Report on the Deliberation Results

November 14, 2016
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Parsabiv Intravenous Injection for Dialysis 2.5 mg Parsabiv Intravenous Injection for Dialysis 5 mg Parsabiv Intravenous Injection for Dialysis 10 mg
Non-proprietary Name	Etelcalcetide Hydrochloride (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	January 14, 2016

Results of Deliberation

In its meeting held on October 31, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

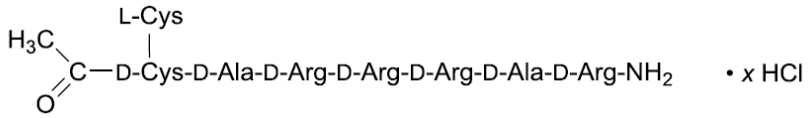
Review Report

October 17, 2016
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.

Brand Name	Parsabiv Intravenous Injection for Dialysis 2.5 mg Parsabiv Intravenous Injection for Dialysis 5 mg Parsabiv Intravenous Injection for Dialysis 10 mg
Non-proprietary Name	Etelcalcetide Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	January 14, 2016
Dosage Form/Strength	Solution for injection: Each vial contains 2.5 mg, 5 mg, or 10 mg of etelcalcetide (as the hydrochloride salt).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{38}H_{73}N_{21}O_{10}S_2 \cdot x$HCl ($4 \leq x \leq 5$)
Molecular weight: 1048.25 (free base)
Chemical name:
N-Acetyl-*S*-[(2*R*)-2-amino-2-carboxyethylsulfanyl]-D-cysteinyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-D-argininamide hydrochloride

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

Results of Review
On the basis of data submitted, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has efficacy in the treatment of secondary hyperparathyroidism in patients on hemodialysis 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 hemodialysis

Dosage and Administration

The usual adult starting dose is 5 mg of etelcalcetide administered 3 times per week. Administer by intravenous injection into the venous line of the dialysis circuit at the end of dialysis during rinse back.

Thereafter, while parathyroid hormone (PTH) and serum calcium levels should be monitored closely, the dose should be titrated based on the PTH and serum calcium levels. The dose range is 2.5 to 15 mg 3 times per week at the end of dialysis during rinse back.

Condition of Approval

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

Attachment

Review Report (1)

September 2, 2016

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

Product Submitted for Approval

Brand Name	Parsabiv Intravenous Injection for Dialysis 2.5 mg Parsabiv Intravenous Injection for Dialysis 5 mg Parsabiv Intravenous Injection for Dialysis 10 mg
Non-proprietary Name	Etelcalcetide Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	January 14, 2016
Dosage Form/Strength	Solution for injection: Each vial contains 2.5 mg, 5 mg, or 10 mg of etelcalcetide (as the hydrochloride salt).
Proposed Indication	Secondary hyperparathyroidism in patients on hemodialysis

Proposed Dosage and Administration

The usual adult starting dose is 5 mg of etelcalcetide administered 3 times per week. Administer by intravenous injection into the venous line of the dialysis circuit at the end of dialysis during rinse back.

Thereafter, while parathyroid hormone (PTH) and serum calcium levels should be monitored closely, the dose should be titrated based on the PTH and serum calcium levels. The dose range is 2.5 to 15 mg 3 times per week at the end of dialysis during rinse back.

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List of Abbreviations

A/G ratio	Ratio of albumin to globulins
AUC	Area Under the Curve
BAP	Bone (specific) alkaline phosphatase
BDC	Bile-duct cannulated
Ca	Calcium
CaSR	Calcium-sensing receptor
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral and bone disorder
Clinical Practice Guideline for CKD-MBD	Clinical Practice Guideline for Management of Chronic Kidney Disease-Mineral and Bone Disorder. Japanese Society for Dialysis Therapy, ed. (*J. Jpn. Soc. Dial. Ther.* 2012; 45: 301-356)
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CYP	Cytochrome P450
Cys	Cysteine
EC_{50}	50% effective concentration
Etelcalcetide	Etelcalcetide hydrochloride
fe	Urinary excretion rate
FAS	Full Analysis Set
GC	Gas chromatography
GLP	Good Laboratory Practice
HEK293	Human Embryonic Kidney 293
hERG	human Ether-a-go-go Related Gene
HPLC	High performance liquid chromatography
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICP-MS	Inductively coupled plasma-mass spectrometry
in silico	via computer simulation
IP-1	Inositol-1-phosphate
iPTH	Intact parathyroid hormone
IV	intravenous
KP-2140	A peptide without D-Cys (removal of D-Cys from M11)
LC/MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LLC-PK1 cells	Lilly Laboratories Cell - Porcine Kidney 1 cells
M10	Glutathione disulfide
M11	Etelcalcetide D-amino acid peptide without L-Cys
M13	L-cysteinyl-L-glycine disulfide
MDCKII cells	Madin Darby canine kidney cells
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P	Phosphorus
PEPT	Peptide transporter
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Terms
PTH	Parathyroid hormone
QbD	Quality by design
QTc	Corrected QT interval
QTca	QT interval corrected using the following formula QTca = QT interval [ms]/(RR interval [ms]/750)$^{0.273}$

QTcF	QT intervals from Fridericia's formula
RH	Relative humidity
S9 fraction	9000 × g supernatant fraction of cell homogenate
SAPC	Serum albumin peptide conjugate
SHPT	Secondary hyperparathyroidism
SH group	Thiol group
SMQ	Standardised MedDRA Queries
$t_{1/2}$	Elimination half life
Tg.rasH2 mouse	CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras) [a hemizygous transgenic mouse carrying the human c-Ha-ras gene]
TRACP-5b	Tartrate resistant acid phosphatase-5b

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

Secondary hyperparathyroidism (SHPT) is a common condition in patients with worsening chronic kidney disease (CKD) and is characterized by excessive secretion of parathyroid hormone (PTH) in response to decreased excretion of phosphorus (P) and low levels of blood calcium (Ca) resulting from inadequate vitamin D activation (Clinical Practice Guideline for Management of Chronic Kidney Disease-Mineral and Bone Disorder. Japanese Society for Dialysis Therapy, ed. 2012. ["Clinical Practice Guideline for CKD-MBD"]). Excessive secretion of PTH in SHPT patients increases bone resorption, which can lead to bone pain and fractures, thereby causing excessive Ca and P release from the bone into blood, which results in cardiovascular calcification, consequently affecting survival prognosis as well (*J Am Soc Nephrol.* 2001;12: 2131-2138, *Hemodial Int.* 2007;11: 340-348). Persistent oversecretion of PTH is associated with parathyroid gland hyperplasia, which contributes to further progression of SHPT. Against this background, Clinical Practice Guideline for CKD-MBD indicates target serum P, Ca, and PTH levels in dialysis patients, and recommends a target serum intact parathyroid hormone (iPTH) range of 60 to 240 pg/mL.

Medication therapies to control PTH in SHPT include active vitamin D preparations and a Ca sensing receptor (CaSR) agonist, cinacalcet hydrochloride. Those agents have been used according to individual patients' conditions. The use of cinacalcet hydrochloride is considered if PTH is high and P or Ca levels are normal or high, and the use of active vitamin D preparations is considered if P or Ca levels are normal or low (Clinical Practice Guideline for CKD-MBD).

Etelcalcetide Hydrochloride (hereinafter referred to as etelcalcetide) is a synthetic peptide made up of 7 D-amino acids linked to L-Cys by a disulfide bond and acts as a CaSR agonist, like cinacalcet hydrochloride. While cinacalcet hydrochloride is available as tablets for oral administration, etelcalcetide is supplied as a solution for injection to be administered via the dialysis circuit at the end of dialysis. Thus, etelcalcetide was developed with a view to improved compliance and a reduced pill burden for dialysis patients who generally limit their water intake and already take oral medications such as phosphate binders.

As of August 2016, etelcalcetide is not approved in any country.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to off-white powder. The properties of the drug substance, including appearance, crystalline polymorphism, optical rotation, pH, thermogravimetric weight loss, glass transition point, hygroscopicity, true density, partition coefficient, isoelectric point, and solubility, have been determined. The drug substance is etelcalcetide hydrochloride. Etelcalcetide is a peptide made up of 7 D-amino acids linked to L-Cys by a disulfide bond. Its structure has been confirmed by amino acid analysis, elemental analysis, MS, NMR (^{1}H-NMR, ^{13}C-NMR), and ultraviolet/visible spectroscopy.

2.1.2 Manufacturing process

The drug substance is synthesized using the following compounds as starting materials.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Using a quality by design (QbD) approach, the control strategy was developed based on studies including the following studies.

- Identification of [redacted], monoisotopic mass, relative retention time (HPLC), [redacted], appearance, optical rotation, appearance of solution, water content, bacterial endotoxins, microbiological quality, [redacted], and content as control quality attributes (CQAs)
- The impact of the drug substance manufacturing process on CQAs
- Control of CQAs (control of material attributes, in-process controls, process control, specification, etc.)

[redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), and [redacted] (Step [redacted]) have been defined as critical steps. To consistently assure the quality of the drug substance, [redacted] in Step [redacted], Step [redacted], and Step [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identification (MS, HPLC, amino acid analysis), optical rotation, purity [appearance of solution, elemental impurities (ICP-MS), related substances (HPLC), [redacted], residual solvents (GC)], water content (coulometric titration method), bacterial endotoxins (turbidimetric technique), microbial limits (membrane filtration method), [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies of the drug substance are presented in Table 1. The photostability study showed that the drug substance is photosensitive.

Table 1. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	−20°C	—	polyethylene bag /aluminum bag (tight container)	24 months

Based on the above, a retest period of 24 months was proposed for the drug substance when stored in a polyethylene bag inside an aluminum bag (a tight container) at ≤ −15°C. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection in a vial (2.2 mL solution) containing 3.17 mg, 6.34 mg, or 12.68 mg of etelcalcetide hydrochloride (equivalent to 2.75 mg, 5.5 mg, or 11 mg of etelcalcetide). It contains the following excipients: sodium chloride, succinic acid, sodium hydroxide, dilute hydrochloric acid, and water for injection. The vial contains a 10% overage to compensate for loss during withdrawal of the solution from the vial.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], [redacted], [redacted], inspection, packaging/labeling, and testing/storage. [redacted] and [redacted] have been defined as critical steps, and process control items and values have been established.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (color reaction, HPLC), pH, purity (related substances [HPLC]), bacterial endotoxins (turbidimetric technique), extractable volume, foreign insoluble matter, insoluble particulate matter, sterility (membrane filtration method), and assay (HPLC).

2.2.4 Stability of drug product

Primary stability studies of the drug product are presented in Table 2. A bracketing approach to stability was adopted, with only vials of the 2.5 mg and 10 mg strengths used for the long-term and accelerated stability studies, and batches of the 5 mg strength were not tested. The photostability study showed that the drug product is photosensitive.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	5°C	−	colorless glass vial/carton	18 months
Accelerated		25°C	60%RH		6 months

Based on the above and in accordance with the ICH Q1E guideline, a shelf-life of 24 months was proposed for the drug product when packaged in a glass vial and stored in a carton, protected from light, in a refrigerator (2°C to 8°C). The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

Primary pharmacodynamic studies were conducted to mainly evaluate the CaSR agonist activity of etelcalcetide and the inhibition of PTH secretion, the prevention of parathyroid gland hyperplasia and vascular calcification, and the control of bone turnover by etelcalcetide. In secondary pharmacodynamic studies, the

ability of etelcalcetide to inhibit radioligand binding to receptors etc. other than the CaSR was tested and the activity of the biotransformation products of etelcalcetide was determined. Safety pharmacology studies were conducted to mainly assess the effects of etelcalcetide on the central nervous system (CNS) and cardiovascular and respiratory systems. A pharmacodynamic drug interaction study of etelcalcetide and cinacalcet hydrochloride was conducted. All doses and concentrations of etelcalcetide in the studies are expressed as free base.

3.1 Primary pharmacodynamics

3.1.1 CaSR agonist activity

3.1.1.1 Human CaSR agonist activity (CTD 4.2.1.1-1 and 4.2.1.1-2, Study Nos. E[redacted]QA001 and 4169-NC-120 [reference data])

HEK293T cells transfected with the human CaSR were treated with 0.03 to 300 μmol/L etelcalcetide in the presence of 1.0 mmol/L Ca, and the intracellular Ca concentrations were measured. Etelcalcetide concentration-dependently increased the intracellular Ca concentration, and the EC_{50} value was 0.53 μmol/L. On the other hand, no increases in the intracellular Ca concentration were observed in untransfected HEK293T cells treated with etelcalcetide.

HEK293T cells transfected with the human CaSR were treated with 0.5 to 500 μmol/L etelcalcetide in the presence or absence of 1.2 mmol/L Ca, and intracellular inositol-1-phosphate (IP-1) accumulation was quantified. While etelcalcetide concentration-dependently increased intracellular IP-1 accumulation in the presence of Ca, almost no increases in intracellular IP-1 accumulation were seen in the absence of Ca.

3.1.1.2 Binding site with human CaSR (CTD 4.2.1.1-3, Study No. 4169-NC-160)

HEK293T cells transfected with the human CaSR were incubated with 0.41 to 300 μmol/L etelcalcetide D-amino acid peptide without L-Cys (M11) or 0.41 to 300 μmol/L KP-2140 (M11 homologue without D-Cys) in the presence of 1.2 mmol/L Ca, and intracellular IP-1 accumulation was quantified. While M11 concentration-dependently increased intracellular IP-1 accumulation, KP-2140 did not increase intracellular IP-1 accumulation.

HEK293T cells transfected with the human CaSR or mutated human CaSR (substitution of Cys482 by Ser482 or Tyr482) were incubated with 2.3 to 300 μmol/L etelcalcetide in the presence of 1.2 mmol/L Ca, and intracellular IP-1 accumulation was quantified. While etelcalcetide increased intracellular IP-1 accumulation in cells transfected with the human CaSR, no increases in intracellular IP-1 accumulation were seen in cells transfected with mutated human CaSR.

3.1.2 Inhibition of PTH secretion

3.1.2.1 *In vitro* inhibition of PTH secretion (CTD 4.2.1.1-4 and 4.2.1.1-5, Study Nos. E[redacted]QA002 and R[redacted]0052)

Primary parathyroid cells from normal rats were treated with 0.01 to 100 μmol/L etelcalcetide in the presence of 1.0 mmol/L Ca, and PTH was quantified from the media. Etelcalcetide concentration-dependently reduced PTH levels in the media, and the EC_{50} value was 0.36 μmol/L.

Isolated parathyroid glands from normal rats were also incubated with 0.1 to 10 μmol/L etelcalcetide in the presence of 0.8, 1.0, or 1.25 mmol/L of Ca, and PTH was quantified from the media. Etelcalcetide concentration-dependently reduced PTH levels in the media. In the presence of 0.8, 1.0, or 1.25 mmol/L of Ca, the EC_{50} values were 1.2, 0.7, and 0.4 μmol/L, respectively.

3.1.2.2 *In vivo* inhibition of PTH secretion (CTD 4.2.1.1-7, Study No. E[redacted]QA001)

A single intravenous dose of etelcalcetide 0.3, 1, or 3 mg/kg or vehicle (0.27% succinate buffer) was administered to 5/6 nephrectomized CKD rats. Plasma PTH, serum Ca, and plasma P levels at 6 hours post-dose are shown in Table 3. In the 5/6 nephrectomized CKD rat model, 2/3 of the left kidney of male rats was surgically removed. One week later, the right kidney was removed. The 5/6 nephrectomized rats were fed a high-P diet (1.0% P) for 4 weeks, beginning 1 week after the second nephrectomy, to further induce SHPT.

Etelcalcetide at all dose levels significantly reduced plasma PTH and serum Ca levels at 6 hours post-dose compared to vehicle control. On the other hand, a significant increase in plasma P was observed in all etelcalcetide groups compared to the vehicle control group.

Table 3. Plasma PTH, serum Ca, and plasma P levels at 6 hours post-dose in 5/6 nephrectomized CKD rats

	n	Plasma PTH (pg/mL)			Serum Ca (mg/dL)		Plasma P (mg/dL)	
		Baseline	6 hours post-dose	Relative plasma PTH [a)]	Baseline	6 hours post-dose	Baseline	6 hours post-dose
Vehicle control	8	1024.3 ± 115.9	796.5 ± 92.6	80.5 ± 7.6	9.53 ± 0.16	8.94 ± 0.12	9.11 ± 0.54	7.51 ± 0.34
Etelcalcetide 0.3 mg/kg	8	944.3 ± 136.2	243.7 ± 88.0	22.8 ± 4.9***	9.29 ± 0.23	7.20 ± 0.20***	8.37 ± 0.54	9.26 ± 0.23***
Etelcalcetide 1 mg/kg	8	914.6 ± 177.7	49.9 ± 6.9	6.4 ± 0.8***	9.27 ± 0.23	6.62 ± 0.28***	8.76 ± 0.50	10.05 ± 0.36***
Etelcalcetide 3 mg/kg	8	944.9 ± 154.0	53.0 ± 6.0	6.1 ± 0.5***	9.40 ± 0.19	5.78 ± 0.22***	8.56 ± 0.45	9.23 ± 0.27**

Mean ± standard error (SE)
a) Plasma PTH at 6 hours post-dose as percent of baseline (%)
**: $P < 0.01$, ***: $P < 0.001$ (vs. vehicle control, t-test)

3.1.3 Prevention of parathyroid gland hyperplasia (CTD 4.2.1.1-8, Study No. 4169-NC-145)

Etelcalcetide 0.3, 1, or 3 mg/kg or vehicle (0.24% succinate buffer) was administered subcutaneously to 5/6 nephrectomized CKD rats 3 times weekly for 6 weeks. Plasma PTH levels, parathyroid chief cell number, and parathyroid gland weight at Week 6 are shown in Table 4. In the 5/6 nephrectomized CKD rat model, 2/3 of the right kidney of male rats was surgically removed. One week later, the left kidney was removed. The 5/6 nephrectomized rats were fed a high-P diet (1.3% P) for 8 weeks, beginning 1 week after the second nephrectomy, to induce parathyroid gland hyperplasia.

A significant reduction in plasma PTH was observed in the etelcalcetide 3 mg/kg group compared to the vehicle control group. Parathyroid cell proliferation was significantly reduced in the etelcalcetide 3 mg/kg group

compared to the vehicle control group. Parathyroid gland weight tended to be lower in all etelcalcetide groups relative to the vehicle control group.

Table 4. Plasma PTH levels, parathyroid cell proliferation, and parathyroid gland weight at Week 6 in 5/6 nephrectomized CKD rats

	n	Plasma PTH (pg/mL)			Parathyroid gland	
		Baseline	Week 6	Relative plasma PTH [a)]	BrdU-positive cell number per section (cells)	Body weight-normalized parathyroid gland weight (mg/kg)
Vehicle control	12	1089 ± 75	1800 ± 276	163 ± 22	127 ± 19	5.6 ± 0.3
Etelcalcetide 0.3 mg/kg	11	1074 ± 101 [b)]	1515 ± 305	145 ± 30	109 ± 13	5.3 ± 0.5
Etelcalcetide 1 mg/kg	11	1117 ± 131 [b)]	1373 ± 257	128 ± 20	74 ± 15	5.1 ± 0.4
Etelcalcetide 3 mg/kg	12	1101 ± 88	636 ± 140	68 ± 19	52 ± 16**	4.4 ± 0.4

Mean ± SE
a) Plasma PTH at Week 6 as percent of baseline (%)
b) n = 12
**: $P < 0.01$ (vs. vehicle control, Bonferroni's multiple comparison test)

3.1.4 Prevention of vascular calcification

3.1.4.1 Prevention of tissue calcification (CTD 4.2.1.1-8, Study No. 4169-NC-145)

Etelcalcetide 3 mg/kg was administered subcutaneously to 5/6 nephrectomized CKD rats 3 times weekly for 6 weeks. Plasma PTH levels at Week 4 and tissue Ca and P content (the heart, aortic arch, and kidney) at Week 6 are shown in Table 5. In the 5/6 nephrectomized CKD rat model, 2/3 of the right kidney of male rats was surgically removed. One week later, the left kidney was removed. Beginning 1 week after the second nephrectomy, the 5/6 nephrectomized rats were fed a vitamin D-deficient and high-P diet (1.25% P) for 8 days, followed by a high-P diet (1.3% P) for 7 weeks, to induce tissue calcification.

A significant reduction in plasma PTH was observed at Week 4 in the etelcalcetide 3 mg/kg group compared to the untreated control group (untreated 5/6 nephrectomized CKD rats). Etelcalcetide at 3 mg/kg significantly reduced Ca content in the aortic arch and tended to reduce Ca content in the heart and kidney from treated animals, compared to untreated controls. Etelcalcetide at 3 mg/kg significantly reduced P content in the heart and aortic arch and tended to reduce P content in the kidney from treated animals, compared to untreated controls.

Table 5. Plasma PTH levels at Week 4 and tissue Ca and P content at Week 6 in 5/6 nephrectomized CKD rats

	n	Plasma PTH (pg/mL)			Tissue Ca content (mg/g)			Tissue P content (mg/g)		
		Baseline	Week 4	Relative plasma PTH [a)]	Heart	Aortic arch	Kidney	Heart	Aortic arch	Kidney
Untreated controls	10	824 ± 71 [b)]	1476 ± 304 [c)]	176 ± 26	1.41 ± 0.86	9.06 ± 4.77 [d)]	6.69 ± 2.63	7.19 ± 0.52	11.65 ± 2.56 [d)]	13.84 ± 1.91
Etelcalcetide 3 mg/kg	11	823 ± 75 [b)]	439 ± 66	64 ± 13**	0.18 ± 0.02	0.99 ± 0.04***	3.09 ± 0.75	6.32 ± 0.10*	6.34 ± 0.21**	11.56 ± 0.47

Mean ± SE
a) Plasma PTH at Week 4 as percent of baseline (%)
b) n = 12
c) n = 11
d) n = 9
*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ (vs. control, unpaired t-test and Mann-Whitney test)

3.1.4.2 Prevention of vascular calcification (CTD 4.2.1.1-9, Study No. R[redacted]0076)

Etelcalcetide 0.3 mg/kg or vehicle (0.24 % succinate buffer) was administered subcutaneously to adenine-induced CKD rats once daily for 4 weeks. Plasma PTH levels, parathyroid chief cell count, parathyroid gland weight, and Ca and P content in the descending aorta at Week 4 are shown in Table 6. In the adenine-induced CKD rat model, male rats were fed a low-protein diet (2.5% protein) for 1 week followed by adenine diet (a low-protein diet supplemented with 0.75% adenine) for 4 weeks to induce vascular calcification.

Plasma PTH was significantly lower at Week 4 in the etelcalcetide 0.3 mg/kg group compared to the vehicle control group. Parathyroid gland weight and cell proliferation were significantly reduced in the etelcalcetide 0.3 mg/kg group compared to the vehicle control group. Ca content in the descending aorta was significantly lower in the etelcalcetide 0.3 mg/kg group than in the control group. P content in the descending aorta was below the lower limit of quantitation (LLOQ) (150 μg/g) in all of 24 rats in the etelcalcetide 0.3 mg/kg group, while it was below the LLOQ in 18 of 24 rats in the vehicle control group. In the remaining 6 rats, the aortic P content was 1725 ± 941 μg/g (mean ± standard error [SE]).

Table 6. Plasma PTH levels, parathyroid cell proliferation, parathyroid gland weight, and tissue Ca and P content at Week 4 in adenine-induced CKD rats

	n	Plasma PTH (pg/mL)			Parathyroid gland		Descending aorta	
		Baseline	Week 4	Relative plasma PTH [a)]	Cell count (cells/μm^2 × 1000)	Body weight-normalized parathyroid gland weight (mg/g)	Ca content (μg/g)	P content (μg/g)
Vehicle control	24	174 ± 12	1048 ± 85	651 ± 58	0.397 ± 0.071	2.49 ± 0.24	631.3 ± 326.4	1725 ± 941
Etelcalcetide 0.3 mg/kg	24	302 ± 21	738 ± 49*	269 ± 25*	0.041 ± 0.006*	1.61 ± 0.15*	47.5 ± 3.3#	Below LLOQ

Mean ± SE

a) Plasma PTH at Week 4 as percent of baseline (%)

*: $P < 0.05$ (vs. vehicle control, Tukey's multiple test), #: $P < 0.05$ (vs. vehicle control, Dunn's multiple comparison test)

3.1.5 Control of bone turnover

3.1.5.1 Effects on bone histomorphometry parameters (CTD 4.2.1.1-10, Study No. R[redacted]0074)

Etelcalcetide 0.3 or 1 mg/kg or vehicle (0.24% succinate buffer) was administered subcutaneously to 5/6 nephrectomized CKD rats once daily for 6 weeks, or cinacalcet hydrochloride 3 or 15 mg/kg or vehicle (0.5% methylcellulose solution) was administered orally to 5/6 nephrectomized CKD rats once daily for 6 weeks. Bone histomorphometric parameters (osteoclast surface, osteoid surface, mineralizing surface, bone formation rate, osteoid volume, mineralization lag time) at Week 6 are shown in Table 7. In the 5/6 nephrectomized CKD rat model, 2/3 of the left kidney of male rats was surgically removed, and the right kidney was removed 1 week later. The dose was reduced to 0.6 mg/kg in the etelcalcetide 1 mg/kg group on and after Day 15 due to loss in body weight for this group.

Osteoclast surface tended to be lower in both etelcalcetide groups than in the vehicle control group. Mineralizing surface was significantly reduced in the etelcalcetide 0.3 mg/kg group compared to the vehicle control group. Osteoid surface, mineralizing surface, bone formation rate, osteoid volume, and mineralization lag time were significantly decreased in the etelcalcetide 1 mg/kg group compared to the vehicle control group.

In contrast, no significant differences were observed in cinacalcet hydrochloride-treated rats when compared to vehicle-treated controls.

Table 7. Bone histomorphometric parameters at Week 6 in 5/6 nephrectomized CKD rats

Treatment group	n	Osteoclast surface (%)	Osteoid surface (%)	Mineralizing surface (%)	Bone formation rate ($\mu m^3/\mu m^2$/day)	Osteoid volume (%)	Mineralization lag time (day)
Vehicle control (0.24% succinate buffer)	12	1.22 ± 0.11	10.81 ± 2.12	43.63 ± 1.64	0.56 ± 0.04	1.65 ± 0.38	0.94 ± 0.14
Etelcalcetide 0.3 mg/kg	12	0.95 ± 0.28	6.67 ± 1.65	36.39 ± 1.77*	0.46 ± 0.03	1.00 ± 0.30	0.68 ± 0.16
Etelcalcetide 1 mg/kg	11	0.83 ± 0.16	3.63 ± 0.70*	30.60 ± 2.43*	0.35 ± 0.04*	0.48 ± 0.08*	0.41 ± 0.06*
Vehicle control (0.5% methylcellulose solution)	13	1.15 ± 0.10	12.54 ± 2.00	34.70 ± 1.88	0.45 ± 0.03	2.46 ± 0.88	1.52 ± 0.40
Cinacalcet hydrochloride 3 mg/kg	10	1.36 ± 0.27	10.07 ± 2.08	33.88 ± 1.71	0.41 ± 0.03	1.89 ± 0.54	1.18 ± 0.29
Cinacalcet hydrochloride 15 mg/kg	10	1.43 ± 0.11	12.06 ± 2.64	31.51 ± 1.99	0.42 ± 0.05	1.81 ± 0.45	1.29 ± 0.23

Mean ± SE

*: $P < 0.05$ (vs. respective vehicle control, Tukey's test)

3.1.5.2 Effects on bone disease (CTD 4.2.1.1-11, Study No. R[redacted]0075)

Etelcalcetide 1 mg/kg or vehicle (0.24% succinate buffer) was administered subcutaneously to 5/6 nephrectomized CKD rats once daily for 42 days. Serum PTH levels, femoral cortical porosity, and bone strength parameters (maximum load, energy to failure, and toughness) on Day 42 are shown in Table 8. In the 5/6 nephrectomized CKD rat model, the left renal artery of male rats was ligated (= 2/3 nephrectomy), and the right kidney was removed 1 week later. The 5/6 nephrectomized rats were fed a high-P and low-Ca diet (1.0% P and 0.6% Ca) for 14 weeks, beginning 3 weeks after the nephrectomy, to further induce SHPT. The dose was reduced to 0.6 mg/kg in the etelcalcetide 1 mg/kg group on and after Day 12 due to loss in body weight for this group.

Femoral cortical porosity was significantly decreased in the etelcalcetide group compared to the vehicle control group. Bone strength parameters were assessed in both groups. Maximum load tended to increase and energy to failure and toughness were significantly greater in the etelcalcetide group than in the vehicle control group.

Table 8. Serum PTH levels, cortical porosity, and bone strength parameters at Week 6 in 5/6 nephrectomized CKD rats

Treatment group	n	Serum PTH (pg/mL)			Cortical porosity (%)	Bone strength parameter		
		Baseline	Day 42	Relative serum PTH [a)]		Maximum load (N)	Energy to failure (N.mm)	Toughness (MPa)
Vehicle control	12	791 ± 129	2205 ± 497	285 ± 44	8.256 ± 2.693	156.3 ± 7.7	71.3 ± 8.1	4.21 ± 0.47
Etelcalcetide 1 mg/kg	13	686 ± 65	90 ± 23*	14 ± 3	2.273 ± 0.734*	178.1 ± 7.8	109.6 ± 10.8*	6.05 ± 0.42*

Mean ± SE

a) Serum PTH at Week 6 as percent of baseline (%)

*: $P < 0.05$ (vs. vehicle control, Tukey's test)

3.2 Secondary pharmacodynamics

3.2.1 Selectivity (CTD 4.2.1.2-3, Study No. 4169-NC-128)

The ability of etelcalcetide (10 μmol/L) to inhibit ligand binding to a panel of 34 receptors, channels, and a transporter was tested. Etelcalcetide inhibited ligand binding to the human muscarinic M_2 receptor, rat sigma σ_2 receptor, and rat adrenergic α_{1A} receptor by ≥30%, but did not inhibit ligand binding to any target by ≥50%.

3.2.2 Activity of biotransformation products (CTD 4.2.1.2-4, Study No. R[redacted]0023)

A study was conducted to determine the activity of the following biotransformation products of etelcalcetide detected in a human mass balance study: a serum albumin conjugate of the D-amino acid peptide backbone (SAPC) and a glutathione disulfide of the D-amino acid peptide backbone (M10). HEK293T cells transfected with the human CaSR were treated with etelcalcetide (0.1-300 μmol/L), SAPC (0.05-100 μmol/L), or M10 (0.1-300 μmol/L) in the presence of 1.2 mmol/L Ca, and intracellular IP-1 accumulation was quantified. Etelcalcetide and M10 concentration-dependently increased intracellular IP-1 accumulation, and the EC_{50} values were 26 and 66 μmol/L, respectively. The activity of SAPC at 100 μmol/L was <14% of the activity observed with etelcalcetide.

3.3 Safety pharmacology

Table 9. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/method of assessment, etc.	Doses	Route of administration	Findings	CTD (Study No.)
CNS	Dog (4 males/group)	clinical signs, body temperature, neurobehavioral examinations (1.5 mg/kg only)	0, 0.3, 1.5 mg/kg	IV	Tremoring, limb stiffness, rapid/shallow breathing, tremors in the hind limbs, and slightly increased body temperature were observed at 1.5 mg/kg. Thus, the no-observed-effect-level (NOEL) for CNS effects in dogs was determined to be 0.3 mg/kg.	4.2.1.3-1 (4169-NC-102)
Cardiovascular system	Dog (4 males/group)	mean blood pressure, heart rate, ECG (unanesthetized and unrestrained)	0, 0.3, 1.5 mg/kg	IV	QTcF prolongation, transient increases in heart rate, and increased blood pressure were observed at 1.5 mg/kg. Thus, the NOEL for cardiovascular effects in dogs was determined to be 0.3 mg/kg.	4.2.1.3-1 (4169-NC-102)
	HEK293 cells (n = 3-4/group)	hERG current	0.0954, 0.286, 0.954, 2.86, 9.54 μmol/L	*In vitro*	Etelcalcetide had no effect on hERG current at doses up to the highest concentration tested (9.54 μmol/L).	4.2.1.3-5 (122036)
Respiratory system	Dog (4 males/group)	respiration rate, blood gases (partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, arterial blood pH, hemoglobin oxygen saturation)	0, 0.3, 1.5 mg/kg	IV	There were no effects on respiration rate or blood gases at doses up to the highest dose (1.5 mg/kg) of etelcalcetide. The NOEL for respiratory effects in dogs was determined to be 1.5 mg/kg.	4.2.1.3-1 (4169-NC-102)

3.4 Pharmacodynamic drug interactions

3.4.1 Interaction with cinacalcet hydrochloride (CTD 4.2.1.4-1, Study No. R[redacted]0030)

Interaction of etelcalcetide with cinacalcet hydrochloride was evaluated using HEK293T cell line transfected with the human CaSR. Intracellular IP-1 accumulation was quantified following individual or combined exposure to etelcalcetide and/or cinacalcet hydrochloride. Intracellular IP-1 accumulation following coadministration of etelcalcetide and cinacalcet hydrochloride was almost comparable to the sum of intracellular IP-1 accumulation that was observed for each compound alone.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

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

Excessive secretion of PTH in SHPT patients induces high bone turnover associated with increased bone resorption, thereby causing excessive Ca and P release from the bone into blood, which results in vascular and

soft tissue calcification and osteitis fibrosa (*J Am Soc Nephrol*. 2001;12: 2131-2138, *Hemodial Int*. 2007;11: 340-348). Sustained overproduction of PTH is associated with parathyroid gland hyperplasia, which contributes to further progression of SHPT.

Etelcalcetide is a CaSR agonist. The CaSR regulates PTH secretion, parathyroid cell proliferation and other effects. A disulfide bond is formed between the SH group of the D-cysteine within etelcalcetide and Cys482 in the CaSR and thereby etelcalcetide allosterically enhances the activation of the receptor by extracellular Ca and inhibits PTH secretion and parathyroid cell proliferation [see Sections "3.1.1 CaSR agonist activity" and "3.1.2.1 *In vitro* inhibition of PTH secretion"]. In the CKD rat model, etelcalcetide inhibited PTH secretion, thus reducing serum Ca levels, which resulted in prevention of ectopic calcification in the heart, kidney, and aorta [see Section "3.1.4 Prevention of vascular calcification"]. Etelcalcetide improved cortical porosity and preserved bone strength by reducing bone turnover [see Section "3.1.5 Control of bone turnover"]. Furthermore, etelcalcetide reduced parathyroid cell proliferation and parathyroid gland hyperplasia [see Section "3.1.3 Prevention of parathyroid gland hyperplasia"]. Based on the above findings, etelcalcetide is considered to be effective in the treatment of SHPT.

The applicant explained the reason why administration of 0.3 to 3 mg/kg of etelcalcetide caused an increase in plasma P in 5/6 nephrectomized CKD rats [see Section "3.1.2.2 *In vivo* inhibition of PTH secretion"], which is as follows:
PTH has been reported to inhibit renal tubular P reabsorption mediated by type II sodium-dependent P cotransporter (*Endocrinol*. 2000;141: 2159-2165). An increase in plasma P observed with etelcalcetide is considered attributable to increased renal tubular P reabsorption in response to the decrease in plasma PTH induced by etelcalcetide. On the other hand, etelcalcetide reduces serum P levels in SHPT patients on dialysis [see Section "7.R.2 Serum Ca levels, serum P levels, and effect on bone turnover"]. This can be explained by that the mechanism by which PTH inhibits P reabsorption is still working in CKD rats, but not in SHPT patients. Differences in blood P response have been reported also with cinacalcet hydrochloride (*Clin Calcium*. 2012;22: 1567-1576). Therefore, an increase in plasma P after administration of etelcalcetide in animals with residual kidney function should be of low relevance to SHPT patients.

Taking account of the results from primary pharmacodynamic studies submitted in the current application, PMDA considers that etelcalcetide is expected to be effective in the treatment of SHPT.

3.R.2 Safety pharmacology study

The results from a safety pharmacology study were submitted in the current application. In the study, administration of a single intravenous dose of 1.5 mg/kg etelcalcetide to dogs caused approximately a 30% decrease in serum Ca at 24 hours post-dose. Findings at around 24 hours after dosing included tremoring, QTc prolongation, and increased body temperature, heart rate, and mean blood pressure.

The applicant's explanation about the reasons for these findings:

As to tremoring, it is known that a decrease in serum Ca causes skeletal muscle spams (tetany) (*Guyton and Hall Textbook of Medical Physiology* 12th, 2011). Animals showed clinical signs including tremoring coincident with maximal decreases in serum Ca. The clinical signs improved or resolved following Ca supplementation or recovery of serum Ca levels with lactated Ringer's solution. Thus, the applicant considers that these clinical signs resulted from a decrease in serum Ca, which is an expected pharmacological effect of etelcalcetide.

The increase in QTc interval is considered a secondary effect of decreased serum Ca for the following reasons: (i) QTc prolongation was temporally associated with maximum decreases in serum Ca levels and normalized following recovery of serum Ca levels, and (ii) etelcalcetide had no effect on hERG channel current *in vitro*.

A slight increase in body temperature and increased heart rate and mean blood pressure are also considered secondary to a decrease in serum Ca or tremoring.

On the above grounds, the no-observed-effect-level (NOEL) for CNS and cardiovascular effects was determined to be 0.3 mg/kg and the NOEL for respiratory effects was determined to be 1.5 mg/kg. The blood etelcalcetide concentration at the NOEL (0.3 mg/kg) in dogs was 0.63 μg/mL at 2 minutes post-dose, and the safety margin is <1-fold when compared with the human C_{max} at the maximum clinical dose (15 mg). However, all of the findings observed in the study submitted were secondary to a decrease in serum Ca, which is an expected pharmacological effect of etelcalcetide. Therefore, etelcalcetide can be used safely in clinical settings by monitoring serum Ca levels and watching for symptoms of hypocalcaemia.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics of etelcalcetide were investigated following administration of etelcalcetide or [^{14}C]-etelcalcetide in rats and dogs. Plasma etelcalcetide concentrations were determined by Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS), and the LLOQ was 1.1 ng/mL in rat plasma and 1.0 ng/mL in dog plasma. Its biotransformation products in plasma were converted to M11 by chemical reduction and then total M11 concentrations were determined by LC/MS/MS. The LLOQ for M11 was 25 ng/mL. [^{14}C]-etelcalcetide-derived radioactivity was determined using liquid scintillation counter, radio-HPLC, and quantitative whole-body autoradiography. The results from the main studies are described in sections below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.1.1-6, 4.2.1.3-1, 4.2.2.2-1, and 4.2.2.2-2, Study Nos. 4169-NC-103, 4169-NC-102, 118436, and 4169-NC-114)

Normal rats, 5/6 nephrectomized rats, bilaterally nephrectomized rats, and normal dogs received etelcalcetide or [^{14}C]-etelcalcetide ([^{14}C]Ac and [^{14}C]Ala) by single intravenous bolus injection or intravenous infusion. Pharmacokinetic parameters in treated animals are shown in Table 10. The primary route of elimination of

etelcalcetide is in the urine [see Section "4.4.1 Urinary, fecal, and biliary excretion in rats"]. There was a trend towards an increase in AUC and prolonged half-life in nephrectomized rats.

Table 10. Plasma pharmacokinetic parameters following intravenous administration of etelcalcetide or [^{14}C]-etelcalcetide

Species	Method of administration	Test article	Dose	Model	n	$AUC_{0\text{-}24h}$ (μg·h/mL)	$t_{1/2}$ (h)
Male rat [a)]	Bolus	Etelcalcetide	0.3 mg/kg	Normal	4	1.26 ± 0.06	1.3
				5/6 nephrectomized	4	1.47 ± 0.17	1.5
				2 × nephrectomized	3	3.90 ± 0.38	6.7
			1.0 mg/kg	Normal	4	3.74 ± 0.17	1.3
				5/6 nephrectomized	4	5.12 ± 0.37	2.2
				2 × nephrectomized	3	11.41 ± 0.58	6.7
		[^{14}C]Ac	2.5 mg/kg	Normal	10	7.42 [d)]	5.8
				2 × nephrectomized	6	134.45 [d)]	23.1
		[^{14}C]Ala		Normal	2	9.28 [d)]	5.0
Male dog [b)]	Bolus	Etelcalcetide	1.5 mg/kg	Normal	4	3.55 ± 0.57 [e)]	10.2 ± 1.0
	Infusion [c)]	Etelcalcetide	1.0 μg/kg/h	Normal	4	0.063 ± 0.009	2.6 ± 0.2
			8.0 μg/kg/h	Normal	4	0.457 ± 0.128	5.8 ± 0.6
			20 μg/kg/h	Normal	4	1.207 ± 0.159	8.2 ± 1.4

a) Mean ± SE for $AUC_{0\text{-}24h}$. $t_{1/2}$ was calculated using the mean plasma concentration in each group. The unit of $AUC_{0\text{-}24h}$ is μg eq.·h/mL when radiolabeled drug was administered.
b) Mean ± SD
c) Infused over 24 hours
d) Blood samples from rats in each group were pooled for analysis.
e) $AUC_{0\text{-}48h}$

4.1.2 Repeated-dose studies (CTD 4.2.3.2-2, 4.2.3.2-4, and 4.2.3.2-6 to 4.2.3.2-8, Study Nos. 4169-NC-107, 119037, 4169-NC-106, 119036, and 4169-NC-132)

The toxicokinetics of etelcalcetide were evaluated in a 28-day repeat-dose (intravenous bolus injection) toxicity study in male and female rats and a 27-day repeat-dose (intravenous bolus injection) toxicity study in male and female dogs. In the studies, etelcalcetide was administered once daily to rats for 28 days or every other day to dogs for 27 days. Plasma pharmacokinetic parameters of etelcalcetide in treated animals are shown in Table 11. The $AUC_{0\text{-}t}$ tended to increase slightly on Day 27 or 28 in the high dose group.

Table 11. Plasma pharmacokinetic parameters following repeated intravenous administration in rats and dogs

Species	Sex	Dose (mg/kg)	$AUC_{0\text{-}t}$ [a)] (μg·h/mL)		$t_{1/2}$ [b)] (h)	
			Day 1	After the last dose [c)]	Day 1	After the last dose [c)]
Rat	Males	0.3	0.48 ± 0.01	0.58 ± 0.04	1.5	1.6
		1.0	1.41 ± 0.10	1.57 ± 0.57	1.6	1.6
		3.0	4.51 ± 0.37	6.17 ± 0.26	1.8	1.7
	Females	0.3	0.62 ± 0.04	0.65 ± 0.07	1.6	1.6
		1.0	2.01 ± 0.11	2.14 ± 0.06	1.6	1.8
		3.0	4.72 ± 1.54	7.81 ± 0.77	1.8	1.8
Dog	Males	0.1	0.26 ± 0.02	0.29 ± 0.01	6.9 ± 2.3	7.2 ± 0.5
		0.3	0.70 ± 0.04	0.81 ± 0.05	6.9 ± 0.2	7.3 ± 0.5
		1.5	4.25 ± 0.75	4.54 ± 1.12	6.8 ± 0.6	7.7 ± 0.3
	Females	0.1	0.24 ± 0.03	0.29 ± 0.03	5.5 ± 2.1	7.1 ± 0.1
		0.3	0.72 ± 0.13	0.89 ± 0.12	7.2 ± 0.9	7.5 ± 0.4
		1.5	3.82 ± 0.22	5.02 ± 0.53	6.2 ± 0.4	8.1 ± 0.7

Mean ± SE, n = 3 (n = 5 for male and female dogs in the 1.5 mg/kg group only)
a) $AUC_{0\text{-}8h}$ in rats, $AUC_{0\text{-}24h}$ in dogs
b) Calculated using the mean plasma concentration in each group in the rat study.
c) Day 28 in rats, Day 27 in dogs

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-1, Study No. 117581)

Following a single intravenous dose of [^{14}C]-etelcalcetide ([^{14}C]Ac) 2.5 mg/kg in male albino rats, tissue radioactivity concentrations were determined at 0.083, 0.25, 0.5, 1, 4, 12, 24, 48, 96, and 168 hours post-dose.[1)] For most tissues, the peak tissue concentration of radioactivity was reached within the first 1 hour post-dose. High radioactivity exposures were observed in the hyaline cartilage, epiphyseal line, intervertebral cartilage, articular cartilage, and renal medulla during the first 1 hour post-dose, and the tissue to plasma radioactivity ratios were 17.0, 14.1, 9.4, 5.8, and 1.8, respectively. Blood to plasma concentration ratios for radioactivity were <0.8 at all time-points through 168 hours post-dose, indicating limited distribution of etelcalcetide into blood cells.

Following a single intravenous dose of [^{14}C]-etelcalcetide ([^{14}C]Ac) 2.5 mg/kg in female albino rats and male pigmented rats, radioactivity concentrations were determined. Similar results as above were obtained, and there were no gender differences in radioactivity distribution or melanin affinity of etelcalcetide.

4.2.2 Placental transfer in rats (CTD 4.2.3.5.3-1, Study No. 116847)

Pregnant rats received etelcalcetide 0.75, 1.5, or 3.0 mg/kg intravenously once daily from gestation day 7 through gestation day 21. Maternal and fetal plasma etelcalcetide concentrations were measured on gestation day 21. The observed mean percent of fetal plasma to maternal plasma concentration was 2.99%, 2.86%, and 2.39% at the 0.75, 1.5, and 3.0 mg/kg dose levels, respectively, indicating low placental transfer of etelcalcetide.

4.3 Metabolism

4.3.1 Biotransformation products in plasma and urine (CTD 4.2.2.2-1. Study No. 118436)

Following a single intravenous dose of [^{14}C]-etelcalcetide ([^{14}C]Ac) 2.5 mg/kg in normal male rats and bilaterally nephrectomized male rats, the biotransformation profiles in plasma were characterized. The abundant components in plasma were intact etelcalcetide, serum albumin peptide conjugate (SAPC), an active biotransformation product, M10 (a glutathione disulfide), and an active biotransformation product, M11 (etelcalcetide D-amino acid peptide without L-Cys).

Following a single intravenous dose of [^{14}C]-etelcalcetide ([^{14}C]Ac) 1.84 mg/kg in bile duct-cannulated (BDC) male rats, the biotransformation profiles in urine were characterized. Predominant compounds in urine included intact etelcalcetide, a biotransformation product, M1 (a thiosulfate disulfide), and a biotransformation product, M3 (acetylated M10).

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1) Radioactivity levels were determined in the following: plasma, blood, cerebrum, cerebellum, pituitary gland, spinal cord, eyes, Harderian gland, thyroid, thymus, lungs, liver, kidneys, renal medulla, renal cortex, adrenal gland, spleen, pancreas, white fat, muscle, bone, epiphyseal line, hyaline cartilage, intervertebral cartilage, articular cartilage, skin, bone marrow, lymph nodes, arterial wall, testis, epididymis, seminal vesicle, prostate gland, stomach, small intestine, large intestine, and bladder.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.2-1, Study No. 118436)

In order to evaluate the urinary, fecal, and biliary excretion of etelcalcetide in rats, recovery of radioactivity (% of total radioactivity administered) was determined following a single intravenous dose of 1.84 or 2.5 mg/kg of [^{14}C]-etelcalcetide ([^{14}C]Ac and [^{14}C]Ala) in bilaterally nephrectomized male rats and BDC rats. While radioactivity elimination was minimal in bilaterally nephrectomized rats, approximately 80% of the etelcalcetide dose was excreted in urine in BDC rats. This suggest that etelcalcetide is eliminated predominantly via renal clearance. There was minor excretion in feces (1.34% to 3.90%) and bile (0.28% to 0.64%).

4.4.2 Excretion in milk in rats (CTD 4.2.2.5-1, Study No. Y[redacted]AG004)

[^{14}C]-etelcalcetide ([^{14}C]Ac) 2.5 mg/kg was administered by single intravenous bolus injection to female rats at 11 days post-parturition. Excretion in mild was assessed at 1, 8, 24, 48, and 72 hours post-dose. The radioactivity concentration in milk reached C_{max} (450 ng eq./mL, which is 3.31-fold that in plasma) at 8 hours post-dose and then decreased with time. The milk/plasma ratios of radioactivity concentration were 1.06 to 1.44 after 24 hours post-dose. Etelcalcetide was shown to transfer into milk.

4.R Outline of the review conducted by PMDA

PMDA's view:

There is no particular problem with the non-clinical pharmacokinetics of etelcalcetide, but the observed trend towards a slight increase in the $AUC_{0\text{-}t}$ of plasma etelcalcetide in the high dose group in rat and dog repeated-dose studies (Table 11) is discussed in Section 6.R.

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity studies of etelcalcetide conducted were repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies and other toxicity studies (e.g., toxicity studies for impurities). Some of the studies were non-GLP studies and thus submitted as reference data. Succinate buffer (10 mmol/L) was used as vehicle.

5.1 Single-dose toxicity (CTD 4.2.3.2-1 and 4.2.3.2-5 [reference data], Study Nos. 2082-NC-100 and 4169-NC-101)

Although no single-dose toxicity studies were conducted, the acute toxicity of etelcalcetide was assessed in rat and dog toxicity studies.

In a 7-day intravenous toxicity study in rats, etelcalcetide 0.5, 2, or 5 mg/kg was administered intravenously once daily. After the first dose, decreases in serum Ca were observed at 5 mg/kg, but there were no changes in clinical observations or mortality.

In a rat micronucleus test (CTD 4.2.3.3.2-1), etelcalcetide 5, 7.5, 10, or 12.5 mg/kg was administered by intravenous infusion once daily. After the first dose, mortality, lethargy, and piloerection were observed at ≥7.5 mg/kg.

In a 7-day intravenous toxicity study in dogs, etelcalcetide 0.5, 2, or 5 mg/kg was administered intravenously once daily. After the first dose, decreases in serum Ca were noted at 2 and 5 mg/kg and lethargy, tremors, convulsions, dyspnea, emesis, etc. at ≥2 mg/kg, but there was no mortality.

The approximate lethal doses by intravenous administration were determined to be 7.5 mg/kg in rats and >5 mg/kg in dogs.

5.2 Repeated-dose toxicity

Intravenous toxicity studies were conducted in rats (6 months) and dogs (6 months). The principal findings were tremors, emesis, convulsions, reduced body weight gain, reduced food intake, and QTc prolongation, which were considered to be directly or secondarily related to decreased serum Ca as an expected pharmacological effect of etelcalcetide. The no-observed-adverse-effect levels (NOAELs) in rats (6 months) and dogs (6 months) were 1 mg/kg and 0.2 mg/kg, respectively. Exposures (AUCs) at NOAELs in rats and dogs were 0.53- and 0.05-fold human exposure at the maximum clinical dose (15 mg), respectively.

5.2.1 Six-month intravenous toxicity study in rats with a 4-week recovery period (CTD 4.2.3.2-4, Study No. 119037)

Etelcalcetide 0.3, 1, or 3 mg/kg or vehicle was administered intravenously to male and female rats once daily for 6 months, and the reversibility after a 4-week recovery period was assessed in animals in the 3 mg/kg and control groups. One male in the 0.3 mg/kg group was found dead on Day 103, which was considered incidental because of no findings suggestive of the cause of death. One female in the 1 mg/kg group was sacrificed moribund due to a deterioration in clinical signs and necropsied on Day 70. Necropsy revealed spontaneous lymphoma. Although 1 male in the 3 mg/kg group was sacrificed moribund and necropsied due to intermittent convulsions. Necropsy and histopathological examination revealed no abnormalities, and therefore the convulsions were considered associated with markedly decreased serum Ca. Findings observed in treated animals were as follows: Decreased serum Ca and increased serum P at ≥0.3 mg/kg, increased cytoplasmic eosinophilia of the parathyroid gland at ≥1 mg/kg, and tremors, decreased general activity, hunched posture, uncoordinated gait, abnormal gait, increased vocalization, decreases in body weight gain and food consumption, an increase in neutrophils, a decrease in lymphocytes, increased serum albumin and A/G ratio, decreased serum potassium and globulins, a decrease in spleen weight, and dark focus with erosion or depressed focus in the gastric mucosa at 3 mg/kg. All changes were reversible after a recovery period. Increased cytoplasmic eosinophilia of the parathyroid gland noted at ≥1 mg/kg was considered to result from the activation of the PTH producing chief cells secondary to persistent and excessive decrease in serum Ca induced by etelcalcetide.

Because decreased general activity, convulsions, and other changes associated with markedly decreased serum Ca were observed at ≥3 mg/kg of etelcalcetide, the NOAEL was determined to be 1 mg/kg/day.

5.2.2 Six-month intravenous toxicity study in dogs with a 4-week recovery period (CTD 4.2.3.2-7, Study No. 119036)

Etelcalcetide 0.2, 0.5, or 0.9 mg/kg or vehicle was administered intravenously to male and female dogs every other day for 6 months, and the reversibility after a 4-week recovery period was assessed in animals in the 0.9 mg/kg and control groups. Findings observed in treated animals were as follows: Decreased serum Ca and increased serum P at ≥0.2 mg/kg, emesis, salivation, reduced general activity, reduced body weight or body weight gain, reduced food intake, QTca prolongation, and decreased reticulocytes at ≥0.5 mg/kg, and tremors at 0.9 mg/kg. All changes were reversible after a recovery period.

The NOAEL was determined to be 0.2 mg/kg.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-5, 4.2.3.3.1-6, and 4.2.3.3.2-1, Study Nos. 4169-NC-104, 4169-NC-105, 4169-NC-112, and 4169-NC-122)

A bacterial reverse mutation assay, a gene mutation test in Chinese hamster ovary cells, a chromosomal aberration test in human peripheral blood lymphocytes, and a rat micronucleus test, and other tests were performed. In the bacterial reverse mutation assay, positive mutagenic responses were seen in two strains of *Salmonella typhimurium* (TA100 and TA1535). However, published literature has reported that SH group-containing amino acids and peptides induce mutations in TA100 strain via reactive oxygen species formed from the SH group (*Science*. 1983;220: 961-963, *Mutagenesis*. 1989;4: 221-227, and other articles). Etelcalcetide also possibly showed a positive response in TA1535 strain through a similar mechanism. The applicant therefore considered that etelcalcetide induced mutations, which is of no mammalian relevance. Etelcalcetide was negative in the gene mutation test in Chinese hamster ovary cells, chromosomal aberration test in human peripheral blood lymphocytes, and rat micronucleus test.

5.4 Carcinogenicity

Carcinogenicity studies were conducted in mice and rats, both of which showed no carcinogenic potential of etelcalcetide. Exposure (AUC) in rats at a dose of 1.6 mg/kg at which no tumors were observed was 0.33-fold human exposure at the maximum clinical dose (15 mg).

5.4.1 Twenty-six-week subcutaneous carcinogenicity study in Tg.rasH2 mice (CTD 4.2.3.4.1-2, Study No. 116846)

Etelcalcetide 0.375/0.3, 0.75/1, or 1.5/3 (males/females) mg/kg or vehicle was administered subcutaneously to male and female Tg.rasH2 mice once daily for 26 weeks. No etelcalcetide-related neoplastic or non-neoplastic lesions were observed in treated animals. Etelcalcetide was not carcinogenic in Tg.rasH2 mice.

5.4.2 Two-year subcutaneous carcinogenicity study in rats (CTD 4.2.3.4.1-5, Study No. 116848)

Etelcalcetide 0.2, 0.4, 0.8, or 1.6 mg/kg or vehicle was administered subcutaneously to male and female rats once daily for 2 years. The neoplastic finding noted was an increased incidence of anterior pituitary adenoma in females of all groups. The incidences of anterior pituitary adenoma were 86% in the 0.2 mg/kg group, 86%

in the 0.4 mg/kg group, 88% in the 0.8 mg/kg group, 71% in the 1.6 mg/kg group, and 77% in the vehicle control group. These values were slightly higher than the historical range of the laboratory (63% to 85%), and the incidence of the change was not dose-dependent. The non-neoplastic finding noted was fibrosis at the injection site. Based on the above, etelcalcetide was not carcinogenic in rats.

5.5 Reproductive and developmental toxicity

Reproductive and developmental toxicity studies conducted were a fertility and embryo-fetal development study in rats, an embryo-fetal development study in rabbits, and a rat study for effects on pre- and postnatal development, including maternal function. The NOAELs for fertility or embryo-fetal development were 3 mg/kg in rats and 1.5 mg/kg in rabbits. Exposures (AUCs) at the NOAELs in rats and rabbits were 1.49- and 3.59-fold human exposure at the maximum clinical dose (15 mg), respectively. The data showed low placental transfer and transfer into milk of etelcalcetide [see Sections “4.2.2 Placental transfer in rats” and “4.4.2 Excretion in mild in rats”].

5.5.1 Fertility and embryo-fetal development study in rats (CTD 4.2.3.5.2-3, Study No. 119088)

Male and female rats received etelcalcetide 0.75, 1.5, or 3 mg/kg or vehicle intravenously once daily for 28 days (males) or 15 days (females) prior to mating, during cohabitation, and through the day before necropsy for males and through gestation day 17 for females. Findings in parental animals included the following; tremors, ataxia, hunched posture, and reduced body weight gain at ≥1.5 mg/kg; and reduced food intake and prolonged periods of diestrus at 3 mg/kg. There were no effects on fertility or embryo-fetal development or fetal external, visceral, or skeletal morphology. The NOAEL for parental general toxicity was determined to be 0.75 mg/kg/day, and the NOAEL for fertility in male and female rats and embryo-fetal development was determined to be 3 mg/kg/day.

5.5.2 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2-6, Study No. 119089)

Pregnant rabbits received etelcalcetide 0.375, 0.75, or 1.5 mg/kg or vehicle intravenously once daily from gestation day 7 through gestation day 19. Two rabbits in the 0.375 mg/kg group, 1 rabbit in the 0.75 mg/kg group, and 1 rabbit in the 1.5 mg/kg group were sacrificed moribund. Body weight and food intake were reduced in these animals. Although the cause for the reduced food intake is unknown, there was no dose-response relationship in mortality. No death occurred at doses up to 2.25 mg/kg in a dose range-finding embryo-fetal development toxicity study in rabbits. Thus, these unscheduled sacrifices were considered unrelated to etelcalcetide. In maternal animals, decreased defecation, reduced body weight gain, and reductions in food intake were observed at ≥1.5 mg/kg. There were no effects on embryo-fetal development. The NOAEL for maternal general toxicity was determined to be 0.75 mg/kg/day, and the NOAEL for embryo-fetal development was determined to be 1.5 mg/kg/day.

5.5.3 Rat study for effects on pre- and postnatal development, including maternal function (CTD 4.2.3.5.3-1, Study No. 116847)

Pregnant rats received etelcalcetide 0.75, 1.5, or 3 mg/kg or vehicle intravenously once daily from gestation day 7 through lactation day 20. One rat in the 3 mg/kg group was sacrificed moribund, and tremors, dehydration,

emaciation, reduced body weight and food intake, and other changes were noted in this animal. Findings in dams were as follows: tremors, salivation, and an increase in the duration of gestation at ≥1.5 mg/kg; and dehydration, hunched posture, and reduced body weight gain and food intake at 3 mg/kg. The applicant explained that the increase in the duration of gestation was due to reduced uterine smooth muscle contractions associated with decreased serum Ca. Findings in pups were as follows: reduced body weight gain at ≥1.5 mg/kg; and a decrease in the number of liveborn pups, an increase in the number of stillborn pups, and a reduction in the percentage of pups surviving at 3 mg/kg. The applicant explained that these findings were associated with deterioration in maternal nutritional status. The NOAEL for maternal general toxicity and pup survival/development was determined to be 0.75 mg/kg/day. The NOAEL for sexual maturation and neurobehavioral and reproductive function in the F1 generation pups was determined to be 3 mg/kg/day.

5.6 Local tolerance (CTD 4.2.3.6-1, Study No. 117458)

A single dose of etelcalcetide 5 mg/mL or vehicle was administered to male dogs via intravenous (right front leg cephalic vein) or paravenous (right hind leg saphenous vein) injection to evaluate local tolerance of etelcalcetide. There were no etelcalcetide-related macroscopic observations at the injection site (irritation scores based on the modified Draize test). Necropsy and histopathological examination of the injection site revealed no effects of etelcalcetide.

5.7 Other toxicity studies

5.7.1 Safety assessment of impurities

5.7.1.1 Four-week intravenous toxicity study of mixture of etelcalcetide and impurities (CTD 4.2.3.7.6-1, Study No. 119181)

Male and female rats received 0.3, 1, or 3 mg/kg etelcalcetide and [redacted] different impurities and degradants potentially present in the drug substance or product, or vehicle intravenously once daily for 4 weeks. Findings observed in treated animals were as follows: Decreased serum Ca and increased serum P at ≥0.3 mg/kg; increased cytoplasmic eosinophilia of the parathyroid gland at ≥1 mg/kg; and tremors, decreased general activity, hunched posture, abnormal gait, increased vocalization, reduced body weight gain, etc., at 3 mg/kg. These findings were consistent with those observed with etelcalcetide drug substance without those impurities, and no toxic changes specific to the added impurities were noted. The NOAEL was determined to be 1 mg/kg/day.

5.7.1.2 Ames assay for Impurity A (CTD 4.2.3.7.6-4, Study No. 118280)

In silico assessment of potential impurities present in the drug substance revealed that Impurity A had a structural alert. Thus, a bacterial reverse mutation assay was performed. As a result, Impurity A was found not to be mutagenic.

5.7.2 Immunogenicity

No immunogenicity studies were conducted. Repeated-dose toxicity studies in rats and dogs showed no findings suggestive of anti-etelcalcetide antibody formation such as decreased plasma etelcalcetide concentrations and the activation of the immune system following repeated administration. In the repeated-

dose toxicity studies in rats and dogs, an increase in neutrophils, a decrease in lymphocytes, and decreases in spleen and thymus weights were noted, which were not direct effects of etelcalcetide but were secondary to stress associated with decreased serum Ca.

5.R Outline of the review conducted by PMDA

According to the applicant's explanation, the NOAELs identified in rat and dog repeated-dose toxicity studies corresponded to a safety margin of <1-fold relative to human exposure at the maximum clinical dose. PMDA asked the applicant to explain whether toxic changes observed in the rat and dog repeated-dose toxicity studies may occur in clinical use.

The applicant's response:

While PTH is involved in the renal excretion of Ca, CaSR agonists increase renal Ca excretion by lowering PTH levels. Because of the fact, healthy animals are more sensitive to the serum Ca lowering effects of a CaSR agonist, relative to SHPT patients who have impaired or no kidney function. All of the toxic changes observed in rats and dogs were directly or secondarily related to decreased serum Ca, which is an expected pharmacological effect of etelcalcetide. Etelcalcetide can be used safely in clinical settings by monitoring serum Ca levels and watching for the symptoms of hypocalcaemia.

PMDA accepted the applicant's explanation.

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

[redacted] formulation was used in Japanese phase I and phase I/II studies and [redacted] formulation in a Japanese phase III study, which were conducted to support the current application.

Plasma and urine etelcalcetide concentrations were determined by LC/MS/MS. The LLOQ was 0.2 ng/mL for etelcalcetide in plasma and 50.0 ng/mL for etelcalcetide in urine. Its biotransformation products in plasma were converted to M11 by chemical reduction and then Total M11 concentrations were determined by LC/MS/MS. The LLOQ for M11 was 50.0 ng/mL.

For the detection of anti-etelcalcetide antibodies, an enzyme-linked immunosorbent assay was used in the Japanese phase I and phase I/II studies, and surface plasmon resonance in the Japanese phase III study.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biomaterials

6.2.1.1 Protein binding (CTD 4.2.2.3-2, Study No. 119313)

When blood from healthy volunteers and CKD patients was incubated with etelcalcetide (50-10,000 ng/mL), the mean plasma protein binding ranged from 42% to 52% and from 37% to 44%, respectively. The plasma

protein binding was independent of concentration over the concentration range tested. There were no differences in plasma protein binding between healthy volunteers and CKD patients.

6.2.1.2 Distribution in blood cells (CTD 4.2.2.3-3, Study No. 118358)

When a ^{14}C-labeled etelcalcetide molecule, [^{14}C]Ac-etelcalcetide (0.1-10.0 μmol/L), was incubated in whole blood obtained from healthy volunteers and CKD patients, the blood to plasma ratios ranged from 0.50 to 0.56 and from 0.64 to 0.69, respectively, indicating no preferential partitioning of etelcalcetide into red blood cells. The blood to plasma ratio was independent of concentration over the concentration range tested, and there were no differences in the blood to plasma ratio between healthy volunteers and CKD patients.

6.2.1.3 Metabolism

6.2.1.3.1 Metabolism of etelcalcetide (CTD 4.2.2.3-3 and 5.3.2.2-1, Study Nos. 118358 and 119917)

[^{14}C]-etelcalcetide ([^{14}C]Ac) at 5 and 10 μmol/L was incubated in human whole blood and with human hepatocytes, liver S9 fraction, and kidney S9 fraction, and its biotransformation was determined after inclubation. In blood, serum albumin peptide conjugate (SAPC) was the predominant product (71.4%), and intact etelcalcetide was also detected (14.1%). Intact etelcalcetide, its biotransformation products (M10 and M11), etc., were mainly identified in hepatocytes, liver S9 fraction, and kidney S9 fraction.

When human liver microsomes and S9 fraction were incubated with etelcalcetide 5 μmol/L and a non-selective cytochrome P450 (CYP) inhibitor, the biotransformation of etelcalcetide was not affected by the CYP inhibitor, indicating that CYP is not involved in the biotransformation of etelcalcetide.

6.2.1.3.2 CYP inhibition and induction (CTD 5.3.2.2-3, 5.3.2.2-4, and 5.3.2.2-5, Study Nos. 4169-NC-124, 119314, and 4169-NC-125)

Etelcalcetide (0.2-5.0 μg/mL) was incubated with human liver microsomes to evaluate its potential to inhibit the activities of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Etelcalcetide did not inhibit the activity of any of the CYP isoforms.

Etelcalcetide 5 μmol/L was incubated with human liver microsomes to determine its time-dependent inhibition of the activities of CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A). Etelcalcetide was not a time-dependent inhibitor of the CYP isoforms.

Human hepatocytes were incubated with etelcalcetide (0.2-10.0 μg/mL) to determine the potential of etelcalcetide to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A4). Etelcalcetide was not an inducer of the CYP isoforms.

6.2.1.3.3 Membrane permeability and transporter substrate and inhibition assays (CTD 5.3.2.3-1 and 5.3.2.3-2, Study Nos. 118052 and 119513)

The permeability of [^{14}C]-etelcalcetide ([^{14}C]Ac) (5 μmol/L) in LLC-PK1 cell monolayers was evaluated. The apparent permeability coefficient of etelcalcetide in the apical to basolateral direction was 0.6×10^{-6} cm/s, and the membrane permeability of etelcalcetide was low.

LLC-PK1 cells transfected with P-glycoprotein and MDCKII cells transfected with breast cancer resistance protein were treated with [^{14}C]-etelcalcetide ([^{14}C]Ac) (1 to 20 μmol/L). Etelcalcetide was not shown to be a substrate of these transporters. The inhibition potential of etelcalcetide was determined by measuring transport of specific substrates of P-glycoprotein and breast cancer resistance protein. Etelcalcetide at concentrations up to 50 μmol/L was not an inhibitor of these transporters.

HEK293 cells transfected with various transporters (organic anion transporter [OAT] 1, OAT3, organic anion transporting polypeptide [OATP] 1B1, OATP1B3, organic cation transporter [OCT] 2, peptide transporter [PEPT] 1, and PEPT2) were treated with [^{14}C]-etelcalcetide ([^{14}C]Ac) (10 μmol/L). Etelcalcetide was not shown to be a substrate of these transporters. The inhibition potential of etelcalcetide was determined by measuring transport of specific substrates of OAT1, OAT3, OATP1B1, OATP1B3, and OCT2. Etelcalcetide at concentrations up to 50 μmol/L was not an inhibitor of these transporters.

Sf9 membrane vesicles expressing bile salt export pump were treated with etelcalcetide (0.007 to 133 μmol/L). Etelcalcetide was not shown to be an inhibitor of the transporter.

6.2.2 Japanese phase I study (CTD 5.3.3.1-1, Study No. ONO-5163-[to 20])

A placebo-controlled, double-blind, randomized, parallel-group study was conducted at 1 site in Japan to evaluate the pharmacokinetics and safety of etelcalcetide in Japanese healthy adults aged 20 to 45 years (target sample size, 16 subjects [6 per etelcalcetide dose group, 4 in the placebo group).

Subjects received a single intravenous dose of 2 or 5 mg of etelcalcetide or placebo in the study.

All of 16 subjects enrolled in this study were included in the safety analysis set, and 12 subjects who received etelcalcetide were included in the pharmacokinetic analysis set.

Plasma and urine pharmacokinetic parameters of etelcalcetide are presented in Table 12.

Table 12. Plasma and urine pharmacokinetic parameters of etelcalcetide following a single intravenous dose in healthy adult subjects

Dose	N	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	fe (%)
2 mg	6	361 ± 43	20 ± 1	—[a)]
5 mg	6	828 ± 104	20 ± 3	28.4 ± 3.5

Mean ± SD
a) Etelcalcetide in urine was not measured.

Safety data were analyzed. Of 4 subjects in the placebo group, 1 (25.0%) experienced an adverse event and its causal relationship to study drug was ruled out. There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

6.2.3 Japanese phase I/II study (CTD 5.3.3.2-1, Study No. ONO-5163-[redacted] [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, double-blind, single- and multiple-dose study and an open-label, uncontrolled, multiple-dose titration study were conducted at 16 sites in Japan to evaluate the pharmacokinetics and safety of etelcalcetide in Japanese patients with SHPT on hemodialysis aged ≥20 years (target sample size, 18 subjects for a single-dose part [4 per etelcalcetide dose group, 6 in the placebo group], 22 subjects for a multiple-dose part [8 per etelcalcetide dose group, 6 in the placebo group], a multiple-dose titration part [21 in the etelcalcetide group]).

6.2.3.1 Single intravenous administration

Subjects received a single intravenous dose of 5, 10, or 20 mg of etelcalcetide or placebo in the study.

All of 18 enrolled subjects were included in the safety analysis set, and all of 12 subjects who received etelcalcetide were included in the pharmacokinetic analysis set.

Plasma pharmacokinetic parameters of etelcalcetide are shown in Table 13. Following administration of etelcalcetide 5, 10, and 20 mg, percent reduction in plasma etelcalcetide concentrations (plasma etelcalcetide concentration immediately after dialysis/plasma etelcalcetide concentration immediately before dialysis ×100) was 35% to 38%.

Table 13. Plasma pharmacokinetic parameters of etelcalcetide following a single intravenous dose in patients with SHPT

Dose	n	$AUC_{0\text{-}t}$ [a] (ng·h/mL)	$t_{1/2}$ (h) [b]
5 mg	4	1110 ± 360	81
10 mg	4	2550 ± 110	130, 180
20 mg	4	5460 ± 680	190

Individual values (Mean ± SD for $AUC_{0\text{-}t}$)
a) AUC up to Day 4 (predialysis)
b) n = 2 for the 10 mg group, n = 1 for others

Safety data were analyzed. Adverse events occurred in 33.3% (2 of 6) of subjects in the placebo group, 25.0% (1 of 4) of subjects in the etelcalcetide 5 mg group, and 25.0% (1 of 4) of subjects in the etelcalcetide 10 mg group. An adverse drug reaction occurred in 16.7% (1 of 6; atrial flutter) of subjects in the placebo group. No adverse events or adverse drug reactions were reported by ≥2 subjects in any group.

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

6.2.3.2 Multiple intravenous administration

Etelcalcetide 2.5 or 5 mg or placebo was administered into the venous line of the dialysis circuit at the end of dialysis during rinse back 3 times weekly for 4 weeks.

All of 22 enrolled subjects were included in the safety analysis set, and all of 16 subjects who received etelcalcetide were included in the pharmacokinetic analysis set.

Plasma pharmacokinetic parameters of etelcalcetide are shown in Table 14, and the plasma etelcalcetide trough concentration over time up to Day 29 is shown in Table 15.

Table 14. Plasma pharmacokinetic parameters of etelcalcetide following multiple intravenous administration in patients with SHPT

	Dose	n	$AUC_{0\text{-}t}$ [a)] (ng·h/mL)	$t_{1/2}$ (h)
Day 1	2.5 mg	8	600 ± 133	33 ± 32
	5 mg	7	1200 ± 560	45 ± 31
Day 27	2.5 mg	8	1830 ± 380	—
	5 mg	8	3860 ± 1840	—

Mean ± SD
a) AUC up to Day 3 (predialysis)

Table 15. Plasma etelcalcetide trough concentration over time following multiple intravenous administration in patients with SHPT [a)]

		Day 3	Day 6	Day 15	Day 20	Day 24	Day 29
2.5 mg	n	8	8	7	7	7	7
	Plasma concentration (ng/mL)	9.0 ± 2.3	14.4 ± 3.0	27.7 ± 7.5	36.6 ± 10.0	39.8 ± 8.8	42.9 ± 9.2
5 mg	n	8	8	8	8	8	8
	Plasma concentration (ng/mL)	17.6 ± 9.6	29.9 ± 14.4	62.3 ± 32.8	72.1 ± 34.9	79.7 ± 34.6	87.7 ± 42.9

Mean ± SD
a) Predialysis plasma etelcalcetide trough concentration

Safety data were analyzed. Adverse events occurred in 33.3% (2 of 6) of subjects in the placebo group, 87.5% (7 of 8) of subjects in the etelcalcetide 2.5 mg group, and 37.5% (3 of 8) of subjects in the etelcalcetide 5 mg group. Adverse drug reactions occurred in 50.0% (4 of 8) of subjects in the etelcalcetide 2.5 mg group and 12.5% (1 of 8) of subjects in the etelcalcetide 5 mg group. No adverse events or adverse drug reactions were reported by ≥2 subjects in any group.

No deaths were reported. An adverse event reported as a serious adverse event or an adverse event leading to treatment discontinuation was cardio-respiratory arrest which occurred in 12.5% (1 of 8) of subjects in the etelcalcetide 2.5 mg group. Its causal relationship to study drug could not be ruled out, but the event resolved after treatment.

6.2.3.3 Multiple intravenous dose titration

The starting dose of etelcalcetide was 5 mg. Dose was titrated and individualized between 2.5 and 15 mg. Etelcalcetide was administered into the venous line of the dialysis circuit at the end of dialysis during rinse back 3 times weekly for 12 weeks.

All of 24 enrolled subjects were included in the safety and pharmacokinetic analysis sets.

Pharmacokinetics was evaluated in 8 subjects who were maintained on 5 mg of etelcalcetide for 8 weeks. The predialysis plasma etelcalcetide trough concentration over time up to Day 57 in these subjects are shown in Table 16.

Table 16. Plasma etelcalcetide trough concentration over time following multiple intravenous administration in patients with SHPT [a)]

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
n	8	8	8	8	8	8	8	8
Plasma concentration (ng/mL)	34.7 ± 10.4	50.9 ± 14.5	70.9 ± 16.1	78.1 ± 23.2	87.4 ± 24.6	94.2 ± 26.4	98.6 ± 25.4	106 ± 30

Mean ± SD

a) Predialysis plasma etelcalcetide trough concentration

Safety analysis showed that the incidence of adverse events was 83.3% (20 of 24 subjects). Adverse events reported by ≥2 subjects were nasopharyngitis (29.2% [7 of 24 subjects]), blood Ca decreased (16.7% [4 of 24 subjects]), vomiting (12.5% [3 of 24 subjects]), and diarrhoea (8.3% [2 of 24 subjects]). Adverse drug reactions occurred in 9 of 24 subjects (37.5%). Adverse drug reactions reported by ≥2 subjects were blood Ca decreased only (16.7% [4 of 24 subjects]).

No deaths were reported. Serious adverse events occurred in 2 of 24 subjects (8.3%) (sepsis [1 subject]; and peripheral arterial occlusive disease, gangrene, and back pain [1 subject]). All those events were considered unrelated to etelcalcetide. The incidence of adverse events leading to treatment discontinuation was 4.2% (1 of 24 subjects; sepsis), and the event was considered unrelated to etelcalcetide.

6.2.4 Foreign mass balance study (CTD 5.3.3.2-2 [reference data], Study No. 20130147 [February to August 2014])

An open-label, uncontrolled study was conducted at 1 site overseas to evaluate the mass balance and safety of etelcalcetide in patients with end stage renal disease receiving hemodialysis aged ≥18 years (target sample size, 6 subjects).

Subjects received a single intravenous dose of [^{14}C]-etelcalcetide 10 mg.

All of 6 enrolled subjects were included in the safety and pharmacokinetic analysis sets.

According to pharmacokinetic analysis, 59.6%, 3.2%, and 4.5% of the administered radioactivity were recovered in dialysate, urine, and feces, respectively, over 176 days post-dose. Hemodialysis was found to be the predominant route of etelcalcetide elimination. The major components in dialysate and urine included intact etelcalcetide and its biotransformation product M13, while SAPC was not detected. On Day 4, 0.005% of radioactivity was recovered from the dialysis apparatus, and there was negligible binding to the dialysis apparatus.

Etelcalcetide existed predominantly in the form of SAPC in plasma, and SAPC represented 72.9% of the total radioactivity in the AUC pooled plasma up to 68 hours post-dose. Intact etelcalcetide accounted for 17.4% of the total radioactive AUC in plasma.

Safety data were analyzed. The incidence of adverse events was 83.3% (5 of 6 subjects), and the incidence of adverse drug reactions was 33.3% (2 of 6 subjects). Adverse events reported by ≥2 subjects were constipation (33.3% [2 of 6 subjects]), and their causal relationship to etelcalcetide could not be ruled out. The incidence of

serious adverse events was 16.7% (1 of 6 subjects; pneumonia), and the event was considered unrelated to etelcalcetide. There were no deaths or adverse events leading to treatment discontinuation.

6.R Outline of the review conducted by PMDA

The applicant's explanation about plasma concentration over time following multiple doses of etelcalcetide in patients with SHPT:

Non-clinical studies [see Section "4.1.2 Repeated-dose studies"] showed a trend towards an increase in the $AUC_{0\text{-}t}$ of plasma etelcalcetide on the last day of multiple dosing in the high dose group. The plasma concentration of etelcalcetide tended to increase slowly until around Day 29 in a 4-week multiple-dose study in patients with SHPT [see Section "6.2.3.2 Multiple intravenous administration"], whereas a 12-week multiple-dose study in patients with SHPT [see Section "6.2.3.3 Multiple intravenous dose titration"] indicated that the plasma concentration is essentially at steady state after Day 29.

The incidence of adverse events did not increase with prolonged treatment in a long-term treatment study of etelcalcetide [see Section "7.R.3.2 Safety of long-term treatment"].

At present, there should be no particular clinical relevant problems with the trend towards an increase in plasma etelcalcetide concentrations after multiple dosing.

PMDA accepted the applicant's explanation.

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

The applicant submitted evaluation data, namely the results from a Japanese phase III study (Study ONO-5163-[redacted]) and a Japanese long-term treatment study (Study ONO-5163-[redacted]).

7.1 Phase III studies

7.1.1 Japanese phase III study (CTD 5.3.5.1-1, Study No. ONO-5163-[redacted] [October 2014 to [redacted] 20[redacted]])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 37 sites in Japan to evaluate the efficacy and safety of etelcalcetide in patients with SHPT on hemodialysis aged ≥20 years (Table 17) (target sample size, 150 subjects [75 per group]).

Table 17. Key inclusion/exclusion criteria

Key inclusion criteria
· Patients with chronic renal failure receiving hemodialysis three times per week
· Predialysis serum iPTH (central laboratory data) ≥300 pg/mL
Key exclusion criteria
· Corrected serum Ca (central laboratory data) <8.4 mg/dL

Following a run-in period of ≤4 weeks, etelcalcetide or placebo was administered into the venous line of the dialysis circuit at the end of dialysis during rinse back 3 times weekly for 12 weeks. Study drug was administered according to the procedures presented in Table 18. Patients receiving P binders (including precipitated calcium carbonate preparations), Ca supplements, or active vitamin D preparations at enrollment were required to maintain stable doses.

Table 18. Dosage regimen

	Etelcalcetide or placebo
Starting dose	**5 mg**
Titration range	**2.5-15 mg**
Target serum iPTH levels	**60-240 pg/mL**
Dose titration algorithm	**As a rule, investigator or sub-investigator titrates the dose every 4 weeks, taking account of serum iPTH levels and tolerability.** **<u>Dose increase</u>** **Increase the dose by 5 mg if all of the following criteria are met and when the investigator or sub-investigator consider that there are no safety or tolerability issues. Increase the dose up to the last dose before dose reduction if the reduced dose is increased for the first time.** **1. Patient has been on a stable dose for ≥4 weeks.** **2. Serum iPTH (central laboratory data) >240 pg/mL.** **3. Corrected serum Ca (central laboratory data) ≥8.4 mg/dL.** **4. No ongoing adverse event that precludes dose increase, such as symptomatic hypocalcemia.** **<u>Dose reduction</u>** **Decrease the dose by 2.5 mg if either of the following criteria is met.** **1. Serum iPTH (central laboratory data) <60 pg/mL. Suspend the dose if the last administered dose is 2.5 mg. Re-initiate at 2.5 mg, as appropriate, once serum iPTH levels are ≥60 pg/mL.** **2. Ongoing adverse event that, in the opinion of investigator or sub-investigator, necessitates dose reduction.** **<u>Dose suspension</u>** **Suspend the dose if any of the following criteria is met.** **1. Predialysis corrected serum Ca <7.5 mg/dL. Re-initiate at a dose 2.5 mg lower than the last administered dose, as a rule, once corrected serum Ca levels are ≥8.4 mg/dL (if the last administered dose is 2.5 mg, re-initiate at a dose of 2.5 mg).** **2. Patient has symptomatic hypocalcemia. Re-initiate at the same dose as the last administered dose or at a dose 2.5 mg lower than the last administered dose, as a rule.** **3. Ongoing adverse event that, in the opinion of investigator or sub-investigator, necessitates dose suspension. Re-initiate at the same dose as the last administered dose or at a dose 2.5 mg lower than the last administered dose, as a rule.**

All of 155 randomized subjects (77 in the placebo group and 78 in the etelcalcetide group) were included in the FAS and in the safety analysis set, and the FAS was used for the primary efficacy analysis. There were 13 discontinuations (9 in the placebo group and 4 in the etelcalcetide group), and the reasons for discontinuation were patient's request (8 subjects [7 in the placebo group and 1 in the etelcalcetide group]), adverse event (2 subjects [2 in the etelcalcetide group]), physician's decision (2 subjects [1 in the placebo group and 1 in the etelcalcetide group]), and withdrawal criteria met (1 subject [1 in the placebo group]).

The primary efficacy endpoint of this study was the proportion of subjects achieving serum iPTH of 60 to 240 pg/mL on Day 85. The results are shown in Table 19. There was a statistically significant difference between the etelcalcetide and placebo groups ($P < 0.0001$; two-sided level of significance of 5%; Mantel-Haenszel test stratified by screening serum iPTH, screening corrected serum Ca, and washout of cinacalcet hydrochloride).

Table 19. Proportion of subjects achieving target serum iPTH levels on Day 85

	Placebo (N = 77)	Etelcalcetide (N = 78)
Proportion of subjects achieving target serum iPTH levels on Day 85 (%) [a]	1.3% (1/77)	59.0% (46/78)
Treatment difference (etelcalcetide − placebo) [b] [95% CI]	60.0% [49.7, 70.4]	
P-value [c]	*P* < 0.0001	

a) Patients who had no serum iPTH data on Day 85 or who required rescue therapy were considered as not achieving the endpoint.
b) Mantel-Haenszel estimator stratified by screening serum iPTH, screening corrected serum Ca, and washout of cinacalcet hydrochloride
c) Mantel-Haenszel test stratified by screening serum iPTH, screening corrected serum Ca, and washout of cinacalcet hydrochloride; two-sided level of significance of 5%

Safety data were analyzed. The incidences of adverse events were 72.7% (56 of 77 subjects) in the placebo group and 65.4% (51 of 78 subjects) in the etelcalcetide group. The incidences of adverse drug reactions were 3.9% (3 of 77 subjects) in the placebo group and 19.2% (15 of 78 subjects) in the etelcalcetide group. Adverse events or adverse drug reactions occurring in ≥2.0% of subjects in either group are shown in Table 20 and Table 21, respectively.

Table 20. Adverse events occurring in ≥2.0% of subjects in either group

	Placebo (N = 77)	Etelcalcetide (N = 78)		Placebo (N = 77)	Etelcalcetide (N = 78)
Total	72.7 (56)	65.4 (51)	Myalgia	1.3 (1)	2.6 (2)
Nasopharyngitis	19.5 (15)	20.5 (16)	Neck pain	0 (0)	2.6 (2)
Vomiting	0 (0)	5.1 (4)	Rash	0 (0)	2.6 (2)
Diarrhoea	2.6 (2)	3.8 (3)	Hypertension	0 (0)	2.6 (2)
Influenza	2.6 (2)	3.8 (3)	Gastroenteritis	3.9 (3)	1.3 (1)
Procedural hypotension	1.3 (1)	3.8 (3)	Upper respiratory tract inflammation	3.9 (3)	1.3 (1)
Nausea	0 (0)	3.8 (3)	Back pain	2.6 (2)	1.3 (1)
Blood Ca decreased	0 (0)	3.8 (3)	Cough	2.6 (2)	1.3 (1)
Adjusted Ca decreased	0 (0)	3.8 (3)	Pruritus	2.6 (2)	1.3 (1)
Headache	3.9 (3)	2.6 (2)	Contusion	6.5 (5)	0 (0)
Constipation	2.6 (2)	2.6 (2)	Abdominal distension	2.6 (2)	0 (0)
Stomatitis	2.6 (2)	2.6 (2)	Pyrexia	2.6 (2)	0 (0)
Bronchitis	2.6 (2)	2.6 (2)	Gingivitis	2.6 (2)	0 (0)
Muscle spasms	2.6 (2)	2.6 (2)	Shunt stenosis	2.6 (2)	0 (0)
Conjunctivitis allergic	1.3 (1)	2.6 (2)	Hypotension	2.6 (2)	0 (0)
Arthralgia	1.3 (1)	2.6 (2)			

MedDRA /J ver.18.0 Incidence % (n)

Table 21. Adverse drug reactions occurring in ≥2.0% of subjects in either group

	Placebo (N = 77)	Etelcalcetide (N = 78)
Total	3.9 (3)	19.2 (15)
Vomiting	0 (0)	3.8 (3)
Adjusted Ca decreased	0 (0)	3.8 (3)
Blood Ca decreased	0 (0)	2.6 (2)

MedDRA /J ver.18.0 Incidence % (n)

No deaths were reported. Serious adverse events occurred in 2.6% (2 of 78) of subjects in the etelcalcetide group (cerebral infarction [1 subject] and haematoma [1 subject]), and both events were considered unrelated to study drug. Adverse events leading to study drug discontinuation occurred in 2.6% (2 of 78) of subjects in the etelcalcetide group (cerebral infarction [1 subject] and rash [1 subject]). A causal relationship between study drug and rash reported by 1 subject in the etelcalcetide group could not be ruled out, but the event was mild in severity.

7.1.2 Japanese long-term treatment study (CTD 5.3.5.2-1, Study No. ONO-5163-[redacted] [October 2014 to [redacted] 2016)

A multicenter, open-label, uncontrolled study was conducted at 41 sites in Japan to evaluate the long-term safety and efficacy of etelcalcetide in patients with SHPT on hemodialysis aged ≥20 years (Table 22) (target sample size, 180 subjects).

Following a run-in period of ≤4 weeks, etelcalcetide was administered into the venous line of the dialysis circuit at the end of dialysis during rinse back 3 times weekly for 52 weeks. Etelcalcetide was administered according to the procedures presented in Table 18. At the discretion of the investigator or sub-investigator, initiation and dose increase of P binders (including precipitated calcium carbonate preparations), Ca supplements, or active vitamin D preparations or other measures were performed, as appropriate, during the treatment period.

Table 22. Key inclusion/exclusion criteria

Key inclusion criteria
· Patients with chronic renal failure receiving hemodialysis three times per week
· Predialysis serum iPTH (central laboratory data) >240 pg/mL
Key exclusion criteria
· Corrected serum Ca (central laboratory data) <8.4 mg/dL

A total of 191 subjects were enrolled in this study. Of these, 190 subjects were included in the FAS and in the safety analysis set, and 1 subject who did not receive etelcalcetide was excluded from the analyses. The FAS was used for the primary efficacy analysis. There were 31 discontinuations, and the reasons for discontinuation were adverse event (14 subjects), the physician's decision (8 subjects including 1 untreated subject), the patient's request (6 subjects), and the exclusion criteria met (3 subjects).

The efficacy analysis showed that the proportions of subjects achieving serum iPTH of 60 to 240 pg/mL on Days 85, 169, and 365 were 60.5% (107 of 177 subjects), 73.8% (127 of 172 subjects), and 87.5% (140 of 160 subjects), respectively.

Safety analysis showed that the incidence of adverse events was 96.8% (184 of 190 subjects). Adverse events occurring in ≥5.0% of subjects are shown in Table 23. The incidence of adverse drug reactions was 27.9% (53 of 190 subjects). Adverse drug reactions occurring in ≥5.0% of subjects were adjusted Ca decreased (9.5% [18 of 190 subjects]) and blood Ca decreased (8.4% [16 of 190 subjects]).

Table 23. Adverse events occurring in ≥5.0% of subjects

	Etelcalcetide (N = 190)		Etelcalcetide (N = 190)
Total	96.8 (184)	Procedural hypotension	7.4 (14)
Nasopharyngitis	57.4 (109)	Constipation	6.3 (12)
Diarrhoea	17.9 (34)	Excoriation	6.3 (12)
Contusion	15.8 (30)	Dermatitis contact	6.3 (12)
Adjusted Ca decreased	10.0 (19)	Eczema	5.8 (11)
Vomiting	9.5 (18)	Vertigo	5.3 (10)
Wound	8.4 (16)	Gastroenteritis	5.3 (10)
Blood Ca decreased	8.4 (16)	Pain in extremity	5.3 (10)
Back pain	8.4 (16)		

MedDRA /J ver.18.0 Incidence % (n)

Death occurred in 1.1% (2 of 190) of subjects (sudden death [1 subject] and brain stem haemorrhage [1 subject]), and a causal relationship between study drug and sudden death could not be ruled out.[2)] The incidence of non-fatal serious adverse events was 13.7% (26 of 190 subjects) (shunt occlusion and hepatocellular carcinoma [2 subjects each]; and atrial fibrillation, cardiac failure congestive, myocardial infarction, cataract, pancreatitis acute/retinal detachment, diverticulum intestinal haemorrhagic/humerus fracture/vertigo, gastrooesophageal reflux disease, haemorrhoids, large intestine perforation, peritoneal perforation, bile duct stone, lobar pneumonia, meningitis listeria/Hashimoto's encephalopathy, renal cyst infection, dehydration, carcinoid tumour, lung adenocarcinoma, lacunar infarction, hydronephrosis/urinary tract infection, aortic dissection, haematoma, and aneurysm ruptured [1 subject each]). The adverse events for which a causal relationship to study drug could not be ruled out were myocardial infarction, gastrooesophageal reflux disease, and aortic dissection (1 subject each), but all those events improved or resolved following treatment discontinuation. The incidence of adverse events leading to study drug discontinuation was 7.4% (14 of 190 subjects) (hepatocellular carcinoma [2 subjects]; gastrooesophageal reflux disease/epistaxis, dyskinesia, hypocalcaemia, myocardial infarction, large intestine perforation, lung adenocarcinoma, dementia Alzheimer's type, meningitis listeria/Hashimoto's encephalopathy, brain stem haemorrhage, sudden death, aortic dissection, and carcinoid tumour [1 subject each]). Except for gastrooesophageal reflux disease/epistaxis, dyskinesia, hypocalcaemia, myocardial infarction, sudden death, and aortic dissection (1 subject each), all those events were considered unrelated to study drug.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following considerations and confirmation in Sections 7.R.1.1 to 7.R.1.3, PMDA considers that the efficacy of etelcalcetide in patients with SHPT on hemodialysis has been demonstrated.

A final decision on the efficacy of etelcalcetide will be made, taking account of comments from expert advisors at the Expert Discussion.

2) On Day 358, the patient had difficulty in speaking and was taken to hospital by ambulance, but died. Since the patient had very severe arteriosclerosis, the death was suspected to be associated with some vascular events. However, the cause of death could not be identified. A causal relationship between study drug and the death could not be ruled out.

7.R.1.1 Primary endpoint

A Japanese phase III study showed a statistically significant difference between the etelcalcetide and placebo groups for the primary endpoint of the proportion of subjects achieving target serum iPTH levels on Day 85 (Table 19). Target serum iPTH levels were established based on the target range of serum iPTH of 60 to 240 pg/mL recommended by Clinical Practice Guideline for CKD-MBD.

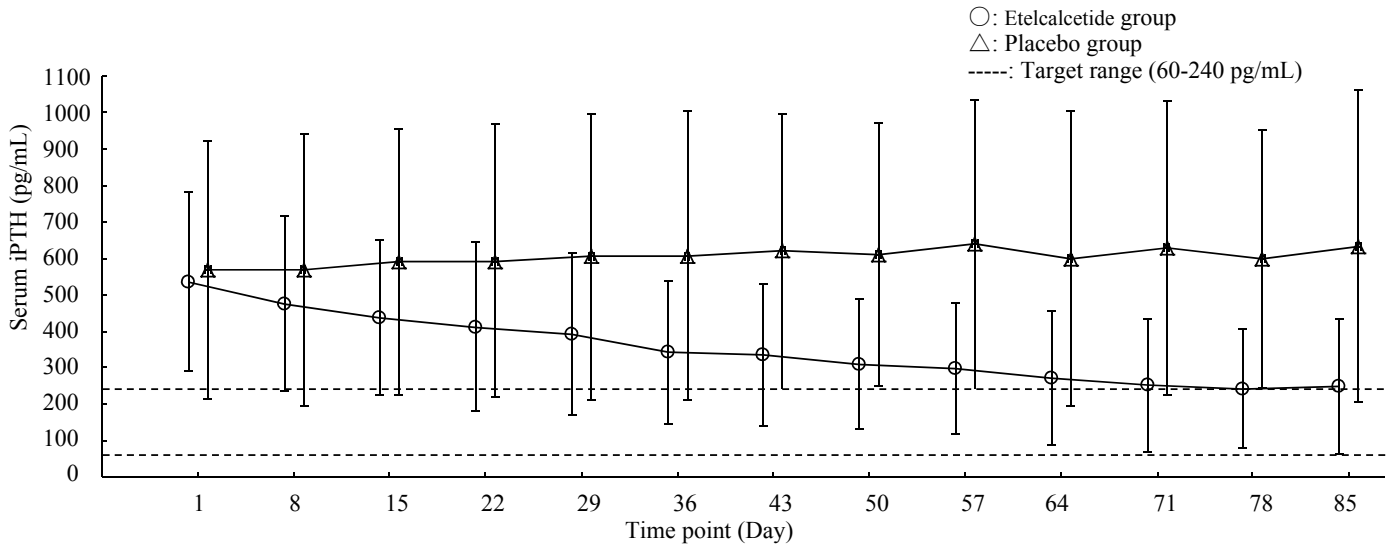
PMDA's view:

The Japanese phase III study has demonstrated the superiority of etelcalcetide over placebo, indicating the efficacy of etelcalcetide in patients with SHPT on hemodialysis.

7.R.1.2 Key secondary endpoint

Among secondary endpoints in the Japanese phase III study, the percent change from baseline to Day 85 in serum iPTH (mean ± SD) was 12.49 ± 29.16% in the placebo group and −52.09 ± 22.82% in the etelcalcetide group. Serum iPTH levels decreased in the etelcalcetide group.

Serum iPTH over time in the Japanese phase III study are shown in Figure 1. While serum iPTH levels decreased over time in the etelcalcetide group, there was no trend towards a decrease in serum iPTH in the placebo group.

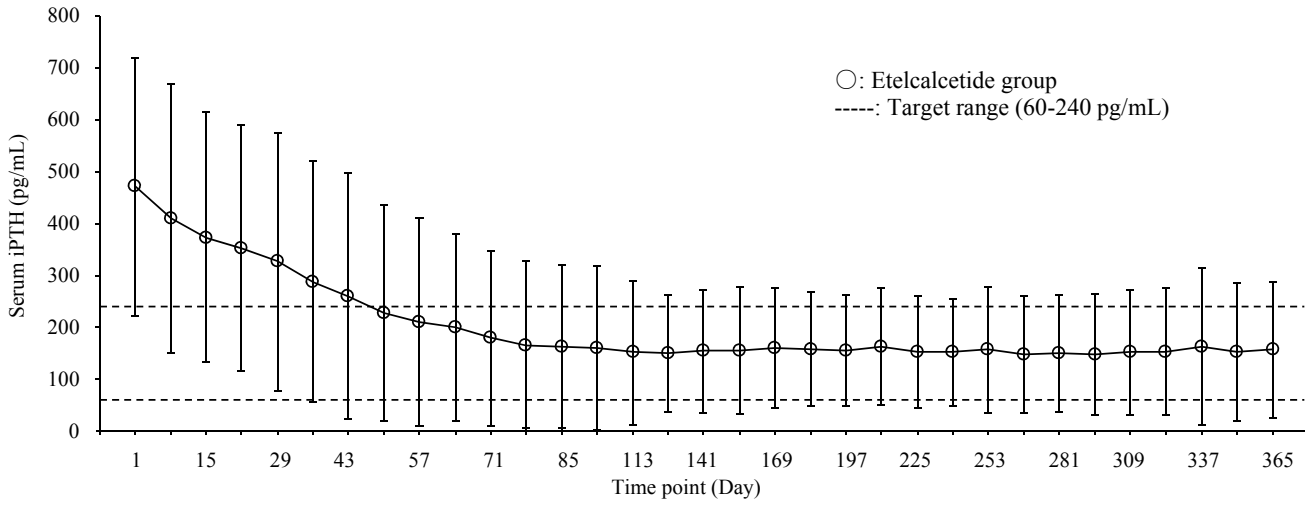


Time point (Day)	1	8	15	22	29	36	43	50	57	64	71	78	85
Placebo (N)	77	76	75	76	76	72	71	71	69	68	66	65	66
Etelcalcetide (N)	78	78	78	77	76	76	76	74	74	75	74	73	74

Figure 1. Serum iPTH (mean ± SD) over time (Japanese phase III study)

7.R.1.3 Efficacy of long-term treatment

Serum iPTH over time and the doses of etelcalcetide in a Japanese long-term treatment study are shown in Figure 2 and Figure 3, respectively. PMDA confirmed that serum iPTH tended to be maintained within the target range by titrating the dose of etelcalcetide.



Time point (Day)	1	15	29	43	57	71	85	113	141	169	197	225	253	281	309	337	365
Etelcalcetide (N)	190	188	189	189	182	180	177	174	175	172	171	166	164	163	161	161	160

Figure 2. Serum iPTH (mean ± SD) over time (Japanese long-term treatment study)

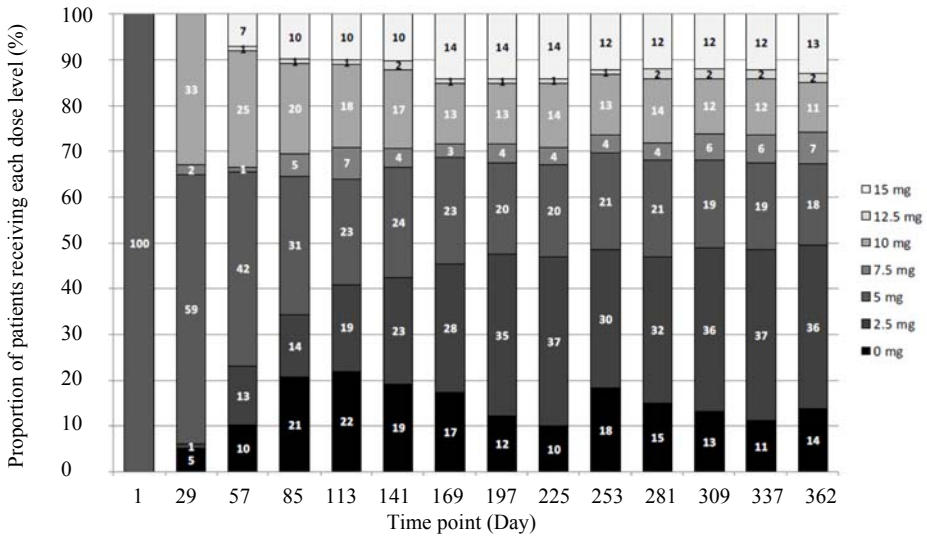


Figure 3. Proportion of patients and change in etelcalcetide dose over time (Japanese long-term treatment study)

7.R.1.4 Efficacy by baseline characteristics

The proportion of subjects achieving target serum iPTH levels on Day 85 was analyzed by baseline characteristics in the Japanese phase III study. The results for each subgroup are shown in Table 24. The proportion of subjects achieving target serum iPTH levels on Day 85 tended to be higher in the etelcalcetide group than in the placebo group across all subgroups.

Table 24. Proportion of subjects achieving target serum iPTH levels on Day 85 by baseline characteristics (Japanese phase III study)

Baseline characteristics	Subgroup	Placebo (N = 77)	Etelcalcetide (N = 78)
Age	<65 years	2.3 (1/43)	57.1 (24/42)
	≥65 years	0 (0/34)	61.1 (22/36)
Previous cinacalcet hydrochloride use	Yes	0 (0/50)	60.0 (30/50)
	No	3.7 (1/27)	57.1 (16/28)
Screening iPTH (pg/mL)	<500	2.4 (1/42)	73.8 (31/42)
	≥500 and <700	0 (0/23)	43.5 (10/23)
	≥700	0 (0/12)	38.5 (5/13)
Screening corrected serum Ca (mg/dL)	≤10.0	1.7 (1/60)	61.7 (37/60)
	>10.0	0 (0/17)	50.0 (9/18)
Baseline P binder use	Yes	1.4 (1/72)	59.5 (44/74)
	No	0 (0/5)	50.0 (2/4)
Baseline active vitamin D preparation use	Yes	1.5 (1/67)	66.7 (42/63)
	No	0 (0/10)	26.7 (4/15)

% (n/N)

7.R.2 Serum Ca levels, serum P levels, and effect on bone turnover

Control of serum Ca and P levels as well as serum iPTH levels is important in the management of SHPT. In patients with SHPT, excessive secretion of PTH increases bone resorption, which could lead to bone pain and fracture. Based on the following considerations and confirmation in Sections 7.R.2.1 to 7.R.2.3, PMDA confirmed that etelcalcetide lowers corrected serum Ca and serum P levels in patients with SHPT on hemodialysis and that etelcalcetide use is associated with a trend towards a decrease in bone resorption. Etelcalcetide-induced oversuppression of bone resorption may lead to an increased risk of adynamic bone disease, etc. The applicant should therefore collect information on the effect of etelcalcetide on bone turnover via post-marketing surveillance or other means.

7.R.2.1 Corrected serum Ca levels

The percent change from baseline to Day 85 in corrected serum Ca in the Japanese phase III study is shown in Table 25. PMDA confirmed that corrected serum Ca tends to decrease in the etelcalcetide group compared to the placebo group.

Table 25. Percent change from baseline to Day 85 in corrected serum Ca (Japanese phase III study)

	Placebo	Etelcalcetide
Corrected serum Ca on Day 1 (mg/dL)	9.48 ± 0.76 (N = 77)	9.58 ± 0.65 (N = 78)
Corrected serum Ca on Day 85 (mg/dL)	9.35 ± 0.69 (N = 68)	8.38 ± 0.52 (N = 74)
Percent change from baseline to Day 85 (%)	−0.55 ± 3.62	−12.35 ± 7.06

Mean ± SD

7.R.2.2 Serum P levels

The percent change from baseline to Day 85 in serum P in the Japanese phase III study is shown in Table 26. PMDA confirmed that serum P tends to decrease in the etelcalcetide group compared to the placebo group.

Table 26. Percent change from baseline to Day 85 in serum P (%) (Japanese phase III study)

	Placebo	Etelcalcetide
Serum P on Day 1 (mg/dL)	6.33 ± 1.41 (N = 77)	5.94 ± 1.44 (N = 78)
Serum P on Day 85 (mg/dL)	6.14 ± 1.61 (N = 68)	5.24 ± 1.66 (N = 74)
Percent change from baseline to Day 85 (%)	−1.25 ± 23.07	−10.60 ± 24.02

Mean ± SD

7.R.2.3 Effect on bone turnover

In the Japanese phase III and long-term treatment studies, a bone formation marker (BAP) and a bone resorption marker (TRACP-5b) were measured to assess bone turnover. BAP and TRACP-5b levels at baseline and at the end of treatment are shown in Table 27. There were little changes from baseline in BAP in both groups in the Japanese phase III study. While there were little changes in TRACP-5b in the placebo group, a reduction from baseline to the end of treatment in TRACP-5b was noted in the etelcalcetide group. Reductions from baseline to the end of treatment in both BAP and TRACP-5b were observed in the Japanese long-term treatment study.

Table 27. BAP and TRACP-5b levels at baseline and at the end of treatment

Study		BAP (μg/L)		TRACP-5b (mU/dL)	
		Baseline	End of treatment [a)]	Baseline	End of treatment [a)]
Japanese phase III study	Placebo	19.56 ± 10.62 (N = 77)	23.01 ± 12.96 (N = 68)	873.3 ± 344.5 (N = 77)	931.0 ± 363.1 (N = 68)
	Etelcalcetide	19.35 ± 8.96 (N = 78)	20.87 ± 11.83 (N = 74)	854.5 ± 351.5 (N = 78)	489.5 ± 267.2 (N = 74)
Japanese long-term treatment study		19.00 ± 11.38 (N = 190)	10.89 ± 5.08 (N = 160)	831.5 ± 432.3 (N = 190)	410.5 ± 284.1 (N = 160)

Mean ± SD (N)
a) Day 85 in the Japanese phase III study and Day 365 in the Japanese long-term treatment study

PMDA's view:

The results of bone turnover biomarkers and other data suggest that etelcalcetide use may be associated with a decrease in bone resorption. Adynamic bone disease potentially results from oversuppression of PTH [see Section "7.R.3.4 Hungry bone syndrome and adynamic bone disease"]. The applicant should collect information on the effect of etelcalcetide on bone turnover in patients with SHPT via post-marketing surveillance or other means.

7.R.3 Safety

Based on the following considerations and confirmation in Sections 7.R.3.1 to 7.R.3.7, PMDA considers that the safety of etelcalcetide is acceptable as long as the dose is titrated appropriately based on serum Ca levels, etc. Meanwhile, the applicant should collect information on the occurrence of hypocalcaemia and cardiovascular events, hungry bone syndrome and adynamic bone disease, and upper gastrointestinal disorders via post-marketing surveillance or other means.

A final decision on the safety of etelcalcetide will be made, taking account of comments from expert advisors at the Expert Discussion.

7.R.3.1 Comparison with placebo

According to the analysis of safety data from the Japanese phase III study, the incidences of vomiting, nausea, blood Ca decreased, and adjusted Ca decreased tended to be higher in the etelcalcetide group than in the placebo group (Table 20), but all of the events were mild or moderate in severity.

No serious adverse drug reactions occurred in either group. An adverse drug reaction leading to study drug discontinuation was not observed in the placebo group. One subject in the etelcalcetide group had an adverse drug reaction leading to study drug discontinuation, i.e. rash, which was mild in severity.

PMDA confirmed that except for hypocalcaemia-related events and upper gastrointestinal disorder-related events, there were no clinically relevant adverse events or trend of occurrence of adverse events in the etelcalcetide group compared to the placebo group. Hypocalcaemia-related events are assessed in Section "7.R.3.3 Hypocalcaemia" and upper gastrointestinal disorder-related events in Section "7.R.3.5 Upper gastrointestinal disorders."

7.R.3.2 Long-term safety of etelcalcetide

Adverse events occurring in ≥5.0% of etelcalcetide-treated subjects in a Japanese long-term treatment study are shown in Table 23. There were no major differences in the occurrence of adverse events between the Japanese long-term treatment and phase III studies. The incidence of adverse events by time to onset is presented in Table 28, and the incidence of adverse events did not increase with increasing duration of treatment.

Table 28. Incidence of adverse events or adverse drug reactions by time to onset (Japanese long-term treatment study)

	Days 1-84	Days 85-168	Days 169-252	Days 253-336	Days 337-	Entire period
Adverse events	68.4 (130/190)	64.6 (115/178)	69.9 (121/173)	71.3 (119/167)	38.7 (63/163)	96.8 (184/190)
Adverse drug reactions	21.6 (41/190)	6.2 (11/178)	5.8 (10/173)	6.0 (10/167)	3.7 (6/163)	27.9 (53/190)
Serious adverse events	3.2 (6/190)	2.2 (4/178)	5.2 (9/173)	4.8 (8/167)	1.8 (3/163)	14.7 (28/190)
Adverse events leading to treatment discontinuation	2.6 (5/190)	0.6 (1/178)	2.9 (5/173)	1.8 (3/167)	0.6 (1/163)	7.4 (14/190)
Hypocalcaemia-related events	16.3 (31/190)	6.7 (12/178)	9.2 (16/173)	7.8 (13/167)	3.7 (6/163)	27.9 (53/190)

MedDRA /J ver.18.0 Incidence % (n/N)

7.R.3.3 Hypocalcaemia

Etelcalcetide is a CaSR agonist and lowers serum Ca levels through reducing PTH secretion [see Section "7.R.2.1 Corrected serum Ca levels"].

The applicant's explanation about the occurrence of hypocalcaemia:

Adverse events classified as "Symptomatic hypocalcemia and potentially associated adverse events" were defined as hypocalcaemia, blood Ca decreased, adjusted Ca decreased, hypoaesthesia, muscle spasms, cardiac failure congestive, feeling abnormal, hypoaesthesia oral, musculoskeletal stiffness, blood pressure decreased, hypotension, and loss of consciousness. Safety data were assessed for those hypocalcaemia-related events.

Hypocalcaemia-related events identified in the data from the Japanese phase III study are shown in Table 29. Hypocalcaemia-related events occurred in 6.5% (5 of 77) of subjects in the placebo group and 10.3% (8 of 78) of subjects in the etelcalcetide group. The events were all mild or moderate in severity. None of these events were serious or led to treatment discontinuation.

Table 29. Hypocalcaemia-related events (Japanese phase III study)

	Placebo (N = 77)	Etelcalcetide (N = 78)
Hypocalcaemia-related events	6.5 (5)	10.3 (8)
Blood Ca decreased	0 (0)	3.8 (3)
Corrected Ca decreased	0 (0)	3.8 (3)
Muscle spasms	2.6 (2)	2.6 (2)
Hypocalcaemia	0 (0)	1.3 (1)
Hypotension	2.6 (2)	0 (0)
Blood pressure decreased	1.3 (1)	0 (0)
Hypoaesthesia	1.3 (1)	0 (0)

MedDRA /J ver.18.0 Incidence % (n)

In the Japanese long-term treatment study, hypocalcaemia-related events occurred in 27.9% (53 of 190) of subjects (corrected Ca decreased [19 subjects]; blood Ca decreased [16 subjects]; hypoaesthesia [5 subjects]; muscle spasms [4 subjects]; loss of consciousness [3 subjects]; blood pressure decreased, cardiac failure congestive, and hypocalcaemia [2 subjects each]; feeling abnormal, musculoskeletal stiffness, and hypoaesthesia oral [1 subject each]). Of which, cardiac failure congestive occurring in 1 subject was reported as a serious adverse event, but the event was considered unrelated to study drug. All other events were mild or moderate in severity. Hypocalcaemia occurring in 0.5% (1 of 190) of subjects was reported as an adverse event leading to treatment discontinuation. Although its causal relationship to etelcalcetide could not be ruled out, the event resolved following discontinuation of etelcalcetide.

The protocols of the Japanese phase III and long-term treatment studies specified that, from the safety point of view, dose increases were to occur unless corrected serum Ca was <8.4 mg/dL and dose suspension was to occur if corrected serum Ca was <7.5 mg/dL.

Data from the Japanese phase III and long-term treatment studies was analyzed to identify the proportion of patients with corrected serum Ca falling below 7.5 or 8.4 mg/dL (see Table 30). Dose was not increased or was suspended in many patients. According to pooled data from the Japanese phase III and long-term treatment studies, the number of dose suspensions in the etelcalcetide group was 274, and the doses before dose suspensions were 2.5 mg for 173 suspensions, 5 mg for 61 suspensions, 7.5 mg for 7 suspensions, 10 mg for 26 suspensions, 12.5 mg for 1 suspension, and 15 mg for 6 suspensions. Moreover, 3.8% (3 of 78) of patients participating in the Japanese phase III study and 1.1% (2 of 190) of patients participating in the long-term treatment study had their dose reduced because their corrected serum Ca was <8.4 mg/dL. The decreased serum Ca levels were considered by the investigator or sub-investigator to be difficult to resolve with rescue therapy with Ca supplements, Ca-containing P binder, or other medications.

Table 30. Proportion of patients experiencing corrected serum Ca <7.5 or <8.4 mg/dL

		<7.5 mg/dL	<8.4 mg/dL
Japanese phase III study	Placebo	0 (0/77)	14.3 (11/77)
	Etelcalcetide	17.9 (14/78)	87.2 (68/78)
Japanese long-term treatment study		21.6 (41/190)	86.3 (164/190)

Incidence % (n/N)

Published literature has reported that hypocalcaemia is associated with cardiovascular risks such as exacerbation of cardiac dysfunction and QT interval prolongation (*Heart Fail.* 2014;Rev 2: 199-205, *Eur J Cardiovasc Prev Rehabil.* 2005;12: 363-368, and other articles). Analyses were performed to identify the

incidence of cardiac failure- or cardiac repolarization-related events (cardiac failure-related events were defined as events coded to "cardiac failure" [narrow SMQ], cardiac repolarization-related events were defined as events coded to "Torsade de pointes/QT prolongation" [narrow SMQ], and events coded to "ventricular tachyarrhythmias" [narrow SMQ]) in clinical use.

In the Japanese phase III study, no cardiac failure- or cardiac repolarization-related events were observed in the placebo group. Cardiac failure- or cardiac repolarization-related events occurred in 1.3% (1 of 78) of subjects in the etelcalcetide group (ventricular extrasystoles), which was mild in severity. There were no serious adverse events or adverse events leading to treatment discontinuation. At the time of onset of ventricular extrasystoles, the corrected serum Ca level was 8.4 mg/dL, which was the patient's lowest value. Thus, ventricular extrasystoles was likely to be associated with hypocalcaemia, but its causal relationship to etelcalcetide was ruled out because the event was considered attributable to a transient, rapid decrease in Ca after dialysis.

In the Japanese long-term treatment study, cardiac failure- or cardiac repolarization-related events occurred in 1.6% (3 of 190) of subjects (cardiac failure congestive [2 subjects] and ventricular extrasystoles [1 subject]). Cardiac failure congestive occurring in 1 subject was reported as a serious adverse event, but its causal relationship to study drug was ruled out. There were no adverse events leading to treatment discontinuation. One patients experiencing cardiac failure congestive had corrected serum Ca of 8.6 to 8.8 mg/dL around the time of onset of the event. The event was considered attributable to cardiac hypertrophy and failure to achieve dry weight. The other patient experiencing cardiac failure congestive had corrected serum Ca of 7.5 to 7.9 mg/dL around the time of onset of the event. The event was considered attributable to poor control of water intake. The corrected serum Ca levels were 8.2 to 8.6 mg/dL around the time of onset of ventricular extrasystoles, and the event was considered attributable to a concomitant illness (old myocardial infarction). Based on the above, all those events were unlikely to be associated with hypocalcaemia.

PMDA's view:
As done in clinical studies, serum Ca levels should be monitored so that the dose can be appropriately reduced or suspended, because (i) hypocalcaemia-related events and cardiac failure- or cardiac repolarization-related events observed in the Japanese phase III and long-term treatment studies were all non-serious, and (ii) a hypocalcaemia-related event leading to treatment discontinuation noted in the etelcalcetide group resolved following treatment discontinuation. Therefore, the applicant should ensure that physicians are informed of the risk of etelcalcetide-related decreases in serum Ca, and the package insert and other information materials should advise that serum Ca should be measured regularly during treatment with etelcalcetide and that the dosage should be appropriately adjusted (by dose reduction/suspension, etc.). The applicant should also collect information on the occurrence of hypocalcaemia and cardiovascular events via post-marketing surveillance or other means.

7.R.3.4 Hungry bone syndrome and adynamic bone disease

Hungry bone syndrome accompanied by hypocalcaemia and hypophosphatemia due to a rapid decrease in PTH, and adynamic bone disease due to a rapid decrease in PTH have been reported overseas with a similar drug,

cinacalcet hydrochloride (Regpara Tablets 12.5 mg, etc. Interview Form, revised in June 2016). The applicant provided the following explanation about the risk of hungry bone syndrome or adynamic bone disease in etelcalcetide-treated patients:

According to data from the Japanese phase III and long-term treatment studies, hungry bone syndrome or adynamic bone disease was not reported. Hungry bone syndrome or adynamic bone disease did not occur in a total of 841 etelcalcetide-treated patients in 3 foreign phase III studies (20120229, 20120230, 20120360). However, in light of the fact that hungry bone syndrome and adynamic bone disease have been reported with a drug with a similar mechanism of action to etelcalcetide, cinacalcet hydrochloride, a relevant precaution will be provided in the package insert.

PMDA's view:

From the standpoint of mechanism of action, the risk of hungry bone syndrome or adynamic bone disease in etelcalcetide-treated patients cannot be ruled out. Thus, a relevant precaution should be provided in the package insert, and information needs to be collected via post-marketing surveillance or other means.

7.R.3.5 Upper gastrointestinal disorders

The most frequently reported adverse reactions to cinacalcet hydrochloride are gastrointestinal symptoms such as nausea/vomiting, stomach discomfort, anorexia, and abdominal distension. The applicant provided the following explanation about the occurrence of upper gastrointestinal disorders:

Upper gastrointestinal disorder-related events reported in the Japanese phase III and long-term treatment studies were identified by MedDRA PTs related to "upper gastrointestinal disorders."

Upper gastrointestinal disorder-related events reported in the Japanese phase III study are shown in Table 31. Upper gastrointestinal disorder-related events occurred in 7.8% (6 of 77) of subjects in the placebo group and 11.5% (9 of 78) of subjects in the etelcalcetide group, which were all mild in severity. None of the events were serious or led to treatment discontinuation.

In the Japanese long-term treatment study, upper gastrointestinal disorder-related events occurred in 29.5% (56 of 190) of subjects, and most of the events were mild or moderate in severity (Table 32). Serious adverse events occurred in 1.1% (2 of 190) of subjects (gastrooesophageal reflux disease and peritoneal perforation [1 subject each]). A causal relationship between the gastrooesophageal reflux disease and etelcalcetide could not be ruled out, but the event improved following treatment discontinuation. Except for this case, there were no adverse events leading to treatment discontinuation.

Table 31. Upper gastrointestinal disorder-related events (Japanese phase III study)

	Placebo (N = 77)	Etelcalcetide (N = 78)
Upper gastrointestinal disorder-related events	**7.8 (6)**	**11.5 (9)**
Vomiting	0 (0)	5.1 (4)
Nausea	0 (0)	3.8 (3)
Gastroenteritis	3.9 (3)	1.3 (1)
Abdominal pain upper	1.3 (1)	1.3 (1)
Gastritis	0 (0)	1.3 (1)
Decreased appetite	0 (0)	1.3 (1)
Abdominal distension	2.6 (2)	0 (0)
Duodenal ulcer	1.3 (1)	0 (0)
Duodenitis	1.3 (1)	0 (0)
Gastritis erosive	1.3 (1)	0 (0)

MedDRA /J ver.18.0 Incidence % (n)

Table 32. Upper gastrointestinal disorder-related events (Japanese long-term treatment study)

	Etelcalcetide (N = 190)		Etelcalcetide (N = 190)
Upper gastrointestinal disorder-related events	**29.5 (56)**	Abdominal distension	0.5 (1)
Vomiting	9.5 (18)	Abdominal pain	0.5 (1)
Gastroenteritis	5.3 (10)	Chronic gastritis	0.5 (1)
Nausea	4.7 (9)	Duodenitis	0.5 (1)
Gastric polyps	3.7 (7)	Dyspepsia	0.5 (1)
Abdominal discomfort	2.6 (5)	Gastric atony	0.5 (1)
Gastritis	2.6 (5)	Hiatus hernia	0.5 (1)
Abdominal pain upper	2.1 (4)	Epigastric discomfort	0.5 (1)
Gastrooesophageal reflux disease	2.1 (4)	Brunner's gland hyperplasia	0.5 (1)
Decreased appetite	1.1 (2)	Peritoneal perforation	0.5 (1)

MedDRA /J ver.18.0 Incidence % (n)

A cinacalcet hydrochloride-controlled phase III study (20120360)[3)] was conducted overseas. Upper gastrointestinal disorder-related events occurred in 32.0% (108 of 338) of subjects in the etelcalcetide group and 37.0% (126 of 341) of subjects in the cinacalcet hydrochloride group. Those adverse events occurring in ≥2.0% of subjects in either group are shown in Table 33. Upper gastrointestinal disorder-related events reported as serious adverse events occurred in 3.3% (11 of 338) of subjects in the etelcalcetide group (gastroenteritis and gastrointestinal haemorrhage [2 subjects each]; abdominal pain, diverticulum, duodenitis haemorrhagic/esophagitis haemorrhagic, haematemesis, vomiting, diabetic gastroparesis, and abdominal hernia [1 subject each]) and 1.8% (6 of 341) of subjects in the cinacalcet hydrochloride group (abdominal pain upper, ascites/vomiting/impaired gastric emptying, gastroenteritis, gastrointestinal necrosis/peritonitis, retroperitoneal haemorrhage, and upper gastrointestinal haemorrhage [1 subject each]). The adverse events for which a causal relationship to study drug could not be ruled out were abdominal pain and diabetic gastroparesis occurring in the etelcalcetide group and ascites/vomiting/impaired gastric emptying occurring in the cinacalcet hydrochloride group. The outcome was reported as "resolved" for all those events. Adverse events leading to treatment discontinuation occurred in 1.5% (5 of 338) of subjects in the etelcalcetide group and 1.5% (5 of 341) of subjects in the cinacalcet hydrochloride group.

3) A multicenter, randomized, double-blind, active-controlled, parallel-group study to demonstrate the non-inferiority of etelcalcetide to cinacalcet hydrochloride in patients with SHPT on hemodialysis aged ≥18 years. The same dosage regimen of etelcalcetide as in the Japanese phase III study was used. Subjects in the cinacalcet hydrochloride group received once-daily oral doses of cinacalcet hydrochloride. The starting dose of cinacalcet was 30 mg and the maximum dose was 180 mg.

Table 33. Upper gastrointestinal disorder-related events occurring in ≥2.0% of subjects in either group (Foreign phase III study [20120360])

	Etelcalcetide (N = 338)	Cinacalcet hydrochloride (N = 341)
Upper gastrointestinal disorder-related events	**32.0 (108)**	**37.0 (126)**
Nausea	18.3 (62)	22.6 (77)
Vomiting	13.3 (45)	13.8 (47)
Abdominal pain	3.8 (13)	3.8 (13)
Decreased appetite	2.4 (8)	1.8 (6)
Dyspepsia	2.1 (7)	1.5 (5)
Gastroenteritis	1.5 (5)	2.1 (7)
Abdominal pain upper	1.2 (4)	2.3 (8)

MedDRA /J ver.17.1 Incidence % (n)

PMDA's view:

There were no major concerns about upper gastrointestinal disorder-related events in the Japanese phase III or long-term treatment studies. On the other hand, in the foreign cinacalcet hydrochloride-controlled phase III study (20120360), the incidence of upper gastrointestinal disorder-related events was similar between the etelcalcetide and cinacalcet hydrochloride groups. Especially, nausea and vomiting were commonly reported in both the etelcalcetide and cinacalcet hydrochloride groups. Although serious upper gastrointestinal disorder-related events or upper gastrointestinal disorder-related events leading to treatment discontinuation were infrequent in the etelcalcetide group, the applicant should continue to collect information on upper gastrointestinal disorder-related events such as nausea and vomiting via post-marketing surveillance or other means and should assess the risk of such events.

7.R.3.6 Hypersensitivity and infusion reaction

Etelcalcetide is a peptide product to be administered into the venous line of the dialysis circuit, and hypersensitivity and infusion reaction may occur. The applicant provided the following explanation about the occurrence of hypersensitivity and infusion reactions:

Hypersensitivity-related events were defined as events coded to hypersensitivity (narrow SMQ) and infusion reactions were defined as events potentially related to serious allergic reactions (blood pressure decreased, hypotension, loss of consciousness, arthralgia, hypertension, myalgia, pruritus, pyrexia, rash, urticaria, pruritus generalised, procedural hypotension, syncope, dyspnoea, eczema nummular, pulmonary congestion, sudden death) for analyses.

In the Japanese phase III study, hypersensitivity-related events occurred in 3.9% (3 of 77) of subjects in the placebo group (conjunctivitis allergic, dermatitis, and urticaria [1 subject each]) and 9.0% (7 of 78) of subjects in the etelcalcetide group (conjunctivitis allergic and rash [2 subjects each]; dermatitis contact, eczema, gingival swelling, and rhinitis allergic [1 subject each]). These events were all mild or moderate in severity, and none of the adverse events were serious or led to treatment discontinuation. Infusion reactions occurred in 11.7% (9 of 77) of subjects in the placebo group (hypotension, pruritus, and pyrexia [2 subjects each]; arthralgia, blood pressure decreased, myalgia, urticaria, pruritus generalised, and procedural hypotension [1 subject each]) and 14.1% (11 of 78) of subjects in the etelcalcetide group (procedural hypotension [3 subjects]; arthralgia, hypertension, myalgia, and rash [2 subjects each]; pruritus [1 subject]). These events were all mild or moderate

in severity, and none of the events were serious. An infusion reaction leading to treatment discontinuation occurred in 1.3% (1 of 78) of subjects in the etelcalcetide group (rash), which was mild in severity.

In the Japanese long-term treatment study, hypersensitivity-related events occurred in 17.9% (34 of 190) of subjects (dermatitis contact [12 subjects]; eczema [11 subjects]; rash [5 subjects]; conjunctivitis allergic [3 subjects]; dermatitis infected [2 subjects]; dermatitis allergic, eczema nummular, urticaria, and contrast media allergy [1 subject each]). These events were all mild in severity, and none of the events were serious or led to treatment discontinuation. Infusion reactions occurred in 26.3% (50 of 190) of subjects (procedural hypotension [14 subjects]; pruritus [8 subjects]; arthralgia and hypertension [7 subjects each]; rash [5 subjects]; loss of consciousness and myalgia [3 subjects each]; blood pressure decreased and pyrexia [2 subjects each]; dyspnoea, eczema nummular, pulmonary congestion, sudden death, syncope, and urticaria [1 subject each]). Except for sudden death,[2)] all these events were mild or moderate in severity, and none of the adverse events were serious or led to treatment discontinuation.

According to an analysis of pooled data from foreign phase III studies (20120229 and 20120230), hypersensitivity-related events occurred in 3.7% (19 of 513) of subjects in the placebo group and 4.4% (22 of 503) of subjects in the etelcalcetide group. None of these adverse events were reported by ≥2.0% of subjects in either group, and most events were mild or moderate in severity. Serious adverse events occurred in 0.2% (1 of 513) of subjects in the placebo group and 0.4% (2 of 503) of subjects in the etelcalcetide group, and all those events were considered unrelated to study drug. Adverse events leading to treatment discontinuation occurred in 0.2% (1 of 513) of subjects in the placebo group and 0.2% (1 of 503) of subjects in the etelcalcetide group. Infusion reactions occurred in 17.7% (91 of 513) of subjects in the placebo group and 19.7% (99 of 503) of subjects in the etelcalcetide group. Those adverse events occurring in ≥2.0% of subjects in either group were hypertension (5.7% [29 of 513 subjects] in the placebo group and 6.2% [31 of 503 subjects] in the etelcalcetide group), hypotension (5.1% [26 of 513 subjects] and 6.0% [30 of 503 subjects], respectively), and pyrexia (3.9% [20 of 513 subjects] and 4.0% [20 of 503 subjects], respectively). These adverse events are symptoms commonly observed in CKD patients, and most of the events were mild or moderate in severity. Serious adverse events occurred in 2.3% (12 of 513) of subjects in the placebo group and 2.4% (12 of 503) of subjects in the etelcalcetide group, and a causal relationship between study drug and 1 case of hypotension in the etelcalcetide group could not be ruled out. Adverse events leading to treatment discontinuation occurred in 0.2% (1 of 513) of subjects in the placebo group and 0.2% (1 of 503) of subjects in the etelcalcetide group.

PMDA's view:

In the Japanese phase III and long-term treatment studies, sudden death[2)] occurred in 1 subject in the etelcalcetide group, but no symptoms suspected of hypersensitivity or infusion reaction were identified. Except for this case, no serious hypersensitivity or infusion reaction was reported in the Japanese phase III or long-term treatment study. However, etelcalcetide is a peptide product and the risk of hypersensitivity cannot be ruled out. A relevant precaution should be provided in the package insert, and information should be collected via post-marketing surveillance or other means.

7.R.3.7 Anti-etelcalcetide antibodies

Etelcalcetide is a peptide product. The applicant provided the following explanation about the incidence of anti-etelcalcetide antibodies and its impact on safety and efficacy:

No subjects tested positive for anti-etelcalcetide antibodies in Japanese phase I and phase I/II studies. In Japanese phase III and long-term treatment studies, 1.3% (1 of 77) of patients and 2.6% (5 of 189) of patients, respectively, tested positive for anti-etelcalcetide antibodies. None of patients in the Japanese phase III study developed anti-etelcalcetide antibodies during treatment with etelcalcetide. In the Japanese long-term treatment study, 1.6% (3 of 189) of patients developed anti-etelcalcetide antibodies during treatment with etelcalcetide. Of the 3 patients who developed anti-etelcalcetide antibodies during treatment with etelcalcetide in the Japanese long-term treatment study, 1 experienced an immunogenicity-related adverse event (hypersensitivity or infusion reaction), i.e. procedural hypotension as an infusion reaction, which was mild in severity. All of these 3 patients had serum iPTH levels within the target range on Day 365.

According to an analysis of pooled data from foreign phase III studies (20120229 and 20120230), of 503 patients included the analysis, 56 tested positive for anti-etelcalcetide antibodies. Of the 56 patients, 13 developed anti-etelcalcetide antibodies during treatment with etelcalcetide. Data were further analyzed for immunogenicity-related adverse events (hypersensitivity or infusion reaction). Hypersensitivity occurred in 4.7% (21 of 447) of antibody-negative patients, but not in patients who developed anti-etelcalcetide antibodies during treatment with etelcalcetide. Infusion reactions occurred in 19.7% (88 of 447) of antibody-negative patients and 7.7% (1 of 13) of patients who developed anti-etelcalcetide antibodies during treatment with etelcalcetide. Furthermore, the presence of anti-etelcalcetide antibodies had no impact on percent change in serum iPTH.

PMDA confirmed that no significant impact of formation of anti-etelcalcetide antibodies on efficacy and safety has been observed at present.

7.R.4 Clinical positioning

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

Excessive secretion of PTH in patients with SHPT induces calcification of blood vessels and soft tissues and osteitis fibrosa and is associated with parathyroid gland hyperplasia, which contributes to further progression of SHPT. Thus, Clinical Practice Guideline for CKD-MBD in Japan recommends the control of serum PTH in patients with SHPT.

In Japan, active vitamin D preparations and cinacalcet hydrochloride are available as medication therapies to control serum PTH in patients with SHPT, from which appropriate one is selected according to individual patients' conditions (Clinical Practice Guideline for CKD-MBD). The use of cinacalcet hydrochloride is considered if serum PTH is high and serum P or Ca levels are normal or high, and the use of active vitamin D preparations is considered if serum P or Ca levels are normal or low. Problems associated with the characteristics of these agents are also known: Active vitamin D preparations are associated with the risk of hypercalcaemia due to enhanced gastrointestinal absorption of Ca, and increase serum P levels. Hence, a sufficient dose of active vitamin D cannot be administered or treatment with active vitamin D preparations has

to be stopped in some patients with high serum P levels. Cinacalcet hydrochloride is a CaSR agonist and is associated with the risk of hypocalcaemia. Also, upper gastrointestinal disorders are relatively common with cinacalcet hydrochloride.

Like cinacalcet hydrochloride, etelcalcetide is a CaSR agonist. A foreign phase III study (20120360)[3)] demonstrated the non-inferiority of the efficacy of etelcalcetide versus cinacalcet hydrochloride. Thus, as with cinacalcet hydrochloride, etelcalcetide will be chosen from among treatment options. Etelcalcetide is a solution for injection to be administered by intravenous injection into the dialysis circuit at the end of hemodialysis. This method of administration ensures that etelcalcetide is administered under the supervision of a physician, thus possibly contributing to improved compliance and a reduced pill burden.

PMDA's view:
A Japanese phase III study in patients with SHPT on hemodialysis demonstrated the efficacy of etelcalcetide [see Section "7.R.1 Efficacy"] and acceptable safety [see Section "7.R.3 Safety"]. Etelcalcetide has therefore been shown to be beneficial for patients with SHPT on hemodialysis. It will become a therapeutic option for such patients.

7.R.5 Indication

PMDA's view:
The Japanese phase III and long-term treatment studies in patients with SHPT on hemodialysis demonstrated the efficacy of etelcalcetide and found no major safety concerns. The proposed indication of "secondary hyperparathyroidism in patients on hemodialysis" is acceptable.

The indication of etelcalcetide will be finalized, taking account of comments from expert advisors at the Expert Discussion.

7.R.6 Dosage and administration

PMDA's view:
There are no particular problems with the dosage regimen of etelcalcetide decided based on the results of the Japanese phase III study. This is based on the considerations presented in Sections 7.R.6.1 and 7.R.6.2. However, a final decision will be made, taking account of comments from expert advisors at the Expert Discussion.

7.R.6.1 Starting dose and maximum dose

The applicant's explanation about why a starting dose of 5 mg and a maximum dose of 15 mg were selected for the Japanese phase III study:
<u>Starting dose of etelcalcetide</u>
Following 4-week administration of 2.5 and 5 mg of etelcalcetide in a multiple-dose part of a Japanese phase I/II study in patients with SHPT on hemodialysis, the mean percent changes from baseline to the end of treatment in serum iPTH were −26.25% and −45.65%, respectively. A starting dose of 5 mg was selected for

the Japanese phase III study because (i) the reduction in serum iPTH was greater with 5 mg of etelcalcetide compared to 2.5 mg and (ii) there were no particular safety concerns about the 5 mg dose.

Maximum dose of etelcalcetide

In a 12-week foreign late phase II study (20120331), 8 patients had their dose up-titrated to 20 mg at Week 9 but 3 of them experienced dose suspension due to adverse events at Weeks 10 to 12 (hypocalcaemia [2 subjects] and papule [1 subject]). The 5 patients staying on etelcalcetide 20 mg at the end of treatment participated in a foreign late phase II open-label extension study (20120334). Etelcalcetide was started at 20 mg in 4 patients and at 22.5 mg in 1 patient. Within 4 weeks of treatment, 4 patients met the criteria for dose suspension (low corrected serum Ca levels, low serum iPTH levels, or adverse events) and experienced dose suspension. Based on the above findings, a maximum dose of 15 mg was selected for foreign phase III studies. In a multiple-dose titration part of the Japanese phase I/II study, the changes from baseline to the end of treatment in serum iPTH by patient's maximum dose (mean ± SD) were −226.1 ± 125.3 pg/mL for 5 mg, −362.5 ± 161.5 pg/mL for 10 mg, and −412.4 ± 130.2 pg/mL for 15 mg. Of 5 patients treated with 15 mg of etelcalcetide, 4 had no safety problems and 1 had blood Ca decreased which resolved following dose reduction. In light of the outcomes, a maximum dose of 15 mg was selected for the Japanese phase III study. The results of the Japanese phase III study demonstrated the superiority of etelcalcetide over placebo for the primary endpoint of the proportion of subjects achieving target serum iPTH levels on Day 85. No clinically relevant safety risk was identified in the study.

In the Japanese phase III and long-term treatment studies, the proportions of patients who were titrated to the maximum dose of 15 mg were 20.5% (16 of 78 patients) and 13.2% (25 of 190 patients), respectively. In the Japanese phase III study, the proportion of patients who were titrated to the maximum dose of 15 mg and who achieved target serum iPTH levels on Day 85 was 43.8% (7 of 16 patients). In the Japanese long-term treatment study, the proportion of patients who were titrated to the maximum dose of 15 mg and who achieved target serum iPTH levels on Day 365 was 76.0% (19 of 25 patients). The safety data from the Japanese phase III and long-term treatment studies were analyzed to identify the incidence of adverse events by dose at onset (see Table 34). There was no increase in the incidence of adverse events with increasing dose.

Table 34. Incidence by dose at onset [a] (Japanese phase III and long-term treatment studies)

Dose at onset of adverse event	Japanese phase III study	Japanese long-term treatment study
Any dose	65.4 (51/78)	96.8 (184/190)
0 mg [b]	26.1 (6/23)	56.0 (70/125)
2.5 mg	33.3 (4/12)	85.9 (85/99)
5 mg	43.6 (34/78)	62.6 (119/190)
7.5 mg	16.7 (1/6)	34.6 (9/26)
10 mg	38.6 (17/44)	64.9 (48/74)
12.5 mg	0 (0/1)	71.4 (5/7)
15 mg	31.3 (5/16)	76.7 (23/30)

MedDRA /J ver.18.0 Incidence % (n/N)

a) A patient with ≥2 episodes of the same adverse event was counted once for each dose level.

b) The following cases were classified as 0 mg:
- the dose was reduced to 0 mg;
- during dose suspension;
- study drug was not administered due to protocol deviations; or
- adverse event occurred after the end of treatment.

On the above grounds, the applicant considered that a starting dose of 5 mg and a maximum dose of 15 mg for patients with SHPT on hemodialysis was justified.

PMDA's view:
There are no particular problems with a starting dose of 5 mg with titration to a maximum dose of 15 mg decided based on the results of the Japanese phase III and long-term treatment studies.

7.R.6.2 Dosing frequency and dose titration

The applicant's explanation about the dosing frequency and dose titration scheme of etelcalcetide:
Hemodialysis removes etelcalcetide. Thus ,etelcalcetide was to be administered 3 times per week at the end of hemodialysis in the Japanese phase III and long-term treatment studies. The dose was allowed to be increased every 4 weeks in the Japanese phase III and long-term treatment studies because serum iPTH, corrected serum Ca, and serum P concentrations were essentially at steady state after 4 weeks of treatment in the Japanese phase I/II study, in which etelcalcetide was administered 3 times weekly at the end of hemodialysis. Because there were no particular safety concerns in the Japanese phase III and long-term treatment studies, the package insert will provide advice stating that the dose may be increased no more frequently than every 4 weeks.

The dose was to be increased by 5 mg and reduced by 2.5 mg in the Japanese phase III and long-term treatment studies (Table 18). Dose increases/reductions and dose suspension were to occur based on serum iPTH and corrected serum Ca levels, and the criteria for dose increase/reduction were established, referring to the target range of serum PTH and corrected serum Ca recommended by Clinical Practice Guideline for CKD-MBD (Table 18). Moreover, eligible patients had to have a corrected serum Ca ≥8.4 mg/dL at baseline because etelcalcetide-induced marked reduction in serum Ca could lead to hypocalcaemia or other symptoms. Eventually, there were no major safety concerns in the Japanese phase III and long-term treatment studies. The dose of etelcalcetide was increased by 5 mg, but the dose was reduced in patients whose corrected serum Ca was <8.4 mg/dL after dose increase and was considered difficult to recover with rescue therapy with Ca supplements or other medications. Because of such reason, the dose was reduced in 2.6% (2 of 78) of patients participating in the Japanese phase III study and 0.5% (1 of 190) of patients participating in the Japanese long-term treatment study. Dose suspension occurred in 3.8% (3 of 78) of patients and 5.3% (10 of 190) of patients, respectively, because the corrected serum Ca fell to <7.5 mg/dL. The dose was reduced in 1.3% (1 of 78) of patients and 7.9% (15 of 190) of patients, respectively, because the serum iPTH fell to <60 pg/mL. Pooled data from the Japanese phase III and long-term treatment studies were analyzed to identify the extent and number of dose reductions in 116 patients who had their dose reduced. The results are shown in Table 35.

Table 35. Extent and number of dose reductions in patients who had their dose reduced (Pooled data from Japanese phase III and long-term treatment studies)

		Dose before dose reduction					
		15 mg	12.5 mg	10 mg	7.5 mg	5 mg	2.5 mg
Extent of dose reduction	2.5 mg	5	2	19	11	86	173
	5 mg	2	0	1	0	61	—
	7.5 mg	0	0	0	7	—	—
	10 mg	1	0	26	—	—	—
	12.5 mg	0	1	—	—	—	—
	15 mg	6	—	—	—	—	—

In light of the above findings, the use of dose increments of 2.5 mg as well as 5 mg should be considered because a certain number of patients required dose reduction/suspension due to the exaggerated pharmacodynamic effects of etelcalcetide.

Clinical Practice Guideline for CKD-MBD recommends that corrected serum Ca should be measured at least once or twice a month. For this reason and others, corrected serum Ca was to be measured once a week until Week 12 in the Japanese phase III and long-term treatment studies and every 2 weeks after Week 12 in the Japanese long-term treatment study. Eventually, there were no major safety concerns about decreased serum Ca levels in the Japanese phase III or long-term treatment studies. Therefore, corrected serum Ca should be measured once a week after the initiation and dose adjustment of etelcalcetide and every 2 weeks while corrected serum Ca is maintained within the target range. This is based on the results of the Japanese phase III and long-term treatment studies.

The dose was to be titrated every 4 weeks based on serum iPTH levels in the Japanese phase III and long-term treatment studies for the following reasons: (i) Clinical Practice Guideline for CKD-MBD recommends that serum PTH should be measured once a month in patients with high blood PTH levels on active treatment with cinacalcet hydrochloride or other therapies, and (ii) serum iPTH concentrations are essentially at steady state after 4-week treatment with etelcalcetide. Eventually, there were no major safety concerns about decreased serum PTH levels in the Japanese phase III and long-term treatment studies. Thus, serum PTH should be measured once a month during treatment with etelcalcetide. To ensure that PTH is within the target range, however, it is recommended that serum PTH should be measured approximately twice a month until PTH levels are stable after the initiation or dose adjustment of etelcalcetide.

PMDA's view:

There are no particular problems with three-times-weekly administration of etelcalcetide at the end of hemodialysis, which was adopted based on the Japanese phase III and long-term treatment studies. The dose may be increased in 2.5 or 5 mg increments no more frequently than every 4 weeks because a certain number of patients required dose reduction/suspension due to serum Ca and PTH falling below the target range. There is little need for specifying the extent of dose reduction for the following reasons: (i) The dose was reduced by >2.5 mg in some patients in the Japanese phase III and long-term treatment studies, and (ii) a dose reduction of >2.5 mg may be needed from the standpoint of safety.

The criteria for initiation, dose increase/reduction, and dose suspension of etelcalcetide, and other procedures are appropriate; etelcalcetide should be initiated in patients with corrected serum Ca ≥8.4 mg/dL, Ca supplements should be started or the dose of etelcalcetide should be reduced if corrected serum Ca is <8.4 mg/dL, and etelcalcetide should be suspended if corrected serum Ca falls to <7.5 mg/dL, based on the Japanese clinical studies. Serum Ca should be measured once a week after the initiation and dose adjustment of etelcalcetide and at least every 2 weeks while serum Ca is maintained within the target range. It is recommended that serum PTH should be measured twice a month until PTH levels are stable and once a month thereafter.

7.R.7 Concomitant medications

Etelcalcetide is expected to be used concomitantly with P binders in patients with SHPT on hemodialysis. PMDA asked the applicant to explain the efficacy and safety of etelcalcetide when used concomitantly with P binders.

The applicant's response:

In a Japanese phase III study, 98.7% (77 of 78) of subjects in the etelcalcetide group were treated concomitantly with P binders during the study period. The proportions of subjects who received etelcalcetide with or without concomitant P binders and who achieved target serum iPTH levels on Day 85 were 59.7% (46 of 77 subjects) and 0% (0 of 1 subjects), respectively. The incidences of adverse events in the former and latter subgroups were 64.9% (50 of 77 subjects) and 100% (1 of 1 subject), respectively. There were no particular clinical problems with use of concomitant P binders. In a Japanese long-term treatment study, 98.4% (187 of 190) of patients were treated concomitantly with P binders during the study period. Although P binders were used concomitantly in most patients, there were no particular efficacy or safety concerns.

A breakdown of P binders used in the etelcalcetide group in the Japanese phase III study is as follows: Ca-containing P binders used in 14.1% (11 of 78) of subjects, P binders without Ca used in 23.1% (18 of 78) of subjects, and both used in 61.5% (48 of 78) of subjects. The proportions of subjects achieving target serum iPTH levels on Day 85 were 63.6% (7 of 11 subjects) among subjects treated concomitantly with Ca-containing P binders and 50.0% (9 of 18 subjects) among those treated concomitantly with P binders without Ca. The incidences of adverse events in the former and latter subgroups were 81.8% (9 of 11 subjects) and 66.7% (12 of 18 subjects), respectively. A breakdown of P binders used in the Japanese long-term treatment study is as follows: Ca-containing P binders used in 15.8% (30 of 190) of subjects, P binders without Ca used in 17.4% (33 of 190) of subjects, and both used in 65.3% (124 of 190) of subjects. The proportions of subjects achieving target serum iPTH levels on Day 365 were 79.2% (19 of 24 subjects) among subjects treated concomitantly with Ca-containing P binders and 96.4% (27 of 28 subjects) among those treated concomitantly with P binders without Ca. The incidences of adverse events in the former and latter subgroups were 93.3% (28 of 30 subjects) and 97.0% (32 of 33 subjects), respectively. There were no major problems with the efficacy and safety of etelcalcetide when used concomitantly with Ca-containing P binders or P binders without Ca in the Japanese phase III and long-term treatment studies.

Based on the above, there should be no particular problems with the efficacy and safety of etelcalcetide when used concomitantly with P binders.

Then, PMDA asked the applicant to explain the efficacy and safety of etelcalcetide when used concomitantly with cinacalcet hydrochloride and active vitamin D preparations, which are recommended for use in patients with SHPT by Clinical Practice Guideline for CKD-MBD.

The applicant's response:
Since cinacalcet hydrochloride is also a CaSR agonist, there should be no possibility of concurrent administration of etelcalcetide with cinacalcet hydrochloride.

On the other hand, since active vitamin D preparations have a different mechanism of action, their concurrent administration with etelcalcetide is envisaged. In the Japanese phase III study, 80.8% (63 of 78) of subjects in the etelcalcetide group reported concomitant use of active vitamin D preparations at baseline. The proportions of subjects achieving target serum iPTH levels on Day 85 were 66.7% (42 of 63 subjects) among subjects treated concomitantly with active vitamin D preparations and 26.7% (4 of 15 subjects) among those not treated concomitantly with active vitamin D preparations (Table 24). The incidences of adverse events in the former and latter subgroups were 60.3% (38 of 63 subjects) and 86.7% (13 of 15 subjects), respectively. There were no particular clinical problems with concomitant use of active vitamin D preparations. In the Japanese long-term treatment study, 98.9% (188 of 190) of patients were treated concomitantly with active vitamin D preparations during the study period. Although active vitamin D preparations were used concomitantly in most patients, there were no particular efficacy or safety concerns.

On the above grounds, there should be no problems with the efficacy and safety of etelcalcetide when used concomitantly with active vitamin D preparations.

PMDA accepted the applicant's explanation about concurrent administration of etelcalcetide with cinacalcet hydrochloride. PMDA confirmed that there have so far been no particular problems with the efficacy and safety of etelcalcetide when used concomitantly with P binders or active vitamin D preparations. The applicant should continue to collect information regarding the effects of concomitant medications on safety and efficacy via post-marketing surveillance or other means.

7.R.8 Post-marketing investigations

The applicant is planning a post-marketing specified use-results survey as shown in Table 36.

Table 36. Outline of specified use-results survey (draft)

Objective	**To ascertain the safety and efficacy of etelcalcetide in patient with SHPT on hemodialysis in routine clinical settings and identify unknown adverse drug reactions and factors affecting safety or efficacy.**
Survey method	**Central registry system**
Population	**Patients with SHPT on hemodialysis**
Target sample size	**1200 patients (number of patients to be analyzed, 1000 patients)**
Survey period	**3 years and 6 months (the enrollment period is 1 year)**
Observation period	**1 year**
Main survey items	**· Patient characteristics (e.g., age, gender, the disease that led to dialysis and a history of other medical conditions, details of dialysis [e.g., dialysis vintage, mode of dialysis, frequency of dialysis, dialysate Ca concentration], previous cinacalcet hydrochloride use) · Administration of etelcalcetide (e.g., dose, treatment duration, reason for etelcalcetide discontinuation) · Details of concomitant therapy (e.g., use of concomitant therapy, name of concomitant therapy, duration of therapy) · Efficacy (e.g., global improvement) · Clinical laboratory values (serum iPTH, corrected Ca, and P levels) · Adverse events (e.g., onset date, seriousness, action taken, outcome, a causal relationship to etelcalcetide)**

PMDA's view:

The applicant should collect information on the occurrence (frequency and severity) of hypocalcaemia-related events, cardiovascular events, hungry bone syndrome and adynamic bone disease, upper gastrointestinal disorder-related events, hypersensitivity, etc., via post-marketing surveillance or other means. The details of the post-marketing surveillance study will be finalized, taking account of comments from the expert advisor at the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.3.2-1, CTD 5.3.5.1-1, CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole were conducted in compliance with GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Although the outcome of the overall assessment of the studies was not affected significantly, the inspection revealed the following findings at a study site (medical institution) used by the applicant. The head of the medical institution was notified of these findings requiring corrective action.

[Findings requiring corrective action]

Study site

● Flaws in the contract for the outsourcing of part of study-related duties

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

On the basis of the data submitted, PMDA has concluded that etelcalcetide has efficacy in the treatment of SHPT in patients on hemodialysis and that etelcalcetide has acceptable safety in view of its benefits. Etelcalcetide is clinically meaningful because it offers a new option for the treatment of SHPT in patients on hemodialysis. PMDA considers that the efficacy, safety, indication, dosage and administration, and post-marketing investigations of etelcalcetide need further discussion.

PMDA has concluded that Parsabiv (etelcalcetide) may be approved if the product is not considered to have any particular problems based on comments from expert advisors at the Expert Discussion.

Review Report (2)

October 13, 2016

Product Submitted for Approval

Brand Name	Parsabiv Intravenous Injection for Dialysis 2.5 mg Parsabiv Intravenous Injection for Dialysis 5 mg Parsabiv Intravenous Injection for Dialysis 10 mg
Non-proprietary Name	Etelcalcetide Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	January 14, 2016

1. Content of the Review

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

1.1 Efficacy, safety, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions on Sections "7.R.1 Efficacy," "7.R.3 Safety," "7.R.5 Indication," and "7.R.6 Dosage and administration" presented in Review Report (1).

Based on comments from the expert advisors at the Expert Discussion, PMDA accepted the proposed indication and dosage and administration as shown below. PMDA requested the applicant to modify the statements in the "Precautions for Dosage and Administration" section of the package insert as follows. The applicant responded appropriately, and PMDA accepted it.

Indication

Secondary hyperparathyroidism in patients on hemodialysis

Dosage and administration

The usual adult starting dose is 5 mg of etelcalcetide administered 3 times per week. Administer by intravenous injection into the venous line of the dialysis circuit at the end of dialysis during rinse back.

Thereafter, while parathyroid hormone (PTH) and serum calcium levels should be monitored closely, the dose should be titrated based on the PTH and serum calcium levels. The dose range is 2.5 to 15 mg 3 times per week at the end of dialysis during rinse back.

Precautions for Dosage and Administration

(1) Ensure that serum calcium is not low (≥8.4 mg/dL) prior to the initiation of etelcalcetide, because etelcalcetide lowers blood calcium.

(2) Measure serum calcium once a week after the initiation and dose adjustment of etelcalcetide and at least every 2 weeks during maintenance. In the event that serum calcium is <8.4 mg/dL, the management shown in the table below is recommended. In order to properly determine the therapeutic effect and safety of etelcalcetide, it is recommended that predose serum calcium should be measured.

<table>
<tr><th colspan="2" rowspan="2">Serum calcium</th><th colspan="3">Management</th></tr>
<tr><th>Action</th><th>Test</th><th>Dose increase/Re-initiation</th></tr>
<tr><td colspan="2"><8.4 mg/dL</td><td>As a rule, do not increase the dose of etelcalcetide, and consider necessary actions including use of calcium supplements and/or vitamin D preparations or reduction of the dose of etelcalcetide.</td><td rowspan="2">Measure serum calcium at least once a week. ECG monitoring is recommended.</td><td>Increase the dose of etelcalcetide once serum calcium levels are ≥8.4 mg/dL.</td></tr>
<tr><td></td><td><7.5 mg/dL</td><td>Immediately stop etelcalcetide.</td><td>Re-initiate etelcalcetide at a dose that is the same as or lower than the last administered dose once serum calcium levels are ≥8.4 mg/dL.</td></tr>
</table>

If symptoms of hypoalbuminemia (serum albumin <4.0 g/dL) are present, corrected calcium levels * should be used.

* Corrected calcium (mg/dL) ＝ serum calcium (mg/dL) − serum albumin (g/dL) + 4.0

(3) The dose may be increased in 5 mg increments no more frequently than every 4 weeks. The use of dose increments of 2.5 mg should also be considered so that serum calcium or PTH does not fall below the target range.

(4) Measure PTH regularly to ensure that PTH is maintained within the target range. It is recommended that PTH should be measured twice a month after the initiation and dose adjustment of etelcalcetide (for approximately 3 months after dose initiation), and once a month once PTH levels are almost stable. In the event that PTH falls below the target range, consider dose reduction or suspension. In order to properly determine the therapeutic effect and safety of etelcalcetide, it is recommended that predose PTH should be measured.

1.2 Risk management plan (draft)

The expert advisors supported PMDA's conclusion presented in Section "7.R.8 Post-marketing investigations" in Review Report (1).

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for etelcalcetide should include the safety and efficacy specifications presented in Table 37, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 38 and a specified use-results survey presented in Table 39.

Table 37. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
· Hypocalcemia · Worsening heart failure · QT prolongation	· Hypersensitivity reactions · Convulsions · Bone metabolism disorder	· None
Efficacy specification		
· Long-term efficacy of etelcalcetide in routine clinical settings		

Table 38. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Specified use-results survey	· Dissemination of information obtained during early post-marketing phase vigilance.

Table 39. Outline of specified use-results survey (draft)

Objective	To ascertain the safety and efficacy of etelcalcetide in patient with SHPT on hemodialysis in routine clinical settings and identify unknown adverse drug reactions and factors affecting safety or efficacy.
Survey method	Central registry system
Population	Patients with SHPT on hemodialysis
Target sample size	1200 patients (number of patients to be analyzed, 1000 patients)
Survey period	3 years and 6 months (the enrollment period is 1 year)
Observation period	1 year
Main survey items	· Patient characteristics (e.g., age, gender, the disease that led to dialysis and a history of other medical conditions, details of dialysis [e.g., dialysis vintage, mode of dialysis, frequency of dialysis, dialysate Ca concentration], previous cinacalcet hydrochloride use) · Administration of etelcalcetide (e.g., dose, treatment duration, reason for etelcalcetide discontinuation) · Details of concomitant therapy (e.g., use of concomitant therapy, name of concomitant therapy, duration of therapy) · Efficacy (e.g., global improvement) · Clinical laboratory values (serum iPTH, corrected Ca, and P levels) · Adverse events (e.g., onset date, seriousness, action taken, outcome, a causal relationship to etelcalcetide)

2. Overall Evaluation

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

Indication

Secondary hyperparathyroidism in patients on hemodialysis

Dosage and Administration

The usual adult starting dose is 5 mg of etelcalcetide administered 3 times per week. Administer by intravenous injection into the venous line of the dialysis circuit at the end of dialysis during rinse back.

Thereafter, while parathyroid hormone (PTH) and serum calcium levels should be monitored closely, the dose should be titrated based on the PTH and serum calcium levels. The dose range is 2.5 to 15 mg 3 times per week at the end of dialysis during rinse back.

Condition of Approval

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