patient was excluded from analysis because of failure to meet the inclusion criteria at baseline. Of the 151 patients receiving study drug, 150 patients (30 in the placebo group, 31 in the evocalcet 0.5 mg group, 30 in the evocalcet 1 mg group, 29 in the evocalcet 2 mg group, 30 in the cinacalcet 25 mg group) were included in the full analysis set (FAS), and the remaining 1 patient in the 2 mg group was excluded from analysis because of lack of baseline serum iPTH data. Of the 150 patients included in the FAS, 144 patients (28 in the placebo group, 30 in the evocalcet 0.5 mg group, 30 in the evocalcet 1 mg group, 28 in the evocalcet 2 mg group, 28 in the cinacalcet 25 mg group) were included in the per protocol set (PPS), and the 6 patients[11] with a compliance rate of <70% during the treatment period with study drug were excluded from analysis. The PPS was used for the primary efficacy analysis. Treatment was discontinued in 11 patients (2 in the placebo group, 1 in the evocalcet 0.5 mg group, 1 in the evocalcet 1 mg group, 4 in the evocalcet 2 mg group, 3 in the cinacalcet 25 mg group). The reasons for the discontinuation were “adjusted serum Ca levels decreased to ≤7.5 mg/dL” in 7 patients (1 in the placebo group, 1 in the evocalcet 1 mg group, 3 in the evocalcet 2 mg group, 2 in the cinacalcet 25 mg group), “adverse events requiring the discontinuation, as judged by the investigator” in 3 patients (1 each in the placebo group, the evocalcet 2 mg group, and the cinacalcet 25 mg group), and “the patient was found to be ineligible for enrollment in the clinical study because of failure to meet the inclusion criteria” in 1 patient (evocalcet 0.5 mg group).

Table 24 shows the results of the primary efficacy endpoint “percent change from baseline (i.e., before the start of study treatment) in iPTH levels at the end of study treatment.” iPTH levels were lower in all evocalcet groups than in the placebo group, and the dose-response profile showed a statistically significant difference in the results of all paired comparisons (paired comparison test, multiplicity adjusted by sampling method, two-sided significance level of 5%).

[10] Cinacalcet hydrochloride was administered to the reference group under open-label conditions in order to confirm the sensitivity of the study.
[11] One patient met an exclusion criterion as well (patient who participated in a clinical study or equivalent study of a drug or a medical device within 12 weeks before the screening test and received study drug or used an unapproved medical device).

Table 24. Percent change from baseline in iPTH levels at the end of study treatment (PPS)

		Placebo (n = 28)	Evocalcet 0.5 mg (n = 30)	Evocalcet 1.0 mg (n = 30)	Evocalcet 2.0 mg (n = 28)	Cinacalcet 25 mg (n = 28)	*P* value[a]
Mean percent change in iPTH levels at the end of study treatment [95% CI]		5.44 ± 25.85 [−4.80, 15.68]	−8.40 ± 25.43 [−18.29, 1.49]	−10.56 ± 22.86 [−20.45, −0.67]	−20.16 ± 34.23 [−30.40, −9.92]	−25.86 ± 27.76 [−36.10, −15.62]	
Difference from placebo [95% CI]		-	−13.84 [−28.08, 0.40]	−16.00 [−30.24, −1.76]	−25.60 [−40.08, −11.12]	−31.30 [−45.78, −16.82]	
Paired comparison pattern	Monotonic decrease	(3, 1, −1, -3)				-	0.002
	Decrease from evocalcet 1 mg	(3, 3, −1, −5)				-	0.009
	Decrease from evocalcet 2 mg	(1, 1, 1, −3)				-	0.029
	Monotonic decrease	(1, 0, 0, −1)				-	0.002
	Monotonic decrease	(5, 1, −3, −3)				-	0.004
	Monotonic decrease	(3, −1, −1, −1)				-	0.007
	Monotonic decrease	(1, 1, −1, −1)				-	0.022

Paired comparison test, multiplicity adjusted by sampling method, two-sided significance level of 5%

Adverse events were observed in 46.7% (14 of 30) of patients in the placebo group, 35.5% (11 of 31) of patients in the evocalcet 0.5 mg group, 46.7% (14 of 30) of patients in the evocalcet 1 mg group, 30.0% (9 of 30) of patients in the evocalcet 2 mg group, and 50.0% (15 of 30) of patients in the cinacalcet 25 mg group. Adverse events reported in ≥5.0% of patients in any group were nasopharyngitis (13.3% [4 of 30] of patients in the placebo group, 16.1% [5 of 31] of patients in the evocalcet 0.5 mg group, 16.7% [5 of 30] of patients in the evocalcet 1 mg group, 6.7% [2 of 30] of patients in the evocalcet 2 mg group, 16.7% [5 of 30] of patients in the cinacalcet 25 mg group) and adjusted calcium decreased (6.7% [2 of 30] of patients in the placebo group, 0% [0 of 31] of patients in the evocalcet 0.5 mg group, 0% [0 of 30] of patients in the evocalcet 1 mg group, 10.0% [3 of 30] of patients in the evocalcet 2 mg group, 3.3% [1 of 30] of patients in the cinacalcet 25 mg group). Adverse drug reactions were observed in 13.3% (4 of 30) of patients in the placebo group, 6.5% (2 of 31) of patients in the evocalcet 0.5 mg group, 6.7% (2 of 30) of patients in the evocalcet 1 mg group, 20.0% (6 of 30) of patients in the evocalcet 2 mg group, and 16.7% (5 of 30) of patients in the cinacalcet 25 mg group. Adverse drug reaction reported in ≥5.0% of patients in any group was adjusted calcium decreased only (6.7% [2 of 30] of patients in the placebo group, 0% [0 of 31] of patients in the evocalcet 0.5 mg group, 0% [0 of 30] of patients in the evocalcet 1 mg group, 10.0% [3 of 30] of patients in the evocalcet 2 mg group, 3.3% [1 of 30] of patients in the cinacalcet 25 mg group).

No death occurred. Serious adverse events were observed in 6.5% (2 of 31) of patients in the evocalcet 0.5 mg group (cholelithiasis and shunt occlusion in 1 patient each) and in 3.3% (1 of 31) of patients in the cinacalcet 25 mg group (thrombotic cerebral infarction). A causal relationship to the study drug was ruled out for all events. Adverse events leading to treatment discontinuation (other than serious adverse events) were observed in 6.7% (2 of 30) of patients in the placebo group (palpitations and adjusted calcium decreased in 1 patient each), 13.3% (4 of 30) of patients in the evocalcet 2 mg group (adjusted calcium decreased in 3 patients, malaise in 1 patient), and in 6.7% (2 of 30) of patients in the

cinacalcet 25 mg group (adjusted calcium decreased and blood calcium decreased in 1 patient each). All of these events were considered to be adverse drug reactions, but the outcome was “recovered” for all of them.

7.2 Phase III studies

7.2.1 Japanese phase III comparative study in patients on HD (CTD 5.3.5.1-2, Study 7580-010 [[redacted]])

A multicenter, randomized, double-blind, parallel-group study in patients with SHPT on HD aged ≥20 years (Table 25) (target sample size, 600 subjects; 300 per group) was conducted at 89 study sites in Japan to investigate the efficacy and safety of evocalcet.

Table 25. Key inclusion/exclusion criteria

Inclusion criteria • Patients with mean iPTH levels >240 pg/mL, at 2 weeks and 1 week before the start of study treatment • Patients with adjusted serum Ca levels ≥9.0 mg/dL at the screening test • Patients with stable chronic renal failure who were receiving HD 3 times a week and had a hemodialysis history of ≥12 weeks before the screening test Exclusion criteria • Patients who used cinacalcet within 2 weeks before the screening test • Patients who received the modified regimen of activated vitamin D or its derivative, P adsorbent, or Ca preparation, or who newly received any of these drugs, within 2 weeks before the screening test • Patients who underwent any change in the dialyzing conditions within 2 weeks before the screening test

The dose of evocalcet or cinacalcet was adjusted according to the criteria as shown in Table 26 to control iPTH levels within the range between ≥60 pg/mL and ≤240 pg/mL (150 pg/mL optimally), and the thus-adjusted study drug was administered orally once daily to subjects for 30 weeks (dose adjustment period, Weeks 0-28; evaluation period, Weeks 28-30).

Table 26. Criteria for dose adjustment

Target iPTH level	≥60 pg/mL and ≤240 pg/mL (the dose should be adjusted to achieve approximately 150 pg/mL iPTH)	
Starting dose	Evocalcet: iPTH levels 1 week before the start of study treatment: • <500 pg/mL: 1 mg • ≥500 pg/mL: 2 mg	Cinacalcet: 25 mg regardless of iPTH levels
Maximum dose	Evocalcet 8 mg	Cinacalcet 100 mg
Increment/ decrement	Evocalcet 1 mg	Cinacalcet 25 mg Cinacalcet may be decreased by 12.5 mg if deemed necessary by the investigator, etc. When the dose was decreased by 12.5 mg, the first increment after the dose reduction is 12.5 mg. In patients receiving 25 mg, the dose is decreased by 12.5 mg if deemed necessary.
Criteria for dose increase	The dose may be increased if all of the following criteria are met: • The current dose has been maintained for ≥3 weeks. • iPTH levels >240 pg/mL at the planned visit immediately before the dose modification. However, dose increase is possible at iPTH levels ≤240 pg/mL if the investigator, etc., considers that the dose may be increased to achieve iPTH levels of approximately 150 pg/mL. • Adjusted serum Ca levels ≥8.4 mg/dL (measured at the central laboratory) at the planned visit immediately before the dose modification.	
Criteria for dose decrease	The dose may be decreased if either of the following criteria is met: • iPTH levels have decreased to <60 pg/mL. • The investigator, etc., considers that the dose should be reduced because of adverse events.	
Dose increase after dose decrease	If adjusted serum Ca is <8.4 mg/dL, dose increase is prohibited.	
Criteria for treatment interruption	Treatment should be interrupted if either of the following is met: • Adjusted serum Ca levels have decreased to ≤7.5 mg/dL. • The investigator, etc., considers that the dose should be reduced because of adverse events.	
Criteria for resumption after treatment interruption	If treatment was interrupted due to the decrease in adjusted serum Ca levels to ≤7.5 mg/dL, the study treatment should be resumed after adjusted serum Ca levels have increased to ≥8.4 mg/dL. The dose at the resumption should be the same as, or lower than, the dose before the interruption (as a general rule, the dose of evocalcet should be lower than the previous dose by 1 mg, and cinacalcet should be lower than the previous dose by 12.5 or 25 mg).	
Dose adjustment period	28 weeks after the start of study treatment	
Evaluation period and dose adjustment	2 weeks after the dose adjustment period The dose at the end of the dose adjustment period should be maintained without adjustment. Dose reduction and treatment interruption are allowed.	
Criteria for use of concomitant activated vitamin D and its derivatives	• If currently in use, no change should be made to the type(s) and the dosage regimen of the concomitant drugs from 2 weeks before the screening test until Week 30 (or discontinuation). • If not in use currently, addition of concomitant drugs is prohibited. If, after the start of study treatment, adjusted serum Ca levels exceeds 11.0 mg/dL, the dose of the activated vitamin D and its derivatives may be reduced or discontinued. After the dose reduction or discontinuation, the dose may be increased to the level prior to the dose reduction or discontinuation. After the start of study treatment, the dose increase or addition of activated vitamin D or its derivatives is possible if either of the following criteria is met: • Adjusted serum Ca levels remains <7.5 mg/dL even after Ca preparation is newly added or increased in dose. • Clinical symptoms possibly associated with hypocalcemia do not resolve even after dose increase or addition of Ca preparation.	

Of 639 randomized patients, 634 patients (317 per group) received the study drug and were included in the safety analysis set. The remaining 5 patients were excluded from analysis because they discontinued the study before the start of study treatment. Of the 634 patients receiving study drug, 623 patients (313 in the evocalcet group, 310 in the cinacalcet group) were included in the FAS, and the remaining 11 patients were excluded from analysis because of no iPTH level data after the start of study treatment. Of the patients included in the FAS, 519 patients (253 in the evocalcet group, 266 in the cinacalcet group) were included in the PPS and the remaining 104 patients (60 in the evocalcet

group, 44 in the cinacalcet group) were excluded from analysis because they met the criteria.[12)] The PPS was used for the primary efficacy analysis. Study treatment was discontinued in 108 patients (61 in the evocalcet group, 47 in the cinacalcet group) who received at least one dose of study drug. The reasons for the discontinuation (one or more reasons in some patients) were "patient's request" in 47 patients (26 in the evocalcet group, 21 in the cinacalcet group), "adverse events requiring the discontinuation, as judged by the investigator" in 33 patients (21 in the evocalcet group, 12 in the cinacalcet group), "study discontinuation for any other reason, as judged by the investigator" in 14 patients (10 in the evocalcet group, 4 in the cinacalcet group), "continued treatment interruption" in 9 patients (2 in the evocalcet group, 7 in the cinacalcet group), "deviation from inclusion criteria" in 7 patients (3 in the evocalcet group, 4 in the cinacalcet group), and "lost to follow-up" in 3 patients (2 in the evocalcet group, 1 in the cinacalcet group).

Table 27 shows results of the primary efficacy endpoint "percentage of patients who achieved the mean iPTH level[13)] of ≥60 pg/mL and ≤240 pg/mL during the evaluation period (Weeks 28-30)." The difference [95% CI] between the evocalcet group and the cinacalcet group was −4.0% [−11.4, 3.5], with the lower limit of the 95% CI exceeding the pre-specified non-inferiority margin (−15%). Thus, the study demonstrated the non-inferiority of evocalcet to cinacalcet.

Table 27. Percentage of patients achieving mean iPTH level ≥60 pg/mL and ≤240 pg/mL during the evaluation period (Weeks 28-30) (PPS)

	Evocalcet (N = 253)	Cinacalcet (N = 266)
Percentage of patients achieving mean iPTH level of ≥60 pg/mL and ≤240 pg/mL [95% CI]	72.7% (n = 184) [66.8, 78.1]	76.7% (n = 204) [71.1, 81.6]
Treatment difference (evocalcet vs. cinacalcet) [95% CI]	−4.0% [−11.4, 3.5]	

Percentage of patients (n)

Adverse events were observed in 90.9% (288 of 317) of patients in the evocalcet group and in 91.2% (289 of 317) of patients in the cinacalcet group. Adverse drug reactions were observed in 44.8% (142 of 317) of patients in the evocalcet group and in 58.7% (186 of 317) of patients in the cinacalcet group. Tables 28 and 29 show adverse events and adverse drug reactions, respectively, reported in ≥3.0% of patients in either group.

12) Some subjects meeting more than one criterion.
- Subjects without iPTH level data in ≥2 of 3 sampling points during the evaluation period (Weeks 28-30): 57 subjects in the evocalcet group, 40 subjects in the cinacalcet group
- Subjects who use prohibited concomitant drugs or therapies: 2 subjects in the evocalcet group, 4 subjects in the cinacalcet group
- Subjects who fail to meet the inclusion criteria or meet the exclusion criteria: 1 subjects in the evocalcet group, 2 subjects in the cinacalcet group
- Subjects for which study drug was prescribed for ≥28 weeks and who achieved a compliance rate of <70% in the period from the start of study treatment to the end of the evaluation period (compliance rate [%] = 100 × "days of administration as per prescription"/"total prescription days": 2 subjects in the evocalcet group, 0 subjects in the cinacalcet group.

13) Mean iPTH level during the evaluation period (pg/mL) = "Sum of iPTH levels observed during the evaluation period"/"number of time points of iPTH level measurement during the evaluation period"

Table 28. Adverse events reported in ≥3.0% of patients in either group

Adverse event	Evocalcet (N = 317)	Cinacalcet (N = 317)	Adverse event	Evocalcet (N = 317)	Cinacalcet (N = 317)
All adverse events	90.9 (288)	91.2 (289)	Pharyngitis	4.1 (13)	1.3 (4)
Nasopharyngitis	31.9 (101)	32.5 (103)	Blood calcium decreased	3.5 (11)	7.6 (24)
Adjusted calcium decreased	11.7 (37)	15.8 (50)	Hypocalcaemia	3.5 (11)	1.3 (4)
Contusion	9.5 (30)	7.6 (24)	Wound	3.5 (11)	2.2 (7)
Vomiting	8.5 (27)	11.7 (37)	Abdominal pain upper	3.2 (10)	1.6 (5)
Diarrhoea	8.2 (26)	9.5 (30)	Pain in extremity	3.2 (10)	3.5 (11)
Nausea	7.3 (23)	14.2 (45)	Back pain	3.2 (10)	2.8 (9)
Shunt stenosis	6.3 (20)	3.8 (12)	Gastroenteritis	2.8 (9)	4.4 (14)
Arthralgia	5.4 (17)	4.7 (15)	Shunt occlusion	2.5 (8)	3.8 (12)
Upper respiratory tract inflammation	5.0 (16)	5.7 (18)	Decreased appetite	2.5 (8)	3.5 (11)
Abdominal discomfort	4.4 (14)	11.0 (35)	Headache	1.9 (6)	3.2 (10)
Influenza	4.4 (14)	4.1 (13)	Hypertension	1.3 (4)	3.5 (11)
Excoriation	4.4 (14)	2.5 (8)			

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver. 19.0; Incidence, % (n)

Table 29. Adverse drug reactions reported in ≥3.0% of patients in either group

Adverse drug reaction	Evocalcet (N = 317)	Cinacalcet (N = 317)
All adverse drug reactions	44.8 (142)	58.7 (186)
Adjusted calcium decreased	11.7 (37)	15.8 (50)
Nausea	5.0 (16)	11.4 (36)
Vomiting	4.4 (14)	6.0 (19)
Blood calcium decreased	3.5 (11)	7.6 (24)
Hypocalcaemia	3.5 (11)	1.3 (4)
Abdominal discomfort	3.2 (10)	9.1 (29)
Diarrhoea	3.2 (10)	3.2 (10)

MedDRA/J ver. 19.0, Incidence; % (n)

Death occurred in 0.3 % (1 of 317) of patients (pancreatitis acute[14]) and is assessed to be an adverse drug reaction. Serious adverse events other than death occurred in 18.0% (57 of 317) of patients in the evocalcet group and in 13.9% (44 of 317) of patients in the cinacalcet group. Table 30 shows serious adverse events reported in ≥2 patients in either group. Serious adverse drug reactions were observed in 2.5% (8 of 317) of patients in the evocalcet group (angina pectoris, cardiac failure congestive, arrhythmia, vertigo positional, liver abscess, breast cancer, colon cancer, and extranodal marginal zone B-cell lymphoma [MALT type] in 1 patient each) and in 1.9% (6 of 317) of patients in the cinacalcet group (cardiac failure congestive, atrial fibrillation, vertigo positional, ascites, gastroenteritis, and cerebral infarction in 1 patient each). Except for cardiac failure congestive,[15] arrhythmia,[16] liver abscess,[17] breast cancer,[18] colon cancer,[19] and extranodal marginal zone B-cell lymphoma (MALT

[14] A 61-year-old male patient complicated with hyperkalaemia, hyperphosphataemia, von Recklinghausen disease, cerebral infarction, osteoporosis, etc. On Day 74 (9 days after the last dose of study drug), the patient experienced idiopathic acute pancreatitis followed by sepsis and multi-organ failure, and died on Day 140. The investigator concluded that the causal relationship between pancreatitis and the study drug could not be ruled out, although the event was very unlikely to be related to the study drug because the pancreatitis developed at 9 days after the last dose of the study drug.

[15] A 54-year-old male patient. At the enrollment, echocardiography showed decreased cardiac function but cardiac catheter test did not reveal any significant stenosis. On Day 43, the patient had congestive cardiac failure. The outcome was reported as “not recovered” on Day 169.

[16] A 63-year-old male patient. On Day 43, electrocardiography showed extrasystole. Although cardiac catheter test did not reveal any significant stenosis, study treatment was interrupted on Day 53, and discontinued on Day 61. The outcome was reported as “not recovered” on Day 64.

[17] A 53-year-old male patient. On Day 166, the patient experienced blood pressure decreased, vomiting, etc., during HD, and subsequently had a diagnosis of liver abscess. The patient underwent liver abscess drainage and other treatments, which led to improvement of the symptoms. However, the outcome was reported as “not recovered” on Day 211.

[18] A 71-year-old female patient. On Day 170, the patient experienced breast cancer whereupon the study was discontinued on Day 197. The outcome was reported as “not recovered.”

[19] A 65-year-old male patient. On Day 64, the patient experienced colon cancer, whereupon the treatment was interrupted on Day 120. The study was discontinued on Day 127. The outcome was reported as “not recovered.”

type)[20] in the evocalcet group and cerebral infarction in the cinacalcet group, the outcomes of other serious adverse events were "recovered" or "recovering."

Table 30. Serious adverse events reported in ≥2 patients in either group

Adverse event	Evocalcet (N = 317)	Cinacalcet (N = 317)	Adverse event	Evocalcet (N = 317)	Cinacalcet (N = 317)
All events	18.0 (57)	13.9 (44)	Coronary artery stenosis	0.6 (2)	0 (0)
Shunt stenosis	1.6 (5)	0.9 (3)	Vascular stent occlusion	0.6 (2)	0 (0)
Pneumonia	0.9 (3)	0.6 (2)	Bile duct stone	0.6 (2)	0 (0)
Angina pectoris	0.9 (3)	0 (0)	Spinal compression fracture	0.6 (2)	0 (0)
Shunt malfunction	0.9 (3)	0 (0)	Gastric cancer	0.6 (2)	0 (0)
Shunt occlusion	0.6 (2)	1.9 (6)	Peripheral arterial occlusive disease	0.6 (2)	0.3 (1)
Pulmonary oedema	0.6 (2)	0.6 (2)	Cardiac failure congestive	0.3 (1)	0.6 (2)
Cardiac failure acute	0.6 (2)	0.3 (1)	Gastroenteritis	0.3 (1)	0.6 (2)
Cholecystitis	0.6 (2)	0.3 (1)	Atrial fibrillation	0 (0)	0.6 (2)
Acute myocardial infarction	0.6 (2)	0 (0)	Cerebral infarction	0 (0)	0.6 (2)

MedDRA/J ver. 19.0; Incidence, % (n)

Adverse events leading to discontinuation or interruption of study drug (other than serious adverse events) were observed in 16.1% (51 of 317) of patients in the evocalcet group and in 26.5% (84 of 317) of patients in the cinacalcet group. Adverse drug reactions leading to discontinuation or interruption of study drug were observed in 15.5% (49 of 317) of patients in the evocalcet group and in 25.6% (81 of 317) of patients in the cinacalcet group. Tables 31 and 32 show adverse events and adverse drug reactions, respectively, leading to discontinuation or interruption of study drug in ≥2 patients in either group.

Table 31. Adverse events leading to discontinuation or interruption of study drug in ≥2 patients in either group

Adverse event	Evocalcet (N = 317)	Cinacalcet (N = 317)
All events	16.1 (51)	26.5 (84)
Adjusted calcium decreased	8.8 (28)	13.6 (43)
Blood calcium decreased	1.9 (6)	6.0 (19)
Hypocalcaemia	1.3 (4)	0.3 (1)
Nausea	0.9 (3)	2.2 (7)
Abdominal discomfort	0.3 (1)	1.3 (4)
Decreased appetite	0.3 (1)	0.9 (3)
Vomiting	0.3 (1)	0.6 (2)
Diarrhoea	0.3 (1)	0.6 (2)
Abdominal distension	0 (0)	0.6 (2)

MedDRA/J ver. 19.0; Incidence, % (n)

[20] A 70-year-old male patient. On Day 94, the patient experienced extranodal marginal zone B-cell lymphoma (MALT type). On Day 211, the outcome was reported as "not recovered."

Table 32. Adverse drug reactions leading to discontinuation or interruption of the study drug in ≥2 patients in either group

Adverse drug reactions	Evocalcet (N = 317)	Cinacalcet (N = 317)
All adverse drug reactions	15.5 (49)	25.6 (81)
Adjusted calcium decreased	8.8 (28)	13.6 (43)
Blood calcium decreased	1.9 (6)	6.0 (19)
Hypocalcaemia	1.3 (4)	0.3 (1)
Nausea	0.9 (3)	2.2 (7)
Abdominal discomfort	0.3 (1)	1.3 (4)
Decreased appetite	0.3 (1)	0.9 (3)
Vomiting	0.3 (1)	0.6 (2)
Abdominal distension	0 (0)	0.6 (2)

MedDRA/J ver. 19.0; Incidence, % (number of patients with events)

7.2.2 Japanese long-term treatment study in patients on HD (CTD 5.3.5.2-1, Study 7580-011 [September 2015 to December 2016])

A multicenter, open-label, uncontrolled study in patients with SHPT on HD aged ≥20 years (Table 33) (target sample size, 120 subjects) was conducted at 15 study sites in Japan to investigate the long-term safety and efficacy of evocalcet.

Table 33. Key inclusion/exclusion criteria

Inclusion criteria • Patients with iPTH levels >240 pg/mL at the screening test (excluding patients receiving cinacalcet) • Patients with adjusted serum Ca levels ≥8.4 mg/dL at the screening test • Patients with stable chronic renal failure who were receiving HD 3 times a week and had a hemodialysis history of ≥12 weeks before the screening test Exclusion criteria • Patients who received the modified regimen of cinacalcet, activated vitamin D or its derivative, P adsorbent, or Ca preparation, or who newly received any of these drugs, within 2 weeks before the screening test • Patients who underwent any change in the dialyzing conditions within 2 weeks before the screening test

The dose of evocalcet was adjusted according to Table 34 to control iPTH levels within the range between ≥60 pg/mL and ≤240 pg/mL (150 pg/mL optimally), and the thus-adjusted study drug was administered orally once daily to subjects for 52 weeks.

Table 34. Criteria for dose adjustment

Target iPTH level	≥60 pg/mL and ≤240 pg/mL (the dose should be adjusted to achieve approximately 150 pg/mL iPTH)
Starting dose	iPTH levels <500 pg/mL at the screening test: evocalcet 1 mg iPTH levels ≥500 pg/mL and adjusted Ca levels <9.0 mg/dL at the screening test: evocalcet 1 mg iPTH levels ≥500 pg/mL and adjusted Ca levels ≥9.0 mg/dL at the screening test: evocalcet 2 mg
Maximum dose	12 mg
Increment/decrement	Increment, 1 mg; decrement, 1 mg as a rule
Criteria for dose increase	The dose may be increased if all of the following criteria are met: • The current dose has been maintained for ≥3 weeks. • iPTH levels >240 pg/mL at the planned visit immediately before the dose modification. However, dose increase is possible at iPTH levels ≤240 pg/mL if the investigator, etc., considers that the dose may be increased to achieve iPTH levels of approximately 150 pg/mL. • Adjusted serum Ca levels ≥8.4 mg/dL (measured at the central laboratory) at the planned visit immediately before the dose modification. • The investigator considers that dose increase does not pose safety problem in the patient.
Criteria for dose decrease	The dose may be decreased if either of the following criteria is met: (the dose may be decreased by >1 mg, if deemed necessary by the investigator.) • iPTH levels have decreased to <60 pg/mL. • The investigator, etc., considers that the dose should be reduced because of adverse events.
Dose increase after dose decrease	If the adjusted serum Ca is <8.4 mg/dL, dose increase is prohibited.
Criteria for interruption	Treatment should be interrupted if either of the following is met: • Adjusted serum Ca levels have decreased to ≤7.5 mg/dL. • The investigator, etc., considers that the dose should be reduced because of adverse events.
Criteria for resumption after interruption	If treatment was interrupted due to the decrease in adjusted serum Ca levels to ≤7.5 mg/dL, the study treatment should be resumed after adjusted serum Ca levels have increased to ≥8.4 mg/dL. The dose at the resumption should be the same as, or lower than, the dose before the interruption.
Criteria for use of concomitant activated vitamin D and its derivatives	• If currently in use, no change should be made to the type(s) and the dosage regimen of the concomitant drugs from 2 weeks before the screening test until Week 0. • If not in use currently, addition of concomitant drugs is prohibited from 2 weeks before the screening test until Week 0. • On and after the next day of the start of study treatment, activated vitamin D and its derivatives may be changed in dose or type, or added.

All of the 137 patients enrolled in the study received study drug and were included in the FAS and the safety analysis set. The FAS was used for the efficacy analysis. Treatment was discontinued in 24 patients. The causes of the discontinuation were “adverse events requiring the discontinuation, as judged by the investigator” in 9 patients, “patient’s request” in 5 patients, “treatment interruption lasting >4 weeks” in 5 patients, “necessary monitoring and tests infeasible due to the patient’s reason” in 4 patients, and “study discontinuation necessitated for any other reason, as judged by the investigator” in 1 patient.

Table 35 shows changes over time in “percentage of patients achieving iPTH levels ≥60 pg/mL and ≤240 pg/mL at each evaluation time point.” The percentage [95% CI] of patients achieving this target level at Week 52 was 72.3% (99 of 137 patients) [64.0, 79.6].

Table 35. Percentage of patients achieving iPTH levels ≥60 pg/mL and ≤240 pg/mL at each evaluation time point (FAS)

Evaluation time point	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
Percentage of patients with iPTH levels ≥60 and ≤240 pg/mL	40.9 (56)	45.3 (62)	49.6 (68)	56.2 (77)	68.6 (94)	70.8 (97)	72.3 (99)

Patients achieving the endpoint, % (number of patients)

Adverse events were observed in 99.3% (136 of 137) of patients. Table 36 shows adverse events reported in ≥5.0% of patients. Adverse drug reactions were observed in 35.0% (48 of 137) of patients.

Adverse drug reactions reported in ≥5.0% of patients were adjusted calcium decreased in 7.3% (10 of 137) of patients, nausea and abdominal discomfort in 5.1% each (7 of 137) of patients.

Table 36. Adverse events reported in ≥5.0% of patients

Adverse event	Evocalcet (N = 137)	Adverse event	Evocalcet (N = 137)
All events	99.3 (136)	Pain in extremity	7.3 (10)
Nasopharyngitis	61.3 (84)	Headache	7.3 (10)
Contusion	16.1 (22)	Stomatitis	6.6 (9)
Diarrhoea	11.7 (16)	Internal haemorrhage	6.6 (9)
Nausea	11.7 (16)	Constipation	5.8 (8)
Upper respiratory tract inflammation	9.5 (13)	Shunt stenosis	5.8 (8)
Abdominal discomfort	8.8 (12)	Dermatitis contact	5.8 (8)
Vomiting	8.8 (12)	Dental caries	5.1 (7)
Arthralgia	8.8 (12)	Influenza	5.1 (7)
Shunt occlusion	8.0 (11)	Back pain	5.1 (7)
Wound	8.0 (11)	Muscle spasms	5.1 (7)
Sloughing of skin	8.0 (11)	Cough	5.1 (7)
Adjusted calcium decreased	7.3 (10)	Pruritus	5.1 (7)

MedDRA/J ver. 19.0; Incidence, % (n)

No death occurred. Serious adverse events were observed in 29.9% (41 of 137) of patients. Serious adverse events reported in ≥2 patients were shunt occlusion in 4.4% (6 of 137) of patients, peripheral arterial occlusive disease in 2.9% (4 of 137) of patients, coronary artery stenosis, shunt stenosis, blood pressure decreased, cerebral infarction, and cataract operation in 1.5% each (2 of 137) of patients. Serious adverse drug reactions were observed in 3.6% (5 of 137) of patients (cardiac failure congestive, cardiomyopathy, cataract, intestinal obstruction, and drug-induced liver injury in 1 patient each). Their outcome was reported as “recovered” or “recovering.”

Adverse events leading to discontinuation or interruption of the study drug (other than serious adverse events) were observed in 16.1% (22 of 317) of patients. Adverse events reported in ≥2 patients were adjusted calcium decreased in 7.3% (10 of 137) of patients and blood calcium decreased in 2.9% (4 of 137) of patients. Adverse drug reactions leading to discontinuation or interruption of study drug (other than serious adverse drug reactions) were observed in 13.9% (19 of 317) of patients (adjusted calcium decreased in 7.3% [10 of 137] of patients, blood calcium decreased in 2.9% [4 of 137] of patients, diarrhea, gastritis erosive, nausea, vomiting, chest discomfort, and pruritus in 0.7% each [1 of 137] of patients).

7.2.3 Japanese open-label clinical study in patients on PD (CTD 5.3.5.2-2, Study 7580-012 [September 2015 to December 2016])

A multicenter, open-label, uncontrolled study in patients with SHPT on PD aged ≥20 years (Table 37) (target sample size, 30 subjects) was conducted at 16 study sites in Japan to investigate the efficacy and safety of evocalcet.

Table 37. Key inclusion/exclusion criteria

Inclusion criteria • Patients with iPTH levels >240 pg/mL at the screening test • Patienst with adjusted serum Ca levels ≥8.4 mg/dL at the screening test • Patients with stable chronic renal failure who had a PD history of ≥16 weeks Exclusion criteria • Patients who used cinacalcet within 2 weeks before the screening test • Patients who received the modified regimen of activated vitamin D or its derivative, P adsorbent, or Ca preparation, or who newly received any of these drugs, within 2 weeks before the screening test • Patients who received a combination therapy with HD or hemodialysis filtration, or underwent any change in the dialyzing conditions, within 4 weeks before the screening test

The dose of evocalcet was adjusted according to Table 38 to control iPTH levels within the range between ≥60 pg/mL and ≤240 pg/mL (150 pg/mL optimally), and the thus-adjusted study drug was administered orally once daily to subjects for a maximum of 52 weeks (dose adjustment period, 30 weeks [Weeks 0-30]; evaluation period, 2 weeks [Weeks 30-32]; extended treatment period,[21] 20 weeks [Weeks 32-52]).

Table 38. Criteria for dose adjustment

Target iPTH level	≥60 pg/mL and ≤240 pg/mL (the dose should be adjusted to achieve approximately 150 pg/mL iPTH)
Starting dose	iPTH levels <500 pg/mL at the screening test: evocalcet 1 mg iPTH levels ≥500 pg/mL and adjusted Ca levels <9.0 mg/dL at the screening test: evocalcet 1 mg iPTH levels ≥500 pg/mL and adjusted Ca levels ≥9.0 mg/dL at the screening test: evocalcet 2 mg
Maximum dose	12 mg (8 mg for the dose adjustment period up to Week 30 and the evaluation period from Week 30 to Week 32, and 12 mg for the extended treatment period from Week 32 to Week 52)
Increment/decrement	1 mg
Criteria for dose increase	The dose may be increased if all of the following criteria are met: • The current dose has been maintained for ≥4 weeks. • iPTH levels >240 pg/mL at the planned visit immediately before the dose modification. However, dose increase is possible at iPTH levels ≤240 pg/mL if the investigator, etc., considers that the dose may be increased to achieve iPTH levels of approximately 150 pg/mL. • Adjusted serum Ca levels ≥8.4 mg/dL (measured at the central laboratory) at the planned visit immediately before the dose modification. • The investigator consideres that dose increase does not pose a safety problem in the patient.
Criteria for dose decrease	The dose may be decreased if either of the following criteria is met: (the dose may be decreased by >1 mg, if deemed necessary by the investigator) • iPTH levels have decreased to <60 pg/mL. • The investigator, etc., considers that the dose should be reduced because of adverse events.
Dose increase after dose decrease	If the adjusted serum Ca is <8.4 mg/dL, dose increase is prohibited.
Criteria for interruption	Treatment should be interrupted if either of the following is met: • Adjusted serum Ca levels have decreased to ≤7.5 mg/dL. • The investigator, etc., considers that the dose should be reduced because of adverse events.
Criteria for resumption after interruption	If treatment was interrupted due to the decrease in adjusted serum Ca levels to ≤7.5 mg/dL, the study treatment should be resumed after adjusted serum Ca levels have increased to ≥8.4 mg/dL. The dose at the resumption should be the same as, or lower than, the dose before the interruption.
Vitamin D and its derivatives, P adsorbent, and Ca preparation	• If currently in use, no change should be made to the type(s) and the dosage regimen of the concomitant drugs from 2 weeks before the screening test until Week 0. • If not in use currently, addition of concomitant drugs is prohibited from 2 weeks before the screening test until Week 0. • On and after the next day of the start of study treatment, activated vitamin D and its derivatives may be changed in dose or type, or added.

Of 42 patients enrolled in the study, 39 patients received study drug and were included in the FAS and the safety analysis set. The remaining 3 patients were excluded from analysis because they

[21] Patients who completed the evaluation period and were considered by the investigator, etc., to be able to continue the study up to Week 52 were allowed to enter the extended treatment period. In other patients, the study was completed at Week 32.

discontinued the study before the start of study treatment. The FAS was used for the primary efficacy analysis. Study treatment was discontinued in 14 patients. The reasons for the discontinuation (some patients with one or more reasons) were “adverse events requiring the discontinuation, as decided by the investigator” in 5 patients, “treatment interruption continued for >4 weeks” in 4 patients, “the patient was found after the start of the study to be ineligible for enrollment in the study because of failure to meet the inclusion criteria” in 2 patients, “patient’s request” in 2 patients, and “study discontinuation for any other reason, as decided by the investigator” in 2 patients, “necessary monitoring and tests infeasible due to the patient’s reason” in 1 patient, and “withdrawal from peritoneal dialysis” in 1 patient.

The primary efficacy endpoint “the percentage of patients achieving mean iPTH level ≥60 pg/mL and ≤240 pg/mL during the evaluation period (Weeks 30-32)” [95% CI] was 71.8% (28 of 39 patients) [55.1, 85.0].

Adverse events occurred in 100% (39 of 39) of patients. Table 39 shows adverse events reported in ≥5.0% of patients. Adverse drug reactions were observed in 46.2% (18 of 39) of patients. Adverse drug reactions reported in ≥5.0% of patients were adjusted calcium decreased in 17.9% (7 of 39) of patients and blood calcium decreased in 5.1% (2 of 39) of patients.

Table 39. Adverse events reported in ≥5.0% of patients

Adverse event	Evocalcet (N = 39)	Adverse event	Evocalcet (N = 39)
All events	100.0 (39)	Conjunctivitis	5.1 (2)
Nasopharyngitis	43.6 (17)	Folliculitis	5.1 (2)
Catheter site infection	28.2 (11)	Pharyngitis	5.1 (2)
Adjusted calcium decreased	17.9 (7)	Rhinitis	5.1 (2)
Hypertension	17.9 (7)	Blood calcium decreased	5.1 (2)
Diarrhoea	10.3 (4)	Blood CPK increased	5.1 (2)
Peritonitis	10.3 (4)	Dehydration	5.1 (2)
Contusion	10.3 (4)	Hyperkalaemia	5.1 (2)
Iron deficiency anaemia	7.7 (3)	Hypokalaemia	5.1 (2)
Vomiting	7.7 (3)	Decreased appetite	5.1 (2)
Gastroenteritis	7.7 (3)	Back pain	5.1 (2)
Hyperphosphataemia	7.7 (3)	Muscle spasms	5.1 (2)
Pruritus	7.7 (3)	Osteoarthritis	5.1 (2)
Rash	7.7 (3)	Insomnia	5.1 (2)
Angina pectoris	5.1 (2)	Sleep apnoea syndrome	5.1 (2)
Myocardial ischaemia	5.1 (2)	Upper respiratory tract inflammation	5.1 (2)
Conjunctival haemorrhage	5.1 (2)	Dermatitis	5.1 (2)
Oedema	5.1 (2)	Pyrexia	5.1 (2)
Bronchitis	5.1 (2)		

MedDRA/J ver. 19.0;Incidence, % (n)

Death occurred in 2.6% (1 of 39) of patients (altered state of consciousness[22)]), but its causal relationship to the study drug was ruled out. Serious adverse events other than death were observed in 41.0% (16 of 39) of patients. Serious adverse events reported in ≥2 patients were peritonitis in 10.3%

22) A 71-year-old female patient. On Day 225, the patient was hospitalized because of pneumonia, which was considered to be a serious adverse event. Its causal relationship to the study drug was ruled out. On Day 236, the patient had a blow to the head due to fall, but cranial computed tomography (CT) revealed no obvious intracranial haemorrhage. On Day 237, consciousness level decreased and, on Day 238, the study was discontinued. The patient died on Day 242. The investigator concluded that the event was caused by meningitis (suspected), which was considered to be accidental and its causal relationship to the study drug was ruled out.

(4 of 39) of patients, catheter site infection in 7.7% (3 of 39) of patients, and angina pectoris in 5.1% (2 of 39) of patients. There were no serious adverse events.

Adverse events leading to discontinuation or interruption of study drug (other than serious adverse events) were observed in 23.1% (9 of 39) of patients. Events reported in ≥5.0% of patients were adjusted calcium decrease in 12.8% (5 of 39) of patients and blood calcium decreased in 5.1% (2 of 39) of patients. Adverse drug reactions leading to discontinuation or interruption of study drug were observed in 20.5% (8 of 39) of patients (adjusted calcium decrease in 5 patients, blood calcium decreased in 2 patients, and eczema in 1 patient).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the results of reviews presented in Sections 7.R.1.1 and 7.R.1.2, PMDA considers that the submitted data have demonstrated the efficacy of evocalcet in patients with SHPT on dialysis. The final decision on the efficacy of evocalcet will be made, taking account of comments raised in the Expert Discussion.

7.R.1.1 Patients on HD

On the basis of the results of reviews presented in Sections 7.R.1.1.1 to 7.R.1.1.4, PMDA considers that the submitted data have demonstrated the efficacy of evocalcet in patients with SHPT on HD.

7.R.1.1.1 Design of Japanese phase III comparative study and results of the primary endpoint

The applicant's explanation about the justification for the design (primary endpoint, control group, evaluation period, and non-inferiority margin) of the Japanese phase III comparative study, a confirmatory study in patients with SHPT on HD:

It was considered appropriate to define the primary efficacy endpoint as the percentage of patients achieving the target iPTH level of ≥60 and ≤240 pg/mL, because the Clinical Practice Guideline for CKD-MBD 2012 recommends that iPTH levels should be maintained within this target range.

Evocalcet is a CaR agonist. Cinacalcet was selected as the control drug because it is also a CaR agonist and is commonly used in and outside Japan to treat patients with SHPT on maintenance dialysis.

The study was designed to consist of the dose adjustment period of 28 weeks and the evaluation period of 2 weeks (Weeks 28-30). In the Japanese phase II study in SHPT patients on HD [see Section 7.1.1], the percent change in iPTH levels and adjusted serum Ca levels at each dose of evocalcet reached the peak within appropriately 2 weeks after the start of treatment. The results indicated that each dose should be maintained for 2 weeks. In the Japanese phase III comparative study, serum iPTH and adjusted serum Ca levels were measured at the central laboratory. Therefore, the same dose of study drug was maintained for at least 3 weeks to allow for the time for reporting the test result. The dose of evocalcet was increased in increments of 1 mg because a gradual dose increase was desirable from safety perspective. The dose adjustment period of 28 weeks was set because the efficacy and safety of

evocalcet could be compared with those of cinacalcet if the dose of evocalcet was increased up to 8 mg, the dose expected to be as effective as the maximum dose of cinacalcet (100 mg) [see Section 7.R.6.1]. The evaluation period of 2 weeks (Weeks 28-30) was set to allow evaluation by multiple tests.

The non-inferiority margin was specified by referring to the data from the clinical studies of cinacalcet. A detailed rationale is presented below. Since cinacalcet has become available in clinical settings in recent years, there is a tendency toward a decrease in the number of patients with severe SHPT (*Official Journal of the Japan Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery*. 2014;31:210-213). For this reason, the efficacy of cinacalcet was investigated in the subpopulation of patients with baseline iPTH level <800 pg/mL in the Japanese phase III study of cinacalcet in patients with SHPT on HD (Study KRN1493/04-A10). In the subpopulation of patients with baseline iPTH level <800 pg/mL, "the percentage of patients achieving iPTH levels ≤250 pg/mL at the end of study treatment (Week 14 or at discontinuation)" was 61.5% (32 of 52 patients) in the cinacalcet group and 3.8% (2 of 52 patients) in the placebo group, with the treatment difference (cinacalcet vs. placebo) being 57.7%. In the Japanese long-term treatment study of cinacalcet in patients with SHPT on HD (Study KRN1493/04-A11), the percentage of patients achieving iPTH levels ≤250 pg/mL reached the steady state at approximately 14 weeks after the start of treatment with cinacalcet, with no major changes thereafter. Based on the above study results, on the assumption that "the percentage of patients achieving iPTH levels≥60 pg/mL and ≤240 pg/mL during the evaluation period (Weeks 28-30)" in the cinacalcet group of the Japanese phase III comparative study is 60%, the difference in the percentage of patients achieving the endpoint between the placebo group and the cinacalcet group is calculated to be 50%. Therefore, the non-inferiority margin was defined as 15%, which is approximately one-third of 50%.

PMDA's view:
There are no particular problems regarding the applicant's explanation about the design (primary endpoint, control group, evaluation period, non-inferiority margin) of the Japanese phase III comparative study in patients with SHPT on HD.

The results of the primary endpoint in the Japanese phase III comparative study were analyzed. The primary endpoint "the percentage of patients achieving the mean iPTH level of ≥60 and ≤240 pg/mL during the evaluation period (Weeks 28-30) (PPS)" [95% CI] was 72.7% (184 of 253 patients) [66.8, 78.1] in the evocalcet group and 76.7% (204 of 266 patients) [71.1, 81.6] in the cinacalcet group (Table 27). The treatment difference (evocalcet vs. cinacalcet) [95% CI] of the percentage of patients achieving the endpoint was −4.0% [−11.4, 3.5], with the lower limit of the 95% CI exceeding the non-inferiority margin of −15%, demonstrating the non-inferiority of evocalcet to cinacalcet. The above results confirmed the efficacy of evocalcet in patients with SHPT on HD.

7.R.1.1.2 Main secondary endpoint in Japanese phase III comparative study

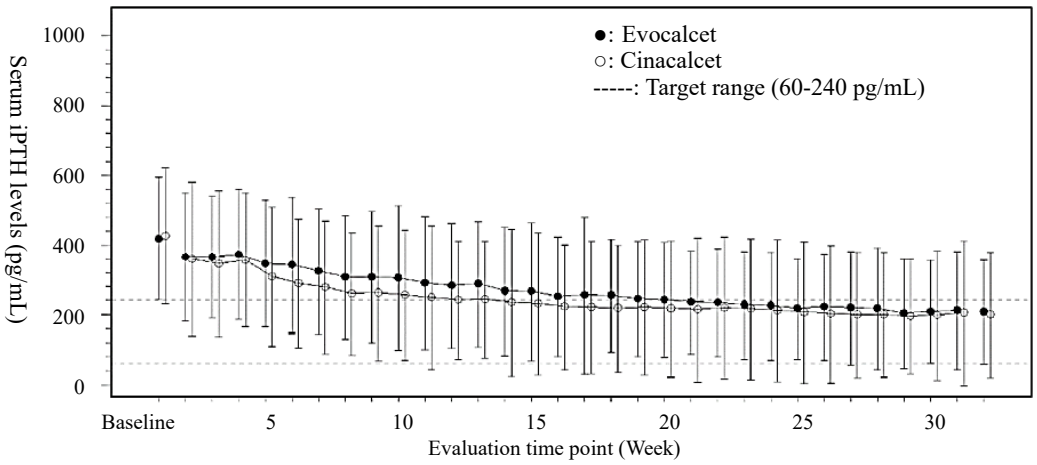
Table 40 shows the mean percent change from baseline in iPTH levels in the evaluation period (Weeks 28-30) in the Japanese phase III comparative study. The decrease in iPTH levels in the evocalcet group was comparable to that in the cinacalcet group.

Table 40. Mean percent change from baseline in iPTH levels in the evaluation period (Weeks 28-30) (Japanese phase III comparative study, PPS)

	Evocalcet (N = 253)	Cinacalcet (N = 266)
Baseline iPTH levels (pg/mL)	418.3 ± 176.9	426.8 ± 195.4
iPTH levels during the evaluation period (Weeks 28-30) (pg/L)	207.8 ± 148.7	199.7 ± 178.7
Mean percent change from baseline in iPTH levels in the evaluation period (%)	−49.6 ± 25.9	−53.6 ± 23.0
Treatment difference (evocalcet vs. cinacalcet) [95% CI]	3.9 [−0.3,8.1]	

Mean ± SD

Figure 1 shows the change over time in serum iPTH levels (mean ± standard deviation [SD]) in the Japanese phase III comparative study. Mean serum iPTH level decreased over time both in the evocalcet group and in the cinacalcet group, reaching the target level (≥60 and ≤240 pg/mL) eventually.



Evaluation time point (Week)	Baseline	2	4	8	12	16	20	24	28	30	Evaluation period (28-30)
Evocalcet (N)	253	253	252	253	251	252	253	251	253	250	253
Cinacalcet (N)	266	266	265	264	264	266	266	265	266	266	266

Figure 1. Change over time in serum iPTH levels (mean ± SD) (Japanese phase III comparative study, PPS)

7.R.1.1.3 Efficacy by patient characteristics in Japanese phase III comparative study

Subgroup analyses by patient characteristics were performed for "the percentage of patients achieving the mean serum iPTH level ≥60 and ≤240 pg/mL during the evaluation period (Weeks 28-30)" in the Japanese phase III comparative study. Table 41 shows the analysis results. No clinically significant difference was observed between evocalcet and cinacalcet in any of the subgroups.

Table 41. Percentage of patients achieving mean iPTH level ≥60 and ≤240 pg/mL, analyzed by patient characteristics
Evaluation period (Weeks 28-30) (Japanese phase III comparative study, PPS)

Patient characteristics	Subgroup	Evocalcet (N = 253)	Cinacalcet (N = 266)
Sex	Male	75.7 (134/177)	77.9 (152/195)
	Female	65.8 (50/76)	73.2 (52/71)
Age	<65	69.5 (98/141)	74.7 (118/158)
	≥65	76.8 (86/112)	79.6 (86/108)
Baseline iPTH level (pg/mL)	<500	80.3 (159/198)	86.4 (172/199)
	≥500	45.5 (25/55)	47.8 (32/67)
Baseline adjusted serum Ca level (mg/dL)	<9.5	68.8 (86/125)	73.1 (87/119)
	≥9.5	76.6 (98/128)	79.6 (117/147)
Use of cinacalcet before screening	No	81.6 (80/98)	82.8 (72/87)
	Yes	67.1 (104/155)	73.7 (132/179)
Use of concomitant activated vitamin D at the start of study treatment	No	41.7 (15/36)	51.7 (15/29)
	Yes	77.9 (169/217)	79.7 (189/237)
Starting dose of evocalcet[a)]	1 mg	80.7 (155/192)	86.4 (178/206)
	2 mg	47.5 (29/61)	43.3 (26/60)

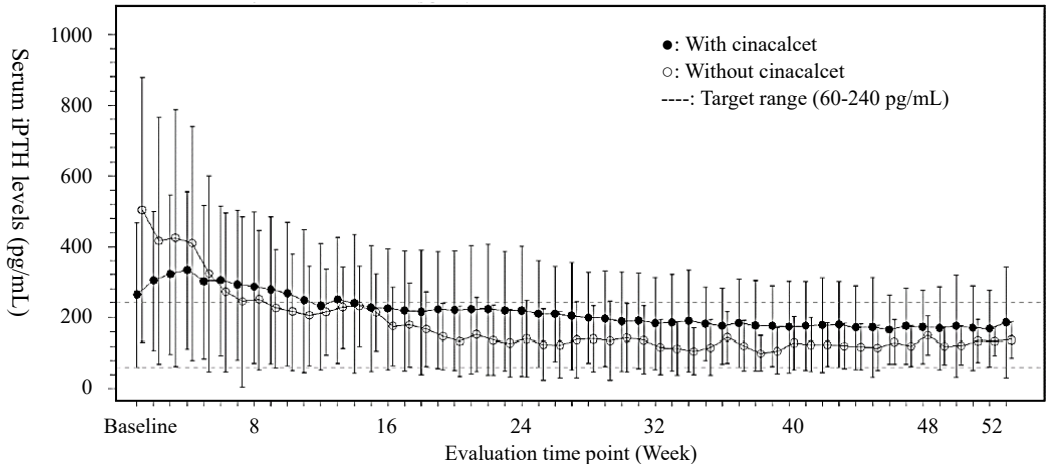
Percentage of patients achieving the endpoint, % (n/N)
a) Patients in the cinacalcet group were divided into 2 groups by iPTH level 1 week before the start of study treatment (<500 pg/mL or ≥500 pg/mL), by referring to the criteria for the starting dose of evocalcet.

7.R.1.1.4 Long-term efficacy in patients on HD

In the Japanese long-term treatment study, patients receiving cinacalcet were eligible for enrollment in the study. Thus, 85.4% (117 of 137) of enrolled patients had received cinacalcet 1 day before treatment with evocalcet. Figure 2 shows the change over time in serum iPTH levels (mean ± SD) in patients receiving, or not receiving, cinacalcet 1 day before treatment with evocalcet. In the subgroup of patients not receiving cinacalcet, serum iPTH levels decreased after the start of treatment with evocalcet and tended to remain within the target range from Week 8 onward. In the subgroup of patients receiving cinacalcet previously (patients who switched from cinacalcet to evocalcet), the mean serum iPTH level tended to increase after the start of treatment with evocalcet. An analysis of data from patients receiving different doses of cinacalcet revealed an increase in the mean iPTH levels in patients who had been treated with cinacalcet at doses of ≥37.5 mg. However, the dose of evocalcet was adjusted from Week 3 onward according to the criteria shown in Table 34.The mean iPTH levels decreased starting at Week 4 and tended to remain within the target range from Week 11 onward.

PMDA's view:

There is no particular problem in the long-term efficacy of evocalcet. However, information on variations in serum iPTH levels in patients who switch from cinacalcet to evocalcet should be collected in the post-marketing surveillance, etc.



Evaluation time point (Week)	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52
Evocalcet (N)	137	136	131	127	126	124	122	122	122	119	117	117	115	113
With cinacalcet (N)	113	112	107	104	104	102	100	100	100	99	97	97	95	93
Without cinacalcet (N)	24	24	24	23	22	22	22	22	22	20	20	20	20	20

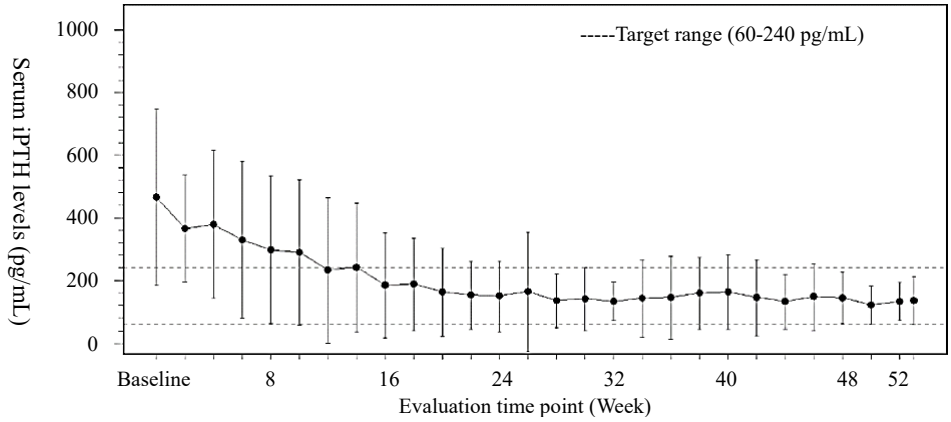
Figure 2. Changes over time in serum iPTH levels (mean ± SD)
(Japanese long-term treatment study)

7.R.1.2 Patients on PD

On the basis of the results of reviews presented in Sections 7.R.1.2.1 and 7.R.1.2.2, PMDA has concluded that the submitted data have demonstrated the efficacy of evocalcet in patients with SHPT on PD.

7.R.1.2.1 Main data of Japanese open-label clinical study

In the Japanese open-label clinical study in patients with SHPT on PD, the primary endpoint "the percentage of patients achieving the mean iPTH level ≥60 and ≤240 pg/mL during the evaluation period (Weeks 30-32)" [95% CI] was 71.8% (28 of 39 patients) [55.1, 85.0], which was comparable to the percentage achieved in patients on HD [see Section 7.2.3]. Figure 3 shows changes over time in serum iPTH levels (mean ± SD), showing that the mean serum iPTH level tended to remain within the target range from Week 12 onward.



Evaluation time point (Week)	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	Evaluation period (30-32)
Evocalcet (N)	39	39	39	38	38	35	34	33	31	28	26	26	25	24	32

Figure 3. Changes over time in serum iPTH levels (mean ± SD)
(Japanese open-label clinical study)

7.R.1.2.2 Efficacy by patient characteristics in Japanese open-label clinical study

Subgroup analyses were performed by patient characteristics for "the percentage of patients achieving the mean iPTH level ≥60 and ≤240 pg/mL during the evaluation period (Weeks 30-32) (FAS)" in the Japanese open-label clinical study in patients with SHPT on PD. Table 42 shows the analysis results. No clinically significant difference was observed between subgroups.

Table 42. Percentage of patients achieving mean iPTH level of ≥60 and ≤240 pg/mL, analyzed by patient characteristics
Evaluation period (Weeks 30-32) (Japanese open-label clinical study, FAS)

Patient characteristics	Subgroup	Evocalcet (N = 39)
Sex	Male	69.6 (16/23)
	Female	75.0 (12/16)
Age	<65	61.9 (13/21)
	≥65	83.3 (15/18)
Baseline iPTH level (pg/mL)	<500	76.9 (20/26)
	≥500	61.5 (8/13)
Baseline adjusted serum Ca level (mg/dL)	<9.5	75.0 (21/28)
	≥9.5	63.6 (7/11)
Use of cinacalcet before screening	No	73.3 (22/30)
	Yes	66.7 (6/9)
Use of concomitant activated vitamin D at the start of study treatment	No	64.3 (9/14)
	Yes	76.0 (19/25)
Starting dose of evocalcet	1 mg	75.0 (24/32)
	2 mg	57.1 (4/7)

Percentage of patients achieving the endpoint, % (n/N)

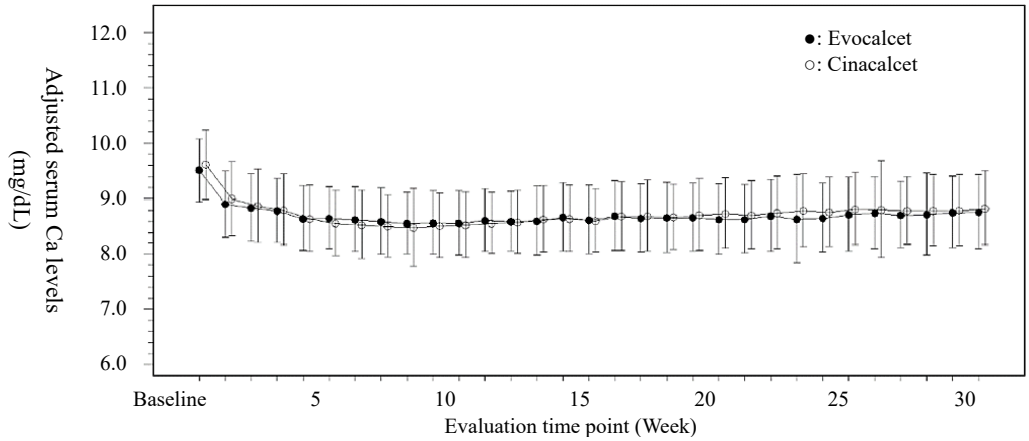
7.R.2 Effect on serum Ca, serum P, and bone metabolism

Since controlling not only serum iPTH levels but also serum Ca and P levels is important in the treatment of SHPT, serum Ca and P levels were investigated. The reviews presented in Sections 7.R.2.1 and 7.R.2.2 below showed that, in the Japanese phase III comparative study, decreases in adjusted serum Ca levels and serum P levels in the evocalcet group were comparable to those in the cinacalcet group. Based on these results, PMDA considers that adjusted serum Ca levels and serum P levels should be closely monitored in patients receiving evocalcet, as is the case with those on

treatment with cinacalcet. The review presented in Section 7.R.2.3 below confirmed that changes in bone metabolism markers in patients receiving evocalcet were similar to those in patients receiving cinacalcet. However, PMDA considers that information on the effect of evocalcet on bone metabolism should be collected in the post-marketing surveillance, etc.

7.R.2.1 Adjusted serum Ca

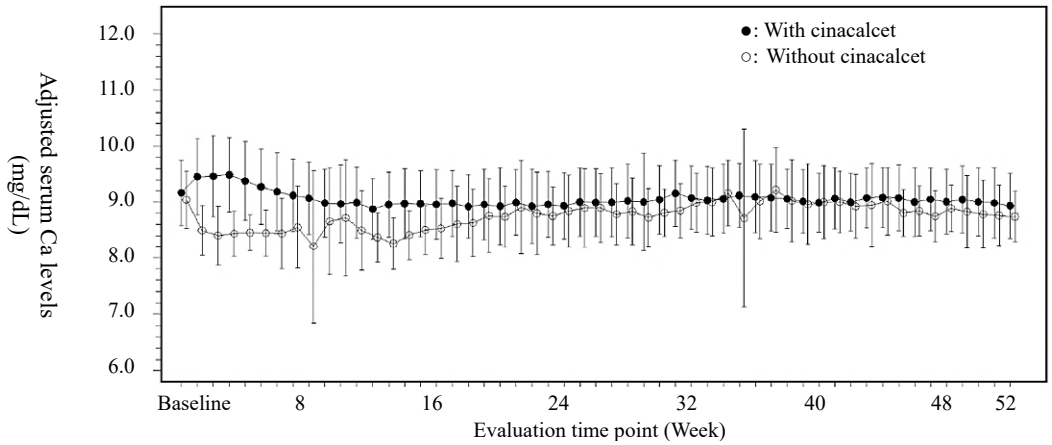
Figure 4 shows changes over time in adjusted serum Ca levels (mean ± SD) in the Japanese phase III comparative study in patients on HD. In patients receiving evocalcet, adjusted serum Ca levels decreased over time until Week 4 in a similar manner to those in patients receiving cinacalcet, and then remained at almost the same level.



Evaluation time point (Week)	Baseline	2	4	8	12	16	20	24	28	30
Evocalcet (N)	253	253	252	253	251	251	253	251	253	250
Cinacalcet (N)	266	266	264	264	264	266	266	265	266	266

Figure 4. Changes over time in adjusted serum Ca levels (mean ± SD)
(Japanese phase III comparative study, PPS)

Figure 5 shows changes over time in adjusted serum Ca levels (mean ± SD) in the long-term treatment study in patients on HD. In the subgroup of patients not receiving cinacalcet 1 day before the start of treatment with evocalcet, adjusted serum Ca levels decreased after the start of treatment with evocalcet, as observed in the Japanese phase III comparative study. In contrast, in the subgroup of patients receiving cinacalcet previously (the population that switched from cinacalcet to evocalcet), serum Ca levels tended to increase after the start of treatment with evocalcet. An analysis of data from patients receiving different doses of cinacalcet revealed an increase in adjusted serum Ca levels in patients treated with ≥37.5 mg of cinacalcet. However, the dose of evocalcet was adjusted from Week 3 onward according to the criteria shown in Table 34. Adjusted serum Ca levels decreased starting at Week 4 and, from Week 8 onward, tended to remain at almost the same level before the switching.



Evaluation time point (Week)	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52
Evocalcet (N)	137	136	131	127	126	124	122	122	122	119	117	117	115	113
With Cinacalcet (N)	113	112	107	104	104	102	100	100	100	99	97	97	95	93
Without Cinacalcet (N)	24	24	24	23	22	22	22	22	22	20	20	20	20	20

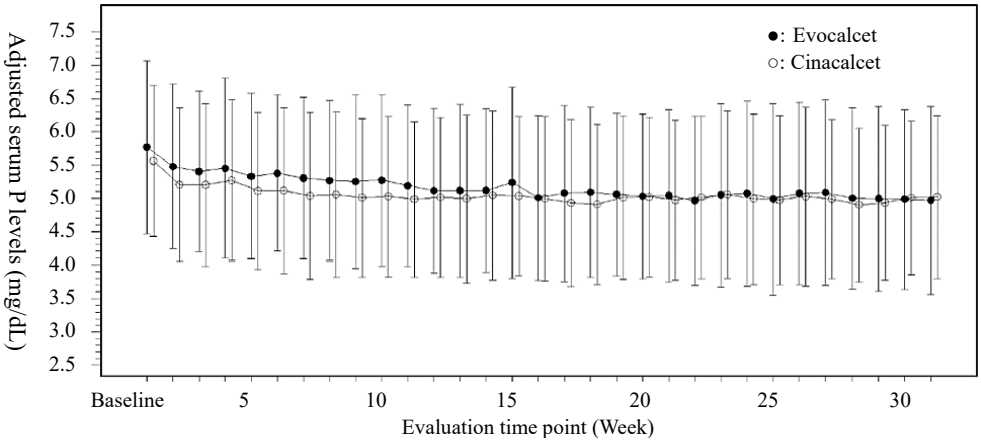
Figure 5. Changes over time in serum Ca levels (mean ± SD)
(Japanese long-term treatment study)

In the Japanese open-label clinical study in patients on PD, adjusted serum Ca levels (mean ± SD) decreased from 9.13 ± 0.50 mg/dL at baseline to 8.52 ± 0.48 mg/dL at Week 2, and then remained at almost the same level, namely 8.73 ± 0.59 mg/dL at Week 24, and 8.60 ± 0.53 mg/dL at Week 52.

PMDA's view:
Attention should be paid to the decrease in adjusted serum Ca levels associated with treatment with evocalcet. This precautionary statement should be included in the package insert of evocalcet [see Sections 7.R.3.3.2 and 7.R.6]. In addition, information on changes in adjusted serum Ca levels after switching from cinacalcet to evocalcet should be collected in the post-marketing surveillance, etc.

7.R.2.2 Serum P

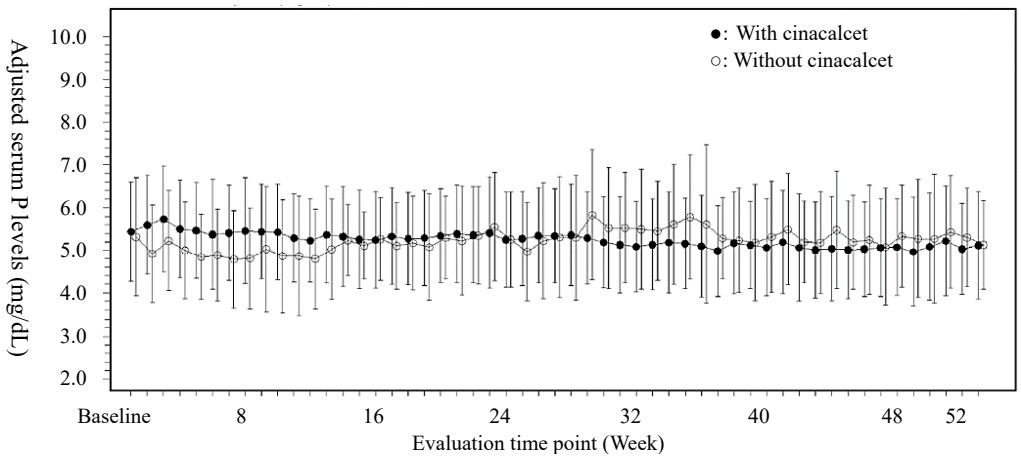
Figure 6 shows changes over time in serum P levels (mean ± SD) in the Japanese phase III comparative study in patients on HD. Serum P levels decreased more gradually in the evocalcet group than in the cinacalcet group and the two groups showed a similar time-course change from Week 18 onward.



Evaluation time point (Week)	Baseline	2	4	8	12	16	20	24	28	30
Evocalcet (N)	253	253	252	253	251	251	253	251	253	250
Cinacalcet (N)	266	266	265	264	264	266	266	265	266	266

Figure 6. Changes over time in serum P levels (mean ± SD)
(Japanese phase III comparative study, PPS)

Figure 7 shows changes over time in serum P levels (mean ± SD) in the long-term treatment study in patients on HD. In the subgroup of patients not receiving cinacalcet 1 day before the start of treatment with evocalcet, serum P levels decreased after the start of treatment with evocalcet, as observed in the Japanese phase III comparative study. In contrast, in the subgroup of patients receiving cinacalcet (the population that switched from cinacalcet to evocalcet), serum P levels tended to increase slightly after the start of treatment with evocalcet but tended to decrease starting at Week 3. However, the dose of evocalcet was adjusted according to the criteria shown in Table 34, and then serum P levels returned to almost the same level as that before the switching by Week 4.



Evaluation time point (Week)	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52
Evocalcet (N)	137	136	131	127	126	124	122	122	122	119	117	117	115	113
With cinacalcet (N)	113	112	107	104	104	102	100	100	100	99	97	97	95	93
Without cinacalcet (N)	24	24	24	23	22	22	22	22	22	20	20	20	20	20

Figure 7. Changes over time in serum P levels (mean ± SD)
(long-term treatment study)

In the Japanese open-label clinical study in patients on PD, serum P levels (mean ± SD) were 4.86 ± 1.07 mg/dL at baseline, 4.87 ± 1.19 mg/dL at Week 24, and 4.48 ± 1.10 mg/dL at Week 52.

PMDA's view:
Evocalcet decreased serum P levels, but only to the same extent as observed in treatment with cinacalcet, showing no tendency of posing any clinical problem. Information on changes in serum P levels after switching from cinacalcet to evocalcet should be collected in the post-marketing surveillance, etc.

7.R.2.3 Effect on bone metabolism

Table 43 shows the levels of bone type alkaline phosphatase (BAP), total procollagen I N-terminal propeptide (total P1NP), and tartrate-resistant acid phosphatase 5b (TRACP-5b) at the start and end of study treatment in the Japanese phase III comparative study and the Japanese long-term treatment study, both in patients on HD, and in the Japanese open-label clinical study in patients on PD.

BAP changed little from baseline in the Japanese phase III comparative study but, in the long-term treatment study and the Japanese open-label clinical study, decreased at the end of study treatment compared to the baseline level. TRACP-5b and total P1NP decreased at the end of study treatment compared to the baseline level in all of the above studies.

Table 43. Bone metabolism markers at the start and end of study treatment (Japanese phase III comparative study, Japanese long-term treatment study, Japanese open-label clinical study)

Study		BAP (μg/L)		TRACP-5b (mU/dL)		Total P1NP (μg/L)	
		Start of treatment	End of treatment[a)]	Start of treatment	End of treatment[a)]	Start of treatment	End of treatment[a)]
Japanese phase III comparative study (PPS)	Evocalcet (N = 253)	17.6 ± 9.9 (253)	16.4 ± 11.0 (250)	783.2 ± 394.5 (253)	462.2 ± 302.4 (250)	437.3 ± 287.5 (253)	286.1 ± 220.5 (250)
	Cinacalcet (N = 266)	17.4 ± 9.9 (266)	17.1 ± 11.0 (266)	859.3 ± 429.5 (266)	561.0 ± 348.9 (266)	446.7 ± 266.9 (266)	320.0 ± 230.3 (266)
Japanese long-term treatment study (N = 137)		16.4 ± 8.0 (137)	14.4 ± 6.0 (113)	670.5 ± 335.2 (137)	473.0 ± 260.3 (113)	358.6 ± 203.0 (137)	230.0 ± 129.4 (113)
Japanese open-label clinical study (N = 39)		17.6 ± 10.4 (39)	13.5 ± 5.0 (24)	646.7 ± 338.3 (39)	301.2 ± 241.2 (24)	282.9 ± 211.3 (39)	177.5 ± 156.4 (24)

Mean ± SD (n)
a) Week 30 in the Japanese phase III comparative study, Week 52 in the Japanese long-term treatment study and in the Japanese open-label clinical study

The applicant's explanation about the effect of evocalcet on bone metabolism, based on the results of the Japanese phase III comparative study, the Japanese long-term treatment study, and the Japanese open-label clinical study:
It is known that, in patients with SHPT, excessive PTH secretion enhances bone turnover, resulting in osteitis fibrosa which is a cause of bone fracture and bone pain. For this reason, PTH levels should be decreased to improve the excessively enhanced bone turnover in these patients (Clinical Practice Guideline for CKD-MBD 2012).

In the Japanese phase III comparative study of evocalcet, a bone formation marker BAP tended to increase transiently and then decrease. A similar tendency was reported in studies of drugs in the same class, i.e., the Japanese phase III placebo-controlled study of cinacalcet (Study KRN1493/04-A10) and

the Japanese phase III study of etelcalcetide hydrochloride (*Nephrol Dial Transplant.* 2017;32:1723-30, etc.). These findings suggest that the transient increase in BAP is attributable to a decrease in PTH levels. On the other hand, in the Japanese long-term treatment study and the Japanese open-label clinical study on evocalcet, BAP decreased and the bone resorption marker TRACP-5b and the bone formation marker total P1NP also decreased. The results with these bone metabolism markers suggest that evocalcet may improve high-turnover bone disorder in patients with SHPT by suppressing excess PTH and maintaining it within the target range.

Thus, although the possibility cannot be excluded that a rapid or excessive decrease in PTH levels may cause abnormal bone metabolism, no abnormal bone metabolism-related adverse drug reactions were observed in Japanese clinical studies. Therefore, evocalcet-induced bone metabolism abnormality can be prevented by controlling PTH levels appropriately and by avoiding extreme hypocalcemia and hypophosphatemia. For this purpose, the following precautionary statements will be included in the package insert of evocalcet: (1) PTH levels should be monitored periodically during the treatment with evocalcet in order to maintain blood PTH levels within the target range, and (2) a rapid or excessive decrease in PTH levels may result in the onset of abnormal bone metabolism-related events such as adynamic bone disease and hungry bone syndrome. Information on the incidence of abnormal bone metabolism-related events will be collected continuously in the post-marketing setting.

PMDA's view:
It is appropriate to include the following precautionary statements in the package insert of evocalcet: (1) PTH levels should be monitored periodically during the treatment with evocalcet in order to maintain blood PTH levels within the target range, and (2) a rapid or excessive decrease in PTH may result in the onset of adynamic bone disease and hungry bone syndrome. Information on the occurrence of abnormal bone metabolism-related events should be collected continuously in the post-marketing setting.

7.R.3 Safety

On the basis of the reviews presented in Sections 7.R.3.1 to 7.R.3.4 below, PMDA considers that the safety of evocalcet in patients with SHPT on dialysis is acceptable provided that the dose of evocalcet is adjusted appropriately while serum Ca levels, etc., is monitored. The final decision on the safety of evocalcet will be made, taking account of comments raised in the Expert Discussion.

7.R.3.1 Patients on HD

7.R.3.1.1 Comparison of safety (evocalcet versus placebo or cinacalcet)

In the Japanese phase II study in patients on HD, clinically relevant adverse events did not tend to occur more frequently in any of the evocalcet groups than in the placebo or cinacalcet group [see Section 7.1]. No death or serious adverse drug reaction occurred in any of the treatment groups.

In the Japanese phase III comparative study in patients on HD, adverse events related to upper gastrointestinal disorder and to hypocalcemia occurred relatively frequently in both evocalcet and cinacalcet groups, but the incidence of adverse events did not tend to be significantly higher in the evocalcet group than in the cinacalcet group. Death occurred in 1 patient in the evocalcet group (acute

pancreatitis). Its causal relationship to study drug could not be ruled out, but what extent evocalcet was related to the event remains unclear, judging from the complications and clinical course.[14)] No clinically significant difference was observed between the evocalcet group and the cinacalcet group in the profiles of serious adverse events and adverse drug reactions or in the profiles of adverse events and adverse drug reactions leading to discontinuation or interruption of study treatment.

PMDA confirmed that there was no clinically significant tendency in the evocalcet group compared with the cinacalcet group. Events related to upper gastrointestinal disorder, which occurred relatively frequently, is discussed in Section 7.R.3.3.1, and events related to hypocalcemia, which require attention during treatment with evocalcet, in Section 7.R.3.3.2.

7.R.3.1.2 Long-term safety

Table 36 shows adverse events reported in ≥5.0% of patients in the Japanese long-term treatment study. There was no clinically significant difference in the profiles of adverse events between the Japanese long-term treatment study and the Japanese phase III comparative study. Table 44 shows the incidence of adverse events by treatment period. There was no clinically significant tendency toward a relationship between the treatment period and the incidence of adverse events.

Table 44. Incidence of adverse events by treatment period (Japanese long-term treatment study)

	Weeks 1-12	Weeks 13-25	Weeks 26-38	Weeks 39-52	Entire period
	N = 137	N = 129	N = 123	N = 119	N = 137
Adverse events	80.3 (110)	76.0 (98)	78.0 (96)	85.7 (102)	99.3 (136)
Adverse drug reactions	21.2 (29)	15.5 (20)	14.6 (18)	9.2 (11)	35.0 (48)
Serious adverse events	8.0 (11)	4.7 (6)	11.4 (14)	12.6 (15)	29.9 (41)
Serious adverse drug reactions	2.2 (3)	0 (0)	0.8 (1)	0.8 (1)	3.6 (5)
Adverse events leading to treatment discontinuation	2.2 (3)	1.6 (2)	2.4 (3)	0.8 (1)	6.6 (9)
Adverse drug reactions leading to treatment discontinuation	0 (0)	0 (0)	1.6 (2)	0 (0)	1.5 (2)
Events related to upper gastrointestinal disorder[a)]	10.9 (15)	8.5 (11)	13.0 (16)	7.6 (9)	24.1 (33)
Events related to hypocalcemia[b)]	4.4 (6)	5.4 (7)	2.4 (3)	2.5 (3)	10.9 (15)

MedDRA/J ver. 19.0; Incidence, % (n)

a) Abdominal discomfort, abdominal distension, nausea, vomiting, decreased appetite, and abdominal pain upper in the preferred terms of Medical Dictionary for Regulatory Activities (MedDRA)

b) Adjusted calcium decreased, blood calcium decreased, and hypocalcaemia in the preferred terms of MedDRA

7.R.3.2 Patients on PD

Table 39 shows adverse events reported in ≥5.0% of patients in the Japanese open-label clinical study in patients on PD. Except for the events related to PD procedures (catheter site infection and peritonitis), adverse events observed in the Japanese open-label clinical study were not significantly different from those observed in the Japanese phase III comparative study or the Japanese long-term treatment study. Table 45 shows the incidences of adverse events by treatment period. There was no clinically significant tendency toward a relationship between the treatment period and the incidence of adverse events.

Table 45. Incidences of adverse events by treatment period (Japanese open-label clinical study)

	Weeks 1-12	Weeks 13-25	Weeks 26-38	Weeks 39-52	Entire period
	N = 39	N = 38	N = 34	N = 27	N = 39
Adverse events	76.9 (30)	76.3 (29)	70.6 (24)	74.1 (20)	100.0 (39)
Adverse drug reactions	25.6 (10)	10.5 (4)	14.7 (5)	18.5 (5)	46.2 (18)
Serious adverse events	10.3 (4)	23.7 (9)	17.6 (6)	11.1 (3)	41.0 (16)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	2.6 (1)	8.8 (3)	3.7 (1)	12.8 (5)
Adverse drug reactions leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Events related to upper gastrointestinal disorder	10.3 (4)	0 (0)	0 (0)	11.1 (3)	15.4 (6)
Events related to hypocalcemia	10.3 (4)	5.3 (2)	8.8 (3)	7.4 (2)	23.1 (9)

MedDRA/J ver. 19.0; Incidence, % (n)

7.R.3.3 Safety by patient characteristics

Table 46 shows the incidence of adverse events, analyzed by patient characteristics, in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study). No clinically significant tendency was observed in any of the subgroups.

Table 46. Incidence of adverse events, analyzed by patient characteristics, in Japanese phase III studies (safety analysis sets in Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study)

Patient characteristics	Subgroup	Japanese phase III comparative study		Japanese long-term treatment study	Japanese open-label clinical study	Total
		Evocalcet (N = 317)	Cinacalcet (N = 317)	Evocalcet (N = 137)	Evocalcet (N = 39)	Evocalcet (N = 493)
Sex	Male	90.1 (200/222)	89.4 (202/226)	100 (81/81)	100 (23/23)	93.3 (304/326)
	Female	92.6 (88/95)	95.6 (87/91)	98.2 (55/56)	100 (16/16)	95.2 (159/167)
Age	<65	91.7 (155/169)	89.0 (161/181)	100 (83/83)	100 (21/21)	94.9 (259/273)
	≥65	89.9 (133/148)	94.1 (128/136)	98.1 (53/54)	100 (18/18)	92.7 (204/220)
Baseline iPTH levels (pg/mL)	<500	89.2 (223/250)	90.4 (216/239)	99.2 (123/124)	100 (26/26)	93.0 (372/400)
	≥500	97.0 (65/67)	93.6 (73/78)	100 (13/13)	100 (13/13)	97.8 (91/93)
Baseline adjusted serum Ca levels (mg/dL)	<9.5	91.0 (141/155)	90.0 (126/140)	99.0 (97/98)	100 (28/28)	94.7 (266/281)
	≥9.5	90.7 (147/162)	92.1 (163/177)	100 (39/39)	100 (11/11)	92.9 (197/212)
Use of cinacalcet before screening	No	90.6 (115/127)	88.6 (93/105)	100 (20/20)	100 (30/30)	93.2 (165/177)
	Yes	91.1 (173/190)	92.5 (196/212)	99.1 (116/117)	100 (9/9)	94.3 (298/316)
Use of concomitant activated vitamin D at the start of treatment	No	94.3 (50/53)	91.7 (33/36)	100 (18/18)	100 (14/14)	96.5 (82/85)
	Yes	90.2 (238/264)	91.1 (256/281)	99.2 (118/119)	100 (25/25)	93.4 (381/408)
Starting dose of evocalcet	1 mg	89.8 (220/245)	-	99.2 (131/132)	100 (32/32)	93.6 (383/409)
	2 mg	94.4 (68/72)	-	100 (5/5)	100 (7/7)	95.2 (80/84)

MedDRA/J ver. 19.0; Incidence, % (n/N)

7.R.3.4 Adverse events of special interests associated with evocalcet

Taking account of the findings that adverse drug reactions related to upper gastrointestinal disorder occured in a certain percentage of patients receiving cinacalcet, a drug in the same class, and that evocalcet decreases blood Ca levels, the applicant investigated events related to upper gastrointestinal disorder or to hypocalcemia.

7.R.3.4.1 Events related to upper gastrointestinal disorder

The applicant's explanation about the events related to upper gastrointestinal disorder observed in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study):

Table 47 shows the incidence of events related to upper gastrointestinal disorder (abdominal discomfort, abdominal distension, nausea, vomiting, decreased appetite, and abdominal pain upper in the preferred terms of Medical Dictionary for Regulatory Activities [MedDRA]) observed in the Japanese phase III studies. Events related to upper gastrointestinal disorder were observed in 21.1% (104 of 493) of patients in all evocalcet groups combined, but most of them were mild in severity, with no severe events observed. In the Japanese phase III comparative study, events related to upper gastrointestinal disorder were observed in 20.5% (65 of 317) of patients in the evocalcet group and in 34.1% (108 of 317) of patients in the cinacalcet group, showing that events related to upper gastrointestinal disorder tends to less frequently occur in the evocalcet group than in the cinacalcet group.

Table 47. Adverse events related to upper gastrointestinal disorder (safety analysis sets in Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study)

	Japanese phase III comparative study		Japanese long-term treatment study	Japanese open-label clinical study	Total
	Evocalcet (N = 317)	Cinacalcet (N = 317)	Evocalcet (N = 137)	Evocalcet (N = 39)	Evocalcet (N = 493)
Events related to upper gastrointestinal disorder	20.5 (65)	34.1 (108)	24.1 (33)	15.4 (6)	21.1 (104)
Vomiting	8.5 (27)	11.7 (37)	8.8 (12)	7.7 (3)	8.5 (42)
Nausea	7.3 (23)	14.2 (45)	11.7 (16)	2.6 (1)	8.1 (40)
Abdominal discomfort	4.4 (14)	11.0 (35)	8.8 (12)	2.6 (1)	5.5 (27)
Abdominal pain upper	3.2 (10)	1.6 (5)	2.2 (3)	0 (0)	2.6 (13)
Decreased appetite	2.5 (8)	3.5 (11)	0.7 (1)	5.1 (2)	2.2 (11)
Abdominal distension	0.6 (2)	2.2 (7)	1.5 (2)	0 (0)	0.8 (4)

MedDRA/J ver. 19.0; Incidence, % (n)

PMDA's view:

There is no clinically significant problems, taking account of the following findings: (1) Most of the events related to upper gastrointestinal disorder such as vomiting and nausea observed in evocalcet-treated patients in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study) were mild, and (2) events related to upper gastrointestinal disorder tended to less frequently occur in the evocalcet group than in the cinacalcet group in the Japanese phase III comparative study. However, information on events related to upper gastrointestinal disorder should be continuously collected in the post-marketing surveillance, etc., because such events occurred in a certain percentage of patients.

7.R.3.4.2 Events related to hypocalcemia

The applicant's explanation about the events related to hypocalcemia observed in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study):

Table 48 shows the incidence of events related to hypocalcemia (blood calcium decreased, adjusted calcium decreased, and hypocalcaemia in the preferred terms of MedDRA) observed in the Japanese phase III studies. Events related to hypocalcemia were observed in 16.8% (83 of 493) of patients in all

evocalcet groups combined, and considered to be adverse drug reactions. However, no serious or severe events occurred and most of them were mild in severity and controllable. In all evocalcet groups combined, hypocalcemia-related events leading to discontinuation or interruption of study treatment were adjusted calcium decreased in 2.4% (12 of 493) of patients, blood calcium decreased in 8.7% (43 of 493) of patients, and hypocalcaemia in 0.8% (4 of 493) of patients. Most of these events resolved after treatment discontinuation or interruption. In the Japanese phase III comparative study, the incidence of hypocalcemia-related events was 18.6% (59 of 317) of patients in the evocalcet group and 24.3% (77 of 317) of patients in the cinacalcet group, showing that hypocalcemia-related events occurred less frequently in the evocalcet group than in the cinacalcet group.

Table 48. Adverse events related to hypocalcemia (safety analysis sets in Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study)

	Japanese phase III comparative study		Japanese long-term treatment study	Japanese open-label clinical study	Total
	Evocalcet (N = 317)	Cinacalcet (N = 317)	Evocalcet (N = 137)	Evocalcet (N = 39)	Evocalcet (N = 493)
Events related to hypocalcemia	18.6 (59)	24.3 (77)	10.9 (15)	23.1 (9)	16.8 (83; mild in 75, moderate in 8)
Adjusted calcium decreased	11.7 (37)	15.8 (50)	7.3 (10)	17.9 (7)	11.0 (54; mild in 48, moderate in 6)
Blood calcium decreased	3.5 (11)	7.6 (24)	3.6 (5)	5.1 (2)	3.7 (18; mild in 17, moderate in 1)
Hypocalcaemia	3.5 (11)	1.3 (4)	0 (0)	0 (0)	2.2 (11; mild in 10, moderate in 1)

MedDRA/J ver. 19.0; Incidence, % (n)

The applicant also investigated other events possibly related to decreased blood Ca levels, namely arrhythmia associated with QT/QTc interval prolongation, adverse events suggestive of pro-arrhythmic potential, and lenticular opacities.

As adverse events related to arrhythmia associated with QT/QTc interval prolongation, incidences of adverse events coded to torsade de pointes/QT prolongation in MedDRA SMQ were investigated. Table 49 shows the incidences of adverse events coded to torsade de pointes/QT prolongation in the Japanese phase III studies. Adverse events coded to torsade de pointes/QT prolongation occurred in 1.6% (8 of 493) of patients in all evocalcet groups combined. Of the 8 patients, 3 patients had electrocardiogram QT prolonged that was considered to be adverse drug reactions. However, there were no serious or severe events. In the Japanese phase III comparative study, adverse events coded to torsade de pointes/QT prolongation occurred in 0.9% (3 of 317) of patients in the evocalcet group and in 2.8% (9 of 317) of patients in the cinacalcet group.

Table 49. Adverse events related to arrhythmia associated with QT/QTc interval prolongation (Safety analysis sets in Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study)

	Japanese phase III comparative study		Japanese long-term treatment study	Japanese open-label clinical study	Total
	Evocalcet (N = 317)	Cinacalcet (N = 317)	Evocalcet (N = 137)	Evocalcet (N = 39)	Evocalcet (N = 493)
Event related to torsade de pointes/QT prolongation	0.9 (3)	2.8 (9)	3.6 (5)	0 (0)	1.6 (8; mild in 6, moderate in 2)
Loss of consciousness	0.3 (1)	0.6 (2)	2.9 (4)	0 (0)	1.0 (5; mild in 3, moderate in 2)
Electrocardiogram QT prolonged	0.6 (2)	2.2 (7)	0.7 (1)	0 (0)	0.6 (3; mild in 3)

MedDRA/J ver. 19.0; Incidence, % (n)

As adverse events suggestive of pro-arrhythmic potential, incidences of events classified as epileptic seizure, sudden death, syncope, torsade de pointes, ventricular fibrillation, ventricular flutter, and ventricular tachycardia in the preferred terms of MedDRA were investigated. Adverse events suggestive of pro-arrhythmic potential were not observed in the Japanese phase III comparative study or the Japanese open-label clinical study, whereas epilepsy was observed in 0.7% (1 of 137) of patients in the Japanese long-term treatment study. Its causal relationship to the study drug was ruled out.

Table 50 shows the incidences of adverse events related to lenticular opacities, i.e., events coded to lens disorder in MedDRA SMQ. Adverse events coded to lens disorder occurred in 2.4% (12 of 493) of patients in all evocalcet groups combined. There were no severe events. Cataract operation in 2 patients and cataract in 1 patient were serious events. None of these patients showed hypocalcemia-related events at the onset of these events. In the Japanese phase III comparative study, adverse events coded to lens disorder occurred in 0.9% (3 of 317) of patients in the evocalcet group and in 1.3% (4 of 317) of patients in the cinacalcet group.

Table 50. Adverse events related to lens disorder (safety analysis sets in Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study)

	Japanese phase III comparative study		Japanese long-term treatment study	Japanese open-label clinical study	Total
	Evocalcet (N = 317)	Cinacalcet (N = 317)	Evocalcet (N = 137)	Evocalcet (N = 39)	Evocalcet (N = 493)
Events coded to lens disorder	0.9 (3)	1.3 (4)	6.6 (9)	0 (0)	2.4 (12; mild in 8, moderate in 4)
Cataract	0.3 (1)	0.3 (1)	4.4 (6)	0 (0)	1.4 (7; mild in 4, moderate in 3)
Cataract operation	0 (0)	0.3 (1)	1.5 (2)	0 (0)	0.4 (2; mild in 1, moderate in 1)
Posterior capsule opacification	0.3 (1)	0 (0)	0 (0)	0 (0)	0.2 (1, mild)
Visual acuity reduced	0.3 (1)	0.3 (1)	0 (0)	0 (0)	0.2 (1, mild)
Visual impairment	0 (0)	0 (0)	0.7 (1)	0 (0)	0.2 (1, mild)
Vision blurred	0 (0)	0.3 (1)	0 (0)	0 (0)	0 (0)

MedDRA/J ver. 19.0; Incidence, % (n)

The excessive pharmacological action of evocalcet may cause a risk of hypocalcemia or arrythmia associated with QT/QTc interval prolongation induced by decreased blood Ca levels. However, the incidences of these events in the evocalcet group were not significantly different from those in the cinacalcet group. Therefore, similarly to cinacalcet, evocalcet is unlikely to pose any clinically significant problem provided that the following precautions are advised: (1) Prior to the start of

treatment with evocalcet, serum Ca levels of the patient should be confirmed not to be low, and (2) serum Ca levels should be monitored appropriately during the treatment with evocalcet.

PMDA's view:
The protocols of the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study) included the criteria specifying that evocalcet should be started in patients with adjusted serum Ca levels ≥8.4 mg/dL, and the criteria for dose increase, dose reduction, and discontinuation based on serum Ca levels (Tables 26, 34, and 38). Therefore, although hypocalcemia-related events were observed in a certain percentage of patients, their incidence did not tend to be higher in the evocalcet group than in the cinacalcet group (Table 48). Also, neither severe hypocalcemia nor serious adverse events associated with hypocalcemia tended to increase in the evocalcet group. No clinically significant tendency was observed in the evocalcet group regarding adverse events related to arrythmia associated with QT/QTc interval prolongation (Table 49), adverse events suggestive of pro-arrhythmic potential, or adverse events related to lenticular opacities (Table 50).

Based on the above, in order to prevent serious adverse events caused by decreased serum Ca levels associated with the use of evocalcet, serum Ca levels should be monitored before and during the treatment with evocalcet, and the dose of evocalcet should be adjusted based on serum Ca levels, as were the cases with the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study) [see Section 7.R.6.2].

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of evocalcet:
In Japan, the Clinical Practice Guideline for CKD-MBD 2012 specifies the target levels for serum P, Ca, and PTH levels, and recommends the administration of activated vitamin D in patients with normal or low serum P or Ca levels, cinacalcet in patients with normal or high serum P or Ca levels, and also cinacalcet patients with high PTH levels. However, upper gastrointestinal disorders such as nausea and vomiting occur in a certain percentage of patients treated with cinacalcet, imposing a burden on patients and contributing to the failure to increase the dose to a sufficiently effective level. In addition to cinacalcet, etelcalcetide hydrochloride, an injection, is approved as a CaR agonist for the treatment of secondary hyperparathyroidism in patients on hemodialysis. In the foreign phase III comparative study of etelcalcetide hydrochloride, the incidences of nausea and vomiting in the etelcalcetide group were similar to those in the cinacalcet group (*JAMA*. 2017;317:156-164).

In the Japanese phase III comparative study in patients on HD, the non-inferiority of evocalcet to cinacalcet was demonstrated, and upper gastrointestinal disorder occurred less frequently in the evocalcet group than in the cinacalcet group. In the Japanese open-label clinical study in patients on PD, the efficacy and safety of evocalcet were similar to those observed in patients on HD. Since cinacalcet is metabolized mainly by CYP3A4 and strongly inhibits CYP2D6, the package insert of cinacalcet provides precautions against co-administration with CYP3A4 inhibitors (such as azole antifungal agents) or with CYP2D6 substrate drugs (such as tricyclic antidepressants). In contrast, evocalcet may be co-administered with CYP3A4 inhibitors and with CYP2D6 substrate drugs because

both the contribution of CYP isoforms to evocalcet metabolism and the inhibition of evocalcet against CYP isoforms are extremely low.

These results demonstrate that the clinical positioning of evocalcet is similar to that of cinacalcet for the treatment of SHPT. At the same time, evocalcet is expected to reduce the onset of upper gastrointestinal disorder compared with cinacalcet and can be used in combination with CYP3A4 inhibitors and CYP2D6 substrate drugs.

PMDA's view:
The Japanese phase III comparative study in patients on HD demonstrated the non-inferiority of evocalcet to cinacalcet, and the Japanese open-label clinical study in patients on HD suggested the efficacy of evocalcet in patients on PD [Section 7.R.1]. Further, the data from Japanese studies (Japanese phase II study, Japanese phase III comparative study, Japanese open-label clinical study, and Japanese long-term treatment study) demonstrated that evocalcet has acceptable safety profiles both in patients on HD and patients on PD [Section 7.R.3]. Based on the above, the clinical positioning of evocalcet is similar to that of cinacalcet and evocalcet serves as one of the options for the treatment of patients with SHPT on maintenance dialysis.

7.R.5 Indication

The Japanese phase III comparative study in patients on HD demonstrated the efficacy of evocalcet [Section 7.R.1.1] and so did the Japanese open-label clinical study in patients on PD [Section 7.R.1.2]. In addition, evocalcet was shown to have acceptable safety profiles by Japanese studies (Japanese phase II study, Japanese phase III comparative study, Japanese open-label clinical study, and Japanese long-term treatment study) [Section 7.R.3]. Based on the above, PMDA considers that evocalcet can be indicated for "secondary hyperparathyroidism in patients on hemodialysis."

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

7.R.6 Dosage and administration

On the basis of the reviews presented in Sections 7.R.6.1 and 7.R.6.2 below, PMDA considers that there is no particular problem in setting the dosage and administration generally in line with the dosage regimen employed in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study). The final decision on the dosage and administration will be made, taking account of comments raised in the Expert Discussion.

7.R.6.1 Starting dose and maximum dose

The applicant's explanation about the starting dose and the maximum dose of evocalcet:
"The mean percent change from baseline in iPTH levels at the end of treatment [95% CI]," which was the primary endpoint of the Japanese phase II study in patients on HD, was −10.56% [−20.45, −0.67] in the evocalcet 1 mg group, −20.16% [−30.40, −9.92] in the evocalcet 2 mg group, and −25.86% [−36.10, −15.62] in the cinacalcet 25 mg group (Table 24). In each of the evocalcet groups and in the cinacalcet 25 mg group, adjusted serum Ca levels decreased after administration of study drug,

showing the maximal change around Day 15 in any of the treatment groups. “The percent decrease from baseline in adjusted Ca levels at Day 15” was −7.38% in the evocalcet 1 mg group, −8.62% in the evocalcet 2 mg group, and −7.70% in the cinacalcet 25 mg group. These results suggested that the effects of 2 mg evocalcet to lower iPTH levels and adjusted serum Ca levels are similar to those of 25 mg cinacalcet.

In the Japanese phase II study, study treatment was discontinued due to adverse events related to decreased blood Ca levels or due to decrease in blood Ca levels in 1 of 30 patients (3.3%) in the evocalcet 1 mg group, 3 of 30 patients (10.0%) in the evocalcet 2 mg group, 1 of 30 patients (3.3%) in the placebo group, and 2 of 30 patients (6.7%) in the cinacalcet 25 mg group, showing a higher incidence of discontinuation in the evocalcet 2 mg group than in the evocalcet 1 mg group. Therefore, for the safety of patients, 1 mg was considered to be appropriate as the recommended starting dose of evocalcet.

However, since the Clinical Practice Guideline for CKD-MBD 2012 classifies patients with iPTH levels ≥500 pg/mL as patients with severe SHPT, the starting dose of 2 mg of evocalcet is expected to exhibit its therapeutic effect promptly in patients with SHPT with iPTH levels ≥500 pg/mL and adjusted Ca levels ≥9.0 mg/dL. The safety of evocalcet administered at the starting dose of 2 mg was evaluated based on the results of the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study), the details of which are provided below. The incidence of adverse events during the early period after the start of study treatment (Weeks 0-7), i.e., the period when the difference in the starting dose is expected to have the greatest effect, was 62.0% (152 of 245) of patients in the subgroup receiving the starting dose of 1 mg and 58.3% (42 of 72) of patients in the subgroup receiving 2 mg in the Japanese phase III comparative study; 67.4% (89 of 132) of patients in the 1 mg subgroup and 80.0% (4 of 5) of patients in the 2 mg subgroup in the Japanese long-term treatment study; and 53.1% (17 of 32) of patients in the 1 mg subgroup and 28.6% (2 of 7) of patients in the 2 mg subgroup in the Japanese open-label clinical study, showing no clear tendency toward higher incidence of adverse events in the evocalcet 2 mg subgroup than in the evocalcet 1 mg subgroup. Table 51 shows the incidences of adverse events and of hypocalcemia-related events within 14 days after the start of study treatment in the Japanese phase III comparative study. No significant difference was observed in the incidences between the starting dose of 1 mg and 2 mg.

Table 51. Incidences of adverse events and hypocalcemia-related events by starting dose of evocalcet within 14 days after the start of study treatment (safety analysis set of Japanese phase III comparative study)

	Evocalcet		Cinacalcet	
	1 mg (N = 245)	2 mg (N = 72)	iPTH <500 pg/mL[a)] (N = 247)	iPTH ≥500 pg/mL[a)] (N = 70)
Adverse events	22.0 (54)	20.8 (15)	28.3 (70)	28.6 (20)
Events related to hypocalcemia	0.8 (2)	1.4 (1)	2.0 (5)	1.4 (1)
Adjusted calcium decreased	0.4 (1)	1.4 (1)	1.2 (3)	0 (0)
Blood calcium decreased	0.4 (1)	0 (0)	0.8 (2)	1.4 (1)
Hypocalcaemia	0 (0)	0 (0)	0 (0)	0 (0)

MedDRA/J ver. 19.0; Incidence, % (n)

a) In the cinacalcet group, results were tabulated by iPTH concentration at the screening test.

As described above, the results of the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study) demonstrated the safety of evocalcet administered to patients with iPTH levels ≥500 pg/mL and adjusted serum Ca levels ≥9.0 mg/dL. The applicant therefore considered that the starting dose of 2 mg of evocalcet is appropriate in this patient population.

Since evocalcet lowers serum Ca levels, it is essential to measure serum Ca levels at baseline. In the Japanese phase III comparative study which used cinacalcet as the comparator, the baseline adjusted serum Ca level of ≥9.0 mg/dL was selected by referring to the package insert of cinacalcet ("Package insert for Regpara Tablets 12.5 mg, etc." eighth edition, revised in June 2015). On the other hand, in the Japanese long-term treatment study and the Japanese open-label clinical study, the baseline adjusted serum Ca level of ≥8.4 mg/dL was selected, taking into account that the Clinical Practice Guideline for CKD-MBD 2012 recommends controlling the adjusted serum Ca levels in patients with SHPT within the range from 8.4 to 10.0 mg/dL. The studies produced no significant safety problems. Based on the above, physicians will be advised to confirm that the baseline serum Ca level is ≥8.4 mg/dL before the start of treatment with evocalcet, as a rule.

The applicant's explanation about the maximum dose of evocalcet:
The maximum dose of evocalcet was 8 mg in the Japanese phase III comparative study and 12 mg in the long-term treatment study and the open-label clinical study, for the reasons shown below.

The Japanese phase III comparative study was a double-blind study. The maximum dose of evocalcet and the treatment duration were determined by referring to the dosage regimen for the comparator cinacalcet and to the results of the Japanese phase II study in patients on HD. In the Japanese phase II study, evocalcet 2 mg and cinacalcet 25 mg exhibited similar lowering effects on iPTH levels and adjusted serum Ca levels, suggesting that the clinical effect of cinacalcet 25 mg is similar to that of evocalcet 2 mg. Since the maximum dose of cinacalcet is 100 mg (4 × 25 mg), a dose of 8 mg (4 × 2 mg) was selected as the maximum dose of evocalcet in the Japanese phase III comparative study. This regimen was expected to allow comparison of the two drugs. Results of the Japanese phase III comparative study confirmed the non-inferiority of evocalcet to cinacalcet and the safety of evocalcet up to 8 mg. In the phase I/II clinical study in patients with SHPT on HD, multiple administration of evocalcet 12 mg was shown to be safe and well tolerated. Therefore, the maximum dose of 12 mg was selected for the Japanese long-term treatment study and the open-label clinical study. Ultimately, evocalcet 12 mg was administered to 10 patients in the Japanese long-term treatment study (Table 53) and to 1 patient in the Japanese open-label clinical study, showing no safety problems. In the 10 patients who received 12 mg in the Japanese long-term treatment study, the dose at Week 24 was 8 or 9 mg. At this time point, none of these patients achieved the target range of iPTH levels (≥60 pg/mL and ≤240 g/mL) but, at Week 52 (the dose was 12 mg), 4 patients achieved the target range. These results suggest that, dose increase to 12 mg (the maximum dose confirmed to be safe in clinical studies) is possible in patients with no adequate response.

In the Japanese phase III comparative study and the Japanese long-term treatment study, approximately 80% of patients were treated with evocalcet at doses ≤6 mg (Tables 52 and 53). Therefore, the dose of evocalcet is to be adjusted within the range from 1 to 6 mg in clinical use.

Table 52. Patients distribution by dose level of evocalcet in Japanese phase III comparative study (PPS)

	Dose of evocalcet								
	0 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	8 mg
Week 1 (N = 253)	0.4 (1)	75.5 (191)	24.1 (61)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 9 (N = 253)	4.7 (12)	15.4 (39)	29.6 (75)	29.2 (74)	15.8 (40)	5.1 (13)	0 (0)	0 (0)	0 (0)
Week 19 (N = 253)	5.5 (14)	14.6 (37)	20.6 (52)	16.6 (42)	15.8 (40)	9.9 (25)	10.7 (27)	4.3 (11)	2.0 (5)
Week 29 (N = 253)	9.9 (25)	15.8 (40)	16.2 (41)	14.2 (36)	13.0 (33)	8.7 (22)	6.7 (17)	7.1 (18)	8.3 (21)

Fraction of patients,% (number of patients)

Table 53. Patient distribution by dose level of evocalcet in Japanese long-term treatment study (FAS)

	Dose of evocalcet												
	0 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	8 mg	9 mg	10 mg	11 mg	12 mg
Week 1 (N = 137)	5.8 (8)	90.5 (124)	3.6 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 12 (N = 129)	8.5 (11)	24.8 (32)	23.3 (30)	20.2 (26)	11.6 (15)	10.9 (14)	0.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Week 24 (N = 124)	4.0 (5)	29.8 (37)	20.2 (25)	14.5 (18)	7.3 (9)	7.3 (9)	0.8 (1)	2.4 (3)	10.5 (13)	2.4 (3)	0.8 (1)	0 (0)	0 (0)
Week 36 (N = 120)	1.7 (2)	32.5 (39)	23.3 (28)	6.7 (8)	9.2 (11)	5 (6)	2.5 (3)	3.3 (4)	3.3 (4)	4.2 (5)	0.8 (1)	1.7 (2)	5.8 (7)
Week 51 (N = 114)	6.1 (7)	27.2 (31)	25.4 (29)	6.1 (7)	6.1 (7)	4.4 (5)	2.6 (3)	3.5 (4)	5.3 (6)	2.6 (3)	0 (0)	1.8 (2)	8.8 (10)

Fraction of patients,% (number of patients)

PMDA's view:

Taking account of the results of the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study) and of the applicant's explanation, there are no particular problems with the usual starting dose of 1 mg of evocalcet and, with the starting dose of 2 mg selected depending on the patient's condition (e.g., iPTH levels ≥500 pg/mL and adjusted serum Ca levels ≥9.0 mg/dL). Given a serum Ca-lowering effect of evocalcet, the package insert should include a precautionary statement advising physicians to confirm that the patient's serum Ca c level is ≥8.4 mg/dL at the start of treatment with evocalcet (if evocalcet is started at a dose of 2 mg in patients with iPTH levels ≥500 pg/mL, adjusted serum Ca levels should be ≥9.0 mg/dL).

According to the applicant's explanation, the proposed dosage and administration statement specified that "the dose of evocalcet is adjusted within the range from 1 to 6 mg," because approximately 80% of patients were treated with evocalcet at doses up to 6 mg in the Japanese phase III comparative study and the Japanese long term treatment study. However, given that (1) the dose of evocalcet was adjusted within the range from 1 to 8 mg in the Japanese phase III comparative study and (2) evocalcet at doses exceeding 6 mg was administered to a certain percentage of patients in the Japanese phase III comparative study (Table 52), it is unnecessary to define the recommended dose of evocalcet as 1 to 6 mg.

As for the maximum dose of evocalcet, 12 mg was administered in a certain number of patients as a result of gradual dose increase according to the criteria for dose adjustment (Tables 34 and 38) in the Japanese long-term treatment study and in the Japanese open-label clinical study, and no particular safety problem was noted in these patients. Since the dose of evocalcet should be increased as necessary while monitoring iPTH and serum Ca levels, there is no problem in increasing the dose up to 12 mg. However, the dose of 12 mg was administered in only a limited number of patients. Information on the safety and efficacy of 12 mg of evocalcet should be collected and evaluated in the post-marketing surveillance, etc.

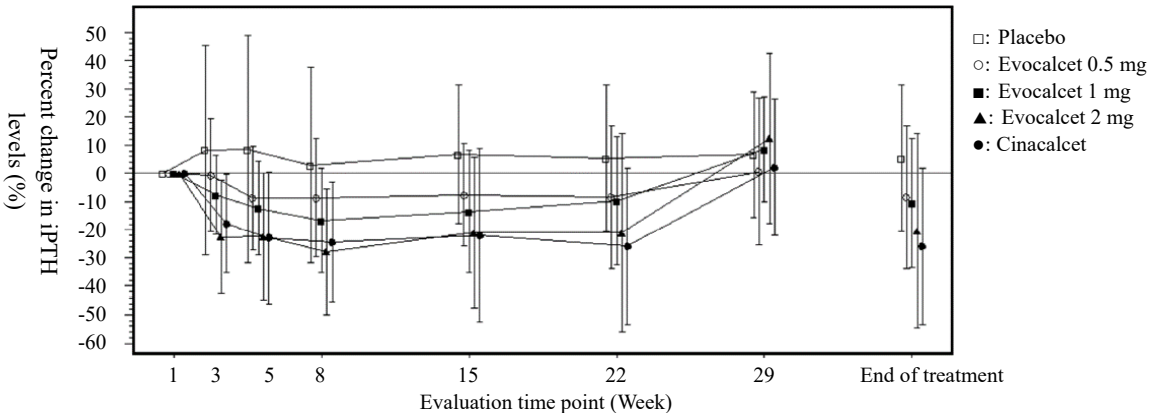
7.R.6.2 Dose adjustment

In the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study), the dose of evocalcet was adjusted according to the criteria shown in Tables 26, 34, and 38, respectively.

The applicant's explanation about the method for dose adjustment during treatment with evocalcet is described in subsections below.

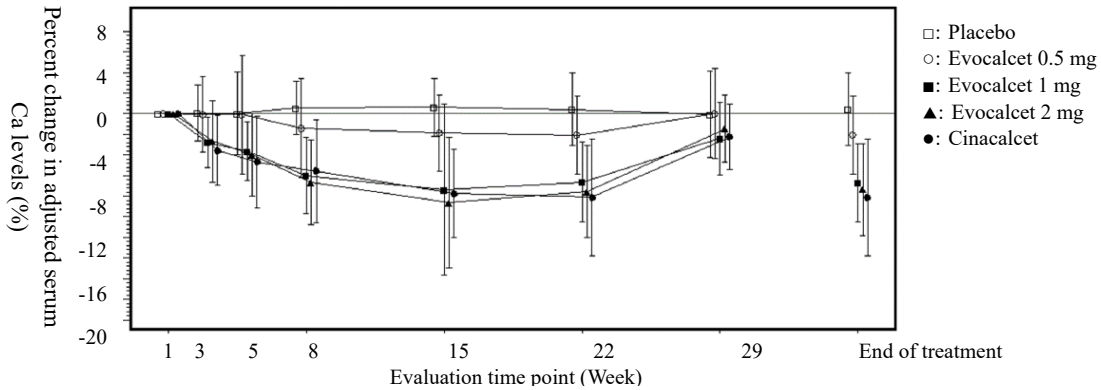
7.R.6.2.1 Increment and interval of dose increase

In the Japanese phase II study, patients received 0.5, 1, or 2 mg of evocalcet. The percent changes in iPTH levels and in adjusted serum Ca levels reached a maximum level within approximately 2 weeks after the start of treatment (Figures 8 and 9).



Evaluation time point (Week)	1	3	5	8	15	22	29	End of treatment
Placebo (N)	28	28	27	28	28	28	28	28
Evocalcet 0.5 mg (N)	30	29	29	30	30	30	30	30
Evocalcet 1 mg (N)	30	28	29	30	30	29	29	30
Evocalcet 2 mg (N)	28	27	27	28	28	25	25	28
Cinacalcet (N)	28	28	28	28	28	28	27	28

Figure 8. Change over time in the percent change in iPTH levels (mean ± SD) (Japanese phase II study, PPS)



Evaluation time point (Week)	1	3	5	8	15	22	29	End of treatment
Placebo (N)	28	28	27	28	28	28	28	28
Evocalcet 0.5 mg (N)	30	29	29	30	30	30	30	30
Evocalcet 1 mg (N)	30	28	29	30	30	29	29	30
Evocalcet 2 mg (N)	28	27	27	28	28	25	25	28
Cinacalcet (N)	28	28	28	28	28	28	27	28

Figure 9. Change over time in the percent change in adjusted serum Ca level (mean ± SD) (Japanese phase II study, PPS)

These results suggest that, in order to avoid rapid decrease in serum Ca levels for safety reason, the dose of evocalcet should not be increased at intervals of <2 weeks, and that the same dose should be maintained for at least 2 weeks. In the Japanese phase III studies, in which serum iPTH and adjusted serum Ca levels were determined at the central laboratory, the dose was increased, in increments of 1 mg, at intervals of ≥3 weeks, taking account of the period until the data of these tests became available. The study results showed no significant safety problem. In the Japanese phase III studies, data on serum iPTH and adjusted serum Ca levels were not available on the same day of the test. However, in clinical practice, there are some medical institutions where test results are available on the same day of test, which will allow dose increase at 2 weeks after the previous dose increase. Therefore, the applicant considered it reasonable to choose to increase the evocalcet dose, in increments of 1 mg, at intervals of ≥2 weeks.

PMDA's view:

There is no particular problem with choosing the increment of 1 mg for the dose of evocalcet in line with the regimen employed in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study). In addition, taking account of the findings that the percent changes in iPTH and adjusted serum Ca levels reached the maximum level at 2 weeks after the start of treatment, the results of tests at 2 weeks after the previous dose increase should be confirmed before the next dose increase. The dose should therefore be increased at intervals of ≥2 weeks.

7.R.6.2.2 Serum Ca

In the Japanese phase III comparative study in which serum Ca levels was measured once every week, adjusted serum Ca levels decreased rapidly 1 week after the start of treatment with evocalcet (Figure 4). Also, adjusted serum Ca levels decreased rapidly 1 week after the dose increase of evocalcet. These results suggest the necessity of once-weekly measurement of serum Ca levels after the start of treatment with evocalcet and during dose adjustment. On the other hand, in the Japanese long-term

treatment study and in the Japanese open-label clinical study, no significant changes in adjusted serum Ca levels were observed once a stable dose of evocalcet was reached. In the open-label clinical study, serum Ca levels were measured once every 2 weeks, but there was no significant safety problem. Based on the above results, the frequency of measurement of serum Ca levels was once every week after the start of treatment with evocalcet and durign dose adjustment, and at least once every 2 weeks when the dose remains unchanged. In patient with decreased serum Ca levels, serum Ca levels should be measured at least once weekly for the safety purpose.

From the safety perspective, the dose of evocalcet should not be increased or maintained in patients with excessively decreased serum Ca levels. The protocols of the Japanese phase III studies specified the criteria for not increasing the dose of evocalcet and for treatment interruption depending on serum Ca levels. The protocol of a Japanese clinical study of cinacalcet specified the following criteria: Dose increase of cinacalcet was prohibited at serum Ca levels <8.4 mg/dL and treatment with cinacalcet had to be interrupted at serum Ca levels ≤7.5 mg/dL. There was no major safety problem in the study. Therefore, the same criteria were used in the Japanese phase III studies of evocalcet. Further, the package insert should advise physicians to consider reduction of the evocalcet dose or use of Ca preparation or vitamin D in patients with an excessive decrease in serum Ca levels, as is the case with cinacalcet.

PMDA's view:
The criteria for the measurement of serum Ca levels during treatment with evocalcet and dose adjustment of evocalcet based on the serum Ca levels are appropriate, The criteria have been defined in line with those employed in the Japanese phase III studies (Japanese phase III comparative study, Japanese long-term treatment study, and Japanese open-label clinical study), and the details of the criteria are as follows: (1) Treatment with evocalcet should be started in patients with adjusted serum Ca levels ≥8.4 mg/dL, (2) Ca should be supplemented with Ca preparation or the dose of evocalcet should be decreased if the adjusted serum Ca has decreased to <8.4 mg/dL, and (3) treatment with evocalcet should be interrupted if the adjusted serum Ca level has decreased to <7.5 mg/dL. Further, serum Ca levels should be measured once every week after the start of treatment with evocalcet and during dose adjustment, and once or more every 2 weeks when the serum Ca level is maintained within the target range.

7.R.6.2.3 PTH

In the Japanese phase III comparative study, iPTH levels were measured once every week. A stable iPTH level was reached 1 to 2 weeks after the start of treatment with evocalcet (Figure 1). On the basis of the finding, it is appropriate to measure iPTH levels twice every month for the dose adjustment of evocalcet. Also, after stable iPTH levels are confirmed, measurement of iPTH levels once every month is sufficient for determining the therapeutic effect and evaluating the safety. The results of the Japanese phase III comparative study and the Japanese open-label clinical study suggest that approximately 3 months are required for dose adjustment before the maintenance dose is reached.

PMDA's view:

Serum PTH levels should be measured twice every month until a stable PTH level is reached (after the start of treatment with evocalcet and during dose adjustment period of approximately 3 months after the start of treatment with evocalcet) and once every month after a stable PTH levels is reached.

7.R.7 Post-marketing investigations

The applicant plans to conduct a specified use-results survey in patients on HD (Table 54) and patients on PD (Table 55) in the post-marketing setting.

Table 54. Outline of the plan for specified use-results survey in patients on HD (draft)

Objective	To confirm the long-term safety and efficacy of evocalcet in patients with SHPT on HD in clinical practice
Survey method	Central registry system
Population	Patients with SHPT on HD
Target sample size	2,400 patients
Survey period	4 years (registration period, 2 years)
Observation period	1 year (52 weeks)
Main survey items	• Patient characteristics (age, sex, history of dialysis, primary disease requiring dialysis, prior treatment for secondary hyperparathyroidism, prior treatment with calcium receptor agonist, concurrent diseases, past history, etc.) • Dialysis therapy (type of dialysis, change in dialyzing method, frequency of dialysis per week, Ca levels in dialysate, etc.) • Use of evocalcet (daily dose, treatment duration, reason for discontinuation, etc.) • Use of activated vitamin D or its derivatives, drugs for treating hyperphosphataemia, calcium preparation, and calcium receptor agonists • Concomitant medication (name of drugs, route of administration, use purpose, etc.) • Laboratory data (serum iPTH levels, adjusted serum Ca levels, serum P levels, etc.) • Electrocardiogram • Adverse events (date of onset, seriousness, outcome, causal relationship to evocalcet, treatments etc.)

Table 55. Outline of the plan for specified use-results survey in patients on PD (draft)

Objective	To confirm the long-term safety and efficacy of evocalcet in patients with SHPT on PD in clinical practice
Survey method	Central registry system
Population	Patients with SHPT on PD
Target sample size	100 patients
Survey period	4 years (registration period, 2 years)
Observation period	1 year (52 weeks)
Main survey items	• Patient characteristics (age, sex, history of dialysis, primary disease requiring dialysis, prior treatment for secondary hyperparathyroidism, prior treatment with calcium receptor agonist, concurrent diseases, past history, etc.) • Dialysis therapy (type of dialysis, change in dialyzing method, exchange frequency per day, fluid volume per exchange, Ca levels in dialysate, etc.) • Use of evocalcet (daily dose, administration period, reason for discontinuation, etc.) • Use of activated vitamin D or its derivatives, drugs for treating hyperphosphataemia, calcium preparation, and calcium receptor agonists • Concomitant medication (name of drugs, route of administration, use purpose, etc.) • Laboratory data (serum iPTH levels, adjusted serum Ca levels, serum P levels, etc.) • Electrocardiogram • Adverse events (date of onset, seriousness, outcome, causal relationship to evocalcet, treatments, etc.)

PMDA considers that the following information should also be collected for investigation. Details of the plan for the post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion.

- Safety and efficacy of evocalcet at the maximum dose (12 mg)

- Safety and efficacy in patients switching from cinacalcet to evocalcet (including investigation on the dose of evocalcet)

- Incidences of events related to upper gastrointestinal disorder, lens disorder, and abnormal bone metabolism

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 5.3.3.2-1, CTD 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.2-1, and CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that the clinical studies, as a whole, were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings requiring corrective action at a study site used by the applicant, although the findings did not significantly affect the overall review of the study. The findings were notified to the head of the study site to seek improvement.

Findings requiring corrective action

A study site

- Defects in the control of study drug (supply of study drug labelled with wrong code to some patients, some inconsistencies in the number of unused study drug between the control record and the actual number)

- Protocol deviations (noncompliance with the criteria for dose increase of study drug, noncompliance with the rule for checking for exclusion criteria before enrollment of subjects in the study [presence or absence of change in dialyzing conditions])

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

On the basis of the data submitted, PMDA has concluded that Orkedia (evocalcet) has efficacy in the treatment of patients with SHPT on maintenance dialysis, and that Orkedia has acceptable safety in view of its benefits. Orkedia is clinically meaningful because it offers a new treatment option for

patients with SHPT on hemodialysis. The efficacy, safety, indication, dosage and administration, and post-marketing investigations should be further evaluated.

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

Review Report (2)

February 19, 2018

Product Submitted for Approval

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	April 27, 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 conclusions in "Section 7.R.1 Efficacy," "Section 7.R.3 Safety," "Section 7.R.5 Indication," and "Section 7.R.6 Dosage and administration" described in the Review Report (1). The following comments on "Section 7.R.6 Dosage and administration" were raised from the expert advisors:

- The dose of evocalcet was increased up to 12 mg while monitoring iPTH and serum Ca levels in the Japanese long-term treatment study and the Japanese open-label clinical study, and the study results showed no particular safety problem. Thus, there is no objection to selecting 12 mg as the maximum dose of evocalcet. However, the dose range of evocalcet investigated in the Japanese phase III comparative study, was from 1 to 8 mg and, in the Japanese long-term treatment study and the Japanese open-label clinical study, only a limited number of patients received evocalcet at a dose exceeding 8 mg. Therefore, the dose of evocalcet should be adjusted appropriately within the range from 1 to 8 mg, and the dose should be increased up to 12 mg only if the patient has an inadequate response.

Taking account of the comment raised in the Expert Discussion, PMDA accepted the proposed indication for evocalcet as shown below. Further, PMDA instructed the applicant to modify the statements of the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package insert as described below. The applicant responded appropriately and PMDA accepted the response.

Indication

Secondary hyperparathyroidism in patients on maintenance dialysis

Dosage and Administration

The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Precautions for Dosage and Administration

(1) Evocalcet lowers blood calcium levels. Treatment with evocalcet should be started after ensuring that serum calcium level is not low (≥8.4 mg/dL as a rule).

(2) The dose of evocalcet should be increased in increments of 1 mg at intervals of ≥2 weeks.

(3) If the PTH level is high (intact PTH ≥500 pg/mL as a rule) and the serum calcium level is ≥9.0 mg/dL, the starting dose of 2 mg once daily should be considered (see the Clinical Studies section).

(4) Serum calcium levels should be measured at least once every week after the start of treatment with evocalcet and during dose adjustment, and at least once every 2 weeks during the maintenance period. If the serum calcium level is <8.4 mg/dL, take the measures as indicated in the following table.

Serum calcium levels	Measures to be taken			
	Medical care		Test	Dose increase/resumption
	Evocalcet			
<8.4 mg/dL	As a general rule, the dose of evocalcet should not be increased (the dose should be decreased as necessary).	Use of calcium and vitamin D preparations should be considered.	Serum calcium should be measured at least once every week. It is desirable to perform electrocardiography.	Increase the dose of evocalcet, if necessary, after confirming that serum Ca has increased to ≥8.4 mg/dL.
≤7.5 mg/dL	Treatment with evocalcet should be interrupted immediately.			Before resumption of treatment with evocalcet, confirm that serum Ca is ≥8.4 mg/dL. The restarting dose should be the same as, or lower than, the dose before the interruption.

Serum calcium test should desirably be performed before treatment with evocalcet in order to accurately evaluate the efficacy and safety of evocalcet. In case of hypoalbuminaemia (serum albumin concentration <4.0 g/dL), it is desirable to use an adjusted serum calcium level as the index.

* Method for calculating adjusted calcium levels:
Adjusted calcium level (mg/dL) = serum calcium level (mg/dL) – serum albumin level (g/dL) + 4.0

(5) PTH levels should be measured periodically to ensure that PTH is maintained within the target range. PTH levels should be measured twice every month after the start of treatment with evocalcet and during dose adjustment (approximately 3 months from the start of treatment), and desirably once every month after an almost stable PTH level is reached. Measurement of PTH

levels before the start of treatment with evocalcet is desirable in order to accurately evaluate the efficacy and safety of evocalcet.

1.2 Risk management plan (draft)

The PMDA's conclusion described in "Section 7.R.7 Post-marketing investigations" of the Review Report (1) was supported by the expert advisors.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for evocalcet should include the safety and efficacy specifications presented in Table 56, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 57 as well as specified use-results surveys presented in Tables 58 and 59.

Table 56. Safety and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypocalcaemia • QT prolongation	• Bone metabolism disorder	• Not applicable
Efficacy specification		
• Not applicable		

Table 57. Summary of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (long-term use in patients on HD) • Specified use-results survey (long-term use in patients on PD)	• Provision of information collected through the early post-marketing phase vigilance

Table 58. Outline of the specified use-results survey in patients on HD (draft)

Objective	To confirm the long-term safety and efficacy of evocalcet in patients with SHPT on HD in clinical practice
Survey method	Central registry system
Population	Patients with SHPT on HD
Target sample size	2,400 patients
Survey period	4 years (registration period, 2 years)
Observation period	1 year (52 weeks)
Main survey items	• Patient characteristics (age, sex, history of dialysis, primary disease requiring dialysis, prior treatment for secondary hyperparathyroidism, prior treatment with calcium receptor agonist, concurrent diseases, past history, etc.) • Dialysis therapy (type of dialysis, change in dialyzing method, frequency of dialysis per week, Ca levels in dialysate, etc.) • Use of evocalcet (daily dose, administration period, reason for discontinuation, etc.) • Use of activated vitamin D or its derivatives, drugs for treating hyperphosphataemia, calcium preparation, and calcium receptor agonists • Concomitant medication (name of drugs, route of administration, use purpose, etc.) • Laboratory data (serum iPTH levels, adjusted serum Ca levels, serum P levels, etc.) • Electrocardiogram • Adverse events (date of onset, seriousness, outcome, causal relationship to evocalcet, medical care, etc.)

Table 59. Outline of the specified use-results survey inpatients on PD (draft)

Objective	To confirm the long-term safety and efficacy of evocalcet in patients with SHPT on PD in clinical practice
Survey method	Central registry system
Population	Patients with SHPT on PD
Target sample size	100 patients
Survey period	4 years (registration period, 2 years)
Observation period	1 year (52 weeks)
Main survey items	• Patient characteristics (age, sex, history of dialysis, primary disease requiring dialysis, prior treatment for secondary hyperparathyroidism, prior treatment with calcium receptor agonist, concurrent diseases, past history, etc.) • Dialysis therapy (type of dialysis, change in dialyzing method, frequency of exchange per day, fluid volume per exchange, Ca levels in dialysate, etc.) • Use of evocalcet (daily dose, administration period, reason for discontinuation, etc.) • Use of activated vitamin D or its derivatives, drugs for treating hyperphosphataemia, calcium preparation, and calcium receptor agonists • Concomitant medication (name of drugs, route of administration, use purpose, etc.) • Laboratory data (serum iPTH levels, adjusted serum Ca levels, serum P levels, etc.) • Electrocardiogram • Adverse events (date of onset, seriousness, outcome, causal relationship to evocalcet, medical care, etc.)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that Orkedia (evocalcet) may be approved after modifying the indications and dosage and administration as shown below, with the following condition. Since Orkedia is a drug with a new active ingredient, the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a biological product or a specified biological product. The drug product and its drug substance are classified as a powerful drug and a poisonous drug, respectively.

Indication

Secondary hyperparathyroidism in patients on maintenance dialysis

Dosage and administration

The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Condition for approval

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

Appendix

List of Abbreviations

Adverse drug reaction	Adverse event for which a causal relationship to study drug cannot be ruled out
ALT	Alanine aminotransferase
APA	Action potential amplitude
APD	Action potential duration
AUC	Area under concentration-time curve
BAP	Bone type alkaline phosphatase
BCRP	Breast cancer resistance protein
BMI	Body Mass Index
C	Carbon
Ca	Calcium
Caco-2 cell	Human colon carcinoma cell line Caco-2
CaR	Calcium-sensing receptor
CHO cell	Chinese hamster ovary cell line CHO
CK	Creatine Kinase
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral and bone disorder
Clinical Practice Guideline for CKD-MBD 2012	Clinical Practice Guideline for the Management of Chronic Kidney Disease-Mineral and Bone Disorder (Clinical Practice Guideline for CKD-MBD) (*Journal of Japanese Society for Dialysis Therapy*, 2012;45:301-356)
Cl	Chloride
CMA	Critical material attribute
C_{max}	Maximum concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CT	Computed tomography
CTD	Common technical document
CYP	Cytochrome P450
EC_{50}	Half maximal effective concentration
Evocalcet	Evocalcet
FAS	Full analysis set
GC	Gas chromatography
GCP	Good clinical practice
HD	Hemodialysis
HEK293 cell	Human embryonic kidney cell line HEK293
hERG	Human ether-à-go-go related gene
HPLC	High performance liquid chromatography
HPLC-RAD	HPLC-radioactivity detector
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E Guideline	"Guideline on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3 2003, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).
IP	Inorganic phosphorus
iPTH	Intact parathyroid hormone
IR	Infrared absorption spectrophotometry
K	Kalium
LC/MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
M1	Metabolite 1, taurine conjugate of evocalcet (active metabolite)

M2	Metabolite 2, glycine conjugate of evocalcet (active metabolite)
M3	Metabolite 3, glucuronate conjugate of evocalcet
M4	Metabolite 4, a metabolite of evocalcet with α-oxidized phenylacetate
M5	Metabolite 5, naphthylethylamine
M6	Metabolite 6, dihydrodiol form of evocalcet
M7	Metabolite 7, naphthyl acetate
M9	Metabolite 9, dihydrodiol form of M5
MATE	Multidrug and toxic extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Master file
mRNA	Messenger RNA
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
Na	Sodium
NMR	Nuclear magnetic resonance spectrometry
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P	Phosphorus
PD	Peritoneal dialysis
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PIF	Photo irritation factor
PMDA	Pharmaceuticals and Medical Device Agency
PPS	Per protocol set
PTH	Parathyroid hormone
PTP	Press through packaging
QbD	Quality by Design
rasH2	c-Ha-ras
RH	Relative humidity
RNA	Ribonucleic acid
SHPT	Secondary hyperparathyroidism
$t_{1/2}$	Elimination half life
t_{max}	Time to reach maximum concentration
total P1NP	Total procollagen I N-terminal propeptide
TRACP-5b	Tartrate-resistant acid phosphatase 5b
UGT	Uridine diphosphate-glucuronosyltransferase
UV	Ultraviolet-visible spectrophotometry
WBP	Whole body plethysmograph