Report on the Deliberation Results

May 6, 2010

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

[Brand name]	Forteo Subcutaneous Injection Cartridge 600 μg Forteo Subcutaneous Injection Kit 600 μg
[Non-proprietary name]	Teriparatide (Genetical Recombination) (JAN*)
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	April 28, 2009

[Results of deliberation]
In the meeting held on April 23, 2010, 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, and the re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

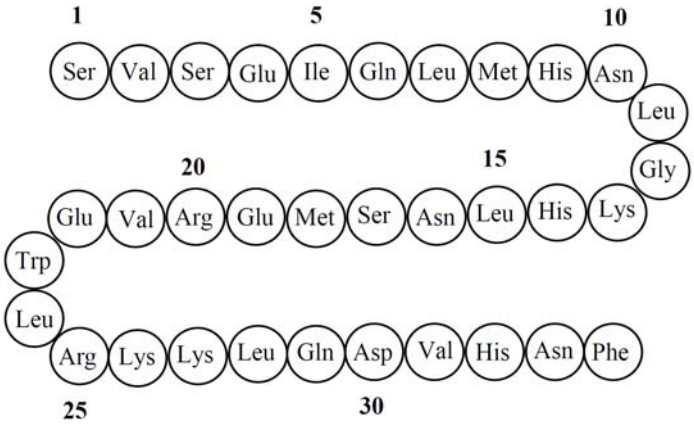
**Japanese Accepted Name (modified INN)*

Review Report

April 6, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] (a) Forteo Subcutaneous Injection Cartridge 600 μg
(b) Forteo Subcutaneous Injection Kit 600 μg
(The brand names have been changed as above. They were initially proposed as Forteo Injection Cartridge 600 μg and Forteo Injection Kit 600 μg, respectively.)
[Non-proprietary name] Teriparatide (Genetical Recombination)
[Applicant] Eli Lilly Japan K.K.
[Date of application] April 28, 2009
[Dosage form/Strength] Solution for injection: (a) One cartridge (2.4 mL) or (b) one kit (2.4 mL) contains 600 μg of Teriparatide (Genetical Recombination).
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Molecular formula: $C_{181}H_{291}N_{55}O_{51}S_2$
Molecular weight: 4117.72
Chemical name or entity:

Teriparatide is a recombinant peptide corresponding to human parathyroid hormone at positions 1-34. Teriparatide consists of 34 amino acid residues.

[Items warranting special mention] None
[Reviewing office] Office of New Drug I

Review Results

April 6, 2010

[Brand name]	Forteo Subcutaneous Injection Cartridge 600 μg, Forteo Subcutaneous Injection Kit 600 μg (The brand names have been changed as above. They were initially proposed as Forteo Injection Cartridge 600 μg and Forteo Injection Kit 600 μg, respectively.)
[Non-proprietary name]	Teriparatide (Genetical Recombination)
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	April 28, 2009
[Items warranting special mention]	None

[Results of review]

Based on the submitted data, the efficacy of the product in the treatment of patients with osteoporosis at high risk for fracture has been demonstrated and its safety is acceptable in view of its observed benefits. It is necessary to continue to collect information on safety in patients with hyperuricaemia, renal impairment, or hepatic impairment and elderly patients, safety issues of hypercalcaemia and cardiovascular disorders, etc., and the effects of antibody formation on safety and efficacy via post-marketing surveillance and to carefully investigate the relationship between teriparatide and the development of osteosarcoma via Foreign Study GHBX, etc. as well as post-marketing surveillance.

As a result of its review, the Pharmaceuticals and Medical Devices Agency concluded that the product may be approved for the following indication and dosage and administration.

[Indication]

Treatment of patients with osteoporosis at high risk for fracture

[Dosage and Administration]

The usual adult dosage of Teriparatide (Genetical Recombination) is 20 μg once daily, administered by subcutaneous injection.

The maximum duration of treatment with Forteo should be 18 months.

Review Report (1)

March 3, 2010

I. Product Submitted for Registration

[Brand name] (a) Forteo Injection Cartridge 600 μg
(b) Forteo Injection Kit 600 μg

[Non-proprietary name] Teriparatide (Genetical Recombination)

[Name of applicant] Eli Lilly Japan K.K.

[Date of application] April 28, 2009

[Dosage form/Strength] Solution for injection: (a) One cartridge (2.4 mL) or (b) one kit (2.4 mL) contains 600 μg of Teriparatide (Genetical Recombination).

[Proposed indication] Treatment of patients with osteoporosis at high risk for fracture

[Proposed dosage and administration]

The usual adult dosage of teriparatide is 20 μg once daily, administered by subcutaneous injection.

II. Summary of the Submitted Data and Outline of Review

The data submitted in the application and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or background of discovery and usage conditions in foreign countries, etc.

At the US National Institutes of Health (NIH) consensus conference in 2000, osteoporosis was defined as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture" and it was shown that bone mineral density (BMD) accounts for approximately 70% of bone strength and bone quality such as bone turnover (bone resorption and formation) accounts for the remaining approximately 30% of bone strength (NIH. *Osteoporosis Prevention, Diagnosis, and Therapy.* NIH Consensus Statement. 2000;17: 1-45).

The goal of therapy for osteoporosis is to prevent fractures and as therapeutic drugs, bisphosphonates, selective estrogen receptor modulators (SERMs), active vitamin D_3 preparations, etc. have been used in Japan. Antiresorptive therapies including bisphosphonates and SERMs increase BMD and prevent fractures by inhibiting osteoclast-mediated bone resorption, but do not restore bone microarchitecture by stimulating bone formation and it is difficult to say that these therapies are adequately effective in patients with osteoporosis at high risk for fracture. According to "Guidelines for Prevention and Treatment of Osteoporosis 2006", it is hard to say that the evidence level for active vitamin D_3 preparations in the prevention of fractures is high, as compared to that for bisphosphonates, etc. Thus, under the current circumstances, osteoporosis therapy with approved drugs is not necessarily satisfactory.

Parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and

kidney and once-daily administration of PTH is known to stimulate bone formation. Teriparatide (Genetical Recombination), the active substance of Forteo Injection Cartridge 600 μg and Forteo Injection Kit 600 μg (the proposed product), is a recombinant peptide corresponding to human PTH (hPTH) at positions 1-34 (rhPTH (1-34) or teriparatide), developed by Eli Lilly and Company.

The clinical development of teriparatide began in 19[redacted] overseas. In December 1998 when foreign phase III trials were underway, the sponsor stopped all ongoing clinical trials involving teriparatide due to the findings of neoplastic bone lesions including osteosarcoma in a rat carcinogenicity study. Then, Eli Lilly and Company conducted a long-term study in monkeys and a follow-up study of patients previously enrolled in the terminated clinical trials and discussed with the US FDA. As a result, it was concluded that teriparatide is unlikely to cause osteosarcoma in humans and it was agreed that the data, etc. from the terminated clinical trials can be included in the NDA package to support the application for teriparatide. Teriparatide was approved in November 2002. The EU marketing authorization was also granted in June 2003. As of January 2010, teriparatide has been approved in 83 countries or regions worldwide.

The clinical development of teriparatide in Japan began in [redacted] 20[redacted] after the approval of teriparatide in the US and EU and a bridging strategy was selected during development. As the usefulness of teriparatide in patients with osteoporosis at high risk for fracture has been confirmed on the basis of extrapolation of foreign clinical data, a marketing application for teriparatide has been filed.

In Japan, teriparatide acetate (of synthetic chemical origin) injection was approved for the indication of "Ellsworth-Howard test" in 1987.

2. Data relating to quality

2.A Summary of the submitted data

"Forteo Injection Cartridge 600 μg" or "Forteo Injection Kit 600 μg" (the drug product placed in disposable kits), submitted for registration, is supplied as a 2.4 mL colorless clear aqueous solution for injection containing 250 μg/mL of rhPTH (1-34) as the active substance, in a cartridge or in a cartridge pre-assembled in a pen-injector, Colter Pen (medical device), respectively. rhPTH (1-34) is a recombinant peptide consisting of 34 amino acid residues ($C_{181}H_{291}N_{55}O_{51}S_2$; molecular weight, 4117.72), which is produced in a recombinant cell by expression of a gene encoding amino acid residues at positions 1-34 of hPTH. The formulations of the two drug products are the same.

2.A.(1) Drug substance

2.A.(1).1) Manufacturing process

2.A.(1).1).(a) Establishment of cell banking system

[redacted][1]

[1] [redacted]

[redacted][2] [redacted] A master cell bank (MCB) was established from the cell line for the development of MCB and a working cell bank (WCB) was established from the MCB.

2.A.(1).1).(b) Characterization and control of cell banks

The MCB and WCB were characterized by phenotype testing (drug resistance, growth requirements), restriction enzyme analysis, and nucleotide sequencing of the rhPTH (1-34)-fusion protein gene and its flanking regions and as purity tests, tests for bacteria and phages were also performed. All test results met the acceptance criteria. Cells at the limit of *in vitro* cell age were characterized (restriction enzyme analysis, nucleotide sequencing of the rhPTH (1-34) fusion protein gene and its flanking regions) and all test results met the acceptance criteria, demonstrating the stability of cells during the production cycle.

As the current MCB is large enough to produce rhPTH (1-34), generation of a new MCB is not scheduled.

A new WCB will be prepared from the MCB and qualified by characterization and purity tests as described above.

2.A.(1).1).(c) Manufacturing process

The manufacturing process for rhPTH (1-34) consists of 12 steps. In the fermentation process for the production of rhPTH (1-34), cells from the WCB are inoculated and fermented in a flask (seed fermentation, Step 1) followed by production fermentation (production fermentation, Step 2). The fermented cells are centrifuged and homogenized to prepare a granular concentrate containing rhPTH (1-34)-fusion protein[3] (Step 3).

[redacted]

[2] [redacted]
[3] [redacted]

In-process controls other than the control of critical intermediates include the specific activity of a granular concentrate containing rhPTH (1-34)-fusion protein and the final solid concentration at Step 3, the acetonitrile concentration in the unfiltered solution at Purification Step 3, the molar yield of rhPTH (1-34) at the end of Purification Step 5 relative to rhPTH (1-34)-fusion protein introduced into Purification Step 4 at Purification Step 5, and the acetonitrile concentration at the end of diafiltration at Purification Step 8. In the course of the regulatory review, endotoxins, total viable count, polymers, biological potency, and the purity of rhPTH (1-34) at Purification Step 9 were added as in-process controls [see "2.B.(1) Process control items" for details].

For process validation, the attributes evaluated for the fermentation process (Step 2) were the fusion protein concentration, restriction enzyme analysis, phenotype analysis, and tests for bacteria and phages. [redacted][4] [redacted][5] [redacted][6] [redacted][7] [redacted]

2.A.(1).1).(d) Controls of critical steps and critical intermediates

[redacted]

2.A.(1).1).(e) Manufacturing process development (comparability)

During pharmaceutical development and after market launch overseas, the following changes were made to the manufacturing process. [redacted]

[4] [redacted]
[5] DHFR fragment
[6] [redacted]
[7] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted][8][redacted]

2.A.(1).2) Characterization

rhPTH (1-34) is a white powder and its general properties including amino acid composition, amino acid sequence, mass spectrum, peptide map, isoelectric point, ultraviolet spectrum, circular dichroism spectra, nuclear magnetic resonance spectrum, X-ray crystallography, fluorescence spectrum, and quaternary structure (ultracentrifugation, size exclusion chromatography, dynamic light scattering), immunochemical properties (a rat 6-month subcutaneous administration study, a monkey 1-year subcutaneous administration study [see "3.(iii).A.(2).2) Rat 6-month administration study and 3.(iii).A.(2).4) Monkey 1-year administration study" for details], biological properties (bioresponse method), solubility, extinction coefficient, and hygroscopicity have been determined. Amino acid composition analysis and amino acid

[8] [redacted]

sequencing showed that the number of residues of each amino acid and primary structure agreed with the theoretical ones. The molecular weight as determined by mass spectrometry was [redacted] Da, which agreed well with the theoretical value (4117.8 Da). [redacted] The circular dichroism spectra showed that α-helix is more stable at pH[redacted] than at pH[redacted] and that the stability of α-helix is not sensitive to increased ionic strength of buffer at pH[redacted]. The nuclear magnetic resonance spectrum and X-ray crystallography confirmed that rhPTH (1-34) does not adopt a stable helical structure in solution and adopts an α-helical structure in its crystal form. The fluorescence spectrum indicated that it does not have a stable three-dimensional structure. Analysis of quaternary structure indicated that it does not self-associate. In studies of immunochemical properties, antibody production was not observed in rats and anti-rhPTH (1-34) IgG antibodies were detected in cynomolgus monkeys in the 10 μg/kg group 1 year after treatment though there was no dose-dependency. However, the antibody levels were low, indicating weak immunogenicity. [redacted] Amino acid analysis, mass spectrum analysis, and analysis by reverse-phase chromatography confirmed that rhPTH (1-34) is not glycosylated and is a single molecular entity that contains no disulfide bonds and there was a correlation between the results by liquid chromatography (HPLC) and those by the bioresponse method. Therefore, only assay by HPLC was included in the proposed specifications for rhPTH (1-34). However, in the course of the regulatory review, biological potency was included in the drug product specifications [see "2.B.(2) Biological potency" for details].

rhPTH (1-34) is freely soluble in water and in buffer (pH[redacted], pH[redacted], pH[redacted]) and showed hygroscopicity as humidity changed from [redacted]% to [redacted]%. Also, the calculated extinction coefficient (1.38 mL/(mg.cm)) almost matched the measured value ([redacted] mL/(mg.cm)).

2.A.(1).3) Product-related substances and impurities

[redacted][9] [10] [11]

[9] [redacted]
[10] [redacted]

[redacted]

No product-related substances exist.

2.A.(1).4) Control of the drug substance

[redacted] During development, the drug substance was tested for endotoxins, total viable count, polymers, and biological potency. However, these are not included in the proposed specifications. Endotoxins is included in proposed specifications of the drug product. Total viable count was low in the pilot-scale and validation lots. Polymers are tested at release form the country of production and are controlled in the manufacturing process. Biological potency is excluded because rhPTH (1-34) does not have a higher order structure. Content is controlled by HPLC assay.

2.A.(1).5) Reference materials

[redacted]

A working reference material is produced similarly to the primary reference material and used in the identity testing and assay of drug substance. [redacted]

[redacted]

[redacted] When stored at [redacted]°C to [redacted]°C, the working reference material is to be re-evaluated at an interval of [redacted] months to [redacted] years.

2.A.(1).6) Container closure system

The container closure system for rhPTH (1-34) is a clear glass bottle with a metal plastisol (polyvinyl chloride resin)-lined screw cap. The cap also has an opaque silicone rubber covering that provides an appropriate torque so it is securely closed.

2.A.(1).7) Stability

The stability of the drug substance was studied as follows:

Long-term testing (-10°C/60 months) and accelerated testing (5°C/6 months) were performed with 3 commercial-scale drug substance lots (Process IIIc) in glass vials ([redacted] mL) with metal screw caps (plastisol-lined). The attributes tested were description (appearance), purity (acetate, related substances [Impurity A, other individual related substances, total related substances]), water content, biological potency, and content. Purity test (polymers) was also conducted in the long-term study. No specific changes occurred in both the long-term and accelerated conditions and the drug substance remained within its specification.

Photostability testing (3 million lx·hr, 1440 W·hr/m^2) was performed with 1 lot (Process IIIc) in glass vials (sealed). The attributes tested were description (appearance), purity (related substances [Impurity A, total related substances]), and content. [redacted]

As preliminary stability studies, long-term testing (-10°C/30 months) and accelerated testing (5°C/6 months) were performed with 3 commercial-scale drug substance lots (Process V) in glass vials ([redacted] mL) with metal screw caps (plastisol-lined). The attributes tested were description (appearance), purity (Impurity A, other individual related substances, total related substances, polymers), water content, and content. No significant changes occurred at the long-term or accelerated condition and the drug substance remained within its specification. In addition, long-term testing (-10°C/24 months) was performed with 3 commercial-scale drug substance lots (Process VI) in glass vials ([redacted] mL) with metal screw caps (plastisol-lined). The attributes tested were description (appearance), purity (Impurity A, other individual related substances, total related substances), water content, and content and showed no specific changes. The long-term testing (as preliminary stability studies) will be continued up to 60 months.

Based on the above, the applicant proposed a re-test period of [redacted] years for the drug substance when stored in airtight containers at -10°C (dark place), which was changed to a shelf-life of [redacted] years in the course of the regulatory review.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

The product is a colorless clear aqueous solution for injection. Each mL contains 250 μg of rhPTH (1-34) as the active substance. It also contains buffering agents (glacial acetic acid, anhydrous sodium acetate), an isotonizing agent (D-mannitol), a preservative (*m*-cresol), pH adjusters (sodium hydroxide, hydrochloric acid), and solvent (water for injection). The primary packaging of "Forteo Injection Cartridge 600 μg" is a 3-mL borosilicate glass cartridge (the volume of drug solution, 2.4 mL). [redacted] "Forteo Injection Kit 600 μg" is a disposable kit comprising a pen-injector called Colter Pen pre-assembled with a cartridge, which is filled with the drug product. The performance of Colter Pen has been confirmed to conform to the Japanese Industrial Standard for Pen-Injectors for Medical Use, JIS T 3226-1 (International Standard ISO 11608-1) and the certification requirements, and Colter Pen has been certified in Japan (Certification No. 221ADBZX00053000). The volume of drug product in the cartridge is the same as that in the injection kit which is sufficient to cover a 28-day dosing period. However, in order to use the cartridge with the dedicated pen-injector Forteo 14 Pen, the pen must be primed before each injection, and thus the cartridge is intended for 14 days of dosing.

2.A.(2).2) Pharmaceutical development

[redacted] The proposed commercial formulation is a preservative-containing drug solution added with pH adjusters. The drug product of the same formulation as proposed for marketing was used in Japanese clinical studies [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" for formulations used in clinical studies (evaluation data)].

2.A.(2).3) Manufacturing process

The manufacturing process for the drug product in cartridges consists of the preparation of the excipient solution (Step 1), the preparation of drug solution (Step 2), sterile filtration (Step 3), filling and closing (Step 4), labeling (Step 5), and packaging (Step 6). The drug product is produced in lot sizes ranging from [redacted] to [redacted] L. Step 3 and Step 4 have been defined as critical steps and the integrity of the sterile filter after each filtration process, the position of the plunger after filling, and the full length of the cartridge are controlled.

The manufacturing process for the drug product in injection kit consists of Steps 1 to 4 of the manufacturing process for the drug product in cartridge, assembling with pen injectors (Step 5), labeling (Step 6), and packaging (Step 7).

If deviation from process control or equipment failure occurs, reprocessing by repeating manufacturing steps such as sterile filtration and transfers between the tanks is to be conducted.

2.A.(2).4) Impurities

[redacted]

2.A.(2).5) Control of the drug product

[redacted] In the course of the regulatory review, biological potency was included in the specifications [see "2.B.(2) Biological potency" for details]. The test for extractable volume of parenteral preparations is not included in the specifications because the fill volume is controlled by the position of the plunger.

2.A.(2).6) Stability

2.A.(2).6).(a) Stability studies to establish storage conditions and a shelf-life

The stability of the drug product was studied as follows:

[redacted]

Under the long-term condition, although the drug product both in cartridge and kit met the specifications, tests for related substances showed increases in related substances over time. Under the accelerated condition, increases in related substances and a decrease in content were observed in the drug product both in cartridge and kit. [redacted]

Photostability testing (1.4 million lx·hr, 720 W·hr/m^2) was performed on 1 lot of each drug product (containing the drug substance produced by Process IIIc) by using samples in cartridge, in cartridge protected from light, in kit, and in secondary-packaged kit. The attributes tested were pH, color, clarity, total related substances (HPLC), *m*-cresol content, and content. No significant changes occurred in any attributes tested

for the drug product in cartridge protected from light, in kit, and in secondary-packaged kit, whereas the light-exposed drug product in cartridge failed to meet the specifications: a significant increase in the total amount of related substances and a decrease in content were observed.

Furthermore, the following preliminary stability studies were performed:

[redacted] Endotoxins, preservative effectiveness, and sterility were also tested in the long-term study.

[redacted] Endotoxins, preservative effectiveness (drug product in cartridges only), sterility, and injection dose accuracy (drug product in kits only) were also tested in the long-term study.

[redacted] The insoluble particulate matter test and sterility test were also conducted in the long-term study.

Under the long-term condition, although the samples remained within the specification, increases in related substances over time and a decrease in content were observed. Also in the accelerated condition, increases in related substances and a decrease in content were observed. [redacted]

[redacted]

2.A.(2).6).(b) In-use stability study

For evaluation of in-use stability, a 29-day study was performed on 1 lot of drug product in kit (drug substance produced by Process V) prior to the beginning of long-term testing and 1 lot of drug product in kit (drug substance produced by Process IV) stored at 5°C for 24 months. Samples were left at 30°C for 30 minutes then at ambient temperature for another 30 minutes daily. The attributes tested were description (appearance), total related substances, *m*-cresol content, and content. During 29-day storage, each rubber closure was penetrated [redacted] times a day, with a new needle each time to withdraw [redacted] μL. No significant changes occurred and the samples remained within the specifications for all attributes tested.

Based on the above study results, a shelf-life of 18 months and an in-use shelf-life of 28 days have been proposed for the drug product when stored at 2°C to 8°C, protected from light.

2.B Outline of the review

2.B.(1) Process control items

Since endotoxins, total viable count, polymers, biological potency, and the purity of rhPTH (1-34) are included in the release specifications for rhPTH (1-34) overseas, PMDA asked the applicant to explain whether these tests need to be performed as in-process controls in Japan.

The applicant responded that endotoxins, total viable count, polymers, biological potency, and the purity of rhPTH (1-34) will be included as process control items at Purification Step 9.

PMDA accepted the response.

2.B.(2) Biological potency

The applicant explained that as rhPTH (1-34) is not glycosylated and is a single molecular entity that contains no disulfide bonds, biological assay may be omitted. PMDA asked the applicant to explain in details about it, showing supporting data.

The applicant responded as follows:

As rhPTH (1-34) is produced in *E. coli*, it is not glycosylated. This has also been confirmed by the finding that the molecular weight of rhPTH (1-34) determined by mass spectrometry had agreed well with its theoretical value. Then, as an amino acid composition analysis and amino acid sequencing have confirmed that rhPTH (1-34) has no cysteine residues, no intramolecular or intermolecular disulfide bonds are formed. The mass spectrum and the results of analysis by HPLC have confirmed that rhPTH (1-34) is a single molecular entity and furthermore, there was a good correlation between these analysis results and results by bioresponse method. Therefore, it can be said that the biological activity of rhPTH (1-34) is derived from the

single molecular entity and the biological potency of rhPTH (1-34) can be assured even without bioresponse method.

PMDA asked the applicant to explain the correlation between the results by HPLC and those by bioresponse method.

The applicant responded as follows:
Samples were prepared so that each had the same total protein content and that the peak areas for rhPTH (1-34) in these samples were approximately [redacted]%, [redacted]%, and [redacted]%, respectively, and were analyzed by HPLC method and by bioresponse method. A good correlation between the peak purity of the main peak as determined by HPLC (% of rhPTH (1-34) peak) and relative potency (%) as determined by bioresponse method. Also when 46 lots manufactured by Process [redacted] to Process [redacted] were analyzed by HPLC method and by bioresponse method, it could not be said that there were differences between the mean measured values by HPLC method and those by bioresponse method.

Considering the difficulty in identifying a correlation between the results by HPLC method and those by bioresponse method as well as the need of specifications that allow the identification of the intended biological activity in the drug product, PMDA instructed the applicant to include biological potency in the specifications.

The applicant responded that biological potency as determined by bioresponse method will be included in the drug product specifications.

PMDA accepted the response.

2.B.(3) Container to store the drug substance
The drug substance is stored in a container with a polyvinyl chloride resin-lined metal screw cap. PMDA asked the applicant to explain if di(2-ethylhexyl) phthalate (DEHP) can leach into the product, etc.

The applicant responded as follows:
The screw cap is lined with a polyvinyl chloride resin gasket, but the bottle is not lined. The drug substance rhPTH (1-34) is put into containers, freeze-dried and stored at ≤-10°C. As the water content of the drug substance is low, chemical interaction between the drug substance and the container cannot occur or very little interaction occurs if any. As the screw cap lining constitutes a small percentage of the inner surface of the container, only a trace amount of rhPTH (1-34) directly contacts the polyvinyl chloride resin lining. Also in long-term stability studies, etc. conducted using bottles similar to the container closure system for the drug substance, no changes that can affect the quality of the drug substance occurred throughout the storage period.

PMDA considered that problems, such as leaching of DEHP from the polyvinyl chloride resin lining during the storage of the drug substance, are unlikely to occur and accepted the response.

2.B.(4) Shelf-life for the drug product

The applicant proposed a shelf-life of 18 months for the drug product. Since significant changes occurred under the accelerated condition and the shelf-life should be based on the data obtained at the long-term storage condition, PMDA requested the applicant to submit 18-month data from the stability study under the long-term storage condition.

The applicant responded that the data will be submitted as soon as they become available.

With respect to this matter, PMDA is requesting the applicant to continue to evaluate the stability of the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

As primary pharmacodynamic studies, the effects of teriparatide in improving trabecular and cortical bone mass, strength, and quality were evaluated *in vivo* in rodent and monkey models of osteoporosis. No studies were performed on the mechanism of action or bone formation effect of teriparatide because a lot of literature already exists. As safety pharmacology studies, the effects of teriparatide on the cardiovascular and central nervous systems were assessed. The effect of teriparatide on the respiratory system was assessed in a safety pharmacology study on general symptoms and central nervous system effects and in monkey repeat-dose toxicity studies. No secondary pharmacodynamic studies or pharmacodynamic drug interaction studies were performed.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Effects on bone tissue in the rodent

3.(i).A.(1).1).(a) Effects of different modes of administration on bone mass-1 (4.2.1.1.1)

Teriparatide, as a total daily dose of 80 μg/kg/day, was given as once-daily subcutaneous injections or as 6 subcutaneous injections within 1 hour (10 minute intervals) or over a 6-hour period (1 hour intervals) (13.3 μg/kg/injection) daily for 18 days to male rats (4 weeks of age, n = 6 per group). Changes in proximal tibial BMD were assessed by quantitative computed tomography (QCT). When teriparatide was given as once daily injections or as 6 injections within 1 hour, BMD increased. Meanwhile, when teriparatide was given as 6 injections over a 6-hour period, BMD decreased.

3.(i).A.(1).1).(b) Effects of different modes of administration on bone mass-2 (4.2.1.1.2)

A single subcutaneous dose of 80 μg/kg of teriparatide was administered or teriparatide (13.3 μg/kg/injection) was given as 6 subcutaneous injections within 1 hour (10 minute intervals) or over a 6-hour period (1 hour intervals) to male rats (4-5 weeks of age, n = 4-6 per group). Changes over time in serum

calcium, phosphorus, and teriparatide concentrations were assessed. After a single dose of teriparatide, serum calcium rapidly decreased to a nadir (10 minutes) and returned to baseline within 40 minutes. Serum phosphorus also decreased to a nadir at 60 to 120 minutes but returned to baseline within 4 hours. Serum teriparatide (mean ± standard error [SE]) rose transiently to a peak (18.6 ± 4.2 ng/mL) at 10 minutes then declined to baseline within 3 to 4 hours. Teriparatide given as 6 injections (10 minute intervals) gave a longer duration of serum calcium and phosphorus depression with a lower nadir than the single dose regimen. Serum teriparatide transiently rose to 2.5 ± 0.6 ng/mL 5 minutes after the first dose and increased to 5.6 ± 0.7 ng/mL 5 minutes after the last dose, but returned to baseline by 4 hours after the first injection. When teriparatide was given as 6 injections (1 hour intervals), serum calcium and phosphorus decreased after each injection followed by a recovery prior to the next dose. Serum teriparatide rose to a C_{max} 5 minutes after each dose (2.2-3.8 ng/mL) and declined to 2% to 10% of the peak values prior to the next dose, but serum teriparatide level remained above baseline until 7 hours after the first dose.

The study showed that the net effect of teriparatide on bone depended on the mode of administration; the net response to teriparatide was bone formation rather than resorption or vice versa. The applicant discussed that the response in bone to teriparatide may be determined by the length of time serum concentrations remain above baseline.

3.(i).A.(1).1).(c) Effects on trabecular bone

3.(i).A.(1).1).(c).i) Effects on bone mass and strength-1 (4.2.1.1.3)

Ovariectomized (OVX) female rats (approximately 6 months of age, n = 20-30 per group) were given teriparatide (8 and 40 μg/kg) or vehicle (20 mM phosphate-buffered saline containing mannitol) once daily by subcutaneous injection for 1 year and the effects of teriparatide on bone mass, quality, and strength of the lumbar vertebrae, femurs, and tibiae were assessed by dual-energy X-ray absorptiometry (DXA), QCT, and bone biomechanical analyses. Sham-ovariectomized female rats (approximately 6 months of age, n = 10) were given vehicle once daily by subcutaneous injection for 1 year. In addition, as the baseline group, sham-operated or OVX female rats (approximately 6 months of age, n = 10 per group) were sacrificed 60 days after OVX. BMD increased in the proximal tibia of OVX female rats treated with teriparatide dose-dependently by up to approximately 2-fold as compared to the OVX vehicle control group. The ultimate load of the lumbar vertebra increased by approximately 2-fold in OVX female rats treated with teriparatide as compared to the OVX baseline group or the OVX vehicle control group, and bone strength parameters such as stiffness and Young's modulus also increased. The ultimate load of the femoral neck also increased by 140% to 175% in OVX females as compared to the OVX vehicle control group. Teriparatide had no effect on body weight. Bone turnover was higher in the baseline group than in the sham-operated group.

Male rats (approximately 6 months of age, n = 20-30 per group) were also studied in the same manner. As in OVX female rats, proximal tibial BMD and bone strength of the lumbar vertebra increased in intact male rats. In the teriparatide group, the mean body weight decreased as compared to the vehicle control group (5% and 8% in the 8 and 40 μg/kg groups, respectively). Bone turnover was higher in the male baseline group as compared to the sham-operated group.

3.(i).A.(1).1).(c).ii) Effects on bone mass and strength-2 (4.2.1.1.4)

OVX female rats (approximately 9 months of age, n = 35 per group) were given teriparatide (8 and 40 μg/kg) or vehicle (20 mM phosphate-buffered saline containing mannitol) once daily by subcutaneous injection for 6 months and the effects of teriparatide on bone mass, quality, and strength of the lumbar vertebrae, femurs, and tibiae were assessed by QCT and bone biomechanical analyses. Sham-operated rats (approximately 9 months of age, n = 35) were given vehicle once daily by subcutaneous injection for 6 months. In addition, as the baseline group, female rats (approximately 9 months of age, n = 26) were sacrificed before randomization. A marked reduction in BMD was observed in the OVX vehicle control group. In the teriparatide group, tibial and femoral metaphyseal BMD increased dose-dependently in OVX female rats and the increases was significant as compared to the OVX vehicle control group. In the teriparatide group, mechanical strength (ultimate load, stiffness, Young's modulus, etc.) of the femoral neck and lumbar vertebrae increased and the increase was significant as compared to the OVX vehicle control group. Teriparatide significantly increased bone strength in OVX females, also as compared to the sham-operated group or the baseline group.

3.(i).A.(1).1).(c).iii) Effect on bone quality (4.2.1.1.4)

This effect was evaluated in the study for "ii) Effects on bone mass and strength-2". As a result, teriparatide improved bone quality parameters related to trabecular connectivity or structural properties in the proximal tibia and lumbar vertebra (bone formation rate, trabecular thickness, trabecular number, trabecular connectivity).

3.(i).A.(1).1).(d) Effects on cortical bone

3.(i).A.(1).1).(d).i) Effects on bone mass and strength-1 (4.2.1.1.3)

These effects were evaluated in the study for "3.(i).A.(1).1).(c).i) Effects on bone mass and strength-1". In the OVX teriparatide group, BMD of the femoral midshaft increased dose-dependently by up to 55% in OVX female rats as compared to the OVX vehicle control group. Similarly, BMD increased dose-dependently by 67% also in male rats. In the OVX teriparatide group, ultimate load increased by approximately 150% to 200% and stiffness and Young's modulus also increased as compared to the baseline group or the vehicle control group. Similarly, in the male teriparatide group, ultimate load increased by approximately 200% and stiffness also increased significantly as compared to the baseline group or the vehicle control group.

3.(i).A.(1).1).(d).ii) Effects on bone mass and strength-2 (4.2.1.1.4)

These effects were evaluated in the study for "3.(i).A.(1).1).(c).ii) Effects on bone mass and strength-2". In the OVX teriparatide group, BMD of the femur shaft increased dose-dependently in OVX female rats and the increase was significant as compared to the vehicle control group. In the OVX teriparatide group, the bone formation rate at the endosteal and periosteal surfaces increased, and increases in the cortical thickness, moment of inertia, ultimate load, and stiffness were also significant as compared to the vehicle control group. These increases caused by teriparatide were significant as compared to the sham-operated group or the baseline group.

3.(i).A.(1).2) Effects on bone tissue in the monkey

3.(i).A.(1).2).(a) Effects on trabecular bone

Effects on bone mass, quality, and strength (4.2.1.1.5)

OVX female cynomolgus monkeys (n = 21-22 per group) were treated with teriparatide (1 or 5 μg/kg/day) or vehicle (20 mM phosphate-buffered saline containing mannitol) once daily by subcutaneous injection from the day after the surgery for 18 months or for 12 months followed by 6-month withdrawal ("1 μg/kg/day-withdrawal group" or "5 μg/kg/day-withdrawal group") and the effects of long-term treatment with teriparatide and the discontinuation of treatment on the trabecular and cortical bones were assessed by DXA, QCT, and bone biomechanical analyses. Sham-operated monkeys (n = 21) were given vehicle once daily by subcutaneous injection for 18 months. The assessment of bone turnover markers showed increases in alkaline phosphatase, osteocalcin, and urinary CrossLaps (C-terminal collagen fragments) in the OVX vehicle control group as compared to the sham-operated group (n = 21) and a bone histomorphometry also showed increased bone formation. BMD and bone strength (ultimate load, stiffness) of the vertebrae and femoral neck decreased in the OVX vehicle control group as compared to the sham-operated group. Vertebral BMD increased dose dependently by 7% to 14% in OVX female animals treated with teriparatide subcutaneously for 18 months as compared to the OVX vehicle control group, and the increase was significant also as compared with the sham-operated group. Bone microarchitecture (mineralized bone volume, trabecular number, etc.) improved and bone strength (ultimate load, stiffness, Young's modulus) increased in OVX female animals treated with teriparatide as compared with the OVX vehicle control group and these values were similar to or greater than those in the sham-operated group. Ultimate load also significantly increased in the proximal femur in OVX female animals treated with teriparatide as compared to the OVX vehicle control group. Although there were no significant differences in alkaline phosphatase, osteocalcin, or urinary CrossLaps between the teriparatide and OVX vehicle control groups, alkaline phosphatase and urinary CrossLaps increased during 6 months of teriparatide treatment. Bone histomorphometry by iliac crest biopsies also showed a significant increase in bone formation as compared to the OVX vehicle control group. While there were no major changes in ultimate load in the 1 μg/kg/day-withdrawal group as compared to the 18-month teriparatide 1 μg/kg/day group, it decreased in the 5 μg/kg/day-withdrawal group as compared to the 18-month teriparatide 5 μg/kg/day group. A similar trend was observed also in ultimate load in the proximal femur. Teriparatide withdrawal did not reverse the increases in trabecular connectivity and bone volume of the lumbar vertebrae caused by teriparatide. Following 18-month subcutaneous administration of teriparatide, the AUC values of serum teriparatide were 0.31 and 2.22 ng·hr/mL in the 1 μg/kg/day and 5 μg/kg/day groups, respectively.

While bone mass and bone strength parameters markedly increased in trabeculae-rich bones (lumbar vertebrae, etc.) in the rat, the increases were marginal in the monkey as compared to the rat. The applicant discussed that these differences in bone tissue response are attributable to species differences in bone physiology, such as the nearly continuous growth of the rat skeleton throughout life (unlike humans and monkeys), faster bone turnover in the rat [11.8-36.5 cycles/year (3-16 months of age)] than in the monkey (7.2-9 cycles/year), and the lack of haversian remodeling in the rat, etc.

3.(i).A.(1).2).(b) Effects on cortical bone (4.2.1.1.5)

Effects on cortical bone were evaluated in the study for "3.(i).A.(1).2).(a) Effects on trabecular bone - Effects on bone mass, quality, and strength". Radial midshaft BMD did not decrease in the OVX vehicle control group as compared to the sham-operated group and no significant differences were observed even between the teriparatide and OVX vehicle control groups. Biomechanical parameters of strength in the humeral midshaft (ultimate load, stiffness, absorption energy) also not significantly decreased in the OVX vehicle control group as compared to the sham-operated group, and no significant changes were observed in the teriparatide group as compared to the OVX vehicle control group. In the teriparatide group, there were no significant alterations in material properties (ultimate stress, toughness) of the femur shaft as compared to the OVX vehicle control group. In the teriparatide 5 μg/kg/day group, the turnover rate of the femur shaft and bone formation rate at the endosteal surface significantly increased as compared to the OVX vehicle control group, and there was also a trend toward increased periosteal bone formation. Furthermore, in the teriparatide 5 μg/kg/day group, cortical bone area and thickness also increased significantly in the humerus as compare to the OVX vehicle control group. A bone histomorphometric analysis revealed no proliferative or neoplastic bone lesions in the teriparatide groups.

3.(i).A.(1).2).(c) Effect of withdrawal after repeat-dose administration of teriparatide (4.2.1.1.6)

OVX female cynomolgus monkeys (n = 30 per group) were given teriparatide 5 μg/kg or vehicle (20 mM phosphate-buffered saline containing mannitol) once daily by subcutaneous injection for 18 months followed by 3-year withdrawal. At the end of treatment period, 6 animals per group were sacrificed and the remaining animals were sacrificed for examination after 3-year withdrawal. At the end of the 18-month treatment period in the teriparatide group, biomechanical parameters (ultimate load, stiffness, absorption energy), material properties (ultimate stress, Young's modulus), and BMD in the lumbar vertebrae increased as compared to the vehicle control group. Biomechanical parameters of strength (ultimate load, stiffness) and BMD also increased in the proximal femur. After 3-year withdrawal, although there were no significant differences in BMD or bone strength of the lumbar vertebrae between the teriparatide and vehicle control groups, stiffness, bone mineral content (BMC), and trabecular bone volume fraction of the proximal femur were 20%, 14%, and 53% higher, respectively, in the teriparatide group as compared to the vehicle control group, and the effects of teriparatide on some parameters of bone mass and bone quality, etc. were still significant as compared to the vehicle control group after 3-year withdrawal.

3.(i).A.(1).3) Sequential studies with synthetic hPTH (1-34) and other osteoporosis treatments

Switching from synthetic hPTH (1-34) to ethinyl estradiol or raloxifene (4.2.1.1.7, Reference data)

OVX or sham-OVX female rats (n = 58 and n = 20, respectively) were given synthetic hPTH (1-34) 80 μg/kg/day by subcutaneous injection for 2 months (restoration period) from 2 months after surgery (loss period). Then, the rats treated with synthetic hPTH (1-34) (n = 6-8 per group) were administered ethinyl estradiol (0.1 mg/kg/day, oral), raloxifene (3 mg/kg/day, oral), synthetic hPTH (1-34) (80 μg/kg/day, subcutaneous injection), or vehicle (20% β-hydroxycyclodextrin, oral) for 2 months (maintenance period). At 2, 4, and 6 months after OVX, X-ray imaging was performed on the isolated distal femurs and the change in bone mass over time was evaluated. As a result, 2-month treatment with synthetic hPTH (1-34) during the

restoration period resulted in a marked increase in bone mass of the distal femoral metaphysis. A further increase in bone mass was observed in rats treated with synthetic hPTH (1-34) for another 2 months during the maintenance period. On the other hand, treatment with vehicle during the maintenance period resulted in a marked decrease in bone mass, which was below the sham-OVX level at the end of the 2-month maintenance period. In rats treated with raloxifene or ethinyl estradiol during the maintenance period, bone mass was maintained at levels achieved at the end of the restoration period, which was significantly higher than that in rats treated with vehicle during the maintenance period. Also when BMD was measured by QCT, similar findings were observed.

The applicant explained that when the affinity for the PTH receptor and stimulation to cAMP production were compared between teriparatide and synthetic hPTH (1-34) to confirm that the biological activity of teriparatide is identical to synthetic hPTH (1-34), no differences were found.

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Cardiovascular effects (4.2.1.3.1, 4.2.1.3.2, 4.2.1.3.3, 4.2.1.3.4)

A single subcutaneous dose of teriparatide (10, 30, 100, 300, 1000 μg/kg) or vehicle (20 mM phosphate-buffered saline) was administered to male rats (n = 4 per group). The actual dose levels for the 10 and 30 μg/kg groups were 4.3 and 22.8 μg/kg, respectively, because the measured content of teriparatide in the dosing solution was lower than the theoretical value. At dose levels of ≥30 μg/kg, diastolic pressure, systolic pressure, and the mean arterial pressure decreased by 18% to 29%, 15% to 23%, and 16% to 25%, respectively, and heart rates increased by 12% to 31% at 30 minutes after dosing as compared to the vehicle control group. A decrease in blood pressure and an increase in heart rates for up to approximately 2.5 hours were significant after dosing as compared with the vehicle control group. No cardiovascular effects were observed in the 10 μg/kg group.

A single subcutaneous dose of teriparatide 6 μg/kg or vehicle (20 mM phosphate-buffered saline containing mannitol) was administered to conscious female beagle dogs (n = 8) in a crossover fashion. The administration of teriparatide caused significant decreases in arterial pressure (systolic pressure, diastolic pressure, mean arterial pressure, pulse pressure) and significant increases in left ventricular inotropy (the peak value of the first derivative of left ventricular pressure, dP/dt_{max}) and heart rate. All these values reached their minimum or maximum during the first 2 hours after dosing, and systolic pressure, diastolic pressure, and the mean arterial pressure (mean ± SE) decreased from baseline by up to 18 ± 4, 10 ± 3, and 15 ± 3 mmHg, respectively. Pulse pressure decreased by up to 24% as compared to the vehicle control group, and left ventricular inotropy and heart rate increased by up to 43% and 79%, respectively, as compared to the vehicle control group. The decreases in systolic pressure, diastolic pressure, and the mean arterial pressure were not significant at 3 to 4 hours after dosing. A marked increase in left ventricular inotropy was observed for 4 to 5 hours after dosing and the increase in heart rate was not significant at 7 hours after dosing. There were no electrocardiographic (qualitative assessment) effects.

3.(i).A.(2).2) Effects on general symptoms and central nervous system (4.2.1.3.5)

Teriparatide (10, 30, 100 μg/kg) or vehicle (20 mM phosphate-buffered saline containing mannitol) was subcutaneously administered to male mice (n = 10 per group) for behavioral pharmacological assessment. No overt clinical signs (Irwin test) were observed up to 24 hours after dosing, and there were no changes in spontaneous activity levels, the threshold for electroshock- or pentylenetetrazole (80, 90, 100, 110 mg/kg)-induced convulsions, or body temperature. When hexobarbital (100 mg/kg) was administered 30 minutes after administration of teriparatide, hexobarbital-induced sleep times were not affected by administration of teriparatide. Based on these results, the no-observed-effect level of teriparatide was estimated to be 100 μg/kg.

3.(i).A.(2).3) Effects on respiratory system (4.2.1.3.5, 4.2.1.3.3, 4.2.1.3.4)

Although the effects of teriparatide on the respiratory system were not assessed in an independent safety pharmacology study, no overt effects including clinical signs suggestive of effects on the respiratory system were observed in a safety pharmacology study for "3.(i).A.(2).2) Effects on general symptoms and central nervous system".

3.(i).B Outline of the review

3.(i).B.(1) Mechanism of action

The applicant explained as follows:

The effects of different modes of the administration of teriparatide on bone mass were studied, and different results were obtained depending on the mode of administration. In *in vivo* studies using animal models of osteoporosis, teriparatide improved bone mass, strength, and microarchitecture of trabecular bone. In monkey studies, teriparatide had no significant effects on bone mass, strength, or material properties of cortical bone, but increased endosteal bone formation. As the primary mechanism of action of teriparatide and its stimulatory effect on bone formation can be explained by the existing literature on PTH, these studies were not performed.

PMDA asked the applicant to explain the mechanism of action and bone formation effect of teriparatide based on the existing information on PTH (1-34) only, rather than based on literature on endogenous PTH (PTH (1-34) has identical sequence to teriparatide).

The applicant responded as follows:

Like endogenous PTH, PTH (1-34) binds to a specific G-protein coupled PTH/PTHrP receptor (Potts JT Jr., *et al., Endocrinology*. 1995; 3 (2): 920-966). Binding of PTH (1-34) to the PTH receptor causes protein kinase A activation via a cAMP-dependent pathway and calcium release from intracellular stores and protein kinase C activation via the diacylglycerol/inositol polyphosphate pathway. Studies of rat bone tissue using molecular biological or histomorphometric techniques showed that PTH (1-34) rapidly induces expression of the c-fos, c-jun, interleukin-6 (IL-6) genes, etc. in trabecular bone, within 1 hour after administration to rats (Onyia JE, et al. *J Bone Miner Res*. 1995; 10 (Suppl 1): S487, Liang JD, et al. *Calc Tissue Int.* 1999; 65 (5):369-373, Pollock JH, et al. *J Bone Miner Res.* 1996; 11 (6): 754-759, Takeda N, et al. *Mech Ageing Dev.*

1999; 108 (1): 87-97). Five-day subcutaneous administration of PTH (1-34) stimulates the expression of extracellular proteins (type I collagen, osteocalcin, osteopontin), which are known as bone formation markers and matrix regulating proteins (matrix metalloproteinase-9, creatine kinase), etc. in rat metaphyseal trabecular bone (McClelland P, et al. *J Bone Miner Res*. 1997; 12 (Suppl 1): S169, McClelland P, et al. *J Cell Biochem*. 1998; 70 (3): 391-401). Once-daily subcutaneous administration of PTH (1-34) increases trabecular and cortical bone mass in axial (vertebrae) and appendicular bones, resulting in increased total body bone mass and increased resistance to fracture in the vertebra and proximal femur *ex vivo* (Hefti E, et al. *Clin Sci*. 1982; 62 (4): 389-396, Simmons HA, et al. *JPET*. 1998; 286 (1): 341-344, Sato M, et al. *Endocrinology*. 1997; 138 (10): 4330-4337). Studies of rat bone tissue using histomorphometric techniques showed that PTH induces trabecular, endosteal, and periosteal mineralization by promoting the differentiation of osteoblast progenitor cells or resting osteoblasts on the surface of bone into mature osteoblasts (Schmidt IU, et al. *Endocrinology*. 1995; 136 (11): 5127-5134, Leaffer D, et al. *Endocrinology*. 1995; 136 (8): 3624-3631, Dobnig H, et al. *Endocrinology*. 1995; 136 (8): 3632-3638) and inhibiting osteoblast apoptosis (Jilka RL, et al. *J Clin Invest*. 1999; 104 (4): 439-446). The skeletal effects of PTH (1-34) differ depending on the mode of administration and bone resorption may exceed bone formation with continuous exposure to PTH (1-34) (e.g. continuous administration), as seen in patients with primary hyperparathyroidism (Melton LJ 3rd, et al. *Arch Intern Med*. 1992; 152 (11): 2269-2273). Actually, it is known that once-daily subcutaneous injections of PTH (1-34) increase the mineral apposition rate, but continuous subcutaneous infusion of PTH (1-34) causes bone loss because bone resorption exceeds bone formation (Hock JM, et al. *J Bone Miner Res*. 1992; 7 (1): 65-72, Uzawa T, et al. *Bone*. 1995; 16: 477-484, Frolik CA, et al. *Bone*. 2003; 33 (3): 372-379).

The existing literature has shown the mechanism of action of PTH (1-34) and the stimulation of bone formation by PTH (1-34) given once daily, and once-daily administration of teriparatide increased trabecular bone mass without cortical thinning in an OVX monkey study. Therefore, considering that teriparatide given once daily is unlikely to affect cortical bone as reported in patients with primary hyperparathyroidism and is expected to increase bone mass, PMDA accepted the applicant's response.

3.(i).B.(2) Effects on fracture healing

As no fracture healing studies have been conducted, PMDA asked the applicant to discuss the effects of teriparatide on fracture healing based on the existing information.

The applicant responded as follows:

The effects of PTH on fracture healing have been investigated in numerous studies using animal models of fracture. Based on a recently published review article about the effects of hPTH (1-34) on fracture healing (Cipriano CA, et al. *HSS J*. 2009; 5 (2): 149–153), the results of representative studies of hPTH (1-34) in rat and monkey models of femoral fracture were summarized and the effects of teriparatide on fracture healing during the reparative phase and during the remodeling phase were discussed. It has been reported that following once-daily subcutaneous injections of hPTH (1-34) 10 μg/kg in a rat model of femoral fracture, the number of osteoprogenitor cells increased in the periosteum proximal to the fracture gap on Day 2 after fracture. The levels of expression of the IGF-I (Insulin-like Growth Factor I) mRNA on Days 4 to 7 and the

expression of bone matrix proteins, i.e. type I collagen, osteonectin, and osteocalcin mRNA on and after Day 7 increased markedly in osteoblast-like cells on trabecular surfaces, as compared to the vehicle control group (Nakajima A, et al. *J Bone Miner Res*. 2002; 17 (11): 2038–2047). Such changes were not observed in the contralateral, non-fractured femurs. Calluses from the group treated with once-daily subcutaneous injections of hPTH (1-34) 30 μg/kg showed significant increases over the vehicle controls with respect to cartilage volume, BMC, BMD, and bone strength by Day 21 after fracture (Alkhiary YM, et al. *J Bone Joint Surg Am*. 2005; 87 (4): 731–741). By Day 35, this cartilage volume decreased and the mineralized bone tissue increased. Following once-daily subcutaneous injections of hPTH (1-34) 10 μg/kg, gene expression of sox 9, type II collagen, and type X collagen (chondrogenesis-related genes) were upregulated transiently on Day 4 or 7 after fracture (Nakazawa T, et al. *Bone*. 2005; 37 (5): 711–719). The cartilage area significantly increased 2 weeks after fracture but the increase was no greater than that in the vehicle control group 3 to 4 weeks after fracture. These results suggest that hPTH (1-34) increases chondrogenesis and stimulates endochondral ossification immediately. After subcutaneous injections of hPTH (1-34) 10 or 30 μg/kg three times weekly for 3 weeks, fractures were produced in rats and treatment was discontinued. The effects of hPTH (1-34) given before fracture were not mechanically or histologically different from those of the vehicle control group, before and after fracture. Meanwhile, when hPTH (1-34) treatment was continued also after fracture, thick, compact bone formation was seen at 6 weeks after fracture and remodeling of woven bone to lamellar bone was accelerated. The ultimate load was increased (Komatsubara S, et al. *Bone*. 2005; 36 (4): 678–687). The stimulation of callus remodeling by hPTH (1-34) has been reported also in a cynomolgus monkey model of femoral fracture. Following twice-weekly subcutaneous injections of hPTH (1-34) 0.75 or 7.5 μg/kg, fracture was produced surgically by cutting the shaft of the femur and fixing with a stainless plate. As a result of hPTH (1-34) treatment continued until 26 weeks after fracture, hPTH (1-34) dose-dependently decreased callus porosity, decreased callus size, increased degree of mineralization of the fracture callus, and increased ultimate stress (an intrinsic mechanical property) (Manabe T, et al. *Bone*. 2007; 40 (6): 1475–1482).

The above results from the studies using rat and monkey models of femoral fracture indicate as follows. Shortly after a fracture, hPTH (1-34) stimulates mesenchymal stem cell proliferation and osteoblast differentiation/induction and increases production of bone matrix proteins by osteoblasts, thereby increasing chondrogenesis. Then hPTH (1-34) stimulates endochondral ossification (callus formation) immediately and quickly restores mechanical stability. During the callus remodeling phase, hPTH (1-34) improves bone quality by accelerating replacement of woven bone with lamellar bone and rapidly restores mechanical bone strength to the previous level. Based on these results, at least the results from the experiments using animal models, in the fracture healing process that begins immediately after the inflammatory phase following a fracture, teriparatide presumably accelerates fracture healing by acting on the entire process from the reparative phase to the remodeling phase.

PMDA accepted the response for the following reason. Although whether or not acceleration of fracture healing by teriparatide, as suggested in animals, occurs in humans is unknown, teriparatide is unlikely to have adverse effects on fracture healing.

3.(i).B.(3) Effect of treatment withdrawal on bones

Concerning bone strength of the proximal femur in OVX monkeys, no major changes were observed in OVX monkeys treated with teriparatide 1 μg/kg/day for 12 months followed by 6-month withdrawal as compared to those treated with teriparatide 1 μg/kg/day for 18 months and there were significant differences from the OVX vehicle control group, whereas bone strength in OVX monkeys treated with teriparatide 5 μg/kg/day for 12 months followed by 6-month withdrawal decreased as compared to those treated with teriparatide 5 μg/kg/day for 18 months and showed no differences from the OVX vehicle control group. The effect of withdrawal differed depending on the dosage regimen. In OVX rats treated with vehicle following withdrawal of synthetic hPTH (1-34) 80 μg/kg, bone mass was below the sham-OVX level. PMDA asked the applicant to discuss the effect of teriparatide withdrawal on bone.

The applicant responded as follows:

In OVX monkeys, bone turnover immediately after withdrawal of teriparatide 5 μg/kg/day may have been unbalanced in favor of bone resorption, which is consistent with the finding that bone loss in OVX rats was suppressed by estrogen or raloxifene administered immediately after withdrawal of synthetic hPTH (1-34) 80 μg/kg. However, in OVX monkeys, bone strength 6 months after withdrawal of 5 μg/kg/day was between the sham-OVX and OVX levels and the decrease in bone strength in the 1 μg/kg/day-withdrawal group was smaller. Thus, the possibility that, after a greater increase in bone mass at a higher dose, treatment withdrawal results in a greater decrease cannot be ruled out. The C_{max} (2.08 ng/mL) at the 5 μg/kg dose in OVX monkeys was approximately 10 times greater than the C_{max} (0.2198 ng/mL) at the clinical dose in Japanese subjects, and the data on increased bone mass and decreased bone mass after treatment withdrawal from the teriparatide 1 μg/kg/day and 1 μg/kg/day-withdrawal groups should be more appropriate for extrapolation to humans. In a study in OVX monkeys treated with teriparatide 5 μg/kg/day for 18 months followed by 3-year withdrawal, bone mass of the vertebrae and proximal femur was significantly reduced after treatment withdrawal. Although bone mass of the proximal femur was still significantly higher than that in the OVX vehicle control group, the increase in bone mass of the vertebrae was completely reversed. Taking account of the above discussion on the non-clinical data, although the skeletal effects of teriparatide are expected to be maintained to some extent also after treatment withdrawal, if bone turnover is shifted in favor of bone resorption and the patient is at risk of bone loss after treatment withdrawal, treatment with anti-resorptives following a cessation of teriparatide therapy should be useful. Based on clinical data, Eastell, et al. (Eastell, et al. *J Bone Miner Res*. 2009; 24 (4): 726-736) and Rittmaster, et al. (Rittmaster, et al. *J Clin Endocrinol Metab*. 2000; 85 (6): 2129-2134) also recommend that after stopping a teriparatide therapy, patients at risk of bone loss should continue receiving anti-resorptives.

According to the applicant's view, teriparatide increased bone strength of the proximal femur in OVX monkeys even at 1 μg/kg/day achieving AUC (0.31 ng·hr /mL) close to the AUC (0.3575 ng·hr/mL) at the clinical dose in humans, therefore data on increased bone mass and decreased bone mass after treatment withdrawal from the teriparatide 1 μg/kg/day and 1 μg/kg/day-withdrawal groups are more appropriate to be

extrapolated to humans than the data from the teriparatide 5 μg/kg/day and 5 μg/kg/day-withdrawal groups. PMDA considered that the applicant's view is convincing and accepted the response.

3.(i).B.(4) Cardiovascular effects

The applicant explained the cardiovascular effects of teriparatide observed in safety pharmacology studies as follows:

Decreased blood pressure, increased heart rate, etc. observed in rats and dogs were considered due to the vasorelaxing, positive chronotropic, and positive inotropic effects of teriparatide and endogenous PTH also has such effects. Although changes in heart rate and blood pressure have been observed also in teriparatide clinical studies, the magnitude of the changes was small and these changes were not considered clinically relevant.

As endogenous PTH has vasorelaxing, positive chronotropic and inotropic effects, the possibility that significant cardiovascular effects of teriparatide as observed in rats and dogs occur also in humans cannot be ruled out, and the dose that caused increases in heart rate and left ventricular inotropic state in dogs (6 μg/kg) was close to a dose that produced therapeutic effects in OVX monkeys (5 μg/kg). PMDA asked the applicant to discuss cardiovascular effects of teriparatide in humans.

The applicant responded as follows:

Although decreased blood pressure and increased heart rate via vascular smooth muscle relaxing action and positive chronotropic effect and positive inotropic effect are known as the cardiovascular effects of PTH (Mok LLS, et al. *Endocr Rev*. 1989; 10 (4): 420-436, Pang PK, et al. *Am J Hypertens*. 1989;2(12, Pt 1):898-902), it has been reported that such cardiac effects of PTH require a concentration higher than that in the main target organs (bone and kidneys) (London GM, et al. *Kidney Int*. 1987; 31 (4): 973-980, Schlüter KD, et al. *Am J Physiol.* 1992;263(6, Pt 2):H1739-1746, Schlüter KD, et al. *Biochem J.* 1995;310(Pt 2):439-444). In a safety pharmacology study in which a single subcutaneous dose of teriparatide (3, 10, 30, 100, 300 μg/kg) was administered to male rats, blood pressure decreased and heart rate increased at dose levels of ≥30 μg/kg while no cardiovascular effects were observed at ≤10 μg/kg. The C_{max} and AUC in male rats following a subcutaneous dose of 30 μg/kg of teriparatide were 8.39 ng/mL and 5.59 ng·hr/mL, respectively, which were 38-fold and 16-fold higher, respectively, than the C_{max} (0.2198 ng/mL) and AUC (0.3575 ng·hr/mL) at the clinical dose (20 μg) in humans in Study GHCS. In an OVX monkey study, teriparatide at doses of 1 and 5 μg/kg increased bone mass. The C_{max} and AUC at 1 μg/kg were 0.88 ng/mL and 0.31 ng·hr/mL, respectively, and the C_{max} and AUC at 5 μg/kg were 2.08 ng/mL and 2.22 ng·hr/mL, respectively. Exposure at 5 μg/kg in monkeys was high, approximately 10-fold (based on C_{max} values) or 6-fold (based on AUC values) the human exposure at the clinical dose (20 μg), and as exposure at 1 μg/kg was close to the human exposure, 1 μg/kg was selected as the therapeutic dose for monkeys. On the other hand, in 3-month (the highest dose, 40 μg/kg) and 1-year (the highest dose, 10 μg/kg) repeat-dose toxicity studies in monkeys, no effects on ECGs including heart rates were observed. The C_{max} at 40 μg/kg in monkeys was 20.3 ng/mL and assuming dose-linearity of AUC, the AUC was estimated to be 18.9 ng·hr/mL and the C_{max} and AUC at 40 μg/kg in monkeys were 23-fold and 61-fold higher, respectively, than those at

the therapeutic dose in monkeys and 92-fold and 53-fold higher, respectively, than those at the clinical dose (20 μg) in humans. Following a single subcutaneous dose of 6 μg/kg of teriparatide in dogs, a decrease in blood pressure and increases in heart rate and left ventricular inotropy were observed. Assuming that the pharmacokinetics of teriparatide in dogs are similar to those in monkeys, the C_{max} and AUC in this study were estimated to be similar to those at 5 μg/kg in monkeys (2.08 ng/mL and 2.22 ng·hr/mL, respectively). In this case, the C_{max} and AUC at which cardiovascular effects were observed in dogs were estimated to be approximately 9.5-fold and 6.2-fold higher, respectively, than those at the clinical dose (20 μg). In clinical studies, orthostatic hypotension occurred predominantly at doses of ≥30 μg, but no clinically relevant cardiovascular effects were observed at doses up to 40 μg. Based on the above, it was inferred that teriparatide is unlikely to have significant effects on the cardiovascular system in humans. However, as orthostatic hypotension occurred predominantly at doses of ≥30 μg/day in clinical studies, precautions against orthostatic hypotension will be included in the package insert.

PMDA considered as follows:
Given that teriparatide even at 1 μg/kg increased bone mass in OVX monkeys and that the C_{max} (0.88 ng/mL) at 1 μg/kg in OVX monkeys was close to the C_{max} (0.2198 ng/mL) at the clinical dose (20 μg) in humans, the applicant's view that 1 μg/kg should be selected as the therapeutic dose for monkeys is justified. The no-observed-adverse-effect level (NOAEL) for effects on cardiac conduction in monkeys was approximately 20-fold higher than the therapeutic dose for monkeys based on C_{max} values and 92-fold higher than the clinical dose (20 μg) in humans based on C_{max} values. The dose at which effects were observed in dogs was 6 μg/kg, and although plasma drug concentrations in dogs were unknown, a 5 μg/kg dose in monkeys was similar to a 6 μg/kg dose in dogs and, assuming that the pharmacokinetics of teriparatide in dogs are similar to those in monkeys, the C_{max} in dogs was considered to be approximately 10-fold higher than the C_{max} at the estimated clinical effective dose in humans. Furthermore, no significant cardiovascular effects other than orthostatic hypotension were observed also in clinical studies. Taking account of these findings, a major concern for humans is unlikely to arise. Therefore, PMDA accepted the response. See "4.(iii).B.(4).4) Cardiovascular disorders" for cardiovascular effects in humans.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics of teriparatide after a single intravenous or subcutaneous dose in rats and monkeys were determined. Based on toxicokinetics in rat and monkey toxicity studies, the repeat-dose pharmacokinetics of teriparatide were determined. Serum concentrations of teriparatide were determined by immunoradiometric assay and the lower limit of quantification was 0.3 ng/mL.

3.(ii).A.(1) Absorption (4.2.2.2.1 to 4.2.2.2.10)

The pharmacokinetic parameters after a single intravenous or subcutaneous dose of teriparatide in male and female rats and male and female monkeys were as shown in Table 1. After subcutaneous administration of teriparatide, C_{max} was reached at 5 to 45 minutes post-dose and the $t_{1/2}$ was 11 to 35 minutes. The

bioavailability (BA) following a 10 μg/kg subcutaneous dose was 55% and 61% in rats and 33% to 39% in monkeys.

Table 1. Pharmacokinetic parameters after a single dose of teriparatide

Animal species	Route of administration	Dose (μg/kg)	Sex	n	t_{max} (min)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	BA (%)	CL (mL/min/kg)	V_β (L/kg)	$t_{1/2}$ (min)
Rat	i.v.	10	♂	3[a)]	3	15 ± 6.7	2.2	—	74.2	0.61	5
			♀	3[a)]	3	20 ± 1.5	2.7	—	62.1	0.48	5
		300	♂	3[a)]	3	1324 ± 302	423.7	—	11.8	0.24	14
			♀	3[a)]	3	1826 ± 42	404.3	—	12.4	0.24	14
	s.c.	10	♂	3[a)]	5	2.6 ± 0.3	1.4	61	—	—	11
			♀	3[a)]	5	2.6 ± 0.1	1.5	55	—	—	14
		100	♂	3[a)]	30	28 ± 2.8	24.0	—	—	—	22.5
			♀	3[a)]	15	15 ± 1.6	11.7	—	—	—	20.4
		300	♂	3[a)]	30	100 ± 9.3	84.7	20	—	—	23.8
			♀	3[a)]	5	47 ± 7.6	34.4	8.5	—	—	17.9
		1000	♂	3[a)]	15	325 ± 88.5	294.2	—	—	—	19.4
			♀	3[a)]	15	179 ± 40.5	119.3	—	—	—	20.0
Monkey	i.v.	10[b)]	♂	5	3	124.8 ± 8.6	26.1 ± 2.1	—	6.6 ± 0.6	0.14 ± 0.01	14 ± 0.6
			♀	5	3	136.7 ± 15.7	29.8 ± 2.8	—	5.8 ± 0.5	0.13 ± 0.01	16 ± 0.6
		10[c)]	♂	2	3	141.5	28.2	—	5.9	0.15	17
			♀	2	3	178.4	36.1	—	4.6	0.09	14
	s.c.	10[b)]	♂	5	30 ± 4.8	8.3 ± 2.1	10.1 ± 1.9	39 ± 6	—	—	26 ± 3.6
			♀	5	45 ± 4.8	7.8 ± 1.4	9.5 ± 1.5	34 ± 6	—	—	25 ± 4.2
		10[c)]	♂	2	30	7.6	10.4	37	—	—	32
			♀	2	17	9.0	11.8	33	—	—	35

Mean ± SE, Parameters other than C_{max} in the rat were calculated from mean serum concentrations.
t_{max}: Time of maximum serum concentration, C_{max}: Maximum serum concentration,
$AUC_{0-\infty}$: Area under the serum concentration-versus-time curve (extrapolated to infinity),
BA: Bioavailability, CL: Serum clearance, V_β: Volume of distribution of β phase, $t_{1/2}$: Serum half-life, —: Not determined
a) No. of animals at each sampling point, b) Cynomolgus monkeys, c) Rhesus monkeys

Male and female rats (n = 3/sex/sampling point/group) were subcutaneously administered 10, 30, 100, or 300 μg/kg/day of teriparatide for 6 weeks. The t_{max} was 5 to 30 minutes, and the C_{max} values in the 100 μg/kg/day group (mean values on Days 8 and 43) were 30 and 64 ng/mL, respectively, in males and 24 and 35 ng/mL, respectively, in females. The AUC_{0-t} values were 22.9 and 44.9 ng·hr/mL, respectively, in males and 15.6 and 26.2 ng·hr/mL, respectively, in females, and the $t_{1/2}$ was 11 to 14 minutes. Male and female rats (n = 3 or 12/sex/sampling point/group) were subcutaneously administered 10, 30, or 100 μg/kg/day of teriparatide for 6 months. The serum concentrations in the 30 and 100 μg/kg/day groups were higher after the last dose compared with the first dose, while the $t_{1/2}$ values after the first and last doses in the 100 μg/kg/day group were 25 to 26 minutes. Female monkeys (n = 5) were subcutaneously administered 5 μg/kg/day of teriparatide for 18 months. The t_{max} values were 25 to 44 minutes and the C_{max} values (mean values on Days 4, 352, 546, and 548) were 2.04, 1.79, 1.62, and 1.85 ng/mL, respectively. The $AUC_{0\text{-}60\ min}$ values were 1.5, 1.4, 1.3, and 1.4 ng·hr/mL, respectively. Also when male and female monkeys (n = 3 or 4/sex/group) were subcutaneously administered 2, 10, 20, or 40 μg/kg/day of teriparatide for 3 months and male and female monkeys (n = 4/sex/group) were subcutaneously administered 0.5, 2, or 10 μg/kg/day of teriparatide for 1 year, no accumulation was detected.

3.(ii).A.(2) Distribution

A distribution study was not performed.

3.(ii).A.(3) Metabolism (4.2.2.4.1)

A metabolite profiling study, etc. were not performed[20].

3.(ii).A.(4) Excretion

An excretion study was not performed.

3.(ii).B Outline of the review

PMDA asked the applicant to explain why non-clinical pharmacokinetic studies of teriparatide (distribution, excretion, metabolite profiling, etc.) were not performed.

The applicant explained the reason for not performing distribution, excretion, and metabolite profiling studies, etc. as follows and discussed the non-clinical pharmacokinetics of teriparatide based on literature reports.

As the durations of elimination half-life of teriparatide in the rat were as short as 11 to 24 minutes (after a single subcutaneous dose of 10-1000 μg/kg), and the absorbed teriparatide was expected to be rapidly catabolized into amino acids and then used for protein biosynthesis. Considering unlikeliness to gain useful information on the exact distribution, metabolites, and mass balance of teriparatide, these studies were not performed ("Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" [PMSB/ELD Notification No. 326 dated February 22, 2000]). It has been reported that following subcutaneous administration of 10 μg/kg of ^{125}I-rhPTH (1-34) to male and female rats, radioactivity was distributed in most tissues/organs excluding the brain by 30 minutes to 1 hour postdosing (Hu Z, et al. *Int J Pharm,* 2006; 317: 144-154). However, this finding should be interpreted carefully taking account of rapidness in *in vivo* metabolism. Although it has been reported that PTH did not cross the placenta in the rat and the monkey (Northrop G, et al. *Am J Obstet Gynecol,* 1977; 129: 449-453, Garel JM & Dumont C. *Horm Metab Res.* 1972; 4: 217-221), no information on hPTH (1-34) has been made available. Teriparatide or PTH (1-34), which has a smaller molecular weight than PTH (1-84), may be more likely to be transferred to the fetus or milk than PTH (1-84) and the possibility that teriparatide is transferred to the fetus or suckling infants through milk cannot be ruled out. Literature on metabolism reports that ^{125}I-labeled bovine PTH (1-34) was metabolized by the dog's liver (D'Amour P, et al. *Am J Physiol.* 1981; 241: E208-E214), that bovine PTH (1-34) was metabolized in an isolated perfused canine tibia model (Martin KJ, et al. *J Clin Invest.* 1978; 62: 256-261), that hPTH (1-34) was rapidly metabolized in an isolated perfused rat liver model (Daugaard H, et al. *Endocrinology.* 1994; 134: 1373-1381, D'Amour P & Huet PM. *Am J Physiol.* 1989; 256: E87-E92), and that hPTH (1-34) was metabolized in rat kidney, lung, and liver homogenates (Liao S, et al. *Amino Acids,* in press), etc. Reports on excretion claims that bovine PTH (1-34) was eliminated by tubular secretion and glomerular filtration in the dog and the rat (Martin KJ et al. *J Clin Invest.* 1977; 60: 808-814) and that hPTH (1-34) was eliminated primarily by glomerular filtration in an isolated rat kidney model (Daugaard H, et al. *Endocrinology.* 1994; 134: 1373-1381), etc.

Following the review on the submitted data, etc., PMDA concluded as follows and accepted the response:

[20] Possible CYP induction has been studied in the monkey.

The pharmacokinetic profile of teriparatide can be discussed to some extent based on existing literature reports, etc. Non-clinical pharmacokinetic studies on the distribution of teriparatide, etc. were not performed, which is unlikely to become a clinically relevant problem.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of teriparatide conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (studies on kidney lesions). As some of the reproductive and developmental toxicity and other toxicity studies were non-GLP studies, the data from these studies were evaluated as reference data.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1, 4.2.3.1.2)

Single-dose toxicity studies were conducted by the subcutaneous route (teriparatide 0, 100, 300, 1000 μg/kg) and the intravenous route (teriparatide 0, 300 μg/kg) in rats (vehicle, 20 mM phosphate buffered saline) and no deaths occurred in either study. The approximate lethal doses by the subcutaneous and intravenous routes were determined to be >1000 μg/kg and >300 μg/kg, respectively, for both males and females. Redness of extremities was seen after dosing, and this finding was considered related to the vasodilating effects of PTH (1-34) (Pang PKT, In *New actions of parathyroid hormone,* Massry SG & Fujita T eds. Plenum Press, New York, 1989; 127-135, Mok LLS, et al. *Endocr Rev*. 1989; 10: 420-436). Although no single-dose toxicity studies in non-rodents have been conducted, in a 3-month subcutaneous administration study in monkeys (4.2.3.2.3), the serum teriparatide concentration 1 hour after administration of teriparatide at the highest dose (40 μg/kg/day) on Day 1 was ≥100-fold the C_{max} at the clinical dose (20 μg) in Japanese female patients (5.3.3.5.1) and no changes in clinical observations and no deaths were observed.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose toxicity studies were conducted by the subcutaneous route in rats (6 weeks, 6 months) and monkeys (3 months, 1 year). As the major effects of teriparatide, increases in serum calcium and alkaline phosphatase activity, decreases in erythrocyte and leukocyte counts and increased extramedullary hematopoiesis, and multifocal mineralization in the kidney were observed in rats, which were considered related to the pharmacological effects of teriparatide or decreased bone marrow space secondary to increased bone formation. In monkeys, decreases in red blood cell parameters and histological changes in the kidney (expanded medullary interstitium, mineralization) were observed. The C_{max} values at the NOAELs (rat, 10 μg/kg/day; monkey, 2 μg/kg/day) in rats (6 months) and monkeys (1 year) were estimated to be approximately 15-fold and approximately 3-fold higher, respectively, than that at the clinical dose (20 μg) in Japanese female patients (5.3.3.5.1) and the AUC values were estimated to be 6.4-fold and 2.2-fold higher, respectively.

3.(iii).A.(2).1) Rat 6-week administration study (4.2.3.2.1)

Male and female rats (8-9 weeks of age) were given 0 (20 mM phosphate-buffered saline containing mannitol), 10, 30, 100, or 300 μg/kg/day of teriparatide by subcutaneous injection for 6 weeks. Decreases in

neutrophil and eosinophil counts, an increase in alkaline phosphatase activity, an increase in globulin, seminiferous tubule degeneration in the testis (stage VII pachytene spermatocyte degeneration), increased extramedullary hematopoiesis in the spleen, and increased femoral trabecular bone mass at ≥10 μg/kg/day, redness in the ears and extremities, decreases in erythrocyte and leukocyte counts, an increase in blood ionized calcium (4 hours post-dose), increased triglycerides, increased urinary calcium excretion, decreased testis weights, and increased spleen weights at ≥100 μg/kg/day, and increased body weight gain, an increase in the efficiency of food utilization, increases in serum total calcium and cholesterol, and decreased prostate weights at 300 μg/kg/day were observed. The decreases in blood cell counts and changes in the spleen were related to decreased bone marrow space secondary to increased bone formation and the increase in serum alkaline phosphatase activity and changes in calcium, and redness in the ears and extremities due to vasodilatation were considered related to the pharmacological effects of teriparatide. Although the changes observed at 10 μg/kg/day including those related to the pharmacological effects of teriparatide would not adversely affect the general condition, as seminiferous tubule degeneration in the testis was observed, the NOAEL in this study was determined to be <10 μg/kg/day. There were no differences in the incidence of histological changes at the injection site (focal hemorrhage, focal granulomatous inflammation, chronic focal inflammation) between the control and 300 μg/kg/day groups and teriparatide showed no irritant effects.

3.(iii).A.(2).2) Rat 6-month administration study (4.2.3.2.2)

Male and female rats (27-28 weeks of age) were given 0 (20 mM phosphate-buffered saline containing mannitol), 10, 30, or 100 μg/kg/day of teriparatide by subcutaneous injection for 6 months. Decreases in erythrocyte, leukocyte, lymphocyte, and neutrophil counts, an increase in serum total calcium, a decrease in albumin, an increase in globulin, estrous cycle abnormalities, reduced pituitary weights, increased femoral length, increased extramedullary hematopoiesis in the spleen, and increased femoral trabecular/cortical bone mass at ≥10 μg/kg/day, an increase in serum inorganic phosphorus, increased urinary excretion of calcium and inorganic phosphorus, bone hypertrophy, and increased spleen weights at ≥30 μg/kg/day, and an increase in blood ionized calcium (4 hours post-dose), an increase in serum alkaline phosphatase activity, multifocal mineralization in the kidney, and increased extramedullary hematopoiesis in the liver at 100 μg/kg/day were observed, and 1 male died at 100 μg/kg/day though its relationship to teriparatide was not clear. Reduced body weight gain was noted in males at 100 μg/kg/day while increased body weight gain and an increase in the efficiency of food utilization at ≥10 μg/kg/day and increased food consumption at 100 μg/kg/day were observed in females. As the changes observed at 10 μg/kg/day including those related to the pharmacological effects of teriparatide would not adversely affect the general condition, the NOAEL in this study was determined to be 10 μg/kg/day. There were no differences in the incidence of histological changes at the injection site (focal dermal hemorrhage, focal subcutaneous hemorrhage, diffuse subcutaneous hemorrhage, chronic inflammatory changes) between the control and 100 μg/kg/day groups and teriparatide showed no irritant effects. Effects on male reproductive organs were noted in the aforementioned 6-week administration study in juvenile rats, but not in this study in adult rats. There was no quantifiable increase in teriparatide-specific IgG in this study.

3.(iii).A.(2).3) Monkey 3-month administration study (4.2.3.2.3)

Male and female cynomolgus monkeys were given 0 (20 mM phosphate-buffered saline containing mannitol), 2, 10, 20, or 40 μg/kg/day of teriparatide by subcutaneous injection for 3 months. Elevation of blood ionized calcium (4 hours post-dose), increased femoral trabecular bone mass, and expanded interstitium in the outer stripe of the medulla in the kidney were observed at ≥2 μg/kg/day, decreases in blood ionized calcium (24 hours post-dose), total serum calcium, and serum inorganic phosphorus levels, and basophilic degeneration/epithelial regeneration in the collecting ducts and distal tubules of the kidney (accompanied by degenerative changes in some regions) at ≥10 μg/kg/day, decreases in erythrocyte count, hemoglobin concentration, and hematocrit, an increase in serum urea, increased kidney weights, and medullary mineralization at ≥20 μg/kg/day, and decreases in serum glucose, potassium, and chloride at 40 μg/kg/day. The renal findings observed at 2 μg/kg/day were minimal and there were no changes that would indicate any effects on renal function. None of these findings including those related to the pharmacological effects of teriparatide would adversely affect the general condition. Thus, the NOAEL in this study was determined to be 2 μg/kg/day. There were no differences in the incidences of histological changes at the injection site (subacute inflammatory changes in the dermis, epidermis, and muscle) between the control and teriparatide groups and teriparatide showed no irritant effects. There was no quantifiable increase in teriparatide-specific IgG in this study.

3.(iii).A.(2).4) Monkey 1-year administration study (4.2.3.2.4)

Male and female cynomolgus monkeys were given 0 (20 mM phosphate-buffered saline containing mannitol), 0.5, 2, or 10 μg/kg/day of teriparatide by subcutaneous injection for 1 year. Increased femoral trabecular bone mass, expansion of the basophilic degeneration in the renal medullary interstitium, and multifocal mineralization of the renal tubule/interstitium were observed at ≥0.5 μg/kg/day, an increase in blood ionized calcium (4 hours post-dose) at ≥2 μg/kg/day, and decreases in erythrocyte count, hemoglobin concentration, and hematocrit and increased kidney weights at 10 μg/kg/day. The renal findings observed at 0.5 and 2 μg/kg/day were minimal and there were no changes that would indicate any effects on renal function. None of these findings including those related to the pharmacological effects of teriparatide would adversely affect the general condition. Thus, the NOAEL in this study was determined to be 2 μg/kg/day. There were no differences in the incidence of histological changes at the injection site (subacute inflammatory changes associated with infiltration of subcutaneous cells) between the control and teriparatide groups and teriparatide showed no irritant effects. Although there were some animals with a quantifiable increase in teriparatide-specific IgG in this study, the levels of teriparatide-specific IgG were all very low and changes in blood ionized calcium were seen also at the end of treatment. Therefore, these levels of anti-teriparatide IgG would not neutralize the pharmacological effects of teriparatide and antibody formation is not considered to affect the results of toxicity studies.

3.(iii).A.(3) Genotoxicity

Genotoxicity studies conducted include a bacterial reverse mutation assay, a gene mutation assay using mouse lymphoma L5178Y $TK^{+/-}$ cells, a chromosomal aberration assay using Chinese hamster ovary cells, and a mouse bone marrow micronucleus test via subcutaneous injection. Although the chromosomal

aberration assay showed an increased incidence of polyploidy at the highest dose (5000 μg/mL), teriparatide is a peptide composed of natural amino acids and is therefore considered to have no genotoxic potential.

3.(iii).A.(4) Carcinogenicity

Concerning the carcinogenicity of teriparatide, a standard 2-year carcinogenicity study in rats showed a dose-related incidence of bone tumors and, furthermore, a second carcinogenicity study showed that the formation of bone tumors was dependent upon the duration of exposure. On the other hand, in a study in ovariectomized monkeys treated with teriparatide for 18 months followed by 3-year withdrawal, proliferative bone lesions including bone tumors were not observed.

Although the mechanism of development of bone tumors observed in rats has not been elucidated, the lesions are considered related to the exaggerated pharmacodynamic effects of teriparatide and it has been discussed that as there are differences in bone physiology between rats and humans (rats do not have Haversian system in cortical bone, the rat skeleton continues to grow longitudinally for most of their lives, bone turnover is faster in rats, etc.), the bone proliferative lesions observed in rats are not necessarily relevant to humans. When 6-month-old rats were treated with 5 μg/kg/day of teriparatide for 20 months, bone tumors were not observed and the C_{max} and AUC at this dose level were estimated to be 6.7-fold and 2.4-fold higher, respectively, than those at the clinical dose (20 μg) in Japanese female patients (5.3.3.5.1).

3.(iii).A.(4).1) Rat carcinogenicity study (4.2.3.4.1.1)

Male and female F344 rats (6-7 weeks of age) were given 0 (20 mM phosphate-buffered saline containing mannitol), 5, 30, or 75 μg/kg/day of teriparatide by subcutaneous injection for 2 years. The incidences of osteosarcoma (males, 0 of 60 rats [0 μg/kg/day], 3 of 60 rats [5 μg/kg/day], 21 of 60 rats [30 μg/kg/day], and 31 of 60 rats [75 μg/kg/day]; females, 0 of 60 rats, 4 of 60 rats, 12 of 60 rats, and 23 of 60 rats, respectively) and osteoblastoma (males, 0 of 60 rats, 0 of 60 rats, 2 of 60 rats, and 7 of 60 rats, respectively; females, 0 of 60 rats, 1 of 60 rats, 1 of 60 rats, and 3 of 60 rats, respectively) were increased at ≥5 μg/kg/day. The incidence of osteoma (males, 0 of 60 rats, 0 of 60 rats, 2 of 60 rats, and 1 of 60 rats, respectively) was increased at ≥30 μg/kg/day and focal osteoblast hyperplasia in bones and an increase in femoral trabecular bone mass were also observed at ≥5 μg/kg/day. Time to first diagnosis of osteosarcoma as a bone nodule at clinical observation or necropsy of animals that died/were killed in extremis was approximately 17 months at 75 μg/kg/day and approximately 20 months at 5 and 30 μg/kg/day. Osteosarcoma occurred at various appendicular and axial skeletal sites and 36% of the animals with a diagnosis of osteosarcoma experienced metastasis. The development of tumors was not observed in tissues other than the bone, and the incidence or severity of non-neoplastic lesions including extramedullary hematopoiesis in the spleen, cystic cartilage degeneration (sternum), chronic progressive nephropathy, renal (renal tubule and pelvis) mineralization, thyroid C-cell hyperplasia, and adrenal medullary hyperplasia increased.

3.(iii).A.(4).2) Rat carcinogenicity study (Additional study) (4.2.3.4.1.2)

Female F344 rats (6-7 weeks of age) were given 0 (20 mM phosphate-buffered saline containing mannitol), 5, or 30 μg/kg/day of teriparatide by subcutaneous injection for 6 months (from approximately 2 months of age

through 8 months of age or from approximately 6 months of age through 12 months of age), for 20 months (from approximately 6 months of age through 26 months of age), or for 24 months (from 2 months of age through 26 months of age, 30 μg/kg/day only). Some of the rats that were treated with 5 or 30 μg/kg/day of teriparatide for 6 months (from approximately 2 months of age through 8 months of age or from approximately 6 months of age through 12 months of age) were kept until 26 months of age. In the histopathological examination of bones at 30 μg/kg/day in rats aged 26 months, while osteosarcoma (1 of 60 rats) was detected in the control group, osteosarcoma (2 of 60 rats each, regardless of age at treatment onset) with a 6-month treatment, osteosarcoma (5 of 60 rats) and osteoma (1 of 60 rats) with a 20-month treatment, and osteosarcoma (9 of 60 rats), osteoma (2 of 60 rats), and osteoblastoma (1 of 60 rats) with a 24-month treatment were observed. Since the incidence of bone tumors increased with increasing treatment duration, the occurrence of bone tumors associated with teriparatide is dependent upon treatment duration. In the groups of rats that were treated for 6 months from 2 months of age through 8 months of age or from 6 months of age through 12 months of age and kept until 26 months of age, no differences in the incidence of bone tumors at 30 μg/kg/day were observed (osteosarcoma, 2 of 60 rats each). The effect of age at the start of the treatment on the induction of bone tumors is not clear. In the group of 6-month-old rats treated with 5 μg/kg/day for 20 months, bone tumors were not observed.

3.(iii).A.(4).3) Study in OVX monkeys treated for 18 months followed by 3-year withdrawal (4.2.3.4.1.3)

OVX cynomolgus monkeys (9-11 years of age, n = 30/group) were given 0 (20 mM phosphate-buffered saline containing mannitol) or 5 μg/kg/day of teriparatide by subcutaneous injection for 18 months. Six animals per group were sacrificed at the end of treatment period and the remaining surviving animals were followed up for 3 years. Bone-specific alkaline phosphatase activity was increased during the treatment period, which resolved upon drug withdrawal. X-ray films revealed no teriparatide-related proliferative changes in bone. The histopathological examination revealed increased trabecular bone mass associated with increases in trabecular thickness and number in the teriparatide group at the end of treatment period, but neoplastic bone lesions or focal bone proliferative lesions were not observed at the end of treatment period or at the end of withdrawal period.

3.(iii).A.(5) Reproductive and developmental toxicity

As reproductive and developmental toxicity studies, studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in mice, rats, and rabbits, and a rat study on pre- and postnatal development, including maternal function were conducted.

In rabbits, the toxicity of teriparatide was enhanced during pregnancy and fetal toxicity (embryonic death) was observed. In mice, the incidence of fetal skeletal variations or abnormalities was slightly increased. In rats, pups exhibited reduced body weight gain and decreased motor activity.

3.(iii).A.(5).1) Rat studies of fertility and early embryonic development to implantation

3.(iii).A.(5).1).(a) Male rat study (4.2.3.5.1.1)

Male rats (approximately 13 weeks of age) were given 0 (20 mM phosphate-buffered saline containing mannitol), 30, 100, or 300 μg/kg/day of teriparatide by subcutaneous injection from 4 weeks prior to and during cohabitation (cohabitation period, up to 2 weeks). Mating with untreated females and fetal examination showed no teriparatide-related effects. Redness of extremities due to vasodilatation at ≥30 μg/kg/day and slightly decreased prostate weights without histological changes at 300 μg/kg/day were observed, which were all considered of little toxicological significance. The NOAEL for general and reproductive toxicity in male animals was determined to be 300 μg/kg/day in this study.

3.(iii).A.(5).1).(b) Female rat study (4.2.3.5.1.2)

Female rats were given 0 (20 mM phosphate-buffered saline containing mannitol), 30, 100, or 300 μg/kg/day of teriparatide by subcutaneous injection from 2 weeks prior to mating until Gestation Day 6 (cohabitation period, up to 2 weeks). Mating with untreated males and fetal examination showed no teriparatide-related effects. Redness of extremities due to vasodilatation at ≥30 μg/kg/day, increased body weight gain (premating period) at ≥100 μg/kg/day, and increased food consumption (premating period) at 300 μg/kg/day were observed, which were all considered of little toxicological significance. The NOAEL for general and reproductive toxicity and early embryonic development in female animals was determined to be 300 μg/kg/day in this study.

3.(iii).A.(5).2) Embryo-fetal development studies

3.(iii).A.(5).2).(a) Mouse study (4.2.3.5.2.1)

Pregnant mice were given 0 (20 mM phosphate-buffered saline containing mannitol), 30, 225, or 1000 μg/kg/day of teriparatide by subcutaneous injection on Gestation Days 6 through 15. The incidence of fetal skeletal variations or abnormalities (interrupted ribs; sternebra bipartite, extra sternebra, and misaligned sternebra; extra rib; extra presacral vertebra; delayed ossification of occipital bone, etc.) was slightly increased at ≥225 μg/kg/day. There were no teriparatide-related effects on maternal fertility. Redness of extremities due to vasodilatation was noted at ≥30 μg/kg/day, which was considered of little toxicological significance. The NOAELs for general and reproductive toxicity in maternal animals and for embryo-fetal developmental toxicity were determined to be 1000 μg/kg/day and 30 μg/kg/day, respectively, in this study.

3.(iii).A.(5).2).(b) Rat study (4.2.3.5.2.2)

Pregnant rats were given 0 (20 mM phosphate-buffered saline containing mannitol), 30, 225, or 1000 μg/kg/day of teriparatide by subcutaneous injection on Gestation Days 6 through 17. There were no teriparatide-related effects on maternal fertility or the embryo/fetus. Redness of extremities due to vasodilatation was noted at ≥30 μg/kg/day, which was considered of little toxicological significance. The NOAEL for general and reproductive toxicity in maternal animals and embryo-fetal developmental toxicity was determined to be 1000 μg/kg/day in this study.

3.(iii).A.(5).2).(c) Rabbit study (Reference data, 4.2.3.5.2.6)

Pregnant rabbits were given 0 (20 mM phosphate-buffered saline containing mannitol), 3, 10, 30, or 100 μg/kg/day of teriparatide by subcutaneous injection on Gestation Days 7 through 19. In dams, vasodilatation

of the ears and decreased body weight at ≥3 μg/kg/day and reduced food consumption, decreased feces, and anuria at ≥30 μg/kg/day were observed. Since increased staining around the vaginal orifice and anus and increased reactivity to touch were noted and 1 of 5 rabbits died on both Gestation Days 16 and 18 at 100 μg/kg/day, the remaining animals were euthanized on Gestation Day 18. As no marked toxicity signs were observed in a pilot study in non-pregnant animals (Reference data, 4.2.3.5.2.5), pregnancy was shown to enhance the toxicity of teriparatide. Red material in the waste tray, indicative of embryotoxicity, was observed at ≥3 μg/kg/day. Based on fetal observation, 1 of 5 dams at 3 μg/kg/day and all dams at ≥10 μg/kg/day had total resorption of the litter and a decrease in the number of live fetuses and an increase in embryonic/fetal mortality rate were also observed at 3 μg/kg/day. In fetuses in the 3 μg/kg/day group assessed for external and skeletal morphology, umbilical torsion (1 of 14 fetuses), absence of arch of cervical vertebra (1 of 13 fetuses), and absent incisor (2 of 13 fetuses) were observed. No NOAEL was determined in this study.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant rats were given 0 (20 mM phosphate-buffered saline containing mannitol), 30, 225, or 1000 μg/kg/day of teriparatide by subcutaneous injection from Gestation Day 6 through Lactation Day 20. In dams, reddened or warm extremities due to vasodilatation were noted at ≥30 μg/kg/day. In the F_1 pups, reduced body weight on Postnatal Day 14 at 1000 μg/kg/day and a post-weaning reduction in body weight gain at ≥225 μg/kg/day were observed and body weight was reduced throughout gestation and lactation in females at 1000 μg/kg/day. In addition, motor activity was reduced on Postnatal Days 23 and 60 at 1000 μg/kg/day. In males at 1000 μg/kg/day, a delay in achievement of balanopreputial separation was noted, which was considered associated with reduced body weight gain and this finding as well as the symptoms in dams were considered of little toxicological significance. The NOAELs for general and reproductive toxicity in maternal animals and for F_1 developmental toxicity were determined to be 1000 μg/kg/day and 30 μg/kg/day, respectively, in this study.

3.(iii).A.(6) Local tolerance

Local tolerance was evaluated in repeat-dose toxicity studies. Teriparatide showed no irritant effects at the injection site in these studies.

3.(iii).A.(7) Other toxicity studies (Studies on kidney lesions)

As histological changes characterized by expanded renal medullary interstitium were observed in repeat-dose toxicity studies in monkeys (4.2.3.2.3, 4.2.3.2.4), additional studies were conducted to assess the reproducibility, effect on renal function, and reversibility of these changes. The studies suggested that the kidney lesions may be related to hypercalcaemia and showed that the kidney lesions were reversible.

3.(iii).A.(7).1) Monkey 4-month administration study with a 3-month reversibility period (4.2.3.7.7.1)

Female cynomolgus monkeys were given 0 (20 mM phosphate-buffered saline containing mannitol, n = 4) or 40 μg/kg/day of teriparatide (n = 8) by subcutaneous injection for 4 months. Two monkeys in the control

group and 5 monkeys in the 40 μg/kg/day group were necropsied at the end of treatment and the remaining animals were observed for 3 months. One animal in the 40 μg/kg/day group exhibited increases in total serum calcium, urea nitrogen, and creatinine and renal failure-like symptoms such as hyposthenuria, polyuria, and dehydration after approximately 2 months of treatment, but the symptoms resolved upon drug withdrawal on Day 83. No apparent effects on renal function were observed in the other animals. The histopathological examination revealed expanded renal medullary interstitium, multifocal subacute inflammation, and multifocal mineralization at the end of treatment period in the 40 μg/kg/day group and especially 2 animals with serious lesions had significant hypercalcaemia. The expanded interstitium was mainly located in the outer stripe of the medulla and histochemical staining suggested that basophilic material resulting in interstitial expansion was acidic mucopolysaccharides. As the severity of the lesions was reduced after a reversibility period, these changes are considered reversible.

3.(iii).A.(7).2) Histopathologic evaluation of kidneys from OVX monkeys given teriparatide for up to 18 months (Reference data, 4.2.3.7.7.2)

In a primary pharmacodynamic study, OVX cynomolgus monkeys (9-10 years of age) were subcutaneously administered 0 (20 mM phosphate-buffered saline containing mannitol), 1, or 5 μg/kg/day of teriparatide for 18 months or 1 or 5 μg/kg/day of teriparatide for 12 months followed by 6-month withdrawal (4.2.1.1.5). The histopathological examination of the kidneys revealed no abnormalities in any animal. Since the calcium content of the diet used in this study (approximately 90 mg/kg body weight) was lower than those used in monkey toxicity studies (estimated at 330-550 mg/kg body weight), it has been inferred that calcium intake from the diet may be related to the kidney lesions.

3.(iii).B Outline of the review

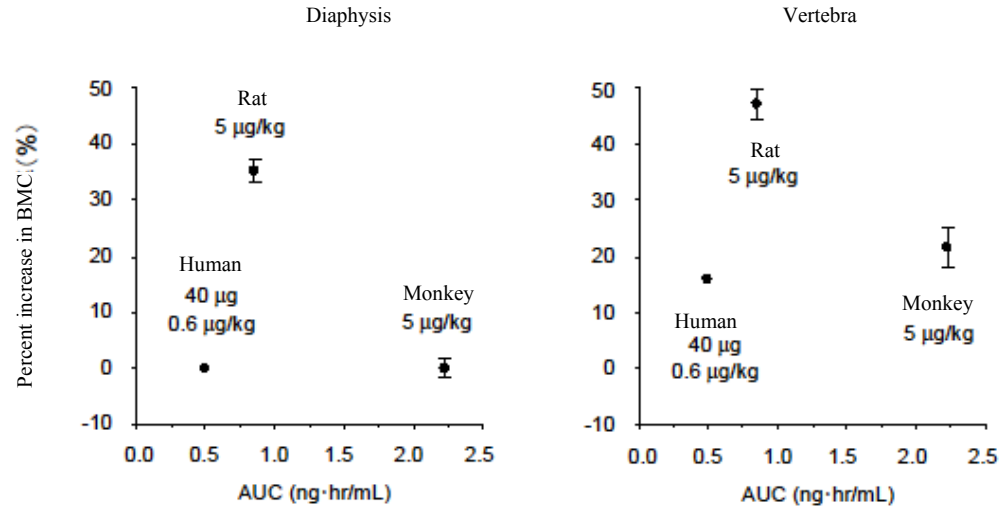
3.(iii).B.(1) Carcinogenicity

3.(iii).B.(1).1) Discussion on osteosarcoma

PMDA asked the applicant to discuss the occurrence of osteosarcoma in rat carcinogenicity studies.

The applicant responded as follows:

As PTH directly acts on osteoblasts via the receptor and stimulates differentiation of progenitor cells, etc. (Dempster DW, et al. *Endocr Rev*. 1993; 14: 690-709), it is considered that bone tumors observed in rat carcinogenicity studies were due to prolonged and continual stimulation by teriparatide of osteoblasts. Moreover, comparison of increases in bone mass caused by teriparatide in rats, monkeys, and humans showed that the magnitude of bone effects in rats is much greater than in humans or monkeys (Figure 1).



Rat : 2 years of treatment with 5 µg/kg/day (n = 27-29, Mean ± SE, 4.2.3.4.1.1)
Monkey : 18 months of treatment with 5 µg/kg/day (n = 22, Mean ± SE, 4.2.1.1.5)
Human : 19 months (median) of treatment with 40 µg in postmenopausal patients with osteoporosis (n = 154 in the placebo group and n = 145 in the 40 µg group for diaphysis; n = 504 in the placebo group and n = 497 in the 40 µg group for vertebra; Mean only, Study GHAC)

Figure 1. Relationship between AUC and percent increase in BMC at cortical (diaphysis) and trabecular (vertebra) bone sites

This greater sensitivity of the rat is thought to be due to the structure of cortical bone (Kimmel DB, In *Osteoporosis,* Marcus R, *et al.* eds. Academic Press, San Diego, 1996; 671-690). As rats do not have Haversian remodeling in cortical bone and cortical bone replacement via osteonal (Haversian lamellae) remodeling does not occur, rats are considered to respond to PTH by extensive apposition of new bone at trabecular, endocortical, and periosteal surfaces (Dempster DW, et al. *Endocr Rev*. 1993; 14: 690-709, Qi H, et al. *J Bone Miner Res*. 1995; 10: 948-955). On the other hand, since humans and monkeys exhibit osteonal remodeling of cortical bone, when PTH stimulates bone turnover, old bone tissue is replaced by new bone tissue and cortical bone mass does not increase dramatically. The rat skeleton continues to grow longitudinally for most of their lives (Kimmel DB, In *Osteoporosis,* Marcus R, et al. eds. Academic Press, San Diego, 1996; 671-690), while longitudinal growth in humans ceases with epiphyseal closure (Compston JE. *Physiol Rev*. 2001; 84: 419-447). Furthermore, the bone turnover rate in humans (postmenopausal women) is 1.4 to 1.6 cycles/year (Recker RR, et al. *J Bone Miner Res*. 1988; 3: 133-144, Eriksen EF, et al. *J Bone Miner Res*. 1990; 5: 311-319, Kimmel DB et al. *Bone Miner*. 1990; 11: 217-235), while the turnover rate in the rat (3-16 months of age) is high, 11.8 to 36.5 cycles/year (Li XJ, et al. *Cell Mater Suppl*. 1991; 1: 25-35). In this way, there are fundamental differences in bone physiology between rats and humans and it is inferred that bone tumors were induced by the exaggerated pharmacodynamic effects of teriparatide in rats. Although a second carcinogenicity study in rats showed that the occurrence of bone tumors associated with teriparatide was dependent upon treatment duration, when taking into account the differences in bone turnover rates in rats, humans, and monkeys, a treatment period not associated with bone tumor formation (20 months) in rats at systemic exposure approximately 2.4 times (AUC ratio) the human exposure at the clinical dose corresponds to approximately 20 cycles of bone turnover (calculated based on 11.8 cycles/year), which is comparable to more than 12 years in postmenopausal women. In addition, bone proliferative lesions were not observed in an 18-month administration study in OVX monkeys (bone turnover rate, 7.2 cycles/year; 4.2.1.1.5) and bone turnover cycles (10.8 cycles) in this study are comparable to about 7 years.

For clinical use of teriparatide, the maximum duration of treatment with teriparatide will be 18 months and teriparatide will be contraindicated in patients at increased baseline risk of osteosarcoma and pediatric and young adult patients with open epiphyseal plates. As long as appropriate patients are selected, the risk of osteosarcoma will not increase.

3.(iii).B.(1).2) Threshold for carcinogenesis

As teriparatide is a non-genotoxic carcinogen, it is considered important to determine the threshold for carcinogenesis in carcinogenic risk assessment. However, a NOEL for carcinogenesis was not established in a standard carcinogenicity study. PMDA asked for the applicant's view on this point.

The applicant responded as follows:

Teriparatide markedly increased bone mass in rats (as previously noted), and proliferative changes in bone observed in carcinogenicity studies are considered associated with increases in bone mass. Rat 6-week and 6-month administration and carcinogenicity studies showed that stimulation of bone formation is dependent upon dose (exposure) and treatment duration. Thus, for tumor development, the duration of treatment was considered important for estimating response in humans, and the second carcinogenicity study was designed to focus on treatment duration, not on the establishment of the NOEL for carcinogenesis. The second study showed that not only dose but also treatment duration are key factors in carcinogenesis induced by teriparatide. No tumors developed in rats treated with teriparatide at a dose equivalent to 2.4 times (AUC ratio) the human exposure for 20 months (about 70% of lifespan of rats). Based on these threshold values for carcinogenesis in terms of the dose and duration of treatment, the risk of osteosarcoma will not be substantially increased in humans treated with teriparatide at the intended clinical dose for up to the maximum duration recommended.

3.(iii).B.(1).3) Risk in premenopausal women

Based on differences in bone turnover rates between rats and humans and the results from a long-term study in OVX monkeys, it has been concluded that the risk of bone tumors in postmenopausal women is low. However, bone turnover in premenopausal women is considered different from that in postmenopausal women. PMDA asked the applicant to explain risks in premenopausal women.

The applicant responded as follows:

The use of teriparatide in premenopausal women is expected to be limited to those with glucocorticoid-induced osteoporosis. For assessment of risks of bone tumors in premenopausal women, findings on bone turnover in premenopausal women and patients with glucocorticoid-induced osteoporosis, epidemiologic studies on osteosarcoma, and the effect of age at treatment onset on tumor development in a carcinogenicity study are considered important. Since bone turnover is lower in premenopausal women with high estrogen levels than in postmenopausal women (Hauschka PV, et al. *Physiol Rev*. 1989; 69: 990-1047, Garnero P, et al. *J Bone Miner Res*. 1996; 11: 337-349, Ravn P, et al. *Bone*. 1996; 19: 291-298, Recker R, et al. *J Bone Miner Res*. 2004; 19: 1628-1633) and bone turnover is also lower in patients with glucocorticoid-induced osteoporosis (Dempster DW, et al. *Calcif Tissue Int.* 1983; 35: 410-417, Dempster

DW. *J Bone Miner Res*. 1989; 4 :137-141, Doga M, et al. *J Endocrinol Invest.* 2008; 31: Suppl-7. 53-58, Minisola S, et al. *J Endocrinol Invest*. 2008; 31: Suppl-7. 28-32, Silverman SL & Lane NE. *Curr Osteoporos Rep*. 2009; 7: 23-26), bone turnover in premenopausal women with glucocorticoid-induced osteoporosis is unlikely to be higher than that in postmenopausal women. Furthermore, an epidemiologic study on osteosarcoma incidence (Mirabello L, et al. *Cancer*. 2009; 115: 1531-1543) has shown that the incidence of osteosarcoma in the age group including premenopausal adult women is lower than those in other age groups, and the second carcinogenicity study in rats did not show that younger animals were more susceptible to bone tumor formation associated with teriparatide. Therefore, risks of osteosarcoma should not increase in premenopausal female patients.

3.(iii).B.(2) Reproductive and developmental toxicity

3.(iii).B.(2).1) Fetal skeletal findings

PMDA asked the applicant to explain the possible relationship between skeletal findings observed in a mouse embryo-fetal development study and teriparatide treatment.

The applicant responded as follows:

Fetal skeletal findings observed in this study were relatively all non-serious, and the incidence of the findings in animals treated with teriparatide was not significantly different from that in the control group and was within the range of historical control data or the difference in incidence between the control and high-dose groups was very small. Thus, these findings are not considered related to teriparatide. Meanwhile, since teriparatide may cross the placenta or changes in maternal blood calcium, etc. may indirectly affect the fetus, their relationship to teriparatide cannot necessarily be ruled out. Based on the above, precaution information concerning skeletal findings will be included in the package insert.

3.(iii).B.(2).2) Effects on pregnancy

PMDA asked the applicant to discuss maternal effects observed in a rabbit embryo-fetal development study.

The applicant responded as follows:

Serious effects were observed in pregnant rabbits at dose levels producing no toxicity signs in non-pregnant rabbits and measurements of blood ionized calcium in pregnant and non-pregnant rabbits indicated that elevations in blood ionized calcium may be delayed in pregnant rabbits. Baseline blood calcium levels are much higher in rabbits than in humans or other mammalians and its homeostasis is different (Buss SL & Bourdeau JE. *Miner Electrolyte Metab*. 1984; 10: 127-132, Redrobe S. *Semin in Avian and Exot Pet Med.* 2002; 11: 94-101). Furthermore, rabbits are considered more sensitive to the effect of PTH on blood ionized calcium than mice or rats. Thus, it is inferred that the toxicities in pregnant rabbits were due to the disruption of calcium homeostasis in the body. Clinically in pregnant patients with hyperparathyroidism, the following events have been reported: higher incidences of excessive hyperemesis gravidarum, urinary calculus, etc., life-threatening complications such as pancreatitis and hypercalcaemic crisis (Norman J, et al. *Clin Endocrinol*. 2009; 71: 104-109), and abortion or fetal death, fetal growth retardation, etc (Graham EM, et al. *J Reprod Med*. 1998; 43: 451-454, Schnatz PF & Curry SL. *Obstet Gynecol Surv*. 2002; 57: 365-376).

However, persistent hypercalcaemia is unlikely to occur at the intended dosing regimen. Teriparatide will be contraindicated in pregnant women or in women who may possibly be pregnant, and the package insert will advise that teriparatide should be used in women of childbearing potential only if the expected therapeutic benefits outweigh the possible risks associated with treatment and that patients should be instructed to use an effective method of birth control during treatment. Therefore, there should be no safety concerns for humans.

3.(iii).B.(3) Nephrotoxicity

PMDA asked the applicant to discuss nephrotoxicity observed in monkeys.

The applicant responded as follows:

In repeat-dose toxicity studies in monkeys, expanded renal medullary interstitium and associated tubular degeneration were observed. The medullary interstitium was expanded by deposition of basophilic material and histochemical staining (Alcian blue staining) suggested that the basophilic material was mucopolysaccharide. Mucopolysaccharide is a component in the extracellular matrix and abundant also in the kidney and is considered to play a physiological role, e.g. contributing to the concentration of urine, due to its high hydrophilicity, water-retaining ability, and negative charge (Murata K, In *Glycosaminoglycans and proteoglycans in physiological and pathological processes of body systems*, Varma RS & Varma R eds. Karger, Basel, 1982; 135-150, Knepper MA, et al. *Am J Physiol*. 2003; 284: F433-F446). Mucopolysaccharide is more abundant in the medulla than in the cortex in the kidney and it has been inferred that such differences in the composition and distribution of mucopolysaccharide are related to different water and electrolyte transport function between the two regions (Murata K. *Renal Physiol*. 1979/1980; 2: 346-352). In the kidney, active turnover of mucopolysaccharides is high in the physiological state and mucopolysaccharides filtered through glomerular capillaries are reabsorbed across the epithelia of the collecting duct and then move into the medullary insterstitium, resulting in morphological changes in the medullary interstitium (Yamaguchi H, et al. *Exp Toxic Pathol*. 1992; 44: 415-420). It seems that due to increased calcium reabsorption in the distal tubule and collecting duct following teriparatide treatment, the balance of mucopolysaccharide production, degradation, and removal in the medulla changed, as a physiological response involving water control in the kidney, resulting in deposition of mucopolysaccharides in the medullary interstitium and expanded interstitium. The degree of the changes was minimal at 2 μg/kg/day (the estimated exposure was approximately 2.2-fold the human exposure based on AUC) in monkey 3-month (4.2.3.2.3) and 1-year (4.2.3.2.4) administration studies and the renal tubules adjacent to the affected regions showed no abnormalities. Thus, these changes are considered an adaptive response and of little toxicological significance, but classified as toxic changes because at a high dose, the expansion of the interstitium became more pronounced and there were animals with lesions in the collecting duct and distal tubule. Also in humans, it has been reported that mucopolysaccharides in the renal medullary interstitium change with physiological conditions such as aging (Inoue G, et al. *Gerontologia*. 1973; 19: 73-78) and the possibility that similar changes occur cannot be ruled out, but it has been suggested that the severity of these changes is correlated with the degree of hypercalcaemia and persistent elevation of calcium is considered a factor causing serious lesions. In Japanese and foreign clinical studies, increases in serum calcium following

administration of teriparatide were transient and furthermore, the incidences of hypercalcaemia were low. Thus, the kidney lesions observed in monkeys are unlikely to become a serious problem in humans.

PMDA accepts the above responses from a toxicological point of view, but considers that the risk of osteosarcoma needs to be further assessed from a clinical point of view [see "4.(iii).B.(4) Safety and 4.(iii).B.(6) Dosage and administration"].

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

In the clinical development of teriparatide, a lyophilized formulation in vials and a liquid formulation in cartridges (250 and 500 μg/mL) were used. The formulations used in clinical studies (evaluation data) were as shown in Table 2. Drug product in cartridges (250 μg/mL) and drug product in disposable kits (drug product in a cartridge pre-assembled in a pen-injector) were proposed for marketing in Japan.

Table 2. Formulations used in clinical studies (evaluation data)

Phase of development	Lyophilized formulation in vials	Liquid formulation in cartridges
Phase I	GHAD, GHBI, GHAE	GHCO, GHBO, GHBO (2) , GHBI, GHAW, GHBC, GHBR, GHBA
Phase II	—	GHCS
Phase III	—	GHDB, GHAC, GHAJ
Phase III/IV	—	GHCA
Phase IV	—	GHBM

Teriparatide in human serum was quantified by immunoradiometric assay and the lower limit of quantification was 50 pg/mL.

As the evaluation data on biopharmaceutics, the results from a foreign clinical study (GHBI) were submitted. As the reference data, the results from foreign clinical studies (GHAK, GHAN, GHAS, GHAT, GHBF, GHCE) were submitted. The results from Study GHBI are described below.

Absolute bioavailability study (5.3.1.1.1, GHBI [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, single-blind, five-period crossover study was conducted in foreign healthy elderly men and women. The primary objective of the study was to determine the absolute bioavailability of teriparatide administered by subcutaneous injection.

Although placebo or 20 or 40 μg of teriparatide was supposed to be given as a single subcutaneous injection or 17.54 μg of teriparatide was supposed to be given as a single intravenous infusion, it was revealed that a single subcutaneous injection of 80 μg of teriparatide was given mistakenly instead of 40 μg of teriparatide. Therefore another treatment period was added to perform a single subcutaneous injection of 40 μg of teriparatide. Calcium (1000 mg/day) and vitamin D (500 IU/day) were orally administered twice daily from 2 weeks prior to the first dose until the fourth dose and from 2 weeks prior to the fifth dose until the end of treatment.

All of 22 subjects treated with study drug[21] were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

According to pharmacokinetic analysis, following subcutaneous administration of 20 μg of teriparatide, the C_{max} (mean [coefficient of variation (CV)]) was 151.0 pg/mL (37.7%) and the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were 165.3 pg·hr/mL (40.9%) and 322.0 pg·hr/mL (41.3%), respectively. Following intravenous administration of teriparatide, the CL was 90.3 L/hr (24.0%) and the V was 18.2 L (32.9%). Following subcutaneous administration of 20 μg of teriparatide, the $AUC_{0\text{-}t}$ values were 143.2 pg·hr/mL (46.5%) in men and 187.4 pg·hr/mL (34.2%) in women and following intravenous administration of teriparatide, the $AUC_{0\text{-}t}$ values were 164.3 pg·hr/mL (19.3%) in men and 223.1 pg·hr/mL (20.0%) in women, showing that total systemic exposure was higher in women than in men. The absolute bioavailability estimated from the population pharmacokinetic analysis assuming a 1-compartment model with first-order absorption and first-order elimination (PPK analysis) was 95% (17%).

Pharmacodynamic analysis indicated that following subcutaneous administration of placebo and teriparatide (placebo, 20, 40, and 80 μg), the maximum changes from baseline in serum total calcium concentrations (geometric means) were 0.072, 0.068, 0.108, and 0.095 mM, respectively. Following subcutaneous administration of teriparatide as compared to placebo, the urinary calcium excretion rate and the serum phosphorus concentration were reduced and the urinary phosphorus excretion rate was increased.

The safety analysis revealed that adverse events for which a causal relationship to teriparatide could not be ruled out occurred in 5 subjects (8 events), 7 subjects (14 events), and 18 subjects (51 events) after subcutaneous administration of teriparatide (20, 40, and 80 μg), respectively, and 14 subjects (25 events) after intravenous administration of teriparatide. The most commonly reported event was headache. Postural hypotension reported by 1 subject after administration of 80 μg of teriparatide was a severe event. Following subcutaneous administration of placebo and teriparatide (placebo, 20, 40, and 80 μg), the changes from baseline in pulse rates (means) were -4.8, -2.8, 1.0, and 6.1 bpm, respectively, in men and -3.7, -1.5, -1.3, and 7.8 bpm, respectively, in women. There were no deaths, other serious adverse events, or adverse events leading to discontinuation.

4.(i).B Outline of the review

Absolute bioavailability

The applicant explained that based on the results of PPK analysis of Study GHBI, the absolute bioavailability of teriparatide administered by subcutaneous injection was 95%. PMDA asked the applicant to also present the value calculated based on non-model-dependent approach and explain the cause for species differences (rat, 55%-61%; monkey, 33%-39%).

[21] Sixteen subjects participated in the additional period in which a single subcutaneous injection of 40 μg of teriparatide was given.

The applicant responded as follows:
As the elimination half-life following intravenous administration of teriparatide was as extremely short as approximately 5 minutes, a non-compartmental analysis requiring frequent blood sampling during the elimination phase was difficult. Moreover, since low concentrations could not be determined, the elimination phase could not be assessed and accurate pharmacokinetic parameters might have not been obtained. Thus, it was not considered appropriate to determine the absolute bioavailability using the pharmacokinetic parameters obtained by a non-compartmental analysis. On the other hand, as data below the lower limit of quantification following subcutaneous administration of low-dose teriparatide were imputed by collectively analyzing data at different dose levels based on PPK approach, the absolute bioavailability was estimated accurately. Species differences in the absolute bioavailability of teriparatide administered by subcutaneous injection may be attributable to species differences in enzyme activity such as peptidase that degrades teriparatide, but the details are unknown as no studies that can explain the cause have been conducted.

PMDA considers as follows:
If most of the blood concentrations during the elimination phase are below the lower limit of quantification, it is difficult to calculate an absolute bioavailability accurately, and the PPK approach may overestimate the absolute bioavailability. Preferably, information on the absolute bioavailability of subcutaneously injected teriparatide should include the calculation method, and the study on species differences should be continued. However, taking account of the short elimination half-life of teriparatide and the submitted efficacy and safety data from clinical studies, the applicant's explanation is acceptable.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As evaluation data, results from foreign clinical studies (GHCO, GHAD, GHBO, GHBO (2), GHAW, GHBC, GHAE, GHBA, GHBR) were submitted. As reference data, results from foreign clinical studies (GHAB, GHAM) were submitted. The results of main studies are described below.

4.(ii).A.(1) Clinical pharmacokinetic and pharmacodynamic studies

4.(ii).A.(1).1) Pharmacokinetics and pharmacodynamics in healthy volunteers

4.(ii).A.(1).1).(a) Phase I single-dose study (5.3.3.1.1, GHCO [[redacted] to [redacted] 20[redacted]])

A randomized, placebo-controlled, single-blind, dose escalation study was conducted in healthy older Japanese and Caucasian women. The primary objective of the study was to evaluate the safety and tolerability of a single subcutaneous dose of teriparatide in Japanese women.

Each subject was to receive single subcutaneous doses of placebo, teriparatide 10 μg (Japanese subjects only), 20 μg, and 60 μg and two subcutaneous doses of teriparatide 40 μg at weekly intervals. Calcium (1000 mg/day) and vitamin D (400 IU/day) were orally administered twice daily from 2 weeks prior to the first dose until the last dose.

All of 33 subjects treated with study drug (18 Japanese subjects, 15 Caucasian subjects) were included in the pharmacokinetic and safety analyses.

The pharmacokinetic parameters following subcutaneous administration of teriparatide were as shown in Table 3. In both Japanese and Caucasian subjects, the C_{max} increased in a dose-proportional manner and the increase in AUC_{0-t} was more than dose-proportional. Following subcutaneous administration of 20 μg of teriparatide, the C_{max} and AUC_{0-t} geometric mean ratios (Japanese/Caucasian) with their 90% confidence intervals (CIs) were 1.37 [1.10, 1.71] and 1.69 [1.28, 2.22], respectively, and 1.04 [0.85, 1.27] and 1.28 [0.99, 1.65], respectively, when adjusted for body weight.

Table 3. Pharmacokinetic parameters following subcutaneous administration of teriparatide

Dose	t_{max} (hr)		C_{max} (pg/mL)		AUC_{0-t} (pg·hr/mL)		CL/F (L/hr)		V_Z/F (L)		$t_{1/2}$ (hr)	
	Japanese (J)	Caucasian (C)	J	C	J	C	J	C	J	C	J	C
10 μg	0.25 (0.25-0.75)	—	119 (43.2)	—	71.8 (76.5)	—	59.7 (30.3)	—	47.5 (48.9)	—	0.551 (0.369-1.21)	—
20 μg	0.25 (0.25-0.75)	0.25 (0.25-0.75)	227 (35.7)	166 (41.3)	222 (53.0)	131 (44.9)	64.5 (38.4)	101 (40.3)	66.0 (37.9)	96.6 (53.9)	0.708 (0.479-1.21)	0.663 (0.317-2.24)
40 μg	0.25 (0.25-1.00)	0.25 (0.25-0.50)	447 (33.2)	333 (42.5)	460 (35.7)	321 (35.7)	69.3 (37.5)	97.8 (34.1)	72.7 (45.0)	104 (45.3)	0.727 (0.38-1.75)	0.735 (0.282-1.65)
60 μg	0.25 (0.25-0.50)	0.25 (0.25-0.50)	671 (38.0)	533 (31.6)	729 (34.3)	552 (37.1)	66.8 (33.3)	81.9 (36.3)	77.7 (45.7)	107 (38.9)	0.806 (0.484-1.36)	0.906 (0.501-2.11)

Geometric mean (CV %), Median (range) for t_{max}, Geometric mean (range) for $t_{1/2}$
CL/F: apparent serum clearance, V_Z/F: apparent volume of distribution

The safety analysis revealed that adverse events for which a causal relationship to teriparatide could not be ruled out occurred in 3 Japanese subjects (3 events), 3 Japanese subjects (3 events), 10 Japanese subjects (10 events), 7 Japanese subjects (9 events), and 13 Japanese subjects (13 events) following subcutaneous administration of 10, 20, 40 (the first dose), 40 (the second dose), and 60 μg of teriparatide, respectively, and in 8 Caucasian subjects (9 events), 18 Caucasian subjects[22] (20 events), 11 Caucasian subjects (11 events), and 20 Caucasian subjects[22] (21 events) following subcutaneous administration of 20, 40 (the first dose), 40 (the second dose), and 60 μg of teriparatide, respectively. The incidence tended to increase with increasing dose. The most commonly reported event was headache. Orthostatic hypotension occurred in 2 Japanese subjects (4 events) and 2 Caucasian subjects (2 events). In both Japanese and Caucasian subjects, supine and standing pulse rates and the serum total calcium concentration increased and the serum phosphorus concentration decreased following subcutaneous administration of teriparatide as compared to placebo. There were no deaths, other serious adverse events, or adverse events leading to discontinuation.

4.(ii).A.(1).1).(b) Study of the effect of teriparatide on calcium homeostasis (5.3.3.1.3, GHAD [to 19])

An open-label study was conducted in foreign healthy postmenopausal women. The primary objective of the study was to determine a level of calcium intake that does not cause hypercalcaemia or hypercalciuria when used in combination with teriparatide and oral vitamin D.

[22] Subjects were counted for each adverse event reported.

Calcium 450, 900, 1200, 1500, or 1700 mg/day was to be taken orally on Days 2 through 29. ^{45}Ca was to be orally administered on Days 15 and 29. 400 IU/day of vitamin D was to be orally administered on Days 2 through 29 (except for the calcium 900 mg/day group), and 40 μg of teriparatide was to be subcutaneously administered once daily on Days 16 through 29.

All of 23 subjects treated with the study drug (6 subjects in the calcium 450 mg/day group, 4 subjects in the 900 mg/day group, 6 subjects in the 1200 mg/day group, 2 subjects in the 1500 mg/day group, 5 subjects in the 1700 mg/day group)[23] were included in the pharmacodynamic[24] and safety analyses, of whom 18 subjects[25] were included in the pharmacokinetic analysis and their blood samples were collected for the analysis.

The pharmacokinetics of teriparatide indicated there were no differences according to calcium intake and the C_{max} values (mean [CV]) after the first dose (n = 18) and the 14th dose (n = 16) were 479 pg/mL (35%) and 438 pg/mL (31%), respectively. The $AUC_{0\text{-}2.5\ h}$ values were 802 pg·hr/mL (27%) and 767 pg·hr/mL (29%), respectively, and the t_{max} was 0.67 to 1.52 hours.

As the pharmacodynamic data of teriparatide, serum ionized calcium and total calcium concentrations were as shown in Table 4, and teriparatide increased these concentrations. Regardless of the amount of calcium taken, teriparatide increased 24-hour urinary calcium excretion and intestinal calcium absorption and the serum 1,25-$(OH)_2$ vitamin D concentration. Teriparatide reduced serum phosphorus and magnesium concentrations.

Table 4. Serum ionized calcium and total calcium $AUC_{0\text{-}8\ h}$

Calcium intake	Serum ionized calcium			Serum total calcium		
	Day before the first dose of teriparatide	First dose of teriparatide	14th dose of teriparatide	Day before the first dose of teriparatide	First dose of teriparatide	14th dose of teriparatide
450 mg/day	9.76 (3.24)	10.34 (3.47)	11.23 (4.01)	18.05 (4.76)	19.13 (5.00)	20.33 (5.26)
900 mg/day	9.61 (2.63)	10.09 (3.79)	10.26 (2.99)	18.77 (2.68)	19.40 (2.81)	19.84 (1.61)
1200 mg/day	9.69 (3.53)	9.88 (3.89)	10.17 (3.44)	18.92 (3.34)	19.32 (3.83)	19.85 (2.58)
1500 mg/day	9.91, 9.48	10.35, 9.88	—	18.79, 18.46	19.71, 18.99	—
1700 mg/day	10.42 (3.68)	10.77 (3.69)	10.99 (4.31)	19.03 (4.19)	19.43 (4.20)	19.77 (4.05)

Unit: mM·hr, Mean (CV %), Values of 2 subjects for 1500 mg/day

The safety analysis revealed that 85 adverse events occurred in 21 subjects and the most commonly reported event was headache. Orthostatic hypotension occurred in 2 subjects. No clinically relevant hypercalcaemia[26] or hypercalciuria was observed. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

[23] The study was conducted in the following order: (1) calcium 900 and 1200 mg/day groups, (2) 450 mg/day group, and (3) 1500 and 1700 mg/day groups.

[24] As 2 subjects in the calcium 1500 mg/day group dropped out on Day 23, pharmacodynamic data on Day 29 are not available.

[25] As 2 subjects in the calcium 1500 mg/day group dropped out on Day 23, pharmacokinetic data on Day 29 are not available.

[26] Hypercalcaemia was initially defined as "a serum ionized calcium concentration of >1.36 mM" and hypercalcaemia did not occur in the calcium 900 or 1200 mg/day group. Although hypercalcaemia did not occur also after the first dose of teriparatide in the calcium 450 mg/day group, as serum ionized calcium concentrations before the 14th dose of teriparatide were high, the post-14th-dose maximum concentration exceeded 1.36 mM in all subjects though the magnitude of the increases after the 14th dose was similar to that after the first dose. Therefore, the investigator and the representative of Lilly Clinical Laboratory Medicine group discussed and concluded that the finding was artifactual, though the cause for high predose serum ionized calcium concentrations was not clear. Then the definition of hypercalcaemia was changed to "a serum total calcium concentration of >11.5 mg/dL and an increase from baseline of ≥1.0 mg/dL".

4.(ii).A.(1).1).(c) Assessment of teriparatide on cardiac conduction and repolarization (5.3.3.1.4, GHBO [[redacted] to [redacted] 20[redacted]])

A randomized, placebo-controlled, single-blind, two-period crossover study was conducted in foreign healthy adult male and female subjects. The primary objective of the study was to assess the effect of teriparatide on cardiac conduction and repolarization.

A single subcutaneous dose of placebo or 20 μg of teriparatide was to be administered in Period 1 and Period 2.

All of 49 subjects treated with the study drug were included in the pharmacodynamic and safety analyses[27].

The pharmacodynamic analysis indicated that the $AUC_{0\text{-}24\ h}$ of serum total calcium (mean ± standard deviation [SD]) was 54.1 ± 1.51 mM·hr following the administration of the placebo and 54.6 ± 1.53 mM·hr following the administration of teriparatide.

Changes in ECG parameters over time were as shown in Table 5.

Table 5. Changes in ECG parameters over time

Measurement time	QT interval	QTcF interval	QTcB interval	RR interval
20 minutes post-dose	-8.30 [-12.30, -4.30]	2.72 [-1.29, 6.72]	8.29 [3.49, 13.08]	-72.16 [-96.63, -47.68]
50 minutes post-dose	-13.49 [-17.94, -9.04]	-2.48 [-5.86, 0.90]	2.90 [-0.74, 6.54]	-76.24 [-99.52, -52.95]
3 hours 45 minutes post-dose	-5.60 [-10.03, -1.18]	-1.95 [-5.14, 1.24]	-0.40 [-4.39, 3.60]	-22.30 [-51.14, 6.53]
5 hours 15 minutes post-dose	-8.52 [-12.99, -4.05]	-5.23 [-8.37, -2.08]	-3.72 [-7.30, -0.15]	-24.49 [-50.52, 1.53]
24 hours post-dose	-6.06 [-12.00, -0.11]	-3.01 [-7.05, 1.02]	-1.75 [-6.31, 2.82]	-13.29 [-43.63, 17.05]

Least-squares mean difference between teriparatide and placebo (teriparatide minus placebo) msec [95% CI]

The safety analysis revealed that 72 adverse events occurred in 28 subjects. Among treatment-emergent adverse events for which a causal relationship to study drug could not be ruled out, those with high incidence were dizziness and headache. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

4.(ii).A.(1).1).(d) Assessment of teriparatide on cardiac conduction and repolarization (A second study) (5.3.3.1.5, GHBO (2) [[redacted] to [redacted] 20[redacted]])

A randomized, placebo-controlled, single-blind, two-period crossover study was conducted in subjects who participated in Study GHBO. The primary objective of the study was to evaluate the pharmacokinetics of teriparatide.

A single subcutaneous dose of placebo or 20 μg of teriparatide was to be administered in Period 1 and Period 2.

[27] In this study, most of the teriparatide serum concentrations were below the lower limit of quantification and several subjects had unexpected changes in serum concentrations over time. Thus, pharmacokinetic analysis was not performed [see "4.(ii).A.(1).1).(d) Assessment of teriparatide on cardiac conduction and repolarization (A second study)"].

All of 12 subjects treated with study drug were included in the pharmacodynamic and safety analyses and 11 subjects excluding 1 subject with missing data were included in the pharmacokinetic analysis.

Pharmacokinetic analysis showed that the t_{max} (mean [CV]) was 21.8 minutes (64.2%), the C_{max} was 117 pg/mL (38.2%), the AUC_{0-t} was 106 pg·hr/mL (42.4%), and the $t_{1/2}$ was 86.6 minutes (44.0%)[28].

Pharmacodynamic analysis showed that the $AUC_{0-24\,h}$ of serum total calcium (mean ± SD) was 53.7 ± 1.62 mM·hr following administration of placebo and 54.6 ± 1.58 mM·hr following administration of teriparatide.

Changes in ECG parameters over time were as shown in Table 6.

Table 6. Changes in ECG parameters over time

Measurement time	QT interval	QTcF interval	QTcB interval	RR interval
20 minutes post-dose	-7.3 [-14.49, -0.10]	-1.34 [-11.45, 8.78]	2.51 [-8.69, 13.72]	-45.88 [-106.45, 14.69]
50 minutes post-dose	-7.78 [-14.15, -1.41]	-0.34 [-8.18, 7.51]	3.6 [-5.89, 13.08]	-58.01 [-93.57, -22.45]
3 hours 45 minutes post-dose	-8.69 [-20.31, 2.93]	-3.75 [-14.74, 7.24]	-1.26 [-13.46, 10.95]	-44.53 [-96.03, 6.96]
5 hours 15 minutes post-dose	-4.06 [-13.98, 5.87]	-4.23 [-13.01, 4.55]	-3.77 [-14.57, 7.03]	5.81 [-51.63, 63.24]
24 hours post-dose	-1.24 [-13.18, 10.70]	0.59 [-6.92, 8.10]	1.95 [-6.83, 10.73]	-17.37 [-98.13, 63.40]

Least-squares mean difference between teriparatide and placebo (teriparatide minus placebo) msec [95% CI]

The safety analysis revealed that 16 adverse events occurred in 8 subjects. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

4.(ii).A.(1).2) Pharmacokinetics and pharmacodynamics in patients with osteoporosis

4.(ii).A.(1).2).(a) PPK analysis of Japanese phase II study (GHCS) (5.3.3.5.1, GHCS_PPK [[redacted] to [redacted]])

Based on the data from Study GHCS for teriparatide concentrations in serum samples collected at 293 time points, a PPK analysis was performed using non-linear mixed effect modeling (software, NONMEM version V). A 1-compartment model with first-order absorption and elimination was selected as the base structural model. The PPK analysis included data on 94 patients (30 patients in the teriparatide 10 μg group, 36 patients in the teriparatide 20 μg group, 28 patients in the teriparatide 40 μg group). The mean age was 71.8 years (Min-Max, 58-85 years), and the mean body weight was 48.4 kg (32.5-77.4 kg). The mean creatinine clearance (C_{CR}) was 62.1 mL/min (35.8-111.3 mL/min)[29]. Covariates evaluated for significance in a step-wise approach included the dose of teriparatide, age, years postmenopausal, body weight, BMI, total body water[30], alcohol use, smoking status, C_{CR}, AST, ALT, alkaline phosphatase, γ-GTP, BUN, and total bilirubin. As a result, body weight was included in the final model as a significant covariate on the apparent

[28] Given that 69% of the concentrations were below the lower limit of quantification in Study GHBO in contrast to 40% in this study, that Study GHBO and this study were conducted at the same site and with the same study design, and that the same lot of study drug was used and samples were analyzed at the same laboratory in Study GHBO and this study, the applicant concluded that the findings in Study GHBO (most of the teriparatide serum concentrations were below the lower limit of quantification and several subjects had unexpected changes in serum concentrations over time) were caused by degradation of teriparatide due to inappropriate handling of samples, not by study drug or subjects.

[29] Calculated using the Cockcroft-Gault formula.

[30] Total body water = -2.097 + [0.1069 × height (cm)] + [0.2466× body weight (kg)]

volume of distribution, and the apparent volume of distribution was estimated to increase with increasing body weight.

4.(ii).A.(1).2).(b) PPK analysis of foreign phase III study (GHAC) (5.3.4.2.1, GHAC_PPK [December 1996 to April 1999])

Based on the data from Study GHAC for teriparatide concentrations in serum samples collected at 1282 time points, a PPK analysis was performed using non-linear mixed effect modeling. A 1-compartment model with first-order absorption and elimination was selected as the base structural model. The PPK analysis included data on 360 patients (182 patients in the teriparatide 20 μg group, 178 patients in the teriparatide 40 μg group). The mean age was 69.4 years (Min-Max, 49-85 years), and the mean body weight was 65.7 kg (40.0-121.0 kg). The mean C_{CR} was 88.7 mL/min (11.7-196.7 mL/min)[31]. Covariates evaluated for significance in a step-wise approach included the dose of teriparatide, the site of injection (abdomen or thigh), age, years postmenopausal, race, body weight, BMI, total body water[30], alcohol use, smoking status, C_{CR}, AST, ALT, alkaline phosphatase, γ-GTP, BUN, and total bilirubin. As a result, the dose of teriparatide as a significant covariate on bioavailability and body weight and the site of injection as significant covariates on the apparent volume of distribution were included in the final model. It was estimated that the bioavailability of the 40 μg dose would be lower relative to the 20 μg dose and that the apparent volume of distribution would increase with increasing body weight and by injection in the thigh rather than in the abdomen.

4.(ii).A.(1).2).(c) PPK analysis of foreign phase III study (GHAJ) (5.3.3.5.2, GHAJ_PPK [October 1997 to March 1999])

Based on the data from Study GHAJ for teriparatide concentrations in serum samples collected at 695 time points, a PPK analysis was performed using non-linear mixed effect modeling. A 1-compartment model with first-order absorption and elimination was selected as the base structural model. The PPK analysis included data on 251 patients (125 patients in the teriparatide 20 μg group, 126 patients in the teriparatide 40 μg group). The mean age was 58.5 years (Min-Max, 31-84 years), and the mean body weight was 75.4 kg (48.2-129.5 kg). The mean C_{CR} was 126.3 mL/min (40.9-310.1 mL/min)[32]. Covariates evaluated for significance in a step-wise approach included the dose of teriparatide, the site of injection (abdomen or thigh), age, race, body weight, BMI, total body water[33], alcohol use, smoking status, C_{CR}, AST, ALT, alkaline phosphatase, γ-GTP, BUN, total bilirubin, and testosterone. As a result, C_{CR} as a significant covariate on the apparent clearance and body weight and the site of injection as significant covariates on the apparent volume of distribution were included in the final model. It was estimated that the apparent clearance would decrease with decreasing C_{CR} and that the apparent volume of distribution would increase with increasing body weight and by injection in the thigh rather than in the abdomen.

[31] Calculated from 24-hour urine collection.
[32] Calculated from 24-hour urine collection.
[33] Total body water = 2.447 - [0.09516 × age (years)] + [0.1074× height (cm)] + [0.3362× body weight (kg)]

4.(ii).A.(1).3) Pharmacokinetics and pharmacodynamics in special populations

4.(ii).A.(1).3).(a) Pharmacokinetics and pharmacodynamics in subjects with renal impairment (5.3.3.3.1, GHAW [19 to 20])

A randomized, single-blind, crossover study was conducted in foreign men and women. The primary objective of the study was to assess the effect of chronic renal impairment on the serum and urinary calcium response to teriparatide.

Subjects were assigned to either of the following two treatments in Period 1 and to the other treatment in Period 2.

Treatment A: A single subcutaneous dose of 40 μg of teriparatide or placebo was to be administered.

Treatment B: A single subcutaneous dose of 40 μg of teriparatide or a single intravenous infusion of furosemide ($C_{CR} \geq$ 90 mL/min, 20 mg; 55-75 mL/min, 40 mg; 31-54 mL/min, 60 mg; 10-30 mL/min, 100 mg) was to be administered.

All of 26 subjects treated with the study drug (9 healthy subjects[34], 12 subjects with mild to moderate renal impairment[35], 5 subjects with severe renal impairment[36]) were included in the pharmacokinetic, pharmacodynamic, and safety analyses[37].

According to the pharmacokinetic analysis, after the administration of teriparatide with placebo, the C_{max} values of teriparatide (mean (CV) in healthy subjects, subjects with mild to moderate renal impairment, and subjects with severe renal impairment) were 241.8 (38.0%), 219.9 (40.5%), and 249.2 (25.1%) pg/mL, respectively. The AUC_{0-t} values were 358.7 (50.5%), 316.7 (49.2%), and 719.9 (87.8%) pg·hr/mL, respectively, and the $t_{1/2}$ values were 60.7 (37.1%), 61.6 (58.0%), and 87.4 (49.0%) minutes, respectively. After the coadministration of teriparatide with furosemide, the C_{max} values of teriparatide were 203.8 (37.0%), 237.6 (59.5%), and 206.2 (33.0%) pg/mL, respectively, and the AUC_{0-t} values were 284.7 (35.8%), 337.2 (67.4%), and 391.6 (46.3%) pg·hr/mL, respectively. The $t_{1/2}$ values were 75.7 (41.5%), 79.4 (91.4%), and 155.0 (54.4%) minutes, respectively.

The pharmacodynamic analysis indicated that the serum ionized calcium concentration, the urinary calcium excretion rate, and the serum 1,25-$(OH)_2$ vitamin D concentration decreased and the serum total calcium concentration was similar in subjects with renal impairment as compared to healthy subjects. Following the coadministration of teriparatide with furosemide, the serum total calcium concentration and the urinary calcium excretion rate increased as compared to teriparatide with placebo, and the serum ionized calcium concentrations was similar between the two treatment groups.

[34] $C_{CR} \geq$ 90 mL/min
[35] C_{CR} = 31-75 mL/min
[36] $C_{CR} \leq$ 30 mL/min
[37] After the coadministration of teriparatide with furosemide, 1 subject withdrew from the study for personal reasons. Thus, the subject did not receive teriparatide + placebo.

The safety analysis revealed that adverse events occurred in 6 healthy subjects, 3 subjects with mild to moderate renal impairment, and 1 subject with severe renal impairment. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

4.(ii).A.(1).3).(b) Pharmacokinetics and pharmacodynamics in subjects with heart failure (5.3.3.3.2, GHBC [to 20])

A placebo-controlled, single-blind study was conducted in foreign subjects with mild or moderate heart failure. The primary objective of the study was to assess the effects of teriparatide on blood pressure and pulse rate.

A single subcutaneous dose of placebo was to be administered on Day 1 and a single subcutaneous dose of 20 μg of teriparatide was to be administered on Day 2 and 3.

All of 13 subjects treated with study drug (2 subjects with mild heart failure, 11 subjects with moderate heart failure) were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

The pharmacokinetic analysis showed that after the administration of teriparatide on Day 3, the t_{max} (mean ± SD) was 33.1 ± 12.8 minutes, and the C_{max} was 118.9 ± 50.0 pg/mL. The $AUC_{0\text{-}t}$ was 135.9 ± 47.62 pg·hr/mL.

The pharmacodynamic analysis indicated that the serum total calcium concentration elevated after the administration of teriparatide as compared to placebo. The maximum concentrations were 2.25 mM after the administration of placebo and 2.34 mM after the administration of teriparatide. The maximum changes from baseline were 0.05 mM after the administration of placebo and 0.12 mM after the administration of teriparatide. The serum phosphorus concentration also increased after the administration of teriparatide as compared to placebo.

The safety analysis revealed that adverse events occurred in 4 subjects, which were all mild in severity and their causal relationship to teriparatide was ruled out. No clinically relevant abnormalities in blood pressure, pulse rate, or ECG were observed. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

4.(ii).A.(1).3).(c) Safety of teriparatide in hypertensive subjects (5.3.3.4.1, GHAE [19 to 19])

A non-randomized, open-label study was conducted in foreign hypertensive women. The primary objective of the study was to evaluate the safety of teriparatide.

A β-adrenergic antagonist or calcium channel antagonist was to be orally administered once daily for 2 weeks and after blood pressure was controlled, the β-adrenergic antagonist or calcium channel antagonist was to be administered in combination with teriparatide 40 μg once daily for 2 or 3 days[38].

All of 14 subjects treated with the study drug (teriparatide administered in combination with a β-adrenergic antagonist in 5 subjects[39]; teriparatide administered in combination with a calcium channel antagonist in 9 subjects[40]) were included in the pharmacodynamic and safety analyses.

The pharmacodynamic analysis indicated that teriparatide increased the serum total calcium concentration and the magnitude of the increases was greater with simultaneous administration of teriparatide and a β-adrenergic antagonist. The maximum concentration was 10.0 mg/dL at 5 hours after administration. Teriparatide reduced the serum phosphorus concentration.

The safety analysis revealed that 36 adverse events occurred in 10 subjects, of which 25 events occurred after the first dose of teriparatide. However, most events were mild in severity and resolved spontaneously. One subject treated with teriparatide for 3 days had orthostatic hypotension with dizziness on all 3 days and was assessed as experiencing symptomatic hypotension. When administered either sequentially or simultaneously with a β-adrenergic antagonist or calcium channel antagonist, teriparatide decreased the blood pressure for up to 4 hours and increased the heart rate. The magnitude of the increases in heart rate up to 4 hours after the administration of teriparatide in combination with a β-adrenergic antagonist was smaller with simultaneous administration than with sequential administration. When administered either sequentially or simultaneously with a calcium channel antagonist, teriparatide caused decreases in the blood pressures other than the standing systolic blood pressure and increases in heart rate, also ≥4 hours after dosing. There were no deaths, other serious adverse events, or teriparatide-related adverse events leading to study discontinuation.

4.(ii).A.(1).4) Drug interaction studies

4.(ii).A.(1).4).(a) Drug interaction study with hydrochlorothiazide (5.3.3.4.2, GHBA [to 20])

A placebo-controlled, single-blind (open-label oral administration) study was conducted in foreign healthy elderly men and women. The primary objective of the study was to evaluate the effect of hydrochlorothiazide (HCTZ) on the serum calcium response by administration of teriparatide.

Placebo was to be administered on Day 1, and 20 or 40 μg of teriparatide was to be subcutaneously administered once daily on Days 2 and 3. HCTZ 25 mg was to be orally administered once daily on Days 4 through 11 with placebo or teriparatide 40 μg administered once daily on Days 9 and 11. Calcium (1000

[38] An antihypertensive drug was to be administered 4 hours after administration of teriparatide ("sequential administration") on Day 1 of coadministration and teriparatide was to be administered simultaneously with the antihypertensive drug on Day 2 (one subject received sequential administration, instead of simultaneous administration, on Day 2, due to the occurrence of transient vomiting after administration of an antihypertensive drug on Day 1). Three subjects received simultaneous administration on Day 3 (1 subject who had transient vomiting after administration of an antihypertensive drug on Day 1, 1 subject who had mild dizziness and decreased blood pressure on Days 1 and 2, 1 subject who had asymptomatic decreased blood pressure and increased heart rate on Day 2).

[39] All 5 subjects received atenolol.

[40] Five subjects received an extended release preparation of nifedipine, 2 subjects received a controlled release preparation of diltiazem hydrochloride, 1 subject received nisoldipine, and 1 subject received felodipine.

mg/day) and vitamin D (500 IU/day) were orally administered twice daily from 2 weeks prior to Day 1 through Day 11.

All of 21 subjects treated with the study drug were included in the safety analysis. Of these subjects, 20 subjects were included in the pharmacodynamic analysis, except 1 subject who had been withdrawn from the study after placebo administration on Day 1 due to the use of prohibited concomitant drugs.

The pharmacodynamic analysis indicated that the serum total calcium $AUC_{0\text{-}24\ h}$ values (mean [CV]; teriparatide 40 μg alone, placebo + HCTZ, and teriparatide + HCTZ) were 53.00 (12.87%), 55.03 (3.747%), and 55.93 (4.562%) mM·hr, respectively. The 24-hour cumulative urinary excretion levels of calcium were 4.81 (42.05%), 4.02 (43.13%), and 4.08 (41.77%) mmol, respectively, and the maximum reductions from baseline in serum intact PTH concentrations were -4.316 (-74.904%), -3.059 (-124.204%), and -8.222 (-56.978%) pg/mL, respectively. The serum phosphorus concentration and the 24-hour cumulative urinary excretion of phosphorus after the administration of teriparatide 40 μg alone were similar to those after the coadministration of teriparatide with HCTZ.

The safety analysis revealed that adverse events for which a causal relationship to teriparatide could not be ruled out occurred in 4 subjects (5 events) within 24 hours after the administration of teriparatide alone and in 1 subject (3 events) within 24 hours after the coadministration of teriparatide with HCTZ. While there were no differences in blood pressure between the coadministration of placebo with HCTZ and the coadministration of teriparatide with HCTZ, the pulse rate increased after the coadministration of teriparatide with HCTZ as compared with the coadministration of placebo with HCTZ. There were no deaths, other serious adverse events, or adverse events leading to study discontinuation.

4.(ii).A.(1).4).(b) Drug interaction study with digoxin (5.3.3.4.3, GHBR [[redacted] to [redacted] 20[redacted]])

A randomized, placebo-controlled, single-blind, crossover study was conducted in foreign healthy men and women. The primary objective of the study was to assess the effect of teriparatide on the pharmacodynamics of digoxin.

A single subcutaneous dose of 20 μg of teriparatide was to be administered on Day 1, and up to 0.5 mg/day of digoxin was to be orally administered on Days 2 to 16 so that a steady state was achieved, and a single subcutaneous dose of placebo or 20 μg of teriparatide was administered on Days 15 and 16.

All of 15 subjects treated with the study drug were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

The pharmacokinetic analysis showed that the serum digoxin concentrations were 0.95 ± 0.16 ng/dL before the coadministration of digoxin with placebo and 0.92 ± 0.17 ng/dL before the coadministration of digoxin with teriparatide, on Day 15 or 16.

As pharmacodynamic data, serum total calcium concentrations were as shown in Table 7. On ECG, the time intervals from the Q wave to the closure of the aortic valve when recorded simultaneously by echocardiogram[41] (least squares mean; teriparatide alone, digoxin + placebo, and digoxin + teriparatide) were 372.8, 349.8, and 348.1 msec, respectively, and the heart rates were 72.6, 66.4, and 68.0 bpm, respectively.

Table 7. Serum total calcium concentration

Measurement time	Change from pretreatment baseline (Serum total calcium concentration for pretreatment baseline)		
	Teriparatide alone	Digoxin + Placebo	Digoxin + Teriparatide
Pretreatment baseline	2.299	2.345	2.334
0.5 hours after dosing	0.018	0.017	0.017
2 hours after dosing	0.050	0.000	0.028
4 hours after dosing	0.025	-0.027	0.025
6 hours after dosing	0.030	-0.033	0.030

Unit: mM, Least squares mean; Arithmetic mean for pretreatment baseline

The safety analysis revealed that 6 adverse events occurred after the administration of teriparatide alone (Day 1), and 23 adverse events occurred after the administration of digoxin alone (Days 2-14). Two adverse events occurred after the coadministration of digoxin with placebo, and 12 adverse events occurred after the coadministration of digoxin with teriparatide. There were no deaths, other serious adverse events, adverse events leading to study discontinuation, or digoxin intoxication.

4.(ii).B Outline of the review

4.(ii).B.(1) Comparison of pharmacokinetics between Japan and overseas

The applicant explained as follows:

The C_{max} and AUC were higher in Japanese subjects than in Caucasian subjects. When adjusted for body weight, the C_{max} and AUC were similar between Japanese and Caucasian subjects. Also, the results of PPK analyses of Studies GHCS, GHAC, and GHAJ showed that there were pharmacokinetic differences due to differences in body weight between Japanese and Caucasian subjects.

PMDA asked the applicant to check if it was appropriate to perform a pooled analysis of Japanese and foreign studies in healthy subjects and patients (GHCO, GHCS, GHAC, and GHAJ) before performing a pooled PPK analysis and to examine the effects of factors, mainly body weights, on the pharmacokinetics of teriparatide to explain the relationship between body weights and the exposure to teriparatide.

The applicant responded as follows:

Based on the data from Studies GHCO, GHCS, GHAC, and GHAJ, which included teriparatide concentrations in serum samples collected from 738 subjects at 2762 time points, PPK analysis was performed using nonlinear mixed effect modeling (software, NONMEM version VI). A 1-compartment model with first order absorption and elimination was selected as the base structural model. As a result, body weight, BUN, age, and dose as significant covariates were included in the final model. The apparent volume of distribution was expected to increase with increasing body weight and decrease with increasing BUN. It

[41] Corrected for heart rate

was also expected that the apparent clearance would decrease with age and the bioavailability of the 40 μg dose would be lower relative to the 10 or 20 μg dose. In this analysis, when race was included alone as a covariate for the apparent volume of distribution in the base model, it showed a significant effect, whereas the effect of race was not significant when race and other factors were included in the model. It was considered that among the other factors included simultaneously, the inclusion of body weight in the model cancelled out the effect of race because body weight is confounded by race. Therefore, as shown by the previous PPK analyses of Studies GHCS, GHAC, and GHAJ, body weight appeared to have a significant effect on the apparent volume of distribution, and it was suggested that the observed pharmacokinetic differences between Japanese and Caucasian subjects were due to body weight differences.

PMDA considers as follows:
The applicant's explanation that the observed pharmacokinetic differences between Japanese and Caucasian subjects were due to body weight differences is understood. On the other hand, given that teriparatide is not a drug that is dosed per body weight, that Studies GHCO and GHBI showed that the incidence of adverse events associated with teriparatide tended to increase with increasing dose, and that a rat carcinogenicity study showed a dose-dependent increase in the incidence of osteosarcoma, attention should be paid to safety when the exposure to teriparatide is increased in Japanese patients, who have a lower body weight than foreign patients. This issue will continue to be discussed in the clinical section [see "4.(iii).B.(2) Clinical data package"].

4.(ii).B.(2) Use in patients with renal impairment
PMDA asked the applicant to explain the exposure and safety after the administration of 20 μg of teriparatide in Japanese patients with renal impairment.

The applicant responded as follows:
Since the exposure in foreign subjects with mild or moderate renal impairment was similar to that in foreign subjects with normal renal function in Study GHAW, there should be no major differences in the exposure or safety also between Japanese patients with mild or moderate renal impairment and Japanese patients with normal renal function. On the other hand, since the $AUC_{0\text{-}t}$ in foreign subjects with severe renal impairment was approximately 1.73-fold that in foreign subjects with normal renal function and the geometric mean ratio of $AUC_{0\text{-}t}$ after the administration of 20 μg of teriparatide (Japanese subjects with normal renal function/foreign subjects with normal renal function) was approximately 1.69 (Study GHCO), the $AUC_{0\text{-}t}$ following the administration of 20 μg of teriparatide in Japanese patients with severe renal impairment is considered comparable to the $AUC_{0\text{-}t}$ following the administration of approximately 35 μg of teriparatide in Japanese patients with normal renal function or following the administration of approximately 58 μg of teriparatide in foreign patients with normal renal function. In Study GHCS, when Japanese patients were treated with 10 to 40 μg of teriparatide for 6 months, the proportion of patients who discontinued from the study and the incidence of adverse events for which a causal relationship to teriparatide could not be ruled out were higher in the teriparatide 40 μg group. However, teriparatide was generally well-tolerated and the reported adverse events were generally mild or moderate in severity. In Study GHCO, the number of adverse

events was higher at 40 μg and 60 μg than at lower dose levels, which was not considered of clinical relevance because all events were mild to moderate in severity and teriparatide increased the serum calcium concentration by up to 5% as compared to placebo. Based on the above, although teriparatide serum concentrations following the administration of 20 μg of teriparatide in Japanese patients with severe renal impairment fall within the range of the teriparatide serum concentration at which safety and tolerability have been demonstrated, as the clearance of teriparatide delayed in subjects with renal impairment in Study GHAW, it will be stated in the package insert that teriparatide should be used with caution in patients with renal impairment.

PMDA considers as follows:
The kidney is the primary site of clearance for teriparatide and delayed clearance of teriparatide due to renal impairment could pose a risk of persistent increase in serum calcium, leading to the exacerbation of renal impairment. From such pharmacokinetic and pharmacodynamic points of view, teriparatide should be used with caution in patients with renal impairment [see "4.(iii).B.(7).1) Patients with renal impairment"].

4.(ii).B.(3) Drug interaction with digitalis preparations
PMDA asked the applicant to explain the safety of teriparatide in patients receiving digitalis preparations, based on the data from Japanese and foreign clinical studies and foreign post-marketing reports.

The applicant responded as follows:
In Japanese clinical studies, only 3 subjects in Study GHDB used digitalis preparations. All of the 3 subjects were in the teriparatide 20 μg group, including 1 subject receiving digoxin and 2 subjects receiving metildigoxin, but hypercalcaemia or digitalis intoxication did not occur. Also in 4 foreign clinical studies (GHAC, GHAJ, GHBM, GHCA) in which digitalis preparations were coadministered to some subjects, digitalis intoxication did not occur. Also in the foreign marketing experience, no cases of digitalis intoxication caused by hypercalcaemia following the coadministration of teriparatide with digitalis preparations have been reported. Based on the above, although there should be no safety concerns at present, as teriparatide transiently increases serum calcium, a precaution statement regarding the use of teriparatide in patients receiving digitalis preparations will be included in the package insert, as in foreign labeling.

PMDA considers as follows:
As teriparatide increases serum calcium, special caution is required from a pharmacodynamic point of view, for use in patients receiving digitalis preparations that have a narrow therapeutic window. Thus, the applicant's response that a precaution statement regarding the use of teriparatide in patients receiving digitalis preparations will be included in the package insert is acceptable. However, information on the safety of teriparatide in concomitant use with digitalis preparations should be further collected even after the market launch.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

Submitted efficacy and safety evaluation data are the results of phase II (GHCS) and phase III (GHDB, a bridging study) studies in Japanese subjects, a clinical pharmacology study in Japanese and Caucasian subjects (GHCO), foreign clinical pharmacology studies (GHBO, GHAD, GHAE, GHAW, GHBA, GHBC, GHBI, GHBR), and foreign phase III and phase IV studies (GHAC [a study to be bridged], GHAJ, GHBM, GHCA, GHBJ). Study GHDB was originally planned to be of a 76-week period. However, while the study was ongoing, an extension of the maximum treatment duration to 24 months was approved in February 2009 in the EU (approved for a maximum treatment period of 18 months in June 2003), and teriparatide had already been approved for a maximum treatment period of 24 months in the US. Thus, the duration of treatment for Study GHDB was extended to 104 weeks and the study was completed in September 2009. In this review, PMDA evaluated Study GHDB based on the data up to 76 weeks of treatment submitted in the course of the review (the data up to 52 weeks of treatment were submitted at filing).

4.(iii).A.(1) Clinical pharmacology studies

See "4.(ii) Summary of clinical pharmacology studies" for the results from Studies GHCO, GHBO, GHAD, GHAE, GHAW, GHBA, GHBC, and GHBR and "4.(i) Summary of biopharmaceutic studies and associated analytical methods" for the results of Study GHBI.

4.(iii).A.(2) Phase II study

Japanese phase II study (5.3.5.1.1, GHCS [April 2005 to March 2006])

A placebo-controlled, randomized, parallel-group study was conducted in Japanese postmenopausal patients with osteoporosis at high risk for fracture[42] (the target sample size of 160 subjects, 40 subjects per group). The primary objective of the study was to assess the dose-response of teriparatide.

Teriparatide 10 μg (0.04 mL), 20 μg (0.08 mL), or 40 μg (0.16 mL) was to be given subcutaneously once daily (at approximately the same time each morning) by self-injection into the abdomen. As three injection volumes were used for the three doses of teriparatide, they were not blinded and subjects in the placebo group received matching volumes of placebo. As background therapy, open-label calcium (up to 610 mg/day) and vitamin D (up to 400 IU/day) were orally administered once daily after the evening meal. The duration of study treatment was 24 weeks.

Of 159 randomized subjects, 154 subjects excluding 3 subjects who did not receive the study drug and 2 subjects with major GCP violations (study drug administration errors) (38 subjects in the placebo group, 38 subjects in the 10 μg group, 39 subjects in the teriparatide 20 μg group, 39 subjects in the 40 μg group) were included in the Full Analysis Set (FAS), which was used as the safety and efficacy populations.

The primary efficacy endpoint of the percent changes in lumbar spine (L2-L4) BMD measured by DXA at the time of last observation was as shown in Table 8 and the percent changes were significantly higher in the

[42] Main criteria for inclusion: patients who were ≥55 years of age at Visit 1 and who met any of the following criteria: (1) lumbar spine (L2-L4) BMD <80% of young adult mean (YAM) and at least 1 moderate or 2 mild vertebral fragility fractures, (2) lumbar spine (L2-L4) BMD <70% of YAM and ≥65 years of age, and (3) lumbar spine (L2-L4) BMD <60% of YAM.

teriparatide groups than in the placebo group ($P < 0.001$, one-sided level of significance of 2.5%, Williams' test).

Table 8. Percent changes from baseline to the time of last observation in lumbar spine (L2-L4) BMD (FAS)

Lumbar spine (L2-L4) BMD	Placebo (n = 38)	Teriparatide 10 μg (n = 38)	Teriparatide 20 μg (n = 39)	Teriparatide 40 μg (n = 39)
Baseline (g/cm^2)	0.630 ± 0.078 (n = 37 [a])	0.620 ± 0.061 (n = 38)	0.627 ± 0.082 (n = 39)	0.626 ± 0.075 (n = 39)
Last observation (g/cm^2)	0.634 ± 0.083 (n = 37 [a])	0.652 ± 0.061 (n = 37 [a])	0.667 ± 0.088 (n = 39)	0.703 ± 0.075 (n = 33 [a])
Percent change from baseline (%)	0.66 ± 2.85 (n = 37 [a])	5.80 ± 4.50 (n = 37 [a])	6.40 ± 4.76 (n = 39)	11.47 ± 5.45 (n = 33 [a])
P-value[b]	—	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean ± SD
a) Subjects without baseline or postbaseline lumbar spine (L2-L4) BMD measurement were excluded from FAS.
b) Williams' test, One-sided level of significance of 2.5%

The secondary endpoints of the percent changes in biochemical markers of bone metabolism were as shown in Table 9.

Table 9. Time course of percent changes from baseline in biochemical markers of bone metabolism (FAS)

Biochemical markers of bone metabolism	Treatment group	Week 4	Week 12	Week 24
Serum PICP[43]	Placebo	-5.38 ± 29.25 (n = 37)	-18.35 ± 21.80 (n = 35)	-14.39 ± 26.02 (n = 33)
	Teriparatide 10 μg	61.39 ± 60.21 (n = 36)	-6.58 ± 33.67 (n = 35)	-21.39 ± 39.60 (n = 35)
	Teriparatide 20 μg	120.06 ± 81.13 (n = 38)	18.30 ± 43.32 (n = 38)	11.10 ± 57.42 (n = 36)
	Teriparatide 40 μg	197.48 ± 132.46 (n = 35)	108.18 ± 66.77 (n = 32)	63.98 ± 77.45 (n = 28)
Serum PINP[44]	Placebo	-10.78 ± 16.43 (n = 35)	-17.54 ± 19.87 (n = 32)	-15.16 ± 25.27 (n = 31)
	Teriparatide 10 μg	56.98 ± 42.73 (n = 36)	34.15 ± 50.57 (n = 33)	31.44 ± 64.56 (n = 35)
	Teriparatide 20 μg	108.89 ± 55.68 (n = 36)	97.69 ± 87.75 (n = 37)	95.09 ± 119.77 (n = 33)
	Teriparatide 40 μg	214.53 ± 177.82 (n = 30)	223.68 ± 133.98 (n = 25)	324.63 ± 239.62 (n = 19)
Serum BAP[45]	Placebo	-3.57 ± 11.42 (n = 36)	-8.80 ± 15.39 (n = 34)	5.59 ± 29.65 (n = 33)
	Teriparatide 10 μg	1.12 ± 21.77 (n = 32)	-7.35 ± 23.82 (n = 31)	6.49 ± 45.13 (n = 31)
	Teriparatide 20 μg	13.50 ± 21.61 (n = 35)	16.72 ± 30.97 (n = 37)	35.48 ± 48.44 (n = 34)
	Teriparatide 40 μg	47.21 ± 61.67 (n = 31)	61.61 ± 57.70 (n = 27)	86.80 ± 74.83 (n = 26)
Serum CTX[46]	Placebo	12.46 ± 39.65 (n = 36)	3.28 ± 41.10 (n = 31)	-13.37 ± 33.79 (n = 30)
	Teriparatide 10 μg	-0.92 ± 32.85 (n = 33)	-1.23 ± 42.83 (n = 31)	-8.85 ± 38.32 (n = 32)
	Teriparatide 20 μg	-1.25 ± 39.69 (n = 33)	27.16 ± 62.06 (n = 36)	35.87 ± 93.91 (n = 29)
	Teriparatide 40 μg	35.66 ± 62.02 (n = 31)	121.48 ± 84.03 (n = 30)	124.53 ± 94.96 (n = 26)

Mean ± SD %

The exploratory endpoints of the percent changes from baseline to the time of last observation in lumbar spine (L1-L4), femoral neck, and total hip BMD measured by DXA were as shown in Table 10.

Table 10. Percent changes from baseline to the time of last observation in lumbar spine (L1-L4), femoral neck and total hip BMD (FAS)

Treatment group	Lumbar spine (L1-L 4)	Femoral neck	Total hip
Placebo	0.94 ± 2.75 (n = 37)	-0.39 ± 4.70 (n = 38)	0.23 ± 3.08 (n = 38)
Teriparatide 10 μg	5.64 ± 4.42 (n = 37)	1.23 ± 4.73 (n = 37)	1.71 ± 2.92 (n = 37)
Teriparatide 20 μg	6.19 ± 4.88 (n = 39)	1.83 ± 7.13 (n = 38)	1.91 ± 3.60 (n = 38)
Teriparatide 40 μg	11.88 ± 5.63 (n = 33)	2.80 ± 7.73 (n = 32)	3.19 ± 5.26 (n = 32)

Mean ± SD %
Subjects without baseline or postbaseline BMD measurement were excluded from FAS.

[43] procollagen I C-terminal propeptide
[44] procollagen I N-terminal propeptide
[45] bone-specific alkaline phosphatase
[46] type I collagen crosslinked C-telopeptide

The safety analysis revealed that the incidences of adverse events were 76.3% (29 of 38 subjects) in the placebo group, 78.9% (30 of 38 subjects) in the teriparatide 10 μg group, 84.6% (33 of 39 subjects) in the teriparatide 20 μg group, and 82.1% (32 of 39 subjects) in the teriparatide 40 μg group. The incidences of adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were 15.8% (6 of 38 subjects) in the placebo group, 13.2% (5 of 38 subjects) in the teriparatide 10 μg group, 15.4% (6 of 39 subjects) in the teriparatide 20 μg group, and 41.0% (16 of 39 subjects) in the teriparatide 40 μg group. Adverse events reported by ≥5% of subjects in any group were as shown in Table 11.

Table 11. Adverse events reported by ≥5% of subjects in any group

Adverse event term	Placebo (n = 38)	Teriparatide 10 μg (n = 38)	Teriparatide 20 μg (n = 39)	Teriparatide 40 μg (n = 39)
Nasopharyngitis	26.3 (10)	18.4 (7)	23.1 (9)	30.8 (12)
Nausea	10.5 (4)	5.3 (2)	10.3 (4)	17.9 (7)
Headache	2.6 (1)	2.6 (1)	2.6 (1)	15.4 (6)
Decreased appetite	0.0 (0)	0.0 (0)	0.0 (0)	10.3 (4)
Diarrhoea	7.9 (3)	7.9 (3)	2.6 (1)	7.7 (3)
Stomach discomfort	0.0 (0)	2.6 (1)	0.0 (0)	7.7 (3)
Eczema	2.6 (1)	10.5 (4)	5.1 (2)	5.1 (2)
Fall	2.6 (1)	13.2 (5)	0.0 (0)	5.1 (2)
Muscle spasms	0.0 (0)	10.5 (4)	2.6 (1)	5.1 (2)
Blood uric acid increased	0.0 (0)	2.6 (1)	7.7 (3)	5.1 (2)
Pain in extremity	0.0 (0)	0.0 (0)	7.7 (3)	5.1 (2)
Vomiting	5.3 (2)	2.6 (1)	5.1 (2)	5.1 (2)
Injection site haemorrhage	0.0 (0)	0.0 (0)	5.1 (2)	5.1 (2)
Dermatitis contact	0.0 (0)	0.0 (0)	2.6 (1)	5.1 (2)
Malaise	7.9 (3)	0.0 (0)	0.0 (0)	5.1 (2)
Pruritus	2.6 (1)	0.0 (0)	0.0 (0)	5.1 (2)
Abdominal pain upper	2.6 (1)	2.6 (1)	7.7 (3)	0.0 (0)
Dizziness	2.6 (1)	0.0 (0)	7.7 (3)	0.0 (0)
Dental caries	0.0 (0)	0.0 (0)	5.1 (2)	2.6 (1)
Constipation	2.6 (1)	2.6 (1)	5.1 (2)	0.0 (0)
Erythema	2.6 (1)	0.0 (0)	5.1 (2)	0.0 (0)
Gingivitis	0.0 (0)	0.0 (0)	5.1 (2)	0.0 (0)
Hyperkeratosis	0.0 (0)	0.0 (0)	5.1 (2)	0.0 (0)
Insomnia	0.0 (0)	0.0 (0)	5.1 (2)	0.0 (0)
Back pain	10.5 (4)	10.5 (4)	0.0 (0)	2.6 (1)
Chest pain	0.0 (0)	10.5 (4)	0.0 (0)	2.6 (1)
Joint sprain	0.0 (0)	10.5 (4)	0.0 (0)	0.0 (0)
Contusion	0.0 (0)	7.9 (3)	2.6 (1)	2.6 (1)
Osteoarthritis	0.0 (0)	7.9 (3)	2.6 (1)	2.6 (1)
Hand fracture	0.0 (0)	5.3 (2)	0.0 (0)	0.0 (0)
Hot flush	0.0 (0)	5.3 (2)	0.0 (0)	0.0 (0)
Pharyngitis	0.0 (0)	5.3 (2)	0.0 (0)	0.0 (0)
Vertigo	5.3 (2)	0.0 (0)	2.6 (1)	0.0 (0)
Gastritis	5.3 (2)	0.0 (0)	0.0 (0)	2.6 (1)
Musculoskeletal stiffness	5.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (n), MedDRA ver.9.0

No deaths were reported. Although serious adverse events occurred in 1 subject in the teriparatide 10 μg group (hand fracture), 1 subject in the teriparatide 20 μg group (transient ischaemic attack), and 1 subject in the teriparatide 40 μg group (decreased appetite), a causal relationship to the study drug was ruled out for all events. No subjects withdrew from the study due to serious adverse events. Adverse events leading to treatment discontinuation occurred in 2 subjects in the teriparatide 20 μg group (blood potassium increased, osteoarthritis) and 4 subjects in the teriparatide 40 μg group (nausea [2 subjects], dyspnoea, malaise) and all of these events except for osteoarthritis were classified as adverse drug reactions.

The predose corrected serum calcium (median) was higher at Week 24 than at baseline in all groups (9.20 mg/dL at baseline and 9.50 mg/dL at Week 24 in the placebo group, 9.30 mg/dL at baseline and 9.65 mg/dL at Week 24 in the teriparatide 10 μg group, 9.30 mg/dL at baseline and 9.70 mg/dL at Week 24 in the teriparatide 20 μg group, 9.40 mg/dL at baseline and 9.70 mg/dL at Week 24 in the teriparatide 40 μg group). At Week 24, the 4- to 6-hour postdose corrected serum calcium (median) was higher than the predose corrected serum calcium in the teriparatide 20 μg and 40 μg groups (the pre-dose and 4- to 6-hour postdose values were 9.50 mg/dL and 9.40 mg/dL, respectively, in the placebo group, 9.65 mg/dL and 9.60 mg/dL, respectively, in the 10 μg group, 9.70 mg/dL and 9.80 mg/dL, respectively, in the 20 μg group, and 9.70 mg/dL and 10.10 mg/dL, respectively, in the 40 μg group).

4.(iii).A.(3) Phase III or IV studies

4.(iii).A.(3).1) Japanese phase III study (5.3.5.1.2, GHDB [February 2007 to September 2009] A bridging study)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with primary osteoporosis at high risk for fracture[47] (the target sample size of 180 subjects; 60 subjects in the placebo group, 120 subjects in the teriparatide 20 μg group). The primary objective of the study was to evaluate the efficacy of teriparatide.

The study consisted of Period 1, Period 2, and Period 3. In Period 1 (double-blind phase, 52 weeks), placebo or teriparatide 20 μg was to be given subcutaneously once daily (at approximately the same time each morning) by self-injection into the abdomen. In Period 2 (open-label phase, 24 weeks) and Period 3 (open-label phase, 28 weeks), all subjects were to receive teriparatide 20 μg following the same dosing regimen. As background therapy, calcium (610 mg/day) and vitamin D (400 IU/day) were orally administered once daily after the evening meal in an open-label manner throughout the study period. For this review, the data up to Period 2 (a total of 76 weeks of treatment [Period 1 and Period 2]) were submitted.

Of 207 randomized subjects, 203 subjects excluding 3 subjects who did not receive the study drug and 1 subject with a major GCP violation (study drug administration errors) (67 subjects in the placebo group, 136 subjects in the teriparatide 20 μg group) were included in the FAS, which was used as the safety and efficacy populations. Five male subjects were assigned to the placebo group and 9 male subjects were assigned to the teriparatide 20 μg group.

The primary efficacy endpoint of the percent changes from baseline to Week 52 in lumbar spine (L2-L4) BMD measured by DXA was as shown in Table 12. The percent change was significantly higher in the teriparatide 20 μg group than in the placebo group ($P < 0.001$, two-sided level of significance of 5%, two-sample t-test).

[47] Main inclusion criteria: patients who were ≥55 years of age at Visit 1 and who met any of the following criteria: (1) lumbar spine (L2-L4) BMD <80% (-1.7 SD) of YAM and at least 1 vertebral fragility fracture, (2) lumbar spine (L2-L4) BMD <70% (-2.6 SD) of YAM and ≥65 years of age, and (3) lumbar spine (L2-L4) BMD <65% (-3.0 SD) of YAM.

Table 12. Percent changes from baseline to Week 52 in lumbar spine (L2-L4) BMD (FAS)

Lumbar spine (L2-L4) BMD	Placebo (n = 63[a)])	Teriparatide 20 μg (n = 131[a)])
Baseline (g/cm^2)	0.631 ± 0.079	0.637 ± 0.069
Last measuring point (g/cm^2)	0.630 ± 0.079	0.699 ± 0.077
Percent change from baseline (%)	0.04 ± 4.34	9.82 ± 5.36
P-value[b)]	*P* < 0.001	

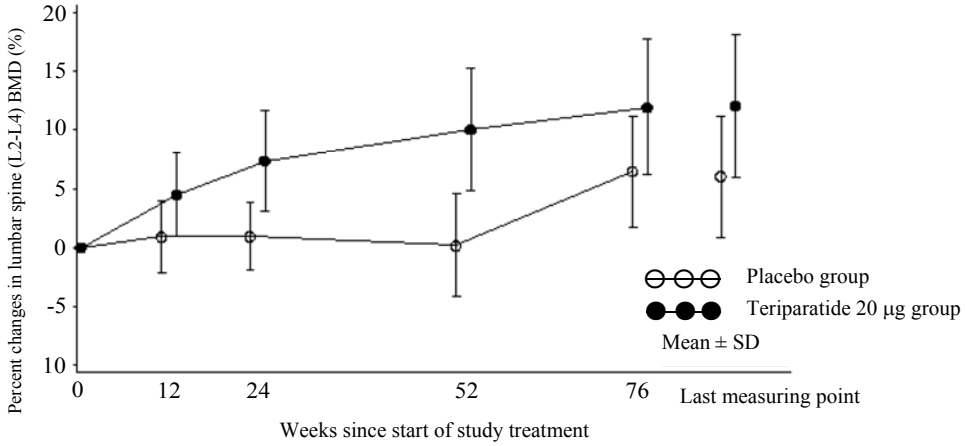
Mean ± SD, Last observation carried forward (LOCF)
a) Subjects without post-baseline lumbar spine (L2-L4) BMD measurement were excluded from FAS.
b) Two-sample t-test, Two-sided level of significance of 5%

The secondary endpoint of the percent changes in lumbar spine (L1-L4), femoral neck, and total hip BMD measured by DXA were as shown in Table 13 and the time course of the percent changes in lumbar spine (L2-L4) BMD was as shown in Figure 2.

Table 13. Percent change in BMD from baseline to Week 52 or 76 (FAS)

Treatment group	Timepoint	Lumbar spine (L1-L4)	Femoral neck	Total hip
Placebo	Week 52	0.23 ± 4.44 (n = 60)	0.44 ± 3.97 (n = 59)	-0.26 ± 3.42 (n = 59)
	Week 76[a)]	6.65 ± 4.66 (n = 55)	1.17 ± 4.81 (n = 54)	1.64 ± 4.63 (n = 54)
Teriparatide 20 μg	Week 52	10.43 ± 5.61 (n = 121)	2.01 ± 4.62 (n = 120)	2.72 ± 4.04 (n = 120)
	Week 76	12.24 ± 5.86 (n = 113)	2.68 ± 4.45 (n = 112)	3.02 ± 3.79 (n = 112)

Mean ± SD %
a) Placebo was administered in Period 1 and teriparatide 20 μg was administered from Week 52 (Period 2).



Treatment group	Baseline	Week 12	Week 24	Week 52	Week 76	Last measuring point in Period 2
Placebo	n = 63	n = 63	n = 61	n = 60	n = 55	n = 59
Teriparatide 20 μg	n = 131	n = 131	n = 127	n = 121	n = 113	n = 118

Figure 2. Time course of percent changes from baseline in lumbar spine (L2-L4) BMD

The time course of the percent changes in biochemical markers of bone metabolism was as shown in Table 14, and the incidence of fracture was as shown in Table 15.

Table 14. Time course of percent changes from baseline in biochemical markers of bone metabolism (FAS)

Biochemical marker of bone metabolism	Treatment group	Week 4	Week 24	Week 52	Week 76
Serum PINP	Placebo[a)]	-9.58 ± 14.39 (n = 66)	-19.10 ± 29.17 (n = 61)	-14.18 ± 29.02 (n = 60)	97.28 ± 131.64 (n = 55)
	Teriparatide 20 μg	90.67 ± 49.85 (n=136)	114.12 ± 112.04 (n = 127)	116.11 ± 139.72 (n = 121)	115.45 ± 174.07 (n=113)
Serum BAP	Placebo[a)]	-9.63 ± 33.62 (n=66)	-28.46 ± 23.81 (n = 60)	-32.24 ± 46.95 (n = 59)	15.71 ± 64.96 (n=55)
	Teriparatide 20 μg	3.74 ± 37.86 (n = 135)	-4.60 ± 43.44 (n = 127)	-17.69 ± 58.12 (n = 120)	17.49 ± 66.40 (n = 113)
Serum CTX	Placebo[a)]	-2.05 ± 28.17 (n = 63)	4.39 ± 37.97 (n = 59)	13.50 ± 39.47 (n = 58)	86.98 ± 132.81 (n = 53)
	Teriparatide 20 μg	2.78 ± 40.73 (n = 124)	82.27 ± 110.54 (n = 119)	84.81 ± 124.23 (n = 113)	85.85 ± 137.13 (n = 104)

Mean ± SD %

a) Placebo was administered in Period 1 and teriparatide 20 μg was administered from Week 52 (Period 2).

Table 15. Incidence of fractures (FAS)

Timepoint	Type of fracture[a)]	Placebo[b)] (n = 67)		Teriparatide 20 μg (n = 136)	
		No. of subjects with fracture (Incidence %)	No. of fracture	No. of subjects with fracture (Incidence %)	No. of fracture
Month 12	New vertebral fracture	4 (6.0)	5	5 (3.7)	7
	Worsened vertebral fracture	0	0	2 (1.5)	3
	Nonvertebral insufficiency fracture	1 (1.5)	1	1 (0.7)	1
	Nonvertebral traumatic fracture	3 (4.5)	3	2 (1.5)	2
Month 18	New vertebral fracture	5 (7.5)	6	5 (3.7)	7
	Worsened vertebral fracture	0	0	2 (1.5)	3
	Nonvertebral insufficiency fracture	1 (1.5)	1	1 (0.7)	1
	Nonvertebral traumatic fracture	3 (4.5)	3	2 (1.5)	2

a) The occurrence of vertebral fracture was determined by central X-ray assessment and the occurrence of nonvertebral fracture was determined by investigators' assessment.

b) Placebo was administered in Period 1 and teriparatide 20 μg was administered from Month 12 (Period 2).

The safety analysis revealed that the incidences of adverse events through Month 12 (at the end of Period 1) were 88.1% (59 of 67 subjects) in the placebo group and 85.3% (116 of 136 subjects) in the teriparatide 20 μg group, and the incidences of adverse drug reactions were 7.5% (5 of 67 subjects) in the placebo group and 12.5% (17 of 136 subjects) in the teriparatide 20 μg group. The incidences of adverse events through Month 18 (at the end of Period 2) were 89.6% (60 of 67 subjects) in the placebo group and 90.4% (123 of 136 subjects) in the teriparatide 20 μg group. The incidences of adverse drug reactions were 13.4% (9 of 67 subjects) in the placebo group and 15.4% (21 of 136 subjects) in the teriparatide 20 μg group. Adverse events reported by ≥5% of subjects in either group were as shown in Table 16.

Table 16. Adverse events reported by ≥5% of subjects in either group

Adverse event term	Month 12 (Period 1)		Month 18 (Period 1 and Period 2)	
	Placebo (n = 67)	Teriparatide 20 μg (n = 136)	Placebo[a)] (n = 67)	Teriparatide 20 μg (n = 136)
Nasopharyngitis	40.3 (27)	27.9 (38)	43.3 (29)	33.1 (45)
Back pain	14.9 (10)	12.5 (17)	23.9 (16)	16.2 (22)
Fall	9.0 (6)	6.6 (9)	10.4 (7)	8.1 (11)
Injection site reaction	11.9 (8)	3.7 (5)	11.9 (8)	3.7 (5)
Eczema	7.5 (5)	3.7 (5)	7.5 (5)	4.4 (6)
Contusion	6.0 (4)	5.9 (8)	7.5 (5)	8.1 (11)
Osteoarthritis	6.0 (4)	6.6 (9)	7.5 (5)	7.4 (10)
Arthralgia	6.0 (4)	5.9 (8)	10.4 (7)	5.9 (8)
Seasonal allergy	6.0 (4)	5.9 (8)	7.5 (5)	5.9 (8)
Dermatitis contact	6.0 (4)	3.7 (5)	6.0 (4)	5.1 (7)
Dizziness	4.5 (3)	5.9 (8)	4.5 (3)	8.1 (11)
Headache	4.5 (3)	6.6 (9)	6.0 (4)	7.4 (10)
Upper respiratory tract inflammation	4.5 (3)	5.9 (8)	4.5 (3)	6.6 (9)
Periarthritis	4.5 (3)	2.2 (3)	6.0 (4)	3.7 (5)
Constipation	3.0 (2)	7.4 (10)	6.0 (4)	8.1 (11)
Cystitis	3.0 (2)	5.1 (7)	6.0 (4)	5.1 (7)
Insomnia	3.0 (2)	2.2 (3)	3.0 (2)	5.1 (7)
Muscle contusion	1.5 (1)	2.9 (4)	1.5 (1)	4.4 (6)
Diarrhoea	0.0 (0)	4.4 (6)	6.0 (4)	5.1 (7)

Incidence % (n), MedDRA ver.12.0

a) Placebo was administered in Period 1 and teriparatide 20 μg was administered from Month 12 (Period 2).

No deaths were reported through Month 18. Through Month 12, serious adverse events occurred in 7 subjects in the placebo group (asthma, anaphylactic reaction, enterocolitis, femoral neck fracture, bronchopulmonary aspergillosis allergic, back pain, and colitis ischaemic, 1 subject each) and 7 subjects in the teriparatide 20 μg group (vertigo positional, blood pressure decreased, chronic respiratory failure, rotator cuff syndrome, abdominal pain, lung adenocarcinoma, colonic polyp, cellulitis, chondrocalcinosis pyrophosphate, breast cancer [abdominal pain and lung adenocarcinoma occurred in 1 subject and colonic polyp, cellulitis, and chondrocalcinosis pyrophosphate occurred in another subject]), and a causal relationship to teriparatide could not be ruled out for the events of blood pressure decreased and breast cancer. Colonic polyp, cellulitis, and chondrocalcinosis pyrophosphate; blood pressure decreased; femoral neck fracture; bronchopulmonary aspergillosis allergic; lung adenocarcinoma; and breast cancer led to study discontinuation. In Period 2, serious adverse events occurred in 2 subjects in the placebo group (pneumonia, artery dissection) and 3 subjects in the teriparatide 20 μg group (vertigo, vomiting, and bronchitis [these 3 events occurred in 1 subject]; cataract; intestinal obstruction), but a causal relationship to the study drug was ruled out for all these events. Artery dissection and intestinal obstruction led to study discontinuation. During treatment with the study drug in Period 1, 4 subjects discontinued the study due to non-serious adverse events, including 1 subject in the placebo group (nephrolithiasis) and 3 subjects in the teriparatide 20 μg group (abdominal pain upper, pulmonary fibrosis, and rash, 1 subject each). In Period 2, 3 subjects in the teriparatide 20 μg group (hepatic function abnormal [1 subject], dizziness postural [2 subjects]) withdrew from the study due to non-serious adverse events. After completing Period 1, 1 subject in the placebo group (back pain) and 1 subject in the teriparatide 20 μg group (nephrolithiasis) withdrew from the study before entering Period 2. The event of nephrolithiasis was classified as an adverse drug reaction.

There were no changes from baseline to Week 52 in the predose corrected serum calcium (median) (both 9.00 mg/dL) in the placebo group while the predose corrected serum calcium was higher at Week 52 than at baseline in the teriparatide 20 μg group (8.90 mg/dL at baseline, 9.20 mg/dL at Week 52). The predose corrected serum calcium at Week 76 was 9.20 mg/dL in the both groups, which was higher than the baseline values.

During the study period, 5.9% of subjects in the teriparatide 20 μg group (8 of 136 subjects) were tested positive for anti-teriparatide antibodies (antibodies), of whom 6 subjects were antibody-positive at baseline. Of these 6 subjects, 3 subjects were tested positive at Weeks 52 and 76. Two subjects were tested negative at Weeks 52 and 76, and 1 subject was tested negative at Week 52, but positive at Week 76. The other 2 subjects were tested negative at baseline and Week 52, but positive at Week 76. BMD changes were similar between antibody-positive and antibody-negative subjects and no adverse events considered to be associated with antibody development (hypoparathyroidism, hypocalcaemia, hyperphosphataemia, etc.) occurred in antibody-positive subjects.

4.(iii).A.(3).2) Foreign phase III study (5.3.5.1.3, GHAC [December 1996 to December 1998 (terminated early)] A study to be bridged)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in foreign postmenopausal patients with osteoporosis[48] (the target sample size of 1476 subjects, 492 patients per group). The primary objective of the study was to compare the proportion of subjects with new vertebral fracture among the teriparatide 20 μg or 40 μg and placebo groups.

Placebo, teriparatide 20 μg or 40 μg was to be subcutaneously administered once daily. As background therapy, calcium (approximately 1000 mg/day) and vitamin D (approximately 400-1200 IU/day) were orally administered once daily in an open-label manner. The planned duration of study treatment was 3 years and the planned duration of the optional extension phase was approximately 2 years. In subjects with an increase in serum calcium above the upper limit of normal or a marked increase in urinary calcium, the dose of calcium was to be reduced or stopped, or the dose of the study drug was to be reduced by half at the discretion of the investigator, and if serum calcium or urinary calcium did not normalize even after the dose reduction of the study drug, the study drug was to be stopped.

On December 8 1998, when this study was in progress, neoplastic bone lesions including osteosarcoma were found in a rat carcinogenicity study, and therefore the sponsor suspended treatment with teriparatide. On December 17 1998, the applicant decided to terminate all ongoing clinical studies with teriparatide including this study. A total of 1637 randomized subjects (541 subjects in the teriparatide 20 μg group, 552 subjects in the teriparatide 40 μg group, 544 subjects in the placebo group) were included in the efficacy and safety populations. The median treatment duration [the 25th percentile, the 75th percentile] was 576.0 [534, 624]

[48] Main inclusion criteria: 30 to 85 years of age; patients with at least 1 moderate or 2 mild nontraumatic vertebral fractures and at least 7 evaluable nonfractured vertebrae. In patients with fewer than 2 moderate fractures and in patients previously treated with therapeutic doses of bisphosphonates or fluorides, the hip or lumbar spine BMD measurement (T-score) was required to be at least 1.0 SD below YAM.

days for the placebo group, 576.0 [532, 625] days for the teriparatide 20 μg group, and was 570.0 [517, 626] days for the teriparatide 40 μg group.

The primary efficacy endpoint was the proportion of subjects with new vertebral fracture, and the primary analysis compared the proportion of subjects with new vertebral fracture in the combined teriparatide group (teriparatide 20 μg and 40 μg) with that in the placebo group. The results of comparison were as shown in Table 17. There was a significant difference in the proportion of subjects with new vertebral fracture between the placebo and combined teriparatide groups (teriparatide 20 μg and 40 μg) ($P < 0.001$, two-sided level of significance of 5%, Pearson's χ^2 test).

Table 17. Proportion of subjects with new vertebral fracture

Treatment group	Proportion of subjects with new vertebral fracture[a)]	*P*-value[b)]	Ratio of proportions[d)] [95% CI]
Placebo	14.3 (64/448 [c)])	$P < 0.001$	—
Combined teriparatide	4.7 (41/878 [c)])		0.327 [0.225,0.476]
Teriparatide 20 μg	5.0 (22/444 [c)])	—	0.347 [0.218,0.553]
Teriparatide 40 μg	4.4 (19/434 [c)])	—	0.306 [0.187,0.503]

a) Proportion % (No. of subjects with fracture/No. of evaluable subjects)
b) Pearson's χ^2 test
c) Subjects without evaluable baseline or the last observation X-ray film were excluded.
d) The ratio of proportions of each teriparatide group to the placebo group

The secondary endpoint of the proportion of subjects with new nonvertebral fracture and the ratio of the proportions of the teriparatide group to the placebo group were as shown in Table 18, and the percent changes in BMD was as shown in Table 19.

Table 18. Proportion of subjects with new nonvertebral fracture

Treatment group	Proportion of subjects with new nonvertebral fracture[a)]	Ratio of proportions [b)] [95% CI]
Placebo	9.7 (53/544)	-
Teriparatide 20 μg	6.3 (34/541)	0.645 [0.426, 0.976]
Teriparatide 40 μg	5.8 (32/552)	0.595 [0.390, 0.908]
Combined teriparatide	6.0 (66/1093)	0.620 [0.438, 0.877]

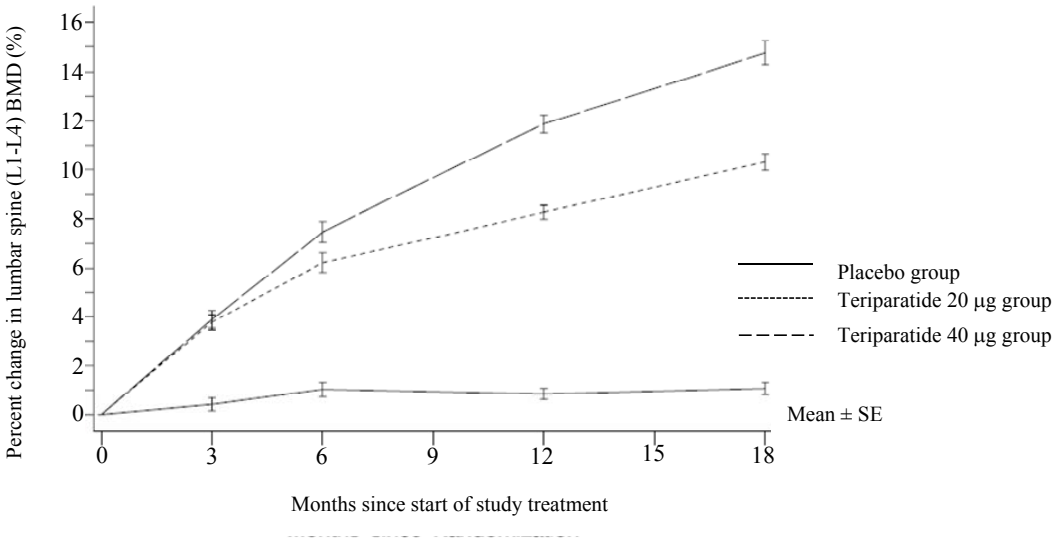
a) Proportion % (No. of subjects with fracture/No. of evaluable subjects)
b) Ratio of proportions of each teriparatide group to the placebo group

Table 19. Percent changes in BMD from baseline to the time of last observation

Treatment group	Lumbar spine (L1-L4)	Femoral neck	Total hip
Placebo	1.13 ± 5.47 (n = 504)	-0.69 ± 5.39 (n = 479)	-1.01 ± 4.25 (n = 230)
Teriparatide 20 μg	9.70 ± 7.41 (n = 498)	2.79 ± 5.72 (n = 479)	2.58 ± 4.88 (n = 222)
Teriparatide 40 μg	13.73 ± 9.69 (n = 497)	5.06 ± 6.73 (n = 482)	3.60 ± 5.42 (n = 232)

Mean ± SD %
Subjects without baseline or postbaseline BMD measurement were excluded.

The time course of the percent change in lumbar spine (L1-L4) BMD was as shown in Figure 3, and the time course of the percent changes in biochemical markers of bone metabolism was as shown in Table 20.



Treatment group	Month 3	Month 6	Month 12	Month 18
Placebo	n = 170	n = 173	n = 467	n = 429
Teriparatide 20 µg	n = 165	n = 162	n = 466	n = 410
Teriparatide 40 µg	n = 165	n = 163	n = 452	n = 407

Figure 3. Time course of percent change in lumbar spine (L1-L4) BMD

Table 20. Time course of percent changes from baseline in biochemical markers of bone metabolism

Biochemical marker of bone metabolism	Treatment group	Week 4	Week 26	Week 52	Week 78
Serum PICP	Placebo	0.09 ± 22.31 (n = 166)	-4.19 ± 21.71 (n = 161)	8.34 ± 29.98 (n = 155)	-2.16 ± 21.95 (n = 21)
	Teriparatide 20 µg	47.51 ± 45.59 (n = 160)	9.84 ± 30.92 (n = 153)	8.31 ± 31.54 (n = 145)	-8.53 ± 23.97 (n = 19)
	Teriparatide 40 µg	84.26 ± 69.49 (n = 164)	34.81 ± 55.01 (n = 150)	29.68 ± 54.50 (n = 137)	6.12 ± 30.65 (n = 18)
Serum BAP	Placebo	3.02 ± 44.02 (n = 164)	-1.62 ± 57.68 (n = 161)	-4.45 ± 42.53 (n = 153)	-12.58 ± 30.83 (n = 21)
	Teriparatide 20 µg	33.89 ± 69.93 (n = 159)	54.34 ± 88.60 (n = 150)	73.20 ± 98.37 (n = 142)	28.77 ± 95.73 (n = 18)
	Teriparatide 40 µg	73.63 ± 101.76 (n = 163)	116.85 ± 119.29 (n = 149)	123.86 ± 127.90 (n = 136)	76.84 ± 120.01 (n = 18)
Urinary NTX[49]	Placebo	29.86 ± 92.59 (n = 158)	25.70 ± 84.85 (n = 154)	30.98 ± 89.75 (n = 151)	48.18±77.68 (n=21)
	Teriparatide 20 µg	29.08 ± 89.08 (n = 160)	129.45 ± 215.33 (n = 150)	154.64 ± 323.31 (n = 145)	64.20 ± 106.08 (n = 18)
	Teriparatide 40 µg	60.85 ± 163.02 (n = 156)	246.24 ± 436.64 (n = 144)	295.36 ± 403.83 (n = 134)	114.07 ± 91.57 (n = 16)
Urinary free DPD[50]	Placebo	12.55 ± 80.61 (n = 159)	16.85 ± 69.77 (n = 154)	17.23 ± 96.72 (n = 148)	24.81 ± 55.82 (n = 21)
	Teriparatide 20 µg	16.09 ± 64.81 (n = 158)	69.34 ± 95.07 (n = 149)	63.70 ± 155.47 (n = 142)	18.04 ± 31.92 (n = 18)
	Teriparatide 40 µg	37.03 ± 82.60 (n = 158)	117.66 ± 150.81 (n = 146)	125.39 ± 165.57 (n = 136)	68.88 ± 77.79 (n = 16)

Mean ± SD %

The safety analysis revealed the incidences of adverse events were 86.9% (473 of 544 subjects) in the placebo group, 82.6% (447 of 541 subjects) in the teriparatide 20 µg group, and 86.2% (476 of 552 subjects) in the teriparatide 40 µg group, and the incidences of adverse drug reactions were 30.5% (166 of 544 subjects) in the placebo group, 34.8% (188 of 541 subjects) in the teriparatide 20 µg group, and 39.5% (218

[49] type I collagen crosslinked N-telopeptide
[50] deoxypyridinoline

of 552 subjects) in the teriparatide 40 μg group. Clinical adverse events reported by ≥5% of subjects in any group were as shown in Table 21.

Table 21. Clinical adverse events reported by ≥5% of subjects in any group (Safety population)

Adverse event term[a)]	Placebo (n = 544)	Teriparatide 20 μg (n = 541)	Teriparatide 40 μg (n = 552)
Any event	86.9 (473)	82.6 (447)	86.2 (476)
Pain	22.6 (123)	22.2 (120)	24.6 (136)
Back pain	22.6 (123)	16.8 (91)	15.8 (87)
Surgical procedure	16.9 (92)	16.1 (87)	15.8 (87)
Accidental injury	15.1 (82)	10.7 (58)	12.9 (71)
Nausea	7.5 (41)	9.4 (51)	17.8 (98)
Headache	8.3 (45)	8.1 (44)	13.0 (72)
Arthralgia	9.0 (49)	10.4 (56)	8.9 (49)
Abdominal pain	9.2 (50)	8.9 (48)	10.0 (55)
Flu syndrome	8.5 (46)	7.2 (39)	10.7 (59)
Asthenia	7.2 (39)	8.9 (48)	10.1 (56)
Bronchitis	10.1 (55)	7.8 (42)	7.6 (42)
Rhinitis	8.6 (47)	9.4 (51)	7.4 (41)
Dizziness	6.1 (33)	9.2 (50)	8.0 (44)
Infection	8.8 (48)	6.8 (37)	6.3 (35)
Hypertension	8.1 (44)	7.6 (41)	6.2 (34)
Urinary tract infection	7.2 (39)	6.3 (34)	6.5 (36)
Cough increased	5.5 (30)	6.7 (36)	6.3 (35)
Rash	5.3 (29)	5.7 (31)	6.0 (33)
Diarrhoea	5.3 (29)	5.9 (32)	5.6 (31)
Constipation	4.8 (26)	5.9 (32)	4.9 (27)
Dyspepsia	4.6 (25)	5.9 (32)	4.5 (25)
Myalgia	5.7 (31)	3.9 (21)	5.1 (28)
Pharyngitis	5.0 (27)	5.7 (31)	3.8 (21)
Ecchymosis	5.5 (30)	4.4 (24)	3.6 (20)
Depression	3.3 (18)	3.9 (21)	5.4 (30)

Incidence % (n)
a) COSTART terms were translated into Japanese, referring to the MedDRA ver.10.0.

A total of 4 subjects in the placebo group (myocardial infarction, cardiovascular disorder, respiratory disorder, and shock, 1 subject each), 6 subjects in the teriparatide 20 μg group (cardiac arrest [2 subjects], pneumonia [1 subject], myocardial infarction [1 subject], death [1 subject], pancreatitis [1 subject]), and 6 subjects in the teriparatide 40 μg group (pneumonia [2 subjects], bladder neoplasm [1 subject], lung cancer [1 subject], cerebrovascular accident [1 subject], iron deficiency anaemia [1 subject]) died. A causal relationship to the study drug was ruled out for all deaths. The incidences of serious adverse events were 20.8% (113 of 544 subjects) in the placebo group, 17.2% (93 of 541 subjects) in the teriparatide 20 μg group, and 19.7% (109 of 552 subjects) in the teriparatide 40 μg group. The incidences of adverse events leading to discontinuation were 5.9% (32 of 544 subjects) in the placebo group, 6.5% (35 of 541 subjects) in the teriparatide 20 μg group, and 10.7% (59 of 552 subjects) in the teriparatide 40 μg group. The main reasons for discontinuation were breast cancer (4 subjects), back pain (2 subjects), asthma (2 subjects), vertigo (2 subjects), and gastrointestinal carcinoma (2 subjects) in the placebo group, headache (3 subjects), dizziness (3 subjects), nausea (2 subjects), pain (2 subjects), back pain (2 subjects), cardiac arrest (2 subjects), cancer (2 subjects), and gastrointestinal carcinoma (2 subjects) in the teriparatide 20 μg group, and nausea (9 subjects), rash (4 subjects), dizziness (3 subjects), headache (3 subjects), pain (3 subjects), back pain (2 subjects), asthenia (2 subjects), pneumonia (2 subjects), dementia (2 subjects), and neoplasm (2 subjects) in the teriparatide 40 μg group.

There were little changes from Month 1 through Month 18 in the 4 to 6-hour post-dose serum calcium (mean ± SD) in all treatment groups (2.30 ± 0.10 mmol/L[51]at Month 1 and 2.30 ± 0.10 mmol/L at Month 18 in the placebo group, 2.38 ± 0.12 mmol/L at Month 1 and 2.39 ± 0.12 mmol/L at Month 18 in the teriparatide 20 μg group, 2.42 ± 0.15 mmol/L at Month 1 and 2.42 ± 0.14 mmol/L at Month 18 in the teriparatide 40 μg group).

One subject (0.2%) in the placebo group, 15 subjects (2.8%) in the teriparatide 20 μg group, and 44 subjects (8.0%) in the teriparatide 40 μg group were tested positive for antibodies during the study period. There was no hypersensitivity and no allergic reaction in these subjects, even though they continued receiving teriparatide after antibodies had developed.

The evaluations of bone biopsies from 37 subjects in the placebo group, 31 subjects in the teriparatide 20 μg group, and 34 subjects in the teriparatide 40 μg group at selected study sites identified no significant histological safety concerns, such as fibrous dysplasia or osteomalacia. No adverse events were detected by bone biopsy in the teriparatide 20 μg group. A transient increase in cortical and trabecular remodeling was seen in the teriparatide 40 μg group at Month 12 but not at the time of last observation. Dose-dependent, histomorphometric effects that were seen at the time of last observation are consistent with the bone formation effect of teriparatide.

4.(iii).A.(3).3) Foreign phase III study (5.3.5.1.4, GHAJ [October 1997 to December 1998 (terminated early)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in foreign male patients with primary osteoporosis[52] (the target sample size of 279 subjects; 93 subjects each in the placebo, 20 μg, and 40 μg groups). The primary objective of the study was to evaluate the effect of treatment with teriparatide 20 μg or 40 μg on lumbar spine BMD.

Placebo or teriparatide 20 μg or 40 μg was to be subcutaneously administered once daily. As background therapy, calcium (1000 mg/day) and vitamin D (400-1200 IU/day) were orally administered once daily. The duration of treatment with the study drug was 24 months. In subjects with an increase in serum calcium above the upper limit of normal or a marked increase in urinary calcium, the dose of calcium was to be reduced or stopped, or the dose of the study drug was to be reduced by half at the discretion of the investigator, and if serum calcium or urinary calcium were yet to normalize even after the dose reduction of the study drug, the study drug was to be stopped.

For the same reason as for the aforementioned Study GHAC, this study was also terminated early. All of 437 randomized subjects (147 subjects in the placebo group, 151 subjects in the 20 μg group, 139 subjects in the 40 μg group) were included in the efficacy and safety populations. The median treatment duration [the 25th

[51] Unit in Japan: mg/dL = 4.008 × mmol/L

[52] Male patients with primary osteoporosis who were 30 to 85 years of age; and lumbar spine or hip BMD (T score) of ≥2.0 SDs below YAM. Primary osteoporosis was defined as bone loss that was either due to hypogonadism or idiopathic. Hypogonadism was defined as low early morning free testosterone or elevated follicle-stimulating hormone or luteinizing hormone. Idiopathic osteoporosis meant that the bone loss was not due to hypogonadisrn or to other secondary causes.

percentile, the 75th percentile] was 328.0 [275, 371] days in the placebo group, 312.0 [263, 367] days in the 20 μg/day group, and was 300.0 [257, 369] days in the 40 μg/day group.

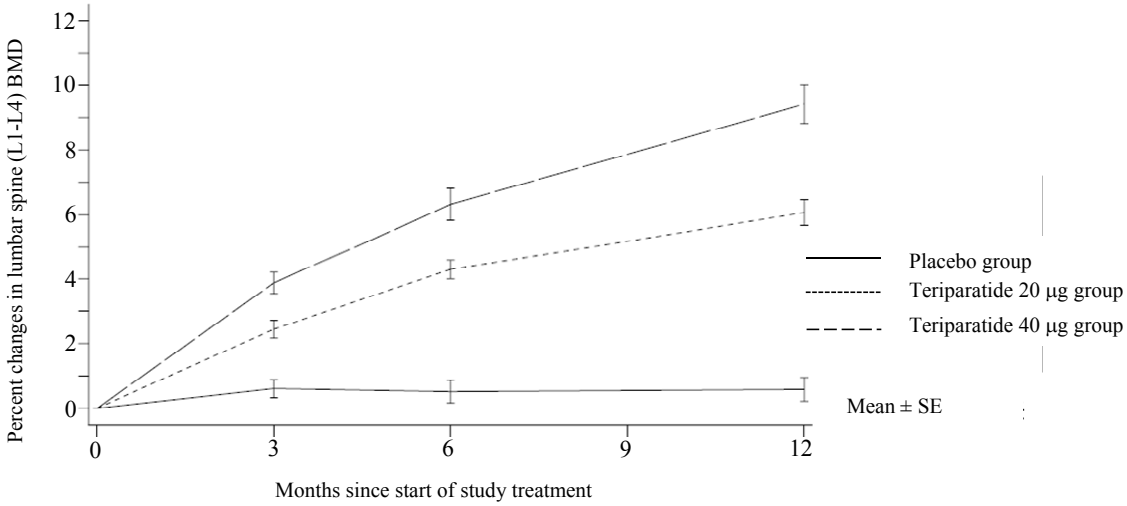
The primary efficacy endpoint of the percent changes from baseline to Month 12 in lumbar spine (L1-L4) BMD measured by DXA was as shown in Table 22 and there were significant differences between the teriparatide 20 μg or teriparatide 40 μg group and the placebo group (both $P < 0.001$, two-sided level of significance of 5%, an analysis of variance (ANOVA) model including treatment and investigator as explanatory variables). No adjustment for multiplicity was performed.

Table 22. Percent changes from baseline to Month 12 in lumbar spine (L1-L4) BMD

Treatment group	Lumbar spine (L1-L4) BMD			
	Baseline (g/cm^2)	Last observation (g/cm^2)	Percent changes from baseline (%)	*P*-value[a) b)]
Placebo (n = 143 [c)])	0.85 ± 0.14	0.86 ± 0.15	0.54 ± 4.19	—
Teriparatide 20 μg (n = 141 [c)])	0.89 ± 0.15	0.95 ± 0.16	5.73 ± 4.46	$P < 0.001$
Teriparatide 40 μg (n = 129 [c)])	0.87 ± 0.14	0.95 ± 0.15	8.75 ± 6.25	$P < 0.001$

Mean ± SD, Last observation carried forward (LOCF)
a) ANOVA model including treatment and investigator as explanatory variables
b) Comparison of the placebo group vs. each of teriparatide groups
c) Subjects without baseline or on-treatment measurement were excluded.

The time course of the percent changes in lumbar spine (L1-L4) BMD, the secondary endpoint, was as shown in Figure 4.



Treatment group	Month 3	Month 6	Month 12
Placebo	n = 141	n = 139	n = 133
Teriparatide 20 μg	n = 139	n = 134	n = 127
Teriparatide 40 μg	n = 127	n = 120	n = 111

Figure 4. Time course of percent change in lumbar spine (L1-L4) BMD

The time course of the percent changes in biochemical markers of bone metabolism was as shown in Table 23.

Table 23. Time course of percent changes from baseline in biochemical markers of bone metabolism

Biochemical marker of bone metabolism	Treatment group	Week 4	Week 26	Week 52	Week 78
Serum PICP	Placebo	-0.96 ± 22.11 (n = 143)	0.41 ± 43.85 (n = 137)	4.13 ± 30.24 (n = 131)	5.04 ± 32.01 (n = 48)
	Teriparatide 20 μg	39.92 ± 37.52 (n = 144)	8.33 ± 39.20 (n = 132)	-6.07 ± 33.02 (n = 125)	-6.61 ± 27.44 (n = 43)
	Teriparatide 40 μg	83.06 ± 78.64 (n = 131)	36.59 ± 54.20 (n = 120)	2.07 ± 28.70 (n = 110)	-10.42 ± 20.13 (n = 39)
Serum BAP	Placebo	0.96 ± 32.30 (n = 143)	-4.74 ± 30.92 (n = 136)	-7.27 ± 34.80 (n = 129)	-5.03 ± 25.29 (n = 48)
	Teriparatide 20 μg	27.63 ± 56.37 (n = 144)	45.14 ± 72.27 (n = 132)	46.56 ± 77.06 (n = 125)	37.75 ± 65.02 (n = 43)
	Teriparatide 40 μg	67.26 ± 94.07 (n = 132)	104.08 ± 112.25 (n = 120)	93.40 ± 117.52 (n = 110)	75.37 ± 103.64 (n = 39)
Urinary NTX	Placebo	-2.75 ± 37.82 (n = 134)	6.20 ± 60.14 (n = 133)	19.51 ± 68.40 (n = 122)	20.46 ± 63.80 (n = 45)
	Teriparatide 20 μg	11.40 ± 56.57 (n = 139)	103.12 ± 290.82 (n = 129)	98.95 ± 279.86 (n = 117)	81.37 ± 136.45 (n = 42)
	Teriparatide 40 μg	39.08 ± 77.67 (n = 126)	215.96 ± 225.47 (n = 112)	187.46 ± 260.14 (n = 103)	105.13 ± 97.28 (n = 38)
Urinary DPD	Placebo	3.63 ± 38.87 (n = 137)	15.50 ± 47.40 (n = 130)	24.87 ± 54.82 (n = 123)	38.81 ± 75.39 (n = 46)
	Teriparatide 20 μg	19.25 ± 54.06 (n = 135)	95.43 ± 316.09 (n = 128)	111.93 ± 442.55 (n = 116)	67.10 ± 118.34 (n = 41)
	Teriparatide 40 μg	46.11 ± 99.51 (n = 123)	131.79 ± 140.74 (n = 110)	120.62 ± 196.36 (n = 102)	79.32 ± 78.34 (n = 37)

Mean ± SD %

The safety analysis revealed that the incidences of adverse events were 76.2% (112 of 147 subjects) in the placebo group, 80.1% (121 of 151 subjects) in the teriparatide 20 μg group, and 80.6% (112 of 139 subjects) in the teriparatide 40 μg group, and the incidences of adverse drug reactions were 14.3% (21 of 147 subjects) in the placebo group, 21.9% (33 of 151 subjects) in the teriparatide 20 μg group, and 36.0% (50 of 139 subjects) in the teriparatide 40 μg group. Adverse events reported by ≥5% of subjects in any group were as shown in Table 24.

Table 24. Adverse events reported by ≥5% of subjects in any group

Adverse event term[a)]	Placebo (n = 147)	Teriparatide 20 μg (n = 151)	Teriparatide 40 μg (n = 139)
Pain	12.9 (19)	17.9 (27)	15.8 (22)
Surgical procedure	12.9 (19)	10.6 (16)	9.4 (13)
Rhinitis	9.5 (14)	9.9 (15)	11.5 (16)
Back pain	12.9 (19)	9.3 (14)	7.9 (11)
Nausea	3.4 (5)	5.3 (8)	18.7 (26)
Asthenia	5.4 (8)	7.9 (12)	11.5 (16)
Arthralgia	6.1 (9)	9.3 (14)	6.5 (9)
Flu syndrome	6.1 (9)	6.0 (9)	10.1 (14)
Infection	8.2 (12)	7.3 (11)	6.5 (9)
Headache	4.1 (6)	5.3 (8)	10.8 (15)
Accidental injury	6.1 (9)	6.0 (9)	5.8 (8)
Bronchitis	4.8 (7)	4.6 (7)	6.5 (9)
Cough increased	5.4 (8)	5.3 (8)	5.0 (7)
Constipation	3.4 (5)	3.3 (5)	5.8 (8)
Dizziness	2.7 (4)	3.3 (5)	6.5 (9)
Hypertension	2.0 (3)	5.3 (8)	3.6 (5)
Sinusitis	2.0 (3)	0.7 (1)	5.0 (7)

Incidence % (n)

a) COSTART terms were translated into Japanese, referring to the MedDRA ver.10.0.

A total of 2 subjects in the teriparatide 20 μg group died (lung cancer, laryngeal cancer: neck differentiated epithelial carcinoma). A causal relationship to the study drug was ruled out for the both deaths. Serious

adverse events occurred in 16 subjects in the placebo group, 15 subjects in the teriparatide 20 μg group, and 14 subjects in the teriparatide 40 μg group. Of the serious adverse events, those reported by ≥2 subjects in either of the teriparatide groups were surgical procedure (4 subjects in the 20 μg group), cough increased (2 subjects in the 20 μg group), accidental injury (2 subjects in the 40 μg group), pyrexia (2 subjects in the 40 μg group), and dyspnoea (2 subjects in the 40 μg group). Serious events reported by 1 subject in the placebo group (cancer), 6 subjects in the teriparatide 20 μg group (laryngeal cancer, pneumonia [lung cancer], addiction, atrial fibrillation, bladder cancer, cerebral haemorrhage), and 4 subjects in the teriparatide 40 μg group (hypercalcaemia, myocardial infarction, somnolence, urticaria) led to study discontinuation. Other than the subjects who died, 4.8% of subjects in the placebo group (7 of 147 subjects; asthenia, renal stone, pain, anaemia, cancer, confusion, and dizziness, 1 subject each), 9.3% of subjects in the teriparatide 20 μg group (14 of 151 subjects; arthralgia [2 subjects], anxiety [2 subjects], asthenia, renal stone, accidental injury, atrial fibrillation, addiction, back pain, bladder cancer, cerebral haemorrhage, depression, and injection site haemorrhage [1 subject each]), and 12.9% of subjects in the teriparatide 40 μg group (18 of 139 subjects; nausea [5 subjects], arthralgia [2 subjects], asthenia [2 subjects], pain, cerebral ischaemia, constipation, headache, hypercalcaemia, myocardial infarction, nervousness, somnolence, and urticaria [1 subject each]) withdrew from the study due to these adverse events.

Although there were no clinically relevant differences in changes in serum calcium from baseline to different timepoints, an increase in serum calcium at 4 to 6 hours post-dose was observed in 16.8% of subjects in the teriparatide 40 μg group, 6.2% of subjects in the teriparatide 20μg group, and 0% of subjects in the placebo group, showing differences among the treatment groups.

Teriparatide-specific binding activity in serum was noted in 2 subjects in the teriparatide groups at Month 12, but it turned out negative during the subsequent study period. Serum calcium, adverse events, and BMD changes in the 2 subjects were similar to those in other subjects.

4.(iii).A.(3).4) Foreign phase III study (5.3.5.2.1, GHBJ [[redacted] 19[redacted] to [redacted] 20[redacted]])

An observational, follow-up study was conducted in patients who had received teriparatide or placebo for up to 24 months in any of Studies GHAC and GHAJ (evaluation data) and GHAF, GHAH, GHAL, GHAU, and GHAV (reference data). The primary objective of the study was to collect safety data following discontinuation of teriparatide treatment. The design of 5 studies (previous studies) (reference data) with patients who were followed in Study GHBJ was as shown in Table 25 [See 4.(iii).A.(3).2) and 4.(iii).A.(3).3) for the design of Studies GHAC and GHAJ].

Table 25. Design of studies with patients who were followed in study GHBJ (excluding Studies GHAC and GHAJ)

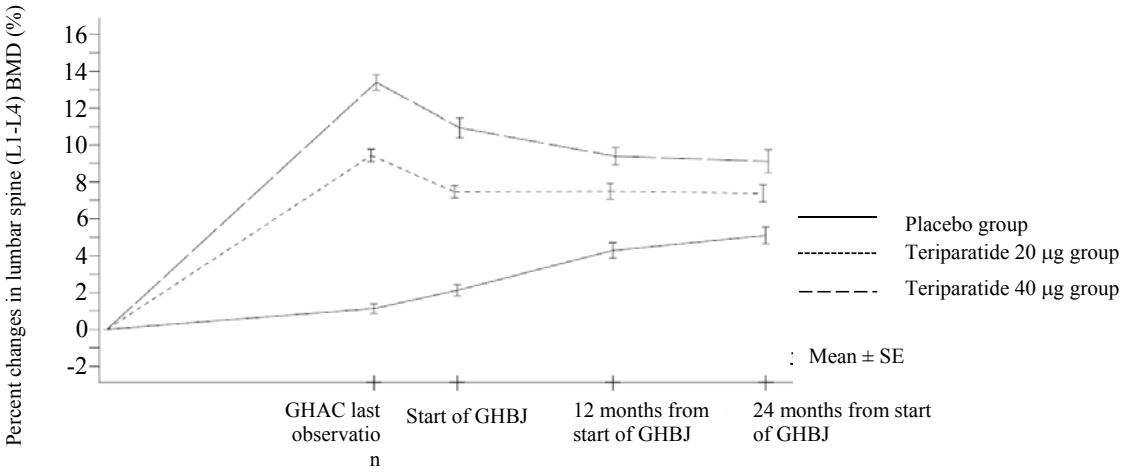
	GHAF (reference data)	GHAH (reference data)	GHAL (reference data)	GHAU (reference data)	GHAV (reference data)
Study population	Postmenopausal patients with osteopenia or osteoporosis	Postmenopausal patients with osteoporosis	Postmenopausal patients with osteoporosis	Postmenopausal women	Postmenopausal patients with osteoporosis
Design	A randomized, double-blind, parallel-group study	A randomized, double-blind, parallel-group study	An open-label, uncontrolled study	A randomized, open-label study	A randomized, open-label study
Study drug /Dosage regimen	Placebo; teriparatide 40 μg subcutaneously administered once daily (HRT): Premarin 0.625 mg/day, Provera 2.5 mg/day	Placebo; ALEN 10 mg orally administered once daily Placebo; teriparatide 40 μg subcutaneously administered once daily	Teriparatide 40 μg subcutaneously administered once daily	No active treatment (background therapy only) Teriparatide 20 μg or 40 μg subcutaneously administered once daily	No active treatment (background therapy only) Teriparatide 40 μg subcutaneously administered once daily
Duration of treatment	Planned: 18 months, Actual (median): 427.0 days for HRT group, 420.5 days for teriparatide 40 μg plus HRT group	Planned: 24 months Actual (median): 418 days for ALEN group, 414 days for teriparatide group	Planned: 24 months Actual (range): 0-79 days	Planned: 3 years Actual (range): 9-100 days for 20 μg group, 16-76 days for 40 μg group	Planned: 42 months Actual (range): 9-55 days
Primary efficacy endpoint	Percent changes in lumbar spine BMD	Percent changes and change in lumbar spine BMD	No analyses performed	No analyses performed	No analyses performed

ALEN: alendronate, HRT: hormone replacement therapy

In this study, teriparatide was not administered, and calcium (1000 mg/day) and vitamin D (400-1200 IU/day) were orally administered[53] as background therapy throughout the study period. The study consisted of a 24-month initial observation phase after enrollment and a subsequent 30-month extension phase (a total of 4.5 years). The primary objective of the study was to collect information on all adverse events during the initial observation phase and serious adverse events during the extension phase. The primary efficacy objective of the study was to assess vertebral fractures in patients with baseline X-ray film in their previous study, and a secondary objective of the study was to compare changes in lumbar spine and total hip BMD. The data from Studies GHAC, GHAJ, GHAF, and GHAH were analyzed separately. The safety data from the 7 studies were analyzed separately. The main results are described below.

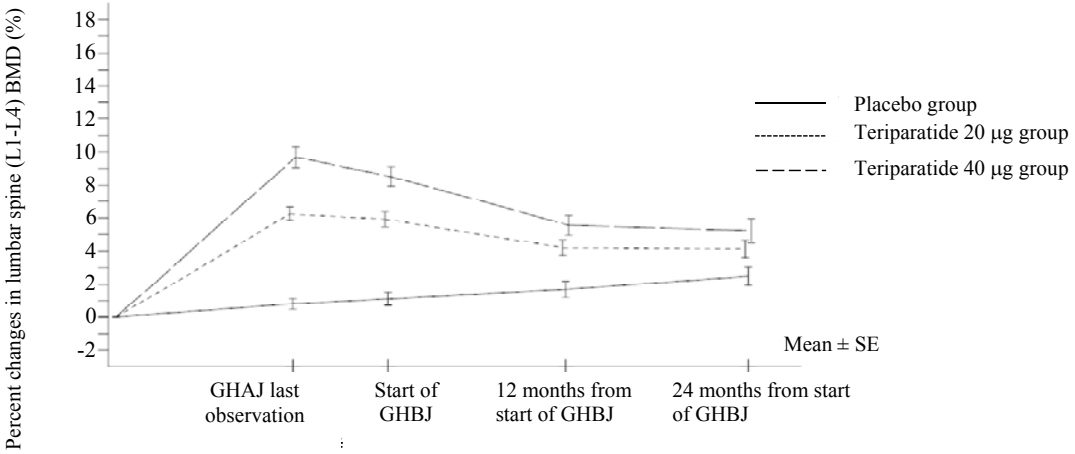
The time course of the percent changes in lumbar spine (L1-L4) BMD was as shown in Figure 5 for the GHAC subset and Figure 6 for the GHAJ subset.

[53] As subjects were allowed to take other osteoporosis drugs at the discretion of their physician, about 60% of subjects in all treatment groups used other osteoporosis drugs during Study GHBJ.



Treatment group	GHAC last observation	Start of GHBJ	12 months from start of GHBJ	24 months from start of GHBJ
Placebo	n = 403	n = 398	n = 367	n = 333
Teriparatide 20 μg	n = 421	n = 422	n = 392	n = 359
Teriparatide 40 μg	n = 397	n = 398	n = 367	n = 342

Figure 5. Percent changes in lumbar spine (L1-L4) BMD in GHAC subset



Treatment group	GHAJ last observation	Start of GHBJ	12 months from start of GHBJ	24 months from start of GHBJ
Placebo	n = 126	n = 127	n = 111	n = 105
Teriparatide 20 μg	n = 120	n = 118	n = 99	n = 104
Teriparatide 40 μg	n = 106	n = 106	n = 96	n = 96

Figure 6. Percent changes in lumbar spine (L1-L4) BMD in GHAJ subset

The incidence of fractures during the observational follow-up period was as shown in Table 26 for the GHAC subset and Table 27 for the GHAJ subset.

Table 26. Incidence of fracture during the observational follow-up period
(from GHAC last observation to 12 months or 24 months from start of GHBJ) in GHAC subset

New vertebral fracture [a)]	Placebo (n = 353)	Teriparatide 20 μg (n = 373)	Teriparatide 40 μg (n = 345)	Combined teriparatide (n = 718)
Proportion of subjects with new vertebral fracture at Month 12 % (n)	19.0 (67)	11.3 (42)	10.4 (6)	10.9 (78)
Ratio of proportions vs. placebo group [95% CI]	—	0.593 [0.415, 0.848]	0.550 [0.377, 0.801]	0.572 [0.424, 0.773]
New nonvertebral fracture[b)]	Placebo (n = 414)	Teriparatide 20 μg (n = 436)	Teriparatide 40 μg (n = 412)	Combined teriparatide (n = 848)
Proportion of subjects with new nonvertebral fracture at Month 24 % (n)	14.5 (60)	12.4 (54)	10.4 (43)	11.4 (97)
Ratio of proportions vs. placebo group [95% CI]	—	0.855 [0.607, 1.203]	0.720 [0.499, 1.040]	0.789 [0.585, 1.065]
New nonvertebral insufficiency fracture [b)]	Placebo (n = 414)	Teriparatide 20 μg (n = 436)	Teriparatide 40 μg (n = 412)	Combined teriparatide (n = 848)
Proportion of subjects with new nonvertebral insufficiency fracture at Month 24 % (n)	8.5 (35)	6.2 (27)	5.1 (21)	5.7 (48)
Ratio of proportions vs. placebo group [95% CI]	—	0.733 [0.452, 1.188]	0.603 [0.357, 1.018]	0.670 [0.440, 1.019]

a) Number of subjects with evaluable x-ray film at GHAC last observation and at 12 months from start of GHBJ
b) Number of all enrolled subjects

Table 27. Incidence of fracture from GHAJ baseline through the observational follow-up period
(to 12 months or 24 months from start of GHBJ) in GHAJ subset

New vertebral fracture [a)]	Placebo (n = 103)	Teriparatide 20 μg (n = 92)	Teriparatide 40 μg (n = 84)	Combined teriparatide (n = 176)
Proportion of subjects with new vertebral fracture at Month 12 % (n)	11.7 (12)	5.4 (5)	6.0 (5)	5.7 (10)
Ratio of proportions vs. placebo group [95% CI]	—	0.466 [0.171, 1.274]	0.511 [0.187, 1.393]	0.488 [0.218, 1.089]
New nonvertebral fracture [b)]	Placebo (n = 127)	Teriparatide 20 μg (n = 121)	Teriparatide 40 μg (n = 107)	Combined teriparatide (n = 228)
Proportion of subjects with new nonvertebral fracture at Month 24 % (n)	5.5 (7)	10.7 (13)	5.6 (6)	8.3 (19)
Ratio of proportions vs. placebo group [95% CI]	—	1.949 [0.805, 4.720]	1.017 [0.353, 2.935]	1.512 [0.653, 3.499]
New nonvertebral insufficiency fracture [b)]	Placebo (n = 127)	Teriparatide 20 μg (n = 121)	Teriparatide 40 μg (n = 107)	Combined teriparatide (n = 228)
Proportion of subjects with new nonvertebral insufficiency fracture at Month 24 % (n)	0.8 (1)	5.0 (6)	0.0 (0)	2.6 (6)
Ratio of proportions vs. placebo group [95% CI]	—	6.298 [0.769, 51.55]	—.	3.342 [0.407, 27.45]

a) Number of subjects with evaluable x-ray film at GHAJ baseline and at 12 months from start of Study GHBJ
b) Number of all enrolled subjects

The safety analysis revealed the incidences of adverse events during the follow-up phase (from the data lock for the previous study to the data lock at 24 months from the start of Study GHBJ) in the GHAC subset were 87.4% (362 of 414 subjects) in the placebo group, 85.8% (374 of 436 subjects) in the teriparatide 20 μg group, and 87.1% (359 of 412 subjects) in the teriparatide 40 μg group. Among adverse events reported by ≥4 subjects and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences among the three treatment groups [the placebo, teriparatide 20 μg, and teriparatide 40 μg groups]) during the treatment phase in GHAC, those reported at a higher incidence in the teriparatide 20 μg or 40 μg group than in the placebo group during the follow-up phase were nausea, depression, nail disorder, otitis externa, glaucoma, dry eye, and headache. For these adverse events except for glaucoma ($P = 0.025$), the Pearson's χ^2 *P*-values for the comparison of incidences during the follow-up phase among the treatment groups were >0.05. Among adverse events newly

occurring in ≥4 subjects during the follow-up phase and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences among the treatment groups), those reported at a higher incidence in the teriparatide 20 μg or 40 μg group than in the placebo group during the follow-up phase were sinusitis, angina pectoris, vasodilatation, bursitis, congestive cardiac failure, and vascular anomaly.

The incidences of adverse events during the follow-up phase in the GHAJ subset were 78.7% (100 of 127 subjects) in the placebo group, 76.9% (93 of 121 subjects) in the teriparatide 20 μg group, and 80.4% (86 of 107 subjects) in the teriparatide 40 μg group. Among adverse events reported by ≥4 subjects and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences among the three treatment groups [the placebo, teriparatide 20 μg, and teriparatide 40 μg groups]) during the treatment phase in GHAJ, those reported at a higher incidence in the teriparatide 20 μg or 40 μg group than in the placebo group during the follow-up phase were dizziness and hernia. For both adverse events, the Pearson's χ^2 *P*-values for the comparison of incidences during the follow-up phase among the treatment groups were >0.05. Among adverse events newly occurring in ≥4 subjects during the follow-up phase and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences among the treatment groups), those reported at a higher incidence in the teriparatide 20 μg or 40 μg group than in the placebo group during the follow-up phase were rectal disorder, amnesia, and tendon disorder.

The incidences of adverse events during the follow-up phase in the GHAF subset were 81.4% (79 of 97 subjects) in the HRT group and 74.5% (70 of 94 subjects) in the teriparatide 40 μg plus HRT group. Among adverse events reported by ≥4 subjects and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences between the two treatment groups [the HRT and teriparatide 40 μg plus HRT groups]) during the treatment phase in GHAF, those reported at a higher incidence in the teriparatide 40 μg plus HRT group than in the HRT group were nausea and somnolence. For both adverse events, the Pearson's χ^2 *P*-values for the comparison of incidences during the follow-up phase between the treatment groups were >0.05. Among adverse events newly occurring in ≥4 subjects during the follow-up phase and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences between the treatment groups), those reported at a higher incidence in the teriparatide 40 μg plus HRT group than in the HRT group during the follow-up phase were arteriosclerosis (*P* = 0.04).

The incidences of adverse events during the follow-up phase in the GHAH subset were 81.1% (43 of 53 subjects) in the ALEN group and 90.4% (47 of 52 subjects) in the teriparatide 40 μg group. Among adverse events reported by ≥4 subjects and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences between the two treatment groups [the ALEN and teriparatide 40 μg groups]) during the treatment phase in GHAH, those reported at a higher incidence in the teriparatide 40 μg group than in the ALEN group were leg cramps, but the Pearson's χ^2 *P*-value for the comparison of incidences during the follow-up phase between the treatment groups was >0.05. Among adverse events newly occurring in ≥4 subjects during the follow-up phase and with a Pearson's χ^2 *P*-value of ≤0.05 (comparison of incidences between the treatment groups), none were reported at a higher incidence in the teriparatide 40 μg group than in the ALEN group during the follow-up phase.

The incidences of mortality in Study GHBJ were as shown in Table 28. There were no major differences among the treatment groups.

Table 28. Incidence of mortality in Study GHBJ

Previous study	Placebo	Teriparatide 20 μg	Teriparatide 40 μg	Teriparatide 40 μg in combination with HRT[a)]	ALEN	HRT
GHAC	3.9 (16/414)	4.8 (21/437)	3.6 (15/412)	—	—	—
GHAJ	2.4 (3/127)	3.3 (4/121)	4.7 (5/107)	—	—	—
GHAF	—	—	—	0.0 (0/99)	—	0.0 (0/104)
GHAH	—	—	0.0 (0/52)	—	3.8 (2/53)	—

% (No. of subjects who died/No. of evaluable subjects)
a) Teriparatide 40 μg plus HRT

The incidences of serious adverse events during the 4.5-year period (median) from teriparatide discontinuation until the end of extension phase by subset of Study GHBJ were as shown in Table 29. There were no differences among the treatment groups and no increases in bone cancer, cardiovascular disease, or vertebral fracture and no osteosarcoma were observed in subjects treated with teriparatide.

Table 29. Incidence of serious adverse events by subset of Study GHBJ

Previous study	Placebo	Teriparatide 20 μg	Teriparatide 40 μg	Teriparatide 40 μg in combination with HRT[a)]	ALEN	HRT
GHAC	35.0 (145/414)	35.5 (155/437)	32.0 (132/412)	—	—	—
GHAJ	24.4 (31/127)	32.2 (39/121)	22.4 (24/107)	—	—	—
GHAF	—	—	—	18.2 (18/99)	—	23.1 (24/104)
GHAH	—	—	13.5 (7/52)	—	28.3 (15/53)	—

Incidence % (No. of subjects with event/No. of evaluable subjects)
a) Teriparatide 40 μg plus HRT

The incidences of tumors in the GHAC subset were as shown in Table 30.

Table 30. Incidence of tumors in GHAC subset
(Tumors [including related tumors] reported by ≥2 subjects treated with teriparatide)

Tumor type	Placebo (n = 414)	Teriparatide 20 μg (n = 437)	Teriparatide 40 μg (n = 412)
Breast cancer	9 (2.2)	5 (1.1)	5 (1.2)
Breast cancer in situ	1 (0.2)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	5 (1.1)	2 (0.5)
Colon cancer stage II	0 (0.0)	0 (0.0)	1 (0.2)
Rectosigmoid cancer stage III	1 (0.2)	0 (0.0)	0 (0.0)
Rectal cancer	0 (0.0)	0 (0.0)	1 (0.2)
Basal cell carcinoma	1 (0.2)	1 (0.2)	3 (0.7)
Skin cancer	0 (0.0)	0 (0.0)	1 (0.2)
Squamous cell carcinoma of skin	0 (0.0)	1 (0.2)	0 (0.0)
Lung neoplasm malignant	1 (0.2)	3 (0.7)	1 (0.2)
Lung adenocarcinoma	0 (0.0)	1 (0.2)	0 (0.0)
Chronic lymphocytic leukaemia	0 (0.0)	0 (0.0)	3 (0.7)
Lymphoma	0 (0.0)	1 (0.2)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	2 (0.5)	1 (0.2)
Meningioma	0 (0.0)	0 (0.0)	2 (0.5)
Ovarian cancer	1 (0.2)	0 (0.0)	1 (0.2)
Ovarian epithelial cancer	0 (0.0)	0 (0.0)	1 (0.2)
Malignant neoplasm of uterine adnexa	0 (0.0)	0 (0.0)	1 (0.2)
Ovarian neoplasm	2 (0.5)	0 (0.0)	0 (0.0)
Renal cell carcinoma stage unspecified	0 (0.0)	0 (0.0)	2 (0.5)
Endometrial cancer	0 (0.0)	0 (0.0)	1 (0.2)
Uterine cancer	0 (0.0)	0 (0.0)	1 (0.2)

n (incidence %), MedDRA ver.7.0

4.(iii).A.(3).5) Foreign phase IV study (5.3.5.1.5, GHBM [April 2001 to May 2003])

A randomized, double-blind, parallel-group study was conducted in foreign postmenopausal patients with osteoporosis[54] (target sample size of 220 subjects, 110 subjects per group). The primary objective of the study was to assess the effect of teriparatide on the percent changes in lumbar spine BMD.

Placebo or teriparatide 20 μg was to be subcutaneously administered once daily and placebo tablet or alendronate (ALEN) tablet 10 mg was to be orally administered once daily. The duration of study treatment was 18 months. As background therapy, calcium (approximately 1000 mg/day) and vitamin D (approximately 400-800 IU/day) were orally administered in an open-label manner. An interim analysis was performed before the completion of the study and the results of an interim efficacy analysis at Month 6 were published in November 2002.

All of 203 treated subjects (102 subjects in the teriparatide group, 101 subjects in the ALEN group) were included in the efficacy and safety populations.

The primary efficacy analysis compared the treatment groups for the changes in lumbar spine (L1-L4) BMD at Month 18 as shown in Table 31. The percent changes from baseline to Month 18 in lumbar spine (L1-L4) BMD and the secondary endpoint of the percent changes from baseline to Month 18 in femoral neck and total hip BMD were as shown in Table 32. The time course of the percent changes from baseline in lumbar spine (L1-L4) BMD was as shown in Figure 7.

Table 31. Changes from baseline to Month 18 in lumbar spine (L1-L4) BMD

Treatment group	Lumbar spine (L1-L4) BMD			
	Baseline (g/cm^2)	Month 18 (g/cm^2)	Changes from baseline (g/cm^2)	*P*-value[b)]
ALEN	0.75 ± 0.10 (n = 101)	0.78 ± 0.08 (n = 74[a)])	0.04 ± 0.03 (n = 74 [a)])	$P < 0.001$
Teriparatide 20 μg	0.75 ± 0.08 (n = 102)	0.83 ± 0.09 (n = 70 [a)])	0.08 ± 0.04 (n = 70 [a)])	

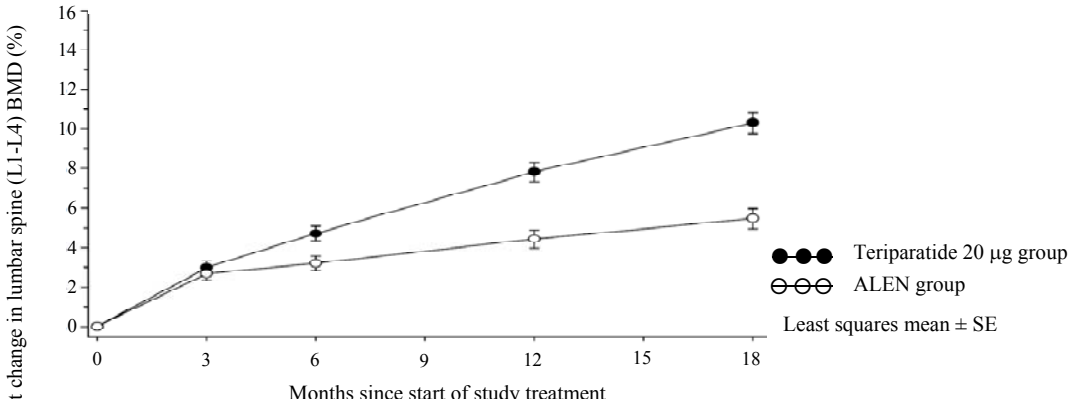
Mean ± SD (n), LOCF
a) Subjects without postbaseline BMD measurement were excluded.
b) A mixed-effects model with repeated measures that included therapy given at the time of a visit as a fixed effect and subject as a random effect

Table 32. Percent changes in BMD at Month 18

Treatment group	Lumbar spine (L1-L4)	Femoral neck	Total hip
ALEN	5.18 ± 3.65 (n = 91)	2.98 ± 5.15 (n = 86)	2.98 ± 3.59 (n = 86)
Teriparatide 20 μg	8.69 ± 6.31 (n = 96)	3.37 ± 4.62 (n = 89)	2.74 ± 4.00 (n = 89)

Mean ± SD % (n), LOCF
Subjects without postbaseline BMD measurement were excluded.

[54] Main inclusion criteria: Ambulatory, postmenopausal women who were 45 to 85 years of age; and lumbar spine (L1-L4) or femoral neck BMD (T-score) of 2.5 to 4.0 SDs below YAM.



Treatment group	Month 0	Month 3	Month 6	Month 12	Month 18
ALEN	n = 101	n = 86	n = 87	n = 83	n = 74
Teriparatide 20 μg	n = 102	n = 88	n = 85	n = 75	n = 70

Figure 7. Time course of percent change in lumbar spine (L1-L4) BMD

The time course of the percent changes in each of biochemical markers of bone metabolism was as shown in Table 33.

Table 33. Time course of percent change from baseline in each of biochemical markers of bone metabolism

Biochemical marker of bone metabolism	Treatment group	Month 1	Month 3	Month 6	Month 12
Serum PICP	ALEN	-4.38 ± 23.46 (n = 90)	-30.22 ± 17.79 (n = 87)	-30.75 ± 20.19 (n = 85)	-34.12 ± 18.98 (n = 76)
	Teriparatide 20 μg	71.29 ± 75.99 (n = 92)	37.13 ± 55.38 (n = 85)	27.78 ± 50.21 (n = 76)	15.08 ± 35.54 (n = 66)
Serum PINP	ALEN	-12.84 ± 27.65 (n = 90)	-53.23 ± 22.68 (n = 87)	-63.06 ± 22.83 (n = 85)	-62.97 ± 29.10 (n = 76)
	Teriparatide 20 μg	114.58 ± 105.62 (n = 92)	169.91 ± 153.39 (n = 86)	265.41 ± 245.03 (n = 76)	252.98 ± 225.82 (n = 66)
Serum BAP	ALEN	0.59 ± 51.65 (n = 90)	-27.57 ± 62.91 (n = 87)	-39.39 ± 55.01 (n = 85)	-48.81 ± 41.26 (n = 76)
	Teriparatide 20 μg	34.07 ± 62.81 (n = 92)	69.81 ± 111.07 (n = 86)	120.35 ± 185.26 (n = 76)	103.64 ± 176.49 (n = 66)
Urinary NTX	ALEN	-41.06 ± 37.43 (n = 86)	-53.40 ± 41.61 (n = 86)	-61.79 ± 19.67 (n = 84)	-57.95 ± 30.14 (n = 75)
	Teriparatide 20 μg	8.99 ± 60.08 (n = 88)	42.15 ± 117.71 (n = 84)	95.38 ± 140.60 (n = 73)	75.15 ± 137.39 (n = 64)

Mean ± SD %

The safety analysis revealed that the incidences of adverse events were 79.2% (80 of 101 subjects) in the ALEN group and 85.3% (87 of 102 subjects) in the teriparatide 20 μg group and the incidences of adverse drug reactions were 22.8% (23 of 101 subjects) in the ALEN group and 28.4% (29 of 102 subjects) in the teriparatide 20 μg group. Adverse events reported by ≥5% of subjects in either group were as shown in Table 34.

Table 34. Adverse events reported by ≥5% of subjects in either group

Adverse event term	ALEN (n = 101)	Teriparatide (n = 102)
Back pain	38.6 (39)	25.5 (26)
Nasopharyngitis	5.9 (6)	11.8 (12)
Headache	5.0 (5)	11.8 (12)
Nausea	6.9 (7)	10.8 (11)
Arthralgia	6.9 (7)	8.8 (9)
Dizziness	5.9 (6)	8.8 (9)
Muscle cramp	4.0 (4)	8.8 (9)
Pain in extremity	6.9 (7)	7.8 (8)
Dyspepsia	4.0 (4)	7.8 (8)
Constipation	3.0 (3)	5.9 (6)
Depression	3.0 (3)	5.9 (6)
Diarrhoea	2.0 (2)	5.9 (6)
Contusion	7.9 (8)	2.9 (3)
Urinary tract infection	7.9 (8)	2.0 (2)
Hypertension	5.9 (6)	2.0 (2)
Meteorism	5.0 (5)	2.0 (2)

Incidence % (n) MedDRA ver.6.0

One subject in the ALEN group died (metastases to liver, adenocarcinoma, haematuria, deep vein thrombosis). Serious adverse events occurred in 14 subjects in the ALEN group (diverticulitis NOS [2 subjects], mitral valve incompetence, haematochezia, lower respiratory tract infection NOS, dengue fever, ankle fracture, pelvic fracture NOS, metastases to liver, adenocarcinoma NOS, haematuria, deep vein thrombosis, cerebrovascular accident, cerebral artery occlusion, bipolar disorder, schizoaffective disorder, bladder prolapse, hypertension NOS, and orthostatic hypotension [1 subject each]. Of these events, metastases to liver, adenocarcinoma, haematuria, and deep vein thrombosis occurred in one subject and bipolar disorder, schizoaffective disorder, and diverticulitis NOS occurred in another subject) and 8 subjects in the teriparatide 20 μg group (anaemia NOS, pancreatitis due to bile duct obstruction, chest pain, cholelithiasis, pneumonia NOS, arthritis NOS, cerebrovascular accident, and bronchitis NOS, 1 subject each). Adverse events leading to study discontinuation occurred in 13 subjects in the ALEN group (abdominal distension, abdominal pain upper, adenocarcinoma, diarrhoea, flushing, pelvic fracture, gastrooesophageal reflux disease, haematochezia, headache, muscle cramp, nausea, oesophagitis, and orthostatic hypotension, 1 subject each) and 18 subjects in the teriparatide 20μg group (chest pain [2 subjects], headache [2 subjects], nausea [2 subjects], abdominal pain, cerebrovascular accident, constipation, dizziness, dysphagia, irritability, nephrolithiasis, oedema, palpitations, pneumonia, rash pruritic, and throat irritation [1 subject each]).

Hypercalcaemia occurred in 2.9% (3 of 102 subjects) of subjects in the teriparatide 20 μg group, which was mild (2 subjects) or moderate (1 subject) in severity.

Iliac crest bone biopsies were obtained from 8 subjects in the teriparatide 20 μg group and 9 subjects in the ALEN group after 6 months of treatment and 8 subjects in the teriparatide 20 μg group and 7 subjects in the ALEN group after 18 months of treatment. Histomorphometric parameters of trabecular bone formation were higher in the teriparatide 20 μg group than in the ALEN group after 6 months of treatment and after 18 months of treatment and those of trabecular bone resorption were lower in the ALEN group than in the teriparatide 20 μg group after 6 months of treatment. Histomorphometric parameters of cortical bone

formation were higher in the teriparatide 20 μg group than in the ALEN group after 6 months of treatment and after 18 months of treatment.

4.(iii).A.(3).6) Foreign phase III/IV study (5.3.5.1.6, GHCA [September 2002 to November 2005])

A randomized, open-label, parallel-group study (Substudy 1) and an uncontrolled study (Substudy 2) were conducted in foreign postmenopausal patients with severe osteoporosis. The primary objective of the study was to compare the changes in lumbar spine BMD of those who had received a 2-year treatment with teriparatide (the target sample size of 405 subjects), a sequential treatment regimen of teriparatide for 1 year followed by 1 year of raloxifene (the target sample size of 135 subjects), and a treatment regimen of teriparatide for 1 year followed by 1 year of no active treatment (the target sample size of 135 subjects) (Substudy 1[55]), and those who had received a 2-year treatment with teriparatide (the target sample size of 135 subjects) (Substudy 2[56]).

In Substudy 1, teriparatide 20 μg was to be subcutaneously administered once daily for 12 months followed by 12 months of once-daily subcutaneous administration of teriparatide 20 μg (teriparatide/teriparatide group), 12 months of once-daily oral administration of a raloxifene hydrochloride 60 mg tablet (teriparatide/raloxifene group), or 12 months of no active treatment (teriparatide/no active treatment group). In Substudy 2, teriparatide 20 μg was to be subcutaneously administered once daily for 24 months. As background therapy, all subjects were orally administered calcium (500 mg/day) and vitamin D (400-800 IU/day).

Of 634 subjects enrolled into Substudy 1, 127[57] subjects withdrew from the study during the first year and 507 subjects (305 subjects in the teriparatide/teriparatide group, 100 subjects in the teriparatide/raloxifene group, 102 subjects in the teriparatide/no active treatment group) were randomized and 504 subjects excluding 3 randomized subjects who did not receive the study drug in the teriparatide/raloxifene group (305 subjects in the teriparatide/teriparatide group, 97 subjects in the teriparatide/raloxifene group, 102 subjects in the teriparatide/no active treatment group) were included in the safety population for Substudy 1. Excluding 1 subject with no measurements for efficacy variables during the second year, 503 subjects (304 subjects in the teriparatide/teriparatide group, 97 subjects in the teriparatide/raloxifene group, 102 subjects in the teriparatide/no active treatment group) were included in the efficacy population for Substudy 1. In Substudy 2, all of 234 enrolled subjects who received the study drug were included in the safety and efficacy populations for Substudy 2.

[55] Postmenopausal women who were ≥55 years of age; lumbar spine (L1-L4), femoral neck, or total hip BMD (T-score) of ≥2.5 SDs below YAM; and the presence of at least one documented preexisting clinical fragility fracture (vertebral or nonvertebral) in the past 3 years.

[56] Patients who met one of the following criteria in addition to the inclusion criteria for Substudy 1: (1) at least one new, documented clinical fragility fracture (vertebral or nonvertebral) despite antiresorptive therapy prescribed in the year prior to this fracture, (2) at least 2 years since initiating antiresorptive therapy, and lumbar spine, total hip, or femoral neck BMD (T-score) of ≥3 SDs below YAM, (3) a decrease of ≥3.5% in BMD at any one site, despite antiresorptive therapy prescribed in the past 2 years.

[57] 49 subjects for personal reasons, 34 subjects due to adverse events, 26 subjects due to deviations from the inclusion criteria, 4 subjects due to death, 4 subjects due to sponsor's decision, 3 subjects due to investigator's decision, 2 subjects due to lost to follow-up, 2 subjects due to poor compliance, 2 subjects due to protocol deviations, 1 subject due to moving away.

In Substudy 1, the primary efficacy endpoint of the time course of the changes from baseline in lumbar spine (L1-L4) BMD was as shown in Table 35.

Table 35. Time course of changes from baseline in lumbar spine (L1-L4) BMD (Substudy 1)

Timepoint	Teriparatide/Teriparatide group (n = 304)	Teriparatide/Raloxifene group (n = 97)	Teriparatide/No active treatment group (n = 102)
Month 6	0.031 ± 0.002 [0.027, 0.035]	0.037 ± 0.004 [0.029, 0.044]	0.031 ± 0.004 [0.024, 0.038]
Month 12	0.052 ± 0.002 [0.048, 0.057]	0.060 ± 0.004 [0.052, 0.068]	0.048 ± 0004 [0.040, 0.057]
Month 18	0.066 ± 0.003 [0.061, 0.071]	0.058 ± 0.005 [0.049, 0.067]	0.037 ± 0.005 [0.028, 0.046]
Month 24	0.079 ± 0.003 [0.073, 0.084]	0.058 ± 0.005 [0.049, 0.068]	0.028 ± 0.005 [0.018, 0.038]

Least squares mean ± SE [95% CI] g/cm^2
A mixed-effects model with repeated measures including treatment, time, and time-treatment interaction as fixed effects and subject as a random effect

In Substudy 2, the lumbar spine (L1-L4) BMD (least squares mean ± SE) increased throughout the study period, i.e. 0.024 ± 0.005 g/cm^2 at Month 6, 0.040 ± 0.005 g/cm^2 at Month 12, 0.058 ± 0.005 g/cm^2 at Month 18, and 0.067 ± 0.005 g/cm^2 at Month 24.

The safety analysis revealed that in subjects treated with teriparatide 20 μg in Substudy 1 or 2, regardless of treatment group, the incidence of adverse events was 72.9% (631 of 866 subjects) and the incidence of adverse drug reactions was 31.1% (269 of 866 subjects). Adverse events reported by ≥3% of the subjects were as shown in Table 36, and the incidences of adverse events by substudy were as shown in Table 37.

Table 36. Adverse events reported by ≥3% of subjects (Total safety population)

Adverse event term	Teriparatide (n = 866)[a)]
Nausea	13.3 (115)
Arthralgia	10.0 (87)
Headache	7.9 (68)
Hypertension	6.7 (58)
Pain in extremity	6.1 (53)
Muscle cramp	5.7 (49)
Diarrhoea	5.3 (46)
Dizziness	4.8 (42)
Nasopharyngitis	4.7 (41)
Back pain	4.2 (36)
Hypercalcaemia	3.7 (32)
Bronchitis	3.6 (31)
Constipation	3.5 (30)
Depression	3.3 (29)
Vomiting	3.2 (28)
Influenza	3.0 (26)

Incidence % (n), MedDRA ver.7.0
a) Pooled data of adverse events that occurred while subjects were treated with teriparatide 20 μg in Substudy 1 or 2, regardless of treatment group

Table 37. Incidences of adverse events[a)] by substudy during the second year

Adverse event term	Substudy 1			Substudy 2	Substudies 1 and 2 combined
	Teriparatide/Teriparatide group (n = 305)	Teriparatide/Raloxifene group (n = 97)	Teriparatide/No active treatment group (n = 102)	Teriparatide/Teriparatide group (n = 199)	Teriparatide/Teriparatide group (n = 504)
Any adverse event	57.0 (174)	54.6 (53)	54.9 (56)	46.2 (92)	52.8 (266)
Arthralgia	3.6 (11)	4.1 (4)	1.0 (1)	7.0 (14)	5.0 (25)
Hypertension	3.9 (12)	2.1 (2)	2.0 (2)	5.5 (11)	4.6 (23)
Urinary tract infection	2.3 (7)	4.1 (4)	2.9 (3)	1.5 (3)	2.0 (10)
Nausea	2.6 (8)	4.1 (4)	1.0 (1)	2.0 (4)	2.4 (12)
Diarrhoea	2.3 (7)	5.2 (5)	1.0 (1)	1.5 (3)	2.0 (10)
Pain in extremity	1.6 (5)	3.1 (3)	2.9 (3)	2.5 (5)	2.0 (10)
Back pain	2.0 (6)	0.0 (0)	2.0 (2)	4.0 (8)	2.8 (14)
Nasopharyngitis	2.3 (7)	1.0 (1)	2.9 (3)	2.0 (4)	2.2 (11)

Incidence % (n), MedDRA ver.7.0

a) Adverse events reported by ≥2% of subjects in either teriparatide/teriparatide group

A total of 8 subjects died, of whom 4 subjects (cerebral ischaemia, drug intoxication, pneumonia, cerebral haemorrhage) died during treatment with teriparatide in the first year and the remaining 4 subjects died during the second year, including 2 subjects (metastatic neoplasm, pneumonia/lung cancer) in the teriparatide/teriparatide group and 1 subject (pancreatic carcinoma) in the teriparatide/raloxifene group in Substudy 1 and 1 subject (chronic obstructive respiratory disease) in Substudy 2. A causal relationship to study drug was ruled out for all of the adverse events leading to death. The incidences of serious adverse events were 15.4% (133 of 866 subjects) in the total safety population and 17.5% (88 of 504 subjects) in subjects treated with teriparatide for 2 years. Serious adverse events reported by ≥0.5% of the subjects throughout the study period were fall (0.8% [7 of 866 subjects]), pneumonia (0.7% [6 of 866 subjects]), atrial fibrillation (0.5% [4 of 866 subjects]), and radius fracture (0.5% [4 of 866 subjects]). Serious adverse events reported by ≥2 subjects during the second year of the study were as shown in Table 38.

Table 38. Serious adverse events reported by ≥2 subjects during the second year of the study

Adverse event term	Substudy 1			Substudy 2	Substudies 1 and 2 combined
	Teriparatide/ Teriparatide group (n = 305)	Teriparatide/ Raloxifene group (n = 97)	Teriparatide/No active treatment group (n = 102)	Teriparatide/ Teriparatide group (n = 199)	Teriparatide/ Teriparatide group (n = 504)
Any serious adverse event	7.5 (23)	9.3 (9)	13.7 (14)	12.1 (24)	9.3 (47)
Fall	0.3 (1)	0.0 (0)	0.0 (0)	1.0 (2)	0.6 (3)
Hypertension	0.3 (1)	0.0 (0)	0.0 (0)	1.0 (2)	0.6 (3)
Radius fracture	0.7 (2)	0.0 (0)	0.0 (0)	0.5 (1)	0.6 (3)
Anaemia	0.3 (1)	0.0 (0)	0.0 (0)	0.5 (1)	0.4 (2)
Pyrexia	0.3 (1)	0.0 (0)	0.0 (0)	0.5 (1)	0.4 (2)
Hip fracture	0.3 (1)	0.0 (0)	0.0 (0)	0.5 (1)	0.4 (2)
Breast cancer	0.3 (1)	0.0 (0)	1.0 (1)	0.5 (1)	0.4 (2)

Incidence % (n), MedDRA ver.7.0

Adverse events leading to study discontinuation occurred in 51 subjects during the first year of the study (Substudy 1, 34 subjects; substudy 2, 17 subjects) and 18 subjects during the second year of the study (Substudy 1, 6 subjects in the teriparatide/teriparatide group, 7 subjects in the teriparatide/raloxifene group, 1 subject in the teriparatide/no active treatment group; Substudy 2, 4 subjects in the teriparatide/teriparatide group). During the first year of the study, the incidence of hypercalcaemia/serum calcium increased was 2.9% (25 of 866 subjects) and the incidence of hypercalciuria was 0.3% (3 of 866 subjects) in Months 0 to 6. The incidence of hypercalcaemia/serum calcium increased was 1.3% (10 of 743 subjects) and the incidence

of nephrolithiasis was 0.3% (2 of 743 subjects), but hypercalciuria did not occur in Months 6 to 12. During the second year of the study, hypercalcaemia occurred in 1.0% of subjects in the teriparatide/teriparatide group (3 of 305 subjects) and 1.0% of subjects in the teriparatide/no active treatment group (1 of 102 subjects). Hypercalcaemia occurring in 1 subject on Day 90 was serious and a total of 2 subjects including this subject withdrew from the study due to hypercalcaemia during the first year of the study.

4.(iii).B Outline of the review

4.(iii).B.(1) Clinical positioning

The applicant explained as follows:

While the effects of bisphosphonates in increasing BMD and preventing fractures are well-documented with ample clinical study data, the drugs are also known to have relatively higher incidences of gastrointestinal disorders as compared with other approved therapeutic drugs for osteoporosis. In addition, other safety issues such as delayed fracture healing (Odvina C, et al. *J Clin Endocrinol Metab.* 2005; 90:1294-1301), the occurrence of femoral shaft fractures (Lenart B, et al. *N Engl J Med.* 2008; 358 (12): 1304-1306), and their relationship with jaw necrosis (Woo SB, et al. *Ann Intern Med.* 2006;144 (10): 753-761) have also been reported. The effect of SERMs (e.g. raloxifene) in preventing new vertebral fractures has been reported to be almost comparable to that of bisphosphonates (Delmas P, et al. *J Clin Endocrinol Metab.* 2002; 87: 3609-3617). However, "Guidelines for Prevention and Treatment of Osteoporosis 2006" states that there is evidence that SERMs increase BMD and prevent vertebral fractures in postmenopausal women with osteoporosis aged less than 80 years, but evidence for the prevention of nonvertebral fractures is not sufficient. In Japan, calcitonin preparations, active-form vitamin D_3 preparations, and vitamin K_2 preparations are also used for the prevention of fractures but are considered not as effective as bisphosphonates or SERMs. On the other hand, teriparatide has been shown to increase BMD and prevent fractures in patients with osteoporosis at high risk for fracture in Foreign Study GHAC. Furthermore, teriparatide has been shown to be more efficacious than a bisphosphonate (alendronate tablet 10 mg/day) in increasing lumbar spine BMD in Foreign Study GHBM. Based on the above, teriparatide is expected to be a first-line drug for patients with osteoporosis at high risk for fracture.

PMDA asked the applicant to explain whether there are differences in the definition of patients with osteoporosis at high risk for fracture between Japan and overseas.

The applicant responded as follows:

As the definition of "patients with osteoporosis at high risk for fracture" had not been established in Japan at the time of initiating a Japanese clinical study with teriparatide, "patients with osteoporosis at high risk for fracture" was defined based on fracture risk factors including previous fracture, low BMD, and advanced age. "Guidelines for Prevention and Treatment of Osteoporosis 2006" states that patients at high risk for fracture can be identified based on BMD, age, etc., and spine fracture status, low BMD, and age have also been reported to be the major risk factors for fracture in foreigners (Chen P *et al. J. Bone Miner. Res.* 2009; 24: 495-502). Furthermore, it has been reported that the ability of these risk factors to predict future fracture risk is not different between the Japanese and US/European populations (Fujiwara S, et al. *J. Bone Miner. Res.*

2003; 18: 1547-1553). Based on the above, there should be no differences in the definition of patients with osteoporosis at high risk for fracture between Japan and overseas.

PMDA considered as follows:
Given that neoplastic bone lesions including osteosarcoma were observed in rats, prior to selecting teriparatide as a therapeutic drug, the appropriateness of the use of teriparatide should be thoroughly examined from a risk/benefit standpoint. The definition of "patients with osteoporosis at high risk for fracture" should be further discussed [see "4.(iii).B.(5) Indication"]. Meanwhile, based on the results of Japanese and foreign clinical studies, the efficacy of teriparatide has been demonstrated [see "4.(iii).B.(3) Efficacy"] and its safety is considered acceptable [see "4.(iii).B.(4) Safety"]. Thus, PMDA accepted the response.

4.(iii).B.(2) Clinical data package

A bridging strategy was used for the development of teriparatide in Japan and a Japanese phase III study (GHDB) was positioned as a bridging study. A foreign phase III study (GHAC) was positioned as a study to be bridged. The applicant concluded that the similarity of clinical study data between Japan and overseas (including the data from these two studies) was demonstrated and constructed a clinical data package by extrapolation of foreign clinical data [see Figure 8].

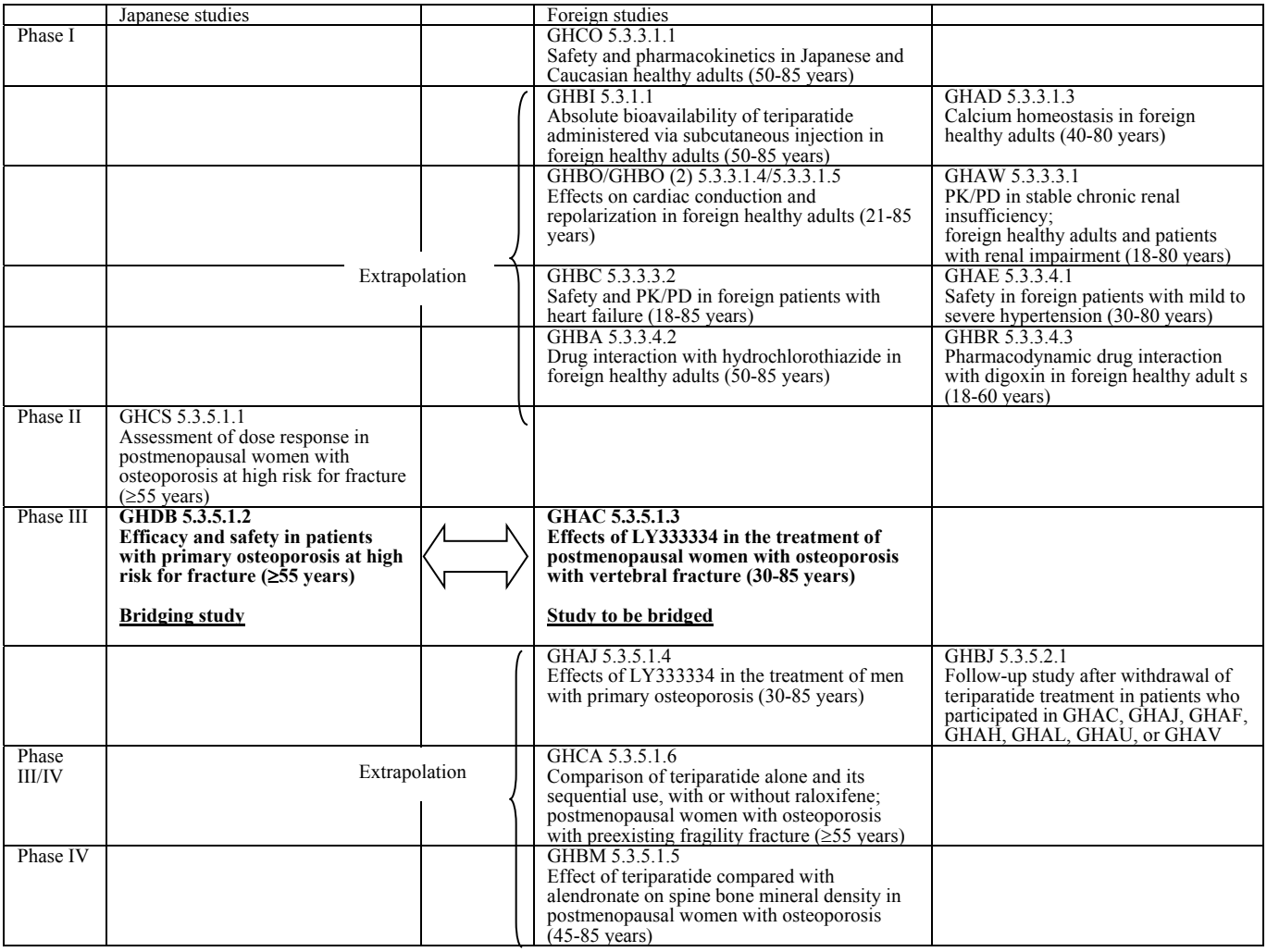


Figure 8. Clinical data package (evaluation data)

The applicant explained the reason for early termination of foreign phase III studies (GHAC, GHAJ) (evaluation data) and the impact of early termination on assessments as follows:

Since neoplastic bone lesions including osteosarcoma were observed in a rat carcinogenicity study, the sponsor (Eli Lilly and Company) suspended treatment with teriparatide in all ongoing clinical studies with teriparatide on December 8, 1998 and advised the study investigators to instruct subjects to complete scheduled visits. Meanwhile, a pre-planned interim analysis of Study GHAC was performed and the Data Monitoring Board evaluated the safety of teriparatide based on the results of the interim analysis on December 17, 1998. The Board found no significant safety issues, but the sponsor decided to terminate all ongoing clinical studies with teriparatide. Then, the sponsor instructed the study investigators to have all subjects complete the close-out visit and follow the procedures for early discontinuation. In both Studies GHAC and GHAJ, about 90% of subjects visited by February 1, 1999 (the close-out visit). As treatment with teriparatide was not continued until the close-out visit and several weeks elapsed between discontinuation of study drug and each subject's close-out visit, it is considered that analyses of biochemical markers of bone metabolism, laboratory data, and specific indices of bone formation and resorption in bone biopsies at the close-out visit underestimated the effect of teriparatide. On the other hand, the results of assessments of

vertebral fractures, BMD, and bone architecture and analysis of adverse events would not have been much different, if treatment with teriparatide had been continued until the close-out visit.

PMDA considers as follows:
Although Studies GHAC and GHAJ were planned to assess the primary endpoint after a prespecified duration of treatment (Study GHAC, 3 years; Study GHAJ, 2 years), the studies were terminated early. While the applicant's explanation is understandable, such early termination made it difficult to provide a clear answer to the hypothesis for the primary efficacy endpoint which was established at the time of planning the study. However, given that teriparatide stimulates bone formation and has been shown to increase lumbar spine BMD earlier and to a greater degree as compared to alendronate (an antiresorptive drug) (Foreign Study GHBM, Figure 7), and taking account of the actual treatment duration in subjects enrolled into the studies (Study GHAC, a median of 19 months; Study GHAJ, a median of 11 months) and the number of subjects, the efficacy and safety of teriparatide can be assessed to a certain degree based on the obtained results.

The applicant assessed the following items based on "On Ethnic Factors in the Acceptability of Foreign Clinical Data" (PMSB/ELD Notification No. 672 dated August 11, 1998) in order to determine whether foreign clinical data including Study GHAC can be extrapolated to Japan. The applicant assessed the similarity of efficacy profiles based on the data from Japanese and foreign placebo-controlled, double-blind studies (Japanese Study GHCS and Foreign Study GHAJ) as well as the bridging study (Japanese Study GHDB) and the study to be bridged (Foreign Study GHAC). On the other hand, the similarity of safety profiles between Japanese and foreign studies was assessed based on the data from a foreign active-controlled, double-blind study (Study GHBM) in addition to the above 4 studies. Adverse events were coded using COSTART or MedDRA in the individual clinical study reports and the version of MedDRA differed depending on the timing of the conduct of the study. MedDRA's lowest level terms (LLTs) assigned to the reported terms recorded in the case report forms were linked to preferred terms (PTs) or system organ classes (SOCs) under a single version of MedDRA for the 5 studies to be recounted for the assessment of the similarity of safety profiles.

4.(iii).B.(2).1) Similarity of pharmacokinetics
Study GHCO showed that the exposure to teriparatide increased in Japanese subjects, who had a lower body weight than Caucasian subjects [see "4.(ii).B.(1) Comparison of pharmacokinetics between Japan and overseas"]. PMDA asked the applicant to explain the safety of teriparatide in Japanese patients.

The applicant responded as follows:
Among all adverse events reported in Japanese Studies GHCS (24 weeks of treatment) and GHDB (12 months of treatment; Period 1, double-blind, parallel-group phase) and Foreign Studies GHAC (a median of 19 months of treatment), GHAJ (a median of 11 months of treatment), and GHBM (18 months of treatment) (studies in patients with osteoporosis), those with an incidence of ≥5% in the pooled teriparatide 20 μg group and with a higher incidence than in the placebo group were constipation, dizziness, headache, osteoarthritis,

arthralgia, contusion, and upper respiratory tract inflammation across the 2 Japanese studies and arthralgia, pain in extremity, nausea, headache, dizziness, nasopharyngitis, cough, constipation, muscle spasms, and diarrhoea across the 3 foreign studies. These studies demonstrated that the trend of occurrence of adverse events was similar between Japanese and foreign patients and there was no trend towards the occurrence of adverse events unique to Japanese patients. In order to assess the effect of body weight differences, the incidence of adverse events was compared according to body weight at baseline (median) (<65 kg vs. ≥65 kg in Foreign Study GHAC; <50 kg vs. ≥50 kg in Japanese Study GHDB). Among subjects treated with teriparatide 20 μg in Foreign Study GHAC, the incidence of adverse events was higher in the subgroup of subjects weighing <65 kg (n = 259) than in the subgroup of subjects weighing ≥65 kg (n = 275) and the incidences of the following adverse events were significantly different between the two subgroups: dizziness (<65 kg, 13.1% [34 of 259 subjects]; ≥65 kg, 4.7% [13 of 275 subjects]; *P* = 0.001) and neck pain (<65 kg, 4.6% (12 of 259 subjects); ≥65 kg, 1.5% (4 of 275 subjects); *P* = 0.041). Among subjects treated with teriparatide 20 μg in Japanese Study GHDB, the incidences of dizziness in the subgroups of subjects weighing <50 kg (n = 77) and ≥50 kg (n = 59) were 7.8% (6 of 77 subjects) and 3.4% (2 of 59 subjects), respectively, through 12 months of treatment and 10.4% (8 of 77 subjects) and 5.1% (3 of 59 subjects), respectively, through 18 months of treatment. The subgroup of subjects weighing <50 kg had an approximately 2-fold higher incidence than the subgroup of subjects weighing ≥50 kg. The incidence of dizziness tended to be higher in the lower body weight group than in the higher body weight group in both Japanese and foreign patients. The incidence of dizziness was 6.3% (11 of 175 subjects) in the pooled teriparatide 20 μg group from the 2 Japanese studies, which was lower than the incidence in the subgroup of subjects weighing <65 kg (similar to body weight of Japanese patients) in Foreign Study GHAC (13.1%) and similar to the incidence in the pooled teriparatide 20 μg group from the 3 foreign studies (7.7% [61 of 794 subjects]). Furthermore, the events of dizziness observed in the 2 Japanese studies were all mild or moderate in severity.

4.(iii).B.(2).2) Similarities of intrinsic and extrinsic ethnic factors

4.(iii).B.(2).2).(a) Intrinsic ethnic factors

4.(iii).B.(2).2).(a).i) Age, gender, body weight

The applicant explained as follows:

The effect of age on the pharmacokinetics of teriparatide was considered small based on the results of PPK analyses of Japanese Study GHCS and Foreign Studies GHAC and GHAJ (patient studies). There were no gender differences in C_{max} after subcutaneous or intravenous administration of teriparatide to healthy adult men and women aged 50 to 84 years in a foreign clinical pharmacology study (GHBI). However, AUC after subcutaneous administration was approximately 23% higher in women than in men and the AUC after intravenous administration was approximately 18% higher in women than in men. These gender differences in AUC were considered attributable to differences in body weight. Also based on differences in the mean body weight of subjects between Japanese Study GHCS and Foreign Study GHAC (patient studies), the apparent volume of distribution in Japanese patients was estimated to be approximately 15% smaller than that in foreign patients and the C_{max} reflecting the apparent volume of distribution was inferred to be higher in Japanese patients. In Study GHCO in Japanese and Caucasian postmenopausal healthy women, the mean

AUC and C_{max} in the teriparatide 40 μg group were approximately 40% and 30% higher, respectively, in Japanese subjects than in Caucasian subjects, but the AUC and C_{max} adjusted for body weight were similar, and there were no differences in safety between Japanese and Caucasian subjects. Taking account of these findings, no dose adjustment is required.

4.(iii).B.(2).2).(a).ii) Baseline lumbar spine BMD

The applicant explained as follows:

In order to establish the criteria for bridging the clinical data between the regions and to design a method for assessing the similarity of efficacy, a subgroup analysis of Foreign Study GHAC based on the tertile of baseline lumbar spine (L1-L4) BMD was performed. The percent change in lumbar spine BMD at the time of last observation tended to be greater in the subgroup of subjects with lower baseline lumbar spine (L1-L4) BMD. YAM of lumbar spine BMD is lower in the Japanese population than in the foreign population. Based on these findings, the percent change in lumbar spine (L1-L4) BMD following treatment with teriparatide was expected to be greater in Japanese patients than in foreign patients and it was considered necessary to investigate the relationship with baseline lumbar spine (L1-L4) BMD for assessment of the similarity of efficacy between Japanese and foreign patients. Likewise, it was also decided to investigate the relationship with baseline lumbar spine (L1-L4) T-score. As a result, baseline lumbar spine (L1-L4) BMD (mean) was lower in Japanese subjects than in foreign subjects (Japanese Study GHDB, 0.6143 g/cm^2; Foreign Study GHAC, 0.8204 g/cm^2) and the percent change in lumbar spine (L1-L4) BMD following treatment with teriparatide was greater in Japanese subjects than in foreign subjects, but it was likely that there are no substantial differences between Japan and overseas for the relationship between the percent change in lumbar spine (L1-L4) BMD and baseline lumbar spine (L1-L4) BMD and T-score [see "4.(iii).B.(2).3).(a).i) Comparison of bridging study and study to be bridged"].

4.(iii).B.(2).2).(a).iii) Drug interactions

The applicant explained as follows:

As teriparatide has a pharmacological effect that leads to a transient increase in serum calcium and orthostatic hypotension has been reported in foreign clinical pharmacology studies, potential drug interactions with calcium channel antagonists, atenolol (a β-adrenergic antagonist), furosemide (a loop diuretic), HCTZ (a thiazide diuretic), and digoxin (a digitalis preparation) were examined (GHAE, GHAW, GHBA, GHBR). As a result, no drug interactions were observed.

4.(iii).B.(2).2).(a).iv) Effects of hepatic, renal, and cardiac functions

The applicant explained as follows:

A number of factors such as Kupffer cells and other macrophages as well as proteinases in hepatocytes or other tissues seem to be involved in the proteolysis of PTH (1-34) (Segre GV, et al. *J Clin Invest.* 1981; 67: 449-457, Bringhurst FR, et al. *Am J Physiol.* 1988; 255: E886-E893, Daugaard H, *Dan Med Bull.* 1996; 43: 203-215, Murray TM, et al. *Endocrine Reviews.* 2005; 26: 78-113). It has also been reported that PTH (1-34) is degraded in the kidney, liver, lung, etc. (Liao S, et al. *Amino Acids*, in press). Since the literature suggested that teriparatide is degraded by various factors in various tissues in the body and hepatic impairment should

have no significant effect on the pharmacokinetics of teriparatide, a study on the effect of hepatic impairment on the pharmacokinetics of teriparatide was not performed. In Foreign Study GHAW, the effect of renal impairment on the pharmacokinetics of teriparatide was assessed. C_{max} and AUC were similar between subjects with normal renal function and subjects with mild or moderate renal impairment. On the other hand, AUC increased by 73% in subjects with severe renal impairment as compared with subjects with normal renal function. As there is no report that the condition of renal impairment itself differs between ethnic groups, it is unlikely that the effect of severe renal impairment on the pharmacokinetics of teriparatide differs by ethnic group. In Foreign Study GHBC, the effects of teriparatide on hemodynamic parameters and ECG findings and the pharmacokinetics of teriparatide were assessed in subjects with mild to moderate heart failure. As a result, there were no safety concerns in subjects with mild or moderate heart failure. There were no clinically relevant changes in hemodynamic parameters, QTc prolongation, and other ECG abnormalities and no clinically relevant pharmacokinetic differences were observed as compared with healthy adult subjects.

As described above, the evaluation of intrinsic ethnic factors revealed difference in body weight between Japanese and foreign patients, but the difference was not considered to affect the efficacy or safety of teriparatide.

4.(iii).B.(2).2).(b) Extrinsic ethnic factors

4.(iii).B.(2).2).(b).i) Definition, diagnosis, treatment, etc. of osteoporosis

The applicant explained as follows:

At the NIH consensus conference in 2000, osteoporosis was defined internationally as “a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture” and it is a common recognition around the world that the prevention of osteoporosis, regardless of gender or age, is important. BMD-based diagnostic criteria were proposed by the WHO in 1994 and have been used widely in Europe and the US. According to the criteria, a person with a T-score of ≤ -2.5 (BMD of ≥2.5 SDs below YAM) has a diagnosis of osteoporosis. In Japan, a person with BMD <70% of YAM is diagnosed with osteoporosis, and 70% of YAM is almost comparable to a T-score of -2.5 SD. The diagnostic criteria for vertebral fracture also are not substantially different between Japan and overseas. The ultimate goal of the prevention and treatment of osteoporosis is to prevent fractures. Each patient undergoes a risk assessment and is treated with dietary therapy, exercise therapy, or pharmacotherapy according to the degree of risk identified. Standard therapeutic drugs are bisphosphonates and SERMs in both Japan and overseas. Except that no bone formation stimulator has been approved in Japan, there are no differences in treatment between Japan and overseas.

4.(iii).B.(2).2).(b).ii) Design of clinical studies

The applicant compared the design of a bridging study with that of a study to be bridged (Table 39 and then explained as follows.

Table 39. Comparison of the design of a bridging study with that of a study to be bridged

	Japanese Study GHDB (Bridging study)	Foreign Study GHAC (Study to be bridged)
Design	A placebo-controlled, randomized, double-blind, parallel-group study	A placebo-controlled, randomized, double-blind, parallel-group study
Duration of treatment	24 months (Period 1, 12-month double-blind comparative phase; Period 2, 6-month open-label phase; Period 3, 6-month open-label phase)	A median of 19 months (although the planned duration of treatment was 3 years, the study was terminated early due to the sponsor's decision)
Treatment group	Placebo, Teriparatide 20 μg	Placebo, Teriparatide 20 μg, Teriparatide 40 μg
Study population	≥55 years of age; patients with primary osteoporosis at high risk for fracture; men or women postmenopausal for ≥5 years (including menopause due to surgery or chemotherapy)	30 to 85 years of age; women postmenopausal for ≥5 years (including menopause due to surgery or chemotherapy); patients with a minimum of one moderate or two mild nontraumatic vertebral fractures
Primary endpoint	Percent change in lumbar spine (L2-L4) BMD	Proportion of subjects with new vertebral (T4-L4) fracture
Key secondary endpoints	biochemical markers of bone metabolism, femoral neck BMD, total hip BMD, lumbar spine (L1-L4) BMD, new vertebral fractures and nonvertebral fractures	biochemical markers of bone metabolism, femoral neck BMD, total hip BMD, lumbar spine (L1-L4) BMD, nonvertebral fractures

In order to evaluate drug efficacy, in both Japan and overseas, the assessment of the effects of teriparatide on the incidence of fractures, BMD, biochemical markers of bone metabolism, etc. is important and BMD assessment is considered a useful predictor of the risk of fracture. Especially, the lumbar spine is the site where changes in BMD following treatment can be measured easily and is a standard measuring site for BMD. In Japan, "Guidelines for Prevention and Treatment of Osteoporosis 2006", etc. states that BMD refers to that measured at the lumbar spine as a rule, and is generally measured at the L2-L4. In contrast, outside Japan, the L1-L4 BMD is measured. The difference between Japan and overseas is whether or not the BMD at L1 is included. Since L1 is the site where deformation and fracture are often found in the elderly, BMD may be overestimated if the BMD at L1 is included. However, the ratio of trabecular or cortical bone is not substantially different L1- and L2-L4, and it is unlikely that responsiveness to drugs differs between L1 and L2-L4. Moreover, there were no major differences between the L1-L4 BMD and the L2-L4 BMD, which were measured at baseline in Japanese Studies GHCS and GHDB (Figure 9). Thus, whether or not the BMD at L1 is included in the measuring sites would not affect the comparison of the percent changes in lumbar spine BMD between Japan and overseas.

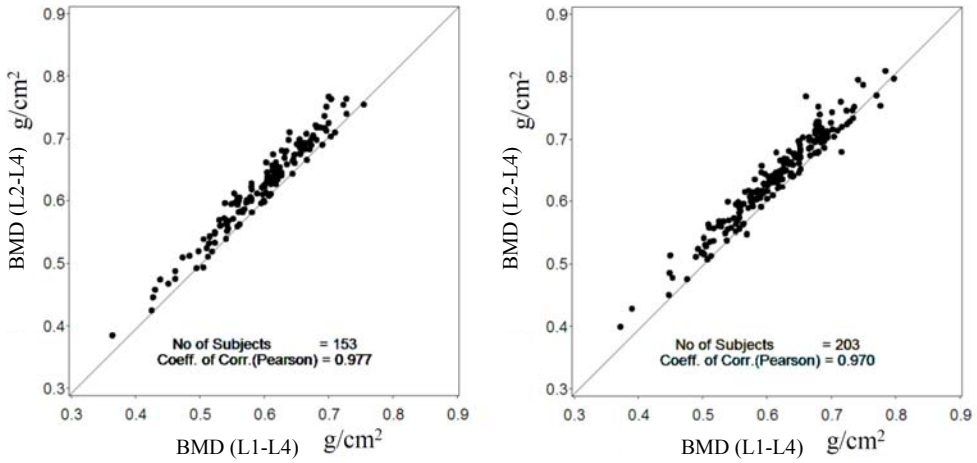


Figure 9. Correlation in baseline lumbar spine BMD between L1-L4 and L2-L4 (Left: Japanese Study GHCS; Right: Japanese Study GHDB)

The primary endpoint of Study GHAC was "the proportion of subjects with new vertebral fractures" whereas that of Study GHDB was "the percent change in lumbar spine (L2-L4) BMD". As the guidelines on

osteoporosis drugs in Europe/the US state that fractures should be assessed in a randomized, double-blind, comparative study, the proportion of subjects with new vertebral fractures was chosen as the primary endpoint and lumbar spine (L1-L4) BMD, etc. were chosen as secondary endpoints for Foreign phase III Study GHAC. The results of Study GHAC were already available at the start of the Japanese clinical study, and it was planned to be utilized in the development of teriparatide. Since a comparative study with the primary endpoint of bone mass can serve as a bridging study and the demonstration of the similarity of improvement in bone mass between Japan and overseas helps the assessment of the foreign clinical data for extrapolation to Japan (Narukawa M. *Iyakuhin Kenkyu*. 2000; 31: 44-52), the percent changes in lumbar spine (L2-L4) BMD was chosen as the primary endpoint and new vertebral fractures and nonvertebral fractures, etc. were chosen as secondary endpoints for Study GHDB. As described above, although the primary endpoint was different between Studies GHDB and GHAC, it was concluded that there was no problem with comparing efficacy between the two studies using lumbar spine (L1-L4) BMD data. For the comparison of efficacy using lumbar spine (L1-L4) BMD data, the relationship between BMD as a surrogate marker and fracture was investigated. BMD accounts for approximately 70% of bone strength, and an epidemiologic study has reported that BMD estimates the risk of spine and hip fracture, regardless of race (Fujiwara S, et al. *J. Bone Miner. Res.* 2003; 18: 1547-1553). However, it has also been reported that the effect of antiresorptive drugs in preventing fractures is partly correlated with an increase in BMD, but it is difficult to explain the effect on fracture prevention with BMD change alone. In contrast, it has been reported that increases in lumbar spine BMD account for 30% to 41% of the vertebral fracture risk reduction with teriparatide treatment (Chen P, et al. *J. Bone Miner. Res.* 2006; 21: 1785-1790). The relationship between increases in BMD and fracture risk reduction seems stronger for teriparatide treatment than for antiresorptive therapy and, in Foreign Study GHBM, teriparatide has been shown to increase lumbar spine BMD more than an antiresorptive drug, alendronate. Furthermore, histomorphometry of bone biopsy specimens from women treated with teriparatide revealed increases in trabecular bone volume and trabecular bone connectivity density, improved trabecular morphology with a shift toward a more plate-like structure, and increased cortical thickness, and teriparatide has been shown to improve microarchitectural deterioration characteristic of osteoporosis to a more normal state (Jiang Y, et al. *J. Bone Miner. Res.* 2003; 18: 1932-1941). It has been reported that increases in lumbar spine and femoral neck BMD are correlated with improvements in trabecular microarchitecture (Chen P, et al. *J. Bone Miner. Res.* 2007; 22: 1173-1180). Based on the above, etc., the relationship between increases in BMD and fracture prevention is strong for teriparatide treatment and BMD assessment as a surrogate marker is considered valid. Due to early termination of Study GHAC, the last measuring points were different and the actual duration of treatment varied from subject to subject depending on the timing of early discontinuation. Thus, it was decided to compare the percent change in lumbar spine (L1-L4) BMD at Month 12 in Study GHAC with the percent change in lumbar spine (L1-L4) BMD at Month 12 (double-blind comparative phase) in Study GHDB because BMD measurement had been scheduled for Month 12 and there were sufficient data at Month 12.

The study population for Study GHAC was determined based on the primary endpoint (the proportion of subjects with new vertebral fractures) and postmenopausal osteoporosis patients with vertebral fracture who were 30 to 85 years of age were included in the study. In Study GHDB taking into account age as well as

previous vertebral fracture and low BMD, patients with primary osteoporosis aged ≥55 years were included. Thus, not only postmenopausal women with osteoporosis but also men with primary osteoporosis (n = 14) were enrolled into this study. Prior vertebral fracture, advanced age, and low BMD are fracture risk factors in men as well as in women and after adjusting for prevalent vertebral fracture, age, and BMD, there was no major gender difference in the incidence of vertebral fractures (Fujiwara S, et al. *J Bone Miner Res*. 2003; 18: 1547-1553). Therefore, it was considered that there were no major differences in the study population between the two studies in terms of the risk of fracture.

As described above, there should be no major differences in extrinsic ethnic factors between Japan and overseas.

4.(iii).B.(2).3) Similarities of efficacy and safety

4.(iii).B.(2).3).(a) BMD-increasing effect

4.(iii).B.(2).3).(a).i) Comparison of bridging study with study to be bridged

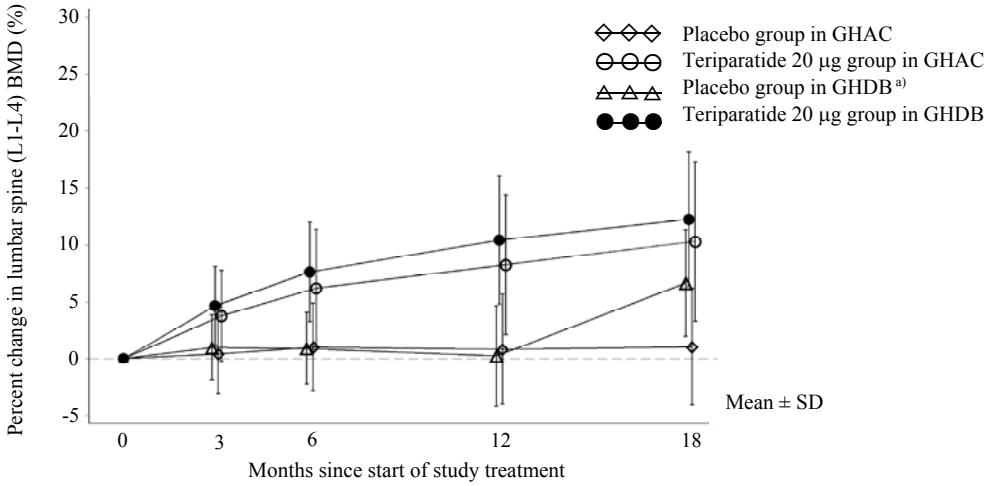
The applicant explained as follows:

As shown in Table 40, the difference between the teriparatide 20 μg and placebo groups for the percent changes from baseline to Month 12 in lumbar spine (L1-L4) BMD (mean) with its 95% confidence interval was 10.20% [8.57, 11.84] in Study GHDB, which was higher than 7.41% [6.70, 8.12] in Study GHAC.

Table 40. Comparison of percent changes from baseline to Month 12 in lumbar spine (L1-L4) BMD

Study	Treatment group	N	Percent change in lumbar spine (L1-L4) BMD (%)		
			Mean	SD	95% CI
GHAC (Study to be bridged)	Placebo	467	0.84	4.87	—
	Teriparatide 20 μg	466	8.25	6.10	—
	(Difference between teriparatide 20 μg and placebo groups)	—	7.41	5.52	[6.70, 8.12]
GHDB (Bridging study)	Placebo	60	0.23	4.44	—
	Teriparatide 20 μg	121	10.43	5.61	—
	(Difference between teriparatide 20 μg and placebo groups)	—	10.20	5.25	[8.57, 11.84]

As shown in Figure 10, the percent changes in lumbar spine (L1-L4) BMD increased with increasing duration of treatment in the teriparatide 20 μg group in both studies and the magnitude of the increases was similar between the two studies.



a) Subjects in the placebo group of Study GHDB received teriparatide 20 μg from Month 12.

Figure 10. Time course of percent changes in lumbar spine (L1-L4) BMD (%) (GHDB and GHAC)

As described in "4.(iii).B.(2).2).(a).ii) Baseline lumbar spine BMD", baseline lumbar spine (L1-L4) BMD (mean) was lower in Japanese subjects than in foreign subjects (Japanese Study GHDB, 0.6143 g/cm^2; Foreign Study GHAC, 0.8204 g/cm^2). In order to assess the effect of differences in baseline lumbar spine BMD between Japanese and foreign subjects on the percent changes in lumbar spine BMD, the relationship between baseline lumbar spine (L1-L4) BMD and the percent changes in lumbar spine (L1-L4) BMD and the relationship between baseline lumbar spine (L1-L4) BMD (T-score) and the percent changes in lumbar spine (L1-L4) BMD were investigated. As shown in Figure 11, the distribution of subjects with respect to the former was similar between the two studies, showing no substantial differences between Japanese and foreign subjects. The distribution of subjects with respect to the latter was also similar between the two studies, within the range of -4 SD to -2 SD of T-score, and the percent change in lumbar spine (L1-L4) BMD tended to be greater with smaller baseline T-score in both studies. As described above, there were no substantial differences between the two studies for the relationship between the percent change in lumbar spine (L1-L4) BMD and baseline lumbar spine (L1-L4) BMD (T-score for teriparatide treatment).

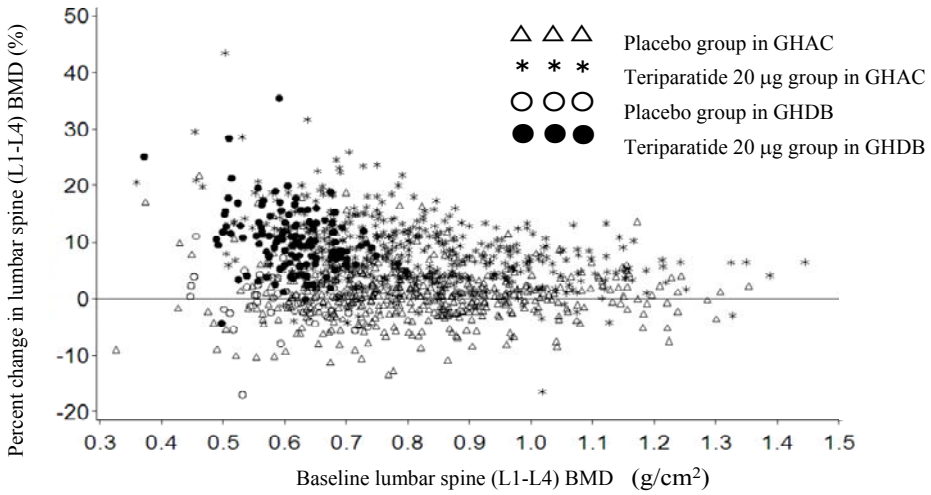


Figure 11. Relationship between baseline lumbar spine (L1-L4) BMD and percent changes in lumbar spine (L1-L4) BMD at Month 12

4.(iii).B.(2).3).(a).ii) Comparison of Japanese phase II study (GHCS) with study to be bridged

The applicant explained as follows:

The dose-response relationship for the percent changes from baseline to Month 6 in lumbar spine (L1-L4) BMD in Study GHCS and GHAC were as shown in Figure 12 and the percent changes in lumbar spine (L1-L4) BMD were greater with increasing dose of teriparatide in both studies.

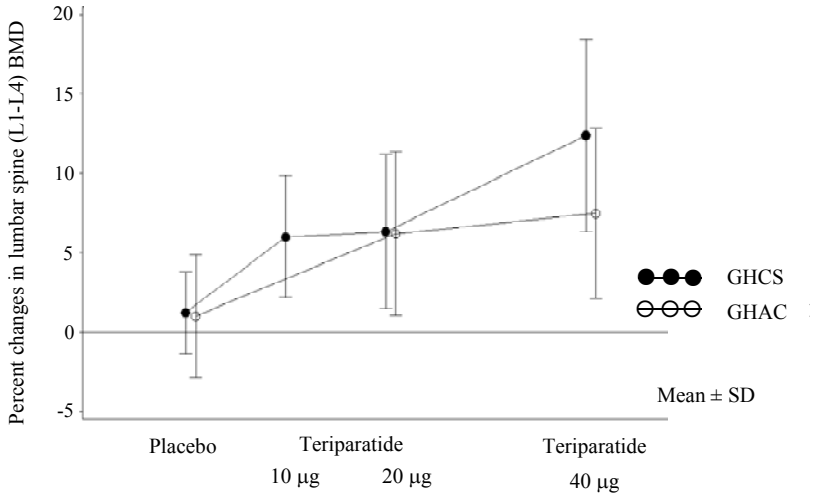


Figure 12. Dose-response relationship for percent changes from baseline to Month 6 in lumbar spine (L1-L4) BMD

4.(iii).B.(2).3).(a).iii) Relationship between gender and BMD-increasing effect

The applicant compared a foreign study in postmenopausal women with osteoporosis (a study to be bridged) (GHAC) with a foreign phase III study in men with primary osteoporosis (GHAJ) and explained as follows:

The time courses of the percent changes in lumbar spine (L1-L4) BMD in Studies GHAC and GHAJ were as shown in Figure 13 and the percent changes from baseline to Month 12 in lumbar spine (L1-L4) BMD (mean ± SD) in the placebo and teriparatide 20 µg groups were 0.84 ± 4.87% and 8.25 ± 6.10%, respectively, in Study GHAC and 0.58 ± 4.22% and 6.07 ± 4.50%, respectively, in Study GHAJ. The difference between the teriparatide 20 µg and placebo groups for the percent changes from baseline to Month 12 in lumbar spine

(L1-L4) BMD was 7.41 ± 5.52% in Study GHAC, which was higher than 5.49 ± 4.36% in Study GHAJ. This seemed to reflect higher baseline lumbar spine (L1-L4) BMD in men than in women because baseline lumbar spine (L1-L4) BMD in the placebo and teriparatide 20 μg groups combined was higher in Study GHAJ, i.e. 0.8205 ± 0.1692 g/cm^2 in Study GHAC and 0.8735 ± 0.1449 g/cm^2 in Study GHAJ.

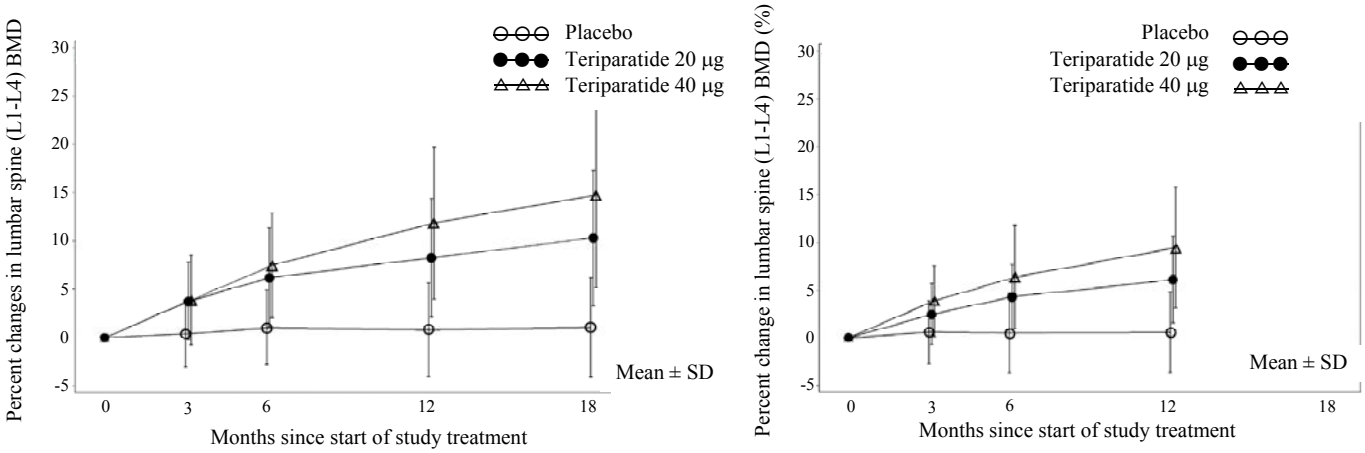


Figure 13. Time course of percent changes in lumbar spine (L1-L4) BMD (Left: Study GHAC; Right: Study GHAJ)

In Japanese Study GHDB, the data from 14 men were compared with the data from all subjects. Increases in lumbar spine (L2-L4) BMD were observed in all men treated with teriparatide and the percent change in lumbar spine (L2-L4) BMD at Month 12 in men treated with teriparatide 20 μg (9.99 ± 4.55%) was similar to that in all subjects treated with teriparatide 20 μg (9.82 ± 5.36%). On the other hand, the percent change in lumbar spine (L1-L4) BMD in foreign men treated with teriparatide 20 μg in Study GHAJ was 5.73 ± 4.46%. The percent change in lumbar spine (L1-L4) BMD was greater in Study GHDB as compared with Study GHAJ, which was considered due to lower baseline lumbar spine (L1-L4) BMD in men in Study GHDB as compared with Study GHAJ (Study GHAJ, 0.8735 ± 0.1449 g/cm^2; Study GHDB, 0.6221 ± 0.0736 g/cm^2). Since there were limited number of men whose lumbar spine BMD at Month 12 was available in Study GHDB (3 subjects in the placebo group, 8 subjects in the teriparatide 20 μg group), a definitive conclusion could not be drawn from the comparison of the data from men in Study GHDB with the data from Study GHAJ (male subjects studied) with respect to the difference between the teriparatide 20 μg and placebo groups for the percent changes in lumbar spine (L1-L4) BMD.

4.(iii).B.(2).3).(b) Effects on biochemical markers of bone metabolism

The applicant explained as follows:

The efficacy evaluation data were used to compare effects on biochemical markers of bone metabolism among the studies. In Japanese Study GHCS, as serum PINP was above the upper limit of quantification and serum CTX was below the detection limit, these values were unmeasurable. Moreover, there were many missing values for serum BAP due to mishandling of samples at the laboratory. Generally, biochemical markers of bone metabolism above the upper limit of quantification or below the detection limit are considered as a reflection of changes in biochemical markers of bone metabolism. Thus, it was considered inappropriate to assess effects on biochemical markers of bone metabolism using the percent changes

calculated from the obtained data. For this reason, serum concentrations of PINP, BAP, and CTX were used for assessment in Study GHCS. In 4 placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, GHAJ), following teriparatide treatment, increases in bone formation markers occurred first and increases in bone resorption markers occurred later. The percent changes in bone formation markers were greater than the percent changes in bone resorption markers. Furthermore, in active-controlled studies GHBM (evaluation data) and GHBZ (reference data), there were increases in markers of bone formation and resorption in the teriparatide group while there were decreases in markers of bone formation and resorption in the alendronate group (an antiresorptive drug). In 3 studies conducted in Asia (GHCB, GHCC, GHCF; all reference data), increases in biochemical markers of bone metabolism were shown following treatment with teriparatide.

4.(iii).B.(2).3).(c) Safety

The applicant performed pooled analyses of adverse events reported in 2 Japanese studies (GHCS, GHDB) and 3 foreign studies (GHAC, GHAJ, GHBM). The data from all the teriparatide groups combined (Japanese studies, 10 μg, 20 μg, 40 μg; foreign studies, 20 μg, 40 μg) and the data of the teriparatide 20 μg groups combined were analyzed separately. The results of a pooled analysis of data from subjects treated with teriparatide 20 μg are shown below.

4.(iii).B.(2).3).(c).i) Results of pooled analysis of data from subjects treated with teriparatide 20 μg in 2 Japanese studies (GHCS, GHDB)

The applicant explained as follows:

Adverse events with an incidence of ≥2% in the teriparatide 20 μg groups combined were as shown in Table 41, of which adverse events with an incidence of ≥5% and with a higher incidence than placebo were constipation, dizziness, headache, osteoarthritis, arthralgia, contusion, and upper respiratory tract inflammation.

Table 41. Adverse events with an incidence of ≥2% in the pooled teriparatide 20 μg group (GHCS and GHDB)

Adverse event term (MedDRA PT)	GHCS Teriparatide 20 μg group (n = 39)	GHDB Teriparatide 20 μg group (n = 136)	Pooled teriparatide 20 μg group (n = 175)	Placebo group (n = 105)
Nasopharyngitis	9 (23.1)	38 (27.9)	47 (26.9)	37 (35.2)
Back pain	0 (0.0)	17 (12.5)	17 (9.7)	14 (13.3)
Constipation	2 (5.1)	10 (7.4)	12 (6.9)	3 (2.9)
Dizziness	3 (7.7)	8 (5.9)	11 (6.3)	4 (3.8)
Headache	1 (2.6)	9 (6.6)	10 (5.7)	4 (3.8)
Osteoarthritis	1 (2.6)	9 (6.6)	10 (5.7)	4 (3.8)
Arthralgia	1 (2.6)	8 (5.9)	9 (5.1)	4 (3.8)
Contusion	1 (2.6)	8 (5.9)	9 (5.1)	4 (3.8)
Fall	0 (0.0)	9 (6.6)	9 (5.1)	7 (6.7)
Upper respiratory tract inflammation	1 (2.6)	8 (5.9)	9 (5.1)	3 (2.9)
Seasonal allergy	0 (0.0)	8 (5.9)	8 (4.6)	5 (4.8)
Cystitis	0 (0.0)	7 (5.1)	7 (4.0)	2 (1.9)
Diarrhoea	1 (2.6)	6 (4.4)	7 (4.0)	3 (2.9)
Eczema	2 (5.1)	5 (3.7)	7 (4.0)	6 (5.7)
Pain in extremity	3 (7.7)	4 (2.9)	7 (4.0)	1 (1.0)
Dermatitis contact	1 (2.6)	5 (3.7)	6 (3.4)	4 (3.8)
Abdominal pain upper	3 (7.7)	2 (1.5)	5 (2.9)	2 (1.9)
Injection site reaction	0 (0.0)	5 (3.7)	5 (2.9)	8 (7.6)
Insomnia	2 (5.1)	3 (2.2)	5 (2.9)	2 (1.9)
Joint sprain	0 (0.0)	5 (3.7)	5 (2.9)	0 (0.0)
Nausea	4 (10.3)	1 (0.7)	5 (2.9)	5 (4.8)
Periodontitis	1 (2.6)	4 (2.9)	5 (2.9)	0 (0.0)
Tooth extraction	1 (2.6)	4 (2.9)	5 (2.9)	0 (0.0)
Arthropod sting	1 (2.6)	3 (2.2)	4 (2.3)	3 (2.9)
Back injury	0 (0.0)	4 (2.9)	4 (2.3)	1 (1.0)
Blood alkaline phosphatase increased	0 (0.0)	4 (2.9)	4 (2.3)	2 (1.9)
Blood uric acid increased	3 (7.7)	1 (0.7)	4 (2.3)	0 (0.0)
Dental caries	2 (5.1)	2 (1.5)	4 (2.3)	0 (0.0)
Dental treatment	1 (2.6)	3 (2.2)	4 (2.3)	0 (0.0)
Erythema	2 (5.1)	2 (1.5)	4 (2.3)	1 (1.0)
Gastroenteritis	0 (0.0)	4 (2.9)	4 (2.3)	1 (1.0)
Muscle spasms	1 (2.6)	3 (2.2)	4 (2.3)	1 (1.0)
Vomiting	2 (5.1)	2 (1.5)	4 (2.3)	3 (2.9)

n (Incidence %), MedDRA ver.11.0
Data at Month 6 for Study GHCS, Data at Month 12 for Study GHDB

4.(iii).B.(2).3).(c).ii) Results of pooled analysis of data from subjects treated with teriparatide 20 μg in 3 foreign studies (GHAC, GHAJ, GHBM)

The applicant explained as follows:

Adverse events with an incidence of ≥2% in the teriparatide 20 μg groups combined were as shown in Table 42, of which adverse events with an incidence of ≥5% and with a higher incidence than placebo were arthralgia, pain in extremity, nausea, headache, dizziness, nasopharyngitis, cough, constipation, muscle spasms, and diarrhoea.

Table 42. Adverse events with an incidence of ≥2% in the pooled teriparatide 20 μg group (GHAC, GHAJ, and GHBM)

Adverse event term (MedDRA PT)	GHAC Teriparatide 20 μg group (n = 541)	GHAJ Teriparatide 20 μg group (n = 151)	GHBM Teriparatide 20 μg group (n = 102)	Pooled teriparatide 20 μg group (n = 794)	Placebo (n = 691)
Back pain	84 (15.5)	13 (8.6)	26 (25.5)	123 (15.5)	132 (19.1)
Arthralgia	90 (16.6)	16 (10.6)	8 (7.8)	114 (14.4)	99 (14.3)
Pain in extremity	52 (9.6)	11 (7.3)	8 (7.8)	71 (8.9)	46 (6.7)
Nausea	50 (9.2)	8 (5.3)	11 (10.8)	69 (8.7)	44 (6.4)
Headache	44 (8.1)	9 (6.0)	12 (11.8)	65 (8.2)	51 (7.4)
Dizziness	47 (8.7)	5 (3.3)	9 (8.8)	61 (7.7)	38 (5.5)
Nasopharyngitis	32 (5.9)	14 (9.3)	12 (11.8)	58 (7.3)	37 (5.4)
Cough	35 (6.5)	8 (5.3)	3 (2.9)	46 (5.8)	35 (5.1)
Bronchitis	36 (6.7)	5 (3.3)	2 (2.0)	43 (5.4)	54 (7.8)
Constipation	32 (5.9)	5 (3.3)	6 (5.9)	43 (5.4)	29 (4.2)
Influenza	33 (6.1)	7 (4.6)	3 (2.9)	43 (5.4)	39 (5.6)
Muscle spasms	29 (5.4)	4 (2.6)	10 (9.8)	43 (5.4)	23 (3.3)
Diarrhoea	32 (5.9)	3 (2.0)	6 (5.9)	41 (5.2)	32 (4.6)
Urinary tract infection	34 (6.3)	2 (1.3)	2 (2.0)	38 (4.8)	39 (5.6)
Dyspepsia	25 (4.6)	4 (2.6)	7 (6.9)	36 (4.5)	24 (3.5)
Depression	20 (3.7)	8 (5.3)	6 (5.9)	34 (4.3)	17 (2.5)
Fatigue	24 (4.4)	7 (4.6)	1 (1.0)	32 (4.0)	30 (4.3)
Musculoskeletal pain	20 (3.7)	6 (4.0)	5 (4.9)	31 (3.9)	22 (3.2)
Insomnia	25 (4.6)	4 (2.6)	1 (1.0)	30 (3.8)	25 (3.6)
Abdominal pain	26 (4.8)	0 (0.0)	2 (2.0)	28 (3.5)	31 (4.5)
Asthenia	23 (4.3)	4 (2.6)	1 (1.0)	28 (3.5)	14 (2.0)
Vomiting	21 (3.9)	2 (1.3)	5 (4.9)	28 (3.5)	18 (2.6)
Oedema peripheral	20 (3.7)	3 (2.0)	4 (3.9)	27 (3.4)	36 (5.2)
Pneumonia	21 (3.9)	3 (2.0)	3 (2.9)	27 (3.4)	21 (3.0)
Abdominal pain upper	18 (3.3)	3 (2.0)	4 (3.9)	25 (3.1)	17 (2.5)
Chest pain	20 (3.7)	3 (2.0)	1 (1.0)	24 (3.0)	23 (3.3)
Fall	17 (3.1)	6 (4.0)	1 (1.0)	24 (3.0)	30 (4.3)
Vertigo	22 (4.1)	2 (1.3)	0 (0.0)	24 (3.0)	17 (2.5)
Dyspnoea	20 (3.7)	3 (2.0)	0 (0.0)	23 (2.9)	15 (2.2)
Pharyngolaryngeal pain	16 (3.0)	5 (3.3)	1 (1.0)	22 (2.8)	14 (2.0)
Cystitis	17 (3.1)	2 (1.3)	1 (1.0)	20 (2.5)	27 (3.9)
Hypercholesterolaemia	15 (2.8)	3 (2.0)	2 (2.0)	20 (2.5)	16 (2.3)
Neck pain	16 (3.0)	2 (1.3)	2 (2.0)	20 (2.5)	21 (3.0)
Osteoarthritis	16 (3.0)	4 (2.6)	0 (0.0)	20 (2.5)	30 (4.3)
Rash	14 (2.6)	3 (2.0)	3 (2.9)	20 (2.5)	13 (1.9)
Cataract	13 (2.4)	4 (2.6)	1 (1.0)	18 (2.3)	20 (2.9)
Myalgia	13 (2.4)	3 (2.0)	2 (2.0)	18 (2.3)	22 (3.2)
Upper respiratory tract infection	11 (2.0)	3 (2.0)	4 (3.9)	18 (2.3)	24 (3.5)
Angina pectoris	16 (3.0)	0 (0.0)	0 (0.0)	16 (2.0)	10 (1.4)
Cataract operation	12 (2.2)	4 (2.6)	0 (0.0)	16 (2.0)	7 (1.0)
Sinusitis	14 (2.6)	1 (0.7)	1 (1.0)	16 (2.0)	24 (3.5)

n (Incidence %), MedDRA ver.11.0

As shown above, when the results of the pooled analysis from 2 Japanese studies were compared with the results of the pooled analysis from 3 foreign studies, the trend of occurrence of common adverse events in the pooled teriparatide 20 μg groups was similar between these analyses, and there was no trend towards the occurrence of adverse events unique to Japan. The safety of teriparatide was considered similar between Japan and overseas. This was also true when the results of a pooled analysis of data from subjects treated with teriparatide (all dose groups) were compared between Japan and overseas.

PMDA asked the applicant to explain any differences in the method of collecting safety information and data handling between Japan and overseas.

The applicant responded as follows:

The severity of adverse events was classified as mild, moderate, or severe in both Japan and overseas. Causality between an adverse event and the study drug was assessed using a 2-point scale (Related, Non-related) in Studies GHCS, GHDB, GHAJ, and GHBM, while a 4-point scale (None, Remote [Unlikely], Possible, Probable) was used in Study GHAC. However, since all adverse events other than those assessed as "None" were treated as "events for which a causal relationship to the study drug could not be ruled out," the classification difference was not considered to affect the assessment of the similarity of adverse events. Although the definition of serious adverse events was almost the same in all studies, cancer and overdose were also defined as serious adverse events in Study GHAC, but not in Study GHDB. However, this difference is not considered to have affected the incidence of cancers in Studies GHDB and GHAC and handling of overdose also is not considered to affect safety assessment.

Concerning the method of counting and analyzing adverse events, event terms were coded in MedDRA LLTs in Japanese Studies GHCS and GHDB. A medical review of coding (reported terms coded in LLTs) was conducted by the sponsor's medical experts. MedDRA was used also for Foreign Study GHBM, while COSTART was used as an adverse event dictionary during the conduct of Studies GHAC and GHAJ. Then, in order to use MedDRA as a unified terminology for reporting adverse events, events entered in the CRFs were re-coded to MedDRA LLTs and a medical review of coding was conducted by the sponsor's medical experts as in the Japanese studies. Adverse events in these studies were tabulated using a dictionary and a version that were available at the time of preparing a clinical study report, resulting in the use of different dictionaries or different versions of MedDRA. For more appropriate comparison of adverse events among the studies, the assigned LLTs were linked to PTs or SOCs (higher in the hierarchy) using the same version of MedDRA and the results of retabulation were presented in the CTD. In all studies, treatment-emergent adverse events were assessed and the number and proportion of subjects with adverse events in each treatment group were compared by PT or SOC. Based on the above, there should be no particular differences in the tabulation and analysis of adverse events.

While predose and 4- to 6-hour postdose serum calcium were measured in Foreign Studies GHAC and GHAJ and Japanese Study GHCS, only predose serum calcium was measured in Japanese Study GHDB. Serum calcium was not measured at 4 to 6 hours postdose in Study GHDB because clinically relevant elevation of serum calcium or hypercalcaemia was not observed following treatment with teriparatide in Study GHCS, which was conducted before the initiation of Study GHDB. Whether or not 4- to 6-hour postdose serum calcium had been measured had little impact on the reported incidence of hypercalcaemia and would not affect the similarity assessment.

Although the method of antibody response assessment (the criteria for antibody positivity) was different between Japan and overseas, antibody formation did not affect efficacy or safety in any study.

As described above, there should be no relevant differences in the method of collecting safety information or data handling between Japan and overseas.

4.(iii).B.(2).4) PMDA's conclusion on the ability to extrapolate foreign clinical data

With respect to the applicant's assessment results mentioned in Sections 4.(iii).B.(2).1), 4.(iii).B.(2).1), and 4.(iii).B.(2).3), PMDA considers as follows:

"4.(iii).B.(2).1) Similarity of pharmacokinetics": The applicant's explanation (the exposure to teriparatide was increased in Japanese subjects than in Caucasian subjects in Study GHCO in Japanese and Caucasian healthy women [see "4.(ii).A.(1).1) Pharmacokinetics and pharmacodynamics in healthy volunteers (a)"] and the observed pharmacokinetic differences were due to differences in body weight) is understandable. However, as it is important to investigate the impact of the differences in exposure on the assessment, pharmacokinetic similarity was assessed via the analyses of the similarities of efficacy and safety (to be described later).

"4.(iii).B.(2).2) Similarities of intrinsic and extrinsic ethnic factors": Although there were differences between Japan and overseas in body weight, measurement sites in the lumbar vertebrae for BMD measurement, and baseline lumbar spine BMD, the submitted data have suggested that these differences do not substantially affect the assessment [see Figure 9 and Figure 11; the impact of body weight-related exposure on assessment is described later]. There are some differences in the use of osteoporosis drugs; active vitamin D_3 preparations are commonly used in Japan but not in foreign countries. Differences are also observed in the clinical trial environment, e.g. bone biopsies were performed at selected sites in foreign clinical studies of teriparatide but not in Japanese clinical studies. However, taking also into account that sodium risedronate hydrate (a bisphosphonate) and raloxifene (SERM) have already been approved based on the extrapolation of foreign clinical data in the osteoporosis area, these differences do not substantially affect the assessment of teriparatide.

"4.(iii).B.(2).3) Similarities of efficacy and safety": Serum BAP was the only biochemical marker of bone metabolism assessed in both Studies GHDB (a bridging study) and GHAC (a study to be bridged), and none of the markers were common to all of 4 placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, GHAJ), and the markers common to 3 studies were serum BAP (GHDB, GHAC, GHAJ) and serum PICP (GHCS, GHAC, GHAJ) only. Although this fact does not deny the effect of teriparatide in improving bone turnover observed in the 4 individual studies, as biochemical markers of bone metabolism that can be assessed for similarity are limited, etc., it is difficult to reach a definite conclusion that effects on biochemical markers of bone metabolism are similar between Japan and overseas.

In BMD-increasing effect, although there were some differences in the study designs between Japanese Study GHDB (a bridging study) and Foreign Study GHAC (a study to be bridged) [see "4.(iii).A.(3) Phase III or IV studies 1) and 2)" and Table 39], the percent changes in lumbar spine (L1-L4) BMD at Month 12 (mean difference vs. placebo) were as high as ≥7% in both studies. In placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, and GHAJ), there were no major differences between Japan and overseas in the percent changes from baseline in lumbar spine (L1-L4) BMD by visit (Table 43).

Table 43. Percent changes from baseline in lumbar spine (L1-L4) BMD by visit
in placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, GHAJ)

Visit	Placebo	Teriparatide 10 μg	Teriparatide 20 μg	Teriparatide 40 μg
Japanese Study GHCS				
Month 3	1.11 ± 2.68 (36)	3.65 ± 4.10 (37)	4.13 ± 3.67 (39)	8.09 ± 4.53 (32)
Month 6	1.25 ± 2.56 (34)	6.01 ± 3.84 (36)	6.35 ± 4.86 (37)	12.40 ± 6.05 (27)
Last observation	0.94 ± 2.75 (37)	5.64 ± 4.42 (37)	6.19 ± 4.88 (39)	11.88 ± 5.63 (33)
Japanese Study GHDB (Bridging study) [a)]				
Month 3	1.00 ± 2.89 (63)	—	4.67 ± 3.45 (131)	—
Month 6	0.91 ± 3.17 (61)	—	7.63 ± 4.37 (127)	—
Month 12	0.23 ± 4.44 (60)	—	10.43 ± 5.61 (121)	—
Last observation	0.11 ± 4.42 (63)	—	10.23 ± 5.74 (131)	—
Foreign Study GHAC (Study to be bridged)				
Month 3	0.42 ± 3.50 (170)		3.78 ± 4.01 (165)	3.89 ± 4.66 (165)
Month 6	1.02 ± 3.88 (173)		6.22 ± 5.14 (162)	7.47 ± 5.37 (163)
Month 12	0.84 ± 4.86 (467)		8.26 ± 6.11 (466)	11.87 ± 7.84 (452)
Month 18	1.06 ± 5.16 (429)		10.31 ± 6.97 (410)	14.76 ± 9.61 (407)
Last observation	1.13 ± 5.47 (504)		9.70 ± 7.41 (498)	13.73 ± 9.69 (497)
Foreign Study GHAJ [b)]				
Month 3	0.61 ± 3.31 (141)		2.44 ± 3.21 (139)	3.87 ± 3.71 (127)
Month 6	0.52 ± 4.18 (139)		4.29 ± 3.41 (134)	6.33 ± 5.40 (120)
Month 12	0.58 ± 4.22 (133)		6.07 ± 4.50 (127)	9.41 ± 6.30 (111)
Last observation	0.54 ± 4.19 (143)		5.73 ± 4.46 (141)	8.75 ± 6.25 (129)

Mean ± SD % (n)
a) The results from Period 1 (double-blind comparative phase) are presented for Study GHDB.
b) For LOCF analysis for Study GHAJ, the last postbaseline data (prior to and including Month 12) for each subject are presented.

When a bridging strategy is used in the osteoporosis area, as a rule, the bridging study needs to be designed in a way which allows a comparison with a study to be bridged (for study population, dose levels selected, duration of treatment, etc.), and the study should be conducted with an endpoint of changes in BMD for about 2 years. Based on the results of these studies, the similarity between Japan and overseas should be assessed to determine whether foreign clinical data (fracture prevention effect) can be extrapolated to the Japanese population. Also, in such osteoporosis bridging study, the assessment of fracture prevention is required as a secondary endpoint. In contrast, there are no foreign data from a dose-finding study of teriparatide with the primary endpoint of BMD changes (in Japan, data on BMD changes were obtained from Study GHCS with 24-week treatment duration) and it is difficult to assess fracture prevention as a secondary endpoint in the Japanese phase II study, GHCS, in view of its duration of treatment (24 weeks). Furthermore, there were some differences in the study designs between Japanese Study GHDB (a bridging study) and Foreign Study GHAC (a study to be bridged) (Table 39), only one dose level of teriparatide was used in Japanese Study GHDB, and multiple foreign clinical studies such as GHAC were terminated early due to neoplastic bone lesions including osteosarcoma observed in rats, etc. Thus, difficulties in the assessment of the similarity between Japan and overseas cannot be denied. In such a case, clinical development in Japan (conduct of a Japanese phase III study to verify the fracture prevention efficacy of teriparatide) may be an option, but given that teriparatide has been approved overseas based on data including those from Foreign Study GHAC with the primary endpoint of fractures, that there have so far been no particular problems in foreign clinical experience with teriparatide, that no drug has been approved in Japan for patients with osteoporosis at high risk for fracture, and that there is a global consensus about the importance of the prevention of fractures in osteoporosis, etc., the conduct of another Japanese phase III study in Japanese patients with osteoporosis is not necessary to verify the fracture prevention efficacy of teriparatide. Taking

also into account that multiple foreign clinical studies were terminated early due to non-clinical findings and that the recommended clinical dose of teriparatide in Japan is expected to be 20 μg from an efficacy and safety standpoint, it is acceptable that considering that another Japanese study of multiple dose levels of ≥20 μg that could serve as a bridging study was not needed. The applicant assessment of the similarity between Japan and overseas is also acceptable as it was based on the data from placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, and GHAJ) in addition to Japanese Study GHDB and Foreign Study GHAC, instead of the data from Japanese Study GHDB and Foreign Study GHAC only. When the BMD-increasing effect of teriparatide 20 μg was assessed taking account of the above, based on Table 43, there were no major differences between Japan and overseas, as previously noted. In addition, Foreign Study GHAC produced consistent results regarding the relationship between BMD increases and fracture prevention for treatment with teriparatide 20 μg (Table 17 to Table 19).

The similarity in safety was assessed based on the data from placebo-controlled, double-blind, comparative studies (GHCS, GHDB, GHAC, GHAJ), an active-controlled study (GHBM), Japanese Study GHDB, Foreign Study GHAC, in addition to the data from the two bridging studies (GHDB and GHAC). This is considered acceptable because it is important to evaluate safety based on the data from as many patients as possible. Based on a pooled analysis of subjects treated with teriparatide 20 μg from 2 Japanese studies (Table 41) and a pooled analysis of subjects treated with teriparatide 20 μg from 3 foreign studies (Table 42), there were no major differences in safety between Japan and overseas. Therefore, a major safety concern is unlikely to arise when teriparatide 20 μg is administered to Japanese patients who have a lower body weight than foreign patients.

Taking account of the overall results of these assessments, the data from Foreign Study GHAC with the primary endpoint of "the proportion of subjects with new vertebral fractures", as a confirmatory study, can be extrapolated to the Japanese population. A final conclusion will be made taking account of comments from the Expert Discussion.

4.(iii).B.(3) Efficacy

4.(iii).B.(3).1) Prevention of new vertebral fractures

The applicant explained as follows:

In Study GHAC, as compared with the placebo group, the combined teriparatide group (the teriparatide 20 μg and 40 μg groups combined) experienced a significant reduction in the proportion of subjects with new vertebral fractures ($P < 0.001$, Pearson's χ^2 test). For an analysis of the proportion of subjects with new vertebral fractures, 311 subjects without evaluable X-ray film at baseline or the time of last observation (97 subjects in the teriparatide 20 μg group, 118 subjects in the teriparatide 40 μg group, 96 subjects in the placebo group) were excluded from the efficacy population. These subjects were classified as unevaluable subjects and a sensitivity analysis in which unevaluable subjects were included in the denominator was conducted. As a result, as shown in Table 44, the proportion of subjects with new vertebral fractures tended to be lower in the combined teriparatide group than in the placebo group.

Table 44. Proportion of subjects with new vertebral fractures (GHAC)

Treatment group		Proportion of subjects with new vertebral fractures [a)]	Ratio of proportion [95% CI]
Placebo		11.8 (64/544)	–
Combined teriparatide		3.8 (41/1093)	0.319 [0.218, 0.465]
	Teriparatide 20 μg	4.1 (22/541)	0.346 [0.216, 0.553]
	Teriparatide 40 μg	3.4 (19/552)	0.293 [0.178, 0.481]

a) Proportion % (No. of subjects with new vertebral fracture/No. of evaluable and unevaluable subjects)
b) Ratio of proportions of each teriparatide group to placebo group
CI: confidence interval

On the other hand, as Study GHAC was terminated early, the duration of study treatment varied from subject to subject. In light of the study population, the occurrence of a fracture is likely to be observed in subjects observed for a longer period of time. Taking account of these effects on assessment, a sensitivity analysis was conducted using person-time methods and, as shown in Table 45, the rate of new vertebral fractures tended to be lower in the combined teriparatide group than in the placebo group.

Table 45. Rate of new vertebral fractures (GHAC)

Treatment group		n	No. of patients with fracture	Total observation time (patient-years)	Rate	Ratio of rate[b)] [95% CI]
Placebo		448 [a)]	64	706.01	0.091	-
Combined teriparatide		878 [a)]	41	1378.02	0.030	0.328 [0.316, 0.341]
	Teriparatide 20 μg	444 [a)]	22	700.50	0.031	0.346 [0.326, 0.368]
	Teriparatide 40 μg	434 [a)]	19	677.52	0.028	0.309 [0.289, 0.331]

a) Subjects without evaluable X-ray film at baseline or at the time of last observation were excluded.
b) Ratio of rates of each teriparatide group to placebo group
CI: confidence interval

Based on the above, PMDA considers as follows:
As compared with the placebo group, the combined teriparatide group (the teriparatide 20 μg and 40 μg groups combined) experienced a significant reduction in the proportion of subjects with new vertebral fractures ($P < 0.001$, Pearson's χ^2 test) and a sensitivity analysis also showed that the risk of new vertebral fractures tended to be lower in the combined teriparatide group than in the placebo group. Thus, teriparatide is expected to prevent new vertebral fractures. In Study GHAC, 19.0% of subjects (311 of 1637 subjects) without evaluable X-ray film at baseline or the time of last observation had no significant effects on assessment, as shown by the above sensitivity analysis results, but measures to eliminate unevaluable cases as much as possible should have been taken.

Given that baseline lumbar spine (L1-L4) BMD was higher in Study GHAC than in the Japanese study, PMDA asked the applicant to explain whether the effect of teriparatide in preventing new vertebral fractures has been shown also in foreign subjects with baseline lumbar spine (L1-L4) BMD comparable to that of Japanese subjects, based on the results from Study GHAC.

The applicant responded as follows:
Baseline lumbar spine (L1-L4) BMD (mean ± SD) in the pooled treatment group was 0.8204 ± 0.1702 g/cm^2 in Study GHAC, which was higher than 0.6143 ± 0.0726 g/cm^2 in Study GHDB. As the maximum baseline lumbar spine (L1-L4) BMD in Study GHDB was 0.797 g/cm^2, a subgroup of subjects with baseline lumbar spine (L1-L4) BMD <0.8 g/cm^2 in Study GHAC were regarded as being comparable to the Japanese population and the effect of teriparatide in reducing new vertebral fractures in this subgroup was assessed

(Table 46). The proportion of subjects with new vertebral fractures was lower in the teriparatide group than in the placebo group at most study visits for identification of fractures.

Table 46. Occurrence of new vertebral fractures by baseline lumbar spine (L1-L4) BMD (GHAC)

Baseline lumbar spine (L1-L4) BMD	Days after the first dose (Study visit for identification of fractures)	Placebo	Teriparatide 20 μg	Teriparatide 40 μg
No measurement	0-365	0/0 (0)	0/0 (0)	1/2 (50.0)
	366-547	0/0 (0)	0/2 (0)	0/0 (0)
	548-730	4/7 (57.1)	0/3 (0)	1/7 (14.3)
	731-912	0/0 (0)	0/0 (0)	0/0 (0)
< 0.8 g/cm^2	0-365	2/11 (18.2)	1/14 (7.1)	0/13 (0)
	366-547	10/44 (22.7)	2/38 (5.3)	1/50 (2.0)
	548-730	26/148 (17.6)	11/175 (6.3)	8/150 (5.3)
	731-912	0/0 (0)	0/0 (0)	0/0 (0)
≥ 0.8 g/cm^2	0-365	2/10 (20.0)	0/8 (0)	0/10 (0)
	366-547	6/62 (9.7)	2/55 (3.6)	3/51 (5.9)
	548-730	14/165 (8.5)	6/148 (4.1)	5/150 (3.3)
	731-912	0/1 (0)	0/1 (0)	0/1 (0)

No. of subjects with fracture/No. of evaluable subjects (Incidence %)

4.(iii).B.(3).2) Prevention of atraumatic nonvertebral fractures

PMDA confirmed the following results:

In Study GHAC, the proportions of subjects with atraumatic nonvertebral fractures (atraumatic fractures are defined as those fractures caused by minimal trauma that normally would not have fractured a nonosteoporotic bone) were 5.5% (30 of 544 subjects) in the placebo group, 2.6% (14 of 541 subjects) in the teriparatide 20 μg group, and 2.5% (14 of 552 subjects) in the teriparatide 40 μg group. The ratio of the proportion of subjects with atraumatic nonvertebral fractures in the teriparatide 20 μg and 40 μg group to that in the placebo group [95% confidence interval] was 0.469 [0.252, 0.875] and 0.460 [0.247, 0.858], respectively. The proportion of subjects with atraumatic nonvertebral fractures tended to be lower in each teriparatide group than in the placebo group.

4.(iii).B.(3).3) Prevention of fractures in male patients

Since the difference between the teriparatide 20 μg and placebo groups in the percent change from baseline to Month 12 in lumbar spine (L1-L4) BMD was greater in Study GHAC (foreign postmenopausal patients with osteoporosis) than in Study GHAJ (foreign male patients with primary osteoporosis) [see "4.(iii).B.(2).3).(a) BMD-increasing effect" iii)], PMDA asked the applicant to explain gender differences in the efficacy of teriparatide (BMD-increasing effect) in detail.

The applicant responded as follows:

Baseline lumbar spine (L1-L4) BMD (mean ± SD) in the placebo and teriparatide 20 μg groups combined was 0.8735 ± 0.1449 g/cm^2 in Study GHAJ, which was higher than 0.8205 ± 0.1692 g/cm^2 in Study GHAC. As shown in Table 47, the percent change in lumbar spine (L1-L4) BMD at Month 12 tended to be greater with lower baseline lumbar spine (L1-L4) BMD in both women in Study GHAC and men in Study GHAJ. Therefore, as the relationship between the response to teriparatide (BMD-increasing effect) and baseline BMD was confirmed to be similar between the two studies, there should be no gender differences in lumbar spine BMD changes following treatment with teriparatide.

Table 47. Relationship between baseline lumbar spine (L1-L4) BMD and percent changes in lumbar spine (L1-L4) BMD at Month 12 (GHAC and GHAJ)

Baseline lumbar spine (L1-L4) BMD (g/cm^2)	Teriparatide 20 μg		Placebo	
	GHAC (Female subjects)	GHAJ (Male subjects)	GHAC (Female subjects)	GHAJ (Male subjects)
< 0.6	15.19 ± 8.36 (30)	—	1.83 ± 7.85 (37)	-1.36 ± 10.34 (8)
≥ 0.6 and < 0.9	8.94 ± 5.73 (301)	6.62 ± 5.02 (71)	0.81 ± 4.88 (291)	0.31 ± 3.53 (75)
≥ 0.9 and < 1.2	5.23 ± 4.43 (125)	5.36 ± 3.87 (49)	0.74 ± 3.63 (127)	1.27 ± 3.58 (49)
≥ 1.2	4.39 ± 3.13 (10)	5.49 ± 2.04 (7)	-0.33 ± 3.63 (12)	3.11 (1)

Mean ± SD % (n)

PMDA's view on 1) to 3) is as follows:

Foreign Study GHAC was terminated early because neoplastic bone lesions including osteosarcoma were observed in rats while the study was in progress. Thus, the data from subjects who did not complete the planned treatment duration (3-year treatment) were summarized. Meanwhile, teriparatide was approved based on the subsequent non-clinical and clinical study data in the US following discussions with the US FDA and as of January 2010, teriparatide has been approved in 83 countries or regions worldwide, including the EU. As previously mentioned, given that no drug indicated for patients with osteoporosis at high risk for fracture has been approved in Japan, that there is a global consensus about the importance of the prevention of fractures in osteoporosis, and that teriparatide stimulates bone formation and has been shown to increase lumbar spine BMD faster and to a greater extent as compared with alendronate (an antiresorptive drug) (Foreign Study GHBM, Figure 7), and taking account of the actual treatment duration in subjects enrolled into the study (Study GHAC, a median of 19 months) and the number of subjects, it is acceptable to assess the fracture prevention efficacy of teriparatide based on the data from Foreign Study GHAC. Based on the submitted data from this study (Table 17), and the results of sensitivity analyses on new vertebral fractures (Table 44 and Table 45), the fracture prevention efficacy of teriparatide 20 μg has been demonstrated. Generally, it takes at least 3 years to assess fracture prevention efficacy ("Guideline for the Clinical Evaluation of Antiosteoporosis Drugs" [PMSB/ELD Notification No. 742 dated April 15, 1999]), but the fracture prevention efficacy of teriparatide was assessed in subjects treated for a median of 19 months in Study GHAC, due to the early termination of the study for the reason as previously stated. The inclusion of the data from Study GHAC in the analysis is acceptable because (1) teriparatide has been approved overseas based on the data from studies including this study and (2) teriparatide stimulates bone formation and has been shown to increase lumbar spine BMD faster and to a greater extent as compared with alendronate (an antiresorptive drug) (Foreign Study GHBM, Figure 7), etc.

Although teriparatide 20 μg was shown to increase lumbar spine (L1-L4) BMD in male patients in the Foreign Study GHAJ (Table 22), the fracture prevention effect of teriparatide was not assessed in the study as it was not an objective of the study. Taking account of these points, the use of teriparatide 20 μg in male patients is not denied. However, it should be cautioned that the efficacy of teriparatide in male patients has not been established.

4.(iii).B.(4) Safety

PMDA concluded as follows:

As described in "4.(iii).B.(2) Clinical data package", based on a pooled analysis of subjects treated with

teriparatide 20 μg in 2 Japanese studies and a pooled analysis of subjects treated with teriparatide 20 μg in 3 foreign studies, there were no major differences in safety between Japan and overseas. Therefore, a major safety concern is unlikely to arise when teriparatide20 μg is administered to Japanese patients, who have a lower body weight than foreign patients, and the safety of teriparatide is acceptable.

PMDA further reviewed the following items.

4.(iii).B.(4).1) Relationship with tumor development

Neoplastic bone lesions including osteosarcoma were observed in a rat carcinogenicity study. PMDA asked the applicant to explain the risk of osteogenic tumors associated with teriparatide.

The applicant responded as follows:

In all clinical studies with teriparatide including post-marketing clinical studies, no occurrence of osteosarcoma was observed in Japanese or foreign subjects during treatment with teriparatide. As of November 26, 2008, the estimated number of patients who were exposed to teriparatide in clinical studies was 13,700. In a follow-up observational study GHBJ, safety was assessed for 5 years following the discontinuation of treatment in subjects who had participated in foreign phase III studies (7 studies), and no occurrence of osteosarcoma was reported in 1943 patients. The estimated number of patients exposed to teriparatide worldwide from November 26, 2002 (market launch) to November 26, 2008 was 651,000, which is equivalent to approximately 1.5 million patient-years. During this period, osteosarcoma was spontaneously reported by 5 patients. The time to diagnosis of osteosarcoma after teriparatide initiation in 4 patients were 14 months, <2 months, 3 months, and 11.5 months, and the remaining 1 subject had preexisting osteosarcoma. The rate of spontaneously reported osteosarcoma was almost comparable to the background rate of osteosarcoma in the general population aged ≥60 years (approximately 4 per 1,000,000 person-years), which is the candidate population for teriparatide therapy (Surveillance Epidemiology and End Results Database: SEER Database). Furthermore, a surveillance study, GHBX, has been ongoing since 2003 to identify newly diagnosed cases of osteosarcoma among men and women 40 years and older and to retrospectively determine whether they have a history of teriparatide treatment. As of December 15, 2008, 1025 patients with osteosarcoma were enrolled in the study in the US, of whom 461 patients completed the study. Also in 5 European countries, a similar surveillance study has been undertaken and 62 of 89 patients with osteosarcoma completed the study. In either study, no cases of osteosarcoma were identified in patients who have a history of teriparatide treatment. It is estimated that 69% of patients with newly diagnosed cases of osteosarcoma in the US have been enrolled into this study. The study was initially planned to be continued for 10 years until 2013, but is now extended to 15 years until 2018. In conclusion, the Study GHBJ, spontaneous reporting during the 6-year post-marketing experience overseas, or Study GHBX has not suggested a causal relationship between teriparatide and the development of osteosarcoma and at present, teriparatide is unlikely to induce osteosarcoma in humans. The applicant is well aware of the importance of investigating the relationship between teriparatide and the development of osteosarcoma in Japanese patients and will continue to closely exchange information on foreign studies and spontaneous reporting with the US headquarters and carefully monitor post-marketing spontaneous reports.

PMDA considers as follows:

Although the applicant's response (no findings suggesting the relationship between teriparatide and the development of osteosarcoma have so far been obtained, primarily from foreign clinical experience) is acceptable, prior to the initiation of treatment with teriparatide, it is necessary to confirm, based on the patient's condition and medical history, etc., that the patient is not at increased baseline risk for osteosarcoma (teriparatide is not contraindicated in the patient) and to fully examine the appropriateness of selecting teriparatide as a therapeutic drug from a risk/benefit standpoint. Given that clinical experience with teriparatide in Japanese patients is limited and that an increased exposure to teriparatide has been suggested in Japanese patients who have a lower body weight than Caucasian patients, it is necessary to continue to carefully investigate the relationship between teriparatide and the development of osteosarcoma in Japanese patients via post-marketing surveillance as well as other studies including the Foreign Study GHBX. Based on the above, the appropriateness of contraindications relating to osteosarcoma specified in the package insert is to be determined taking account of comments from the Expert Discussion.

4.(iii).B.(4).2) Hypercalcaemia

The applicant explained as follows:

PTH is known as a hormone that controls calcium homeostasis. In the Study GHCS and the Studies GHAC and GHAJ in foreign countries, serum calcium concentration increased transiently 4 to 6 hours after dosing of teriparatide. Increased serum calcium concentration returned to baseline prior to the next dose while no persistent hypercalcaemia was observed, and therefore increases in calcium level were not considered of clinical relevance. In Japanese Study GHDB, increases from baseline in serum calcium and corrected serum calcium (both medians) were observed in the placebo and teriparatide 20 μg groups, but the magnitude of the increases was small. In Japanese and foreign placebo-controlled studies, hypercalcaemia was not observed in the placebo groups but observed in 1 teriparatide-treated subject each in Studies GHDB, GHAC, and GHAJ, 3 teriparatide-treated subjects in Study GHBM, and 32 teriparatide-treated subjects in Study GHCA. In Study GHCA, the upper limit of normal of serum calcium was defined site by site, and a serum calcium level exceeding the upper limit of normal was reported as hypercalcaemia. Increased serum calcium is a pharmacological effect of PTH. Teriparatide increased serum calcium (though transiently), and hypercalcaemia was reported though at a low frequency. Thus, patients should be fully informed of the elevation of serum calcium level. Patients should also be advised to stop the use of teriparatide and consult their physicians promptly when any symptom of suspected persistent elevation of serum calcium level is observed. As teriparatide in combination with active vitamin D_3 preparations may further increase serum calcium, it is recommended that teriparatide should not be used with active-form vitamin D_3 preparations. From a safety point of view, the following precaution statement will be included in the package insert: if marked, persistent hypercalcaemia is noted even within 16 hours after dosing of teriparatide, the patient should be monitored for symptoms such as nausea/vomiting, constipation, lethargy, and muscular weakness and promptly treated in an appropriate manner.

PMDA accepts the applicant's response that the inclusion of a precaution statement regarding hypercalcaemia associated with teriparatide in the "Important Precautions" section of the package insert is appropriate. Nevertheless, information on hypercalcaemia should be further collected via post-marketing surveillance.

4.(iii).B.(4).3) Gastrointestinal disorders

PMDA asked the applicant to explain gastrointestinal disorders associated with teriparatide in view of increased cAMP, Ca^{2+} change, and effects on smooth muscle.

The applicant responded as follows:

PTH has been reported to increase cAMP via adenylyl cyclase and relax smooth muscles in the gastrointestinal tract (Pang PKT, In:Massry SG, Fujita T. *eds*. New actions of parathyroid hormone. New York: Plenum Press. 1989). Increases in teriparatide blood concentration after dosing are transient and teriparatide is not considered to cause persistent relaxation of gastrointestinal smooth muscle or persistent hypercalcaemia that leads to gastrointestinal disorders. However, the incidences of nausea, vomiting, constipation, diarrhoea, abdominal pain, abdominal pain upper, abdominal pain lower, and gastroenteritis in Japanese and foreign clinical studies were assessed. According to a pooled analysis of Japanese Studies GHCS and GHDB, the incidences of the above-mentioned adverse events in the placebo and teriparatide 20 μg groups were 4.8% (5 of 105 subjects) and 2.9% (5 of 175 subjects), respectively, for nausea; 2.9% (3 of 105 subjects) and 2.3% (4 of 175 subjects), respectively, for vomiting; 2.9% (3 of 105 subjects) and 6.9% (12 of 175 subjects), respectively, for constipation; 2.9% (3 of 105 subjects) and 4.0% (7 of 175 subjects), respectively, for diarrhoea; 1.0% (1 of 105 subjects) and 1.1% (2 of 175 subjects), respectively, for abdominal pain; 1.9% (2 of 105 subjects) and 2.9% (5 of 175 subjects), respectively, for abdominal pain upper; 0% and 0.6% (1 of 175 subjects), respectively, for abdominal pain lower; and 1.0% (1 of 105 subjects) and 2.3% (4 of 175 subjects), respectively, for gastroenteritis. The incidences of constipation, diarrhoea, abdominal pain, abdominal pain upper, abdominal pain lower, and gastroenteritis tended to be higher in the teriparatide 20 μg group than in the placebo group. None of these adverse events reported more frequently in the teriparatide 20 μg group were severe. On the other hand, according to a pooled analysis of Foreign Studies GHAC, GHAJ, and GHBM, the incidences of the above-mentioned adverse events in the placebo and teriparatide 20 μg groups were 6.4% (44 of 691 subjects) and 8.7% (69 of 794 subjects), respectively, for nausea; 2.6% (18 of 691 subjects) and 3.5% (28 of 794 subjects), respectively, for vomiting; 4.2% (29 of 691 subjects) and 5.4% (43 of 794 subjects), respectively, for constipation; 4.6% (32 of 691 subjects) and 5.2% (41 of 794 subjects), respectively, for diarrhoea; 4.5% (31 of 691 subjects) and 3.5% (28 of 794 subjects) , respectively, for abdominal pain; 2.5% (17 of 691 subjects) and 3.1% (25 of 794 subjects), respectively, for abdominal pain upper; 0.4% (3 of 691 subjects) and 0.3% (2 of 794 subjects), respectively, for abdominal pain lower; and 1.0% (7 of 691 subjects) and 0.8% (6 of 794 subjects), respectively, for gastroenteritis. The incidences of nausea, vomiting, constipation, diarrhoea, and abdominal pain upper tended to be higher in the teriparatide 20 μg group than in the placebo group. Among these adverse events reported more frequently in the teriparatide 20 μg group, only serious cases were compared. As a result, no serious events were reported more frequently in the teriparatide 20 μg group than in the placebo group. Based on the above, a causal

relationship between relaxation of gastrointestinal smooth muscle via increased cAMP or elevation of blood calcium, which can be caused by the pharmacological effect of teriparatide, and gastrointestinal disorders cannot be ruled out. However, among the aforementioned adverse events reported at a higher incidence with teriparatide, none of them were serious.

PMDA accepts the applicant's response. However, teriparatide has a pharmacological effect that may increase cAMP causing the relaxation of gastrointestinal smooth muscle or the elevation of blood calcium, for which a causal relationship with gastrointestinal disorders cannot be ruled out. In view of the above clinical study results, information on gastrointestinal disorders should be further collected via post-marketing surveillance.

4.(iii).B.(4).4) Cardiovascular disorders

PMDA asked the applicant to explain the effects of teriparatide on the cardiovascular system.

The applicant responded as follows:

PTH has been reported to lower blood pressure by relaxing vascular smooth muscle via adenylyl cyclase and have positive chronotropic and positive inotropic effects on cardiac muscle (Mok LLS et al. *Endocr Rev*. 1989;10 (4): 420-436, Pang PKT In: Massry SG, Fujita T. eds. New actions of parathyroid hormone. New York: Plenum Press. 1989; p127-135). In clinical studies (evaluation data) (GHCS, GHDB, GHAC, GHAJ, GHBM, GHCA), the incidence of orthostatic hypotension with teriparatide 20 μg was 0.7% (1 of 136 subjects) in Study GHDB and 0.1% (1 of 866 subjects) in Study GHCA and both were mild in severity. According to a pooled analysis of Japanese Studies GHCS and GHDB, cerebral infarction, cerebral circulatory failure, stroke, cerebral haemorrhage, lacunar infarction, subarachnoid haemorrhage, angina pectoris, myocardial infarction, acute coronary syndrome, or cardiac failure was not reported and the incidences of other cerebral circulatory failure and cardiovascular adverse events in the placebo and teriparatide 20 μg groups were 1% (1 of 105 subjects) and 0% (0 of 175 subjects), respectively, for amnesia and 3.8% (4 of 105 subjects) and 6.3% (11 of 175 subjects), respectively, for dizziness. The incidence of dizziness tended to be higher in the teriparatide 20 μg group.

In Foreign Studies GHAC, GHAJ, GHCA, and GHBM, cardiovascular/cerebrovascular adverse events that occurred more frequently in subjects treated with teriparatide 20 μg or 40 μg than in placebo-treated subjects and at an incidence of ≥1.0% in the teriparatide 20 μg or 40 μg group were angina pectoris (28 of 1660 subjects [1.7%] in the teriparatide 20 μg group, 10 of 691 subjects [1.4%] in the teriparatide 40 μg group, 10 of 691 subjects [1.4%] in the placebo group), atrial fibrillation (12 of 1660 subjects [0.7%], 9 of 691 subjects [1.3 %], 4 of 691 subjects [0.6%]), palpitations (26 of 1660 subjects [1.6%], 18 of 691 subjects [2.6%], 8 of 691 subjects [1.2%]), tachycardia (13 of 1660 subjects [0.8%], 16 of 691 subjects [2.3%], 6 of 691 subjects [0.9%]), dizziness (105 of 1660 subjects [6.3%], 53 of 691 subjects [7.7%], 38 of 691 subjects [5.5%]), syncope (30 of 1660 subjects [1.8%], 4 of 691 subjects [0.6%], 7 of 691 subjects [1.0%]), hot flush (24 of 1660 subjects [1.4%], 4 of 691 subjects [0.6%], 3 of 691 subjects [0.4%]), hypotension (8 of 1660 subjects [0.5%], 11 of 691 subjects [1.6%], 7 of 691 subjects [1.0%]), and varicose vein (13 of 1660 subjects [0.8%],

13 of 691 subjects [1.9%], 8 of 691 subjects [1.2%]). These events were reported at an incidence of ≤1.0% as serious adverse events or were not reported as serious adverse events.

The incidence of dizziness was higher in the teriparatide group than in the placebo group in all of Japanese and foreign clinical studies and its relationship to the pharmacological effect of teriparatide cannot be ruled out. However, many of the events were mild to moderate in severity and no serious events were reported in Japanese clinical studies.

Based on the above, the incidences of serious cardiovascular/cerebrovascular adverse events were low and teriparatide is not considered to affect the cardiovascular/cerebrovascular safety. Precaution information concerning dizziness is included in the "Important Precautions" section of the package insert.

PMDA considers as follows:
The inclusion of precaution information concerning orthostatic hypotension and dizziness in the package insert is appropriate. Given that PTH exerts its pharmacological effects on vascular smooth muscle and cardiac muscle, it is necessary to continue to collect information on cardiovascular disorders via post-marketing surveillance.

4.(iii).B.(4).5) Hyperuricemia
PMDA asked the applicant to explain the risk of increases in blood uric acid associated with teriparatide.

The applicant responded as follows:
PTH has been reported to have directly act to increase the renal tubular reabsorption of uric acid (Kippen I *et al. J Pharmacol Exp Ther*. 1977;201: 218-225), thereby reducing uric acid clearance (Dunzendorfer U and Schmidt-Gayk H. *Endokrinologie*. 1981; 77: 353-359). It is known that such effect of PTH increases blood uric acid concentrations in hyperparathyroidism. However, teriparatide is eliminated rapidly with an elimination half-life of approximately 1 hour, and the increase in blood uric acid concentrations is considered unrelated to the pathology of hyperparathyroidism. As patients with hyperuricemia were excluded from clinical studies with teriparatide, there are no data from hyperuricemia patients treated with teriparatide. Based on the data from 5 studies in which blood uric acid levels were assessed over time, blood uric acid levels at baseline and the last observation and changes from baseline to the last observation in blood uric acid levels were assessed. In all studies, blood uric acid tended to increase from baseline to the last observation in the teriparatide group. The proportions of subjects with blood uric acid concentrations above the upper limit of normal following study treatment were 12.9% (69 of 534 subjects) in the teriparatide 20 μg group, 17.5% (95 of 542 subjects) in the teriparatide 40 μg group, and 3.7% (20 of 536 subjects) in the placebo group in Study GHAC, 24.3% (33 of 136 subjects) in the teriparatide 20 μg group, 24.0% (29 of 121 subjects) in the teriparatide 40 μg group, and 5.8% (8 of 139 subjects) in the placebo group in Study GHAJ, 1.1% (1 of 94 subjects) in the alendronate group and 1.0% (1 of 101 subjects) in the teriparatide 20 μg group in Study GHBM, 8.1% (3 of 37 subjects) in the teriparatide 10 μg group, 25.6% (10 of 39 subjects) in the teriparatide 20 μg group, 23.7% (9 of 38 subjects) in the teriparatide 40 μg group, and 0% (0 of 38 subjects) in the

placebo group in Study GHCS, and 19.1% (26 of 136 subjects) in the teriparatide 20 μg group and 4.5% (3 of 67 subjects) in the placebo group in Study GHDB. An adverse event of gout occurred in 6 subjects in Study GHAC, including 1 of 541 subjects (0.2%) in the teriparatide 20 μg group, 2 of 552 subjects (0.4%) in the 40 μg group, and 3 of 544 subjects (0.6%) in the placebo group. In Study GHAJ, gout occurred in 0 of 151 subjects (0%) in the teriparatide 20 μg group, 1 of 139 subjects (0.7%) in the teriparatide 40 μg group and 1 of 147 subjects (0.7%) in the placebo group. In Studies GHBM, GHCS, GHDB, and GHCA, gout were not reported. These findings indicate that teriparatide tends to increase blood uric acid concentrations but does not induce high-blood-uric-acid-associated adverse events. However, taking into account that there are no data from patients with hyperuricemia treated with teriparatide, after the market launch, the applicant will pay close attention to hyperuricemia-related adverse drug reactions.

Given that the proportion of subjects with blood uric acid concentrations above the upper limit of normal was higher in the teriparatide group than in the placebo group in Study GHDB, PMDA considers that it is necessary to collect information on hyperuricemia via post-marketing surveillance.

4.(iii).B.(4).6) Nephrolithiasis

PMDA asked the applicant to explain the risk of nephrolithiasis associated with teriparatide.

The applicant responded as follows:

According to a pooled analysis of Foreign Studies GHAC, GHAJ, and GHBM, the incidences of nephrolithiasis were 0.4% (3 of 691 subjects) in the placebo group, 0.5% (4 of 794 subjects) in the teriparatide 20 μg group, and 0.1% (1 of 691 subjects) in the teriparatide 40 μg group. According to a pooled analysis of Japanese Studies GHCS and GHDB, the incidences of nephrolithiasis were 1.0% (1 of 105 subjects) in the placebo group, 0.6% (1 of 175 subjects) in the teriparatide 20 μg group, and 0% (0 of 39 subjects) in the teriparatide 40 μg group. In addition, the incidences of nephrolithiasis at the end of 18-month treatment in Study GHDB were 1.5% (1 of 67 subjects) in the placebo group and 0.7% (1 of 136 subjects) in the teriparatide 20 μg group. The incidence of nephrolithiasis did not increase in the teriparatide groups in Japanese or foreign studies.

PMDA considers as follows:

Given that teriparatide treatment resulted in the increased incidence of hypercalcaemia and increased blood uric acid, it is appropriate that the package insert recommends careful administration for patients with urolithiasis or a history of urolithiasis. It is necessary to continue to collect information on nephrolithiasis via post-marketing surveillance.

4.(iii).B.(4).7) Antibody formation

PMDA asked the applicant to explain antibody formation following treatment with teriparatide and the effects of antibody formation on the efficacy and safety of teriparatide.

The applicant responded as follows:

In Japanese clinical studies, a screening test and a confirmatory test were performed and antibody positivity was defined as a screening test result above a pre-specified threshold and inhibitory activity detected by a confirmatory test. In foreign clinical studies, 2 types of antibody test (binding assay and inhibition assay) were performed and antibody positivity was defined as a ≥2-fold increase from baseline in the binding assay and ≥40% inhibitory activity in the inhibition assay. During 18-month treatment in Study GHDB, 8 subjects in the teriparatide 20 μg group tested positive for antibodies. Of these, 6 subjects were tested positive also at baseline. BMD changes were similar between antibody-positive and antibody-negative subjects. No adverse events possibly associated with antibody formation such as hypoparathyroidism, hypocalcaemia, or hyperphosphataemia and no decrease in serum calcium below the lower limit of normal were observed in these subjects. All of the subjects who developed antibodies completed the 18-month study period. In Study GHAC, 1 subject (0.2%) in the placebo group, 15 subjects (2.8%) in the teriparatide 20 μg group, and 44 subjects (8.0%) in the teriparatide 40 μg group were tested positive at Month 3, Month 12, or the last observation. A subgroup analysis of antibody-positive vs. antibody-negative subjects showed no effects of antibody formation on serum calcium, adverse events, or BMD. There was no hypersensitivity or no allergic reaction in the antibody-positive subjects, even though they continued treatment with teriparatide after being found to be antibody-positive. When 51 of the 59 subjects with a positive antibody test at the end of the study were followed after the discontinuation of teriparatide, antibody-positive subjects decreased over time and 72% of the subjects were tested negative for antibodies by the end of the 54-month follow-up period. The changes in serum calcium (mean) during the follow-up period in antibody-positive subjects were 0.016 mmol/L in the teriparatide 20μg group and -0.087 mmol/L in the teriparatide 40 μg group, and the change was significant in the teriparatide 40 μg group (P = 0.5351 and P = 0.0001, respectively). However, none of the antibody-positive subjects had hypocalcaemia during the follow-up period. There were no clinically relevant changes in serum total protein or albumin in antibody-positive subjects. In Study GHAJ, no subjects were tested positive for antibodies throughout the study period.

PMDA considers as follows:
The applicant's explanation that antibody formation had no particular effects on the efficacy or safety of teriparatide in Japanese or foreign clinical studies is understandable. As the information on antibody formation in Japanese patients is limited, it is necessary to continue to collect information on antibody formation via post-marketing surveillance.

4.(iii).B.(5) Indication
PMDA asked the applicant to explain the relationship between the intended population for teriparatide (patients with osteoporosis at high risk for fracture) and the WHO quantitative fracture risk assessment tool (FRAX), which has recently been used in various countries.

The applicant responded as follows:
Based on an epidemiological study of the Japanese population, previous fracture, low BMD, and age have been reported to be the main risk factors for fracture also in FRAX. Based on T-scores for femoral neck BMD and age of Japanese women without risk factors, 10-year probabilities of fracture were assessed using

FRAX and showed that the FRAX value increases with increasing age and decreases with increasing T-score (Fujiwara S, et al. *Osteoporos Int.* 2008; 19: 429-435). Comparisons of 10-year probabilities of fracture in the presence of clinical risk factors of previous fracture, parental history of fracture, use of glucocorticoids, secondary osteoporosis, alcohol, and smoking have shown that the fracture probability is highest with the existence of previous fracture (Fujiwara S, et al. *Osteoporos Int.* 2008; 19: 429-435). Therefore, there should be no major differences between the fracture risk defined for the intended population for teriparatide and the fracture risk calculated using FRAX. However, limitations on the use of FRAX in determining thresholds for therapeutic intervention includes the following: (1) Thresholds need to be determined according to the medical environment and health economics in the country where FRAX is used; (2) FRAX may only be used in untreated osteoporotic patients; and (3) FRAX calculates a probability of fracture in the next 10 years, which means that fracture probabilities in elderly people with short life expectancy are underestimated. In addition to these limitations, there has so far been no consensus among relevant academic societies in Japan and overseas and the regulatory authorities on FRAX-based intervention thresholds, etc. Therefore, it is not appropriate to define the intended population for teriparatide by FRAX values at present.

PMDA considers the relationship between the definition of patients with osteoporosis at high risk for fracture and the quantitative fracture risk estimated by FRAX as follows:
The extent of the consistency between the actual risk and the future risk estimated with the use of the Japanese FRAX model for fractures in Japanese patients is to be assessed through a vast amount of accumulated data on teriparatide and other drugs including post-marketing data. Thus, the applicant's explanation that it is not appropriate to determine the intended population for teriparatide based on FRAX values at present is understandable. Although there is no major problem with the proposed indication of treatment of patients with osteoporosis at high risk for fracture, it is necessary to continue to review the appropriateness of the statement included in the Precautions for Indications, in view of the characteristics of patients included in clinical studies and the definition of fracture risk in Japan and overseas at the time of conducting clinical studies and at present. The above conclusions is to be finalized taking account of comments from the Expert Discussion.

4.(iii).B.(6) Dosage and administration

4.(iii).B.(6).1) Mode of administration

4.(iii).B.(6).1).(a) Dosing frequency

The applicant explained as follows:
As the skeletal effects (bone formation or resorption) of PTH (1-34) depend on dosing schedule, the relationship between daily dosing frequency of teriparatide and change in bone mass was investigated in rats. An efficacious dose of teriparatide (as a total daily dose of 80 μg/kg/day) had to be given in a single injection or multiple injections to induce an increase in bone mass. Multiple injections at said dose had to be delivered rapidly within a short time period. On the other hand, prolonged exposure to teriparatide by multiple subcutaneous injections over a 6-hour period rather resulted in significant loss of bone mass. These results confirmed that the once-daily dosing schedule of teriparatide is an important factor for inducing an increase in bone mass. In a clinical pharmacology study in foreign healthy adult subjects (11 men and 11 women)

(GHBI), 20, 40, and 80 μg of teriparatide were subcutaneously administered or 17.54 μg of teriparatide was intravenously administered and the absolute bioavailability of teriparatide administered by subcutaneous injection was estimated at approximately 95%. As the observed gender differences in AUC were attributable to differences in body weight and no gender differences in C_{max} or safety were observed, the differences in AUC were not considered of clinical relevance. A clinical pharmacology study in foreign postmenopausal healthy women (n = 24) (GHAD) showed that there was no accumulation of teriparatide after 14 days of once-daily subcutaneous administration of teriparatide 40 μg. Based on the above, once-daily dosing is justified.

PMDA considers that there is no problem with the proposed once-daily dosing regimen for teriparatide.

4.(iii).B.(6).1).(b) Injection site

PMDA asked the applicant to explain the appropriateness of the proposed injection sites for teriparatide (a wide area of the abdomen or thigh, etc.).

The applicant responded as follows:

Among subjects with serum teriparatide concentrations measured in Studies GHAC and GHAJ, 211 subjects and 156 subjects, respectively, subcutaneously injected teriparatide in the abdomen and 149 subjects and 95 subjects, respectively, subcutaneously injected teriparatide in the thigh. In both studies, although the C_{max} was slightly decreased when teriparatide was injected into the thigh relative to the abdomen, the differences in the C_{max} according to injection site were small (Figure 14), suggesting that whether teriparatide is subcutaneously injected into the abdomen or thigh is of no clinical relevance.

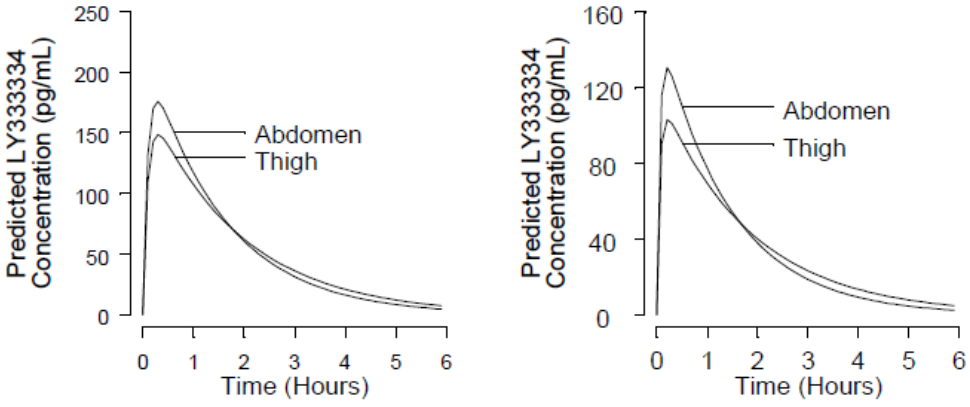


Figure 14. Predicted serum teriparatide concentrations following a single dose of teriparatide 20 μg in foreign female patients (GHAC; median body weight, 66 kg; Left) and foreign male patients (GHAJ; median body weight, 75 kg; Right)

Among subjects for whom the injection site of teriparatide was known in Studies GHAC and GHAJ, the different injection sites were compared for events reported by ≥5% of subjects in the pooled teriparatide 20 μg group from Studies GHAC, GHAJ, and GHBM. Except that nasopharyngitis was more commonly reported when teriparatide was injected into the abdomen (abdomen, 28 subjects [15.6%]; thigh, 6 subjects [4.3%]), no differences according to injection site were observed. Although teriparatide was not injected into

the thigh in Japanese clinical studies, it is unlikely that adverse events increase when teriparatide is injected into the thigh, as the C_{max} is expected to be lower when teriparatide is injected into the thigh relative to the abdomen. Based on the above, injecting teriparatide into the abdomen or thigh is appropriate. Taking into account that injection sites other than the abdomen or thigh have never been used, the "Precautions in use" section of the package insert will advise that teriparatide should be injected into the abdomen or thigh and that injection sites should be rotated regularly over an extensive area.

PMDA considers that there is no major problem with injecting teriparatide into the abdomen or thigh and that it is necessary to caution against consecutive injections into the same site. Thus, PMDA accepted the response.

4.(iii).B.(6).2) Dose

The applicant explained as follows:

In Japanese Study GHCS, the percent change from baseline to the last observation in lumbar spine (L2-L4) BMD (mean) was significantly higher at all dose levels of teriparatide than in the placebo group, i.e. 0.66% in the placebo group, 5.80% in the teriparatide 10 μg group, 6.40% in the teriparatide 20 μg group, and 11.47% in the teriparatide 40 μg group ($P < 0.001$ in all teriparatide treatment groups, Williams' test). Of the biochemical markers of bone metabolism (serum PINP, serum PICP, serum BAP, serum CTX), all markers of bone formation and resorption increased in the teriparatide 20 μg and 40 μg groups while a bone formation marker (serum BAP) and a bone resorption marker (serum CTX) did not increase in the teriparatide 10 μg group. Adverse events for which a causal relationship to study drug could not be ruled out and adverse events leading to discontinuation occurred more frequently in the teriparatide 40 μg group as compared with other treatment groups. Furthermore, in Period 1 (double-blind comparative phase) of Japanese Study GHDB, the efficacy (BMD-increasing effect) and good tolerability of teriparatide 20 μg subcutaneously administered for 12 months were confirmed. In Foreign Study GHAC, the ratio of the proportion of subjects with new vertebral fractures in the teriparatide 20 μg group to that in the placebo group was 0.347 [0.218, 0.553], showing that the proportion of subjects with new vertebral fractures was lower in the teriparatide 20 μg group than in the placebo group. Based on these findings, the proposed dose of 20 μg of teriparatide was justified.

PMDA considers as follows:

In Japanese Study GHCS, significant differences between the teriparatide and placebo groups were observed in the percent changes in lumbar spine (L2-L4) BMD as the primary endpoint. There was a trend towards dose-dependent increases in the percent changes in lumbar spine (L2-L4) BMD (Table 8). The percent changes in lumbar spine (L2-L4) BMD were similar to the percent changes in lumbar spine (L1-L4) BMD (Table 8, Table 10), and the incidence of adverse events was similar between the teriparatide 20 μg and 40 μg groups (20 μg group, 84.6%; 40 μg group, 82.1%), but the incidence of adverse drug reactions was higher in the teriparatide 40 μg group (20 μg group, 15.4%; 40 μg group, 41.0%). The mean difference between the teriparatide 20 μg and placebo groups in the percent changes in lumbar spine (L1-L4) BMD was greater in Japanese Study GHDB than in Foreign Study GHAC (Japanese Study GHDB, 10.20%; Foreign Study GHAC, 7.41%), but the percent change in lumbar spine (L1-L4) BMD was greater in the teriparatide 20 μg

group than in the placebo group in both studies. In Foreign Study GHAC, the ratio of the proportion of subjects with new vertebral fractures in the teriparatide 20 μg group to that in the placebo group [95% confidence interval] was 0.347 [0.218, 0.553] and the proportion was lower in the teriparatide 20 μg group than in the placebo group. Based on the findings above, there is no major problem with the proposed dose of 20 μg/day of teriparatide, which is the same as the approved dose overseas.

4.(iii).B.(6).3) Maximum duration of treatment

The applicant explained as follows:

Due to neoplastic bone lesions (including osteosarcoma) observed in a rat carcinogenicity study with teriparatide, Eli Lilly and Company decided to terminate all clinical studies with teriparatide. After that, no osteosarcoma was observed in a monkey long-term study. Osteosarcoma considered teriparatide-related was not reported in clinical studies with teriparatide or an observational follow-up study in subjects who had participated in the terminated clinical studies. Thus, osteosarcoma, which was observed in rats, is unlikely to occur in humans. However, as the risk of osteosarcoma in humans is unknown, it was decided to establish the maximum treatment duration based on the duration of treatment used in the past clinical studies. Teriparatide has been approved for a maximum treatment period of 24 months in the US and Europe. In Japan, on the premise that safety would be confirmed by 18-month data from Study GHDB, an application for approval of teriparatide with the maximum treatment duration of 18 months was filed and 18-month data were submitted later. Japanese Study GHDB was completed in September 2009 after an extension of treatment duration to 24 months to gain experience with 24 months of treatment with teriparatide.

PMDA considers as follows:

The risk of osteosarcoma cannot be completely excluded in humans. In foreign countries, teriparatide has been approved for the maximum treatment duration of 24 months based on the duration of treatment used in clinical studies in patients with osteoporosis with the mentioned risk being taken into account. Thus, also in Japan, the maximum duration of treatment should be 18 months based on the results of Japanese Study GHDB (18-month data evaluated in this review).

In addition, PMDA requested the applicant to specify the maximum duration of treatment in the "Dosage and Administration" section of the package insert also in Japan, because the relationship between teriparatide and the development of osteosarcoma is still being studied overseas and because the "DOSAGE AND ADMINISTRATION" section of the US label states that the use of the drug for more than 2 years during a patient's lifetime is not recommended and the "Posology and Method of Administration" section of the EU label states that the maximum total duration of treatment with the drug should be 24 months.

The applicant responded that the maximum duration of treatment is going to be specified in the "Dosage and Administration" section of the package insert also in Japan, as in other countries.

PMDA accepted the response, as the applicant responded that the maximum duration of treatment will be specified in the "Dosage and Administration" section of the package insert. The applicant is being requested to consider exactly how it should be described.

4.(iii).B.(7) Special populations

4.(iii).B.(7).1) Patients with renal impairment

PMDA asked the applicant to explain the safety of teriparatide in patients with renal impairment.

The applicant responded as follows:

The percent changes in lumbar spine BMD at Month 12 by C_{CR} in Japanese Study GHDB is shown in Table 48. BMD increased in the teriparatide 20 μg group as compared with the placebo group in all C_{CR} subgroups and there was no C_{CR} subgroup-by-treatment interaction ($P = 0.764$, two-way ANOVA).

Table 48. Percent changes in lumbar spine BMD at Month 12 by C_{CR} (Study GHDB)

C_{CR}	Placebo	Teriparatide 20 μg	Difference from placebo [95% CI]
≥ 30 and < 50	0.11 ± 3.11 (8)	10.82 ± 5.82 (19)	10.71 [6.20, 15.23]
≥ 50 and < 80	-0.33 ± 4.72 (35)	9.67 ± 5.36 (84)	10.00 [7.94, 12.06]
≥ 80	0.65 ± 4.17 (20)	9.60 ± 5.18 (28)	8.96 [6.14, 11.78]

C_{CR}: creatinine clearance (mL/min), CI: confidence interval
Mean ± SD (n)

In the safety analysis, there were no apparent differences in the occurrence of adverse events (MedDRA system organ classes) according to C_{CR} and there were no adverse events with a significantly higher incidence in the teriparatide 20 μg group than in the placebo group in any C_{CR} category. C_{CR} change by C_{CR} in Japanese Study GHDB was as shown in Table 49 and teriparatide reduced C_{CR} in all C_{CR} subgroups. As C_{CR} was decreased also in the placebo group in the C_{CR} categories of ≥50 mL/min and <80 mL/min and of ≥80 mL/min, these decreases in C_{CR} were likely to reflect age-related decrease in renal function (Miller PD, et al. *Osteoporos Int.* 2007; 18 (1): 59-68) and it was not considered that C_{CR} is further decreased by renal impairment.

Table 49. C_{CR} changes at Month 12 by C_{CR} (Study GHDB)

C_{CR}	Placebo	Teriparatide 20 μg	Difference from placebo [95% CI]
≥ 30 and < 50	1.8 ± 4.3 (9)	-4.0 ± 4.0 (20)	-5.7 [-9.1, -2.4]
≥ 50 and < 80	-1.2 ± 6.4 (37)	-2.8 ± 5.1 (87)	-1.6 [-3.7, 0.5]
≥ 80	-0.6 ± 5.3 (21)	-2.6 ± 11.4 (29)	-2.0 [-7.4, 3.4]

C_{CR}: creatinine clearance calculated using the Cockcroft & Gault formula (mL/min), CI: confidence interval
Mean ± SD (n)

In Study GHAC, as shown in Table 50, although 1 subject with C_{CR} <30 mL/min each in the teriparatide 20 μg and 40 μg groups had decreased C_{CR} (-0.7 mL/min and -0.2 mL/min, respectively), decreased C_{CR} was not observed in the teriparatide or placebo group in the C_{CR} categories of ≥30 mL/min and <50 mL/min and of ≥50 mL/min and <80 mL/min. In the C_{CR} category of ≥80 mL/min, C_{CR} did not decrease in the teriparatide group, but it decreased in the placebo group (-3.0 ± 16.8 mL/min). Especially in the C_{CR} category of ≥30 mL/min and <50 mL/min, the decrease in C_{CR} and the difference from placebo as seen in Study GHDB were not observed.

Table 50. C_{CR} changes at Month 12 by C_{CR} (Study GHAC)

C_{CR}	Placebo	Teriparatide 20 μg	Difference from placebo [95% CI]	Teriparatide 40 μg	Difference from placebo [95% CI]
< 30	2.4 (2)	-0.7 (1)	—	-0.2 (1)	—
≥ 30 and < 50	3.2 ± 6.7 (37)	3.1 ± 5.9 (35)	-0.1 [-3.1, 2.9]	1.4 ± 6.6 (51)	-1.9 [-4.7, 1.0]
≥ 50 and < 80	2.5 ± 9.3 (255)	1.2 ± 8.8 (260)	-1.4 [-2.9, 0.2]	0.8 ± 10.3 (248)	-1.7 [-3.4, 0.0]
≥ 80	-3.0 ± 16.8 (184)	0.8 ± 15.3 (171)	3.8 [0.4, 7.1]	2.2 ± 16.1 (154)	5.1 [1.6, 8.7]

C_{CR}: creatinine clearance calculated using the Cockcroft & Gault formula (mL/min), CI: confidence interval
Mean ± SD (n)

In Study GHAJ, as shown in Table 51, although 1 subject with C_{CR} <30 mL/min in the teriparatide 20 μg group had decreased C_{CR} (-4.1 mL/min), decreased C_{CR} was not observed in the teriparatide or placebo group in the C_{CR} categories of ≥30 mL/min and <50 mL/min and of ≥50 mL/min and <80 mL/min. As in Study GHAC, C_{CR} was decreased (-0.5 ± 9.7 mL/min) in the placebo group in the C_{CR} category of ≥80 mL/min. The number of subjects with C_{CR} ≥30 mL/min and <50 mL/min was limited. C_{CR} decreased in Japanese Study GHDB, which was presumably associated partly with aging, while Studies GHAC and GHAJ showed no decreases in C_{CR}. These study results indicate that at least, there is no clear relationship between C_{CR} change and teriparatide and that teriparatide does not worsen renal function. However, as the clearance of teriparatide was delayed in subjects with severe renal impairment, teriparatide should be used with caution in patients with severe renal impairment. Thus, the relevant precaution statement will be included in the package insert.

Table 51. C_{CR} changes at Month 12 by C_{CR} (Study GHAJ)

C_{CR}	Placebo	Teriparatide 20 μg	Difference from placebo [95% CI]	Teriparatide 40 μg	Difference from placebo [95% CI]
< 30	—	-4.1 (1)	—	—	—
≥ 30 and < 50	6.9 (1)	3.3 (2)	—	—	—
≥ 50 and < 80	2.2 ± 8.2 (41)	2.1 ± 8.1 (34)	-0.1 [-3.8,3.7]	1.8 ± 10.2 (29)	-0.3 [-4.7,4.1]
≥ 80	-0.5 ± 9.7 (90)	1.5 ± 12.9 (89)	2.0 [-1.3,5.4]	5.1 ± 14.6 (80)	5.6 [1.9,9.3]

C_{CR}: creatinine clearance calculated using the Cockcroft & Gault formula (mL/min), CI: confidence interval
Mean ± SD (n)

PMDA considers as follows:

As the magnitude of the decreases in C_{CR} tended to be greater in the teriparatide 20 μg group than in the placebo group in Japanese Study GHDB, teriparatide should be used with caution in patients with renal impairment. For example, renal function tests should be performed periodically. It is also necessary to continue to collect information on patients with renal impairment via post-marketing surveillance. A final conclusion is to be made taking account of comments from the Expert Discussion.

4.(iii).B.(7).2) Patients with hepatic impairment

PMDA asked the applicant to explain the safety of teriparatide in patients with hepatic impairment.

The applicant responded as follows:

PPK analyses of Foreign Studies GHAC and GHAJ showed no effects of AST and ALT on the pharmacokinetics of teriparatide. Liver function test results from Japanese Study GHDB and Foreign Study GHAC showed no consistent trend in changes in ALT, AST, γ-GTP, and other liver function parameters

suggestive of any adverse effects on the liver, except for increased serum alkaline phosphatase, which was considered due to bone formation activity. In Japanese Study GHDB, patients with hepatic impairment were defined as patients with preexisting liver function-related diseases or laboratory findings (i.e. blood alkaline phosphatase increased, cholelithiasis, gallbladder polyp, gamma-glutamyltransferase increased, haemangioma of liver, hepatic steatosis, hypertonic bladder, pancreatic atrophy) or patients with baseline AST or ALT >2 times the upper limit of normal and a subgroup analysis of 14 subjects who met this definition (4 subjects in the placebo group, 10 subjects in the teriparatide 20 μg group) was performed. Increased lumbar spine BMD was also observed as compared with placebo also in this subgroup, which was not different from the results in the overall population. In the safety analysis, increased AST and ALT were reported as adverse events only in the placebo group and these adverse events were not observed in the teriparatide 20 μg group. None of other adverse events were characteristic of this subgroup.

PMDA asked the applicant to explain the risk of transient hypercalcaemia in patients with hepatic impairment.

The applicant responded as follows:
In Foreign Studies GHAC and GHAJ, serum calcium 4 to 6 hours after dosing of study drug in patients with hepatic impairment as defined above was as shown in Table 52 and there were no differences between subjects with and without hepatic impairment, except that serum calcium tended to be slightly higher in subjects with hepatic impairment in the teriparatide 40 μg group.

Table 52. 4- to 6-hour postdose serum calcium in subjects with or without hepatic impairment
(Pooled analysis of Studies GHAC and GHAJ)

Treatment group	Without hepatic impairment		With hepatic impairment	
	Mean ± SD (n)	Difference from placebo [95% CI]	Mean ± SD (n)	Difference from placebo [95% CI]
Placebo	9.54 ± 0.47 (177)	—	9.31 ± 0.29 (3)	—
Teriparatide 20 μg	10.19 ± 0.63 (249)	0.65 [0.54, 0.76]	9.77 ± 0.39 (7)	0.46 [-0.12, 1.04]
Teriparatide 40 μg	10.49 ± 0.64 (346)	0.95 [0.84, 1.06]	10.82 ± 0.59 (5)	1.51 [0.59, 2.43]

Note: As 4- to 6-hour postdose serum calcium was measured at multiple timepoints in each study, the maximum value of each subject was used for analysis.

In Studies GHAC, GHAJ, and GHDB, hypercalcaemia did not occur in the subgroup of subjects with hepatic impairment. Although it is difficult to draw a conclusion from this subgroup analysis because of the limited number of subjects with hepatic impairment, at least the possibility of increased risk of hypercalcaemia associated with teriparatide in patients with mild or moderate hepatic impairment, who were not excluded from clinical studies, is considered low.

PMDA asked the applicant to explain the safety of teriparatide in patients with mild, moderate, or severe hepatic impairment, based on foreign post-marketing reports, etc.

The applicant responded as follows:
Approximately 735,000 patients are estimated to have been exposed to teriparatide since the approval of teriparatide overseas until the end of November 2009. Around the same period (from November 26, 2002 to

November 26, 2009), healthcare professionals reported approximately 17,500 adverse events. Among the patients experiencing adverse events, 35 patients assigned a code for hepatic impairment had 133 adverse events, including 48 serious events. There was no consistent trend in adverse events reported more than once.

PMDA considers as follows:
Although there are no particular problems with the safety and efficacy of teriparatide in patients with mild or moderate hepatic impairment, who were not excluded from clinical studies, it is necessary to advise that teriparatide should be used with caution in patients with severe hepatic impairment, etc. Given that the safety of teriparatide in Japanese patients with hepatic impairment has not fully been investigated, it is necessary to continue to collect information on patients with hepatic impairment via post-marketing surveillance.

4.(iii).B.(7).3) Elderly
PMDA asked the applicant to explain the safety of teriparatide in the elderly.

The applicant responded as follows:
According to a subgroup analysis of adverse events by age in Japanese Study GHDB (≤64 years, 65-74 years, ≥75 years), there was a trend towards a lower incidence of nasopharyngitis in the subgroup of subjects ≥75 years of age, a lower incidence of back pain in the subgroup of subjects 65 to 74 years of age, and a higher incidence of headache in the subgroup of subjects 65 to 74 years of age. On the other hand, according to a pooled analysis of Foreign Studies GHAC and GHAJ, no similar trend was observed and the trend was different between the teriparatide and placebo groups as follows. The incidence of nausea was higher in subjects ≤64 years of age in the teriparatide group while the incidence of nausea increased with age in the placebo group. The incidence of chest pain was higher in subjects ≥75 years of age in the teriparatide group while the incidence of chest pain was lower in subjects ≥75 years of age in the placebo group. As shown above, although there were slight differences in the incidences of adverse events according to the age group, no marked differences in the trend of occurrence were observed.

The results of a pooled analysis of 4- to 6-hour postdose serum calcium by age (≤64 years, 65-74 years, ≥75 years) across Studies GHAC and GHAJ are shown in Table 53. The 4- to 6-hour postdose serum calcium concentration (mean) was higher in the teriparatide group than in the placebo group, but there was no trend towards an increase with age.

Table 53. 4- to 6-hour postdose serum calcium by age (Pooled analysis of Studies GHAC and GHAJ)

Treatment group	≤ 64 years		65-74 years		≥ 75 years	
	Mean ± SD (n)	Difference from placebo [95% CI]	Mean ± SD (n)	Difference from placebo [95% CI]	Mean ± SD (n)	Difference from placebo [95% CI]
Placebo	9.46 ± 0.42 (93)	—	9.65 ± 0.51 (72)	—	9.47 ± 0.50 (15)	—
Teriparatide 20 μg	10.11 ± 0.77 (107)	0.66 [0.48, 0.83]	10.22 ± 0.49 (101)	0.56 [0.41, 0.71]	10.24 ± 0.51 (48)	0.78 [0.47, 1.08]
Teriparatide 40 μg	10.43 ± 0.65 (126)	0.97 [0.82, 1.13]	10.54 ± 0.65 (173)	0.88 [0.71, 1.05]	10.53 ± 0.60 (52)	1.06 [0.72, 1.40]

Note: As 4- to 6-hour postdose serum calcium was measured at multiple timepoints in each study, the maximum value of each subject was used for analysis.

In Studies GHAC, GHAJ, and GHDB, hypercalcaemia occurred in 1 subject aged 65 to 74 years in the teriparatide 20 μg group and 2 subjects aged 65 to 74 years in the teriparatide 40 μg group, but not in the subgroup of subjects aged ≥75 years. Due to the limited number of subjects with hypercalcaemia, it is difficult to conclude from these results that there is a consistent aging-associated trend in the occurrence of hypercalcaemia following treatment with teriparatide.

PMDA considers as follows:
Although there have so far been no particular problems with the safety of teriparatide in the elderly, teriparatide is expected to be used in relatively older patients, and elderly patients often have reduced physiological functions and are therefore considered more vulnerable to nausea and dizziness, etc., which are commonly reported with teriparatide. Thus, careful administration to elderly patients should be reminded in the package insert and further information should be gathered on elderly patients via post-marketing surveillance.

4.(iii).B.(8) Post-marketing surveillance plan
The applicant is to conduct a long-term specified use-results survey with a 18-month observation period and a target number of patients of 600 (including 100 patients who have completed a minimum of 12 months of treatment) in order to characterize the safety profile of long-term treatment with teriparatide (nature, incidence, time to onset, seriousness, and outcome, etc. of adverse drug reactions) in patients with osteoporosis at high risk for fracture in routine clinical settings.

PMDA considers that it is necessary to continue to investigate safety in patients with hyperuricemia, renal impairment, or hepatic impairment and in elderly patients, safety issues of hypercalcaemia and cardiovascular disorders, etc., and the effects of antibody formation on safety and efficacy, etc. via post-marketing surveillance and is requesting the applicant to carry out the investigation. PMDA also considers that the relationship between teriparatide and the development of osteosarcoma needs to be further studied carefully not only through post-marketing surveillance but also via Foreign Study GHBX, etc. A final conclusion on these matters is to be made taking account of comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in s the new drug application. As no particular problems were found, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

A GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1, 5.3.5.1.2, 5.3.5.1.2-1). Protocol deviations (the procedure prior to the start of administration) were found and some of the source documents (x-ray films) for some subjects were not retained at some trial sites. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

Based on the submitted data, the efficacy of teriparatide in the treatment of patients with osteoporosis at high risk for fracture has been demonstrated. Although its safety is considered acceptable, further information should to be collected via post-marketing surveillance on safety in patients with hyperuricemia, renal impairment, or hepatic impairment and in elderly patients, safety issues of hypercalcaemia cardiovascular disorders, etc., and on the effects of antibody formation on safety and efficacy. The relationship between teriparatide and the development of osteosarcoma should be further studied carefully not only through post-marketing surveillance but also via Foreign Study GHBX, etc.

Teriparatide may be approved for the indication of treatment of patients with osteoporosis at high risk for fracture if it can be concluded that there are no particular problems based on comments from the Expert Discussion.

Review Report (2)

April 6, 2010

I. Product Submitted for Registration

[Brand name] Forteo Injection Cartridge 600 μg, Forteo Injection Kit 600 μg
[Non-proprietary name] Teriparatide (Genetical Recombination)
[Name of applicant] Eli Lilly Japan K.K.
[Date of application] April 28, 2009

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, 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) Ability to extrapolate foreign clinical data (Study GHAC)

The following conclusion by PMDA was supported by the expert advisors:

The efficacy analyses showed no major differences in the percent change from baseline in lumbar spine (L1-L4) BMD by observation period between Japanese Study GHDB (a bridging study) and Foreign Study GHAC (a study to be bridged). The pooled safety analyses of placebo-controlled, double-blind comparative studies (GHCS, GHDB, GHAC, GHAJ) and an active-controlled study (GHBM) showed no major differences between Japan and overseas. Therefore, it was considered that the data from Study GHAC with the primary endpoint of "the proportion of subjects with new vertebral fractures" can be extrapolated to the Japanese population.

(2) Relationship with the development of osteosarcoma

The following conclusion by PMDA was supported by the expert advisors [see "(6) Post-marketing surveillance"]:

Although the applicant's response that no findings suggesting the relationship between teriparatide and the development of osteosarcoma have so far been obtained primarily from foreign clinical experience is acceptable, prior to the initiation of treatment with teriparatide, the patient's condition and medical history, etc. should be assessed to confirm that the patient is not at increased baseline risk for osteosarcoma (contraindication) and the appropriateness of selecting teriparatide as a therapeutic drug should be thoroughly examined from a risk/benefit standpoint. Given that clinical experience with teriparatide in Japanese patients is limited and that an increased exposure to teriparatide in Japanese patients, who have a lower body weight than Caucasian patients, has been suggested, the relationship between teriparatide and the development of

osteosarcoma in Japanese patients should be further studied carefully not only through post-marketing surveillance but also via Foreign Study GHBX, etc.

(3) Indication

PMDA considered as follows:

Although there is no major problem with the proposed indication of "treatment of patients with osteoporosis at high risk for fracture", the appropriateness of the "Precautions for Indications" section should be reviewed, taking account of the characteristics of patients included in clinical studies and the definition of fracture risk in Japan and overseas at the time of conducting clinical studies and at present.

Based on the above, PMDA sought comments from the expert advisors about the appropriateness of the proposed indication and the statement for the Precautions of Indications.

The expert advisors supported PMDA's conclusion that there is no major problem with the proposed indication of "treatment of patients with osteoporosis at high risk for fracture". At the same time, they made the following comments on the "Precautions for Indications" section.

- The "Precautions for Indications" section presented by the applicant includes generalized inclusion criteria specified for Japanese Study GHDB and does not necessarily accurately describe patients with osteoporosis at high risk for fracture.
- It should be noted that the fracture risk factors listed in the "Guidelines for Prevention and Treatment of Osteoporosis 2006" include the risk factors for fall leading to fracture, such as tall height and the use of hypnotics or antihypertensives.
- Although there are no terms to describe severe osteoporosis at present, the "Precautions for Indications" section presented by the applicant is considered generally appropriate.

Based on the comments from the Expert Discussion, PMDA instructed the applicant to consider including a statement in the "Precautions for Indications" section of the package insert that teriparatide should be indicated for patients with risk factors for fracture such as low bone mineral density, previous fracture, advanced age, and a family history of femoral neck fracture, by reference to the overseas labels and the "Guidelines for Prevention and Treatment of Osteoporosis 2006".

The applicant responded that these risk factors for fracture were going to be listed in the "Precautions for Indications" section, and PMDA reviewed and accepted the content of the package insert.

(4) Dosage and administration

PMDA considered as follows:

The risk of osteosarcoma cannot be completely excluded in humans. In foreign countries, teriparatide was approved with the maximum treatment duration of 24 months based on the duration of treatment used in clinical studies in patients with osteoporosis with the mentioned risk being taken into account. Thus, also in Japan, the maximum duration of treatment should be 18 months based on the results from Japanese Study

GHDB (18-month data evaluated in this review). The maximum duration of treatment needs to be specified in the "Dosage and Administration" section of the package insert also in Japan, as in other countries.

Based on the above, PMDA sought comments from the expert advisors about the proposed modification as shown below.

[Dosage and Administration] (at filing of the application)
The usual adult dosage of teriparatide is 20 μg once daily, administered by subcutaneous injection.

[Dosage and Administration] (after modification)
The usual adult dosage of Teriparatide (Genetical Recombination) is 20 μg once daily, administered by subcutaneous injection.
The maximum duration of treatment with Forteo should be 18 months.

The above conclusion by PMDA and the proposed modification to the Dosage and Administration statement were generally supported by the expert advisors, but some expert advisors commented that the modified Dosage and Administration statement was not clear on whether 18 months refers to a total duration of 18 months or a continuous period of 18 months.

In response to the expert advisors' comment, PMDA instructed the applicant to modify the Dosage and Administration statement as suggested by PMDA and to include the following statements in the "Precautions for Dosage and Administration" section: the total duration of treatment with teriparatide should not exceed 18 months; and an 18-month course of teriparatide should not be repeated.

The applicant responded that the Dosage and Administration statement would be modified as follows and that the following descriptions would be included in the "Precautions for Dosage and Administration" section.

[Dosage and Administration]
The usual adult dosage of Teriparatide (Genetical Recombination) is 20 μg once daily, administered by subcutaneous injection.
The maximum duration of treatment with Forteo should be 18 months.

[Precautions for Dosage and Administration]
(1) As the safety of Forteo has not been established beyond 18 months of treatment, the recommended treatment duration should not be exceeded.
(2) Even if Forteo is once withdrawn and then is readministered, the total duration of treatment with Forteo should not exceed 18 months. The 18-month course of Forteo should not be repeated.

PMDA accepted the response.

(5) Use in patients with renal impairment

The following conclusion by PMDA was supported by the expert advisors:

As the magnitude of the decreases in C_{CR} tended to be greater in the teriparatide 20 μg group than in the placebo group in Japanese Study GHDB, teriparatide should be used with caution in patients with renal impairment, e.g. renal function tests should be performed periodically.

Based on the above, PMDA instructed the applicant to include a precaution in the package insert to the effect that renal function tests should be performed periodically in patients with renal impairment.

The applicant responded that a precaution would be added in the “Important Precautions" section of the package insert to the effect that renal function tests should be performed periodically in patients with renal impairment.

PMDA accepted the response.

(6) Post-marketing surveillance

PMDA considered as follows:

Safety in patients with hyperuricemia, renal impairment, or hepatic impairment and in elderly patients, safety issues of hypercalcaemia, cardiovascular disorders, etc., and the effects of antibody formation on safety and efficacy, etc., should be further studied via post-marketing surveillance. The relationship between teriparatide and the development of osteosarcoma also needs to be further studied carefully not only through post-marketing surveillance but also via Foreign Study GHBX, etc.

The above conclusion by PMDA was supported by the expert advisors. The advisors also gave a comment that a long-term follow-up study would be needed for osteosarcoma.

Based on the above, PMDA instructed the applicant to reconsider the post-marketing surveillance study of teriparatide.

The applicant responded as follows:

A long-term specified use-results survey is planned to be conducted as post-marketing surveillance of teriparatide with a target number of patients of 1800, an enrollment period of 3 years, and an 18-month observation period. Enrolled patients will be stratified by the presence or absence of renal or hepatic impairment, elderly or non-elderly, and men or women. The incidence, trend, nature of adverse drug reactions, etc. will be exploratory analyzed so as to take safety measures as appropriate. With respect to safety issues on hyperuricemia, nephrolithiasis, hypercalcaemia, cardiovascular disorders, etc., the amounts of accumulated data on the events from post-marketing surveillance are to be assessed appropriately to ensure that the incidences of these events are comparable to the incidences of adverse drug reactions in Japanese and foreign clinical studies. It is difficult to perform antibody assay in routine clinical practice to

assess antibody formation-related safety and efficacy. However, when an adverse event reported from post-marketing surveillance is likely due to antibody formation, the presence or absence of an antibody is going to be examined. Antibody testing will also be performed on samples offered by medical institutions or patients on request. In addition, because the estimated annual rate of osteosarcoma in people ≥60 years of age is as extremely low as 1 in 250,000 in the US, the relationship between teriparatide and the development of osteosarcoma is difficult to be assessed via post-marketing surveillance unless newly diagnosed osteosarcoma can be identified appropriately. In efforts to pursue assessment methods for the risk of teriparatide-associated osteosarcoma, the applicant will ask the relevant academic societies if medication histories of patients can be incorporated into the current osteosarcoma registry. Patient notebooks are going to be made available to patients, in which the risk of osteosarcoma will be warned and patients who are going to be transferred to another hospital will be advised to present the notebook to his or her new physician. Besides, efforts are to be made to gather detailed information from spontaneous reports on globally common osteosarcoma-related matters to be looked into, and gathered foreign and Japanese data will be assessed scientifically and medically so that appropriate safety measures will be taken as needed. Once the results of Foreign Study GHBX become available, relevant information will be provided to medical practice in an appropriate manner using publications or by other means.

PMDA accepted the response.

(7) Shelf-life for the drug product

The applicant presented 18-month data from an ongoing long-term stability study (5°C) on commercial-scale lots of the drug product in cartridge and in kit (3 lots each) and then explained the stability of the drug product as follows:

For both the drug product in cartridge and in kit, there were over-time increases in related substances tested. However, the increases were all within the specifications, and the specifications for all the attributes tested were met, indicating the good stability of the drug product. Thus, the proposed shelf-life of 18 months for the drug product was justified.

PMDA concluded that there is no problem with the proposed shelf-life of 18 months for the drug product and accepted the response.

(8) Brand names

The applicant proposed that the Japanese brand names should be modified as follows, based on “Handling of labels and brand names of drugs for the prevention of medical accident” (PMSB Notification No. 935 dated September 19, 2000).

At filing of the application		After modification (The underlined parts have been changed.)
Forteo <u>Injection</u> Cartridge 600 μg	→	Forteo <u>Subcutaneous Injection</u> Cartridge 600 μg
Forteo <u>Injection</u> Kit 600 μg	→	Forteo <u>Subcutaneous Injection</u> Kit 600 μg

III. Overall Evaluation

Based on the above review, PMDA has concluded that teriparatide may be approved for the following indication and dosage and administration. As the proposed product is a drug with a new active ingredient, the re-examination period should be 8 years. Neither the drug substance nor the drug product is classified as poisonous drug or powerful drug, and the product is not classified as biological product or specified biological product.

[Indication]
Treatment of patients with osteoporosis at high risk for fracture

[Dosage and Administration]
The usual adult dose of Teriparatide (Genetical Recombination) is 20 μg once daily, administered by subcutaneous injection.
The maximum duration of treatment with Forteo should be 18 months.