Report on the Deliberation Results

March 3, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ostabalo Subcutaneous Injection Cart 3 mg
Non-proprietary Name	Abaloparatide Acetate (JAN*)
Applicant	Teijin Pharma Limited
Date of Application	May 27, 2020

Results of Deliberation

In its meeting held on February 25, 2021, the First Committee on New Drugs concluded that the product may be approved, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

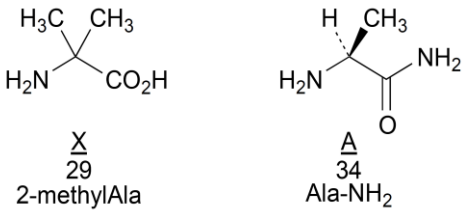
February 3, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Ostabalo Subcutaneous Injection Cart 3 mg
Non-proprietary Name	Abaloparatide Acetate
Applicant	Teijin Pharma Limited
Date of Application	May 27, 2020
Dosage Form/Strength	Aqueous injection: Each 1.5 mL cartridge contains 3.53 mg of Abaloparatide Acetate (3 mg of abaloparatide)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure

AVSEHQLLHD KGKSIQDLRR RELLEKLLXK LHTA • $x H_3C-CO_2H$



Molecular formula: $C_{174}H_{300}N_{56}O_{49} \cdot xC_2H_4O_2$

Molecular weight: 3960.59 (free base)

Chemical name: Abaloparatide acetate is an acetate salt of Abaloparatide consisting of 34 amino acid residues. Abaloparatide is a synthetic peptide analog of human parathyroid hormone-related protein (hPTHrP) corresponding to amino acid sequence of hPTHrP at positions 1 - 34 whose amino acid residues at positions 22, 23, 25, 26, 28, 29, 30, 31 and 34 are substituted by Glu, Leu, Glu, Lys, Leu, 2-methylAla, Lys, Leu and Ala-NH_2, respectively.

Items Warranting Special Mention None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in treating patients with osteoporosis at high risk of fracture, 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 approval condition.

Indication

Treatment for patients with osteoporosis at high risk of fracture

Dosage and Administration

The usual adult dosage is 80 μg of abaloparatide administered subcutaneously once daily. Duration of abaloparatide therapy should not exceed 18 months.

Approval Condition

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

Attachment

Review Report (1)

December 25, 2020

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

Product Submitted for Approval

Brand Name	Ostabalo Subcutaneous Injection Cart 3 mg
Non-proprietary Name	Abaloparatide Acetate
Applicant	Teijin Pharma Limited
Date of Application	May 27, 2020
Dosage Form/Strength	Aqueous injection: Each 1.5 mL cartridge contains 3.53 mg of Abaloparatide Acetate (3 mg of abaloparatide)

Proposed Indication

Treatment for patients with osteoporosis at high risk of fracture

Proposed Dosage and Administration

The usual adult dosage is 80 μg of abaloparatide administered subcutaneously once daily. Duration of abaloparatide therapy should not exceed 18 months.

Table of Contents

List of Abbreviations

See Appendix.

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

Abaloparatide acetate (abaloparatide) discovered by Ipsen (France) is a synthetic polypeptide comprising N-terminal 34 amino acid residues of human parathyroid hormone-related protein (hPTHrP) with partial modifications. Similarly to parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP) binds to PTH1 receptor which is expressed mainly in osteoblasts and, thereby, enhances (1) osteogenesis by promoting the growth and differentiation of osteoblasts through cyclic adenosine monophosphate (cAMP) production, etc., and (2) bone resorption by promoting the differentiation of osteoclast precursors to osteoclasts through the regulation of receptor activator of NF kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expression. However, intermittent administration leads to osteogenesis-dominant conditions, resulting in an increased bone mass and bone density.

Recently, the applicant submitted the application for marketing approval of abaloparatide with the claim that the efficacy and safety of abaloparatide in patients with osteoporosis at high risk of fracture have been confirmed by clinical studies, etc.

Abaloparatide was approved in the US in April 2017. In Europe, an application was submitted in November 2015. However, a refusal of the marketing authorization was issued in March and July in 2018 based on the conclusion that the benefit of abaloparatide fails to outweigh the risk, for the following reasons: Results of the foreign phase III study (Study BA058-05-003) suggested that (1) abaloparatide does not meet the efficacy criteria for non-spinal fracture required by the Guidelines for clinical evaluation of osteoporosis in Europe,[1)] and that (2) the incidence of palpitations was higher in the abaloparatide group than in the placebo group and in the teriparatide group, abaloparatide increases heart rate, and a matter of concern for postmenopausal women, the main intended population of abaloparatide, who have an increased cardiovascular risk.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is white powder, and its general properties, including description, hygroscopicity, pH, optical rotation, isoelectric point, and solubility, have been determined.

The chemical structure of the drug substance has been elucidated by amino acid analysis, electrospray ionization-mass spectrometry (ESI-MS), gas chromatography-mass spectrometry (GC-MS), circular dichroism spectroscopy, and differential scanning calorimetry.

2.1.2 Manufacturing process

The drug substance is synthesized using the following starting materials [redacted][2)][redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted].

1) "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis" (CPMP/EWP/552/95, Rev. 2))
2) [redacted]

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted].

[redacted] and [redacted] were defined as critical steps. [redacted] is controlled as the critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (ultra-high performance liquid chromatography [UHPLC], liquid chromatography-mass spectrometry [LC-MS]), optical rotation, acetate (high performance liquid chromatography [HPLC]), purity ([redacted] [HPLC], related substance [1] [UHPLC], related substance [2] [UHPLC], residual solvents [gas chromatography (GC)]), water content, bacterial endotoxins, microbial limit, and assay (UHPLC, mass balance). Related substance (2) (UHPLC) was added to the specifications during the review process.

2.1.4 Stability of drug substance

Table 1 shows the main stability studies conducted on the drug substance. Results demonstrated the stability of the drug substance. A photostability testing showed that the drug substance is light-stable.

Table 1. Stability studies of drug substance

Study	Primary batch	Storage condition	Storage form	Storage period
Long-term testing	3 commercial batches	[redacted] ± 5°C	[redacted] bottle with [redacted] screw cap	[redacted] months
Accelerated testing	3 commercial batches	5 ± 3°C		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance stored at ≤[redacted]°C in [redacted] bottle with [redacted] screw cap.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection containing 3.53 mg of the drug substance (3 mg of abaloparatide) in each cartridge (1.5 mL). The drug product contains, as excipients, sodium acetate hydrate, glacial acetic acid, phenol, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of drug solution preparation, sterile filtration/filing, and packaging/labeling. [redacted] and [redacted] were defined as critical steps.

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (UHPLC, [redacted]), pH, purity (related substances [UHPLC]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, phenol (UHPLC), and assay (UHPLC). Identification ([redacted]) was added to the specifications during the review process.

2.2.4 Stability of drug product

Table 2 shows the main stability studies conducted on the drug product. Results of the long-term testing demonstrated the stability of the drug product, whereas the accelerated testing showed an increase in related substances and a decrease in the strength. The photo-stability testing showed that the drug product is photostable.

Table 2. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	4 commercial batches	5 ± 3°C	Ambient	Glass cartridge with double-layered rubber disc[a)]-attached aluminum cap and chlorobutyl rubber plunger	36 months
Accelerated testing	4 commercial batches	25 ± 2°C	60% RH		6 months

a) Consists of 2 layers: bromobutyl rubber (in contact with the drug product) and polyisoprene.

Based on the above, a shelf life of 36 months was proposed for the drug product when stored at 2°C to 8°C in a glass cartridge with a double-layered rubber disc (bromobutyl rubber)-attached aluminum cap and a chlorobutyl rubber plunger.

2.R Outline of the review conducted by PMDA

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

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

In primary pharmacodynamic studies, binding activity to human PTH receptor and its mechanism of action *in vitro* and the activity to increase bone density in ovariectomized (OVX) rats, monkeys, etc., *in vivo* were investigated. In secondary pharmacodynamic studies, abaloparatide was tested for its binding to various receptors. In safety pharmacology studies, the effect of abaloparatide on the central nervous, cardiovascular, gastrointestinal, renal function, respiratory, and blood coagulation systems was evaluated. No pharmacodynamic drug-drug interaction study was conducted. Results of the main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effect on human PTH receptor (CTD 4.2.1.1-1)

HEK293 cells engineered to express human PTH1 receptor (HEK-C21 cells) were incubated with abaloparatide, hPTH (1-34), or hPTHrP (1-34) (all 0.003-300 nmol/L), and HEK293 cells engineered to express human PTH2 receptor (HEK-BP16 cells) were incubated with abaloparatide, hPTH (1-34), or hPTHrP (1-34) (all 0.01-100 nmol/L). The binding affinity of abaloparatide, human parathyroid hormone (hPTH) (1-34), and hPTHrP (1-34) to human PTH1 receptor and to human PTH2 receptor was evaluated using the acidification rate of extracellular fluid as the index.[3)] Half maximal effective concentration (EC_{50}) (mean ± standard error [SE]) of abaloparatide was 0.17 ± 0.05 nmol/L for HEK-C21 cells but incalculable for HEK-BP16 cells. EC_{50} (mean ±SE) of hPTH (1-34) was 0.26 ± 0.08 and 4.32 ± 0.56 nmol/L, respectively, for HEK-C21 cells and for HEK-BP16 cells. EC_{50} of hPTHrP (1-34) was 0.21 ± 0.05 nmol/L for HEK-C21 cells and incalculable for HEK-BP16 cells.

3) pH variation of extracellular fluid caused by ligand binding.

HEK-C21 cells were incubated with abaloparatide (0.003-10 μmol/L), hPTH (1-34) (0.01-30 μmol/L), or hPTHrP (1-34) (0.01-30 μmol/L), HEK-BP16 cells were incubated with abaloparatide (0.01-100 μmol/L), hPTH (1-34) (0.01-100 μmol/L), or hPTHrP (1-34) (0.01-100 μmol/L), and cAMP concentration in the culture fluid was measured. Abaloparatide increased cAMP in the culture fluid of HEK-C21 cells with EC_{50} of 0.17 ± 0.06 nmol/L, but EC_{50} was incalculable for HEK-BP16 cells. EC_{50} of hPTH (1-34) was 0.40 ± 0.16 and 1.41 ± 0.24 nmol/L, respectively, for HEK-C21 cells and for HEK-BP16 cells. EC_{50} of hPTHrP (1-34) was 0.48 ± 0.13 nmol/L for HEK-C21 cells but was incalculable for HEK-BP16 cells.

3.1.1.2 cAMP production in human and rat osteoblast-like cell lines (CTD 4.2.1.1-2 to 4.2.1.1-3)

Human osteoblast-like cells (Saos-2 cells) were incubated with abaloparatide, hPTH (1-34), or hPTHrP (1-34) (all 0.046-100 nmol/L), rat osteoblast-like cells (UMR-106 cells) were incubated with abaloparatide, hPTH (1-34), or hPTHrP (1-34) (all 0.0061-100 nmol/L), and cAMP concentration was measured. cAMP increased in both cell lines in the presence of abaloparatide; EC_{50} (mean ± standard deviation [SD]) was 5.10 ± 0.67 nmol/L for human osteoblast-like cells and 0.84 ± 0.05 nmol/L for rat osteoblast-like cells. EC_{50} of hPTH (1-34) was 3.92 ± 0.86 nmol/L for human osteoblast-like cells and 1.18 ± 0.10 nmol/L for rat osteoblast-like cells. EC_{50} of hPTHrP (1-34) was 3.76 ± 0.01 nmol/L for human osteoblast-like cells and 0.80 ± 0.10 nmol/L for rat osteoblast-like cells.

3.1.1.3 Binding affinity to active conformation of human PTH1 receptor and response of cAMP-production signal (CTD 4.2.1.1-4)

Abaloparatide, hPTH (1-34), hPTHrP (1-36), or LA-PTH, a peptide with a high selective affinity to R^0 structure, was added to the membrane fraction of HEK293 cells engineered to express pGloSensor-22F, a cAMP reporter plasmid, (GP-2.3 cells), and their binding affinity to RG form (G protein-binding form of PTH1 receptor) and to R^0 form structure (non-G protein-binding form) was evaluated by the competitive inhibition method using radioactive ligand. Mean half maximal inhibition concentration (IC_{50}) against RG and R^0 forms was 0.20 and 316 nmol/L, respectively, with abaloparatide, 0.33 and 3.9 nmol/L, respectively, with hPTH (1-34), 0.32 and 35 nmol/L, respectively, with hPTHrP (1-36), and 0.38 and 0.83 nmol/L, respectively, with LA-PTH.

GP-2.3 cells were cultured in the presence of luciferin and a test substance (abaloparatide [0.1 nmol/L], hPTH (1-34) [0.3 nmol/L], hPTHrP (1-36) [1 nmol/L], or LA-PTH [0.3 nmol/L]), followed by an exchange of the culture fluid with a culture medium with luciferin but without the test substance, and the amount of emission was measured over time to evaluate the reactivity of cAMP-producing signal. Results showed that E_{max} (mean ± SE) of abaloparatide, hPTH (1-34), hPTHrP (1-36), and LA-PTH was 0.172 ± 0.009, 0.148 ± 0.011, 0.157 ± 0.016, and 0.133 ± 0.009 cps, respectively. AUC (mean ± SE) of the amount of emission after removal of the test substance was 4.298 ± 0.561, 8.664 ± 1.698, 4.953 ± 1.125, and 14.682 ± 2.763 cps•min, respectively, in cells that had been incubated with abaloparatide, hPTH (1-34), hPTHrP (1-36), or LA-PTH.

3.1.1.4 Effect on osteoclast differentiation factor (CTD 4.2.1.1-5)

Human osteoblast-like cells (Saos-2 cells) were incubated with abaloparatide (100 nmol/L), hPTH (1-34) (100 nmol/L), or vehicle.[4)] After 6 hours, the culture fluid of a portion of cells was changed to a new culture medium not containing the test substance, whereas the remaining cells continued to be cultured without any treatment. The gene expression levels of RANKL, osteoprotegerin (OPG), and M-CSF in cells were investigated by real-time polymerase chain reaction (PCR). In cells without culture medium exchange, addition of abaloparatide or hPTH (1-34) induced increased gene expression level of RANKL, decreased gene expression level of OPG, increased RANKL/OPG ratio of gene expression level, and increased gene expression level of M-CSF, with abaloparatide and hPTH (1-34) showing similar tendencies. In cells that underwent medium exchange, the gene expression level of RANKL at 24 and 48 hours after addition of the test substance was lower in cells pretreated with abaloparatide than in cells pretreated with hPTH (1-34), the gene expression level of OPG at 48 hours after addition of the test substance was higher in cells pretreated with abaloparatide than in cells pretreated with hPTH (1-34), and the RANKL/OPG ratio of gene expression level and the gene expression level of M-CSF at 24 to 72 hours after addition of the test substance were lower in cells pretreated with abaloparatide than in cells pretreated with hPTH (1-34).

3.1.2 *In vivo* studies

3.1.2.1 A 12-month administration study in OVX rats (CTD 4.2.1.1-7)

OVX was performed on female rats (6-month-old, n = 10-18/group) and, from 3 months after OVX, abaloparatide 1, 5, 25 μg/kg or vehicle[5)] was administered subcutaneously once daily for 12 months. A sham operation group (6-month-old, n = 18) received vehicle[5)] in a similar manner.

Bone density of the lumbar spine and femur was measured over time[6)] by dual-energy X-ray absorptiometry (DXA) or peripheral quantitative computed tomography (pQCT). The percent change from baseline in the bone density of the lumbar spine and femur was higher in the abaloparatide group than in the OVX/vehicle group throughout the treatment period, and the extent of the increase was dose dependent.

Bone strength was measured on the lumbar spine (compaction test), shaft of femur (three-point bending test), and femoral neck (shearing test) isolated after 12 months of treatment. The maximum load, stiffness, and breaking energy of the lumbar spine, the maximum load and stiffness of the shaft of femur, and the maximum load and stiffness of the femoral neck were generally higher in the abaloparatide group than in the OVX/vehicle group, with the extent of the increase being dose dependent. The maximum load of the lumbar spine, shaft of femur, and femoral neck isolated after 12 months of treatment showed a positive correlation with the bone density of the corresponding site.

Bone morphology measurement was performed on the sponge bone of the lumbar spine and tibia and on the cortical bone of tibial diaphysis isolated after 12 months of treatment. For the sponge bone of the lumbar spine and tibia, the bone mass, trabecular thickness, and trabecular number were higher, but the trabecular separation was narrower, in the abaloparatide group than in the OVX/vehicle group.

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4) Distilled water containing 0.1% BSA
5) Physiological saline
6) Measured after 0, 12 to 13, 25 to 26, and 51 to 52 weeks of treatment.

Osteoclast surface in the abaloparatide group was not different from that in the OVX/vehicle group. The osteoblast surface, osteoid surface, and mineralizing surface as well as the bone formation rate were greater in the abaloparatide group than in the OVX/vehicle group. For cortical bone of tibial diaphysis, the cortical area and cortical width were greater, and the medullary area was smaller, in the abaloparatide group than in the OVX/vehicle group. The eroded surface of endosteum in the abaloparatide group was not different from that in the OVX/vehicle group. Periosteal perimeter, periosteal mineral apposition rate, periosteal bone formation rate, and endosteal perimeter tended to be greater in the abaloparatide group than in the OVX/vehicle group.

Measurement of bone metabolism markers over time[7)] showed that serum osteocalcin (OC) concentration was higher in the abaloparatide 5 and 25 μg/kg groups than in the OVX/vehicle group throughout the treatment period, and that serum procollagen type I N-terminal propeptide (P1NP) concentration was higher in the abaloparatide 25 μg/kg group than in the OVX/vehicle group throughout the treatment period. Serum type I collagen C-telopeptides (CTX) concentration did not show a difference between the abaloparatide group and the OVX/vehicle group throughout the treatment period. The urine deoxypyridinoline (DPD)/Cr ratio was lower in the abaloparatide 5 μg/kg group than in the OVX/vehicle group only during Week 30 to 31 of treatment.

Serum calcium concentration was higher in the abaloparatide 25 μg/kg group than in the OVX/vehicle group only during Week 30 to 31 but, at other time points, no difference was observed between treatment groups.

3.1.2.2 A 16-month administration study in OVX monkeys (CTD 4.2.1.1-8)

OVX was performed on female monkeys (9-18 years old, n = 16-17/group) and, from 9 months after OVX, abaloparatide 0.2, 1, 5 μg/kg or vehicle[5)] was administered subcutaneously once daily for 16 months. A sham operation group (9-18 years old, n = 16) received vehicle[5)] in a similar manner.

Bone density of the lumbar spine and femur was measured over time[8)] by DXA. The percent change from baseline in the bone density of the lumbar spine and proximal femur was higher in all abaloparatide groups than in the OVX/vehicle group throughout the treatment period, and the extent of the increase was similar between the abaloparatide 1 and 5 μg/kg groups, and greater in these groups than in 0.2 μg/kg group. The femoral bone density was not different among dose groups.

Bone strength was measured on the lumbar spine (compaction test), shaft of femur (three-point bending test), and femoral neck (shearing test) isolated after 16 months of treatment. The maximum load of the lumbar spine was greater in the abaloparatide 5 μg/kg group than in the OVX/vehicle group, while no difference was observed in the maximum load, stiffness, and breaking energy of the femoral shaft and neck between the abaloparatide groups and the OVX/vehicle group.

Bone morphology measurement was performed on the sponge bone of the lumbar spine and on the cortical bone of the femoral shaft isolated after 16 months of treatment. For the sponge bone of the

7) Measured after 0, 11 to 12, 30 to 31, and 47 to 48 weeks of treatment.
8) Measured after 0, 16 to 17, 33 to 34, 51 to 52, and 68 to 69 weeks of treatment.

lumbar spine, no difference was observed between the abaloparatide groups and the OVX/vehicle group in the bone mass, trabecular thickness, trabecular separation, trabecular number, osteoclast surface, eroded surface, osteoblast surface, osteoid area, mineralizing surface, mineral apposition rate, or bone formation rate. Micro-CT analysis showed that volumetric bone density, bone mineral content, and bone volume were higher, and structural model index was lower, in the abaloparatide ≥1 μg/kg groups than in the OVX/vehicle group, while no difference was observed in trabecular thickness, trabecular separation, trabecular number, tissue mineral density, or structural anisotropy. For the cortical bone of the femoral shaft, no difference was observed between the abaloparatide groups and the OVX/vehicle group in the cortical area, medullary area, cortical thickness, cortical porosity, endosteal eroded surface, periosteal perimeter, periosteal mineral apposition rate, periosteal bone formation rate, or endosteal mineral apposition rate. Endosteal perimeter and endosteal bone formation rate were higher in the abaloparatide 5 μg/kg group than in the OVX/vehicle group.

Measurement of bone metabolism markers over time[9)] showed that serum bone alkaline phosphatase (BAP) concentration in the abaloparatide groups was not different from that in the OVX/vehicle group throughout the treatment period, whereas blood P1NP concentration tended to be higher in the abaloparatide groups than in the OVX/vehicle group throughout the treatment period. There was no difference in serum CTX concentration or in urine N-terminal telopeptide of type I Collagen (NTX)/Cr ratio between the abaloparatide groups and the OVX/vehicle group throughout the treatment period.

Changes in serum calcium concentration over time showed no difference between the abaloparatide groups and the OVX/vehicle group throughout the treatment period.

3.1.2.3 A 4-week administration study in OVX rats, comparison with hPTH (1-34) (CTD 4.2.1.1-9)

OVX was performed on female rats (12 weeks old, n = 9/group), and abaloparatide or hPTH (1-34) at 0.062, 0.19, 0.56, 1.67, or 5 nmol/kg, or vehicle[10)] was administered subcutaneously once daily for 4 weeks. A sham operation group (12 weeks old, n = 9) received vehicle[10)] in a similar manner.

Measurement of the bone density of the lumbar spine by DXA after 26 days of treatment showed that the bone density was higher in groups receiving ≥0.19 nmol/kg of abaloparatide or hPTH (1-34) than in the OVX/vehicle group, showing a dose-dependent increase in all groups.

Bone strength was measured on the lumbar spine (compaction test) isolated on the next day of the final dose. The maximum load, stiffness, and breaking energy of the lumbar spine were higher in the abaloparatide and the hPTH (1-34) groups than in the OVX/vehicle group, generally showing a dose-dependent increase in all groups.

Bone metabolism markers were measured on the next day of the final dose. Blood P1NP concentration and the urine DPD/Cr ratio were higher in the abaloparatide and the hPTH (1-34) groups than in the OVX/vehicle group, generally showing a dose-dependent increase in all groups.

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9) Measured at baseline and at 0, 14 to 15, 32 to 33, 50 to 51, and 67 to 68 weeks after treatment.
10) Physiological saline containing 0.1% rat serum

3.1.2.4 A 4-week administration study in male mice, comparison with hPTH (1-34) (CTD 4.2.1.1-10)

Abaloparatide or hPTH (1-34) at 30 μg/kg was administered subcutaneously to male mice (6 weeks old, n = 13/group) once or in 2 or 3 divided doses every day for 4 weeks. An untreated group (6 weeks old, n = 6) was included in the study.

The bone density of the lumbar spine and femur was measured by DXA after 26 days of treatment. The bone density was higher in both the abaloparatide and the hPTH (1-34) groups than in the untreated group, showing a tendency of an increase with the dosing frequency. The extent of the increase was greater in the abaloparatide group than the hPTH (1-34) group of the same dosing frequency.

Bone metabolism markers were measured after 28 days of treatment. Serum P1NP concentration was higher in both the abaloparatide and the hPTH (1-34) groups receiving ≥2 divided doses than in the untreated group; the higher the dosing frequency, the greater the extent of the increase. Serum P1NP concentration was higher in the group receiving abaloparatide in ≥2 divided doses than in the group receiving hPTH (1-34) at the same frequency. The urine DPD/Cr ratio was higher in groups receiving abaloparatide or hPTH (1-34) in ≥2 divided doses than in the untreated group and in the group receiving abaloparatide or hPTH (1-34) once daily. No difference was detected between the abaloparatide group and the hPTH (1-34) group.

A histological analysis of femoral distal-metaphysis isolated 28 days after treatment showed that the alkaline phosphatase (ALP)-positive area was higher in the groups receiving abaloparatide or hPTH (1-34) in ≥2 divided doses than in the untreated group; the higher the dosing frequency, the greater the extent of the increase. The ALP-positive area was higher in all abaloparatide groups than in groups receiving hPTH (1-34) in the same dosing frequency. The number of TRAP-positive osteoclasts per unit bone surface was higher in the abaloparatide and hPTH (1-34) groups than in the untreated group. Compared with the number of TRAP-positive osteoclasts in the group receiving hPTH (1-34) in the same dosing frequency, the number was not different in the group receiving abaloparatide once daily or in 2-divided doses, but lower in the group receiving abaloparatide in 3-divided doses.

3.1.2.5 A 4-week administration study in a rat closed femoral fracture model (CTD 4.2.1.1-11 to 4.2.1.1-12)

Closed fracture of the right femoral shaft was performed on male rats (11 weeks old, n = 12/group) and, starting from the day of the operation, abaloparatide 10 μg/kg was administered subcutaneously once daily for 4 weeks or vehicle[10)] was administered subcutaneously once daily for 4 or 6 weeks.

Measurement of the bone density at the site of the fracture by DXA showed that the density was higher in the abaloparatide group than in the vehicle group (4- or 6-week administration).

Bone strength (maximum load) at the fracture site of the femur isolated after 4 weeks (after 6 weeks in the vehicle group [6-week administration]) was measured by a 4-point bending test. The maximum

load at the fracture site in the abaloparatide group was higher than that in the vehicle group (4-week administration) but not different from that in the vehicle group (6-week administration).

3.1.2.6 Study on OVX rats with defective spine (CTD 4.2.1.1-13)

OVX was performed on female rats (8 weeks old, n = 6/group) and, 32 to 36 days after the operation, the lumbar spine was partially deleted. Starting from the day of the removal, abaloparatide 30 μg/kg or vehicle[10)] was administered subcutaneously once daily for 6 weeks at the maximum.

The lumbar spine isolated after 3 days, 1 week, 2 weeks, 4 weeks, and 6 weeks of treatment were subjected to measurement of the bone mineral content, bone structure parameters of the sponge bone, and bone strength (maximum load) at the defective site by micro-CT and compaction test. The bone mineral content at the defective site after ≥2 weeks of treatment was higher in the abaloparatide group than in the OVX/vehicle group.

As for the bone structure parameters of the sponge bone at the defective site, bone volume, trabecular thickness, and trabecular number were higher, and the trabecular separation was lower, in the abaloparatide group than in the OVX/vehicle group.

The maximum load of the lumbar spine at the defective site increased from ≥2 weeks of treatment in the abaloparatide group than in the OVX/vehicle group.

Measurement of bone metabolism markers over time[11)] showed that serum P1NP concentration was higher in the abaloparatide group than in the OVX/vehicle group throughout the treatment period. Serum CTX concentration did not differ between the abaloparatide group and the OVX/vehicle group throughout the treatment period.

Measurement of serum calcium concentration over time[11)] showed no difference between the abaloparatide group and the OVX/vehicle group throughout the treatment period.

3.1.2.7 Study on parathyroidectomized rats (CTD 4.2.1.1-14)

After male rats (n = 5-6/group) were fed on a calcium-deficient diet for 4 days, parathyroidectomy was performed. Immediately after the operation, a single dose of abaloparatide, hPTH (1-34), or hPTHrP (1-34) (5, 20, 80, or 320 μg/kg each) or vehicle[12)] was administered subcutaneously. Non-parathyroidectomized rats fed on a calcium-deficient diet were included in the untreated group.

Plasma calcium concentration was measured at 6 hours after parathyroidectomy. The concentration was lower in the vehicle group than in the untreated group, while the concentration in the abaloparatide, hPTH (1-34), and hPTHrP (1-34) groups was higher than that in the vehicle group. Plasma calcium concentration in the abaloparatide 320 μg/kg group was lower than that in the hPTH (1-34) or hPTHrP (1-34) group receiving the same dose.

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11) Measured after 3 days and 1, 2, 4, and 6 weeks of treatment.
12) Physiological saline containing 2% rat serum

3.2 Secondary pharmacodynamics

3.2.1 Off-target selectivity (CTD 4.2.1.2-1)

The binding or inhibitory effect of abaloparatide to 229 types of receptors, enzymes, etc., was evaluated. Abaloparatide 10 μmol/L exhibited ≥50% inhibitory activity against 4 targets, i.e., IC_{50} of 3.29 μmol/L and K_i of 1.56 μmol/L against bombesin receptor (BB1), IC_{50} of 5.56 μmol/L and Ki of 1.59 μmol/L against N-formyl peptide receptor-like 1 (FPRL1) receptor, IC_{50} of 4.89 μmol/L and K_i of 3.43 μmol/L against orexin receptor (OX1), and IC_{50} of 8.68 μmol/L and Ki of 6.13 μmol/L against vasoactive intestinal peptide (VIP)1 receptor.

3.3 Safety pharmacology

The applicant submitted the results of the studies listed in Table 3 as the data on the safety pharmacology.

Table 3. Summary of safety pharmacology studies

Body system	Test system	Evaluation items/methods	Dose of abaloparatide	Route of administration	Findings	CTD
Central nervous	Wistar rats (4 females/group)	Irwin method	0.2, 1, 5, 25, 125, 625 μg/kg	i.v. or s.c.	≥0.2 μg/kg i.v. administration: Excitation without dose-dependency	4.2.1.3-1
	Wistar rats (10 females/group)	Photocell method	0, 1, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-2
	Wistar rats (10 females/group)	Number of sleeping animals, sleep latency, sleep length	0, 1, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-3
	Wistar rats (15 females/group)	Electroshock intensity	0, 1, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-4
	Wistar rats (10 females/group)	Clonic convulsion, tonic convulsion, and latent time to death after pentylenetetrazole administration, and number of animals showing each of the above symptoms	0, 1, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-5
Cardiovascular	hERG-introduced HEK293 cells (3 specimens)	hERG current	0, 10, 30 μmol/L	*In vitro*	30 μmol/L: Suppression of hERG channel current.	4.2.1.3-7
	Isolated rabbit Purkinje fibers (4-6 specimens)	Cardiac action potential parameters	0.3, 3, 10 μmol/L	*In vitro*	3 and 10 μmol/L: Mild suppression of repolarization of cardiac myocytes 10 μmol/L: Early after depolarization	4.2.1.3-8
	Dogs (3/sex)	Blood pressure, heart rate, ECG, etc.	0, 0.03, 0.1, 0.3, 1, 3 μg/kg	i.v.	≥0.1 μg/kg: Decreases in blood pressure and total peripheral resistance, increases in heart rate and the maximum upstroke velocity of the left ventricular pressure 3 μg/kg: A transient decrease in maximum upstroke velocity of the left ventricular pressure ≥0.3 μg/kg: Increased cardiac output, decreased stroke volume, increased tension time index, decreases in ejection time and isovolumetric contraction time 1 μg/kg: Increased left cardiac work 3 μg/kg: Decreased tension-time index and decreased left cardiac work ≥0.3 μg/kg: Decreased left ventricular diastolic pressure 3 μg/kg: Mild decrease in pulmonary artery pressure and increase in pulmonary artery wedge pressure 0.03 μg/kg: Mild transient increase in renal blood flow velocity and decreased renal arteriolar resistance ≥0.1 μg/kg: Increased renal blood flow velocity and decreased renal arteriolar resistance	4.2.1.3-9

					3 μg/kg: Decreased renal blood flow velocity ≥0.3 μg/kg: Decreased PR and QT intervals 3 μg/kg: Decreased QTc interval	
	Dogs (2/sex)	Blood pressure, heart rate, ECG	0, 1, 3, 10 μg/kg	s.c.	≥1 μg/kg: Increased heart rate ≥3 μg/kg: Decreased blood pressure	4.2.1.3-10
Respiratory	Wistar rats (6-8 females/group)	Inspiration time, expiration time, inspiratory capacity, maximum expiratory volume, tidal volume, respiration rate, relaxation time, resting phase, and airway resistance index	0, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-11
Gastrointestinal	Wistar rats (8 females)	Total length of small intestine, charcoal transport distance	0, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-12
	Wistar rats (8 females)	Scoring of gastric and duodenal inflammation and ulcer	0, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-13
	Wistar rats (7-8/group)	Gastric acid volume, free acidity, total acidity, gastric pH	0, 5, 25, 125 μg/kg	s.c.	125 μg/kg: Decreased gastric fluid volume and mild decrease in gastric-acid secretion	4.2.1.3-14
Renal function	Wistar rats (11-12 females/group)	Urinary pH, urinary volume, urinary electrolytes, etc.	0, 5, 25, 125 μg/kg	s.c.	≥25 μg/kg: Mild increase in urinary sodium and calcium	4.2.1.3-15
Blood coagulation	Wistar rats (8 females/group)	Bleeding time	0, 5, 25, 125 μg/kg	s.c.	No effect	4.2.1.3-16

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of abaloparatide

The applicant's explanation:

Abaloparatide is a synthetic polypeptide consisting of modified N-terminal 34 amino acid residues of human PTHrP. Abaloparatide binds to PTH1 receptor expressed mainly in osteoblasts, thereby increasing the intracellular cAMP concentration, resulting in protein kinase A (PKA) activation through signal transduction, which in turn leads to enhancement of growth and differentiation of osteoblasts, thereby promoting bone formation through induction of bone mineralization. Also, abaloparatide promotes bone resorption by osteoclasts by regulating the expression of osteoclast differentiation factors (RANKL, M-CSF, etc.), thereby promoting the differentiation of osteoclast precursors into osteoclasts. When abaloparatide is administered intermittently, its osteogenic effect outweighs the bone-resorptive effect, thereby exhibiting a bone mass-increasing effect.

In vitro studies showed that abaloparatide selectively binds to human PTH1 receptor and induces human PTH1 receptor-mediated cAMP production. The active PTH1 receptor is present in 2 forms, RG conformation and R^0 conformation. In RG conformation, when the ligand-bound receptor is internalized from the cell surface in the cytoplasm, it does not produce cAMP anymore, resulting in a

transient cAMP production. In R^0 conformation, in contrast, the internalized ligand-bound receptor continues to produce cAMP (*Nat Chem Biol.* 2009;5:734-42, *Nat Chem Biol*. 2009;5:707-8). A reporter assay using HEK293 cells showed a higher binding selectivity of abaloparatide to RG conformation (the G-protein-bound form) than hPTH (1-34). Also, AUC of emission after the removal of the test substance was lower with abaloparatide. These results suggest that the cAMP-producing activity of abaloparatide is transient compared with that of hPTH (1-34). As for the effect on osteoclasts, addition of abaloparatide or hPTH (1-34) to a human osteoblast-like cells increased the RANKL/OPG ratio of gene expression level and also increased the gene expression level of M-CSF. When the duration of the treatment with the test substance was transient, the effect of abaloparatide was smaller than that of hPTH (1-34). RANKL and M-CSF are expressed in osteoblasts and induce the differentiation of osteoclast precursors to osteoclasts. OPG acts as a decoy receptor of RANKL excreted from osteoblast and suppresses the osteoclast differentiation-enhancing effect of RANKL (*Nat Rev Endocrinol*. 2011;7:647-56), suggesting the possibility that the osteoclast differentiation-enhancing effect of abaloparatide is weaker than that of hPTHrP (1-34).

As for *in vivo* studies, a 12-month subcutaneous administration of abaloparatide in OVX rats and a 16-month subcutaneous administration of abaloparatide in monkeys showed, compared with the OVX/vehicle group, a tendency of increased bone density and bone strength of the lumbar spine, as well as the improvement or improving tendency of the bone structure. Also, bone formation marker levels increased, while bone resorption marker levels did not increase. The bone formation rate of the cortical bone of the femoral shaft increased, while osteoclast surface and eroded surface did not increase. In the study in monkeys receiving abaloparatide, bone morphology measurement of the lumbar spine did not detect any difference in the changes of osteogenic parameters between the abaloparatide group and the OVX/vehicle group, probably due to the lower bone metabolic turnover and to lower response to drugs affecting bone metabolism in monkeys than in rodents. Also, increased bone density and bone strength were observed when abaloparatide was administered subcutaneously to a rat model of closed femoral fracture. In addition, subcutaneous administration of abaloparatide to OVX rats with defective spine tended to increase bone mineral content and bone strength, and improved or tended to improve bone structure. As for the comparison with hPTH, when abaloparatide or hPTH (1-34) was subcutaneously administered to male mice in 2 or 3 divided doses, bone density and serum concentration of P1NP, an osteogenic marker, were higher in the abaloparatide group than in the hPTH (1-34) group of the same dosing frequency, while the increase in the urine DPD/Cr ratio, a bone resorption marker, showed no difference. The ALP-positive area was higher in the abaloparatide group than in the hPTH (1-34) group of the same dosing frequency, whereas the number of TRAP-positive osteoclasts did not differ between the abaloparatide group and the hPTH (1-34) group receiving the study drug once daily or in 2 divided doses, but it was lower in the abaloparatide group than in the hPTH (1-34) group receiving 3 divided doses. These results suggest that abaloparatide expanded the anabolic window (difference between the osteogenic effect and bone resorptive effect) more than hPTH (1-34) in mice by increasing the dosing frequency.

The above results demonstrate that abaloparatide enhances bone metabolism through the PTH1 receptor-mediated effect and, by intermittent subcutaneous administration, preferentially promotes bone formation, thereby increasing bone density and bone strength. Abaloparatide is thus expected to

be effective against osteoporosis. Also, the balance between the osteogenic and bone-resorptive effect of abaloparatide is different from that of hPTH (1-34), suggesting that abaloparatide exhibits a more potent bone mass-increasing effect by increasing the ratio of the osteogenic effect relative to the bone-resorbing effect compared with hPTH (1-34).

Safety pharmacology studies showed the effects of abaloparatide on the cardiovascular system such as decreased blood pressure, increased heart rate, increased maximum upstroke velocity of left ventricular pressure, and increased cardiac output, etc. PTHrP and PTH are known to increase heart rate and cardiac contraction (positive chronotropic and inotropic actions) and to dilate peripheral blood vessels (e.g., *Endocrinology*. 1995;136:3024-30, *Circulation*. 1997;96:3704-9). The above effects observed in safety pharmacology studies are considered to be due to pharmacological effects of abaloparatide.

PMDA's view:
The *in vitro* studies demonstrated the binding of abaloparatide to PTH1 receptor and PTH1 receptor-mediated cAMP production. *In vivo* studies showed that (1) studies on ovariectomized rats and monkeys showed increased osteogenic markers and a tendency of increased bone density and bone strength, (2) a rat model of closed femoral fracture showed increased bone density and bone strength, and (3) vertebra-defective OVX rats showed increased bone mineral content and bone strength. On the other hand, abaloparatide did not exhibit any clear effect on bone resorption. The above results demonstrate the osteogenic effect of abaloparatide mediated by PTH1 receptor expressed on osteoblasts. Thus, results of nonclinical studies suggest that abaloparatide exhibits an osteogenic effect that outweighs its bone-resorbing effect. As for the difference in the pharmacological effect between abaloparatide and hPTH (1-34), abaloparatide may be different from hPTH (1-34) in its extent in bone density-increasing and osteogenic effects, given the following: (1) *In vitro* studies showed that abaloparatide is highly selective for RG conformation of PTH1 receptor, the conformation reported to have only a transient cAMP-producing activity, and (2) a study in male mice showed that bone density, serum P1NP concentration (a bone metabolism marker), and the ALP-positive area (a differentiation marker of bone cells) were higher in the abaloparatide group than in the hPTH (1-34) group. However, in OVX rats, no clear difference was observed between the abaloparatide group and the hPTH (1-34). Efficacy of abaloparatide against osteoporosis in humans, including the comparison with hPTH (1-34), is discussed in Section "7.R.1 Efficacy." Effects on the cardiovascular system (positive chronotropic and inotropic actions and peripheral vasodilator actions) reported with PTHrP and PTH were also observed in safety pharmacology studies of abaloparatide. Safety in cardiovascular systems in humans is discussed in Section "7.R.2 Safety."

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

A single dose of abaloparatide or ^{125}I-labeled abaloparatide was administered intravenously or subcutaneously to rats, and pharmacokinetics was investigated. Also, pharmacokinetics in repeated subcutaneous administration of abaloparatide was investigated based on the toxicokinetics in toxicity studies using rats and monkeys. Serum abaloparatide concentration was measured by radioimmunoassay (RIA). The lower limit of quantitation was 80 pg/mL. Plasma abaloparatide concentration was measured by RIA or liquid chromatography-tandem mass spectrometry

(LC-MS/MS). The lower limit of quantitation was 100 or 500 pg/mL (RIA) in rats and 500 pg/mL (RIA) or 20 pg/mL (LC-MS/MS) in monkeys. Radioactivity in biomaterials was measured by a gamma counter or a quantitative whole-body autoradiography. Anti-abaloparatide antibody was measured by RIA. Results of the main studies are described below.

4.1 Absorption

4.1.1 Single-dose administration (CTD 4.2.2.2-1)

A single dose of abaloparatide was administered intravenously or subcutaneously to male and female rats, and pharmacokinetics of abaloparatide was investigated. Table 4 shows the calculated pharmacokinetic parameters of abaloparatide.

Table 4. Pharmacokinetic parameters of abaloparatide in single intravenous or subcutaneous administration of abaloparatide

Route of administration	Dose[a)]	Sex	No. of animals	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	BA (%)
IV	10 μg/kg	Male	3/time point	-	8.63	-	0.84	1.09	0.35	-
		Female	3/time point	-	9.23	-	0.52	1.04	0.28	
SC	10 μg/kg	Male	3/time point	2.992	3.44	0.249	0.75	-	-	38.94
		Female	3/time point	2.389	2.54	0.250	1.27	-	-	27.27

Mean; -, Not calculated; IV, Intravenous administration; SC, Subcutaneous administration
C_{max}, Maximum serum concentration; $AUC_{0\text{-}inf,}$ Area under the serum concentration-time curve from time 0 to infinity; t_{max}, Time to maximum serum concentration; $t_{1/2}$, Elimination half-life; CL, Clearance; V_{ss}, Distribution volume; BA, Absolute bioavailability
a) Dose expressed in terms of abaloparatide

4.1.2 Repeated-dose administration (CTD 4.2.1.1-7 and 4.2.1.1-8, 4.2.3.2-5, 4.2.3.2-8)

Abaloparatide was administered subcutaneously once daily to male and female rats and monkeys. Table 5 shows the pharmacokinetic parameters of abaloparatide.

Table 5. Pharmacokinetic parameters of abaloparatide in repeated subcutaneous administration

Animal species	Dose (μg/kg)	Sex	No. of animals	Time point of measurement	C_{max} (ng/mL)	AUC_{0-t} (ng •h/mL)	t_{max} (h)	$t_{1/2}$ (h)
OVX rats	1	Female	3/time point	Day 1	0.396	0.219	0.25	0.209
			3/time point	Day 176	0.828	0.353	0.25	0.214
			3/time point	Day 358	0.879, 0.888[a)]	0.515	0.25	0.265
	5	Female	3/time point	Day 1	2.51	1.43	0.25	0.287
			3/time point	Day 176	3.94	1.59	0.25	0.224
			3/time point	Day 358	4.11	2.08	0.25	0.289
	25	Female	3/time point	Day 1	5.62	4.31	0.25	0.389
			3/time point	Day 176	22.8	21.0	0.50	0.586
			3/time point	Day 358	13.7	14.4	0.25	0.565
Rats	10	Male	3/time point	Day 1	1.94	1.22	0.25	-
			3/time point	Day 90	6.60	5.14	0.08	0.417
			3/time point	Day 181	3.30	2.60	0.08	-
		Female	3/time point	Day 1	2.85	1.47	0.25	-
			3/time point	Day 90	4.31	3.06	0.50	-
			3/time point	Day 181	4.35	2.78	0.25	-
	25	Male	3/time point	Day 1	5.74	3.27	0.25	-
			3/time point	Day 90	13.2	12.0	0.08	0.460
			3/time point	Day 181	9.64	12.3	0.25	-
		Female	3/time point	Day 1	4.94	2.75	0.25	-
			3/time point	Day 90	14.1	10.1	0.25	0.922
			3/time point	Day 181	9.13	10.5	0.25	1.10
	70	Male	3/time point	Day 1	12.8	9.47	0.25	0.272
			3/time point	Day 90	49.3	48.5	0.25	0.445
			3/time point	Day 181	40.1	44.2	0.50	0.639
		Female	3/time point	Day 1	11.1	8.68	0.50	-
			3/time point	Day 90	37.8	38.6	0.50	0.734
			3/time point	Day 181	28.8	29.2	0.25	0.634
OVX monkeys	0.2	Female	3	Day 1	0.0986 ± 0.0266	0.0803 ± 0.0390	0.5 [0.25, 0.50]	0.314[b)]
		Female	13	Day 267	0.130 ± 0.126	0.135 ± 0.239	0.5 [0.25, 0.5]	-
		Female	15	Day 483	0.155 ± 0.205	0.220 ± 0.563	0.5 [0.25, 1.0]	0.359, 0.393
	1	Female	7	Day 1	0.422 ± 0.162	0.261 ± 0.0998	0.25 [0.25, 0.30]	0.374 ± 0.0602
		Female	16	Day 267	0.232 ± 0.113	0.183 ± 0.125	0.25 [0.25, 0.50]	0.475 ± 0.258
		Female	12	Day 483	0.207 ± 0.0792	0.150 ± 0.101	0.25 [0.25, 0.25]	0.343 ± 0.0515
	5	Female	13	Day 1	1.390 ± 0.668	0.841 ± 0.551	0.25 [0.25, 0.30]	0.354 ± 0.0794
		Female	13	Day 267	1.020 ± 1.330	1.360 ± 2.900	0.25 [0.25, 0.32]	0.531 ± 0.378
		Female	14	Day 483	0.851 ± 0.771	0.946 ± 1.620	0.25 [0.25, 0.50]	0.415 ± 0.259
Monkeys	10	Male	4	Day 1	2.240 ± 0.302	3.493 ± 0.522	0.625 ± 0.250	-
			3	Day 271	2.527 ± 0.607	4.147 ± 2.102	0.750 ± 0.433	-
		Female	4	Day 1	3.355 ± 0.792	4.421 ± 0.404	0.438 ± 0.125	0.565[b)]
			3	Day 271	3.653 ± 0.725	5.342 ± 1.437	0.500 ± 0.0	-
	25	Male	4	Day 1	11.198 ± 2.854	16.897 ± 5.322	0.688 ± 0.375	0.719[b)]
			4	Day 271	9.423 ± 3.676	15.581 ± 7.315	0.563 ± 0.315	0.909, 0.708[c)]
		Female	4	Day 1	8.168 ± 0.637	10.422 ± 3.215	0.438 ± 0.125	0.890[b)]
			4	Day 271	7.658 ± 2.905	11.661 ± 4.686	0.500 ± 0.0	0.972 [b)]
	70/50[d)]	Male	5	Day 1	23.560 ± 9.036	32.282 ± 26.520	0.350 ± 0.137	0.572 ± 0.140
			5	Day 271	16.702 ± 6.076	28.578 ± 18.602	0.500 ± 0.306	1.11 ± 0.34[e)]
		Female	6	Day 1	34.467 ± 13.745	40.852 ± 25.733	0.333 ± 0.129	0.530 ± 0.125
			3	Day 271	18.300 ± 2.587	27.728 ± 6.416	0.333 ± 0.144	0.677 ± 0.225

Parameter values are calculated from means at each measuring time point in rats, and mean ± SD in monkeys (in OVX monkeys, t_{max} is expressed in median [range]).
Individual values for ≤2 animals; -, Not calculated
C_{max}, Maximum plasma concentration; AUC_{0-t}, Area under the plasma concentration-time curve from time 0 to the last measurable concentration; t_{max}, Time to the maximum plasma concentration; $t_{1/2}$, Elimination half-life
a) 2/time point, b) n = 1, c) n = 2, d) On Day 147, dose was changed from 70 μg/kg to 50 μg/kg, e) n = 3

In the 12-month repeated administration study in OVX rats, anti-abaloparatide antibody was detected in 1 of 18 animals at Month 6 in the 1 μg/kg group; and in 2 of 18 animals at Month 6, and in 2 of 17 animals at Month 12 in the 25 μg/kg group. In the 39-week repeated administration study in male and female monkeys, the antibody was detected in 1 of 9 animals at Month 39 in the 70/50 μg/kg group. In the 16-month repeated administration study in OVX monkeys, anti-abaloparatide antibody was not detected.

4.2 Distribution (CTD 4.2.2.3-1, 4.2.2.3-2)

Following a single subcutaneous administration of ^{125}I-labeled abaloparatide to male rats (n = 8) at 100 μg/kg, the radioactivity concentration reached the maximum level at 0.5 or 2 hours after administration in most of the tissues. The maximum radioactivity concentration in each tissue except for the administration site was highest in the kidney cortex, followed in descending order by the kidney, kidney medulla, pancreas, liver, and skeletal muscle. The maximum radioactivity concentration in the blood was 108 ng Eq/g, whereas the concentration in the above tissues was 872, 808, 570, 308, 152, and 144 ng Eq/g, respectively. In all of the brain tissues examined (cerebellum, olfactory lobe, cerebrum, spinal cord, and brain medulla), the radioactivity concentration reached the maximum level (61.3, 59.4, 57.6, 54.0, and 48.3 ng Eq/g, respectively) at 2 hours after administration. The radioactivity disappeared from most of these tissues within 168 hours.

The plasma protein-binding (mean, ultracentrifugation method) of abaloparatide (250-2000 pg/mL) was 65.4% to 78.1% in dogs and 43.8% to 58.1% in monkeys [for data on humans, see Section "6.2.1 Studies using human biomaterials"].

4.3 Metabolism (CTD 4.2.2.4-3)

Following a single subcutaneous administration of ^{125}I-abaloparatide at 100 μg/kg to male and female rats (n = 3/time point), the rate of unchanged abaloparatide in plasma to the administered radioactivity, at 0.25 and 0.5 hours after administration, was 20.21% and 12.91%, respectively, in males and 9.88% and 6.36%, respectively, in females. In both males and females, 8 types of metabolites were detected. The rate of the metabolites to the administered radioactivity, at 0.25 and 0.5 hours after administration, was 1.18% to 40.21% and 0.82% to 58.52%, respectively, in males and 1.03% to 54.30% and 0.74% to 45.29%, respectively, in females. A total of 17 and 16 types, respectively, of metabolites were detected within 48 hours after administration in the urine of males and females. The cumulative urinary excretion rate of each metabolite relative to the administered radioactivity was 0.845% to 15.7% in males and 0.271% to 40.7% in females. Three and one type, respectively, of metabolites were detected in the feces of males and females within 48 hours after administration. The cumulative fecal excretion rate of each metabolite relative to the administered radioactivity was 0.0772% to 1.27% in males and 1.14% in females.

4.4 Excretion (CTD 4.2.2.3-1)

Following a single subcutaneous administration of ^{125}I-abaloparatide at 100 μg/kg to 3 each of male and female rats, the cumulative urinary excretion rate (mean) relative to the administered radioactivity within 168 hours after administration was 82.2% and 93.7%, respectively, in males and females, and the cumulative fecal excretion rate was 4.82% and 4.45%, respectively, in males and females.

4.R Outline of the review conducted by PMDA

On the basis of the results of the nonclinical pharmacokinetic studies submitted, PMDA concluded that there were no particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

As toxicology studies of abaloparatide, the applicant submitted the data of single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other studies (safety of impurities). In *in vivo* studies, physiological saline was used as vehicle, unless specified otherwise.

5.1 Single-dose toxicity

The acute toxicity of abaloparatide was evaluated from the results of single intravenous and subcutaneous toxicity studies in mice and rats (Table 6).

Table 6. Summary of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (OF1)	i.v.	0, 50	Decreased motility from 30 minutes after administration until next day	>50	4.2.3.1-1
Male and female mice (OF1)	s.c.	0, 50	No findings	>50	4.2.3.1-2
Male and female rats (SD)	i.v.	0, 50	5-15 minutes after administration: Sedation, dyspnea, and staggering gait 30 minutes after administration: Sedation, dyspnea, and lateral position 1 hour after administration: Decreased motility	>50	4.2.3.1-3
Male and female rats (SD)	s.c.	0, 50	No findings	>50	4.2.3.1-4

5.2 Repeated-dose toxicity

Repeated subcutaneous dose toxicity studies were conducted in rats (4, 13, and 26 weeks) and monkeys (4, 13, and 39 weeks) (Table 7). Changes associated with the pharmacological action of abaloparatide were increased osteoblasts and osteoclasts, increased trabeculae, mineral deposition in kidney, heart, etc., associated with increased plasma calcium concentration, and decreased red blood cell count associated with decreased medullary cavity.

In the 26-week repeated subcutaneous dose toxicity study in rats, the exposure ($AUC_{0\text{-}t}$; 12.3 ng•h/mL in males, 10.5 ng•h/mL in females) at the no observed adverse effect level (NOAEL) (25 μg/kg/day) was approximately 13 (male) and 11 (female) times the exposure ($AUC_{0\text{-}t}$, 921.81 pg•h/mL) in humans at the clinical dose (80 μg once daily) of abaloparatide. Similarly, in the 39-week repeated subcutaneous dose toxicity study in monkeys, the exposure ($AUC_{0\text{-}t}$; 4147 pg•h/mL in males, 5342 pg•h/mL in females) at the lowest dose (10 μg/kg/day) was approximately 4 (male) and 5 (female) times the exposure in humans at the clinical dose of abaloparatide.

Table 7. Summary of repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (μg/kg/day)	Main findings	NOAEL (μg/kg/day)	Attached document CTD
Male and female rats (SD)	s.c.	4 weeks	0, 15, 70, 300	≥15: Transient reddening of limbs and scrotum, increased urinary calcium/creatinine ratio, decreases in red blood cell count, platelet count, hemoglobin, and MCHC, increased MCV, increased trabeculae in femur, thickened trabeculae, subendosteal fibroblast proliferation, increased osteoblasts and osteoclasts, fibrous bone formation, decreased medullary cavity, extramedullary hematopoiesis in liver and spleen ≥70: Increased plasma calcium concentration 300: Transient tachypnea, decreased hematocrit, increased reticulocyte rate, increased urinary inorganic phosphorus/creatine ratio	15	4.2.3.2-3
Male and female rats (SD)	s.c.	13 weeks	0, 10, 25, 70	≥10: Reddening of limbs and scrotum, decreased red blood cell count, increased MCV, increased fibrinogen, decreased APTT (male), increases in total erythroid cell ratio and polychromatic erythroblast ratio in bone marrow (male), decreased A/G ratio, decreased inorganic phosphorus, increased trabeculae in femur and lumbar spine, thickened trabeculae, subendosteal fibroblast proliferation in femur, increased osteoblasts and osteoclasts, fibrous bone formation, decreased medullary cavity, extramedullary hematopoiesis and megakaryocytosis in spleen ≥25: Increased urinary calcium/creatinine ratio, decreased hemoglobin and hematocrit, decreased TRAP, increased urea, decreased 25-hydroxycholecalciferol (male) 70: Decreased MCHC, increased reticulocyte rate, decreased prothrombin time (male), increased ALP, increased plasma calcium concentration, subendosteal fibroblast proliferation and osteoblast proliferation in lumbar spine	25	4.2.3.2-4
Male and female rats (SD)	s.c.	26 weeks	0, 10, 25, 70	≥10: Reddening of skin, decreases in red blood cell count, hemoglobin, and hematocrit, increased reticulocyte count, increased MCV, decreased A/G ratio, hyperostosis in femur and sternum, thickening of cortical bones and trabeculae and decreased medullary cavity, extramedullary hematopoiesis in spleen, mineral deposition in renal pelvis, vacuolization of zona glomerulosa of the adrenal cortex ≥25: Increased ALP 70: Decreased APTT and prothrombin time (male)	25	4.2.3.2-5
Male and female cynomolgus monkeys	s.c.	4 weeks	0, 100, 200, 450	≥100: Decreases in red blood cell count, hemoglobin, and hematocrit, increased reticulocyte rate, increased ALP, decreased albumin and A/G ratio, subendosteal fibroblast proliferation in sternum, increased osteoblasts and osteoclasts, fibrous bone formation, decreased medullary cavity ≥200: Increased myeloid/erythroid ratio 450: Increased urinary calcium/creatinine ratio	100	4.2.3.2-6

Male and female cynomolgus monkeys	s.c.	13 weeks + 4-week withdrawal	0, 10, 50, 200	≥10: Increased plasma calcium concentration ≥50: Subendosteal fibroblast proliferation in femur, increased osteoblasts and osteoclasts, and fibrous bone formation 200: Increased renal weight, mineral deposition in renal tubules, degeneration/necrosis of tubular epithelium, peritubular fibrosis, and basophilic renal tubules * One of 6 each of males and females in the 200 μg/kg/day group died of cardiac disorder (mineral deposition, degeneration/necrosis of cardiac muscles) and renal disorder (mineral deposition, degeneration/necrosis of tubular epithelium) due to increased plasma calcium concentration. Reversible	50	4.2.3.2-7
Male and female cynomolgus monkeys	s.c.	39 weeks + 4-week withdrawal	0, 10, 25, 70/50[a)]	≥10: Decreases in red blood cell count, hemoglobin, and hematocrit, increased urea nitrogen and ALP, decreased inorganic phosphorus concentration, mineral deposition in renal tubules ≥25: Increased renal weight, mineral deposition in lung and mandibular gland 70/50: Decreased body weight, decreased reticulocyte count, mineral deposition in heart and urinary bladder, hyperplasia of renal tubules * The following animals were moribund-sacrificed each at the indicated timing because of aggravation of clinical conditions associated with mineral deposition in kidney and heart due to increased serum calcium concentration: 1 of 4 males in the 10 μg/kg/day group on Day 144, 1 of 6 males in the 70/50 μg/kg/day group on Day 54, and 2 of 6 females in the 70/50 μg/kg/day group on Day 55 and 110, respectively. Reversible	<10	4.2.3.2-8

a) On Day 147, the dose was decreased from 70 μg/kg/day to 50 μg/kg/day.

5.3 Genotoxicity

The following genotoxicity studies were conducted: *In vitro* bacterial reverse mutation assay and chromosomal aberration assay using human lymphocytes, and an *in vivo* micronucleus assay in mice (Table 8). No genotoxicity was observed in any of the studies.

Table 8. Summary of genotoxicity studies

Study		Test system	S9 (treatment duration)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	−/+	0, 78.125[a], 156.25, 312.5, 625, 1250, 2500, 5000[b]	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvr*A	−/+			
	Chromosomal aberration assay in mammalian cultured cells	Human lymphocytes	− (3 hours) + (3 hours)	0, 3200, 4000, 5000	Negative	4.2.3.3.1-2
			− (20 hours) + (3 hours)	−: 0, 1886, 2610, 3612 +: 0, 3612, 4250, 5000		
In vivo	Micronucleus assay in rodents	Male mice (ICR) Bone marrow		0, 32.5, 65, 130 (2 days, s.c.)	Negative	4.2.3.3.2-1

a) Only *Salmonella typhimurium* strain TA1537 was used.
b) *Salmonella typhimurium* strain TA1537 was not used.

5.4 Carcinogenicity

A 104-week subcutaneous carcinogenicity study was conducted in rats. A significant increase in the incidence of bone neoplastic lesion (osteoblastoma and osteosarcoma) was observed in the abaloparatide group, whereas no abaloparatide-associated neoplastic lesion was observed in tissues other than bone (Table 9).

Table 9. Summary of carcinogenicity test

Test system	Route of administration	Treatment duration	Main lesions	Sex	Dose (μg/kg/day)					Non-carcinogenic dose (μg/kg/day)	Attached document CTD
					0	10	25	50	PTH		
				Number	60	60	59/61[a]	60	60		
Male and female rats (F344)	s.c.	104 weeks	Bone: Osteoblastoma	Male	0	1	15	20	10	<10	4.2.3.4.1-1
				Female	0	8	7	9	4		
			Bone: Osteosarcoma (primary)	Male	1	31	46	52	39		
				Female	1	11	22	37	24		
			Non-neoplastic lesions	Male and female	Osteofibrous dysplasia, hyperostosis, osteoblast hyperplasia, mineral deposition in heart and kidney, alveolar histiocytosis, enhanced extramedullary hematopoiesis in spleen, dilatation/bleeding/inflammation of urinary bladder						

a) One animal assigned to male group at the start of the study turned out to be a female pseudohermaphrodite at necropsy, which was re-assigned to the female group, resulting in 59 males and 61 females.

5.5 Reproductive and developmental toxicity

As the reproductive and developmental toxicity study of abaloparatide in male animals, a study of fertility and early embryonic development to implantation was conducted in rats by subcutaneous administration. No reproductive and developmental toxicity study of abaloparatide was conducted in female animals (Table 10).

Table 10. Summary of reproductive and developmental study

Study	Test system	Route of administration	Treatment period	Dose (μg/kg/day)	Main findings	NOAEL (μg/kg/day)	Attached document CTD
Study of fertility and early embryonic development to implantation	Male rats (SD)	s.c.	43-45 days (14 days before mating to 1 day before necropsy)	0, 10, 25, 70	None	General toxicity, fertility: 70	4.2.3.5.1-1

5.6 Local tolerance

Local tolerance studies were conducted in male rabbits by subcutaneous, intravenous, and perivenous administration. Results showed a favorable local tolerance profile of abaloparatide (Table 11).

Table 11. Summary of local tolerance studies

Test system	Application site	Testing method	Main findings	Attached document CTD
Male NZW rabbits	s.c.	2 mL of approximately 50.6 μg/mL solution or 1 mL of 100 μg/mL solution administered as a single dose	None	4.2.3.6-1
	i.v.	2 mL of approximately 50.6 μg/mL solution administered into auricular vein as a single dose	None	4.2.3.6-2
	Perivascular	0.2 mL of approximately 50.6 μg/mL solution administered around auricular vein as a single dose	None	

5.7 Other toxicity studies

5.7.1 Toxicity of impurities

Related Substance X was subjected to a repeated subcutaneous dose toxicity study in rats. The study revealed no new toxicities associated with Related Substance X (Table 12). A bacterial reverse mutation assay and a chromosomal aberration assay using human lymphocytes were conducted. In both assays, Related Substance X showed no genotoxicity (Table 13).

Table 12. Summary of repeated-dose toxicity study of Related Substance X

Test system	Route of administration	Treatment duration	Dose (μg/kg/day)[a)]	Main findings	Attached document CTD
Male and female SD rats	s.c.	28 days	0, 70 + 0, 65 + 5, 21 + 49	Except for abaloparatide-related findings, there were no toxicity findings associated with Related Substance X.	4.2.3.7.6-4

a) Dose is expressed in terms of abaloparatide plus Related Substance X.

Table 13. Summary of genotoxicity studies of Related Substance X

Study	Test system	S9 (treatment)	Concentration	Results	Attached document CTD
Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	−/+	0, 5, 16, 50, 160, 500, 1600, 5000 (μg/plate)	Negative	4.2.3.7.6-2
	Escherichia coli: WP2*uvr*A	−/+			
Chromosomal aberration assay in mammalian cultured cells	Human lymphocytes	−: 3 hours −: 24 hours +: 3 hours	0, 245, 350, 500 (μg/mL)	Negative	4.2.3.7.6-3

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following reviews, PMDA has concluded that the clinical use of abaloparatide does not pose any particular concern from the toxicological point of view.

5.R.1 Effect on female fertility

No reproductive and developmental toxicity study was conducted on female animals. PMDA asked the applicant to explain the effect of abaloparatide on the reproductive performance of females and on the development of the offspring.

The applicant's explanation:
The findings observed in the toxicity studies and the safety pharmacology studies of abaloparatide are related to the pharmacological action of abaloparatide, and resembled those observed with existing PTH drugs (teriparatide [genetical recombination] and teriparatide acetate). Accordingly, the effect of abaloparatide on female reproductive performance was investigated as shown below, by taking account of the findings from the existing PTH drugs.

Repeated-dose toxicity studies of abaloparatide in rats and monkeys showed no abnormal findings in the reproductive organs of females (CTD 4.2.3.2.3 to 4.2.3.2.8).

The following findings are reported on teriparatide (genetical recombination) and teriparatide acetate[13]:

- Studies of fertility and early embryonic development to implantation did not show an effect on the reproductive function of parental animals or on embryos.
- A study of fertility and embryo-fetal development in rabbit showed that teriparatide (genetical recombination) increased abortion and the rates of embryo-fetal motility from low doses, supposedly due to the disruption of calcium homeostasis in the body.
- Studies for effects on pre- and postnatal development, including maternal function showed that neither teriparatide (genetical recombination) nor teriparatide acetate had an effect on maternal animals during the perinatal or lactation period, and that teriparatide (genetical recombination) reduced weight gain and decreased locomotor activity in F1 offspring.

These results suggest that abaloparatide is unlikely to have any adverse effect on fertility and early embryonic development to implantation in female animals or on maternal animals during the perinatal or lactating period. On the other hand, the toxicity on maternal animals and embryos/fetuses of rabbits is considered to be a class effect of PTH drugs and may possibly occur with abaloparatide as well. Abaloparatide is unlikely to be excreted in milk and, even if it is contained in milk, oral absorption is quite unlikely because it is a peptide drug. Nevertheless, the effect on neonates cannot be completely excluded. Accordingly, abaloparatide needs to be contraindicated in pregnant women or in women who may possibly be pregnant, and the following precautions will be provided: (1) For lactating women, whether to continue breast feeding should be decided by considering the benefits of treatment and the benefits of breast feeding, (2) excretion of abaloparatide in milk is unknown, (3) abaloparatide should be administered to women with potentially pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment, (4) effective contraceptive measures should be taken during the treatment with abaloparatide, and (5) treatment should be discontinued in case of pregnancy.

PMDA's view:
Developmental toxicities, including those due to the pharmacological action have been observed with existing PTH drugs, which suggests that abaloparatide, a drug with similar pharmacological action, also has a risk of developmental toxicity. Therefore, the following proposals of the applicant are

[13] *J Reprod Med*. 1998;43:451-4, *Miner Electrolyte Metab*. 1984;10:127-32, Review Report of "Forteo S.C. Injection Kit 600 μg" (July 2010), etc.

appropriate: (1) Abaloparatide is contraindicated in pregnant women as is the case with existing PTH drugs, and (2) a precaution is provided against the use in lactating women and women with potentially pregnant.

5.R.2 Carcinogenicity

The applicant's explanation about bone neoplastic lesion observed in carcinogenicity studies on abaloparatide:

PTH enhances the differentiation of precursor cells to osteoblasts, stimulates osteoblasts, and has a bone anabolic effect, and stimulates the growth of osteosarcoma cells (*Endocr Rev*. 1993;14:690-709, *Endocrinology*. 1997;138:4330-7, *J Toxicol Sci*. 2012;37:617-29, etc.). Approved drugs teriparatide (genetical recombination) and teriparatide acetate are also reported to cause bone neoplastic lesions such as osteosarcoma in carcinogenicity studies in rats. Similarly to PTH, PTHrP is known to affect osteoblasts through PTH1 receptor (*J Endocrinol*. 2005;187:311-25, *Bone.* 2007;40:1434-46, etc.). Bone neoplastic lesions observed in the carcinogenic study in rats on abaloparatide, a hPTHrP analog with modified N-terminal 34 amino acid sequences of human PTHrP, are considered to have arisen as a result of the direct effect of abaloparatide on osteoblasts through PTH1 receptor over a long time period. However, it is known that there are significant differences between rats and humans in the bone metabolic turn over associated with bone physiology, osteogenesis, and the mechanism of action of PTHs on bones, as described below. Due to these differences, rats may be highly sensitive to PTHs unlike humans. Thus, results of the carcinogenicity study in rats do not suggest bone tumorigenesis in humans.

- The bone turnover rate in rats (3-16 months old) is 12 to 34 times/year (*Cells and Materials.* 1991;Suppl 1:25-35), whereas the rate in healthy postmenopausal women is 1 time/year (*Bone Miner.* 1990;11:217-35).
- Growth plates are observed even in aged rats, and growth along the longitudinal axis continues (*Cells and Materials*. 1991;Suppl 1:11-18, *J Histochem Cytochem*. 2003;51:373-83). In humans, in contrast, epiphyses close at the age of 15 to 17 (*Contemp Top Lab Anim Sci*. 2002;41:21-6), terminating the growth along the longitudinal axis.
- In humans, PTHs do not have an anabolic effect on the cortical bone region (*J Musculoskelet Neuronal Interact.* 2001;2:33-47, *N Engl J Med.* 2001;344:1434-41, etc.). In rats, in contrast, PTHs have an anabolic effect on cortical bones and sponge bones (*Endocr Rev.* 1993;14:690-709, *Endocrinology*. 2002;143:3230-42, etc.). The difference in the anabolic effect is related to the low level of the remodeling of osteon (Haversian lamellar system) in cortical bones of rats (*Osteoporosis*. Academic Press; 1996:671-90).

PMDA accepted the applicant's explanation. The risk of bone tumor caused by abaloparatide is further discussed in Section "7.R.2.7 Osteosarcoma."

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

Table 14 shows the breakdown of formulations mainly used in clinical studies in the development of abaloparatide. In the following, the study code numbers are expressed in abbreviated forms by

omitting “ITM-058-” (Japanese studies) or “BA-058-” (foreign studies, except Study 2-52-52127-001), such as Study 001 in place of Study ITM-058-001 and Study 05-001 in place of Study BA-058-05-001.

Table 14. Breakdown of formulations used in clinical studies

Formulation		Development phase (study code number)	
		Japanese studies	Foreign studies
Lyophilized product		Phase I studies (Japanese Studies 001, 002)	Phase I studies (Study 2-52-52127-001, Foreign Study 05-001)
Cartridge	0.5 mg/mL	-	Phase II study (Foreign Study 05-002)
	1 mg/mL		
	2 mg/mL[a)]	Phase I study (Japanese Study 003) Phase II study (Japanese Study 004) Phase III study (Japanese Study 301)	Phase I studies (Foreign Studies 05-001B, 05-011, and 05-012) Phase II study (Foreign Study 05-002) Phase III study (Foreign Study 05-003)

-, Not applicable; a) Proposed formulation

Abaloparatide in human biomaterials was measured by RIA. The lower limit of quantitation of plasma abaloparatide concentration was 10 to 20 pg/mL. Anti-abaloparatide antibody in human serum was measured by RIA, and neutralizing antibody by cell-based assay (CBA). Anti-PTH antibody in human serum was measured by RIA, and neutralizing antibody by CBA.

6.2 Clinical pharmacology

The applicant submitted evaluation data from 4 Japanese studies (Japanese Studies 001, 002, 003, and 004) and from 4 foreign studies (Foreign Studies 05-001B, 05-011, 05-012, and 05-002). The applicant also submitted reference data from 2 foreign studies (Foreign Studies 2-52-52127-001 and 05-001) and results of a population pharmacokinetic analysis including the data of 7 foreign studies (Foreign Studies 05-003, 05-004,[14)] 05-006,[15)] 05-008,[16)] 05-010,[17)] 05-011, and 05-012) involving healthy subjects, subjects with renal impairment, or patients with osteoporosis. Data of studies using human biomaterials were also submitted. In the following, the dose of Ostabalo Subcutaneous Injection (Ostabalo) is expressed in the amount of abaloparatide. Results of the main studies are described below.

6.2.1 Studies using human biomaterials (CTD 4.2.2.3-2, 4.2.2.4-2, 4.2.2.6-1 to 4.2.2.6-3)

The mean plasma protein-binding (ultracentrifugation method) of abaloparatide (250-2000 pg/mL) in humans was 71.6% to 79.1% in men and 61.5% to 75.4% in women.

Metabolism of abaloparatide was investigated using human liver and kidney homogenates. The residual rate of abaloparatide after 1-hour incubation was 64.6% to 79.9% and 30.8% to 54.5%, respectively. Six types of metabolites were detected in both samples at the ratio of 0.9% to 13.3% in human liver homogenate and 0.8% to 23.7% in human kidney homogenate.

14) A study investigating the safety and pharmacokinetics of abaloparatide in a single subcutaneous or transdermal administration in non-Japanese postmenopausal women
15) A study investigating the safety and pharmacokinetics of abaloparatide in a single subcutaneous or transdermal administration in non-Japanese postmenopausal women
16) A study investigating the safety and pharmacokinetics of abaloparatide in a single subcutaneous and a single or multiple transdermal administration in non-Japanese postmenopausal women
17) A study investigating the safety and pharmacokinetics of abaloparatide in a single subcutaneous or intravenous administration in non-Japanese healthy adults

The inhibitory effect of abaloparatide (0.4374-2000 nmol/L) against each cytochrome P450 (CYP) isoform (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) was investigated using human liver microsomes. Abaloparatide showed neither a direct nor time-dependent inhibitory effect against any of the CYP isoforms.

The activity of abaloparatide (2-2000 nmol/L) to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated using human liver cells. mRNA expression level of CYP1A2 and CYP3A4 increased at ≥600 nmol/L and at 2000 nmol/L of abaloparatide, respectively, whereas no increase in mRNA was observed with any CYP isoform up to 200 nmol/L of abaloparatide, suggesting that abaloparatide is unlikely to induce drug-drug interaction due to the CYP-inducing effect.[18)]

The apparent membrane permeability coefficient ratio (from basolateral surface to apical surface [B→A] / from apical surface to basolateral surface [A→B], mean value) of ^{3}H-labeled digoxin (1 μmol/L), a substrate of P-glycoprotein (P-gp), in Caco-2 cells was 13.9. The ratio was 1.29 in the presence of zosuquidar (2 μmol/L), a P-gp inhibitor, and 12.0 and 15.4, respectively, in the presence of abaloparatide (2 and 2000 nmol/L). The inhibitory effect of abaloparatide (2 and 2000 nmol/L) against intracellular uptake of ^{3}H-labeled estrone sulfate, a breast cancer resistant protein (BCRP) substrate, was investigated. Results showed that abaloparatide had no inhibitory effect.

Using HEK293 cells engineered to express organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, or OATP1B3, the inhibitory effect of abaloparatide (2 and 2000 nmol/L) against intracellular uptake of substrates of their transporters was investigated. Abaloparatide had no effect on any of the transporters.

6.2.2 Studies in healthy adults

6.2.2.1 Phase I study in Japanese postmenopausal women (CTD 5.3.3.1-3, Japanese Study 003 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study in Japanese postmenopausal women (target sample size, 33 subjects) was conducted to investigate the safety, pharmacokinetics, and pharmacodynamics of abaloparatide in a single or multiple subcutaneous administration.

In Step 1, placebo or abaloparatide 80 μg was administered subcutaneously as a single dose. In Step 2, placebo or abaloparatide 80 μg was administered subcutaneously once daily for 7 days. In Step 3, placebo or abaloparatide 20 μg was administered subcutaneously once daily for 7 days, followed by subcutaneous administration of placebo or abaloparatide 40 μg once daily for 7 days, then by subcutaneous administration of placebo or abaloparatide 80 μg once daily for 7 days.[19)]

All of the 22 randomized subjects (11 in each step [3 in the placebo group, 8 in the abaloparatide group]) were included in the full analysis set (FAS), safety analysis population, and

[18)] In Japanese Study 004 in Japanese patients with postmenopausal osteoporosis, C_{max} of abaloparatide in multiple subcutaneous administration of abaloparatide 80 μg was 0.132 nmol/L at Week 9.

[19)] Throughout Steps 1 and 2, vomiting occurred in only 1 subject (Step 2), failing to meet a criterion for proceeding to Step 3 "Occurrence of vomiting in ≥2 subjects in Steps 1 and 2 combined," whereupon the study was terminated.

pharmacodynamics analysis population, and 16 subjects receiving abaloparatide were included in the pharmacokinetics analysis population.

Table 15 shows the pharmacokinetic parameters of abaloparatide in plasma in a single or multiple administration of abaloparatide 80 μg.

Table 15. Pharmacokinetic parameters of abaloparatide in a single or multiple administration of abaloparatide 80 μg

Dosing method		No. of subjects	C_{max} (pg/mL)	AUC [a)] (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Single		8	431.61 ± 126.54	666.67 ± 134.09	0.50 [0.25, 1.07]	1.01 ± 0.25	118.68 ± 21.62	169.48 ± 38.05
Multiple	Day 1	8	510.11 ± 155.61	744.11 ± 237.98	0.38 [0.25, 1.00]	1.10 ± 0.29	111.53 ± 30.94	168.87 ± 36.97
	Day 7	8	443.60 ± 132.48	857.56 ± 229.42	0.38 [0.25, 1.00]	1.16 ± 0.20	100.57 ± 26.10	164.47 ± 35.56

Mean ± SD, t_{max} is expressed in median [range].
C_{max}, Maximum plasma concentration; AUC, Area under the concentration-time curve; t_{max}, Time to maximum plasma concentration; $t_{1/2}$, Elimination half life
CL/F, Apparent clearance; V_z/F, Apparent distribution volume
a) $AUC_{0\text{-}t}$ in single-dose administration, AUC_{tau} in multiple administration

Table 16 shows changes over time in bone metabolism markers from baseline following a single subcutaneous administration of placebo or abaloparatide 80 μg.

Table 16. Changes over time in serum bone metabolism markers from baseline following a single subcutaneous administration of placebo or abaloparatide 80 μg

Bone metabolism markers in serum	Treatment group	No. of subjects	Hour 2	Hour 4	Hour 8	Day 2	Day 8	Day 15
P1NP (ng/mL)	Placebo	3	-1.03 ± 0.15	8.43 ± 9.86	3.23 ± 12.04	-0.70 ± 6.44	2.47 ± 6.72	2.30 ± 5.99
	Abaloparatide 80 μg	8	-2.59 ± 9.40	-8.81 ± 7.99	-5.98 ± 8.45	-1.78 ± 7.90	4.03 ± 8.46	8.53 ± 17.51
P1CP (ng/mL)	Placebo	3	-16.00 ± 10.21	-20.40 ± 4.33	-18.40 ± 7.99	-18.80 ± 5.92	-10.00 ± 7.33	-11.20 ± 7.03
	Abaloparatide 80 μg	8	-20.40 ± 13.41	-19.50 ± 12.66	-18.90 ± 12.38	1.50 ± 7.77	1.80 ± 7.14	0.15 ± 8.23
BAP (U/L)	Placebo	3	-0.57 ± 1.34	0.23 ± 0.81	-0.40 ± 1.21	0.17 ± 1.17	1.13 ± 0.76	0.43 ± 0.31
	Abaloparatide 80 μg	8	-0.53 ± 0.74	-0.16 ± 1.97	-1.03 ± 2.32	-0.05 ± 1.48	-0.33 ± 2.32	-0.14 ± 1.91
OC (ng/mL)	Placebo	3	-1.80 ± 1.31	-2.17 ± 3.09	-6.60 ± 5.52	-0.33 ± 0.58	-2.27 ± 3.10	-0.20 ± 1.06
	Abaloparatide 80 μg	8	0.04 ± 3.21	-1.93 ± 3.52	-1.81 ± 3.76	-0.81 ± 5.00	-0.96 ± 5.84	1.93 ± 2.31
CTX (ng/mL)	Placebo	3	-0.15 ± 0.07	-0.09 ± 0.11	-0.38 ± 0.23	-0.06 ± 0.18	0.01 ± 0.22	-0.05 ± 0.17
	Abaloparatide 80 μg	8	0.11 ± 0.10	0.25 ± 0.17	-0.40 ± 0.22	-0.01 ± 0.07	-0.01 ± 0.09	0.00 ± 0.11
TRACP-5b (mU/dL)	Placebo	3	8.3 ± 25.1	11.7 ± 12.9	-19.3 ± 10.6	30.7 ± 3.1	35.0 ± 42.6	56.3 ± 56.0
	Abaloparatide 80 μg	8	26.9 ± 37.7	7.0 ± 35.8	1.0 ± 33.7	22.1 ± 31.3	28.0 ± 56.4	36.8 ± 32.2

Mean ± SD

Table 17 shows changes over time in bone metabolism markers from baseline in multiple subcutaneous administration of placebo or abaloparatide 80 μg.

Table 17. Changes over time in serum bone metabolism markers from baseline in multiple subcutaneous administration of placebo or abaloparatide 80 μg

Bone metabolism maker in serum	Treatment group	No. of subjects	Before administration on Day 3 after the first dose	Day 8 after the first dose	Day 14 after the first dose
P1NP (ng/mL)	Placebo	3	6.57 ± 3.68	-2.90 ± 5.12	-11.07 ± 26.82
	Abaloparatide 80 μg	8	11.96 ± 11.78	39.58 ± 32.77	34.89 ± 26.50
P1CP (ng/mL)	Placebo	3	0.00 ± 13.63	-4.80 ± 16.50	6.40 ± 23.59
	Abaloparatide 80 μg	8	23.25 ± 18.39	41.55 ± 37.65	32.40 ± 29.89
BAP (U/L)	Placebo	3	0.10 ± 2.86	1.03 ± 2.78	-0.47 ± 1.16
	Abaloparatide 80 μg	8	-1.23 ± 1.51	-0.16 ± 2.06	1.21 ± 2.64
OC (ng/mL)	Placebo	3	1.77 ± 11.62	4.37 ± 9.11	2.80 ± 7.80
	Abaloparatide 80 μg	8	-2.11 ± 5.56	2.89 ± 4.64	2.89 ± 4.26
CTX (ng/mL)	Placebo	3	-0.01 ± 0.06	0.07 ± 0.04	0.08 ± 0.21
	Abaloparatide 80 μg	8	0.09 ± 0.07	0.10 ± 0.12	-0.03 ± 0.09
TRACP-5b (mU/dL)	Placebo	3	0.0 ± 102.1	102.7 ± 97.7	142.0 ± 108.6
	Abaloparatide 80 μg	8	18.1 ± 28.2	82.3 ± 54.6	102.6 ± 61.0

Mean ± SD

Anti-abaloparatide antibody was evaluated before abaloparatide administration and Day 14 or 15. There were no subjects positive for anti-abaloparatide antibody.

Adverse events and adverse drug reactions were observed in 1 of 3 subjects each in the placebo group and in 2 of 8 subjects each in the abaloparatide group in the single-dose administration (Step 1); and in 2 of 3 subjects each in the placebo group and in 6 of 8 subjects each in the abaloparatide group in the multiple administration (Step 2). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2.2 Phase I study in non-Japanese postmenopausal women (CTD 5.3.3.1-6: Foreign Study 05-001B [[redacted] to [redacted], 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study in non-Japanese postmenopausal women (target sample size, 40 subjects) was conducted to investigate the safety, pharmacokinetics, and pharmacodynamics of abaloparatide in multiple subcutaneous administration.

Placebo or abaloparatide 80, 100, 120, or 160 μg[20)] was administered subcutaneously once daily for 7 days. All of the 30 randomized subjects (6 in the placebo group, 8 each in the 80, 100, and 120 μg abaloparatide groups) were included in the safety analysis population and the pharmacodynamics analysis population, and 24 subjects receiving abaloparatide were included in the pharmacokinetics analysis population.

Table 18 shows pharmacokinetic parameters of abaloparatide in plasma in multiple subcutaneous administration of abaloparatide 80, 100, or 120 μg.

[20)] Study proceeding to the abaloparatide 160 μg group was cancelled for the following reasons: (1) One subject in the abaloparatide 120 μg group discontinued the study because of an adverse event (vomiting) which was considered to be an adverse drug reaction, and (2) the incidence of nausea was high in the 120 μg group (4 of 8 subjects).

Table 18. Pharmacokinetic parameters of abaloparatide in multiple subcutaneous administration of abaloparatide

Treatment group	Time point of measurement	No. of subjects	C_{max} (pg/mL)	AUC[a)] (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)
Abaloparatide 80 µg	After the first dose	8	702 ± 175	1247.6 ± 485.4	0.52 [0.26, 2.03]	1.30 ± 0.26	68.64 ± 23.16
	Day 7	8	812 ± 118	1622.3 ± 640.8	0.51 [0.25, 0.52]	1.65 ± 0.69	58.58 ± 28.73
Abaloparatide 100 µg	After the first dose	8	688 ± 66.1	1245.1 ± 482.2	0.51 [0.25, 1.50]	1.20 ± 0.79	86.01 ± 32.14
	Day 7	8	837 ± 270	1445.9 ± 598.4	0.51 [0.25, 1.01]	1.39 ± 0.73	83.38 ± 47.12
Abaloparatide 120 µg	After the first dose	8	952 ± 285	1552.2 ± 659.3	0.52 [0.25, 0.53]	1.20 ± 0.33	84.65 ± 27.97
	Day 7	7	956 ± 338	1600.7 ± 675.2	0.51 [0.25, 0.52]	1.13 ± 0.36	85.31 ± 30.79

Mean ± SD; t_{max} is expressed in median [range]
C_{max}, Maximum plasma concentration; AUC, Area under the concentration-time curve; t_{max}, Time to maximum plasma concentration; $t_{1/2}$, Elimination half-life; CL/F, Apparent clearance
a) $AUC_{0\text{-}t}$ in a single-dose administration, AUC_{tau} in multiple administration

Table 19 shows changes over time in bone metabolism markers from baseline in multiple subcutaneous administration of placebo or abaloparatide 80, 100, or 120 µg.

Table 19. Changes over time in serum bone metabolism markers from baseline in multiple subcutaneous administration of placebo or abaloparatide 80 µg

Bone metabolism maker in serum	Treatment group	No. of subjects	Before administration on Day 3 after the first dose	Day 8 after the first dose	Day 14 after the first dose
P1NP (ng/mL)	Placebo	6	6 ± 7	3 ± 10	-4 ± 8
	Abaloparatide 80 µg	8	12 ± 7	23 ± 11	14 ± 13
	Abaloparatide 100 µg	8	9 ± 8	28 ± 18	18 ± 13
	Abaloparatide 120 µg	7	12 ± 6	26 ± 7	13 ± 5
P1CP (ng/mL)	Placebo	6	8 ± 18	5 ± 21	-10 ± 16
	Abaloparatide 80 µg	8	30 ± 31	39 ± 31	12 ± 23
	Abaloparatide 100 µg	8	19 ± 30	34 ± 39	10 ± 19
	Abaloparatide 120 µg	7	18 ± 11	31 ± 12	11 ± 12
BAP (U/L)	Placebo	6	-0.6 ± 1.7	-0.2 ± 1.5	-1.2 ± 1.6
	Abaloparatide 80 µg	8	-0.9 ± 1.5	2.2 ± 2.2	2.7 ± 3.4
	Abaloparatide 100 µg	8	-0.8 ± 1.4	1.3 ± 1.4	3.2 ± 2.6
	Abaloparatide 120 µg	7	-0.5 ± 1.2	0.7 ± 2.0	-0.1 ± 2.1
OC (ng/mL)	Placebo	6	1.0 ± 2.1	2.5 ± 1.3	0.6 ± 2.1
	Abaloparatide 80 µg	8	-1.0 ± 0.8	3.8 ± 2.2	7.4 ± 6.4
	Abaloparatide 100 µg	8	-2.6 ± 2.3	3.8 ± 1.9	7.6 ± 5.5
	Abaloparatide 120 µg	7	-3.2 ± 2.6	3.8 ± 1.7	7.5 ± 3.9
CTX (ng/mL)	Placebo	6	-0.07 ± 0.18	-0.05 ± 0.15	-0.02 ± 0.06
	Abaloparatide 80 µg	8	0.10 ± 0.12	0.08 ± 0.08	-0.03 ± 0.06
	Abaloparatide 100 µg	8	0.05 ± 0.09	0.04 ± 0.10	-0.02 ± 0.03
	Abaloparatide 120 µg	7	0.02 ± 0.09	-0.03 ± 0.10	-0.07 ± 0.07

Mean ± SD

Anti-abaloparatide antibody was evaluated before abaloparatide administration and Day 14. There were no subjects positive for anti-abaloparatide antibody.

Adverse events and adverse drug reactions were observed in 6 of 6 subjects each in the placebo group, in 8 of 8 subjects and in 6 of 8 subjects, respectively, in the abaloparatide 80 µg group, in 8 of 8 subjects and in 6 of 8 subjects, respectively, in the abaloparatide 100 µg group, and in 8 of 8 subjects each in the abaloparatide 120 µg group. There were no deaths nor serious adverse events. An adverse event leading to treatment discontinuation (vomiting) was observed in 1 subject in the abaloparatide 120 µg group. The event was considered to be an adverse drug reaction.

6.2.3 Studies in patients

6.2.3.1 Japanese phase II study in Japanese patients with postmenopausal osteoporosis (CTD 5.3.5.1-1, Japanese Study 004 [November 2013 to June 2015])

A placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients with postmenopausal osteoporosis (target sample size, 150 subjects [50 in the abaloparatide 40 μg group, 50 in the abaloparatide 80 μg group, 50 in the placebo group] was conducted to investigate the efficacy and safety of abaloparatide [for the details of the study design and for the efficacy and safety results, see Section "7.1.1 Japanese phase II study in Japanese patients with postmenopausal osteoporosis"].

Table 20 shows pharmacokinetic parameters[21)] of abaloparatide in plasma in multiple once daily subcutaneous administration of abaloparatide 40 or 80 μg.

Table 20. Pharmacokinetic parameters of abaloparatide in multiple once daily subcutaneous administration

Treatment group	Time point of measurement	No. of subjects	C_{max} (pg/mL)	AUC_{0-t} (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)
Abaloparatide 40 μg	Week 9	17	343.69 ± 143.08	559.93 ± 257.06	0.47 [0.23, 0.53]	1.26 ± 0.40	76.76 ± 54.53
	Week 36	17	219.27 ± 173.20	365.31 ± 317.91	0.50 [0.25, 0.58]	2.09 ± 3.03	108.95 ± 65.10
Abaloparatide 80 μg	Week 9	19	523.57 ± 118.59	921.81 ± 304.48	0.50 [0.22, 1.50]	1.37 ± 0.62	88.20 ± 44.41
	Week 36	19	264.00 ± 182.23	407.38 ± 278.03	0.50 [0.25, 0.63]	1.65 ± 1.39	194.36 ± 122.06

Mean ± SD; t_{max} is expressed in median [range]
C_{max}, Maximum plasma concentration; AUC_{0-t}, Area under the plasma concentration-time curve from time 0 to the last measurable concentration; t_{max}, Time to the maximum plasma concentration, $t_{1/2}$, Elimination half-life; CL/F, Apparent clearance

Anti-abaloparatide antibody was evaluated before abaloparatide administration and up to Week 48 or at treatment discontinuation. Anti-abaloparatide antibody was positive at least once in 14.8% (8 of 54) of subjects in the abaloparatide 40 μg group and in 28.3% (15 of 53) of subjects in the abaloparatide 80 μg group.[22)] Neutralizing antibody was observed in 2 subjects each in the abaloparatide 40 and 80 μg groups.

6.2.3.2 Foreign phase II study in non-Japanese patients with postmenopausal osteoporosis (CTD 5.3.5.1-3, Foreign Study 05-002 [April 2007 to May 2009])

A placebo- and active drug-controlled, randomized, double-blind, parallel-group study in non-Japanese patients with postmenopausal osteoporosis (target sample size, 225 subjects [45 per group]) was conducted to investigate the efficacy and safety of abaloparatide [for the details of the study design and for the efficacy and safety results, see Section "7.1.2 Foreign phase II study in non-Japanese patients with postmenopausal osteoporosis"].

Table 21 shows abaloparatide concentration in plasma at 90 minutes after administration in multiple once daily subcutaneous administration of abaloparatide 20, 40, or 80 μg.

21) Drug concentration measurement was performed only at some of the study sites.
22) Anti-abaloparatide antibody was positive in 16.7% (9 of 54) of subjects in the abaloparatide 40 μg group and in 30.2% (16 of 53) of subjects in the abaloparatide 80 μg group, including the results of the antibody test at plasma abaloparatide concentration measurement.

Table 21. Abaloparatide concentration in plasma at 90 minutes after administration in multiple once daily subcutaneous administration of abaloparatide

Treatment group	No. of subjects	After the first dose	Week 4	Week 20
Abaloparatide 20 μg	43	49.0 ± 29.1	60.4 ± 36.8	67.6 ± 31.1
Abaloparatide 40 μg	43	93.6 ± 65.5	110.5 ± 74.5	116.6 ± 91.1
Abaloparatide 80 μg	45	184.3 ± 135.4	231.3 ± 148.3	221.3 ± 145.1

Unit, pg/mL; mean ± SD

Anti-abaloparatide antibody was evaluated before abaloparatide administration and at Weeks 24 and 48. Anti-abaloparatide antibody was positive at least once in 11.6% (5 of 43) of subjects in the abaloparatide 20 μg group, in 14.0% (6 of 43) of subjects in the abaloparatide 40 μg group, and in 11.1% (5 of 45) of subjects in the abaloparatide 80 μg group. Neutralizing antibody was detected in 1 subject in the abaloparatide 40 μg group.

6.2.4 Studies of intrinsic factors

6.2.4.1 Pharmacokinetic study in subjects with renal impairment (CTD 5.3.3.3-1, Foreign Study 05-011 [[redacted] to [redacted] 20[redacted]])

An open-label, parallel-group study in non-Japanese subjects with normal renal function and those with renal impairment (target sample size, 32 subjects) was conducted to investigate the pharmacokinetics and safety of abaloparatide in groups classified by the extent of renal impairment (creatinine clearance [Ccr; mL/min][23]: normal, ≥90; mild, ≥60 and <90; moderate, ≥30 and <60; severe, ≥15 and <30).

Abaloparatide 80 μg was administered subcutaneously as a single dose.

A total of 32 subjects (8 per group) were included in the safety analysis population and the pharmacodynamics analysis population. A total of 31 subjects, excluding 1 subject with moderate renal impairment with abaloparatide level below the lower limit of quantitation in 9 of 13 samples, were included in the pharmacokinetics analysis population.

Table 22 shows pharmacokinetic parameters in subjects with normal renal function and subjects with renal impairment. The geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} in subjects with mild, moderate, and severe renal impairment to those in subjects with normal renal function were 1.03 [0.79, 1.35] and 1.17 [0.81, 1.68], 1.28 [0.97, 1.70] and 1.68 [1.15, 2.45], and 1.44 [1.10, 1.89] and 2.13 [1.49, 3.06], respectively.

[23] Ccr calculated by Cockcroft-Gault equation.

Table 22. Pharmacokinetic parameters in subjects with normal renal function and in subjects with renal impairment

Subjects	No. of subjects	C_{max} (pg/mL)	AUC_{inf} (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Subjects with normal renal function	8	431.0 ± 142.0	576.4 ± 213.6	0.38 [0.25, 0.50]	1.13 ± 0.35	169.5 ± 104.0	268.6 ± 173.2
Subjects with mild renal impairment	8	444.0 ± 153.4	652.1 ± 201.7	0.26 [0.25, 0.55]	1.20 ± 0.77	137.3 ± 55.2	218.9 ± 118.6
Subjects with moderate renal impairment	7	574.9 ± 135.6	955.6 ± 306.8	0.28 [0.25, 1.02]	1.48 ± 0.43	92.4 ± 32.4	191.4 ± 70.9
Subjects with severe renal impairment	8	639.0 ± 270.6	1240.5 ± 514.9	0.25 [0.25, 0.50]	1.85 ± 0.81	78.1 ± 39.5	181.4 ± 53.3

Mean ± SD; t_{max} is expressed in median [range]
C_{max}, Maximum serum concentration; $AUC_{nf,}$ Area under the serum concentration-time curve from time 0 to infinity; t_{max}, Time to maximum plasma abaloparatide concentration; $t_{1/2}$, Elimination half-life; CL/F, Apparent clearance; V_z/F, Apparent distribution volume

Adverse events and adverse drug reactions were observed in 3 of 8 subjects and in 0 of 8 subjects, respectively, in subjects with normal renal function, in 1 of 8 subjects and in 0 of 8 subjects, respectively, in subjects with mild renal impairment, in 1 of 8 subjects and in 0 of 8 subjects, respectively, in subjects with moderate renal impairment, and in 2 or 8 subjects and in 0 of 8 subjects, respectively, in subjects with severe renal impairment. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.5 Pharmacodynamics

6.2.5.1 QT/QTc evaluation study (CTD 5.3.4.1, Study 05-012 [[redacted] to [redacted] 20[redacted]])

A placebo- and moxifloxacin-controlled, randomized, double-blind, 4-period cross-over study[24)] in non-Japanese healthy adults (target sample size, 56 subjects) was conducted to investigate the effect of a single subcutaneous administration of abaloparatide on QTc interval, using a single oral administration of moxifloxacin 400 mg as the positive control.

In each treatment period, placebo, abaloparatide 80 or 240 μg was administered subcutaneously as a single dose, or moxifloxacin 400 mg was administered orally as a single dose. A 5-day washout period was instituted between treatment periods.

All of 55 treated subjects were included in the safety analysis population. A total of 53 subjects, excluding 2 subjects unavailable for pharmacokinetics evaluation, were included in the pharmacokinetics analysis population, and 52 subjects, excluding 3 subjects with missing QT/QTc interval measurement at baseline and at least 1 time point after administration, were included in the pharmacodynamics analysis population.

C_{max} (mean ± SD) of abaloparatide in plasma following a single subcutaneous administration of abaloparatide 80 or 240 μg was 511.5 ± 150.4 pg/mL and 1125.5 ± 453.5 pg/mL, respectively, and AUC_{inf} was 774.0 ± 396.2 pg•h/mL and 1771.4 ± 992.6 pg•h/mL, respectively.

24) The positive control moxifloxacin was administered under unblinded conditions.

In electrocardiogram (ECG), the adjusted mean[25)] [90% CI] of the difference between the abaloparatide 80 or 240 μg group and the placebo group in the estimated change in QTcI[26)] interval from baseline was −4.6 [−7.3, −2.0] to 5.3 [2.7, 8.0] and −6.0 [−8.6, −3.4] to 7.1 [4.4, 9.7] ms, respectively, with the upper limit of the 90% confidence interval falling below 10 ms. In the moxifloxacin group, the difference from the placebo group in the adjusted mean[25)] [90% CI] reached the maximum level (11.2 [7.6, 14.8] ms) at 4 hours after administration, with the lower limit of the 90% confidence interval exceeding 5 ms.

The incidence of adverse events and adverse drug reactions was 11.8% (6 of 51) of subjects and 9.8% (5 of 51) of subjects in the placebo group, 40.4% (21 of 52) of subjects and 36.5% (19 of 52) of subjects, respectively, in the abaloparatide 80 μg group, 73.1% (38 of 52) of subjects and 69.2% (36 of 52) of subjects, respectively, in the abaloparatide 240 μg group, and 22.0% (11 of 50) of subjects and 12.0% (6 of 50) of subjects in the moxifloxacin group. Neither death nor serious adverse event was observed. Adverse events leading to treatment discontinuation were observed in 1 subject (nasal congestion) in the abaloparatide 80 μg group and in 1 subject (blood pressure increased) in the moxifloxacin group. One subject in the abaloparatide 80 μg group turned positive for serum human chorionic gonadotropin; the study was discontinued in this subject.

6.2.6 Population pharmacokinetics (CTD 5.3.3.5-1)

A population pharmacokinetic analysis (software, NONMEM [ver.7.3]) was conducted using plasma abaloparatide concentration data at a total of 5204 time points obtained from 973 subjects (74 males and 899 females; 817 subjects with osteoporosis, 156 subjects without osteoporosis; anti-abaloparatide antibody, positive in 308, negative in 509) in 7 foreign studies in patients with osteoporosis (Foreign phase III study 05-003, foreign phase I studies 05-004,[14)] 05-006,[15)] 05-008,[16)] 05-010,[17)] 05-011, and 05-012).

Characteristics (mean [range]) of subjects included in the population pharmacokinetic analysis were as follows: Age, 64.6 [18, 85]; body weight, 63.1 [37.0, 100.4] kg, body mass index (BMI), 25.2 [18.0, 34.4] kg/m^2; Ccr, 84.1 [21.5, 213.1] mL/min, and PTH concentration, 33.9 [6.7, 101.3] pg/mL.

A 2-compartment model with the first-order absorption and the first-order elimination processes was constructed as a basic model. The following parameters were evaluated in a stepwise manner as potential covariates of each of the following values: With/without osteoporosis and dose as covariates of absolute bioavailability; Ccr and positive/negative for anti-abaloparatide antibody (positive [low titer,[27)] high titer[28)]], negative) as covariates of absorption rate constant, Ccr, positive/negative for anti-abaloparatide antibody, positive/negative for neutralizing antibody, PTH concentration, dose, sex, and body weight as covariates of systemic clearance, and positive/negative for anti-abaloparatide antibody and sex as covariates of distribution volume of the central compartment (V_2). The results showed that the following parameters were included in the final model: With/without osteoporosis as the covariate of the absolute bioavailability; Ccr and positive/negative for anti-abaloparatide antibody

[25)] Estimated based on an analysis of the covariance (ANCOVA) model including timing of administration, treatment, and interaction between timing of administration and treatment as factors and baseline QTcI as the covariate.
[26)] QT interval adjusted for baseline QT interval and for heart rate in each subject
[27)] Antibody titer 1:1 or <1:1
[28)] Antibody titer >1:10

as covariates of systemic clearance; and positive/negative for anti-abaloparatide antibody as the covariate of distribution volume of the central compartment (V_2). Parameter values in each of the subjects included in the population pharmacokinetic analysis were estimated using the final model. Among subjects with osteoporosis receiving subcutaneous administration of abaloparatide 80 μg, the estimated AUC (median [range]) was 1461 [745, 2314], 822 [580, 1153], and 575 [435, 828] pg•h/mL, respectively, in anti-abaloparatide antibody-negative subjects, anti-abaloparatide antibody-positive (low titer[27)]) subjects, and anti-abaloparatide antibody-positive (high titer[28)]) subjects; 1444 [745, 1932] and 745 [435, 2509] pg•h/mL, respectively, in neutralizing antibody-negative and -positive subjects; and 1679 [1142, 2314], 1477 [1214, 1773], 1302 [745, 1492], and 1194 [929, 1317] pg•h/mL, respectively, in subjects with Ccr of ≥30 and <60 mL/min, ≥60 and <90 mL/min, ≥90 and <120 mL/min, and ≥120 mL/min.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese subjects

The applicant's explanation about the pharmacokinetics in Japanese and non-Japanese subjects:

Table 23 shows the pharmacokinetics of abaloparatide following a single or multiple subcutaneous administration of Ostabalo or lyophilized abaloparatide 80 μg to Japanese postmenopausal women or to non-Japanese healthy adults or postmenopausal women. C_{max} and AUC of abaloparatide tended to vary from study to study. With no significant difference observed in the characteristics of subjects (age, body weight, height, etc.), factors that caused different tendencies among studies could not be identified.

Table 23. Pharmacokinetic parameters following a single or multiple subcutaneous administration of Ostabalo or lyophilized abaloparatide 80 μg

Formulation	Study	Subjects	Dosage regimen	No. of subjects	C_{max} (pg/mL)	AUC [b)] (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)
Lyophilized formulation	Japanese Study 001[c)]	Healthy adults (postmenopausal women)	Single dose	6	404 ± 105	1214 ± 299	0.50 [0.50, 1.00]	2.32 ± 0.63	64.7 ± 14.4
	Japanese Study 002[d)]	Healthy adults (postmenopausal women)	Multiple dose	8	503 ± 161	1162 ± 454	0.50 [0.25, 0.53]	2.00 ± 0.70	77.5 ± 39.5
	Foreign Study 2-52-52127-001[e)]	Healthy adults (postmenopausal women or elderly men)	Single dose	6	588 ± 56	2360 ± 690	1.00 [0.50, 1.02]	5.13 ± 4.40	31.7 ± 14.5
	Foreign Study 05-001[f)]	Healthy adults (postmenopausal women)	Multiple dose	8	436 ± 69	1080 ± 409	0.51 [0.50, 1.00]	1.69 ± 0.43	82.7 ± 27.0
Ostabalo	Japanese Study 003	Healthy adults (postmenopausal women)	Multiple dose	8	444 ± 132	858 ± 229	0.38 [0.25, 1.00]	1.16 ± 0.20	100.6 ± 26.1
	Foreign Study 05-001B	Healthy adults (postmenopausal women)	Multiple dose	8	812 ± 118	1622 ± 641	0.51 [0.25, 0.52]	1.65 ± 0.69	58.6 ± 28.7

Mean ± SD; t_{max} is expressed in median [range]

C_{max}, Maximum plasma concentration; AUC, Area under the concentration-time curve; t_{max}, Time to maximum plasma concentration; $t_{1/2}$, Elimination half-life; CL/F, Apparent clearance

a) For multiple administration, data on Day 7 are shown.
b) $AUC_{0\text{-}t}$ in single-dose administration, AUC_{tau} in multiple administration
c) A placebo-controlled, randomized, double-blind, parallel-group study in Japanese healthy postmenopausal women receiving a single subcutaneous dose of lyophilized abaloparatide to investigate the safety, pharmacokinetics, and pharmacodynamics.
d) A placebo-controlled, randomized, double-blind, parallel-group study in Japanese healthy postmenopausal women receiving multiple subcutaneous dose of lyophilized abaloparatide to investigate the safety, pharmacokinetics, and pharmacodynamics.
e) A placebo-controlled, randomized, double-blind, parallel-group study in non-Japanese healthy postmenopausal women and elderly men receiving a single subcutaneous dose of lyophilized abaloparatide to investigate the safety, pharmacokinetics, and pharmacodynamics.
f) A placebo-controlled, randomized, double-blind, parallel-group study in non-Japanese healthy postmenopausal women receiving multiple subcutaneous dose of lyophilized abaloparatide to investigate the safety, pharmacokinetics, and pharmacodynamics.

In Japanese Study 004 in Japanese patients with osteoporosis, CL/F (mean ± SD) at Week 9 after administration of abaloparatide 80 μg was 88.2 ± 44.4 L/h, which was not significantly different from CL/F (82.5 ± 26.8 L/h) in non-Japanese patients with osteoporosis in Foreign Study 05-003 estimated by the population pharmacokinetic analysis. Changes in plasma abaloparatide concentration over time after multiple administration of abaloparatide 80 μg in Foreign Study 05-003 were predicted based on the population pharmacokinetic model and were compared with the observed values of abaloparatide concentration in multiple administration of abaloparatide 80 μg in Japanese patients with osteoporosis in Study 004 (13 patients negative for anti-abaloparatide antibody). Most of the plasma abaloparatide concentrations observed in Japanese patients with osteoporosis were within the 90% prediction interval of plasma abaloparatide concentration after administration of abaloparatide 80 μg in Foreign Study 05-003.

These results suggest that there is no significant difference between Japanese and non-Japanese in the pharmacokinetics of abaloparatide.

PMDA's view:
The pharmacokinetics of abaloparatide tended to differ between Japanese and foreign clinical studies mainly in postmenopausal women, but the cause has not been elucidated. Thus, there may be a difference in the pharmacokinetics between Japanese and non-Japanese subjects. Efficacy and safety of abaloparatide in Japanese and non-Japanese subjects, including the possible effect of the above difference, are discussed further in Sections "7.R.1 Efficacy" and "7.R.2 Safety."

6.R.2 Administration to patients with renal impairment

The applicant's explanation:
Abaloparatide is considered to be excreted mainly from the kidney. Foreign Study 05-011 showed that the exposure to abaloparatide (C_{max} and AUC_{inf}) increases in a manner dependent on the severity of renal impairment (Table 22). The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} in patients with renal impairment to that in patients with normal renal function was 1.03 [0.79, 1.35] and 1.17 [0.81, 1.68], respectively, in patients with mild renal impairment, 1.28 [0.97, 1.70] and 1.68 [1.15, 2.45], respectively, in patients with moderate renal impairment, and 1.44 [1.10, 1.89] and 2.13 [1.49, 3.06], respectively, in patients with severe renal impairment. The mean elimination half-life of abaloparatide did not significantly differ between patients with mild renal impairment and patients with normal renal function, whereas the mean elimination half-life in patients with moderate and severe renal impairment (1.48 and 1.85 hours, respectively) was longer than that in patients with normal renal function (1.13 hours). However, plasma abaloparatide concentration at 24 hours after administration was below the lower limit of quantitation in all subjects, which suggested that the time-course change in plasma abaloparatide concentration in multiple administration is not significantly different from that observed after single-dose administration, even in subjects with moderate or severe renal impairment. In Foreign Study 05-012 in non-Japanese healthy adults, C_{max} (mean ± SD) of plasma abaloparatide following the administration of abaloparatide 80 μg or 240 μg (the maximum tolerable dose) was 511.5 ± 150.4 and 1125.5 ± 453.5 pg/mL, respectively, and AUC_{inf} was 774.0 ± 396.2 and 1771.4 ± 992.6 pg•h/mL, respectively. C_{max} and AUC_{inf} at abaloparatide 240 μg (the maximum tolerable dose) were 2.20 times and 2.28 times those at abaloparatide 80 μg. These results suggest that exposure to

abaloparatide (C_{max} and AUC_{inf}) increases in a manner dependent on the severity of renal impairment. Thus, when abaloparatide is administered to patients with severe renal impairment, AUC of abaloparatide in plasma may possibly increase up to approximately twice that observed in patients without renal impairment, but it is unlikely to exceed the plasma abaloparatide concentration observed at 240 μg (the maximum tolerable dose of abaloparatide).

These results suggest that abaloparatide administration to patients with renal impairment is unlikely to pose any clinical problem from the point of view of pharmacokinetics.

PMDA's view:
For pharmacokinetics in patients with renal impairment, the exposure to abaloparatide increases in a manner dependent on the severity of the renal impairment. However, the applicant explained that abaloparatide administration to patients with up to severe renal impairment is unlikely to pose any clinical problem from the point of view of pharmacokinetics. PMDA accepted the applicant's explanation. The safety of abaloparatide administration to patients with renal impairment and appropriateness of providing precautions are discussed in Section "7.R.5.2 Patients with renal impairment."

6.R.3 Effect of antibody production on pharmacokinetics

The applicant's explanation about the effect of anti-abaloparatide antibody and neutralizing antibody detected at or after baseline on the pharmacokinetics of abaloparatide:
In Japanese Study 004, the pharmacokinetics of abaloparatide, anti-abaloparatide antibody, and neutralizing antibody was measured. Table 24 shows the pharmacokinetic parameters in anti-abaloparatide antibody-negative and -positive subjects[29)] and in neutralizing antibody-negative and -positive subjects.[30)] Exposure to abaloparatide tended to be lower in anti-abaloparatide antibody-positive subjects and neutralizing antibody-positive subjects than in anti-abaloparatide-negative subjects.

[29)] Among patients evaluated for pharmacokinetics, patients who were positive for anti-abaloparatide antibody at least once within 48 weeks after abaloparatide administration.
[30)] Among patients evaluated for pharmacokinetics, patients who were positive for neutralizing antibody at least once within 48 weeks after abaloparatide administration.

Table 24. Pharmacokinetic parameters in anti-abaloparatide antibody-negative and -positive subjects and in neutralizing antibody-negative and -positive subjects in Japanese Study 004

Treatment group	Time point of measurement	Antibody		No. of subjects	C_{max} (pg/mL)	AUC_{0-t} (pg•h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Abaloparatide 40 µg	Week 9	ADA	Negative	15	342.6 ± 98.3	560.3 ± 213.1	0.25 [0.23, 0.50]	1.20 ± 0.26[a)]
			Positive	2	41.7, 661.6	98.2, 1016.2	0.53, 0.53	0.91, 2.40
		Neutralizing antibody	Negative	15	342.6 ± 98.3	560.3 ± 213.1	0.25 [0.23, 0.50]	1.20 ± 0.26[a)]
			Positive	2	41.7, 661.6	98.2, 1016.2	0.53, 0.53	0.91, 2.40
	Week 36	ADA	Negative	15	244.5 ± 168.8	406.8 ± 315.9	0.32 [0.25, 0.50]	1.29 ± 0.39[b)]
			Positive	2	28.5, 31.8	32.5, 76.0	0.58, 0.58	12.53[c)]
		Neutralizing antibody	Negative	15	244.5 ± 168.8	406.8 ± 315.9	0.32 [0.25, 0.50]	1.29 ± 0.39[b)]
			Positive	2	28.5, 31.8	32.5, 76.0	0.58, 0.58	12.53[c)]
Abaloparatide 80 µg	Week 9	ADA	Negative	13	493.1 ± 113.2	882.9 ± 345.5	0.50 [0.22, 1.5]	1.52 ± 0.71[d)]
			Positive	6	589.7 ± 110.6	1006.0 ± 186.7	0.40 [0.25, 0.50]	1.07 ± 0.16
		Neutralizing antibody	Negative	17	528.4 ± 122.8	919.9 ± 321.8	0.50 [0.22, 1.50]	1.40 ± 0.65[e)]
			Positive	2	418.7, 546.3	863.8, 1012.7	0.25, 0.50	1.11, 1.12
	Week 36	ADA	Negative	11	278.1 ± 202.0	425.6 ± 322.8	0.48 [0.25, 0.55]	1.32 ± 0.51[f)]
			Positive	6	238.1 ± 153.1	374.0 ± 192.2	0.50 [0.25, 0.63]	2.24 ± 2.25[g)]
		Neutralizing antibody	Negative	15	277.1 ± 187.0	421.1 ± 288.8	0.50 [0.25, 0.63]	1.30 ± 0.47[d)]
			Positive	2	65.9, 265.2	153.6, 455.2	0.25, 0.50	1.25, 6.22

Mean ± SD; Individual value if n = 2: t_{max} is expressed in median [range]; ADA, Anti-abaloparatide antibody
C_{max}, Maximum plasma concentration; AUC_{0-t}, Area under the plasma concentration-time curve from time 0 to the last measurable concentration; t_{max}, Time to the maximum plasma concentration, $t_{1/2}$, Elimination half life
a) n = 14, b) n = 13, c) n = 1, d) n = 12, e) n = 16, f) n = 9, g) n = 5

Similarly, in Foreign Study 05-002, the pharmacokinetics of abaloparatide, anti-abaloparatide antibody, and neutralizing antibody was measured. Table 25 shows plasma abaloparatide concentration at 90 minutes after administration in anti-abaloparatide antibody-negative and -positive subjects and in neutralizing antibody-negative and -positive subjects. The effect of anti-abaloparatide antibody and neutralizing antibody to decrease exposure tended to increase with dose, although there are limitations to the evaluation because of the limited number of anti-abaloparatide antibody-positive or neutralizing antibody-positive subjects.

Table 25. Plasma abaloparatide concentration at 90 minutes after administration in anti-abaloparatide antibody-negative and -positive subjects and in neutralizing antibody-negative and -positive subjects in Foreign Study 05-002

Treatment group	Antibody	After the first dose	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
Abaloparatide 20 µg	ADA-negative	47.2 ± 26.1 (n = 28)	58.7 ± 27.0 (n = 26)	65.1 ± 33.5 (n = 22)	71.5 ± 41.6 (n = 22)	61.7 ± 30.8 (n = 23)	66.9 ± 35.6 (n = 24)	69.8 ± 29.5 (n = 23)
	ADA-positive	60.5 ± 43.2 (n = 5)	72.8 ± 56.8 (n = 5)	85.0 ± 44.4 (n = 4)	86.2 ± 39.5 (n = 4)	87.2 ± 27.8 (n = 4)	92.2 ± 22.5 (n = 4)	78.2 ± 24.0 (n = 4)
	Neutralizing antibody-negative	49.3 ± 28.9 (n = 33)	61.0 ± 32.6 (n = 31)	68.1 ± 35.1 (n = 26)	73.8 ± 40.8 (n = 26)	65.5 ± 31.3 (n = 27)	70.5 ± 34.9 (n = 28)	71.1 ± 28.5 (n = 27)
	Neutralizing antibody-positive	-	-	-	-	-	-	-
Abaloparatide 40 µg	ADA-negative	108.5 ± 65.2 (n = 27)	121.0 ± 61.0 (n = 27)	111.8 ± 73.8 (n = 26)	121.0 ± 72.2 (n = 24)	126.6 ± 56.6 (n = 24)	130.8 ± 75.0 (n = 27)	135.0 ± 87.4 (n = 29)
	ADA-positive	48.6 ± 13.9 (n = 4)	103.4 ± 34.8 (n = 3)	69.5, 207.0 (n = 2)	110.8 ± 95.0 (n = 5)	140.9 ± 97.4 (n = 3)	62.0 ± 35.3 (n = 5)	30.8 ± 6.1 (n = 3)
	Neutralizing antibody-negative	102.2 ± 64.8 (n = 30)	119.2 ± 58.7 (n = 30)	113.7 ± 73.8 (n = 28)	122.4 ± 74.2 (n = 28)	123.5 ± 55.8 (n = 26)	120.0 ± 74.3 (n = 32)	128.0 ± 88.6 (n = 31)
	Neutralizing antibody-positive	58.2 (n = 1)	-	-	31.60 (n = 1)	250.0 (n = 1)	-	37.9 (n = 1)
Abaloparatide 80 µg	ADA-negative	193.3 ± 139.8 (n = 38)	219.7 ± 133.2 (n = 36)	247.0 ± 152.4 (n = 33)	273.5 ± 156.0 (n = 31)	257.7 ± 147.7 (n = 26)	251.7 ± 117.1 (n = 26)	267.1 ± 133.9 (n = 25)
	ADA-positive	139.6 ± 53.9 (n = 4)	123.7 ± 52.8 (n = 4)	127.2 ± 47.1 (n = 5)	136.0 ± 62.94 (n = 5)	115.1 ± 40.7 (n = 5)	109.9 ± 17.5 (n = 5)	89.5 ± 34.4 (n = 5)
	Neutralizing antibody-negative	188.2 ± 134.5 (n = 42)	210.1 ± 130.3 (n = 40)	231.3 ± 148.3 (n = 38)	254.4 ± 153.72 (n = 36)	234.7 ± 145.7 (n = 31)	228.9 ± 119.5 (n = 31)	237.5 ± 143.7 (n = 30)
	Neutralizing antibody-positive	-	-	-	-	-	-	-

Mean ± SD (Number of subjects); Individual values for ≤2 subjects; -, Not applicable; ADA, Anti-abaloparatide antibody

Systemic clearance and distribution volume of the central compartment (median [range]) in Foreign Study 05-003, estimated based on the population pharmacokinetics model, were investigated in subgroups with and without anti-abaloparatide antibody and subgroups with and without neutralizing antibody (those positive for anti-abaloparatide antibody or neutralizing antibody at least once were regarded as positive). Table 26 shows the results. Systemic clearance and distribution volume increased in subjects with anti-abaloparatide antibody or neutralizing antibody.

Table 26. Population pharmacokinetic parameters in subjects negative or positive for anti-abaloparatide antibody or neutralizing antibody

Antibody	Positive/negative of antibody	CL (L/h)	V_2 (L)	AUC (pg•h/mL)
Anti-abaloparatide antibody	Negative[a)] (n = 817)	54.7 [34.6, 107]	50.4 [26.2, 122]	1461 [745, 2314]
	Positive (low titer[b)]) (n = 210)	97.3 [69.4, 138]	119 [71.9, 195]	822 [580, 1153]
	Positive (high titer[c)]) (n = 81)	139 [96.6, 184]	308 [227, 490]	575 [435, 828]
Neutralizing antibody	Negative (n = 108)	55.4 [41.4, 107.3]	49.5 [30.5, 122.1]	1444 [745, 1932]
	Positive (n = 188)	107 [31.9, 184]	132 [37.1, 381]	745 [435, 2509]

Median [range]; CL, Systemic clearance; V_2, Distribution volume of the central compartment; AUC, Area under the concentration-time curve
a) Subjects negative at the start of the study, b) antibody titer 1:1 or <1:1, c) antibody titer >1:10

The above results suggested the possibility that the exposure to abaloparatide is reduced by anti-abaloparatide antibody or neutralizing antibody.

PMDA's view:
Results of the clinical studies conducted suggest that production of anti-abaloparatide antibody or neutralizing antibody are induced by abaloparatide and that the exposure to abaloparatide tends to decrease in antibody-positive subjects. Effects of anti-abaloparatide antibody or neutralizing antibody on the safety and efficacy are discussed further in Section "7.R.2.8 Antibody production."

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

The applicant submitted efficacy and safety evaluation data in the form of results data from 5 clinical studies, as shown in Table 27. In Foreign Studies 05-002 and 05-003, teriparatide (genetical recombination) preparation was used as the control.

Table 27. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of subjects treated	Outline of dosage regimen	Main endpoints
Evaluation	Japan	004	II	Patients with postmenopausal osteoporosis	160	Placebo or abaloparatide 40, 80 μg was administered subcutaneously once daily for 48 weeks.	Efficacy Safety
	Foreign	05-002	II	Patients with postmenopausal osteoporosis	221	Placebo, abaloparatide 20, 40, 80 μg or teriparatide was administered subcutaneously once daily for 24 weeks.	Efficacy Safety
	Japan	301	III	Patients with osteoporosis	212	Placebo or abaloparatide 80 μg was administered subcutaneously once daily for 18 months.	Efficacy Safety
	Foreign	05-003	III	Patients with postmenopausal osteoporosis	2460	Placebo, abaloparatide 80 μg, or teriparatide was administered subcutaneously once daily for 18 months.	Efficacy Safety
	Foreign	05-005	III	Patients with postmenopausal osteoporosis	1133	Alendronate 70 mg was administered orally once weekly for 24 months to subjects who had received placebo or abaloparatide in Foreign Study 05-003.	Efficacy Safety

The results from the main studies are described below.

7.1 Phase II studies

7.1.1 Japanese phase II study in Japanese patients with postmenopausal osteoporosis (CTD 5.3.5.1-1, Japanese Study 004 [November 2013 to June 2015])

A placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients with postmenopausal osteoporosis at high risk of fracture (target sample size; 150 subjects, 50 per group) was conducted to investigate the efficacy, safety, and dose-response of abaloparatide [for pharmacokinetics, see Section "6.2.3.1 Japanese phase II study in Japanese patients with postmenopausal osteoporosis"].

The main inclusion criteria were patients aged ≥55 and ≤85 years (menopause at age ≥43 and ≥3 years before informed consent) with osteoporosis at high risk of fracture who met any of the following criteria: (a) Bone density of the lumbar spine <80% of young adult mean (YAM) and ≥1 fragility fracture of vertebral body, (b) bone density of the lumbar spine ≤70% of YAM or ≤−2.5SD and ≥65 years of age, or (c) bone density of the lumbar spine <65% of YAM. In this study, dynamic allocation procedure was used with the bone density of the lumbar spine (L2-L4) at the test before the provisional registration as the allocation factor.

The study consisted of a run-in period (≤8 weeks) and a treatment period (48 weeks).

Placebo, abaloparatide 40 or 80 μg was administered subcutaneously in the abdomen (self-injection using a pen injector) once daily under blinded conditions. Throughout the study period, calcium (610 mg/day) and natural vitamin D_3 (400 IU/day) were administered orally in the form of New Calcichew D_3 once daily after dinner as the basic medication.

Of 164 randomized subjects, all of the 160 receiving the study drug (53 in the placebo group, 54 in the abaloparatide 40 μg group, 53 in the abaloparatide 80 μg group) were included in the safety analysis population. A total of 157 subjects, excluding 3 subjects in the placebo group without efficacy data after the study drug administration because of the study discontinuation, were included in FAS, and the

FAS was handled as the primary efficacy analysis population. Study discontinuation occurred in 21 subjects; 7 subjects in the placebo group (subject's request in 3 subjects, ≥5% decrease in bone density in 2 subjects, adverse event in 1 subject, and subjects who did not meet the inclusion criteria or met the exclusion criteria in 1 subject), 6 subjects in the abaloparatide 40 μg group (adverse events in 4 subjects, subject's request in 1 subject, and other in 1 subject), and 8 subjects in the abaloparatide 80 μg group (subject's request in 6 subjects, subjects who did not meet the inclusion criteria or met the exclusion criteria in 1 subject, and other in 1 subject).

Table 28 shows the results of the percent change from baseline in the bone density of the lumbar spine (L2-L4) at the last evaluation time point (Week 48), the primary efficacy endpoint. A significant increase was obtained in both abaloparatide groups compared to the placebo group, and the increase was significantly greater in the abaloparatide 80 μg group than in the 40 μg group.

Table 28. Percent change from baseline in the bone density of the lumbar spine (L2-L4) at the last evaluation time point (Japanese Study 004, FAS)

Endpoint	Placebo	Abaloparatide 40 μg	Abaloparatide 80 μg
Bone density at baseline (g/cm^2)	0.642 ± 0.064 (n = 50)	0.641 ± 0.071 (n = 54)	0.648 ± 0.066 (n = 53)
Bone density at the final evaluation (g/cm^2)	0.647 ± 0.065 (n = 49)	0.683 ± 0.077 (n = 50)	0.723 ± 0.070 (n = 49)
Percent change from baseline (%) [a) b)]	0.50 ± 0.69 (n = 49)	7.12 ± 0.68 (n = 50)	12.03 ± 0.69 (n = 49)
Difference from placebo [b)]	-	6.62 [4.70, 8.54]	11.52 [9.59, 13.45]
P value[c)]	-	<0.001	<0.001
Difference between 40 μg and 80 μg[b)]	-	4.91 [2.98, 6.83]	
P value[c)]	-	<0.001	

Mean ± SD (number of subjects); Percent change is expressed in least squares mean ± SE; The difference from the placebo group is expressed in least squares mean [95% CI].

a) Evaluated in subjects in FAS, except for 8 subjects without DXA data measured after the start of treatment due to study discontinuation (3 in the 40μg group, 4 in the 80 μg group, 1 in the placebo group) and 1 subject in the 40 μg group who used systemic corticosteroid, a prohibited concomitant medication.

b) The analysis of covariance (ANCOVA) model using treatment group as the factor and bone density (continuous variable) of the lumbar spine (L2-L4) at the provisional registration as the covariate.

c) Adjusted for multiplicity of the test by comparing the placebo group and the abaloparatide 80 μg group, the placebo group and the abaloparatide 40 μg group, and the abaloparatide 80 μg group and the abaloparatide 40 μg group, using a closed testing procedure at one-sided significance level of 2.5%.

Table 29 shows the results of percent change from baseline in the bone density of the lumbar spine (L2-L4), femur (proximal), and femur (neck) at Week 48, the secondary endpoint. X-ray evaluation showed a new spinal fracture in 1 subject (abaloparatide 80 μg group).

Table 29. Percent change from baseline in bone density at each observation time point at Week 48 (Japanese Study 004, FAS[a)])

Evaluation site	Evaluation time point	Placebo	Abaloparatide 40 μg	Abaloparatide 80 μg
Lumbar spine (L2-L4)	Week 12	0.77 ± 3.28 (n = 46)	4.04 ± 3.99 (n = 50)	6.53 ± 3.08 (n = 46)
	Week 24	1.09 ± 3.10 (n = 48)	6.25 ± 5.04 (n = 49)	9.47 ± 4.82 (n = 48)
	Week 48	0.76 ± 2.69 (n = 46)	7.22 ± 5.69 (n = 48)	11.90 ± 5.56 (n = 47)
	Final evaluation	0.50 ± 3.01 (n = 49)	7.17 ± 5.59 (n = 50)	11.98 ± 5.59 (n = 49)
Femur (proximal)	Week 12	0.98 ± 1.92 (n = 46)	1.21 ± 1.87 (n = 50)	1.30 ± 1.49 (n = 45)
	Week 24	0.62 ± 2.04 (n = 48)	1.64 ± 1.80 (n = 49)	2.13 ± 1.70 (n = 4)
	Week 48	0.42 ± 1.90 (n = 43)	1.49 ± 2.20 (n = 48)	2.90 ± 2.21 (n = 47)
	Final evaluation	0.41 ± 2.22 (n = 49)	1.58 ± 2.22 (n = 50)	2.90 ± 2.16 (n = 49)
Femur (neck)	Week 12	0.81 ± 2.93 (n = 46)	1.01 ± 2.96 (n = 50)	1.44 ± 2.46 (n = 45)
	Week 24	0.57 ± 3.55 (n = 48)	1.97 ± 2.65 (n = 49)	1.75 ± 2.77 (n = 48)
	Week 48	0.87 ± 2.99 (n = 43)	1.47 ± 2.51 (n = 48)	2.33 ± 3.29 (n = 47)
	Final evaluation	0.64 ± 3.26 (n = 49)	1.49 ± 2.47 (n = 50)	2.35 ± 3.22 (n = 49)

Unit, %; Mean ± SD (number of subjects evaluated)

a) Evaluated in subjects in FAS, except for 8 subjects without DXA data after the start of treatment due to study discontinuation (3 in the 40 μg group, 4 in the 80 μg group, 1 in the placebo group) and 1 subject in the 40 μg group who used systemic corticosteroid, a prohibited concomitant medication.

Figure 1 shows changes over time in the percent change from baseline in bone metabolism markers at each observation time point.

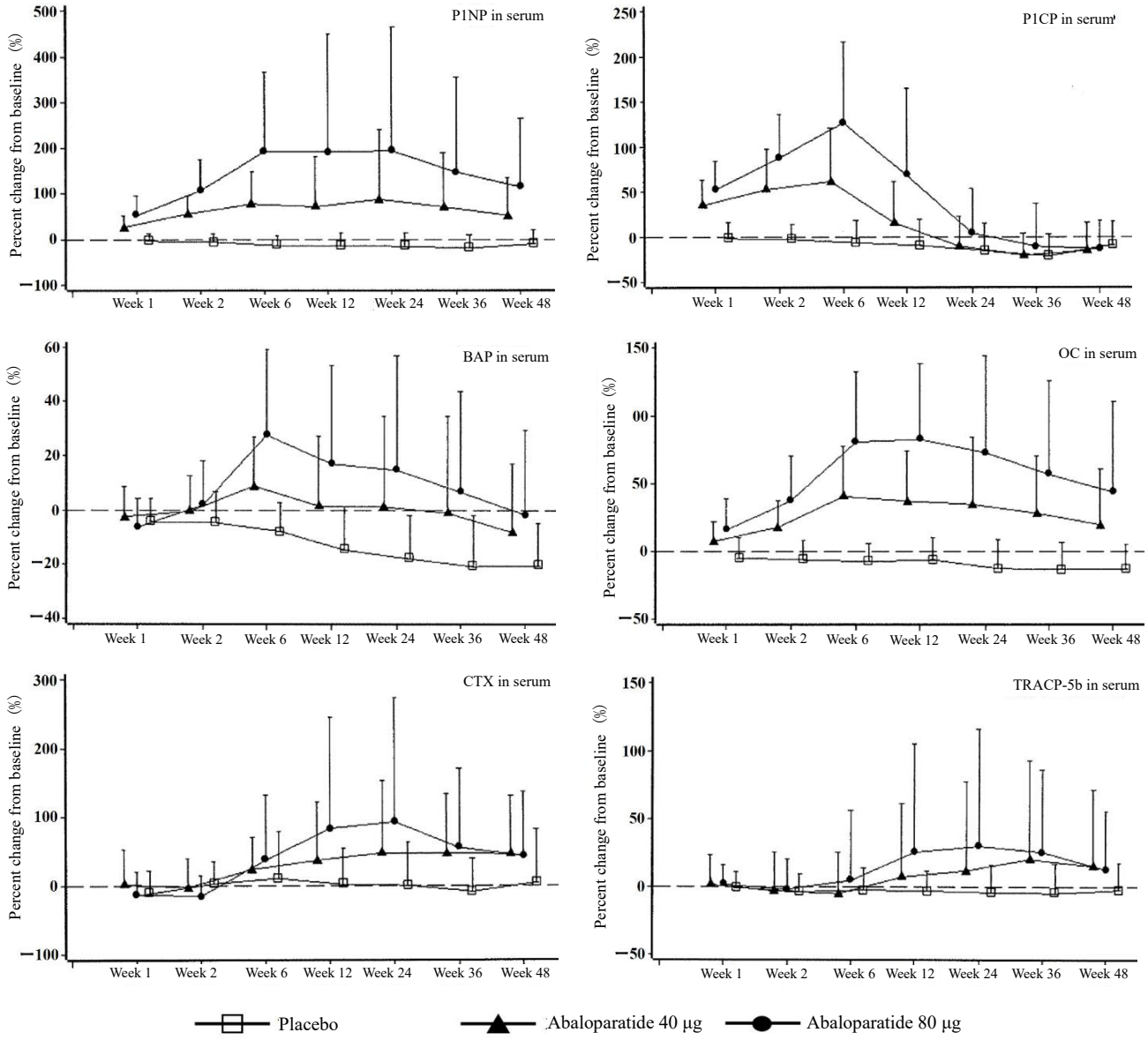

Figure 1. Percent change from baseline in bone metabolism markers at each observation time point (mean + SD) (Japanese Study 004, FAS)

Table 30 shows the incidences of adverse events or adverse drug reactions reported by ≥5% of subjects in any group within Week 48.

Table 30. Incidences of adverse events or adverse drug reactions reported by ≥5% of subjects in any group (Japanese Study 004; up to Week 48, safety analysis population)

Event	Placebo (n = 53)		Abaloparatide 40 μg (n = 54)		Abaloparatide 80 μg (n = 53)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	75.5 (40)	5.7 (3)	90.7 (49)	14.8 (8)	81.1 (43)	17.0 (9)
Nasopharyngitis	41.5 (22)	0 (0)	33.3 (18)	0 (0)	32.1 (17)	0 (0)
Headache	1.9 (1)	0 (0)	16.7 (9)	5.6 (3)	11.3 (6)	3.8 (2)
Pain in extremity	0 (0)	0 (0)	5.6 (3)	0 (0)	9.4 (5)	0 (0)
Back pain	9.4 (5)	0 (0)	14.8 (8)	1.9 (1)	7.5 (4)	0 (0)
Dizziness	1.9 (1)	0 (0)	3.7 (2)	1.9 (1)	7.5 (4)	0 (0)
Arthralgia	11.3 (6)	1.9 (1)	9.3 (5)	0 (0)	5.7 (3)	0 (0)
Contusion	9.4 (5)	0 (0)	5.6 (3)	0 (0)	5.7 (3)	0 (0)
Blood urine present	5.7 (3)	0 (0)	1.9 (1)	0 (0)	5.7 (3)	0 (0)
Cystitis	3.8 (2)	0 (0)	1.9 (1)	0 (0)	5.7 (3)	0 (0)
Conjunctivitis	0 (0)	0 (0)	1.9 (1)	0 (0)	5.7 (3)	0 (0)
Injection site bruising	5.7 (3)	0 (0)	5.6 (3)	0 (0)	3.8 (2)	0 (0)
Periodontitis	1.9 (1)	0 (0)	5.6 (3)	0 (0)	3.8 (2)	0 (0)
Oropharyngeal pain	1.9 (1)	0 (0)	5.6 (3)	0 (0)	1.9 (1)	0 (0)
Dental caries	1.9 (1)	0 (0)	7.4 (4)	0 (0)	1.9 (1)	0 (0)
Diarrhoea	1.9 (1)	0 (0)	7.4 (4)	0 (0)	1.9 (1)	0 (0)
Stomatitis	1.9 (1)	0 (0)	7.4 (4)	0 (0)	1.9 (1)	0 (0)
Malaise	1.9 (1)	1.9 (1)	11.1 (6)	1.9 (1)	1.9 (1)	0 (0)
Tooth fracture	0 (0)	0 (0)	5.6 (3)	0 (0)	1.9 (1)	0 (0)
Eczema	1.9 (1)	0 (0)	5.6 (3)	0 (0)	0 (0)	0 (0)
Upper respiratory tract inflammation	0 (0)	0 (0)	5.6 (3)	0 (0)	0 (0)	0 (0)

Incidence in % (number of subjects with events), Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.16.0

No death occurred. Serious adverse events were observed in 3.7% (2 of 54) of subjects (pneumonia and colitis in 1 subject each) in the abaloparatide 40 μg group. A causal relationship to the study drug was ruled out for both of them. Adverse events leading to treatment discontinuation were observed in 7.4% (4 of 54) of subjects (oedema peripheral/tinnitus/feeling hot/headache, headache, asthma, and palpitations in 1 subject each) in the abaloparatide 40 μg group. The events observed in 3 subjects (oedema peripheral/tinnitus/feeling hot/headache, headache, and palpitations in 1 subject each) were assessed to be adverse drug reactions.

7.1.2 Foreign phase II study in non-Japanese patients with postmenopausal osteoporosis (CTD 5.3.5.1-3, Foreign Study 05-002 [April 2007 to May 2009])

A placebo-controlled, randomized, parallel-group study [31)] in non-Japanese patients with postmenopausal osteoporosis at high risk of fracture[32)] (target sample size; 225 subjects, 45 per group) was conducted to investigate the efficacy, safety, and dose response of abaloparatide [for pharmacokinetics, see Section "6.2.3.2 Foreign phase II study in non-Japanese patients with postmenopausal osteoporosis"].

The main inclusion criteria were patients aged ≥55 and ≤85 years (menopause ≥5 years before informed consent) with osteoporosis at high risk of fracture who met any of the following criteria (a) to (c): (a) The T score of bone density of the lumbar spine (L1-L4) or femur (neck) was ≤−2.5 by DXA, (b) the T score of bone density ≤−2.0 and a history of fragility fracture of forearm, upper arm, vertebral body, sacral bone, pelvis, femur (proximal), femur (neck), or shinbone within the past 5 years,

31) Placebo was used in a double-blinded manner to each dose of abaloparatide, and teriparatide was used in an unblinded manner to each dose of placebo and abaloparatide.
32) US, UK, Argentina, and India

or (c) other risk factors such as ≥65 years of age or the patient's mother had osteoporosis-related fracture or a history of diagnosis of osteoporosis based on the bone density criteria.

The study consisted of a screening period (2-4 weeks), a run-in period (4 weeks), a treatment period (24 weeks), an extended period (24 weeks), and a follow-up period (4 weeks). Subjects who showed no change or increase in bone density from baseline at least 1 measuring time point during the treatment period and did not experience any serious adverse drug reaction proceeded to the extended period.

Placebo, abaloparatide 20, 40, or 80 μg, or teriparatide 20 μg was self-injected subcutaneously at the periumbilical area once daily. The same dosage regimen was employed during the extended period. From the run-in period throughout the follow-up period, calcium (500-1000 mg/day) and natural vitamin D_3 (400-800 IU/day) were administered orally in the form of New Calcichew D_3 as the basic medication once daily in the evening.

Of 222 randomized subjects, 221 subjects receiving the study drug (45 in the placebo group, 43 in the abaloparatide 20 μg group, 43 in the abaloparatide 40 μg group, 45 in the abaloparatide 80 μg group, 45 in the teriparatide group) were included in the safety analysis population and in the intent-to-treat (ITT) population. A total of 155 subjects who completed the 24-week study without any serious protocol violation (37 in the placebo group, 29 in the abaloparatide 20 μg group, 29 in the abaloparatide 40 μg group, 28 in the abaloparatide 80 μg group, 32 in the teriparatide group) were included in the efficacy analysis population. Among them, 55 subjects (11 in the placebo group, 13 in the abaloparatide 20 μg group, 10 in the abaloparatide 40 μg group, 7 in the abaloparatide 80 μg group, 14 in the teriparatide group) participated in the extended period, and all of them were included in the population for extended period analysis. During the treatment period (24 weeks), 38 subjects discontinued the study, including 4 subjects in the placebo group (subject's request in 2 subjects, and lost to follow-up in 2 subjects), 10 subjects in the abaloparatide 20 μg group (unable to comply with the study procedure in 3 subjects, subject's request in 2 subjects, lost to follow-up in 2 subjects, adverse event in 1 subject, and other in 2 subjects), 7 subjects in the abaloparatide 40 μg group (unable to comply with the study procedure in 2 subjects, subject's request in 1 subject, adverse event in 1 subject, lost to follow-up in 1 subject, excluded for management purpose in 1 subject, and other in 1 subject), 11 subjects in the abaloparatide 80 μg group (subject's request in 4 subjects, adverse events in 3 subjects, unable to comply with the study procedure in 1 subject, excluded for management purpose in 1 subject, poor compliance in 1 subject, and protocol deviation in 1 subject), and 6 subjects in the teriparatide group (unable to comply with the study procedure in 2 subjects, adverse events in 2 subjects, subject's request in 1 subject, and poor compliance in 1 subject). During the extended period, 7 subjects discontinued the study, including 1 subject in the placebo group (other in 1 subject), 2 subjects in the abaloparatide 20 μg group (subject's request in 1 subject and other in 1 subject), 2 subjects in the abaloparatide 40 μg group (adverse event in 1 subject and protocol deviation in 1 subject), 1 subject in the abaloparatide 80 μg group (adverse event in 1 subject), and 1 subject in the teriparatide group (other in 1 subject).

Table 31 shows the results of "the percent change from baseline in the bone density in the lumbar spine (L1-L4), femur (neck), radius, and ultradistal ulna up to Week 24, the primary efficacy endpoint.

Table 31. Percent change from baseline in bone density at each observation time point (Foreign Study 05-002, efficacy analysis population)

Endpoint	Observation time point	Placebo (n = 37)	Abaloparatide 20 μg (n = 29)	Abaloparatide 40 μg (n = 29)	Abaloparatide 80 μg (n = 28)	Teriparatide (n = 32)
Lumber spine (L1-L4)	Week 12	1.58 ± 3.67 (n = 37)	2.50 ± 2.44 (n = 29)	3.25 ± 3.89 (n = 29)	4.61 ± 3.11 (n = 28)	3.49 ± 3.78 (n = 31)
	Week 24	1.44 ± 3.39 (n = 37)	3.50 ± 1.74 (n = 29)	4.92 ± 4.05 (n = 29)	6.73 ± 4.34 (n = 28)	5.98 ± 4.22 (n = 32)
Femur (neck)	Week 12	1.03 ± 2.68 (n = 36)	1.88 ± 2.96 (n = 29)	1.41 ± 4.20 (n = 29)	1.89 ± 3.09 (n = 27)	0.56 ± 3.01 (n = 30)
	Week 24	0.35 ± 4.73 (n = 36)	2.30 ± 2.85 (n = 29)	1.45 ± 4.45 (n = 29)	2.88 ± 4.08 (n = 28)	0.62 ± 4.01 (n = 32)
Radius and ultradistal ulna	Week 12	0.52 ± 4.71 (n = 37)	2.12 ± 4.96 (n = 28)	0.12 ± 4.21 (n = 29)	-0.79 ± 5.67 (n = 28)	-0.33 ± 4.84 (n = 31)
	Week 24	-2.46 ± 8.88 (n = 37)	0.39 ± 7.46 (n = 29)	0.03 ± 7.24 (n = 29)	-1.82 ± 9.72 (n = 28)	-1.29 ± 8.70 (n = 32)

Unit, %; Mean ± SD (number of subjects evaluated)

Figure 2 shows the percent change from baseline in bone metabolism markers up to Week 24.

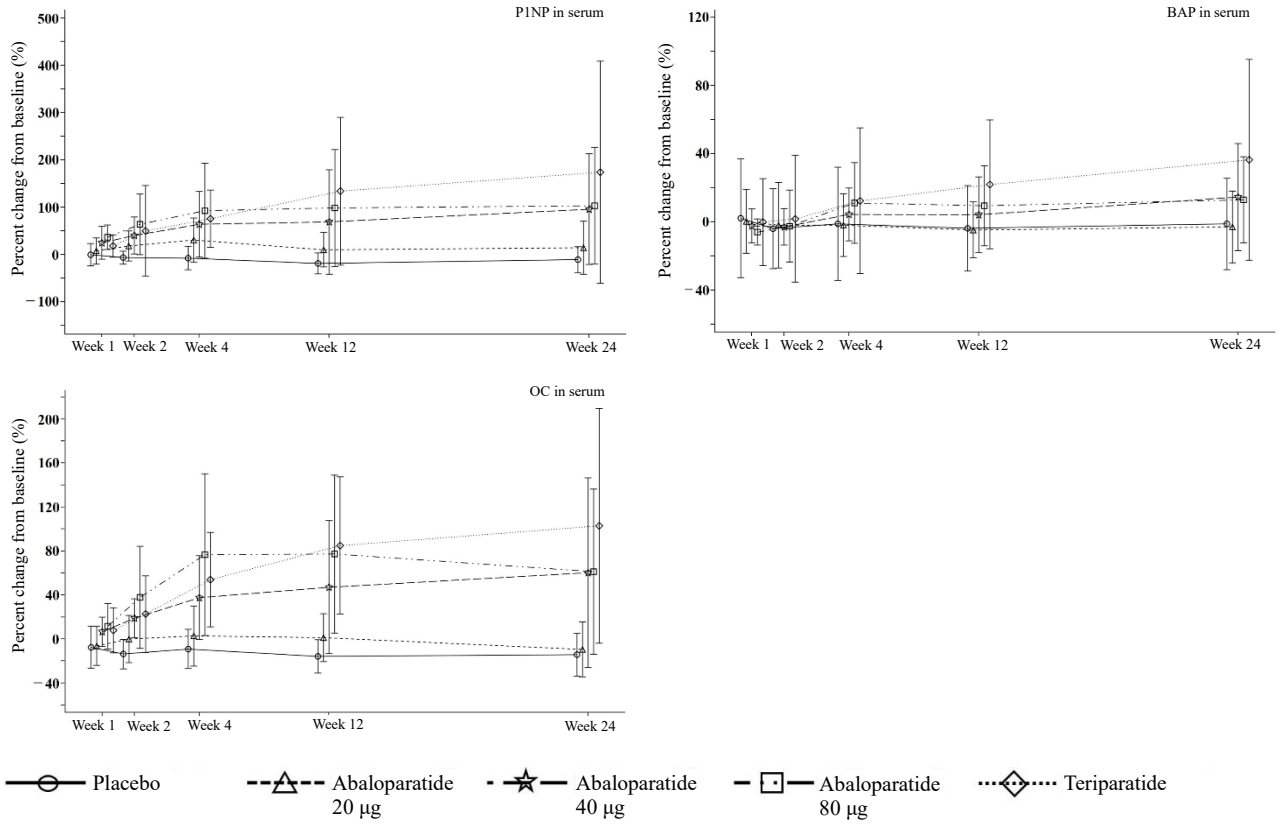

Figure 2. Percent change from baseline in bone metabolism markers at each observation time point (mean ± SD) (Foreign Study 05-002, efficacy analysis population)

Table 32 shows the percent change in bone density at the lumbar spine (L1-L4), femur (neck), radius and ultradistal ulna in the population for extended period analysis. Figure 3 shows the percent change from baseline in bone metabolism markers.

Table 32. Percent change from baseline in bone density at each observation time point (Foreign Study 05-002, population for extended period analysis)

Evaluation site	Observation time point	Placebo (n = 11)	Abaloparatide 20 μg (n = 13)	Abaloparatide 40 μg (n = 10)	Abaloparatide 80 μg (n = 7)	Teriparatide (n = 14)
Lumbar spine (L1-L4)	Week 12	0.55 ± 2.38 (n = 11)	2.12 ± 3.04 (n = 13)	4.45 ± 5.75 (n = 10)	5.77 ± 2.90 (n = 7)	2.96 ± 4.08 (n = 13)
	Week 24	0.96 ± 2.49 (n = 11)	2.45 ± 2.00 (n = 12)	5.51 ± 5.15 (n = 10)	7.52 ± 4.37 (n = 7)	5.84 ± 4.86 (n = 14)
	Week 48	0.74 ± 3.54 (n = 10)	5.14 ± 3.16 (n = 11)	9.84 ± 5.31 (n = 9)	12.94 ± 3.25 (n = 6)	8.63 ± 6.80 (n = 13)
Femur (neck)	Week 12	2.04 ± 3.78 (n = 11)	2.15 ± 2.86 (n = 13)	1.00 ± 2.08 (n = 10)	2.10 ± 3.37 (n = 7)	1.16 ± 3.05 (n = 12)
	Week 24	2.17 ± 4.00 (n = 11)	2.06 ± 3.49 (n = 12)	2.31 ± 6.29 (n = 10)	2.28 ± 2.06 (n = 7)	2.01 ± 3.39 (n = 14)
	Week 48	1.02 ± 3.76 (n = 10)	3.91 ± 2.41 (n = 11)	1.78 ± 4.25 (n = 9)	4.10 ± 1.43 (n = 6)	2.21 ± 6.02 (n = 13)
Radius and ultradistal ulna	Week 12	0.10 ± 3.52 (n = 11)	0.34 ± 2.56 (n = 12)	0.73 ± 3.83 (n = 10)	0.95 ± 5.10 (n = 7)	-0.67 ± 4.21 (n = 13)
	Week 24	-0.84 ± 3.67 (n = 11)	-3.75 ± 9.66 (n = 13)	-0.82 ± 10.25 (n = 10)	-3.04 ± 12.58 (n = 7)	-4.38 ± 11.41 (n = 14)
	Week 48	-0.60 ± 2.85 (n = 10)	1.40 ± 4.64 (n = 11)	2.88 ± 5.42 (n = 9)	3.09 ± 4.81 (n = 6)	2.16 ± 7.00 (n = 13)

Unit, %; Mean ± SD (number of subjects evaluated)

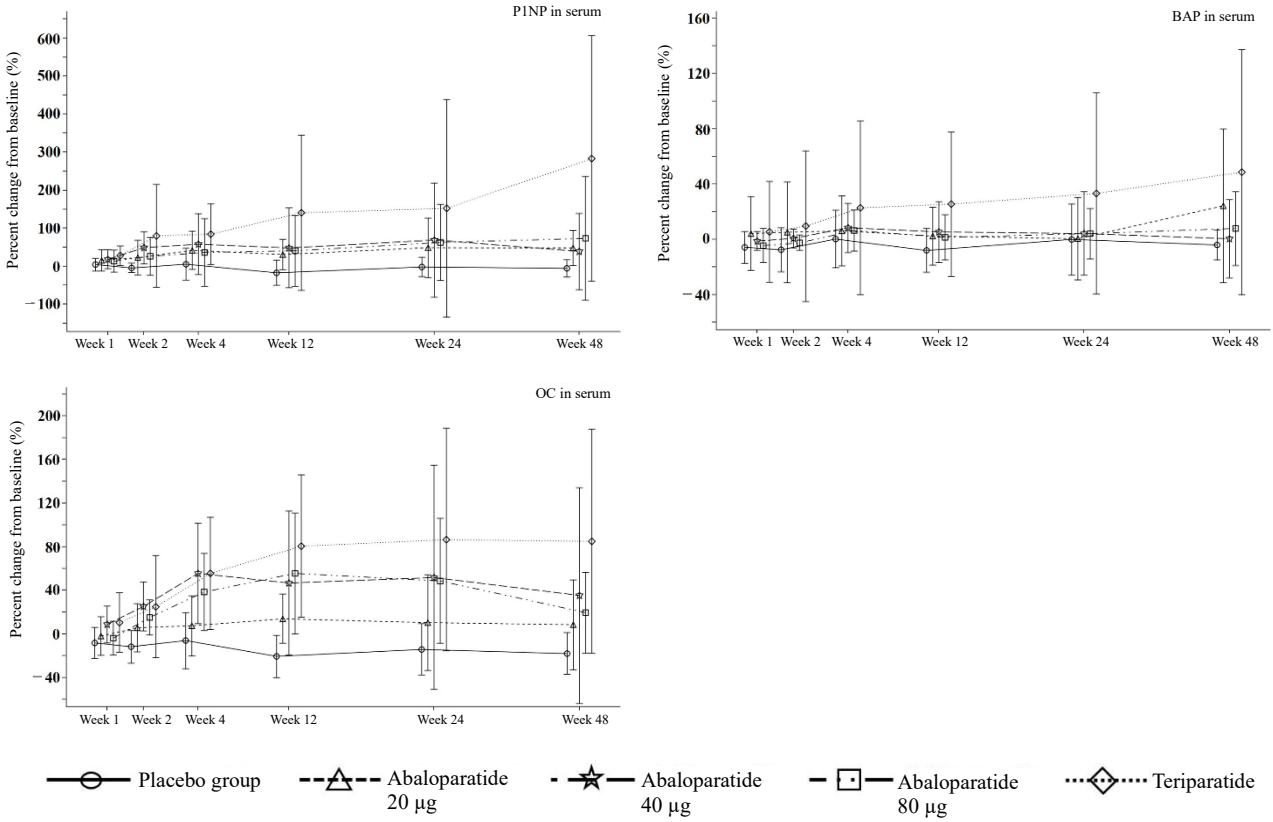

Figure 3. Percent change from baseline in bone metabolism markers at each observation time point (mean ± SD) (Foreign Study 05-002, population for extended period analysis)

Table 33 shows the incidences of adverse events reported by ≥5% of subjects in any group within Week 28[33)] (24-week administration period and 4-week follow-up period) and corresponding adverse drug reactions.

33) Within the 24-week administration period in subjects who participated in the extended period.

Table 33. Incidences of adverse events reported by≥5% of subjects in any treatment group and corresponding drug adverse reactions (Foreign Study 05-002; up to Week 28,[a] safety analysis population)

Event	Placebo (n = 45)		Abaloparatide 20 μg (n = 43)		Abaloparatide 40 μg (n = 43)		Abaloparatide 80 μg (n = 45)		Teriparatide (n = 45)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	73.3 (33)	26.7 (12)	72.1 (31)	20.9 (9)	76.7 (33)	34.9 (15)	77.8 (35)	37.8 (17)	77.8 (35)	28.9 (13)
Headache	6.7 (3)	2.2 (1)	4.7 (2)	0 (0)	14.0 (6)	7.0 (3)	13.3 (6)	11.1 (5)	13.3 (6)	4.4 (2)
Influenza	15.6 (7)	0 (0)	4.7 (2)	0 (0)	7.0 (3)	0 (0)	11.1 (5)	0 (0)	13.3 (6)	0 (0)
Dizziness	4.4 (2)	2.2 (1)	0 (0)	0 (0)	9.3 (4)	4.7 (2)	11.1 (5)	8.9 (4)	4.4 (2)	0 (0)
Diarrhoea	0 (0)	0 (0)	2.3 (1)	0 (0)	11.6 (5)	0 (0)	8.9 (4)	0 (0)	6.7 (3)	0 (0)
Hypercalciuria	8.9 (4)	6.7 (3)	7.0 (3)	7.0 (3)	4.7 (2)	0 (0)	8.9 (4)	8.9 (4)	11.1 (5)	8.9 (4)
Nasopharyngitis	4.4 (2)	0 (0)	11.6 (5)	0 (0)	7.0 (3)	0 (0)	6.7 (3)	0 (0)	13.3 (6)	0 (0)
Bronchitis	6.7 (3)	0 (0)	11.6 (5)	0 (0)	4.7 (2)	0 (0)	6.7 (3)	0 (0)	4.4 (2)	0 (0)
Gastroenteritis	0 (0)	0 (0)	2.3 (1)	0 (0)	7.0 (3)	0 (0)	6.7 (3)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	0 (0)	0 (0)	0 (0)	0 (0)	2.3 (1)	0 (0)	6.7 (3)	2.2 (1)	4.4 (2)	0 (0)
Palpitations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6.7 (3)	4.4 (2)	2.2 (1)	2.2 (1)
Urinary tract infection	2.2 (1)	0 (0)	9.3 (4)	0 (0)	2.3 (1)	0 (0)	4.4 (2)	0 (0)	11.1 (5)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	11.6 (5)	2.3 (1)	4.4 (2)	4.4 (2)	4.4 (2)	2.2 (1)
Hypercalcaemia	2.2 (1)	2.2 (1)	2.3 (1)	2.3 (1)	7.0 (3)	7.0 (3)	4.4 (2)	2.2 (1)	8.9 (4)	8.9 (4)
Cough	0 (0)	0 (0)	4.7 (2)	0 (0)	7.0 (3)	2.3 (1)	4.4 (2)	0 (0)	2.2 (1)	0 (0)
Vomiting	0 (0)	0 (0)	7.0 (3)	0 (0)	4.7 (2)	0 (0)	2.2 (1)	0 (0)	2.2 (1)	0 (0)
Back pain	11.1 (5)	2.2 (1)	7.0 (3)	2.3 (1)	14.0 (6)	2.3 (1)	2.2 (1)	0 (0)	2.2 (1)	0 (0)
Arthralgia	11.1 (5)	0 (0)	4.7 (2)	0 (0)	14.0 (6)	2.3 (1)	2.2 (1)	0 (0)	6.7 (3)	2.2 (1)
Sciatica	0 (0)	0 (0)	0 (0)	0 (0)	7.0 (3)	0 (0)	2.2 (1)	0 (0)	0 (0)	0 (0)
Injection site haematoma	8.9 (4)	6.7 (3)	4.7 (2)	2.3 (1)	7.0 (3)	4.7 (2)	2.2 (1)	0 (0)	11.1 (5)	2.2 (1)
Injection site haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2.2 (1)	2.2 (1)	6.7 (3)	6.7 (3)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	7.0 (3)	2.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	2.2 (1)	0 (0)	4.7 (2)	0 (0)	2.3 (1)	0 (0)	0 (0)	0 (0)	6.7 (3)	0 (0)
Hypertriglyceridaemia	0 (0)	0 (0)	9.3 (4)	0 (0)	2.3 (1)	0 (0)	0 (0)	0 (0)	2.2 (1)	0 (0)
Pain in extremity	6.7 (3)	0 (0)	2.3 (1)	0 (0)	4.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence in % (number of subjects with events), MedDRA/J ver.21.1

a) Data up to Week 24 were collected in subjects who participated in the extended period.

Table 34 shows the incidences of adverse reported by ≥2 subjects in any treatment group within Week 52 (24-week administration period, 24-week extended period, and 4-week follow-up period) and corresponding adverse drug reactions.

Table 34. Incidences of adverse events reported by ≥2 subjects in any treatment group and corresponding adverse drug reactions (Foreign Study 05-002; up to Week 52, population for extended period analysis)

Event	Placebo (n = 11)		Abaloparatide 20 μg (n = 13)		Abaloparatide 40 μg (n = 10)		Abaloparatide 80 μg (n = 7)		Teriparatide (n = 14)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	90.9 (10)	36.4 (4)	84.6 (11)	30.8 (4)	70.0 (7)	30.0 (3)	85.7 (6)	28.6 (2)	78.6 (11)	21.4 (3)
Nasopharyngitis	0 (0)	0 (0)	7.7 (1)	0 (0)	10.0 (1)	0 (0)	28.6 (2)	0 (0)	7.1 (1)	0 (0)
Influenza	0 (0)	0 (0)	0 (0)	0 (0)	20.0 (2)	0 (0)	14.3 (1)	0 (0)	14.3 (2)	0 (0)
Bronchitis	0 (0)	0 (0)	7.7 (1)	0 (0)	0 (0)	0 (0)	14.3 (1)	0 (0)	21.4 (3)	0 (0)
Anaemia	9.1 (1)	0 (0)	15.4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7.1 (1)	0 (0)
Dyspepsia	9.1 (1)	0 (0)	15.4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site haematoma	18.2 (2)	9.1 (1)	0 (0)	0 (0)	10.0 (1)	10.0 (1)	0 (0)	0 (0)	7.1 (1)	0 (0)
Gastroenteritis	0 (0)	0 (0)	7.7 (1)	0 (0)	20.0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	9.1 (1)	0 (0)	23.1 (3)	0 (0)	10.0 (1)	0 (0)	0 (0)	0 (0)	21.4 (3)	0 (0)
Dyslipidaemia	0 (0)	0 (0)	7.7 (1)	0 (0)	20.0 (2)	0 (0)	0 (0)	0 (0)	7.1 (1)	0 (0)
Arthralgia	27.3 (3)	0 (0)	7.7 (1)	0 (0)	20.0 (2)	0 (0)	0 (0)	0 (0)	14.3 (2)	7.1 (1)
Back pain	18.2 (2)	9.1 (1)	7.7 (1)	0 (0)	10.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pain in extremity	27.3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence in % (number of subjects with events), MedDRA/J ver.21.1

No death occurred. Serious adverse events were observed in 2.2% (1 of 45) of subjects (bronchitis) in the placebo group, 2.3% (1 of 43) of subjects (serous cystadenocarcinoma ovary/ascites) in the abaloparatide 20 μg group, and 2.2% (1 of 45) of subjects (diverticulitis) in the abaloparatide 80 μg group during the administration period; and in 14.3% (1 of 7) of subjects (fascial hernia) in the abaloparatide 80 μg group during the extended period. A causal relationship to the study drug was ruled out for all of them. During the administration period, adverse events leading to treatment discontinuation occurred in 2.3% (1 of 43) of subjects (ascites) in the abaloparatide 20 μg group, 2.3% (1 of 43) of subjects (nausea/fatigue) in the abaloparatide 40 μg group, 4.4% (2 of 45) of subjects (headache in 2 subjects) in the abaloparatide 80 μg group, and 4.4% (2 of 45) of subjects (dermatitis allergic and headache/asthenia in 1 subject each) in the teriparatide group. Fatigue in 1 subject in the abaloparatide 40 μg group, headache in 2 subjects in the abaloparatide 80 μg group, and headache/asthenia in 1 subject in the teriparatide group were assessed to be adverse drug reactions. During the extended period, adverse events leading to treatment discontinuation occurred in 10.0% (1 of 10; syncope) of subjects in the abaloparatide 40 μg group and in 14.3% (1 of 7; fascial hernia) of subjects in the abaloparatide 80 μg group. Syncope in 1 subject in the abaloparatide 40 μg group was assessed to be an adverse drug reaction.

7.2 Phase III studies

7.2.1 Japanese phase III study in Japanese patients with osteoporosis (CTD 5.3.5.1-2, Japanese Study 301 [April 2017 to August 2019])

A placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients with osteoporosis at high risk of fracture (target sample size; 195 subjects, 130 in the abaloparatide group, 65 in the placebo group) was conducted to investigate the efficacy and safety of abaloparatide.

The main inclusion criteria were patients aged ≥55 and ≤85 years with osteoporosis at high risk of fracture who met any of the following 3 criteria (women had to have experienced menopause at age ≥43 and ≥3 years before informed consent): (a) Bone density of the lumbar spine <80% of YAM and ≥1 fragility fracture of vertebral body, (b) bone density of the lumbar spine ≤70% of YAM or ≤−2.5SD and ≥65 years of age, or (c) bone density of the lumbar spine <65% of YAM. In this study, dynamic allocation procedure was used with the bone density of the lumbar spine (L1-L4) at the test before the provisional registration and sex as the allocation factors.

The study consisted of a run-in period (≤8 weeks) and a treatment period (78 weeks).

Placebo or abaloparatide 80 μg was administered subcutaneously into the abdomen under blinded conditions (self-injection using an automatic injector). Throughout the study period, calcium (610 mg/day) and natural vitamin D_3 (400 IU/day) were administered orally as the basic medication in the form of New Calcichew D_3 once daily after dinner.

Of 213 randomized subjects, all of the 212 subjects receiving the study drug (72 in the placebo group, 140 in the abaloparatide group) were included in the safety analysis population, and 206 subjects (70 in the placebo group, 136 in the abaloparatide group), excluding 6 subjects without evaluable data of bone density of the lumbar spine after the study drug administration, were included in FAS. The FAS

was handled as the primary efficacy analysis population. The study discontinuation occurred in 54 subjects, including 15 subjects in the placebo group (subject's request in 5 subjects, adverse events in 3 subjects, physician's discretion [based on adjusted serum calcium level] in 1 subject, physician's discretion [based on reason other than adjusted serum calcium level] in 1 subject, and other in 5 subjects) and 39 subjects in the abaloparatide group (subject's request in 19 subjects, physician's discretion [based on reason other than adjusted serum calcium level] in 7 subjects, physician's discretion [based on adjusted serum calcium level] in 2 subjects, adverse events in 2 subjects, and other in 9 subjects).

Table 35 shows the results of the percent change from baseline in the bone density of the lumbar spine (L1-L4) in the entire population and in subjects with postmenopausal osteoporosis at the final evaluation time point (Week 78), the primary efficacy endpoint. A significant increase was observed in abaloparatide compared with placebo.

Table 35. Percent change from baseline in bone density of the lumbar spine (L1-L4) at the final evaluation (Japanese Study 301, FAS)

Endpoint	Entire population		Patients with postmenopausal osteoporosis	
	Placebo (n = 70)	Abaloparatide (n = 136)	Placebo (n = 64)	Abaloparatide (n = 122)
Bone density at baseline (g/cm^2)	0.646 ± 0.062	0.649 ± 0.073	0.643 ± 0.063	0.644 ± 0.073
Bone density at the final evaluation (g/cm^2)	0.659 ± 0.071	0.742 ± 0.091	0.656 ± 0.071	0.734 ± 0.084
Rate of change from baseline (%)	3.78 ± 1.21	16.33 ± 0.99	1.93 ± 0.88	14.15 ± 0.64
Difference from placebo[a)]	-	12.55 [10.30, 14.80]	-	12.22 [10.07, 14.36]
P value[b)]	-	<0.001	-	<0.001

Mean ± SD, Percent change is expressed in least squares mean ± SE; The between-group difference is expressed in least squares mean [95% CI], Last observation carried forward (LOCF).

a) The ANCOVA model using the treatment group and sex as factors and bone density of the lumbar spine (L1-L4) at the provisional registration as covariates.

b) Two-sided significance level of 5%. Adjusted for multiplicity of the test by confirming the superiority of abaloparatide to placebo in the entire population, followed by the confirmation in the population of patients with postmenopausal osteoporosis, using a closed testing procedure.

Table 36 shows the results of the percent change from baseline in bone density of the lumbar spine (L1-L4), femur (proximal), and femur (neck) up to Week 78, the main secondary endpoints. X-ray evaluation showed a new spinal fracture in 3 of 70 subjects (4.3%) in the placebo group but in none of the subjects in the abaloparatide group.

Table 36. Percent change from baseline in bone density at each observation time point up to Week 78 (Japanese Study 301, FAS)

Endpoint	Observation time point	Placebo	Abaloparatide
Lumbar spine (L1-L4)	Week 12	1.11 ± 3.21 (n= 68)	5.74 ± 4.30 (n= 135)
	Week 24	1.35 ± 3.20 (n= 68)	9.20 ± 6.22 (n= 129)
	Week 48	2.11 ± 3.74 (n= 66)	13.28 ± 8.07 (n= 115)
	Week 78	2.15 ± 3.73 (n= 57)	15.35 ± 8.86 (n= 102)
	At the final evaluation	1.97 ± 3.85 (n= 70)	14.65 ± 9.28 (n= 136)
Femur (proximal)	Week 12	-0.26 ± 2.16 (n= 68)	1.82 ± 2.44 (n= 135)
	Week 24	-0.06 ± 2.38 (n= 68)	2.25 ± 2.57 (n= 129)
	Week 48	0.34 ± 2.56 (n= 65)	3.46 ± 3.25 (n= 114)
	Week 78	-0.22 ± 3.04 (n= 57)	4.35 ± 3.32 (n= 101)
	At the final evaluation	-0.22 ± 2.96 (n= 70)	4.04 ± 3.64 (n= 136)
Femur (neck)	Week 12	-0.25 ± 3.38 (n= 68)	1.81 ± 3.08 (n= 135)
	Week 24	-0.14 ± 4.19 (n= 68)	2.05 ± 3.41 (n= 129)
	Week 48	0.96 ± 4.02 (n= 65)	3.47 ± 4.29 (n= 114)
	Week 78	0.40 ± 4.41 (n= 57)	4.75 ± 5.18 (n= 101)
	At the final evaluation	0.17 ± 4.24 (n= 70)	4.45 ± 4.88 (n= 136)

Unit, %; Mean ± SD (number of subjects evaluated)

Figure 4 shows changes over time from baseline in the percent change in bone metabolism markers at each observation time point.

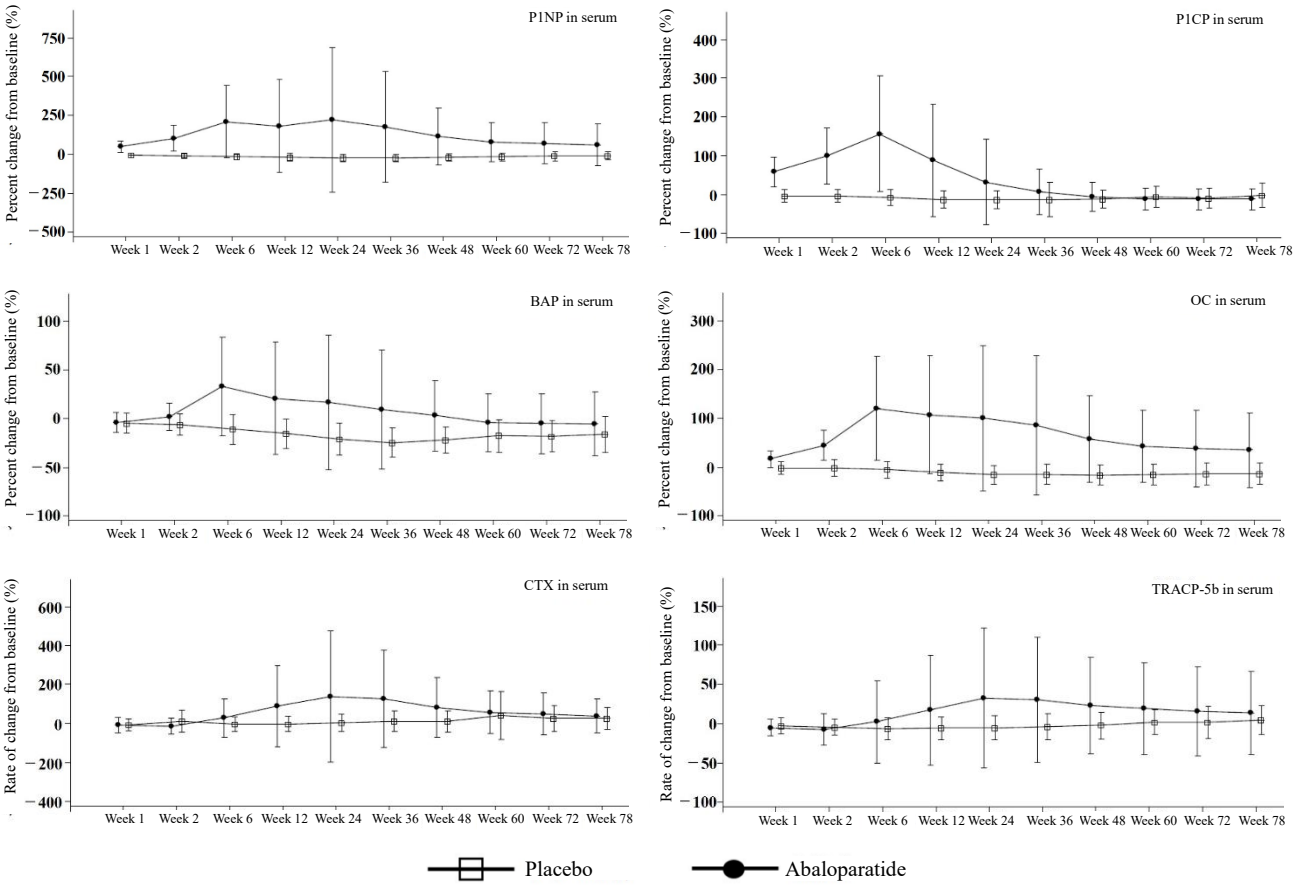

Figure 4. Percent change from baseline in bone metabolism markers at each observation time point (mean ± SD) (Japanese Study 301, FAS)

Table 37 shows the incidence of adverse events reported by ≥5% of subjects in any treatment group and corresponding adverse drug reactions.

Tale 37. Incidence of adverse events reported by ≥5% of subjects in any treatment group and corresponding adverse drug reactions

(Japanese Study 301; at Week 78, safety analysis population)

Event	Placebo (n = 72)		Abaloparatide (n = 140)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	73.6 (53)	13.9 (10)	85.0 (119)	32.1 (45)
Nasopharyngitis	50.0 (36)	0 (0)	57.9 (81)	0 (0)
Headache	11.1 (8)	0 (0)	13.6 (19)	2.1 (3)
Injection site bruising	9.7 (7)	5.6 (4)	7.9 (11)	4.3 (6)
Contusion	5.6 (4)	0 (0)	7.9 (11)	0 (0)
Nausea	8.3 (6)	1.4 (1)	6.4 (9)	5.7 (8)
Abdominal discomfort	4.2 (3)	0 (0)	6.4 (9)	1.4 (2)
Blood uric acid increased	0 (0)	0 (0)	5.7 (8)	3.6 (5)
Back pain	8.3 (6)	0 (0)	5.0 (7)	0 (0)
Eczema	5.6 (4)	0 (0)	5.0 (7)	0 (0)
Dizziness	4.2 (3)	0 (0)	5.0 (7)	2.1 (3)
Osteoarthritis	4.2 (3)	0 (0)	5.0 (7)	0 (0)
Vertigo	2.8 (2)	1.4 (1)	5.0 (7)	0 (0)
Palpitations	1.4 (1)	0 (0)	5.0 (7)	5.0 (7)
Blood calcium increased	1.4 (1)	1.4 (1)	5.0 (7)	4.3 (6)
Cataract	6.9 (5)	0 (0)	0 (0)	0 (0)

Incidence in % (number of subjects with events), MedDRA/J ver.21.1

No death occurred. Serious adverse events were observed in 13.9% (10 of 72) of subjects (diverticulitis, metastases to bone, metastases to liver/neuroendocrine carcinoma, symblepharon, laryngeal oedema, diverticulum intestinal haemorrhagic, enterocolitis/calculus urinary, ankle fracture, radius fracture, and pelvic fracture in 1 subject each) in the placebo group, and in 5.0% (7 of 140) of subjects (pneumonia in 2 subjects, ovarian neoplasm, hypotension/herpes zoster, ileus, subdural haematoma/brain contusion, and cataract operation in 1 subject each) in the abaloparatide group. A causal relationship to the study drug was ruled out for all of them. Adverse events leading to treatment discontinuation were observed in 5.6% (4 of 72) of subjects (metastases to bone, metastases to liver/neuroendocrine carcinoma, blood calcium increased, liver function test increased in 1 subject each) in the placebo group and in 2.9% (4 of 140) of subjects (blood calcium increased in 2 subjects, palpitations and nausea in 1 subject each) in the abaloparatide group. All events except for metastases to bone and metastases to liver/neuroendocrine carcinoma in 2 subjects in the placebo group were assessed to be adverse drug reactions.

7.2.2 Foreign phase III study in patients with postmenopausal osteoporosis (CTD 5.3.5.1-4, Foreign Study 05-003 [March 2011 to October 2014])

A placebo-controlled, randomized, parallel-group study [34)] in non-Japanese patients with postmenopausal osteoporosis at high risk of fracture[35)] (target sample size; 2400 subjects, 800 per group) was conducted to investigate the efficacy and safety of abaloparatide.

The main inclusion criteria were patients aged ≥50 and ≤85 years (women had to have experienced menopause ≥5 years before informed consent) with osteoporosis at high risk of fracture who met any of the following 4 criteria: (a) The bone density T score of the lumbar spine (L1-L4) or femur (neck)

34) Placebo was used in a double-blinded manner to abaloparatide, and teriparatide was used in an unblended manner to placebo or abaloparatide.

35) US, Estonia, Czech Republic, Denmark, Poland, Lithuania, Romania, Argentina, Brazil, and Hong Kong

of >−5.0 and ≤−2.5 by DXA and ≥2 mild or more or ≥1 moderate lumbar or thoracic vertebral fracture confirmed by X-ray imaging, (b) the bone density T score of the lumbar spine (L1-L4) or femur (neck) of >−5.0 and ≤−2.5 and a history of fragility fracture of forearm, upper arm, sacral bone, pelvis, hip, femur, or shinbone within the past 5 years, (c) patients aged ≥65 years who met the criteria for fracture in (a) or (b) with the bone density T score of the lumbar spine (L1-L4) or femur (neck) of >−5.0 and ≤−2.0, or (d) patients aged ≥65 years who did not meet the criteria for fracture in (a) or (b) with the bone density T score of the lumbar spine (L1-L4) or femur (neck) of >−5.0 and ≤−3.0.

The study consisted of a screening period (≤2 months), a pre-administration period (1 week), a treatment period (18 months), and a follow-up period (1 month).

Placebo, abaloparatide 80 μg, or teriparatide 20 μg was administered subcutaneously (self-injection using a pen injector) at the periumbilical area once daily for 18 months. Throughout the study period, calcium (500-1000 mg/day) and natural vitamin D_3 (400-800 IU/day) were administered orally as the basic medication once daily in the evening.

All of 2463 randomized subjects (821 in the placebo group, 824 in the abaloparatide group, 818 in the teriparatide group) were included in ITT, and 2460 subjects receiving the study drug (820 in the placebo group, 822 in the abaloparatide group, 818 in the teriparatide group) were included in the safety analysis population. A total of 2118 subjects (711 in the placebo group, 690 in the abaloparatide group, 717 in the teriparatide group), excluding 342 subjects without evaluable X-ray data of the lumbar spine before and after study drug administration, were included in the modified intent-to-treat (mITT) population.[36)] ITT was handled as the primary efficacy analysis population, while the primary endpoint was analyzed in mITT. The study discontinuation occurred after the start of the study drug administration in 562 subjects, including 184 subjects in the placebo group (adverse events in 53 subjects, consent withdrawal in 48 subjects, refusal of treatment in 33 subjects, >7% decrease from baseline in bone density of the lumbar spine or femur in 12 subjects, poor compliance in 10 subjects, unable to observe the study procedure in 7 subjects, lost to follow-up in 5 subjects, death during the study period in 5 subjects, protocol deviation in 4 subjects, hypersensitivity reaction to the study drug in 1 subject, other in 6 subjects), 218 subjects in the abaloparatide group (adverse events in 89 subjects, consent withdrawal in 47 subjects, refusal of treatment in 31 subjects, lost to follow-up in 15 subjects, unable to observe treatment procedure in 11 subjects, poor compliance in 6 subjects, serious complication in 4 subjects, protocol violation in 4 subjects, death during the treatment period in 3 subjects, >7% decrease from baseline in bone density of the lumbar spine or femur in 1 subject, excluded for management purpose in 1 subject, hypercalcaemia or hypercalciuria in 1 subject, other in 5 subjects), and 160 subjects in the teriparatide group (adverse events in 53 subjects, consent withdrawal in 45 subjects, refusal of treatment in 19 subjects, lost to follow-up in 10 subjects, poor compliance in 9 subjects, unable to observe the treatment procedure in 5 subjects, serious complication in 5 subjects, protocol violation in 5 subjects, death during the treatment period in 2 subjects, serious adverse drug reaction in 2 subjects, >7% decrease from baseline in bone density of the lumbar spine or femur in 1 subject, hypercalcaemia or hypercalciuria in 1 subject, other in 3 subjects).

[36)] Subjects in ITT population with evaluable X-ray imaging of the lumbar spine both before and after the start of treatment

Table 38 shows the results of the incidence of new spinal fracture within 18 months from baseline, the primary endpoint. The incidence was significantly lower in the abaloparatide group than in the placebo group, and in the teriparatide group than in the placebo group.

Table 38. Incidence of new spinal fracture within 18 months from baseline (Foreign Study 05-003, mITT[a])

Endpoint	Placebo (n = 711)	Abaloparatide (n = 600)	Teriparatide (n = 717)
New spinal fracture [95% CI][b]	4.22 (30) [2.97, 5.96]	0.58 (4) [0.23, 1.48]	0.84 (6) [0.38, 1.81]
Decrease in relative risk [95% CI][c]	-	-0.86 [-0.95, -0.61]	-0.80 [-0.92, -0.53]
P value[d]	-	<0.0001	<0.0001

Rate of new fracture in % (number of subjects with new fractures)
a) Subjects evaluated for spinal fracture at baseline and at least once after baseline.
b) Confidence interval by Wilson-Score method
c) Confidence interval by Wald method
d) Fisher's exact test (two-sided significance level of 5%)

Table 39 shows the results of the incidence of non-spinal fracture until the end of the follow-up period from baseline (Month 19), the main secondary endpoint. Table 40 shows the percent change in bone density of the lumbar spine (L1-L4), femur (proximal), and femur (neck) from baseline up to Months 6, 12, and 18.

Table 39. Incidence of non-spinal fracture, etc. (Foreign Study 05-003, ITT)

Endpoint		Placebo (n = 821)	Abaloparatide (n = 824)	Teriparatide (n = 818)
All non-spinal fractures[b]	Incidence	4.0 (33)	2.2 (18)	2.9 (24)
	Hazard ratio to placebo[a] [95% CI]	-	0.57 [0.32, 1.00]	0.72 [0.42, 1.22]
Clinical fracture[c]	Incidence	6.0 (49)	3.3 (27)	4.3 (35)
	Hazard ratio to placebo[a] [95% CI]	-	0.57 [0.35, 0.91]	0.71 [0.46, 1.09]
Main osteoporotic fracture[d]	Incidence	4.1 (34)	1.2 (10)	2.8 (23)
	Hazard ratio to placebo[a] [95% CI]	-	0.30 [0.15, 0.61]	0.67 [0.39, 1.14]
Clinical wrist fracture[e]	Incidence	1.8 (15)	0.8 (7)	2.1 (17)
	Hazard ratio to placebo[a] [95% CI]	-	0.49 [0.20, 1.19]	1.13 [0.56, 2.25]
Non-spinal fracture regardless of the extent of external injury	Incidence	4.5 (37)	2.4 (20)	3.2 (26)
	Hazard ratio to placebo[a] [95% CI]	-	0.56 [0.32, 0.96]	0.69 [0.42, 1.14]
Clinical spinal fracture	Incidence	1.1 (9)	0.1 (1)	0.4 (3)
	Hazard ratio to placebo[a] [95% CI]	-	0.11 [0.01, 0.89]	0.33 [0.09, 1.22]

Incidence in % (number of subjects with fracture); LOCF; -, Not calculated
a) Calculated by the Cox proportional hazard model
b) Clinical fractures of shoulder joint, clavicle, humerus, forearm bones (radius, ulna), wrist (carpals), hand (metacarpals), rib, pelvis (ilium, ischium, pubis, sacrum, coccyx), femur, lower leg bones (tibia and fibula, except patella), ankle (astragalus, calcaneus), foot (tarsal, metatarsal), coccyx, etc., and clinical fracture related to fragility fracture (excluding fractures of vertebral body, sternum, patella, toe phalanges, finger bones, skull, and facial bone; pathological fracture, severe traumatic fracture [fall from a place equal to or higher than body height, or from stool, chair, or ladder], and severe injury other than fall)
c) Regardless of the site.
d) Clinical fracture of vertebral body, proximal femur, wrist, humerus, forearm bone, and shoulder joint
e) Clinical fracture regardless of the extent of external injury

Table 40. Percent change in bone density at each observation time point from baseline (ITT)

Endpoint	Observation time point		Placebo (n = 821)	Abaloparatide (n = 824)	Teriparatide (n = 818)
Lumbar spine (L1-L4)	Baseline (g/m^2)		0.823 ± 0.100 (n = 821)	0.829 ± 0.109 (n = 823)	0.831 ± 0.108 (n = 818)
	Percent change (%)	Month 6	0.56 ± 3.34 (n = 821)	5.90 ± 5.17 (n = 823)	4.84 ± 4.31 (n = 818)
		Month 12	0.39 ± 3.53 (n = 821)	8.19 ± 6.72 (n = 823)	7.40 ± 5.38 (n = 818)
		Month 18	0.48 ± 3.82 (n = 821)	9.20 ± 7.54 (n = 823)	9.12 ± 6.28 (n = 818)
Femur (proximal)	Baseline (g/m^2)		0.767 ± 0.098 (n = 820)	0.766 ± 0.090 (n = 822)	0.773 ± 0.094 (n = 818)
	Percent change (%)	Month 6	0.29 ± 2.11 (n = 820)	2.07 ± 2.55 (n = 822)	1.33 ± 2.38 (n = 818)
		Month 12	0.10 ± 2.45 (n = 820)	2.87 ± 3.06 (n = 822)	2.03 ± 2.92 (n = 818)
		Month 18	-0.08 ± 2.77 (n = 820)	3.44 ± 3.51 (n = 822)	2.81 ± 3.33 (n = 818)
Femur (neck)	Baseline (g/m^2)		0.732 ± 0.099 (n = 820)	0.730 ± 0.091 (n = 822)	0.737 ± 0.096 (n = 818)
	Percent change (%)	Month 6	-0.12 ± 2.84 (n = 820)	1.54 ± 3.07 (n = 82)	0.80 ± 2.90 (n = 818)
		Month 12	-0.37 ± 3.09 (n = 820)	2.21 ± 3.56 (n = 822)	1.41 ± 3.38 (n = 818)
		Month 18	-0.44 ± 3.57 (n = 820)	2.90 ± 4.21 (n = 822)	2.26 ± 3.57 (n = 818)

Mean ± SD (number of subjects evaluated), LOCF

Figure 5 shows changes over time from baseline in the percent change in bone metabolism markers at each observation time point.

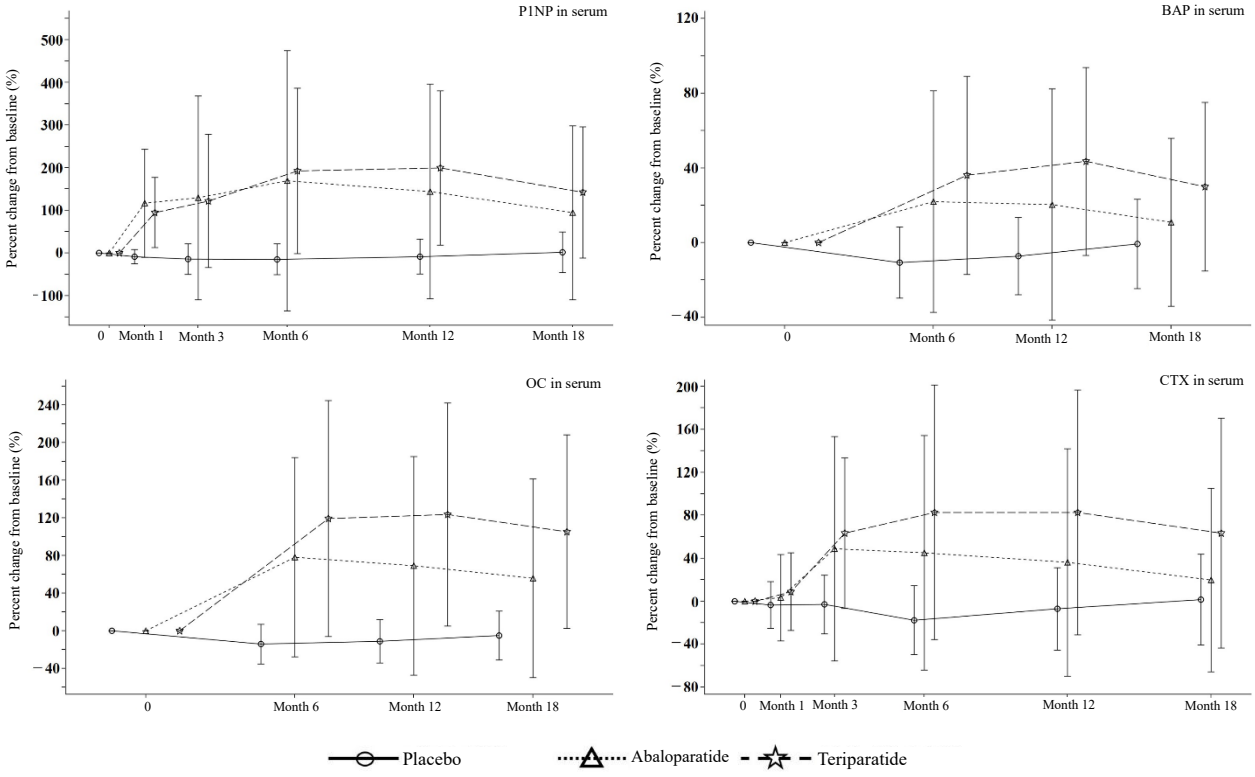

Figure 5. Percent change from baseline in bone metabolism markers at each observation time point (mean ± SD)
(Foreign Study 05-003, population for bone metabolism analysis[37])

Table 41 shows the incidence of adverse events reported by ≥5% of subjects in any treatment group and corresponding adverse drug reactions.

[37] Safety analysis population consisting of subjects with bone metabolism markers evaluated before the start of treatment and at least once after the start of treatment

Table 41. Incidence of adverse events reported by ≥5% of subjects in any treatment group and corresponding adverse drug reactions (Foreign Study 05-003, safety analysis population)

Event	Placebo (n = 820)		Abaloparatide (n = 822)		Teriparatide (n = 818)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	87.6 (718)	24.9 (204)	89.4 (735)	38.0 (312)	88.9 (727)	35.8 (293)
Hypercalciuria	9.0 (74)	6.7 (55)	11.3 (93)	9.9 (81)	12.5 (102)	9.5 (78)
Dizziness	6.1 (50)	2.2 (18)	10.0 (82)	6.3 (52)	7.3 (60)	4.9 (40)
Arthralgia	9.8 (80)	1.0 (8)	8.6 (71)	0.4 (3)	8.6 (70)	0.9 (7)
Back pain	10.0 (82)	0.1 (1)	8.5 (70)	1.0 (8)	7.2 (59)	0.6 (5)
Upper respiratory tract infection	7.7 (63)	0 (0)	8.3 (68)	0 (0)	8.9 (73)	0 (0)
Nausea	3.0 (25)	1.1 (9)	8.3 (68)	5.4 (44)	5.1 (42)	3.2 (26)
Headache	6.0 (49)	1.8 (15)	7.5 (62)	3.8 (31)	6.2 (51)	3.2 (26)
Hypertension	6.6 (54)	0.2 (2)	7.2 (59)	0.2 (2)	5.0 (41)	0.4 (3)
Influenza	4.8 (39)	0 (0)	6.3 (52)	0 (0)	4.2 (34)	0 (0)
Nasopharyngitis	8.0 (66)	0 (0)	5.8 (48)	0 (0)	6.5 (53)	0 (0)
Urinary tract infection	4.6 (38)	0.1 (1)	5.2 (43)	0.4 (3)	5.0 (41)	0.1 (1)
Palpitations	0.4 (3)	0.2 (2)	5.1 (42)	3.2 (26)	1.6 (13)	1.0 (8)
Pain in extremity	6.0 (49)	0.2 (2)	4.9 (40)	0.2 (2)	5.1 (42)	0.7 (6)
Constipation	5.1 (42)	1.0 (8)	4.5 (37)	1.0 (8)	4.2 (34)	0.6 (5)

Incidence in % (number of subjects with events), MedDRA/J ver.17.1

Death occurred in 11 subjects, including 5 subjects in the placebo group (sudden death, intestinal obstruction, aortic dissection, myocardial infarction, and gastrointestinal carcinoma in 1 subject each), 3 subjects in the abaloparatide group (sepsis, myocardial ischaemia, and bronchiectasis in 1 subject each), and 3 subjects in the teriparatide group (pancreatic carcinoma, general physical condition decreased, and cardio-respiratory arrest in 1 subject each). A causal relationship to the study drug was ruled out for all of them. Serious adverse events occurred in 11.0% (90 of 820) of subjects in the placebo group, 9.7% (80 of 822) of subjects in the abaloparatide group, and 10.0% (82 of 818) of subjects in the teriparatide group. Hypercalcaemia, drug eruption, and hypertension in 3 subjects in the teriparatide group were assessed to be adverse drug reactions. Adverse events leading to treatment discontinuation occurred in 6.0% (49 of 820) of subjects in the placebo group, 9.9% (81 of 822) of subjects in the abaloparatide group, and 6.7% (55 of 818) of subjects in the teriparatide group. Table 42 shows events considered to be adverse drug reactions.

Table 42. Adverse drug reactions leading to treatment discontinuation (Foreign Study 05-003, safety analysis population)

Treatment group	Incidence of adverse drug reactions leading to treatment discontinuation	Event
Placebo	2.9% (24/820)[a)]	Nausea/pain in extremity/headache, myocardial ischaemia, malaise, blood pressure decreased, malaise/electrocardiogram QT prolonged, dizziness, nocturia, nausea/abdominal pain, arthralgia, dyspepsia, hypoaesthesia, vertigo, nasal pruritus, dry mouth, headache/hyperhidrosis/constipation, malaise/arrhythmia, asthenia, hypertension, osteoarthritis, abdominal pain, eczema, palpitations/dizziness/insomnia, electrocardiogram QT prolonged, and urticaria in 1 subject each
Abaloparatide	6.3% (52/822)[a)]	Nausea in 7 subjects, headache in 4 subjects, palpitations and dizziness in 3 subjects each, myocardial ischaemia, electrocardiogram QT prolonged, rash pruritic, hypotension, asthenia, and nausea/dizziness in 2 subjects each, neck pain/hypertension/headache/flushing/palpitations/back pain/tachycardia, acute stress disorder/palpitations/dizziness, urticaria/dizziness, restlessness/dizziness/dysgeusia, bundle branch block right, malaise, nausea/restlessness, electrocardiogram QT prolonged/electrocardiogram ST segment depression/palpitations, nausea/visual impairment/dizziness, tachycardia, dermatitis atopic, back pain, abdominal discomfort, heart rate increased, abdominal pain upper, liver function test increased, post procedural discomfort, blood pressure increased, orthostatic hypotension, procedural hypotension, hypercalcaemia, headache/dizziness, and nausea/headache/fatigue in 1 subject each
Teriparatide	4.5% (37/818)[a)]	Dizziness in 5 subjects, hypercalcaemia in 4 subjects, nausea, asthenia, abdominal pain upper and pain in 2 subjects each, vomiting/post procedural discomfort, headache/dizziness, hypertension, allergic oedema/urticaria, drug eruption, dyspepsia, atrial fibrillation, drug intolerance, osteoporosis, blood pressure fluctuation, blood parathyroid hormone increased, blood alkaline phosphatase increased, nausea/vertigo/cervicobrachial syndrome, headache/spinal pain, headache, headache/feeling hot/dizziness, rash, eczema, electrocardiogram QT prolonged, and electrocardiogram PR shortened in 1 subject each

MedDRA/J ver.21.1, a) Incidence in % (number of subjects with events/number of subjects evaluated)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in patients with postmenopausal osteoporosis

The applicant's explanation:

Osteoporosis is internationally defined as "a skeletal disorder characterized by compromised bone strength that increases a risk of fracture." Also, regarding the diagnostic criteria for osteoporosis in Japan, "Guidelines on the management and treatment of primary osteoporosis (ver. 2012) [in Japanese]" (*Osteoporosis Japan.* 2013;21:9-21) was worked out for international consistency. Thus, there is no significant difference in the definition of osteoporosis between Japan and foreign countries. The objective of the treatment of osteoporosis is prevention of a fracture risk and maintenance and improvement of activity of daily living and QOL, which is a common understanding worldwide. Therapeutic agents for osteoporosis are largely classified into antiresorptive agents and osteogenesis promoters. Medications currently used in Japan and other countries are mainly antiresorptive agents, osteogenesis promoters, and calcium metabolism improving agents. Antiresorptive agents include bisphosphonates, female hormones, selective estrogen receptor modulators, calcitonin, ipriflavone, and anti-RANKL antibody, osteogenesis promoters include PTH and anti-sclerostin antibody, and active vitamin D_3 is available as a calcium metabolism improving agent. The situation does not significantly differ between Japan and other countries. Based on the above, the efficacy of abaloparatide was investigated mainly in Japanese Study 301 and Foreign Study 05-003 which were conducted mainly to confirm the activity to increase bone density and the activity to inhibit fracture, respectively.

The activity of abaloparatide to increase bone density was investigated first in dose-finding studies, Japanese Study 004 and Foreign Study 05-002. Abaloparatide was administered at 40 and 80 μg in Japanese Study 004, and at 20, 40 and 80 μg in Foreign Study 05-002. Figure 6 shows changes over time from baseline in the bone density of the lumbar spine (L1-L4) up to Week 48. In both studies, the percent change in the bone density of the lumbar spine (L1-L4) increased with the increase in the dose of abaloparatide, showing similar dose responses.

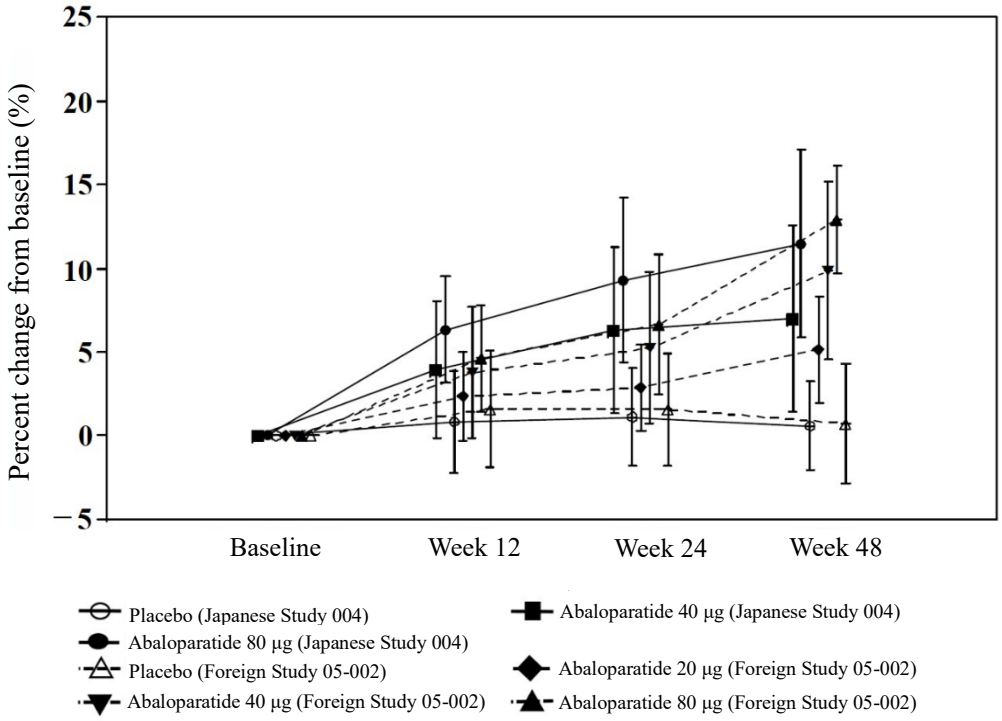

Figure 6. Percent change in the bone density of the lumbar spine (L1-L4) in Japanese Study 004 (FAS) and Foreign Study 05-002 (ITT, data at Week 48 are those of the population for extended period analysis) (mean ± SD)

Next, Japanese Study 301 was conducted using the percent change from baseline in bone density of the lumbar spine (L1-L4) at Month 18 as the primary endpoint. Results demonstrated the superiority of abaloparatide to placebo, as shown in Table 35. Bone density of the lumbar spine (L1-L4) was evaluated also in Foreign Study 05-003 investigating the fracture-preventing effect of abaloparatide. Therefore, similarity of results between Japanese Study 301 and Foreign Study 05-003 was investigated as described below.

For patients investigated in Japanese Study 301 and Foreign Study 05-003, inclusion criteria in Japanese Study 301 were patients who met the following criteria: (a) Bone density of the lumbar spine <80% of YAM and ≥1 fragility fracture of vertebral body, (b) bone density of the lumbar spine ≤70% of YAM or ≤−2.5SD and ≥65 years of age, or (c) bone density of the lumbar spine <65% of YAM. In Foreign Study 05-003, the following inclusion criteria were employed with consideration given to the primary endpoint of incidence of new spinal fracture: (a) Patients aged ≥50 years, a history of the lumbar spine or thoracic spine fracture or fragility fracture, and low bone density of the lumbar spine or femur (neck) (T score >−5.0 and ≤−2.5; >−5.0 and ≤−2.0 in patients aged ≥65 years) or (b) among

patients without lumbar spine or thoracic spine fracture and without a history of fragility fracture, patients aged ≥65 years with extremely low bone density of the lumbar spine or femur (neck) (T score >−5.0 and ≤−3.0). The risk of fracture when bone density decreases by approximately 1SD is similar between patients with and without existing fracture (*Journal of Clinical and Experimental Medicine.* 2005;212:139-42), and 80% in YAM roughly corresponds to T score of −1.7, 70% to T score of −2.6, and 65% to T score of −3.0 (*J Bone Miner Metab*. 1998;16:139-50). Thus, both Japanese Study 301 and Foreign Study 05-003 were conducted in patients with osteoporosis at high risk of fracture. A history of spinal fracture, advanced age, and low bone density are risk factors of fracture in men as well as women, and the incidence of spinal fracture adjusted for existing spinal fracture and bone density does not significantly differ between men and women (*J Bone Miner Res.* 2003;18:1547-53). Accordingly, Japanese Study 301 included male patients with primary osteoporosis in addition to patients with postmenopausal osteoporosis.

Table 43 shows the percent change from baseline in bone density of the lumbar spine (L1-L4) at Month 18 in the placebo group and the abaloparatide 80 μg group of Japanese Study 301 and Foreign Study 05-003. The percent change in bone density of the lumbar spine (L1-L4) in the abaloparatide 80 μg group tended to be greater in Japanese Study 301 than in Foreign Study 05-003.

Table 43. Comparison of the percent change from baseline in bone density of the lumbar spine (L1-L4) at Month 18

Study	Foreign Study 05-003 (ITT)		Japanese Study 301 (FAS)		Female subjects in Japanese Study 301 (FAS)	
Treatment group	Placebo (n = 821)	Abaloparatide 80 μg (n = 823)	Placebo (n = 70)	Abaloparatide 80 μg (n = 136)	Placebo (n = 64)	Abaloparatide 80 μg (n = 122)
Percent change in bone density of the lumbar spine (L1-L4) (%)	0.48 ± 3.82	9.20 ± 7.54	1.97 ± 3.85	14.65 ± 9.28	1.89 ± 3.87	14.16 ± 8.27
Between-group difference [95% CI]	8.72 [8.14, 9.30]		12.68 [10.39, 14.96]		12.27 [10.11, 14.43]	

Mean ± SD; The between-group difference is expressed in mean; LOCF

Table 44 shows the baseline characteristics of female subjects in Japanese Study 301 and subjects in Foreign Study 05-003, both separately for the placebo group and the abaloparatide group. The mean values of body weight, BMI, bone density of the lumbar spine (L1-L4), femur (proximal), and femur (neck), bone density T scores of the lumbar spine (L1-L4), femur (proximal), and femur (neck) tended to be smaller in Japanese Study 301 than in Foreign Study 05-003.

Table 44. Baseline characteristics of patients with postmenopausal osteoporosis in Japanese and foreign phase III studies

Subject characteristics		Female subjects in Japanese Study 301 (FAS)		Foreign Study 05-003 (ITT)	
		Placebo (n = 64)	Abaloparatide 80 μg (n = 122)	Placebo (n = 821)	Abaloparatide 80 μg (n = 824)
Age (years)		68.6 ± 5.2	68.2 ± 6.0	68.2 ± 6.5	68.9 ± 6.5
Height (cm)		152.9 ± 4.6	152.8 ± 6.1	156.0 ± 7.3	156.1 ± 7.2
Body weight (kg)		50.4 ± 5.7	50.7 ± 7.6	61.2 ± 10.2	61.1 ± 10.0
BMI (kg/m^2)		21.5 ± 2.4	21.7 ± 3.1	25.1 ± 3.6	25.0 ± 3.5
Bone density (g/m^2)	Lumbar spine (L1-L4)	0.646 ± 0.067	0.642 ± 0.072	0.823 ± 0.100	0.829 ± 0.109[a)]
	Femur (proximal)	0.655 ± 0.074	0.655 ± 0.083	0.767 ± 0.098[b)]	0.766 ± 0.090[c)]
	Femur (neck)	0.527 ± 0.056	0.525 ± 0.072	0.732 ± 0.099[b)]	0.730 ± 0.091 [c)]
T score of bone density of the lumbar spine (L1-L4)		-3.64 ± 0.61	-3.68 ± 0.66	-2.92 ± 0.82	-2.87 ± 0.89[a)]
T score of bone density of femur (proximal)		-2.32 ± 0.60	-2.36 ± 0.67	-1.89 ± 0.78[b)]	-1.89 ± 0.72[c)]
T score of bone density of femur (neck)		-2.87 ± 0.52	-2.90 ± 0.64	-2.15 ± 0.68[b)]	-2.16 ± 0.63[c)]
Number of existing spinal fractures	0	78.1 (50)	56.6 (69)	77.0 (632)	78.5 (647)
	1	17.2 (11)	32.0 (39)	14.7 (121)	16.3 (134)
	≥2	4.7 (3)	11.5 (14)	8.2 (67)	5.2 (43)

Mean ± SD; Existing spinal fractures are expressed in percentage of subjects (number of subjects with events)
a) n = 823, b) n = 820, c) n = 822

The effect of the baseline characteristics of subjects on the percent change in the bone density of the lumbar spine (L1-L4) of the 2 studies was compared, separately for each subject characteristic. The percent change tended to be higher in Japanese Study 301 than in Foreign Study 05-003 in all subpopulations tested (Table 45). In the population with higher-than-median body weight or bone density of femur (neck), the percent change in the bone density of the lumbar spine (L1-L4) was lower in Japanese Study 301 than in Foreign Study 05-003, but only a limited number of Japanese subjects were included in this comparison. Comparison among subpopulations showed that the percent change in bone density of the lumbar spine (L1-L4) tended to be higher in the subpopulation with less-than-median baseline parameter value, for all characteristics tested in both in Japanese and foreign studies. In contrast, the percent change in bone density of the lumbar spine (L1-L4) was similar regardless of the presence/absence or number of existing spinal fractures, both in Japanese and foreign studies.

Table 45. Percent change (%) from baseline in bone density of the lumbar spine (L1-L4) at Month 18 in patients with postmenopausal osteoporosis in Japanese and foreign phase III studies, by subject characteristics

Subject characteristics [a)]		Female patients in Japanese Study 301 (FAS)		Foreign Study 05-003 (ITT)	
		Placebo	Abaloparatide 80 μg	Placebo	Abaloparatide 80 μg
All		1.89 ± 3.87 (n = 64)	14.16 ± 8.27 (n = 122)	0.48 ± 3.82 (n = 821)	9.20 ± 7.54 (n = 823)
Body weight (kg)	<60.8	2.05 ± 3.83 (n = 62)	14.99 ± 8.19 (n = 109)	0.19 ± 3.73 (n = 407)	9.48 ± 7.98 (n = 409)
	≥60.8	-3.6, -2.3 (n = 2)	7.26 ± 5.35 (n = 13)	0.77 ± 3.89 (n = 414)	8.93 ± 7.07 (n = 414)
BMI (kg/m^2)	<24.8	1.98 ± 3.88 (n = 59)	15.09 ± 8.55 (n = 103)	0.06 ± 3.69 (n = 405)	10.03 ± 7.86 (n = 406)
	≥24.8	0.95 ± 4.06 (n = 5)	9.13 ± 3.82 (n = 19)	0.90 ± 3.91 (n = 416)	8.40 ± 7.13 (n = 417)
Number of existing spinal fractures	0	1.47 ± 3.70 (n = 50)	14.40 ± 8.64 (n = 69)	0.41 ± 3.79 (n = 632)	9.25 ± 7.51 (n = 647)
	1	4.39 ± 4.02 (n = 11)	13.20 ± 6.29 (n = 39)	0.59 ± 3.86 (n = 121)	9.06 ± 7.44 (n = 134)
	≥2	-0.18 ± 3.19 (n = 3)	15.66 ± 11.19 (n = 14)	1.04 ± 4.05 (n = 67)	8.86 ± 8.38 (n = 42)
T score of bone density of the lumbar spine (L1-L4)	<−3.0	1.73 ± 3.78 (n = 57)	14.76 ± 8.69 (n = 102)	0.69 ± 4.08 (n = 374)	9.80 ± 8.29 (n = 376)
	≥−3.0	3.25 ± 4.68 (n = 7)	11.14 ± 4.80 (n = 20)	0.31 ± 3.58 (n = 447)	8.70 ± 6.80 (n = 447)
Bone density of the lumbar spine (L1-L4)	<0.817	1.80 ± 3.83 (n = 63)	14.16 ± 8.27 (n = 122)	0.62 ± 4.03 (n = 412)	9.73 ± 8.18 (n = 408)
	≥0.817	7.57 (n = 1)	-	0.35 ± 3.60 (n = 409)	8.68 ± 6.81 (n = 415)
Bone density of femur (proximal)	<0.764	1.73 ± 3.65 (n = 60)	14.55 ± 8.51 (n = 111)	0.43 ± 3.86 (n = 419)	9.65 ± 7.73 (n = 401)
	≥0.764	4.34 ± 6.61 (n = 4)	10.26 ± 3.73 (n = 11)	0.53 ± 3.78 (n = 401)	8.78 ± 7.33 (n = 422)
Bone density of femur (neck)	<0.731	1.89 ± 3.87 (n = 64)	14.22 ± 8.29 (n = 121)	0.19 ± 3.80 (n = 416)	9.48 ± 7.69 (n = 403)
	≥0.731	-	7.58 (n = 1)	0.79 ± 3.82 (n = 404)	8.96 ± 7.38 (n = 419)

Mean ± SD (number of subjects evaluated); -, Not applicable; LOCF

a) The median values of baseline characteristics of subjects in Foreign Study 05-003 were used as cut-off values.

The relationship between the percent change in bone density of the lumbar spine (L1-L4) and the baseline bone density of the lumbar spine (L1-L4) in Japanese and foreign phase III studies was further investigated as follows. In Japanese Study 301 (female subjects) and Foreign Study 05-003, the baseline value (mean ± SD) of the bone density of the lumbar spine (L1-L4) in the abaloparatide 80 μg group and the placebo group was 0.642 ± 0.072 and 0.646 ± 0.067 g/cm^2, respectively, in Japanese Study 301 and 0.829 ± 0.109 and 0.823 ± 0.010 g/cm^2, respectively, in Foreign Study 05-003, showing that the baseline bone density of the lumbar spine (L1-L4) was lower in subjects in Japanese Study 301 than in subjects in Foreign Study 05-003. The percent change (mean ± SD) from baseline in bone density of the lumbar spine (L1-L4) at Month 18 in the abaloparatide 80 μg group was 14.16% ± 8.27% in Japanese Study 301 (female patients) and 9.20% ± 7.54% in Foreign Study 05-003, showing the tendency that the lower the baseline bone density of the lumbar spine (L1-L4), the higher the percent change in bone density of the lumbar spine (L1-L4). On the other hand, the amount of the change from baseline in bone density of the lumbar spine (L1-L4) at Month 18 was similar between Japanese and foreign studies, i.e., 0.090 ± 0.050 g/cm^2 in Japanese Study 301 (female patients) and 0.075 ± 0.061 g/cm^2 in Foreign Study 05-003.

The above results suggest that the lower baseline values in Japanese Study 301 contributed to the apparently higher percent change from baseline in bone density of the lumbar spine (L1-L4) in Japanese Study 301 than in Foreign Study 05-003. Also given the absolute amount of change from baseline in bone density of the lumbar spine (L1-L4), the efficacy of abaloparatide is likely to be similar between Japanese and non-Japanese patients.

As for the fracture-preventing effect, Japanese Study 301 had not included the plan to test the hypothesis of the fracture-preventing effect as the primary analysis. However, the percentage of subjects who experienced new spinal fracture before study completion was 4.3% (3 of 70 of subjects) in the placebo group and 0% (0 of 136 of subjects) in the abaloparatide group, with the between-group difference (abaloparatide group − placebo group) [95% CI] of the cumulative incidence of new spinal fractures being −4.3% [−11.86, −0.35]%. The percentage of subjects who experienced new non-spinal fracture before the study completion was 2.9% (2 of 70 of subjects) in the placebo group and 2.2% (3 of 136 of subjects) in the abaloparatide group, with the between-group difference (abaloparatide group − placebo group) [95% CI] of the rate of cumulative incidence of new non-spinal fractures being −0.7% [−7.78, 3.92]%. Foreign Study 05-003 was conducted with the main objective of confirming the fracture-preventing effect of abaloparatide. Table 38 shows the results of the incidence of new spinal fracture, the primary endpoint. The rate of fracture within Month 18 was 4.22% (30 of 711) of subjects in the placebo group and 0.58% (4 of 690) of subjects in the abaloparatide group, showing a significantly lower rate in the abaloparatide group than in the placebo group, thereby confirming the fracture-preventing effect of abaloparatide. Table 39 shows the incidence of all non-spinal fractures, which was 4.0% (33 of 821) of subjects in the placebo group and 2.2% (18 of 824) of subjects in the abaloparatide group, with the hazard ratio [95% CI] to the placebo group being 0.57 [0.32, 1.00].

As for the effect on bone metabolism markers (P1NP, BAP, OC, and CTX) in Japanese Study 301 and Foreign Study 05-003, their values showed little difference in the placebo group between before and after treatment in both studies, and a similar trend was observed in the abaloparatide group as well (Figures 4 and 5).

The above results demonstrate the effect of abaloparatide to increase bone density, suggesting that abaloparatide is effective in preventing fracture in Japanese patients as is the case with non-Japanese patients confirmed in Foreign Study 05-003.

Regarding the comparison with conventional PTH drugs, in Foreign Study 05-003 conducted using teriparatide as the active control, the percent change from baseline in bone density of the lumbar spine (L1-L4) was similar between the abaloparatide group and the teriparatide group at Month 18, whereas, at Months 6 and 12, the extent of the increase tended to be greater in the abaloparatide group than in the teriparatide group. The percent change in bone density of femur (proximal) and femur (neck) tended to be greater in the abaloparatide group than in the teriparatide group at all time points of measurement (Table 40). As for the fracture-preventing effect, the incidence of new spinal fracture within Month 18 was 4.22% (30 of 711) of subjects in the placebo group, 0.58% (4 of 690) of subjects in the abaloparatide group, and 0.84% (6 of 717) of subjects in the teriparatide group, with the rate being significantly lower in the abaloparatide group and in the teriparatide group than in the placebo

group. The decrease in the relative risk [95% CI] was −0.86 [−0.95, −0.61] in the abaloparatide group and −0.80 [−0.92, −0.53] in the teriparatide group (Table 38). The incidence of non-spinal fracture at Month 19 estimated by the Kaplan-Meier method was 4.7% in the placebo group, 2.7% in the abaloparatide group and, and 3.3% in the teriparatide group.

PMDA's view:
The effect of abaloparatide to increase bone density in patients with postmenopausal osteoporosis was investigated in Japanese Study 301, which demonstrated the superiority of abaloparatide to placebo in the percent change in bone density of the lumbar spine (L1-L4), the primary endpoint. Foreign Study 05-003 also demonstrated increased bone density compared with the placebo group, and that abaloparatide is equally or more effective than teriparatide in increasing bone density. As for the fracture-preventing effect, Foreign Study 05-003 demonstrated the superiority of abaloparatide to placebo in the incidence of new spinal fracture within 18 months from baseline, the primary endpoint. Regarding the comparison between Japanese and foreign clinical studies, although the percent change in bone density of the lumbar spine (L1-L4) tended to be greater in Japanese Study 301 than in Foreign Study 05-003, no significant difference was observed in the amount of the change, suggesting that the lower baseline bone density in patients enrolled in Japanese Study 301 than that in patients in Foreign Study 05-003 may possibly have caused the apparent difference in the percent change. Although the pharmacokinetics of abaloparatide may possibly differ between Japanese and non-Japanese subjects [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese subjects"], changes over time in bone metabolism markers showed similar tendencies between Japanese Study 301 and Foreign Study 05-003. Also, both in Japanese and foreign phase II studies (Japanese Study 004 and Foreign Study 05-002), the dose-response relationship was observed in the percent change from baseline in the bone density of the lumbar spine over the dose range of abaloparatide of up to 80 μg. Furthermore, the incidence of new spinal fracture observed in Japanese Study 301 was not inconsistent with the result observed in Foreign Study 05-003.

The above results, together with the results of comparison with conventional PTH drug, demonstrate the fracture-preventing effect of abaloparatide in patients with postmenopausal osteoporosis, suggesting the efficacy in Japanese patients with postmenopausal osteoporosis as well.

7.R.1.2 Efficacy in male patients with osteoporosis

The applicant's explanation:
For the efficacy in male patients with osteoporosis, Table 46 shows the percent change in bone density from baseline in Japanese Study 301, separately for male and female patients. In the abaloparatide group, bone density increased in all sites evaluated in male patients, showing no tendency of difference from the increase observed in female patients. Also, the change over time in body metabolism markers (P1NP and CTX) did not show any tendency of difference between male and female patients (Figure 7).

Table 46. Percent change (%) from baseline in bone density at the final evaluation time point (Month 18) in men and women (Japanese Study 301, FAS)

Evaluation site	Men		Women	
	Placebo (n = 6)	Abaloparatide (n = 14)	Placebo (n = 64)	Abaloparatide (n = 122)
Lumbar spine (L1-L4)	2.78 ± 3.88	18.86 ± 15.35	1.89 ± 3.87	14.16 ± 8.27
Femur (proximal)	0.49 ± 1.53	5.39 ± 3.23	-0.28 ± 3.06	3.89 ± 3.66
Femur (neck)	0.61 ± 1.27	6.07 ± 5.29	0.13 ± 4.42	4.26 ± 4.82

Mean ± SD

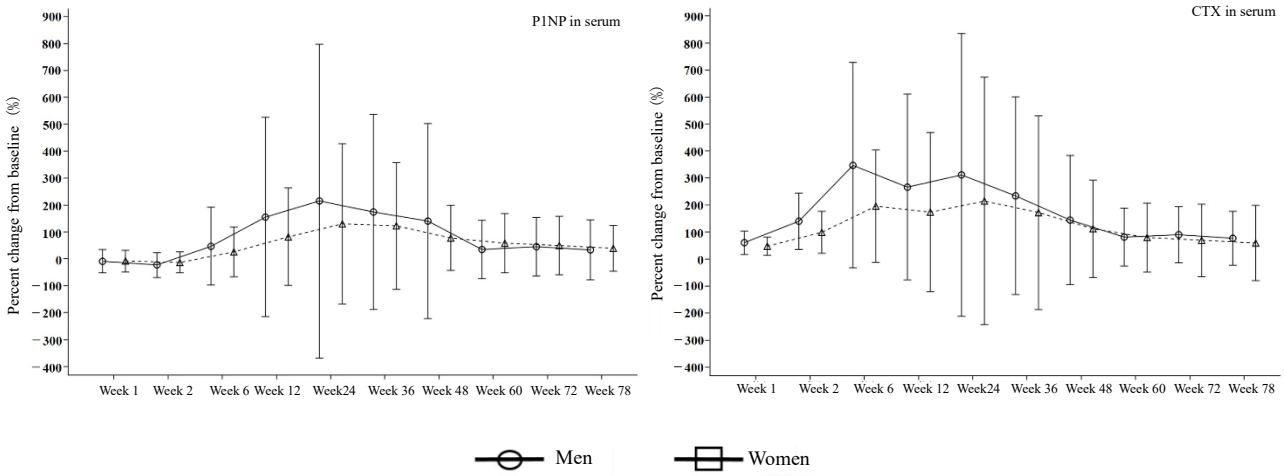

Figure 7. Percent change from baseline in bone metabolism markers at each observation time point, by sex (Japanese Study 301, FAS)

The above results show that the activity to increase bone density and the changes over time in bone metabolism markers in male patients with osteoporosis are similar to those observed in patients with postmenopausal osteoporosis, suggesting that abaloparatide is effective in preventing bone fracture in male patients with osteoporosis as well.

PMDA's view:
A comparison of the percent change in bone density in male patients with osteoporosis and in patients with postmenopausal osteoporosis in Japanese Study 301 showed that the percent change increased in the abaloparatide group compared to the placebo group in both patient populations, and that there was no tendency of any significant difference in the extent of the increase between the 2 populations. Based on these results, abaloparatide is expected to be effective in male patients with osteoporosis as well.

7.R.2 Safety

The applicant's explanation:
In Japanese Study 004, the incidences of adverse events and adverse drug reactions were higher in the abaloparatide group than in the placebo group, but there was no tendency of a dose-dependent increase in the incidence (Table 47). Serious adverse events were observed in 2 subjects in the abaloparatide 40 μg group, but their causal relationship to the study drug was ruled out. In Japanese Study 301, the incidence of adverse events did not significantly differ between groups, whereas the incidence of adverse drug reactions was higher in the abaloparatide group than in the placebo group. The main adverse drug reactions with a higher incidence in the abaloparatide group than in the placebo group were palpitations (0% [0 of 72] of subjects in the placebo group, 5.0% [7 of 140] of subjects in the

abaloparatide group), nausea (1.4% [1 of 72] of subjects in the placebo group, 5.7% [8 of 140] of subjects in the abaloparatide group), and blood calcium increased (1.4% [1 of 72] of subjects in the placebo group, 4.3% [6 of 140] of subjects in the abaloparatide group).

Table 47. Incidence of adverse events in Japanese clinical studies (safety analysis population)

Event		Japanese Study 004 (Week 52)			Japanese Study 301	
		Placebo (n = 53)	Abaloparatide 40 μg (n = 54)	Abaloparatide 80 μg (n = 53)	Placebo (n = 72)	Abaloparatide 80 μg (n = 140)
All adverse events		75.5 (40)	90.7 (49)	81.1 (43)	80.6 (58)	91.4 (128)
All adverse drug reactions		5.7 (3)	14.8 (8)	17.0 (9)	13.9 (10)	32.1 (45)
Death		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events		0 (0)	3.7 (2)	0 (0)	13.9 (10)	5.0 (7)
Adverse events leading to treatment discontinuation		0 (0)	7.4 (4)	0 (0)	5.6 (4)	2.9 (4)
Severity	Mild	15.1 (8)	14.8 (9)	17.0 (9)	9.7 (7)	14.3 (20)
	Moderate	60.4 (32)	70.4 (38)	64.2 (34)	68.1 (49)	77.1 (108)
	Severe	0 (0)	5.6 (3)	0 (0)	2.8 (2)	0 (0)

Incidence in % (number of subjects with events)

Table 48 shows the incidence of adverse events in foreign studies. In Foreign Study 05-002, the incidence of adverse events up to Week 28[38)] was not significantly different among treatment groups. The incidence of adverse drug reactions was higher in the abaloparatide 40 and 80 μg groups than in the placebo, abaloparatide 20 μg, and teriparatide groups. None of the adverse events and adverse drug reactions showed a dose-dependent increase in the incidence. Of adverse drug reactions observed within 28 weeks, those that occurred at a higher frequency in the abaloparatide 80 μg group than in the placebo group included headache (2.2% [1 of 45] of subjects in the placebo group, 11.1% [5 of 45] in the abaloparatide 80 μg group) and dizziness (2.2% [1 of 45] of subjects in the placebo group, 8.9% [4 of 45] of subjects in the abaloparatide 80 μg group). Serious adverse events were observed in 1 subject in the placebo group (bronchitis), in 1 subject in the abaloparatide 20 μg group (serious cystadenocarcinoma ovary/ascites), and in 1 subject in the abaloparatide 80 μg group (diverticulitis). A causal relationship to the study drug was ruled out for all of them. No significant difference was observed in the incidence of adverse events or adverse drug reactions observed among treatment groups of the population for extended period analysis for 52 weeks (48-week treatment period and 4-week follow-up period) (Table 48). In Foreign Study 05-003, the incidence of adverse events was not significantly different among treatment groups, whereas the incidence of adverse drug reactions in the abaloparatide group was higher than that in the placebo group, but not different to that in the teriparatide group (Table 48). Adverse drug reactions with a higher incidence in the abaloparatide group than in the placebo group were hypercalciuria (6.7% [55 of 820] of subjects in the placebo group, 9.9% [81 of 822] of subjects in the abaloparatide group, 9.5% [78 of 818] of subjects in the teriparatide group), dizziness (2.2% [18 of 820] of subjects in the placebo group, 6.3% [52 of 822] of subjects in the abaloparatide group, 4.9% [40 of 818] of subjects in the teriparatide group), nausea (1.1% [9 of 820] of subjects in the placebo group, 5.4% [44 of 822] of subjects in the abaloparatide group, 3.2% [26 of 818] of subjects in the teriparatide group), headache (1.8% [15 of 820] of subjects in the placebo group, 3.8% [31 of 822] of subjects in the abaloparatide group, 3.2% [26 of 818] of subjects in the teriparatide group), palpitations (0.2% [2 of 820] of subjects the placebo group, 3.2% [26 of 822] of subjects in the abaloparatide group, 1.0% [8 of 818] of subjects in the teriparatide

38) 24-week treatment period and 4-week follow-up period. Up to Week 24 in subjects who participated in the extended period.

group), and back pain (0.1% [1 of 820] of subjects in the placebo group, 1.0% [8 of 822] of subjects in the abaloparatide group, 0.6% [5 of 818] of subjects in the teriparatide group).

Table 48. Incidence of adverse events in foreign clinical studies (safety analysis population)

Event		Foreign Study 05-002 (28 weeks)[a]					Foreign Study 05-003		
		Placebo (n = 45)	Abaloparatide 20 μg (n = 43)	Abaloparatide 40 μg (n = 43)	Abaloparatide 80 μg (n = 45)	Teriparatide (n = 45)	Placebo (n = 820)	Abaloparatide 80 μg (n = 822)	Teriparatide (n = 818)
All adverse events		73.3 (33)	72.1 (31)	76.7 (33)	77.8 (35)	77.8 (35)	87.6 (718)	89.4 (735)	88.9 (727)
All adverse drug reactions		26.7 (12)	20.9 (9)	34.9 (15)	37.8 (17)	28.9 (13)	24.9 (204)	38.0 (312)	35.8 (293)
Death		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.6 (5)	0.4 (3)	0.4 (3)
Serious adverse events		2.2 (1)	2.3 (1)	0 (0)	2.2 (1)	0 (0)	11.0 (90)	9.7 (80)	10.0 (82)
Adverse events leading to treatment discontinuation		0 (0)	2.3 (1)	2.3 (1)	4.4 (2)	4.4 (2)	6.0 (49)	9.9 (81)	6.7 (55)
Severity	Mild	40.0 (18)	48.8 (21)	37.2 (16)	37.8 (17)	44.4 (20)	40.1 (329)	42.5 (349)	42.4 (347)
	Moderate	31.1 (14)	18.6 (8)	37.2 (16)	35.6 (16)	31.1 (14)	40.1 (329)	40.4 (332)	40.3 (330)
	Severe	2.2 (1)	4.7 (2)	2.3 (1)	4.4 (2)	2.2 (1)	7.3 (60)	6.6 (54)	6.1 (50)
		Foreign Study 05-002 (52 weeks)[b]							
		Placebo (n = 11)	Abaloparatide 20 μg (n = 13)	Abaloparatide 40 μg (n = 10)	Abaloparatide 80 μg (n = 7)	Teriparatide (n = 14)			
All adverse events		90.9 (10)	84.6 (11)	70.0 (7)	85.7 (6)	78.6 (11)			
All adverse drug reactions		36.4 (4)	30.8 (4)	30.0 (3)	28.6 (2)	21.4 (3)			
Death		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Serious adverse events		0 (0)	0 (0)	0 (0)	14.3 (1)	0 (0)			
Adverse events leading to treatment discontinuation		0 (0)	0 (0)	10.0 (1)	14.3 (1)	0 (0)			
Severity	Mild	63.6 (7)	76.9 (10)	40.0 (4)	42.9 (3)	57.1 (8)			
	Moderate	18.2 (2)	7.7 (1)	30.0 (3)	42.9 (3)	14.3 (2)			
	Severe	9.1 (1)	0 (0)	0 (0)	0 (0)	7.1 (1)			

Incidence in % (number of subjects with events)
a) 24-week treatment period and 4-week follow-up period. Up to Week 24 in patients who participated in the extended period.
b) 48-week treatment period and 4-week follow-up period.

As for the incidences of adverse events by the time to onset, the pooled analysis of Japanese studies (pooled analysis of the placebo group and the abaloparatide 80 μg group in Japanese Study 004, and Japanese Study 301) showed that the incidence of adverse events and adverse drug reactions was the highest during the period up to Week 12 in all treatment groups and that the incidence did not increase in later periods (Table 49). As for the incidences of adverse events during the early treatment period (up to Day 14), the main adverse events with a higher incidence in the abaloparatide group than in the placebo group were palpitations (1.4% [1 of 72] of subjects in the placebo group, 3.6% [5 of 140] of subjects in the abaloparatide group) and headache (0% [0 of 72] of subjects in the placebo group, 3.6% [5 of 140] of subjects in the abaloparatide group). An adverse event leading to treatment discontinuation was nausea in 1 subject during the early stage of the treatment, but it resolved without intervening treatment. During the early stage of the treatment, neither serious nor severe adverse events were observed.

Table 49. Incidence of adverse events by the time to onset (pooled analysis of Japanese studies, safety analysis population)

Event	Evaluation period	Placebo (n = 125)	Abaloparatide (n = 193)
All adverse events	Week 0-12	52.0 (65)	65.8 (127)
	Week 12-24	11.2 (14)	9.8 (19)
	Week 24-36	6.4 (8)	5.7 (11)
	Week 36-48	5.6 (7)	4.1 (8)
	Week 48-60	2.4 (3)	1.6 (3)
	Week 60-72	0.8 (1)	1.0 (2)
	Week 72-	0 (0)	0.5 (1)
All adverse drug reactions	Week 0-12	5.6 (7)	20.2 (39)
	Week 12-24	1.6 (2)	3.1 (6)
	Week 24-36	2.4 (3)	2.6 (5)
	Week 36-48	0.8 (1)	1.0 (2)
	Week 48-60	0 (0)	0.5 (1)
	Week 60-72	0 (0)	0.5 (1)
	Week 72-	0 (0)	0 (0)

Incidence in % (number of subjects with events)

In the pooled analysis of foreign studies (pooled analysis of the placebo group, the abaloparatide 80 μg group, and the teriparatide group in Foreign Study 05-002, the abaloparatide group in Foreign Study 05-007,[39)] and Foreign Study 05-003), the incidence of adverse events was the highest during the period up to Week 12, and the incidence did not increase in later periods (Table 50). In Foreign Study 05-003, adverse events with a higher incidence during the early stage of treatment (up to Day 14) in the abaloparatide group than in the placebo and teriparatide groups were dizziness (2.3% [19 of 820] of subjects in the placebo group, 5.7% [47 of 822] of subjects in the abaloparatide group, 3.4% [28 of 818] of subjects in the teriparatide group), headache (2.0% [16 of 820] of subjects in the placebo group, 4.5% [37 of 822] of subjects in the abaloparatide group, 2.7% [22 of 818] of subjects in the teriparatide group), and palpitations (0.1% [1 of 820] of subjects in the placebo group, 2.3% [19 of 822] of subjects in the abaloparatide group, 0.6% [5 of 818] of subjects in the teriparatide group). The incidence of nausea (1.1% [9 of 820] of subjects in the placebo group, 3.8% [31 of 822] of subjects in the abaloparatide group, 2.7% [22 of 818] of subjects in the teriparatide group) was higher in the abaloparatide group than in the placebo group, but it did not significantly differ between the abaloparatide and teriparatide groups.

[39)] A placebo-controlled, double-blind study in non-Japanese patients with postmenopausal osteoporosis conducted to investigate the efficacy and safety of subcutaneous administration of abaloparatide 80 μg (open-label, reference group) and dermal application of abaloparatide patch (50, 100, or 150 μg, or placebo), once daily for 6 months

Table 50. Incidence of adverse events by the time to onset (pooled analysis of foreign studies, safety analysis population)

Event	Evaluation period	Placebo (n = 865)	Abaloparatide (n = 918)	Teriparatide (n = 863)
All adverse events	Week 0-12	54.2 (469)	62.6 (575)	57.4 (495)
	Week 12-24	12.3 (106)	10.7 (98)	12.2 (105)
	Week 24-36	8.8 (76)	5.2 (48)	8.2 (71)
	Week 36-48	4.4 (38)	5.0 (46)	4.8 (41)
	Week 48-60	3.5 (30)	2.5 (23)	3.0 (26)
	Week 60-72	1.2 (10)	1.6 (15)	1.4 (12)
	Week 72-	2.5 (22)	1.2 (11)	1.6 (14)
All adverse drug reactions	Week 0-12	14.3 (124)	27.5 (252)	22.1 (191)
	Week 12-24	3.2 (28)	3.9 (36)	4.8 (41)
	Week 24-36	2.3 (20)	2.3 (21)	3.9 (34)
	Week 36-48	1.6 (14)	2.4 (22)	2.3 (20)
	Week 48-60	1.7 (15)	1.1 (10)	1.0 (9)
	Week 60-72	0.2 (2)	0 (0)	0.2 (2)
	Week 72-	1.2 (10)	1.0 (9)	1.0 (9)

Incidence in % (number of subjects with events)

Thus, the incidences of palpitations, headache, nausea, and dizziness during the early stage of treatment tended to be slightly higher in the abaloparatide group than in other groups, while there was no tendency of occurrence of serious adverse events, adverse events leading to treatment discontinuation, or severe adverse events at higher incidences during the early treatment period in all of the treatment groups. As for the safety in the long-term administration, the incidence of adverse events was the highest during the period up to Week 12 and tended to decrease toward the later periods.

Table 51 shows the incidence of adverse events by sex in Japanese Study 301. The safety in male patients with osteoporosis was difficult to evaluate because of the limited number of the subjects, but the incidence of adverse events did not significantly differ between male and female subjects.

Table 51. Incidence of adverse events reported by ≥5% of subjects in any group of the entire population, by sex (Japanese Study 301, safety analysis population)

Event	Placebo (n = 72)		Abaloparatide (n = 140)	
	Women (n = 66)	Men (n = 6)	Women (n = 126)	Men (n = 14)
All events	78.8 (52)	6 (100)	91.3 (115)	92.9 (13)
Nasopharyngitis	47.0 (31)	83.3 (5)	59.5 (75)	42.9 (6)
Headache	12.1 (8)	0 (0)	14.3 (18)	7.1 (1)
Contusion	6.1 (4)	0 (0)	8.7 (11)	0 (0)
Injection site bruising	10.6 (7)	0 (0)	7.9 (10)	7.1 (1)
Nausea	9.1 (6)	0 (0)	6.3 (8)	7.1 (1)
Abdominal discomfort	4.5 (3)	0 (0)	6.3 (8)	7.1 (1)
Back pain	9.1 (6)	0 (0)	5.6 (7)	0 (0)
Eczema	6.1 (4)	0 (0)	5.6 (7)	0 (0)
Osteoarthritis	4.5 (3)	0 (0)	5.6 (7)	0 (0)
Palpitations	1.5 (1)	0 (0)	5.6 (7)	0 (0)
Blood uric acid increased	0 (0)	0 (0)	4.8 (6)	14.3 (2)
Dizziness	4.5 (3)	0 (0)	4.8 (6)	7.1 (1)
Vertigo	3.0 (2)	0 (0)	4.8 (6)	7.1 (1)
Blood calcium increased	1.5 (1)	0 (0)	4.8 (6)	7.1 (1)
Cataract	4.5 (3)	33.3 (2)	0 (0)	0 (0)

Incidence in % (number of subjects with events), MedDRA/J ver.21.1

PMDA's view:

Investigation of the incidence of adverse events in Japanese and foreign clinical studies showed that adverse events with a higher incidence in the abaloparatide group than in the placebo group were mostly observed with conventional PTH drugs and that the incidences of serious adverse events and adverse events leading to treatment discontinuation in the abaloparatide group were not significantly different from those in the placebo group or the teriparatide group. Taking account of the mechanism of action of abaloparatide, results of the Japanese and foreign clinical studies, and the following reviews on the individual noteworthy adverse events associated with abaloparatide, the safety of abaloparatide is acceptable provided that safety precautions are taken appropriately based on the following reviews. It was confirmed that there is no particular safety concern in male patients with osteoporosis compared with patients with postmenopausal osteoporosis.

7.R.2.1 Cardiovascular events

The applicant's explanation:

In the pooled analysis of Japanese studies, the incident of cardiovascular-related adverse events[40)] was 7.2% (9 of 125) of subjects in the placebo group and 14.0% (27 of 193) of subjects in the abaloparatide group, being higher in the abaloparatide group than in the placebo group. This difference was mainly due to the difference in the incidences of palpitations (1.6% [2 of 125] of subjects in the placebo group, 4.1% [8 of 193] of subjects in the abaloparatide group) and supraventricular extrasystoles (0.8% [1 of 125] of subjects in the placebo group, 2.1% [4 of 193] of subjects in the abaloparatide group). A serious cardiovascular event was observed in 1 subject in the abaloparatide group (subdural haematoma) but not in the placebo group. A cardiovascular-related adverse event leading to treatment discontinuation was observed in 1 subject in the abaloparatide group (palpitations) but not in the placebo group.

In the pooled analysis of foreign studies, the incidence of cardiovascular-related adverse events was 13.4% (116 of 865) of subjects in the placebo group, 17.4% (160 of 918) of subjects in the abaloparatide group, and 12.6% (109 of 863) of subjects in the teriparatide group, being higher in the abaloparatide group than in the placebo and teriparatide groups. This difference was mainly due to the difference in the incidence of palpitations (0.3% [3 of 865] of subjects in the placebo group, 5.2% [48 of 918] of subjects in the abaloparatide group, 1.6% [14 of 863] of subjects in the teriparatide group). Serious cardiovascular-related adverse events occurred in 2.0% (17 of 865) of subjects in the placebo group, 2.0% (18 of 918) of subjects in the abaloparatide group, and 1.6% (14 of 863) of subjects in the teriparatide group. Events reported by ≥2 subjects in the abaloparatide group were myocardial ischaemia, supraventricular tachycardia, and transient ischaemic attack in 2 subjects each. The incidence of cardiovascular-related adverse events leading to treatment discontinuation were 0.8% (7 of 865) of subjects in the placebo group, 2.3% (21 of 918) of subjects in the abaloparatide group, and 0.8% (7 of 863) of subjects in the teriparatide group. Events reported by ≥2 subjects in the

[40)] Events coded to terms in the following MedDRA:
MedDRA Standardised MedDRA queries (SMQ): Ischaemic heart disease (SMQ) broad, Cardiac arrhythmias (SMQ) broad, Cardiac failure (SMQ) broad, Cardiomyopathy (SMQ) broad, Embolic and thrombotic events (SMQ) broad, Ischaemic central nervous system vascular conditions (SMQ) narrow, Pulmonary hypertension (SMQ) broad, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ) narrow, Haemorrhagic central nervous system vascular conditions (SMQ) narrow
MedDRA Preferred terms (PT): Aortic aneurysm, Aortic valve stenosis, Arteriosclerosis, Arteritis coronary, Carotid bruit, Coronary artery aneurysm, Coronary artery dilatation, Coronary artery perforation, Electrocardiogram QT interval abnormal, Electrocardiogram ST-T change, Femoral artery aneurysm, Ischaemia, Peripheral artery aneurysm, Peripheral vascular disorder

abaloparatide group were palpitations in 7 subjects, electrocardiogram QT prolonged and myocardial ischaemia in 3 subjects each, and tachycardia in 2 subjects.

In Foreign Study 05-005, an open label, uncontrolled study orally administering alendronate 70 mg once weekly for 24 months to subjects who had completed Foreign Study 05-003, the incidence of cardiovascular-related adverse events was 9.0% (52 of 580) of subjects in the group receiving placebo in Foreign Study 05-003 and 8.9% (49 of 553) of subjects in the group receiving abaloparatide in Foreign Study 05-003. Serious cardiovascular-related adverse events occurred in 2.8% (16 of 580) of subjects in the group receiving placebo in Foreign Study 05-003 and in 2.5% (14 of 553) of subjects in the group receiving abaloparatide in Foreign Study 05-003, showing no difference in the incidence between the groups.

The incidence of major adverse cardiovascular events (MACE) was investigated based on the concept of 3 point-MACE (nonfatal myocardial infarction, nonfatal cerebral stroke, and cardiovascular death).[41)] There were no cases of MACE in the pooled analysis of the Japanese studies, whereas the incidence of MACE in the pooled analysis of the foreign studies was 1.8% (16 of 865) of subjects in the placebo group, 1.0% (9 of 918) of subjects in the abaloparatide group, and 1.4% (12 of 863) of subjects in the teriparatide group. In Foreign Study 05-005, the incidence was 1.6% (9 of 580) of subjects in the group receiving placebo in Foreign Study 05-003 and 2.2% (12 of 553) of subjects in the group receiving abaloparatide in Foreign Study 05-003.

The incidence of adverse events classified to cardiac disorders (system organ class [SOC]) was investigated, separately for subjects with and without concurrent cardiac disorders (SOC). In the pooled analysis of Japanese studies, the incidence was 0% (0 of 6) of subjects in the placebo group and 9.1% (1 of 11) of subjects in the abaloparatide group among subjects with concurrent cardiac disorders and 3.4% (4 of 119) of subjects in the placebo group and 8.8% (16 of 182) of subjects in the abaloparatide group among subjects without concurrent cardiac disorders. Thus, the incidence of adverse events classified as cardiac disorders (SOC) did not differ between subjects with and without the concurrent diseases, although simple comparison of the incidence is inadequate because of the limited number of subjects with concurrent cardiac disorders. In the pooled analysis of foreign studies, the incidence of adverse events classified as cardiac disorders (SOC) was 11.2% (13 of 116) of subjects in the placebo group, 13.1% (18 of 137) of subjects in the abaloparatide group, and 7.3% (8 of 110) of subjects in the teriparatide group among subjects with concurrent cardiac disorders, and 4.7% (35 of 749) of subjects in the placebo group, 10.4% (81 of 781) of subjects in the abaloparatide group, and 6.4% (48 of 753) of subjects in the teriparatide group among subjects without concurrent cardiac disorders, showing no difference between subjects with and without the concurrent diseases. The incidence of serious adverse events classified as cardiac disorders (SOC) was 2.6% (3 of 116) of subjects in the placebo group and 1.5% (2 of 137) of subjects in the abaloparatide group among subjects with concurrent cardiac disorders and 0.5% (4 of 749) of subjects in the placebo group and

41) Events corresponding to (a) or (b) below:
(a) Events coded to any of the following terms in MedDRA (PT): Acute myocardial infarction, Myocardial infarction, Myocardial ischaemia, Basal ganglia stroke, Cerebrovascular accident, Ischaemic stroke, Haemorrhage intracranial, Lacunar infarction, Transient ischaemic attack, Cerebral thrombosis, Cardiac operation
(b) All deaths (except those not corresponding to cardiovascular events)

0.9% (7 of 781) of subjects in the abaloparatide group among subjects without concurrent cardiac disorders, showing no difference between subjects with and without concurrent cardiac disorders.

Thus, the incidence of cardiovascular-related adverse events in Japanese and foreign clinical studies was higher in the abaloparatide group than in the placebo and teriparatide groups, but this difference was likely due mainly to the difference in the incidence of palpitations considered to be related to increased heart rate, and the incidence of MACE did not differ between the abaloparatide group and the placebo or teriparatide group. In the study administering alendronate for 24 months after administering abaloparatide or placebo for 18 months, the incidence of MACE did not tend to be higher in the population who had received abaloparatide than in the population who had received placebo, suggesting that abaloparatide is unlikely to cause cardiovascular events. However, it is considered useful to check for the incidence of MACE in patients with a broad range of characteristics in clinical practice, taking into account that the pharmacological effect of abaloparatide suggests a possible effect on the cardiovascular system, that MACE, once manifested, may result in a serious outcome although there was no between-group difference in the incidence of MACE in clinical studies, suggesting that MACE is not related to abaloparatide, and that the characteristics of subjects enrolled in clinical studies are limited. Accordingly, the incidence of MACE will be investigated in the post-marketing surveillance. Further investigations were conducted on the incidence of palpitations and orthostatic hypotension, as described below.

7.R.2.1.1 Palpitations

The applicant's explanation:

In the pooled analysis of Japanese studies, the incidence of palpitation-related adverse events[42)] was 3.2% (4 of 125) of subjects in the placebo group and 7.3% (14 of 193) of subjects in the abaloparatide group, being higher in the abaloparatide group than in the placebo group. This difference was mainly due to the difference in the incidence of palpitations (1.6% [2 of 125] of subjects in the placebo group, 4.1% [8 of 193] of subjects in the abaloparatide group). Palpitation-related serious adverse events were not observed either in the placebo group or in the abaloparatide group. An adverse event leading to treatment discontinuation was observed in 1 subject in the abaloparatide group but not in the placebo group.

In the pooled analysis of foreign studies, the incidence of palpitation-related adverse events was 2.7% (23 of 865) of subjects in the placebo group, 8.6% (79 of 918) of subjects in the abaloparatide group, and 3.8% (33 of 863) of subjects in the teriparatide group, being higher in the abaloparatide group than in the placebo and teriparatide groups. These differences were mainly due to the difference in the incidence of palpitations (0.3% [3 of 865] of subjects in the placebo group, 5.2% [48 of 918] of subjects in the abaloparatide group, 1.6% [14 of 863] of subjects in the teriparatide group). The incidence of palpitation-related serious adverse events was 0% (0 of 865) of subjects in the placebo group, 0.3% (3 of 918) of subjects in the abaloparatide group, and 0.3% (3 of 863) of subjects in the teriparatide group. Adverse events leading to treatment discontinuation occurred in 0.1% (1 of 865) of

[42)] Events coded to terms in the following MedDRA PTs: Extrasystoles, Tachycardia, Tachycardia paroxysmal, Tachyarrhythmia, Postural orthostatic tachycardia syndrome, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Supraventricular tachyarrhythmia, Ventricular extrasystoles, Ventricular tachycardia, Ventricular tachyarrhythmia, Heart rate abnormal, Heart rate increased, Heart rate irregular, Pulse abnormal, Palpitations

subjects in the placebo group, 1.1% (10 of 918) of subjects in the abaloparatide group, and 0.1% (1 of 863) of subjects in the teriparatide group.

Table 52 shows the results of heart rate evaluation in Foreign Study 05-003. The heart rate increased from baseline in the abaloparatide group and the teriparatide group compared to the placebo group, but the heart rate before administration at each time point was similar to that before the start of the treatment.

Table 52. Changes over time from baseline in heart rate before and after study drug administration at each observation time point (Foreign Study 05-003, safety analysis population)

Observation time point		Evaluation time point[a)]	Placebo (n = 820)	Abaloparatide (n = 822	Teriparatide (n = 818)
Baseline		-	65.6 ± 9.6 (n = 820)	66.1 ± 10.1 (n = 822)	66.3 ± 9.4 (n = 818)
Day 1	Amount of change	After administration	1.2 ± 7.1 (n = 815)	7.9 ± 8.5 (n = 817)	5.3 ± 7.5 (n = 816)
Month 1		Before administration	0.1 ± 7.5 (n = 760)	0.1 ± 7.8 (n = 746)	0.5 ± 7.2 (n = 775)
		After administration	1.7 ± 8.3 (n = 770)	7.4 ± 9.6 (n = 754)	5.7 ± 9.1 (n = 785)
Month 3		Before administration	-0.2 ± 7.7 (n = 734)	0.2 ± 7.4 (n = 707)	0.2 ± 7.5 (n = 743)
		After administration	1.3 ± 8.6 (n = 742)	7.6 ± 10.0 (n = 709)	5.4 ± 8.9 (n = 751)
Month 6		Before administration	-0.2 ± 7.8 (n = 709)	0.0 ± 7.9 (n = 676)	0.3 ± 7.8 (n = 720)
		After administration	1.1 ± 8.5 (n = 713)	6.8 ± 10.0 (n = 676)	6.3 ± 9.3 (n = 723)
Month 9		Before administration	-0.1 ± 8.5 (n = 683)	0.1 ± 7.9 (n = 654)	0.4 ± 8.5 (n = 697)
		After administration	1.7 ± 9.0 (n = 690)	7.3 ± 10.2 (n = 655)	5.8 ± 9.8 (n = 702)
Month 12		Before administration	-0.3 ± 8.1 (n = 667)	-0.1 ± 8.0 (n = 625)	0.1 ± 7.8 (n = 680)
		After administration	1.5 ± 8.7 (n = 669)	7.1 ± 10.3 (n = 626)	6.1 ± 9.0 (n = 681)

Unit, bpm; Mean ± SD
a) Heart rate 1 hour after administration

Thus, although palpitations occurred after abaloparatide administration in some subjects, there were only a few palpitation-related adverse events that were serious or led to treatment discontinuation.

7.R.2.1.2 Orthostatic hypotension

The applicant's explanation:

The PTH receptor-mediated pharmacological effect of abaloparatide may possibly cause dilation of peripheral blood vessels, thereby decreasing blood pressure. Therefore, abaloparatide-associated orthostatic hypotension was investigated as follows. In the pooled analysis of Japanese studies, orthostatic hypotension-related adverse events[43)] occurred in 8.0% (10 of 125) of subjects in the placebo group and 16.6% (32 of 193) of subjects in the abaloparatide group; the incidence was higher in the abaloparatide group than in the placebo group. This difference was mainly due to the difference in the incidences of dizziness (3.2% [4 of 125] of subjects in the placebo group, 5.7% [11 of 193] of subjects in the abaloparatide group), palpitations (1.6% [2 of 125] of subjects in the placebo group, 4.1% [8 of 193] of subjects in the abaloparatide group), and vertigo (1.6% [2 of 125] of subjects in the placebo group, 3.6% [7 of 193] of subjects in the abaloparatide group). An orthostatic hypotension-related serious adverse event was observed in 1 subject (hypotension) in the abaloparatide group but not in the placebo group. An adverse event leading to treatment discontinuation was observed in 1 subject (palpitations) in the abaloparatide group but not in the placebo group.

43) Events coded to terms in the following MedDRA PTs: Blood pressure ambulatory decreased, Loss of consciousness, Blood pressure diastolic decreased, Somnolence, Blood pressure orthostatic decreased, Dizziness postural, Blood pressure decreased, Presyncope, Blood pressure systolic decreased, Gait disturbances, Diastolic hypotension, Loss of control of legs, Orthostatic hypotension, Balance disorder, Hypotension, Dysstasia, Blood pressure orthostatic abnormal, Diplopia, Heart rate orthostatic increased, Visual impairment, Depressed level of consciousness, Cardiac discomfort, Dizziness, Tachyarrhythmia, Vertigo, Sinus tachycardia, Vision blurred, Asthenia, Fall, Autonomic nervous system imbalance, Syncope, Fatigue, Palpitations, Listless, Tachycardia, Malaise, Altered state of consciousness, Muscle weakness conditions, Lethargy

In the pooled analysis of foreign studies, orthostatic hypotension-related adverse events occurred in 14.2% (123 of 865) of subjects in the placebo group, 24.4% (224 of 918) of subjects in the abaloparatide group, and 18.7% (161 of 863) of subjects in the teriparatide group; the incidence was higher in the abaloparatide group than in the placebo and teriparatide groups. These differences were mainly due to the difference in the incidences of dizziness (6.0% [52 of 865] of subjects in the placebo group, 10.3% [95 of 918] of subjects in the abaloparatide group, 7.2% [62 of 863] of subjects in the teriparatide group) and palpitations (0.3% [3 of 865] of subjects in the placebo group, 5.2% [48 of 918] of subjects in the abaloparatide group, 1.6% [14 of 863] of subjects in the teriparatide group). Orthostatic hypotension-related serious adverse events occurred in 0.2% (2 of 865) of subjects in the placebo group, 0.4% (4 of 918) of subjects in the abaloparatide group, and 0.5% (4 of 863) of subjects in the teriparatide group. Adverse events leading to treatment discontinuation occurred in 1.3% (11 of 865) of subjects in the placebo group, 2.8% (26 of 918) of subjects in the abaloparatide group, and 1.6% (14 of 863) of subjects in the teriparatide group.

In Foreign Study 05-003, blood pressure was measured at supine and standing positions before and at 60 minutes after administration at each visit and, if systolic pressure decreased by ≥20 mmHg or diastolic blood pressure decreased by ≥10 mmHg when the posture was changed from supine to standing potion, the subject was diagnosed with orthostatic hypotension. Orthostatic hypotension occurred before or at 60 minutes after administration in 26.5% (217 of 820) of subjects in the placebo group, 27.9% (229 of 822) of subjects in the abaloparatide group, and 25.1% (205 of 818) of subjects in the teriparatide group. The incidence of orthostatic hypotension did not differ between before and after administration at any evaluation time point. There was no tendency of an increase in safety concern at any specific time point in all of the treatment groups. There was no between-group difference in the incidence of orthostatic hypotension before and after administration at any time point from 1 month after the start of the treatment (Table 53).

Table 53. Incidence of orthostatic hypotension before or after abaloparatide administration at each observation time point (Foreign Study 05-003, safety analysis population)

Observation time point	Evaluation time point	Placebo (n = 820)	Abaloparatide (n = 822)	Teriparatide (n = 818)
All time points	Before or after administration	26.5 (217/820)	27.9 (229/822)	25.1 (205/818)
	Before administration	16.5 (135/820)	15.5 (127/822)	16.0 (131/818)
	60 minutes after administration	16.4 (134/819)	17.1 (140/821)	15.5 (127/817)
Day 1	Before or after administration	5.5 (45/820)	6.4 (53/822)	4.9 (40/818)
	Before administration	2.7 (22/819)	2.6 (21/822)	1.8 (15/818)
	60 minutes after administration	3.2 (26/818)	4.1 (34/821)	3.5 (29/817)
Month 1	Before or after administration	6.9 (54/779)	7.0 (53/758)	7.8 (61/787)
	Before administration	4.0 (31/771)	3.7 (28/752)	4.7 (37/780)
	60 minutes after administration	4.0 (31/776)	4.2 (32/755)	3.4 (27/785)
Month 3	Before or after administration	6.6 (49/747)	8.2 (58/711)	8.6 (65/754)
	Before administration	3.9 (29/739)	4.2 (30/711)	4.9 (37/751)
	60 minutes after administration	3.4 (25/745)	4.2 (30/711)	4.2 (32/754)
Month 6	Before or after administration	8.3 (59/714)	7.8 (53/679)	7.2 (52/726)
	Before administration	4.4 (31/712)	5.0 (34/678)	4.8 (35/725)
	60 minutes after administration	5.3 (38/714)	3.7 (25/677)	3.7 (27/722)
Month 9	Before or after administration	8.3 (57/690)	8.7 (57/657)	7.7 (54/703)
	Before administration	5.0 (34/685)	5.5 (36/655)	4.4 (31/703)
	60 minutes after administration	4.2 (29/690)	3.8 (25/656)	4.1 (29/703)
Month 12	Before or after administration	9.4 (63/672)	9.0 (57/630)	6.7 (46/682)
	Before administration	6.0 (40/671)	4.0 (25/628)	4.8 (33/682)
	60 minutes after administration	4.8 (32/671)	5.6 (35/630)	3.1 (21/681)

Incidence in % (number of subjects with events/number of subjects evaluated)

Thus, the Japanese and foreign clinical studies showed that abaloparatide tended to increase the incidence of orthostatic hypotension-related adverse events, and some of them were serious. However, abaloparatide had no clear effect on orthostatic hypotension when analyzed based on the blood pressure decrease in postural change from supine to standing position.

Based on the investigation on palpitations and orthostatic hypotension in Sections 7.R.2.1.1 and 7.R.2.1.2 above, the following caution statement will be included in the Important Precautions section of the package insert: (1) Abaloparatide may cause orthostatic hypotension, dizziness, palpitations, tachycardia, etc., (2) the patient should be kept as quiet as possible for approximately 30minutes after administration and, if any of these symptoms occur, he/she should sit or lie down until the symptoms resolve, and (3) the patient should be careful when performing potentially hazardous activities because dizziness or lightheadedness may occur.

PMDA's view on cardiovascular events, including palpitations and orthostatic hypotension described individually in Sections 7.R.2.1.1 and 7.R.2.1.2:
In clinical studies, cardiovascular-related adverse events occurred at a higher incidence in the abaloparatide group than in the placebo group and in the teriparatide group, and adverse events leading to treatment discontinuation occurred more frequently in the abaloparatide group. The main cause of the difference was palpitation-related events. Also, orthostatic hypotension tended to occur more frequently in the abaloparatide group than in the placebo group and in the teriparatide group. The higher incidence in the abaloparatide group than in the placebo group is considered to be caused by the positive chronotropic and inotropic actions, and peripheral vasodilator actions of abaloparatide, judging from the following findings: (1) PTH drugs are known to have positive chronotropic and inotropic actions, and peripheral vasodilator actions, (2) in clinical studies, the incidences of palpitations and orthostatic hypotension tended to be higher in the teriparatide group than in the

placebo group, and (3) in the safety pharmacology studies of abaloparatide, abaloparatide increased heart rate and decreased blood pressure. On the other hand, the incidences of serious palpitations and orthostatic hypotension were similar between the abaloparatide group and the placebo or teriparatide group. Also, there was no tendency of an increase in the incidences of serious cardiovascular-related adverse events or MACE in the abaloparatide group compared with the incidences in the placebo or teriparatide group. Similarly, in Foreign Study 05-005 in which subjects were followed up for 24 months after abaloparatide administration, there was no tendency of an increase in cardiovascular events in the group receiving abaloparatide in Foreign Study 05-003 than in the group receiving placebo in Foreign Study 05-003. These results suggest that the effect of abaloparatide on the cardiovascular system is within acceptable limits, but precautions against orthostatic hypotension and palpitations should be provided in the package insert to inform patients of the possible risks. Also, attention should be paid to the finding that the incidences of palpitations and orthostatic hypotension in the abaloparatide group were higher even than those in the teriparatide group. The incidence of cardiovascular events associated with abaloparatide should be carefully watched for in the post-marketing settings.

7.R.2.2 Nausea

The applicant's explanation:

In the pooled analysis of Japanese studies, nausea-related adverse events[44)] occurred in 7.2% (9 of 125) of subjects in the placebo group and in 6.7% (13 of 193) of subjects in the abaloparatide group, showing no between-group difference. Nausea-related serious adverse events were not observed either in the placebo or abaloparatide group, and nausea-related adverse events leading to treatment discontinuation was observed in 1 subject in the abaloparatide group but not in the placebo group.

In the pooled analysis of foreign studies, nausea-related adverse events occurred in 3.2% (28 of 865) of subjects in the placebo group, 8.6% (79 of 918) of subjects in the abaloparatide group, and 6.0% (52 of 863) of subjects in the teriparatide group; the incidence was higher in the abaloparatide group than in the placebo and teriparatide groups. These differences were mainly due to the difference in the incidence of nausea (2.9% [25 of 865] of subjects in placebo group, 8.0% [73 of 918] of subjects in abaloparatide group, 5.1% [44 of 863] of subjects in the teriparatide group). Nausea-related serious adverse events occurred in 0% (0 of 865) of subjects in the placebo group, 0.1% (1 of 918) of subjects in the abaloparatide group, and 0% (0 of 863) of subjects in the teriparatide group. Nausea-related adverse events leading to treatment discontinuation occurred in 0.2% (2 of 865) of subjects in the placebo group, 1.4% (13 of 918) of subjects in the abaloparatide group, and 0.5% (4 of 863) of subjects in the teriparatide group.

Thus, in the clinical studies conducted, nausea-related adverse events occurred more frequently in the abaloparatide group than in the placebo group, but most of them were mild in severity and were unlikely to result in a serious outcome.

44) Events coded to terms in the following MedDRA High level term (HLT)s: Nausea and vomiting symptoms

PMDA's view:
In foreign clinical studies, nausea-related adverse events occurred at a higher incidence in the abaloparatide group than in the placebo or teriparatide group, with some of events leading to treatment discontinuation. However, the incidence of nausea-related serious adverse events does not pose any particular concern when compared with the incidence in the placebo or teriparatide group and, in Japanese clinical studies, the incidence did not significantly differ between the abaloparatide group and the placebo group, suggesting that the risk of abaloparatide-induced nausea is clinically acceptable. Precautions for nausea should be provided in the Important Precautions section of the package insert as are the cases with drugs in the same class.

7.R.2.3 Hypercalcaemia

The applicant's explanation:
Abaloparatide may increase calcium concentration in the blood by its PTH receptor-mediated bone resorptive effect, calcium resorption-enhancing effect in renal tubules, and calcium absorption-enhancing effect in the intestinal tract. Therefore, incidences of hypercalcaemia-related adverse events in clinical studies were investigated.

In the pooled analysis of Japanese studies, hypercalcaemia-related adverse events[45)] occurred in 0.8% (1 of 125) of subjects in the placebo group and 4.1% (8 of 193) of subjects in the abaloparatide group; the incidence was higher in the abaloparatide group than in the placebo group. Hypercalcaemia-related serious adverse events were not observed either in the placebo group or abaloparatide group. Adverse events leading to treatment discontinuation occurred in 1 subject in the placebo group and 2 subjects in the abaloparatide group. Hypercalcaemia, defined as adjusted serum calcium level of >10.5 mg/dL, occurred in 1.6% (2 of 125) of subjects in the placebo group and 10.4% (20 of 193) of subjects in the abaloparatide group; the incidence was higher in the abaloparatide group than in the placebo group. Changes over time in adjusted serum calcium level were investigated in Japanese Study 301. The mean pre-dose level on the day at the start of treatment was 9.34 mg/dL in the placebo group and 9.33 mg/dL in the abaloparatide group. Throughout the study period, there were only small variations in the level in the placebo group before administration at each observation time point (mean level, 9.26-9.54 mg/dL; mean change, −0.08 to 0.19 mg/dL) whereas, in the abaloparatide group, the level tended to increase from Week 3 (mean level, 9.37-9.68 mg/dL; mean change, 0.04-0.37 mg/dL). The level at 4 hours after administration at each time point changed little throughout the study period in the placebo group (mean level, 9.29-9.51 mg/dL; mean change, −0.06 to 0.16 mg/dL). In the abaloparatide group, the level did not change on the starting day of treatment (mean level, 9.34 mg/dL; mean change, 0.01 mg/dL) but increased at Week 24, 48, and 72 (mean level, 9.76-9.81 mg/dL; mean change, 0.42-0.51 mg/dL). At each observation time point, the level after administration tended to be higher than the level before administration, while the increase in the level at 4 hours after administration was transient.

In the pooled analysis of foreign studies, hypercalcaemia-related adverse events occurred in 0.7% (6 of 865) of subjects in the placebo group, 1.9% (17 of 918) of subjects in the abaloparatide group, and

[45)] Events coded to terms in the following MedDRA PTs: Calcium ionised abnormal, Calcium ionised increased, Blood calcium abnormal, Blood calcium increased, Hypercalcaemia, Hypercalcaemic nephropathy, adjusted calcium increased

4.5% (39 of 863) of subjects in the teriparatide group; the incidence was lower in the abaloparatide group than in the teriparatide group. Hypercalcaemia-related serious adverse events occurred in 0% (0 of 865) of subjects in the placebo group, 0% (0 of 918) of subjects in the abaloparatide group, and 0.1% (1 of 863) of subjects in the teriparatide group. Hypercalcaemia-related adverse events leading to treatment discontinuation occurred in 0% (0 of 865) of subjects in the placebo group, 0.2% (2 of 918) of subjects in the abaloparatide group, and 0.5% (4 of 863) of subjects in the teriparatide group. Hypercalcaemia, defined as adjusted serum calcium level of ≥10.7 mg/dL (upper limit of reference range + 0.3 mg/dL) or ≥2.67 mmol/L, occurred in 0.35% (3 of 862) of subjects in the placebo group, 3.38% (31 of 916) of subjects in the abaloparatide group, and 6.16% (53 of 861) of subjects in the teriparatide group; the incidence in the abaloparatide group was higher than in the placebo group and lower than in the teriparatide group. Changes over time in adjusted serum calcium level were investigated in Foreign Study 05-003. At any of the observation time points, there was no difference in the level before administration at each observation time point among abaloparatide group, teriparatide group, and placebo group, whereas the level at 4 hours after administration increased in both the abaloparatide group and the teriparatide group. The mean change in the level at 4 hours after administration was −0.01 to 0.03 mg/dL in the placebo group, 0.22 to 0.45 mg/dL in the abaloparatide group, and 0.25 to 0.55 mg/dL in the teriparatide group; the extent of increase in the abaloparatide group tended to be smaller than in the teriparatide group. The increase in the level at 4 hours after abaloparatide administration was transient.

Thus, hypercalcaemia-related adverse events tended to occur more frequently in the abaloparatide group than in the placebo group in clinical studies, and a transient increase in adjusted calcium level in serum was observed at 4 hours after abaloparatide administration. The increase in serum calcium level was small in extent and did not persist, suggesting that the increase does not pose any clinical problem. However, severe hypercalcaemia may lead to psychiatric symptoms, disturbance in consciousness, acute renal failure, etc. Abaloparatide should be contraindicated in patients with hypercalcaemia. The Important Precautions section of the package insert will include the description that patients should be instructed to promptly consult a physician if symptoms suggesting increased serum calcium level are noted. Co-administration of active vitamin D preparation may additively increase serum calcium level. Also, co-administration of digitalis preparation with abaloparatide may augment the effect of digitalis due to the increased serum calcium level. These effects should be described in the Interactions section of the package insert, to raise caution.

PMDA's view:
In Japanese and foreign clinical studies, hypercalcaemia-related adverse events occurred at a higher incidence in the abaloparatide group than in the placebo group, and serum calcium level tended to increase albeit transiently. However, in foreign clinical studies, the extent of the increase in hypercalcaemia-related adverse events and in serum calcium level did not tend to be higher in the abaloparatide group than in the teriparatide group. Nevertheless, given that severe hypercalcaemia poses clinical problems, the applicant's plan to raise caution against an increase in serum calcium level, as are the cases with PTH drugs, drugs in the same class, is appropriate.

7.R.2.4 Injection site reaction

The applicant's explanation:

In the pooled analysis of Japanese studies, injection site reaction-related adverse events[46)] occurred in 11.2% (14 of 125) of subjects in the placebo group and 13.5% (26 of 193) of subjects in the abaloparatide group; the incidence did not significantly differ between groups. Injection site reaction-related serious adverse events and adverse events leading to treatment discontinuation were not observed either in the placebo group or the abaloparatide group. In the pooled analysis of foreign studies, injection site reaction-related adverse events occurred in 4.2% (36 of 865) of subjects in the placebo group, 4.7% (43 of 918) of subjects in the abaloparatide group, and 3.7% (32 of 863) of subjects in the teriparatide group; the incidence was not different among the groups. Injection site reaction-related serious adverse events were not observed in all of the placebo, abaloparatide, or teriparatide group. Injection site reaction-related adverse events leading to treatment discontinuation occurred in 0% (0 of 865) of subjects in the placebo group, 0.1% (1 of 918) of subjects in the abaloparatide group, and 0% (0 of 863) of subjects in the teriparatide group.

Of local symptoms at the injection site reported in patient's diaries in Foreign Study 05-003, redness was the most frequently observed injection site reaction in all treatment groups. At Month 1, redness occurred at 1 hour after administration in 28.3% (207 of 731) of subjects in the placebo group, 57.7% (423 of 733) of subjects in the abaloparatide group, and 63.8% (473 of 741) of subjects in the teriparatide group. At Month 12, the incidence of redness at 1 hour after administration was 17.0% (99 of 583) of subjects in the placebo group, 33.9% (180 of 531) of subjects in the abaloparatide group, and 36.3% (214 of 589) of subjects in the teriparatide group. During the study period, most of redness, swelling, pain, and tenderness were mild, and the incidence of severe redness was 1.5% (11 of 751) of subjects in the placebo group, 3.9% (29 of 740) of subjects in the abaloparatide group, and 4.4% (33 of 750) of subjects in the teriparatide group.

Thus, in Foreign Study 05-003, local reactions at the injection site occurred more frequently in abaloparatide group than in placebo group, judging from the patient's diaries. However, there was no between-group difference in the incidence of injection site-related adverse events in Japanese and foreign clinical studies, and all of them were non-serious, suggesting that they do not pose any significant clinical problem.

PMDA's view:

The patient's diaries in Foreign Study 05-003 showed that local symptoms at the injection site occurred more frequently in the abaloparatide group than in the placebo group, but the pooled analysis of Japanese and foreign studies showed that there is no significant difference in the incidence of injection site reactions between the abaloparatide group and the placebo group. Also taking into account that most of the injection site reactions were mild, the applicant's explanation that the adverse reactions are unlikely to pose any clinically significant problem is acceptable.

[46)] Events coded to terms in the following MedDRA HLTs: "Administration site reactions NEC," "Application and instillation site reaction," and "Injection site reaction"

7.R.2.5 Hypersensitivity

The applicant's explanation:

In the pooled analysis of Japanese studies, hypersensitivity reaction-related adverse events[47)] occurred in 7.2% (9 of 125) of subjects in the placebo group and 12.4% (24 of 193) of subjects in the abaloparatide group; the incidence was higher in the abaloparatide group than in the placebo group. This was mainly due to the difference in the incidences of urticaria (0% [0 of 125] of subjects in the placebo group, 2.6% [5 of 193] of subjects in the abaloparatide group) and dermatitis (0% [0 of 125] of subjects in the placebo group, 2.1% [4 of 193] of subjects in the abaloparatide group). Hypersensitivity reaction-related serious adverse events occurred in 1 subject in the placebo group but not in the abaloparatide group. Hypersensitivity-related adverse events leading to treatment discontinuation did not occur either in the placebo group or in the abaloparatide group.

In the pooled analysis of foreign studies, hypersensitivity reaction-related adverse events occurred in 5.8% (50 of 865) of subjects in the placebo group, 4.9% (45 of 918) of subjects in the abaloparatide group, and 6.1% (53 of 863) of subjects in the teriparatide group; the incidence was not different among the groups. Hypersensitivity reaction-related serious adverse events occurred in 0.2% (2 of 865) of subjects in the placebo group, 0% (0 of 918) of subjects in the abaloparatide group, and 0.2% (2 of 863) of subjects in the teriparatide group. Hypersensitivity-related adverse events leading to treatment discontinuation occurred in 0.5% (4 of 865) of subjects in the placebo group, 0.4% (4 of 918) of subjects in the abaloparatide group, and 0.7% (6 of 863) of subjects in the teriparatide group. Anaphylaxis was not observed in the pooled analysis of Japanese studies and pooled analysis foreign studies, but serious anaphylaxis was reported in 3 patients after the market launch in foreign countries.

Thus, as far as the Japanese and foreign clinical studies are concerned, abaloparatide-induced hypersensitivity reaction is unlikely to pose clinical problems.

PMDA's view:

In the Japanese clinical studies, hypersensitivity-related adverse events were observed more frequently in the abaloparatide group than in the placebo group. However, no serious adverse events were observed either in Japanese or foreign clinical studies, and the incidence did not tend to be higher in the abaloparatide group than in the teriparatide group. On the other hand, serious anaphylactic reactions were reported after the market launch in foreign countries, warranting caution. Precautions for anaphylaxis should be provided in the package insert.

7.R.2.6 Hyperuricaemia

The applicant's explanation:

In the pooled analysis of Japanese studies, adverse events related to blood uric acid increased[48)] occurred in 0.8% (1 of 125) of subjects in the placebo group and 8.3% (16 of 193) of subjects in the abaloparatide group; the incidence was higher in the abaloparatide group than in the placebo group. Serious adverse events related to blood uric acid increased did not occur either in the placebo group or in the abaloparatide group. Similarly, there were no adverse events relate to blood uric acid increased

47) Events corresponding to "Hypersensitivity" in MedDRA SMQ (narrow)

48) Events coded to terms in the following MedDRA PTs: Blood uric acid abnormal, Blood uric acid increased, Hyperuricaemia, Hyperuricosuria, Urine uric acid abnormal, Urine uric acid increased

leading to treatment discontinuation in either group. In the pooled analysis of foreign studies, adverse events related to blood uric acid increased occurred in 0.5% (4 of 865) of subjects in the placebo group, 1.6% (15 of 918) of subjects in the abaloparatide group, and 2.1% (18 of 863) of subjects in the teriparatide group; the incidence was not significantly different among the groups. Serious adverse events related to blood uric acid increased did not occur in all of the placebo group, the abaloparatide group, or the teriparatide group. Similarly, there were no adverse events related to blood uric acid increased leading to treatment discontinuation in any group.

Changes over time in blood uric acid level in Japanese Study 301were investigated. The level did not change throughout the study period in the placebo group whereas, in the abaloparatide group, the level increased at Week 3 and continued to increase up to Week 78. The observed blood uric acid level (mean) at Week 78 was 4.74 mg/dL in the placebo group and 5.85 mg/dL in the abaloparatide group. The mean change from baseline was −0.06 mg/dL in the placebo group and 0.98 mg/dL in the abaloparatide group; the change was greater in the abaloparatide group than in the placebo group. Among subjects with increased blood uric acid level, 1.4% (1 of 72) of subjects in the placebo group and 27.1% (38 of 140) of subjects in the abaloparatide group met the criteria of abnormal variations[49]; the incidence was higher in the abaloparatide group than in the placebo group. In Foreign Study 05-003, blood uric acid level changed little from baseline in the placebo group whereas, in the abaloparatide group, the level increased over time up to Month 6, tended to decrease from Month 9 up to Month 18, and the mean change at Month 18 was 0.75 mg/dL. The trend in the teriparatide group was similar to that observed in the abaloparatide group, with the mean change at Month 18 being 0.93 mg/dL. Among subjects with the baseline blood uric acid level within the reference range, 5.5% (44 of 803) of subjects in the placebo group, 25.4% (203 of 800) of subjects in the abaloparatide group, and 29.7% (238 of 801) of subjects in the teriparatide group exceeded the upper limit of the reference range in their maximum changes in blood uric acid level after administration. At the end of the treatment, the level exceeded the upper limit of the reference range in 2.1% (17 of 803) of subjects in the placebo group, 11.0% (88 of 800) of subjects in the abaloparatide group, and 13.7% (110 of 801) of subjects in the teriparatide group.

Thus, abaloparatide may possibly increase blood uric acid level, but no serious adverse events or adverse events leading to treatment discontinuation were observed in clinical studies. An abaloparatide-induced increase in serum calcium and uric acid levels are risk factors of urolithiasis. In the pooled analysis of Japanese studies, urolithiasis-related adverse events[50] occurred in 1.6% (2 of 125) of subjects in the placebo group and 1.6% (3 of 193) of subjects in the abaloparatide group. A urolithiasis-related serious adverse event occurred in 1 subject in the placebo group but not in the abaloparatide group. Urolithiasis-related adverse events leading to treatment discontinuation did not occur either in the placebo group or in the abaloparatide group. In the pooled analysis of foreign

[49] Events corresponding to either (a) or (b) below:
(a) Blood uric acid level was “within the reference range” at baseline but “outside the reference range” after administration:
Variation “to ≥120% of the upper limit of the reference range,” “to ≤80% of the lower limit of the reference range,” or “by ≥50% from baseline.”
(b) Blood uric acid level was “outside the reference range” at baseline and “outside the reference range” after administration (excluding the cases where “the deviation of the value from the reference range” after administration was less than that at baseline):
Variation from “baseline value exceeded the upper limit of the reference range” to “value after administration is ≥120% of the upper limit of the reference range”; variation from “the baseline value is lower than the lower limit of the reference range” to “the value after administration is ≤80% of the lower limit of the reference range”; or variation of “≥50% from baseline value.”

[50] Events corresponding to the following term of MedDRA (High level group term [HLGT]): Urolithiases

studies, urolithiasis-related adverse events occurred in 1.6% (14 of 865) of subjects in the placebo group, 1.9% (17 of 918) of subjects in the abaloparatide group, and 2.2% (19 of 863) of subjects in the teriparatide group. A urolithiasis-related serious adverse event occurred in 1 subject in the placebo group but not in the abaloparatide group or the teriparatide group. Urolithiasis-related serious adverse events leading to treatment discontinuation did not occur either in the placebo group, the abaloparatide group, or the teriparatide group. Thus, there is no significant difference in the incidence of urolithiasis-related adverse events between the abaloparatide group and the placebo group, casting doubt on the possibility of abaloparatide causing urolithiasis. Nevertheless, since abaloparatide may possibly aggravate the symptoms of patients with current or past urolithiasis, precautions will be provided in the Precautions Concerning Patients with Specific Backgrounds section of the package insert.

PMDA's view:
In Japanese and foreign clinical studies, adverse events related to blood uric acid increased occurred more frequently in the abaloparatide group than in the placebo group, whereas the foreign clinical study confirmed that the incidence did not tend to be higher in the abaloparatide group than in the teriparatide group. As for urolithiasis-related adverse events, the incidence did not significantly differ between the abaloparatide group and the placebo group, suggesting that an abaloparatide-induced increase in blood uric acid level will not pose any significant clinical problem. Nevertheless, patients with past or current urolithiasis should be alerted, as is the case with PTH drugs, drugs in the same class.

7.R.2.7 Osteosarcoma

The applicant's explanation:
In Japanese clinical studies, there were no osteosarcoma-related adverse events.[51)] In the pooled analysis of foreign studies, osteosarcoma-related adverse events occurred in 0.7% (6 of 865) of subjects in the placebo group, 1.4% (13 of 918) of subjects in the abaloparatide group, and 1.4% (12 of 863) of subjects in the teriparatide group. Bone pain was all of the events observed. Neither serious adverse events nor adverse events leading to treatment discontinuation were observed in all of the groups.

Osteosarcoma-related events were reported after the market launch in foreign countries, but no osteosarcoma was reported. Reported events were bone pain and pathological fracture, all of which were non-serious.

Thus, no osteosarcoma was reported in Japanese or foreign clinical studies or after the market launch. It remains unknown whether abaloparatide causes osteosarcoma in humans, as observed in rats. However, given the possibility that the change observed in nonclinical studies, once manifested, may result in a serious outcome, abaloparatide will be contraindicated in patients at high risk of osteosarcoma (patients with Paget's disease of bone, patients with high alkaline phosphatase level of

[51)] Events corresponding to the following MedDRA terms:
MedDRA (HLT): Bone sarcomas, Cartilage sarcomas, Extraskeletal Ewing's sarcomas, Extraskeletal chondrosarcomas, Extraskeletal osteosarcomas, "Bone neoplasms unspecified malignancy," Bone neoplasms malignant (excl sarcomas)
MedDRA (PT): Pathological fracture, Malignant joint neoplasm, Cartilage neoplasm, Joint neoplasm, Fibrosarcoma, Fibrosarcoma metastatic, Bone pain

unknown cause, pediatric and young patients with open epiphyseal line, patients who in the past received radiation therapy possibly affecting bones). Further information on osteosarcoma will be collected after the market launch.

PMDA's view:
Currently, results of the Japanese and foreign clinical studies and post-marketing data in foreign countries do not suggest any clear relationship between abaloparatide and onset of osteosarcoma. However, taking account of the finding in the nonclinical studies that abaloparatide induced bone neoplastic lesions as is the case with conventional PTH drugs, the applicant's following plan is appropriate: (1) Abaloparatide is contraindicated in patients at high risk of osteosarcoma, and (2) Associated information is collected continuously after the market launch.

7.R.2.8 Antibody production

The applicant's explanation:
In Japanese Study 004, anti-abaloparatide antibody was observed in none of the subjects in the placebo group, in 16.7% (9 of 54) of subjects in the abaloparatide 40 μg group, and in 30.2% (16 of 53) of subjects in the abaloparatide 80 μg group. As shown in Figure 54, the incidence of adverse events did not significantly differ between anti-abaloparatide antibody-negative and -positive subjects. No serious adverse events were observed in anti-abaloparatide antibody-positive subjects. Neutralizing anti-abaloparatide antibody was detected in 3.7% (2 of 54) of subjects in the abaloparatide 40 μg group and in 3.8% (2 of 53) of subjects in the abaloparatide 80 μg group.

In Japanese Study 301, anti-abaloparatide antibody was not detected in any of the subjects in the placebo group. In the abaloparatide group, anti-abaloparatide antibody was positive in 40 subjects at one or more time points. Table 54 shows the incidence of adverse events and adverse drug reactions, separately for subjects with and without anti-abaloparatide antibody production, and the incidence of hypersensitivity-related adverse events. Neither the incidence of adverse events, adverse drug reactions, nor hypersensitivity-related adverse events differ between subjects with and without anti-abaloparatide antibody production.

Table 54. Incidence of adverse events in Japanese clinical studies, by anti-abaloparatide antibody production (safety analysis population)

Event	Anti-abaloparatide antibody	Japanese Study 004 (Week 52)[a]			Japanese Study 301	
		Placebo (n = 53)	Abaloparatide 40 μg (n = 54)	Abaloparatide 80 μg (n = 53)	Placebo (n = 72)	Abaloparatide 80 μg (n = 140)
All adverse events	Yes	-	100 (9/9)	93.8 (15/16)	-	90.0 (36/40)
	No	75.5 (40/53)	88.9 (40/45)	75.7 (28/37)	80.6 (58/72)	92.0 (92/100)
All adverse drug reactions	Yes	-	22.2 (2/9)	12.5 (2/16)	-	32.5 (13/40)
	No	5.7 (3/53)	13.3 (6/45)	18.9 (7/37)	13.9 (10/72)	32.0 (32/100)
Hypersensitivity-related adverse events[b]	Yes	-	11.1 (1/9)	12.5 (2/16)	-	15.0 (6/40)
	No	5.7 (3/53)	6.7 (3/45)	5.4 (2/37)	8.3 (6/72)	14.0 (14/100)

Incidence in % (number of subjects with events/number of subjects evaluated)
a) Including the results of the antibody test at plasma drug concentration measurement, b) Events corresponding to "Hypersensitivity (narrow)" in Standardised MedDRA queries (SMQ)

At Week 24 of Foreign Study 05-002, anti-abaloparatide antibody was positive in 2 subjects in the abaloparatide 20 μg group, 6 subjects in the abaloparatide 40 μg group, and 5 subjects in the

abaloparatide 80 μg group. During the extended period, an additional 3 subjects in the abaloparatide 20 μg group became positive for the antibody, and 1 subject in the abaloparatide 40 μg group and 3 subjects in the abaloparatide 80 μg group were still positive at Week 48. Adverse events occurred in 81.3% (13 of 16) of subjects among anti-abaloparatide antibody-positive subjects; the incidence and the types of events observed were not significantly different from those observed in the entire population of the study.

In the abaloparatide group of Foreign Study 05-003, anti-abaloparatide antibody was positive in 49.2% (300[52)] of 610) of subjects who underwent evaluation for the antibody at Week 18. Neutralizing antibody was detected in 67.7% (201 of 297) of subjects of them. No difference was observed in the safety profile between anti-abaloparatide antibody- or neutralizing antibody-positive subjects and antibody-negative subjects (Table 55).

Table 55. Incidence of adverse events in Foreign Study 05-003 (safety analysis population)

Event	Anti-abaloparatide antibody negative (n = 310)	Anti-abaloparatide antibody positive		
		All subjects positive for anti-abaloparatide antibody (n = 300)	Neutralizing antibody negative (n =96)	Neutralizing antibody positive (n =201)
All adverse events	91.0 (282)	92.3 (277)	93.8 (90)	91.5 (184)
Serious adverse events	9.4 (29)	8.7 (26)	8.3 (8)	8.5 (17)
Hypersensitivity-related adverse events[a)]	4.5 (14)	6.0 (18)	5.2 (5)	6.5 (13)

Incidence in % (number of subjects with events)
a) Events corresponding to "Hypersensitivity (narrow)" in SMQ

In order to evaluate the effect of anti-abaloparatide antibody on the efficacy of abaloparatide, the percent change in the bone density of the lumbar spine (L1-L4) from baseline in the abaloparatide group of Japanese Study 301 and Foreign Study 05-003 (Table 56), and the incidence of fracture in the abaloparatide group of Foreign Study 05-003 (Table 57) were investigated, separately for subjects positive and negative for anti-abaloparatide production. Results showed no significant difference between subjects with and without antibody production.

[52)] A total of 300 anti-abaloparatide antibody-positive subjects consisted of (1) 297 subjects tested positive for the antibody at Week 18 and (2) 3 subjects who were not tested at Week 18 due to insufficient amount of the test sample but handled as "positive" based on the results of Month 12.

Table 56. Percent change in bone density of the lumbar spine (L1-L4) from baseline, by subjects negative and positive for anti-abaloparatide antibody production (abaloparatide group of Japanese Study 301 and Foreign Study 05-003)

Study	Endpoint	Anti-abaloparatide antibody negative	Anti-abaloparatide antibody positive		
			All subjects positive for anti-abaloparatide antibody	Neutralizing antibody-negative	Neutralizing antibody-positive
Japanese Study 301	Baseline level[a] (g/cm^2)	0.656 ± 0.071 (n = 96)	0.631 ± 0.077 (n = 40)	0.631 ± 0.085 (n = 18)	0.631 ± 0.072 (n = 22)
	Percent change at Week 18[b] (%)	14.04 ± 8.87 (n = 96)	16.11 ± 10.17 (n = 40)	16.16 ± 7.24 (n = 18)	16.06 ± 12.23 (n = 22)
Foreign Study 05-003	Baseline level[a] (g/cm^2)	0.832 ± 0.104 (n = 310)	0.829 ± 0.111 (n = 300)	0.843 ± 0.122 (n = 96)	0.823 ± 0.105 (n = 201)
	Percent change at Week 18[b] (%)	11.17 ± 7.19 (n = 307)	11.35 ± 7.141 (n = 298)	11.98 ± 7.23 (n = 95)	11.10 ± 7.07 (n = 200)

Mean ± SD (number of subjects with events)
a) FAS, b) Population for antibody analysis

Table 57. Incidence of fracture, by anti-abaloparatide antibody production (abaloparatide group of Foreign Study 05-003, population for antibody analysis)

Endpoint	Anti-abaloparatide antibody negative	Anti-abaloparatide antibody positive		
		All anti-abaloparatide antibody positive subjects	Neutralizing antibody negative	Neutralizing antibody positive
New spinal fracture[a]	0.97 (3/308)	0.33 (1/299)	1.04 (1/96)	0 (0/200)
New non-spinal fracture	3.23 (10/310)	2.00 (6/300)	3.13 (3/96)	1.49 (3/201)
Clinical fracture	4.52 (14/310)	3.00 (9/300)	5.21 (5/96)	1.99 (4/201)
Main osteoporotic fracture	1.61 (5/310)	1.33 (4/300)	3.13 (3/96)	0.50 (1/201)

Incidence (number of subjects with events/number of subjects evaluated)
a) Analysis of subjects included both in the antibody analysis population and in mITT.

In Japanese and foreign clinical studies, some subjects became antibody positive after abaloparatide administration, but the antibody production did not have any significant effect on the safety or efficacy of abaloparatide.

PMDA's view:
In Japanese and foreign clinical studies, many subjects became positive for anti-abaloparatide antibody after abaloparatide administration and some of them were positive for neutralizing antibody. Also, the exposure to abaloparatide tended to decrease in antibody-positive subjects [see Section "6.R.3 Effect of antibody production on pharmacokinetics"]. However, the antibody is unlikely to pose any clinically significant problem, judging from the findings that the antibody production had no significant effect on the incidence of fracture, percent change in bone density, or the safety profile up to Week 18.

7.R.3 Clinical positioning and indication

The applicant's explanation:
The objective of drug therapies for osteoporosis is prevention of fracture. In patients with osteoporosis at high risk of fracture due to extensive decrease in bone mass, treatment with osteogenesis promoters, such as PTH and anti-sclerostin antibody, which increase bone mass and rebuild bone structure is considered to be effective (*N Engl J Med*. 2001;344:1434-41). In Japan, teriparatide (genetical recombination) and teriparatide acetate (PTH drugs) and an anti-sclerostin antibody romosozumab (genetical recombination) are approved as therapeutic drugs for "treatment for patients with

osteoporosis at high risk of fracture." Teriparatide (genetical recombination) is effective in increasing bone density and preventing spinal and non-spinal fractures, while it does not prevent the fracture of proximal femur and the decrease in bone density of radius, showing uneven efficacy depending on the site of bones. Teriparatide acetate increases bone density and prevents spinal fracture, but it does not prevent non-spinal fracture and fracture of proximal femur. Romosozumab (genetical recombination) promotes osteogenesis and inhibits bone resorption by a mechanism different from that of PTH, thereby increasing bone mass. In a placebo-controlled study of romosozumab (genetical recombination), 1-year treatment with romosozumab (genetical recombination) is reported to enhance bone mass and prevent spinal fracture. However, the treatment for 1 year was ineffective in preventing non-spinal fracture and fracture of proximal femur. Instead, a sequential therapy with romosozumab (genetical recombination) for 1 year followed by denosumab for 1 year is reported to significantly prevent non-spinal fracture (*N Engl J Med.* 2016;375:1532-43). Thus, although several osteogenesis promoters are currently available, there are demands for new osteogenesis promoters that exhibit a greater bone mass-increasing effect than that of conventional agents in a short period of time and promptly exhibit efficacy in preventing spinal and non-spinal fractures.

Foreign Study 05-003 demonstrated that the incidence of new spinal fracture is significantly lower in the abaloparatide group than in the placebo group and that the incidence of non-spinal fracture is also lower in the abaloparatide group than in the placebo group. In addition, abaloparatide had an early onset of efficacy in increasing the bone density of the lumbar spine, proximal femur, and femoral neck, and tended to increase the bone density of proximal femur and femoral neck in particular to a greater extent than did teriparatide. As for the changes over time in serum concentration of CTX, a bone resorption marker, the level increased after abaloparatide administration but returned to a level similar to that of placebo after 18 months, whereas, after teriparatide administration, serum CTX concentration remained at a higher level than that of abaloparatide throughout the treatment period (Figure 5), suggesting that the bone-resorbing effect of abaloparatide is weaker than that of teriparatide. Based on the above results, abaloparatide is expected to fulfill the unmet needs not satisfied by conventional therapeutic agents and is thus highly useful in patients with osteoporosis at high risk of fracture.

As for the indication of abaloparatide, since patients with osteoporosis at high risk of fracture were investigated in Japanese Study 301 and Foreign Study 05-003, the proposed indication is "treatment for patients with osteoporosis at high risk of fracture." By referring to important risk factors for diagnosing patients with osteoporosis at high risk of fracture, described in the diagnostic criteria, etc., published by The Japanese Society for Bone and Mineral Research and the Japan Osteoporosis Society, the following precautions were included in the Precautions Concerning Indications section: "Abaloparatide should be administered to patients with a risk factor of fracture, such as low bone density, existing fracture, advanced age, a family history of femoral neck fracture, etc."

PMDA's view:
In Foreign Study 05-003 in patients with postmenopausal osteoporosis at high risk of fracture, the effect of abaloparatide to prevent new spinal fracture has been confirmed. Given the above results and the results of Japanese Study 301 in Japanese patients with osteoporosis at high risk of fracture,

abaloparatide is expected to be effective in Japanese patients with postmenopausal osteoporosis and also in Japanese male patients with osteoporosis [see Section "7.R.1 Efficacy"]. As for safety, abaloparatide has an acceptable safety profile, provided that adequate precautions are provided [see Section "7.R.2 Safety"]. Regarding the comparison with teriparatide, the incidences of orthostatic hypotension and palpitations tended to be higher in the abaloparatide group than in the teriparatide group. However, the incidence of new spinal fracture up to Month 18, an efficacy endpoint, in Foreign Study 05-003 was 0.58% (4 of 690) of subjects in the abaloparatide group and 0.84% (6 of 717) of subjects in the teriparatide group, and bone density of the lumbar spine (L1-L4), femur (proximal), and femur (neck) increased more rapidly in the abaloparatide group than in the teriparatide group. In addition, the percent change in the bone density of femur (proximal, neck) at Month 18 tended to be higher in the abaloparatide group than in the teriparatide group. These results suggest that abaloparatide is well qualified as a treatment option for patients with osteoporosis at high risk of fracture, as with conventional PTH drugs, and that the indication of abaloparatide should be "treatment for patients with osteoporosis at high risk of fracture." The applicant's plan to provide precautions in the Precautions Concerning Indications section by referring to the diagnostic criteria, etc., published by The Japanese Society for Bone and Mineral Research and the Japan Osteoporosis Society, is acceptable.

7.R.4 Dosage and administration

The applicant's explanation:

In the dose-finding Foreign Study 05-002, placebo, abaloparatide 20, 40, 80 μg, or teriparatide 20 μg was administered subcutaneously once daily for 24 weeks to patients with postmenopausal osteoporosis. Results showed a dose-dependent increase in the bone density of the lumbar spine (L1-L4), one of a primary endpoint. Abaloparatide 80 μg was well tolerated without any safety problems [see Section "7.1.2 Foreign phase II study in non-Japanese patients with postmenopausal osteoporosis"]. In Foreign Study 05-003, placebo, abaloparatide 80 μg, or teriparatide 20 μg was administered subcutaneously once daily for 18 months to patients with postmenopausal osteoporosis. The results showed that the incidence of new spinal fracture, another primary endpoint, was significantly lower in the abaloparatide group than in the placebo group. Also, the percent change in the bone density of the lumbar spine (L1-L4), a secondary endpoint, was greater in the abaloparatide group than in the placebo group [see Section "7.2.2 Foreign phase III study in patients with postmenopausal osteoporosis"]. In Japanese Study 004, the Japanese phase II study, placebo, abaloparatide 40 μg, or 80 μg was administered subcutaneously once daily for 48 weeks to patients with postmenopausal osteoporosis. In this study as well, the percent change in the lumbar spine (L2-L4), the primary endpoint, increased in a dose-dependent manner. The incidence of adverse events did not significantly differ between the abaloparatide 40 μg and 80 μg groups; no dose-dependent increase was observed in any adverse events [see Section "7.1.1 Japanese phase II study in Japanese patients with postmenopausal osteoporosis"]. Based on the above, the optimal dose of abaloparatide is considered to be 80 μg for Japanese patients as well. Accordingly, in Japanese Study 301, placebo or abaloparatide 80 μg was administered subcutaneously once daily for 18 months to patients with osteoporosis. The percent change in the bone density of the lumbar spine (L1-L4), the primary endpoint, was significantly higher in the abaloparatide 80 μg group than in the placebo group. As for safety, administration of abaloparatide 80 μg for 18 months was well tolerated [see Section "7.2.1

Japanese phase III study in Japanese patients with osteoporosis"]. Based on the above, the recommended clinical dose of abaloparatide was concluded to be 80 μg once daily.

The upper limit of the treatment period was determined to be 18 months because the longest period of treatment with abaloparatide in Japanese clinical studies was 18 months. Switching from other PTH drugs to abaloparatide has never been done in patients, leaving the safety of such a treatment unestablished. Also, the upper limit of the treatment period with abaloparatide after such a switching has not been investigated. The above information will be included in the Precautions Concerning Dosage and Administration section to raise caution.

PMDA's view:
In Japanese and foreign phase II studies, a dose-response relationship of the bone density of the lumbar spine, etc., was confirmed up to abaloparatide 80 μg, and no safety problem was observed within the range up to 80 μg. In Japanese study 301, the superiority of once daily administration of abaloparatide 80 μg to placebo was demonstrated in the percent change in the bone density of the lumbar spine (L1-L4), the primary endpoint. Also, in Foreign Study 05-003, the superiority of once daily administration of abaloparatide 80 μg to placebo was demonstrated in the incidence of new spinal fracture up to Month 18, the primary endpoint. In addition, abaloparatide 80 μg possesses an acceptable safety profile, as demonstrated in Japanese Study 301 and Foreign Study 05-003. It is therefore appropriate to determine the dosage regimen of abaloparatide as "once daily subcutaneous administration of abaloparatide 80 μg."

In nonclinical studies of conventional PTH drugs, the upper limit of the treatment period was included in the dosage regimen in order to avoid bone neoplastic lesions such as osteosarcoma, adverse drug reactions observed in nonclinical studies. Similarly, bone neoplastic lesions were observed in carcinogenicity studies of abaloparatide in rats [see Section "5.R.2 Carcinogenicity"]. It is therefore appropriate to determine the upper limit of the treatment period as 18 months, as employed in Japanese and foreign phase III studies, and include the limit in the dosage regimen. The applicant's plan of providing precautions for switching from conventional PTH drugs to abaloparatide is also appropriate.

7.R.5 Populations with special backgrounds

7.R.5.1 Elderly patients

The applicant's explanation:
Table 58 shows the incidence of adverse events by age group in the pooled analysis of Japanese studies and pooled analysis of foreign studies. In either of the analyses, no significant difference was observed among age groups in the incidences of adverse events, adverse drug reactions, serious adverse events, or adverse events leading to treatment discontinuation. Among adverse events of special interest, hypercalcaemia-related events and blood uric acid increased-related events occurred slightly more frequently in patients aged ≥75 years in the pooled analysis of the Japanese studies, but there are limitations to the interpretation of the results because of the limited number of patients aged ≥75 years.

Thus, there was no safety concern on the administration of abaloparatide in elderly patients in clinical studies, suggesting that abaloparatide does not have a high risk in elderly patients.

Table 58. Incidence of adverse events by age group (pooled analyses of Japanese and foreign clinical studies, safety analysis populations)

Event	Age (years)	Pooled analysis of Japanese studies		Pooled analysis of foreign studies		
		Placebo (n = 125)	Abaloparatide 80 µg (n = 193)	Placebo (n = 865)	Abaloparatide 80 µg (n = 918)	Teriparatide (n = 863)
All adverse events	<65	88.9 (24/27)	90.9 (40/44)	84.4 (157/186)	85.4 (164/192)	87.2 (156/179)
	≥65 and <75	72.2 (57/79)	89.5 (111/124)	87.7 (465/530)	89.9 (510/567)	88.1 (458/520)
	≥75	89.5 (17/19)	80.0 (20/25)	87.2 (130/149)	89.9 (143/159)	91.5 (150/164)
All adverse drug reactions	<65	14.8 (4/27)	22.7 (10/44)	19.9 (37/186)	34.9 (67/192)	30.7 (55/179)
	≥65 and <75	11.4 (9/79)	30.6 (38/124)	26.6 (141/530)	40.7 (231/567)	36.7 (191/520)
	≥75	0 (0/19)	24.0 (6/25)	25.5 (38/149)	33.3 (53/159)	36.6 (60/164)
Serious adverse events	<65	3.7 (1/27)	6.8 (3/44)	9.1 (17/186)	5.7 (11/192)	7.8 (14/179)
	≥65 and <75	7.6 (6/79)	2.4 (3/124)	9.4 (50/530)	9.7 (55/567)	8.7 (45/520)
	≥75	15.8 (3/19)	4.0 (1/25)	16.1 (24/149)	12.6 (20/159)	14.0 (23/164)
Adverse events leading to treatment discontinuation	<65	3.7 (1/27)	4.5 (2/44)	4.8 (9/186)	8.9 (17/192)	3.4 (6/179)
	≥65 and <75	2.5 (2/79)	1.6 (2/124)	5.5 (29/530)	10.4 (59/567)	7.7 (40/520)
	≥75	5.3 (1/19)	0 (0/25)	7.4 (11/149)	9.4 (15/159)	6.7 (11/164)
Cardiovascular-related adverse events	<65	0 (0/27)	13.6 (6/44)	11.8 (22/186)	17.7 (34/192)	10.1 (18/179)
	≥65 and <75	7.6 (6/79)	15.3 (19/124)	13.0 (69/530)	18.2 (103/567)	13.8 (72/520)
	≥75	15.8 (3/19)	8.0 (2/25)	16.8 (25/149)	14.5 (23/159)	11.6 (19/164)
Palpitations-related adverse events	<65	0 (0/27)	9.1 (4/44)	1.1 (2/186)	9.4 (18/192)	2.2 (4/179)
	≥65 and <75	3.8 (3/79)	7.3 (9/124)	2.8 (15/530)	9.9 (56/567)	4.0 (21/520)
	≥75	5.3 (1/19)	4.0 (1/25)	4.0 (6/149)	3.1 (5/159)	4.9 (8/164)
Orthostatic hypotension-related adverse events	<65	7.4 (2/27)	20.5 (9/44)	9.1 (17/186)	21.4 (41/192)	14.0 (25/179)
	≥65 and <75	6.3 (5/79)	16.1 (20/124)	14.7 (78/530)	26.1 (148/567)	20.0 (104/520)
	≥75	15.8 (3/19)	12.0 (3/25)	18.8 (28/149)	22.0 (35/159)	19.5 (32/164)
Nausea-related adverse events	<65	3.7 (1/27)	2.3 (1/44)	3.2 (6/186)	7.8 (15/192)	7.8 (14/179)
	≥65 and <75	8.9 (7/79)	8.1 (10/124)	2.5 (13/530)	9.5 (54/567)	6.0 (31/520)
	≥75	5.3 (1/19)	8.0 (2/25)	6.0 (9/149)	6.3 (10/159)	4.3 (7/164)
Hypercalcaemia-related adverse events	<65	3.7 (1/27)	0 (0/44)	1.1 (2/186)	1.6 (3/192)	3.4 (6/179)
	≥65 and <75	0 (0/79)	4.8 (6/124)	0.8 (4/530)	1.9 (11/567)	4.2 (22/520)
	≥75	0 (0/19)	8.0 (2/25)	0 (0/149)	1.9 (3/159)	6.7 (11/164)
Blood uric acid increased-related adverse events	<65	3.7 (1/27)	6.8 (3/44)	0.5 (1/186)	1.6 (3/192)	4.5 (8/179)
	≥65 and <75	0 (0/79)	6.5 (8/124)	0.4 (2/530)	1.6 (9/567)	1.3 (7/520)
	≥75	0 (0/19)	20.0 (5/25)	0.7 (1/149)	1.9 (3/159)	1.8 (3/164)

Incidence in % (number of subjects with events/number of subjects evaluated)

PMDA's view:

In the pooled analysis of Japanese studies, hypercalcaemia-related events and blood uric acid increased-related events in the abaloparatide group occurred at high incidences in the age group of ≥75 years, but the results were obtained from a limited number of subjects, and no similar tendencies were observed in the pooled analysis of foreign studies. The incidences of other adverse events were not significantly different among subjects of different age groups.

7.R.5.2 Patients with renal impairment

The applicant's explanation:

In Foreign Study 05-011 in patients with renal impairment, adverse events occurred in 3 of 8 subjects with normal renal function (Ccr ≥90 mL/min), in 1 of 8 subjects with mild renal impairment (≥60 mL/min and <90 mL/min), in 1 of 8 subjects with moderate renal impairment (≥30 mL/min and <60 mL/min), and in 2 of 8 subjects with severe renal impairment (≥15 mL/min and <30 mL/min); the incidence was the highest in subjects with normal renal function. Headache was the adverse event with the highest incidence; it occurred in 2 of 8 subjects with normal renal function and in 1 of 8 subjects with moderate renal impairment. All other adverse events occurred in 1 subject each. All adverse events were mild, and their causal relationship to the study drug was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation. The exposure to

abaloparatide was higher in subjects with severe renal impairment than in subjects with normal renal function, i.e., 1.4 times in C_{max} and 2.1 times in AUC_{inf}. Plasma abaloparatide concentration increased in accordance with the severity of renal impairment, while the incidence of adverse events or abnormalities in laboratory tests, vital signs, or ECG parameters did not increase with the increase in the severity of renal impairment.

Table 59 shows the incidence of adverse events by renal function in the pooled analysis of Japanese studies. There were no subjects with severe renal impairment (Ccr <30 mL/min) because patients with clinically severe renal impairment were excluded from enrollment in these studies. There was no difference in the incidence of adverse events, adverse drug reactions, serious adverse events, or adverse events leading to treatment discontinuation among groups of different severity of renal impairment in the abaloparatide group. Among adverse events of special interest in the abaloparatide group, adverse events related to palpitation, orthostatic hypotension, and blood uric acid increased tended to occur at higher incidences with the extent of renal impairment. Among adverse events related to orthostatic hypotension and blood uric acid increased, the only serious event observed was hypotension (an orthostatic hypotension-related event) in 1 subject with mild renal impairment. This event resolved while the treatment was continued, and its causal relationship to the study drug was ruled out.

Table 59 shows the incidence of adverse events by renal function in the pooled analysis of foreign studies. There were only 4 subjects with severe renal impairment (1 in the placebo group, 2 in the abaloparatide group, 1 in the teriparatide group) because patients with clinically severe renal impairment were excluded from enrollment in the studies. There was no significant difference in the incidence of adverse events or adverse drug reactions among groups of different severity of renal impairment in the abaloparatide group.

There was no significant difference in the incidence of serious adverse events or adverse events leading to treatment discontinuation among groups of different severity of renal impairment in the abaloparatide group. Among adverse events of special interest in the abaloparatide group, the incidence of nausea-related adverse events tended to slightly increase with the increase in the severity of renal impairment. No serious nausea was observed. No adverse events of special interest were observed in the 2 subjects with severe renal impairment in the abaloparatide group.

Table 59. Incidence of adverse events, by severity of renal impairment (pooled analyses of Japanese and foreign studies, safety analysis population)

Event	Renal impairment	Pooled analysis of Japanese studies		Pooled analysis of foreign studies		
		Placebo (n = 125)	Abaloparatide 80 μg (n = 193)	Placebo (n = 865)	Abaloparatide 80 μg (n = 918)	Teriparatide (n = 863)
All adverse events	Normal	50.0 (1/2)	85.7 (12/14)	90.4 (47/52)	95.5 (63/66)	89.3 (50/56)
	Mild impairment	78.4 (80/102)	87.7 (128/146)	86.3 (465/539)	88.3 (520/589)	88.1 (476/540)
	Moderate impairment	81.0 (17/21)	93.9 (31/33)	87.5 (239/273)	88.9 (232/261)	89.1 (237/266)
	Severe impairment	-	-	100 (1/1)	100 (2/2)	100 (1/1)
All adverse drug reactions	Normal	0 (0/2)	35.7 (5/14)	40.4 (21/52)	56.1 (37/66)	48.2 (27/56)
	Mild impairment	11.8 (12/102)	25.3 (37/146)	25.2 (136/539)	37.2 (219/589)	37.0 (200/540)
	Moderate impairment	4.8 (1/21)	36.4 (12/33)	21.6 (59/273)	36.4 (95/261)	29.3 (78/266)
	Severe impairment	-	-	0 (0/1)	0 (0/2)	100 (1/1)
Serious adverse events	Normal	0 (0/2)	7.1 (1/14)	7.7 (4/52)	21.2 (14/66)	5.4 (3/56)
	Mild impairment	4.9 (5/102)	3.4 (5/146)	10.0 (54/539)	8.1 (48/589)	9.4 (51/540)
	Moderate impairment	23.8 (5/21)	3.0 (1/33)	11.7 (32/273)	9.2 (24/261)	10.5 (28/266)
	Severe impairment	-	-	100 (1/1)	0 (0/2)	0 (0/1)
Adverse events leading to treatment discontinuation	Normal	0 (0/2)	0 (0/14)	7.7 (4/52)	10.6 (7/66)	3.6 (2/56)
	Mild impairment	2.9 (3/102)	2.7 (4/146)	5.8 (31/539)	8.7 (51/589)	7.6 (41/540)
	Moderate impairment	4.8 (1/21)	0 (0/33)	5.1 (14/273)	12.6 (33/261)	4.9 (13/266)
	Severe impairment	-	-	0 (0/1)	0 (0/2)	100 (1/1)
Cardiovascular-related adverse events	Normal	0 (0/2)	21.4 (3/14)	9.6 (5/52)	16.7 (11/66)	16.1 (9/56)
	Mild impairment	7.8 (8/102)	11.6 (17/146)	12.8 (69/539)	17.7 (104/589)	9.6 (52/540)
	Moderate impairment	4.8 (1/21)	21.2 (7/33)	15.0 (41/273)	17.2 (45/261)	18.0 (48/266)
	Severe impairment	-	-	100 (1/1)	0 (0/2)	0 (0/1)
Palpitations-related adverse events	Normal	0 (0/2)	0 (0/14)	1.9 (1/52)	12.1 (8/66)	3.6 (2/56)
	Mild impairment	3.9 (4/102)	6.8 (10/146)	2.4 (13/539)	8.8 (52/589)	3.1 (17/540)
	Moderate impairment	0 (0/21)	12.1 (4/33)	2.9 (8/273)	7.3 (19/261)	5.3 (14/266)
	Severe impairment	-	-	100 (1/1)	0 (0/2)	0 (0/1)
Orthostatic hypotension-related adverse events	Normal	0 (0/2)	0 (0/14)	21.2 (11/52)	22.7 (15/66)	21.4 (12/56)
	Mild impairment	8.8 (9/102)	16.4 (24/146)	13.0 (70/539)	23.3 (137/589)	17.0 (92/540)
	Moderate impairment	4.8 (1/21)	24.2 (8/33)	15.4 (42/273)	27.2 (71/261)	21.1 (56/266)
	Severe impairment	-	-	0 (0/1)	50.0 (1/2)	100 (1/1)
Nausea-related adverse events	Normal	0 (0/2)	7.1 (1/14)	3.8 (2/52)	6.1 (4/66)	10.7 (6/56)
	Mild impairment	7.8 (8/102)	7.5 (11/146)	3.2 (17/539)	8.1 (48/589)	5.2 (28/540)
	Moderate impairment	4.8 (1/21)	3.0 (1/33)	3.3 (9/273)	10.3 (27/261)	6.8 (18/266)
	Severe impairment	-	-	0 (0/1)	0 (0/2)	0 (0/1)
Hypercalcaemia-related events adverse events	Normal	0 (0/2)	7.1 (1/14)	0 (0/52)	1.5 (1/66)	7.1 (4/56)
	Mild impairment	1.0 (1/102)	4.8 (7/146)	0.6 (3/539)	2.2 (13/589)	3.9 (21/540)
	Moderate impairment	0 (0/21)	0 (0/33)	1.1 (3/273)	1.1 (3/261)	5.3 (14/266)
	Severe impairment	-	-	0 (0/1)	0 (0/2)	0 (0/1)
Blood uric acid increased-related adverse events	Normal	0 (0/2)	7.1 (1/14)	0 (0/52)	0 (0/66)	1.8 (1/56)
	Mild impairment	1.0 (1/102)	4.8 (7/146)	0.4 (2/539)	1.4 (8/589)	1.7 (9/540)
	Moderate impairment	0 (0/21)	24.2 (8/33)	0.7 (2/273)	2.7 (7/261)	3.0 (8/266)
	Severe impairment	-	-	0 (0/1)	0 (0/2)	0 (0/1)

Incidence in % (number of subjects with events/number of subjects evaluated)

Thus, the incidences of adverse events related to palpitation, orthostatic hypotension, and blood uric acid increased in the pooled analysis of Japanese studies and the incidence of nausea-related adverse events in the pooled analysis of foreign studies tended to increase slightly in accordance with the extent of renal impairment. However, the only serious event observed was hypotension in a subject with mild impairment in the pooled analysis of Japanese studies, and its causal relationship to the study drug was ruled out, suggesting that these events are unlikely to pose any significant clinical problem in patients with renal impairment. Also, abaloparatide accumulation in blood did not occur in multiple administration even in patients with severe renal impairment, suggesting that abaloparatide is eliminated promptly enough given the dosing interval of abaloparatide. Thus, abaloparatide concentration in blood is unlikely to exceed the level observed following the administration of the maximum tolerated dose of abaloparatide (240 μg) even in patients with severe renal impairment [see Section "6.R.2 Administration to patients with renal impairment"]. These results suggest that abaloparatide is unlikely to pose clinical problems in patients with renal impairment, including

patients with severe impairment. However, since plasma abaloparatide concentration increases with the increase in the severity of renal impairment, resulting in the increase in the exposure to abaloparatide, and since there is only limited experience of abaloparatide administration to patients with severe renal impairment, the package insert will include the following precautions: (1) Patients with renal impairment should periodically be tested for renal function and (2) delayed elimination of abaloparatide from blood occurs in patients with severe renal impairment. Also, the information that no clinical study was conducted in patients undergoing hemodialysis will be provided.

PMDA's view:
Regarding the safety in patients with or without renal impairment, results of Japanese and foreign clinical studies did not clearly show that the incidences of all adverse events, serious adverse events, or adverse events leading to treatment discontinuation were higher in patients with renal impairment. However, the applicant's plan to provide cautions for patients with renal impairment in the package insert is appropriate, taking account of the observations (1) that the incidences of adverse events related to palpitation, orthostatic hypotension, and blood uric acid increased in the pooled analysis of Japanese studies and the incidence of nausea-related adverse events in the pooled analysis of foreign studies tended to increase in accordance with the severity of renal impairment, and (2) that the exposure to abaloparatide in plasma increases in accordance with the severity of renal impairment [see Section "6.R.2 Administration to patients with renal impairment"].

7.R.5.3 Patients with hepatic impairment

The applicant's explanation:
Results of nonclinical studies suggest that abaloparatide is degraded by multiple proteases into amino acids and metabolized in the kidney. Accordingly, hepatic impairment is unlikely to affect the systemic exposure to abaloparatide. Therefore, no clinical study in patients with hepatic impairment was conducted. In the pooled analysis of Japanese studies, either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeded the upper limit of the reference range and was ≤2 times the upper limit of the reference range in 2 subjects in the placebo group and 4 subjects in the abaloparatide group. There were no subjects in any treatment group with AST or ALT level of >2 times the upper limit of the reference range. Of the above 4 subjects in the abaloparatide group, all of them had adverse events, 1 subject had a serious adverse event, but none had adverse events leading to treatment discontinuation. In the pooled analysis of foreign studies, either AST or ALT exceeded the upper limit of the reference range and was ≤2 times the upper limit of the reference range in 12 subjects in the placebo group, 14 subjects in the abaloparatide group, and 15 subjects in the teriparatide group. Either AST or ALT exceeded twice the upper limit of the reference range and was ≤3 times the upper limit of the reference range in 1 subject in the abaloparatide group, and either AST or ALT was >3 times the upper limit of the reference range in 1 subject in the teriparatide group. Of 14 subjects in the abaloparatide group with either AST or ALT exceeding the upper limit of the reference range and ≤2 times the upper limit of the reference range, 12 subjects had adverse events, 3 subjects had serious adverse events, and 2 subjects had adverse events leading to treatment discontinuation. In the subject with either AST or ALT exceeding 2 times the upper limit of reference range and ≤3 times the upper limit of the reference range, an adverse event was observed in 1 subject in the abaloparatide group, which was non-serious but led to treatment discontinuation. Because of the limited number of subjects

with hepatic impairment, there are limitations to the comparison of the incidence of adverse events by hepatic impairment. Nevertheless, investigations on adverse events of special interest such as cardiovascular-related adverse events (including palpitations and orthostatic hypotension), hypercalcaemia, adverse events related to blood uric acid increased, and nausea suggested that hepatic function had no clear effect on the incidence of these adverse events.

PMDA's view:
Because of the limited number of subjects with hepatic impairment enrolled in Japanese and foreign clinical studies, there are limitations to the investigation. Nevertheless, no particular problems were observed in the studies. Also, given the pharmacokinetic profile of abaloparatide, hepatic impairment is unlikely to affect the safety profile of abaloparatide.

7.R.6 Post-marketing investigations

The applicant's explanation:
In the Japanese and foreign clinical studies, cardiovascular-related adverse events tended to occur more frequently in the abaloparatide group than in the teriparatide or placebo group. This difference is considered to be due to the difference in the incidence of palpitations associated with increased heart rate. The incidence of MACE did not differ between the abaloparatide group and the teriparatide or placebo group. On the other hand, parathyroid hormone is known to dilate vascular smooth muscles, exhibits positive chronotropic/inotropic action, and peripheral vasodilator actions, and these effects were confirmed in nonclinical studies of abaloparatide as well. MACE may possibly result in a serious outcome, and it is helpful to confirm in clinical practice the incidence of MACE among patients with more diverse characteristics than those in subjects enrolled in clinical studies. Therefore, the applicant plans to conduct a post-marketing surveillance to create a database for comparing the incidence of serious cardiovascular-related adverse events associated with abaloparatide or with drugs in the same class. The detailed design for the surveillance will be worked out later. Currently, the applicant plans to evaluate the relative risk of serious cardiovascular-related adverse events in patients with osteoporosis at high risk of fracture, divided into the exposure group (patients treated with abaloparatide) and the control group (patients treated with teriparatide).

PMDA's view:
Parathyroid hormones including abaloparatide are known to act on the cardiovascular system, exhibiting positive chronotropic and inotropic actions, and peripheral vasodilator actions. Given that palpitations, etc., occurred more frequently in the abaloparatide group than in the teriparatide group in foreign clinical studies, the possibility cannot be ruled out that abaloparatide affects the cardiovascular system more than does teriparatide. In Japanese and foreign clinical studies, however, no difference was observed in the incidence of serious cardiovascular events or MACE between the abaloparatide group and the placebo or teriparatide group, suggesting that, currently, the observed difference in the incidence of palpitations does not pose any clinically significant problem. Nevertheless, it will be necessary to continuously investigate whether abaloparatide poses any particular safety problem compared with drugs in the same class after the market launch. The policy and the outline of the post-marketing surveillance proposed by the applicant appear to be appropriate currently, but the detail

of the post-marketing surveillance will be concluded, also taking account of the comments raised in 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 Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that abaloparatide has efficacy in treating patients with osteoporosis at high risk of fracture, and that abaloparatide has acceptable safety in view of its benefits. Abaloparatide, a PTHrP derivative, is clinically meaningful because it offers a new treatment option for patients with osteoporosis at high risk of fracture.

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

Review Report (2)

February 3, 2021

Product Submitted for Approval

Brand Name	Ostabalo Subcutaneous Injection Cart 3 mg
Non-proprietary Name	Abaloparatide Acetate
Applicant	Teijin Pharma Limited
Date of Application	May 27, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's view:

Abaloparatide-associated increase in bone density in patients with postmenopausal osteoporosis was investigated in clinical studies. Japanese Study 301 demonstrated the superiority of abaloparatide to placebo in the percent change in bone density of the lumbar spine (L1-L4), the primary endpoint. In foreign Study 05-003, abaloparatide increased bone density more than placebo and as much as or more than teriparatide. As for the fracture-preventing effect, Foreign Study 05-003 demonstrated the superiority of abaloparatide to placebo in the incidence of new spinal fracture within 18 months from baseline, the primary endpoint. Further, results from the Japanese study (Study 301) were consistent with those from the foreign study (Study 05-003); PMDA therefore considers that abaloparatide is expected to be effective in Japanese patients with postmenopausal osteoporosis. Japanese Study 301 showed no tendency of a clear difference in the increase in bone density (i.e. the percent change in bone density from baseline) between male and postmenopausal female patients with osteoporosis. Thus, abaloparatide is expected to be effective in male patients with osteoporosis as well.

At the Expert Discussion, the following comment was raised from the expert advisors:

The study results of male patients with osteoporosis should be interpreted with care because the study included only a limited number of male patients.

However, PMDA's conclusion (i.e., abaloparatide is expected to be effective in both male and postmenopausal female patients with osteoporosis) was supported by the expert advisors.

1.2 Safety

PMDA's view on the safety of abaloparatide:

In the Japanese and foreign clinical studies, some events occurred more frequently in the abaloparatide group than in the placebo group, but most of them are known to occur with conventional PTH drugs as well. Further, the clinical studies showed no significant difference in the incidence of serious adverse events or adverse events leading to treatment discontinuation between the abaloparatide group and the placebo or teriparatide group.

In Japanese and foreign clinical studies, among adverse events of special interest associated with abaloparatide, cardiovascular-related adverse events tended to occur more frequently in the abaloparatide group than in the placebo or teriparatide group, and events leading to treatment discontinuation also tended to occur more frequently in the abaloparatide group than in the other groups. The main cause of these tendencies was palpitation-related events. In addition, orthostatic hypotension tended to occur more frequently in the abaloparatide group than in the placebo or teriparatide group. On the other hand, the incidence of serious events related to palpitations or orthostatic hypotension was similar between the abaloparatide group and the placebo or teriparatide group. Also, neither serious adverse events related to the cardiovascular system nor MACE occurred more frequently in the abaloparatide group than in the placebo or teriparatide group. Based on these findings, the cardiovascular effects of abaloparatide is considered to be acceptable at present. Nevertheless, the package insert should include a precautionary statement regarding palpitations and orthostatic hypotension to inform patients about these events. Attention should be paid to occurrences of abaloparatide-associated cardiovascular events after the market launch.

In addition to the above, PMDA reviewed each of the following noteworthy adverse events associated with abaloparatide: Nausea, hypercalcaemia, injection site reactions, hypersensitivity, hyperuricaemia, osteosarcoma, and antibody production. As a result, PMDA considers that the safety of abaloparatide is acceptable provided that appropriate safety alerts are issued.

PMDA's conclusions (i.e., the safety of abaloparatide, including the effect on the cardiovascular system, is acceptable at present) were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- The post-marketing surveillance should investigate the incidence of cardiovascular events by sex, concurrent heart disease including cardiac failure (yes/no), concomitant antihypertensive agents (yes/no), and renal impairment (yes/no), for the following reasons:
  (1) The risk of ischemic heart disease has been reported to differ by sex.
  (2) Abaloparatide increases heart rate, and therefore may pose a risk in patients with cardiac failure.
  (3) Orthostatic hypotension may pose a safety problem in patients using antihypertensive drugs.
  (4) Patients with renal impairment are at risk of cardiovascular calcification.

Based on the above, PMDA instructed the applicant to investigate, in the post-marketing surveillance, the incidences of serious cardiovascular events by sex, concurrent heart disease including cardiac

failure (yes/no), antihypertensive drugs (yes/no), and renal impairment (yes/no). The applicant agreed. PMDA confirmed that the applicant took appropriate actions. PMDA has also confirmed that there are no major concerns on the incidences of serious cardiovascular events in foreign countries after the marketing.

1.3 Clinical positioning and indication

PMDA's view:

Both Japanese Study 301 and Foreign Study 05-003 enrolled patients with osteoporosis at high risk of fracture. Results of these studies show that abaloparatide is expected to be effective in Japanese male and postmenopausal female patients with osteoporosis with acceptable safety. As for a comparison between abaloparatide and conventional PTH drugs, in foreign clinical studies, palpitations and orthostatic hypotension tended to occur more frequently in the abaloparatide group than in the teriparatide group, but the incidence of serious cardiovascular events did not differ. In view of these results and the incidence of spinal fracture and the percent change in the bone density in the abaloparatide and teriparatide groups, abaloparatide can be considered as a treatment option for patients with osteoporosis at high risk of fracture, as with conventional PTH drugs. The indication of abaloparatide should be "treatment for patients with osteoporosis at high risk of fracture," the same indication of conventional PTH drugs. The applicant plans to include a precautionary statement in the Precautions Concerning Indications section of the package insert. (The statement will be prepared based on the diagnostic criteria, etc., published by the Japanese Society for Bone and Mineral Research and the Japan Osteoporosis Society.) This applicant's plan is appropriate.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration

PMDA's view:

The Japanese and foreign phase II studies demonstrated the dose-response relationship between abaloparatide therapy up to 80 μg and the bone density of the lumbar spine. Also, the Japanese and foreign phase III studies confirmed the efficacy of abaloparatide 80 μg with acceptable safety. It is therefore appropriate to determine the dosage of abaloparatide as "once daily subcutaneous administration of 80 μg." Bone neoplastic lesions were observed in the carcinogenicity study in rats. Therefore the Dosage and Administration section should state that the duration of abaloparatide therapy should not exceed 18 months (which is the treatment period employed in the Japanese and foreign phase III studies). The following precautionary statements regarding switching from conventional PTH drugs to abaloparatide should be included in the Precautions Concerning Dosage and Administration section:

(1) Switching from other PTH drugs to abaloparatide has never been done in patients. The safety of abaloparatide therapy switched from other PTH drugs has not been established, as with drugs in the same class.
(2) The maximum duration of abaloparatide therapy after switching from other PTH drugs has not been investigated.

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA and made the following comments:

- Abaloparatide has the same pharmacological effect as that of conventional PTH drugs. Therefore precautionary statements regarding the safety of abaloparatide therapy switched from other PTH drugs should include further information such as associated specific risks.

Taking account of this comment raised at the Expert Discussion, PMDA instructed the applicant to take the following actions:

- Ensure that the package insert states that bone neoplastic lesions were observed in nonclinical studies of abaloparatide.
- Define the maximum duration of abaloparatide therapy as 18 months
- Disseminate the following information: The maximum duration of treatment has been established also for conventional PTH drugs because bone neoplastic lesions were observed in their nonclinical studies, as with abaloparatide.

The applicant agreed. PMDA confirmed that appropriate actions were taken by the applicant.

1.5 Patient population with special characteristics

PMDA reviewed the safety in patients with special characteristics: age (elderly patients), renal impairment, and hepatic impairment. As for the safety in patients with or without renal impairment, the incidence of adverse events did not significantly increase in patients with renal impairment either in Japanese or foreign clinical studies. However, the incidences of adverse events related to orthostatic hypotension, palpitation, blood uric acid increased, and nausea tended to increase slightly depending on the severity of renal impairment. Also, the exposure to abaloparatide in plasma increased depending on the severity of renal impairment. Therefore, the applicant's plan to include the following precautionary statements for patients with renal impairment in the package insert is appropriate:

(1) Patients with renal impairment should be periodically tested for renal function.
(2) Elimination of abaloparatide from blood is delayed in patients with severe renal impairment.

PMDA has concluded that precautionary statements for elderly patients and patients with hepatic impairment are not needed.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.6 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), with the following comments:

Abaloparatide may have a greater osteogenic effect than conventional PTH drugs, and the conventional PTH drugs are known to have a risk of causing ectopic calcification in the cardiovascular system. Cardiovascular events should therefore be evaluated in the post-marketing surveillance of abaloparatide.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for abaloparatide should include the safety specifications presented in Table 60, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 61.

Table 60. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Orthostatic hypotension • Anaphylaxis	• Hypercalcaemia • Osteosarcoma • Cardiovascular events	• Administration to patients with renal impairment • Administration to male patients
Efficacy specification		
None		

Table 61. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey (cardiovascular events)	• Disseminate information gathered during early post-marketing phase vigilance

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 approval condition. The re-examination period is 8 years because the product is a drug with a new active ingredient. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Treatment for patients with osteoporosis at high risk of fracture

Dosage and Administration

The usual adult dosage is 80 μg of abaloparatide administered subcutaneously once daily. Duration of abaloparatide therapy should not exceed 18 months.

Approval Condition

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

Appendix

List of Abbreviations

A→B	From apical surface to basolateral surface
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
B→A	From basolateral surface to apical surface
BAP	Bone alkaline phosphatase
BB1	Bombesin receptor
BCRP	Breast cancer resistant protein
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CBA	Cell-based assay
Ccr	Creatinine clearance
C_{max}	Maximum concentration
CTX	Type I collagen C-telopeptides
CYP	Cytochrome P450
DPD	Deoxypyridinoline
DXA	Dual-energy X-ray absorptiometry
EC_{50}	Half maximal effective concentration
ECL	Electrochemiluminescent assay
ELISA	Enzyme-linked immunosorbent assay
ESI-MS	Electrospray ionization-mass spectrometry
FAS	Full analysis set
FPRL1	N-formyl peptide receptor-like 1
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
hERG	Human ether-a-go-go related gene
HLGT	High level group term
HLT	High level term
HPLC	High performance liquid chromatography
hPTH	Human parathyroid hormone
IC_{50}	Half maximal inhibition concentration
ITT	Intent-to-treat
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
M-CSF	Macrophage colony-stimulating factor
MCV	Mean corpuscular volume
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mITT	Modified intent-to-treat
NTX	N-terminal telopeptide of type I Collagen
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OC	Osteocalcin
OCT	Organic cation transporter
OPG	Osteoprotegerin

OVX	Ovariectomized
OX1	Orexin receptor
P1CP	Procollagen type I C-terminal propeptide
P1NP	Procollagen type I N-terminal propeptide
PCR	Polymerase chain reaction
P-gp	P-glycoprotein
PKA	Protein kinase A
PMDA	Pharmaceuticals and Medical Devices Agency
pQCT	Peripheral quantitative computed tomography
PT	Preferred terms
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide
RANKL	Receptor activator of NF kappa B ligand
RIA	Radioimmunoassay
SMQ	Standardised MedDRA queries
SOC	System organ class
TRACP-5b	Tartaric acid-resistant acid phosphate-5b
UHPLC	Ultra-High performance liquid chromatography
VIP	Vasoactive intestinal peptide
YAM	Young adult mean