Patent Right	Date	June 22, 2022	Court	Intellectual Property High Court, Fourth Division
	Case number	2021 (Gyo-Ke) 10115		
- A case in which the court held that there was an error in the determination in a decision made by the JPO to the effect that an invention relating to osteoporosis could not have been easily conceived of by a person skilled in the art based on a cited invention				

Case type: Rescission of Trial Decision to Maintain
Result: Granted
References: Article 29, paragraph (2) of the Patent Act
Related rights, etc.: Patent No. 6198346
Decision of the JPO: Invalidation Trial No. 2019-800062

Summary of the Judgment

1. This case is a lawsuit to seek rescission of a decision made by the JPO (the "JPO Decision") to the effect that a request for a trial for invalidation of a patent relating to an invention titled "PTH-containing therapeutic/prophylactic agent for osteoporosis, characterized in that PTH is administered once a week in a unit dose of 100 to 200 units" (Patent No. 6198346) is groundless.

The major issue is whether there is a lack of an inventive step (the ease in conceiving of Differences 1 through 3).

In this judgment, the court rescinded the JPO Decision which found that Inventions 1 and 2 involve an inventive step.

2. Claim 1 of the patent in question after the correction ("Invention 1") states as follows.

"An agent for the treatment or prevention of osteoporosis that contains PTH (1-34) or salt thereof as the active ingredient, characterized in that PTH (1-34) or salt thereof is administered once a week in a unit dose of 200 units over a duration exceeding 48 weeks to 72 weeks or longer, which is for the inhibition of bone fractures to treat osteoporosis patients who satisfy all of the following conditions (1) through (3) below:
(1) Age 65 years or older
(2) Prevalent bone fractures
(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher."

3. Differences 1 through 3 between Invention 1 and Exhibit Ko 1 Invention , which is the primary prior art, are as follows.

(Difference 1)

In the case of Invention 1, the "specified osteoporosis patients" are "osteoporosis patients who satisfy all of the following conditions (1) through (3) below:

(1) Age 65 years or older

(2) Prevalent bone fractures

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher," whereas in the case of Exhibit Ko 1 Invention, they are "subjects between the ages of 45 and 95 years who were defined as osteoporosis based on the diagnostic criteria proposed by a Committee supported by the Ministry of Health and Welfare, with a total score higher than 4 as a result of defining osteoporosis in terms of multiple factors weighted in the form of scores."

(Difference 2)

The "therapeutic or prophylactic agent for osteoporosis" is specified to be one "for the inhibition of bone fractures" in Invention 1, whereas there is no such specification in Exhibit Ko 1 Invention.

(Difference 3)

The agent is specified to be "administered ... over a duration exceeding 48 weeks to 72 weeks or longer" in Invention 1, whereas there is no such specification in Exhibit Ko 1 Invention.

4. In this judgment, the court held that, because the composition of Invention 1 relating to Differences 1 through 3 could have been easily conceived of by a person skilled in the art, there was an error in the determination in the JPO Decision which found that Invention 1 involves an inventive step. The court further ruled that there was also an error in the determination in the JPO Decision which found that Invention 2 involves an inventive step on the basis that Invention 1 involves an inventive step.

5. The outline of the court's determinations relating to Differences 1 through 3 in this judgment is as follows.

(1) Regarding Difference 1

The following can be said as a result of examining the conditions of Invention 1, which are "(1) Age 65 years or older" (Condition (1)), "(2) Prevalent bone fractures" (Condition (2)), and "(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher" (Condition (3)) (the "Three Conditions"). As Condition (2) and Condition (3) are the same as conditions applied for the diagnosis of osteoporosis under the diagnostic criteria of Exhibit Ko 5, it is not difficult at all for a person skilled in the art to apply Condition (2) and Condition (3) for screening osteoporosis patients to whom the therapeutic agent for osteoporosis is to be

administered once a week in a unit dose of 200 units as referred to in Exhibit Ko 1 Invention.

In addition, as there is common general technical knowledge that the incidence of osteoporosis increases with age, it is only a natural choice and not difficult at all for a person skilled in the art to apply, in addition to Condition (2) and Condition (3), a condition similar to Condition (1) specifying that the osteoporosis patients to be administered the agent are those aged 65 or older, by focusing on the fact that age is cited, along with low bone density and prevalent bone fractures, as the multiple risk factors for bone fractures caused by osteoporosis.

It follows that it is not particularly difficult for a person skilled in the art who comes across Exhibit Ko 1 Invention to specify the subject patients for administration of the osteoporosis therapeutic agent to be patients who satisfy all of the Three Conditions.

(2) Regarding Difference 2

The following common general technical knowledge existed at the time: osteoporosis is a bone disease characterized by decreased bone strength and involving increased risk for bone fractures, and the purpose of the treatment of osteoporosis is to prevent bone fractures; and "bone strength" consists of two factors—bone density and bone quality—and bone density accounts for almost 70% of bone strength. Therefore, it should be said that a person skilled in the art would understand the fact that an increase in bone density contributes to prevention of bone fractures.

It follows that a person skilled in the art could have easily conceived of using the osteoporosis therapeutic agent referred to in Exhibit Ko 1 Invention for the inhibition of bone fractures.

(3) Regarding Difference 3

When examining the condition in Invention 1 to "make the administration period 'a duration exceeding 48 weeks to 72 weeks or longer,'" according to the statements in the Description, it is difficult to find the significance of a critical range in "48 weeks" and "72 weeks or longer," and no particular technical meaning can be found in the limitation in the Invention which defines the start and the end of a period by stating a specific period, that is, "a duration exceeding 48 weeks to 72 weeks or longer." It is reasonable to regard that the specific period merely indicates that the bone fracture incidence declined as the PTH administration was continued over a discretionary period.

As of the base date for determining the patentability of Invention 1, it was known that bone density increases and the occurrence of bone fractures decreases through daily administration of a PTH preparation over a duration exceeding 48 weeks.

In the case of Exhibit Ko 1 Invention, on the other hand, when PTH was

administered once a week in a unit dose of 200 units, the lumbar spine bone mineral density (BMD) continuously increased over the duration up to 48 weeks, significantly increasing by 8.1% after 48 weeks, and in Group H, which was administered PTH in a unit dose of 200 units, vertebral bone fractures did not occur during the administration period of 48 weeks. While a person skilled in the art would understand, according to common general technical knowledge, that such increase in bone density contributes to preventing bone fractures, the test in Exhibit Ko 1 Document, which involves administration over a duration up to 48 weeks, shows a continuous increase in the lumbar spine BMD although the increase rate has a tendency to gradually decline, and does not provide any basis for finding that the lumbar spine BMD turns to a decrease after 48 weeks.

According to the above, it can be said that, based on the report that had been made concerning daily administration of PTH over a duration exceeding 48 weeks and the resulting increase in bone density and decrease in the occurrence of bone fractures, a person skilled in the art could have easily conceived of also administering the therapeutic agent for osteoporosis referred to in Exhibit Ko 1 Invention over a duration exceeding 48 weeks for increasing bone density and preventing bone fractures, and could have arrived at Invention 1 as a result.

(4) The unpredicted and outstanding effects of the Invention as asserted by the plaintiff are as follows: [i] an outstanding inhibitory effect on bone fractures, indicating a 79% relative risk reduction (RRR) in comparison to the placebo, after 72 weeks (Effect [i]); [ii] an effect that the inhibitory effect on bone fractures is intensified through continuous administration of the agent (Effect [ii]); and [iii] an effect of completely inhibiting bone fractures in practice after 48 weeks (Effect [iii]).

When examining Effect [i], while a person skilled in the art has an understanding that an increase in bone density contributes to prevention of bone fractures, the disclosed fact that Exhibit Ko 1 Invention increased bone density by 8.1% in 48 weeks makes it easy for a person skilled in the art to understand that the osteoporosis therapeutic agent in Exhibit Ko 1 Invention exhibits an effect of inhibiting bone fractures. Then, in order to confirm Effect [i], there is a need to compare between the inhibitory effect on bone fractures in high-risk patients (patients who satisfy all of the Three Conditions) and that in low-risk patients (patients who do not satisfy all or part of the Three Conditions). However, it cannot be concluded from the statements in the Description that the degree to which bone fracture occurrence is inhibited among high-risk patients is higher compared to such degree among low-risk patients. According to the above, it should be said that Effect [i] is not based on the statements in the

Description.

When examining Effect [ii], the Description merely compares between patients to whom the osteoporosis therapeutic agent referred to in the Invention was administered and patients to whom a placebo was administered, and does not indicate that the inhibitory effect on bone fractures is higher in patients who satisfy all of the Three Conditions than in patients who do not. In addition, Exhibit Ko 2 Document states that, when 20 or 40 μg of PTH was administered daily for an average of 17 or 18 months, the rate of inhibition of bone fractures by PTH administration became higher as the administration period became longer. Therefore, it was within the scope of expectation for a person skilled in the art that the inhibitory effect on bone fractures would be intensified through continuous administration of the agent.

Effect [iii] only refers to a fact indicating a test result that no new vertebral fractures were found when administration went beyond 48 weeks, which can hardly be found to mean that the osteoporosis therapeutic agent referred to in the Invention is a therapeutic agent that completely inhibits bone fractures in practice after 48 weeks of administration (a complete wonder drug). The defendant also does not allege that the osteoporosis therapeutic agent referred to in the Invention has such effect. While it is natural to consider that the inhibitory effect on bone fractures will continue to a certain extent even after 48 weeks in Exhibit Ko 1 Invention, given that no vertebral fractures were found during 48-week administration also in Exhibit Ko 1 Invention, even though it is merely a fact indicating a test result, it can be understood that the bone fracture incidence was originally low. Accordingly, even if the number of bone fractures during the period exceeding 48 weeks to 72 weeks was zero in the Invention, one cannot go so far as to say that this fact itself was surprising for a person skilled in the art. Rather, it can be said that this fact was within the scope of expectation for a person skilled in the art.

Judgment rendered on June 22, 2022
2021 (Gyo-Ke) 10115 Case of seeking rescission of the JPO decision
Date of conclusion of oral argument: May 11, 2022

Judgment

Plaintiff: Nichi-Iko Pharmaceutical Co., Ltd.

Defendant: Asahi Kasei Pharma Corporation

Main text

1. The decision made by the Japan Patent Office (the "JPO") on August 11, 2021, for the case of Invalidation Trial No. 2019-800062 shall be rescinded.
2. The Defendant shall bear the court costs.

Facts and reasons

No. 1 Claim

Same as the main text.

No. 2 Outline of the case

This case is a lawsuit to seek rescission of a decision made by the JPO (the "JPO Decision") to the effect that a request for a trial for invalidation of a patent is groundless.

1. History of procedures at the JPO (The facts are not disputed between the parties.)

(1) On May 25, 2015, the Defendant filed a patent application for an invention titled "PTH-containing therapeutic/prophylactic agent for osteoporosis, characterized in that PTH is administered once a week in a unit dose of 100 to 200 units" (Patent Application No. 2015-105266; a part of Patent Application No. 2011-530844 of which the international filing date is September 8, 2010 [priority claim: September 9, 2009; Patent Application No. 2009-208039] filed as a new application; hereinafter referred to as the "Application"), and obtained registration of a patent right for that application on September 1, 2017 (Patent No. 6198346; number of claims: 2) (the patent relating to this registration is hereinafter referred to as the "Patent").

(2) On August 29, 2019, the Plaintiff filed a request for a trial for invalidation with regard to Claims 1 and 2 of the Patent (Invalidation Trial No. 2019-800062).

On November 26, 2020, the JPO gave an advance notice of a trial decision to invalidate the patent with regard to the inventions pertaining to Claims 1 and 2 of the

Patent. In response, the Defendant made a request for correction to correct Claim 2 of the Patent on January 29, 2021 (this correction is hereinafter referred to as the "Correction").

On August 11, 2021, the JPO rendered a trial decision (hereinafter referred to as the "JPO Decision") stating as follows: "Correction is allowed for Claim [2] according to the correction of claims of Patent No. 6198346 as stated in the attached written request for correction. The request for a trial for invalidation of the inventions pertaining to Claims 1 and 2 of Patent No. 6198346 is groundless." A certified copy of the JPO Decision was served on the Plaintiff on August 18, 2021.

(3) On September 16, 2021, the Plaintiff filed the present action seeking rescission of the JPO Decision.

2. Statement of the claims

The statement of the claims for the inventions pertaining to Claims 1 and 2 of the Patent after the Correction (hereinafter referred to as "Invention 1" and the like in the order of the claim number, and Inventions 1 and 2 are collectively referred to as the "Invention" in some cases) is as follows. The description of the Invention, including the drawings, is referred to as the "Description."

(1) Invention 1

"An agent for the treatment or prevention of osteoporosis that contains PTH (1-34) or salt thereof as the active ingredient, characterized in that PTH (1-34) or salt thereof is administered once a week in a unit dose of 200 units over a duration exceeding 48 weeks to 72 weeks or longer, which is for the inhibition of bone fractures to treat osteoporosis patients who satisfy all of the following conditions (1) through (3) below:

(1) Age 65 years or older

(2) Prevalent bone fractures

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher."

(2) Invention 2

"An agent for the treatment or prevention of osteoporosis that contains PTH (1-34) or salt thereof as the active ingredient, characterized in that PTH (1-34) or salt thereof is administered once a week in a unit dose of 200 units over a duration exceeding 48 weeks to 72 weeks or longer, which is for the inhibition of bone fractures to treat osteoporosis patients who satisfy all of the following conditions (1) through (3) below, wherein said PTH (1-34) or salt thereof is human PTH (1-34) acetate and said inhibition of bone fractures is for reducing the incidence of new vertebral fractures to 0% when the agent is administered over a duration exceeding 48 weeks and up to 72 week:

(1) Age 65 years or older

(2) Prevalent bone fractures

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher."

3. Summary of the JPO Decision

In the JPO Decision, the JPO stated that the Correction satisfies all of the requirements for correction, and determined as follows: [i] it cannot be said that Inventions 1 and 2 could have been easily made by a person skilled in the art even based on the invention described in Exhibit Ko 1"Effect of an Intermittent Weekly Dose of Human Parathyroid Hormone (1-34) on Osteoporosis: A Randomized Double-Masked Prospective Study Using Three Dose Levels" (*Osteoporosis International*, vol. 9, no.4, p.296–306, 1999) (the document is hereinafter referred to as "Exhibit Ko 1 Document" and the invention is hereinafter referred to as "Exhibit Ko 1 Invention") and the common general technical knowledge as of the international filing date of the original application, which is found to be the base date for determining the patentability of the Patent (September 8, 2010; hereinafter referred to as the "the Base Date"); [ii] it cannot be said that Inventions 1 and 2 could have been easily made by a person skilled in the art even based on the publicly known invention identified from a lecture of which content was published in Exhibit Ko 14-1 "Teriparachido sakusan'en [PTH (1-34)] no shū 1 kai kanketsu hika tōyo ni okeru shinki tsuitai kossetsu yokusei kōka" (The inhibitory effect on new vertebral fractures of intermittent weekly subcutaneous administration of teriparatide acetate [PTH (1-34)]) (*Osteoporosis Japan*, vol. 17, extra issue no. 1, p. 189, September 11, 2009) and from a broadcast program of which content was recorded in Exhibit Ko 14-2 "Kotsusoshōshō chiryōyō hito fukukōjōsen horumon seizai teriparachido sakusan'en" (Teriparatide acetate—a human parathyroid hormone preparation for the treatment of osteoporosis) (hereinafter referred to as "Exhibit Ko 14 Invention") and the common general technical knowledge as of the Base Date; [iii] Inventions 1 and 2 do not violate the support requirement (Article 36, paragraph (6), item (i) of the Patent Act), as they are stated in the detailed explanation of the invention in the description of the Patent (the description, including the drawings, is hereinafter referred to as the "Description"), and are within the extent of inventions for which a person skilled in the art is able to recognize that the problems to be solved by the inventions may be solved based on the statement of the detailed explanation of the invention or on matters suggested thereby; [iv] the statement of the detailed explanation of the invention for the Invention does not violate the enablement requirement (Article 36, paragraph (4), item (i) of the Patent Act), as a person skilled in the art is able to

work the Invention based on the statement of the Description and the common general technical knowledge as of the filing date; and [v] it cannot be said that Inventions 1 and 2 constitute the invention described in Exhibit Ko 12 "International Publication No. 2011/030774" (hereinafter the document is referred to as "Exhibit Ko 12 Document" and the invention is referred to as "Exhibit Ko 12 Invention"), because, while the Application satisfies the requirements for division of an application, Exhibit Ko 12 Document was published on March 17, 2011, after September 8, 2010, which is the filing date of the original application.

The summary of the JPO Decision regarding each issue is as follows.

(1) Regarding whether there is a lack of novelty based on Exhibit Ko 1 Invention (Grounds for Invalidation 3)

A. Finding of Exhibit Ko 1 Invention

An agent for the treatment of osteoporosis that contains hPTH (1-34) as the active ingredient, wherein 200 units of hPTH (1-34) are subcutaneously injected every week to treat subjects between the ages of 45 and 95 years who were defined as osteoporotic based on the diagnostic criteria proposed by a Committee supported by the Ministry of Health and Welfare, with a total score higher than 4 as a result of defining osteoporosis in terms of multiple factors weighted in the form of scores.

B. Common features between Invention 1 and Exhibit Ko 1 Invention

An agent for the treatment or prevention of osteoporosis that contains hPTH (1-34) as the active ingredient, wherein 200 units of hPTH (1-34) are administered once a week to treat osteoporosis patients.

C. Differences between Invention 1 and Exhibit Ko 1 Invention

(A) Difference 1

In the case of Invention 1, the "specified osteoporosis patients" are "osteoporosis patients who satisfy all of the following conditions (1) through (3) below:

(1) Age 65 years or older

(2) Prevalent bone fractures

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher,"

whereas in the case of Exhibit Ko 1 Invention, they are "subjects between the ages of 45 and 95 years who were defined as osteoporotic based on the diagnostic criteria proposed by a Committee supported by the Ministry of Health and Welfare, with a total score higher than 4 as a result of defining osteoporosis in terms of multiple factors weighted in the form of scores."

(B) Difference 2

The "agent for the treatment or prevention of osteoporosis" is specified to be one "for the inhibition of bone fractures" in Invention 1, whereas there is no such specification in Exhibit Ko 1 Invention.

(C) Difference 3

The agent is specified to be "administered ... over a duration exceeding 48 weeks to 72 weeks or longer" in Invention 1, whereas there is no such specification in Exhibit Ko 1 Invention.

(Hereinafter, "(1) Age 65 years or older" is referred to as "Condition (1)," "(2) Prevalent bone fractures" is referred to as "Condition (2))," "(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher" is referred to as "Condition (3)," and Conditions (1) through (3) are collectively referred to as the "Three Conditions." In addition, osteoporosis patients who satisfy all of the Three Conditions are referred to as "patients satisfying the Three Conditions" or "high-risk patients," and osteoporosis patients who do not satisfy all or part of the Three Conditions are referred to as "patients not satisfying the Three Conditions" or "low-risk patients.")

D. Ease in conceiving of the Differences

(A) Difference 1

The presence or absence of bone fractures, bone density, and age are important factors for diagnosing the progression of osteoporosis, but they are irrelevant to the process in Exhibit Ko 1 Invention of selecting osteoporosis patients who satisfy all of the Three Conditions as the patients to whom PTH is to be applied. In addition, the prior art documents have no description or suggestion that motivates the selection of osteoporosis patients who satisfy all of the Three Conditions.

Therefore, a person skilled in the art could not have easily conceived of the matters that define Invention 1 relating to Difference 1.

(B) Difference 2

Although patients with a high risk of bone fractures cannot be judged based on bone density measurements alone, factors such as the bone strength are not checked in Exhibit Ko 1 Document, and even based on statements in the prior art documents, it cannot be determined that the "agent for the treatment or prevention of osteoporosis" of Exhibit Ko 1 Invention is "for the inhibition of bone fractures."

(C) Difference 3

Exhibit Ko 1 Document indicates that, if the agent is administered over a duration exceeding 48 weeks in a clinical trial including administration of 200 units, a considerable number of patients are expected to drop out, and therefore 48 weeks were

thought to be the limit of duration of administration in the test planning phase. As a result of the trial, as many as 22% of the patients (more than half the patients experiencing side effects) dropped out without being able to withstand the trial in the case of administration of 200 units, which means that an excessively high dropout rate was observed even with a duration of 48 weeks.

In the experiment in Exhibit Ko 3 "SAITO Mitsuru et al., 'Teriparachido (hPTH1-34) no shū ikkai tōyo wa kotsuryō/kotsushitsu wo kaizenshi kotsu kyōdo wo zōkyō suru: ransō tekitshutsu saru ni taisuru 18 kagetsu tōyo no kentō" (Weekly administration of teriparatide (hPTH1-34) improves the bone mass/bone quality and enhances the bone strength: a study on 18-month administration to ovariectomized monkeys' (*The Journal of the Japanese Orthopaedic Association*, vol. 82, no. 8, S1159, 2-8-23, 2008)" (hereinafter referred to as "Exhibit Ko 3 Document"), PTH is subcutaneously injected once a week over a duration of 18 months to ovariectomized (OVX) monkey models. As humans and monkeys are different animal species, it cannot be said that the agent has a similar effect on both monkeys and humans, and its inhibitory effect on bone fractures is also unknown. Therefore, it cannot be said that the statements in Exhibit Ko 3 Document serve as a motivation for continuing treatment for a duration of 18 months in Exhibit Ko 1 Invention. Exhibit Ko 2 "EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS (*J Med*, vol. 344, no.19, p.1434–1441, 2001)" (hereinafter referred to as "Exhibit Ko 2 Document") relates to a clinical trial in which 20 μg or 40 μg of PTH is administered subcutaneously daily over a period of 17 to 18 months (about 74 to 78 weeks) on average for the treatment of osteoporosis in postmenopausal women. As the dropout rate due to side effects is less than half of 22%, which is the dropout rate at 48 weeks (about 12 months) in the case of Exhibit Ko 1 Invention, it cannot be said that the statements in Exhibit Ko 2 Document serve as a motivation for continuing treatment for a duration exceeding 48 weeks in Exhibit Ko 1 Invention.

E. Effect of Invention 1

When the relative risk reduction (hereinafter referred to as the "RRR") of bone fractures in comparison to the placebo (control) is calculated based on the Description [Table 35], the RRR between 0 to 24 weeks in the case of administering the agent to patients who satisfy all of the Three Conditions for a duration of 24 weeks was about 54%, the RRR between 24 to 48 weeks in the case of administering the agent to patients who satisfy all of the Three Conditions for a duration of 48 weeks was about 82%, and the RRR between 48 to 72 weeks in the case of administering the agent to patients who

satisfy all of the Three Conditions for a duration of 72 weeks was about 100%. Therefore, it is found that the rate of reducing the risk of bone fractures in comparison to the placebo group rises by continuing weekly administration of 200 units of PTH to patients satisfying the Three Conditions in the long term.

In addition, Experiment Result Certificate I (Exhibit Ko 64; hereinafter referred to as "Exhibit Ko 64 Certificate") in Attachment 3 indicates the following RRR for the case of administering the test drug (200 units of PTH once a week) to patients satisfying the Three Conditions and patients not satisfying the Three Conditions who satisfy Condition (1) but do not satisfy at least one of Condition (2) or Condition (3), over a duration exceeding 48 weeks to 72 weeks or longer, and the case of administering the control (placebo) to these patients over a duration exceeding 48 weeks to 72 weeks or longer:

[i] Administration over a duration exceeding 48 weeks (Table 2)	Patients satisfying the Three Conditions	About 51%
	Patients not satisfying the Three Conditions	About 43%
[ii] Administration over a duration of 72 weeks or longer (Table 3)	Patients satisfying the Three Conditions	About 59%
	Patients not satisfying the Three Conditions	About 36%

According to this, when administering the agent for a duration of 72 weeks or longer, the RRR for patients satisfying the Three Conditions was as much as about 23% (59 minus 36) larger than that for patients not satisfying the Three Conditions, meaning that the agent demonstrated an extremely high inhibitory effect on bone fractures in patients satisfying the Three Conditions when administered for 72 weeks or longer. In addition, when administering the agent for a duration exceeding 48 weeks, the difference between the RRR for patients satisfying the Three Conditions and that for patients not satisfying the Three Conditions remained at about 8% (51 minus 43). Considering these results, patients satisfying the Three Conditions are found to be a patient group that is particularly suitable for long-term administration of 72 weeks or longer. Furthermore, Experiment Result Certificate J (Exhibit Ko 68; hereinafter referred to as "Exhibit Ko 68 Certificate") in Attachment 4 confirms the validity of Exhibit Ko 64 Certificate.

Due to the above, Invention 1, which specified the usage of "administering the agent over a duration exceeding 48 weeks to 72 weeks or longer" and selected patients

satisfying the Three Conditions as the subject patients for administration, is an invention for which the patient group and usage are specially limited to those for which a conspicuous pharmacological effect is demonstrated, and this effect cannot be predicted from the prior art documents.

F. Summary on Invention 1

Given the above, Invention 1 could not have been easily made by a person skilled in the art based on Exhibit Ko 1 Invention.

G. Regarding Invention 2

Invention 2 limits "PTH (1-34) or salt thereof" of Invention 1 to "human PTH (1-34) acetate," and limits the purpose, "for the inhibition of bone fractures," of Invention 1 by stating that "said inhibition of bone fractures is for reducing the incidence of new vertebral fractures to 0% when the agent is administered over a duration exceeding 48 weeks and up to 72 week." Therefore, Invention 2 also could not have been easily made by a person skilled in the art based on Exhibit Ko 1 Invention based on the same grounds as those for Invention 1.

(2) Regarding whether there is a lack of an inventive step based on Exhibit Ko 14 Invention (Grounds for Invalidation 4)

A. Finding of Exhibit Ko 14 Invention

An agent for the treatment of osteoporosis that contains teriparatide acetate as the active ingredient, characterized in that 100 units of teriparatide acetate are administered once a week over a duration up to 78 weeks, which is for the inhibition of new vertebral fractures to treat patients who are diagnosed to have osteoporosis based on the diagnostic criteria for primary osteoporosis and have one to five prevalent vertebral fractures and whose average age is 71.6 years.

B. Common features between Invention 1 and Exhibit Ko 14 Invention

An agent for the treatment or prevention of osteoporosis that contains PTH (1-34) or salt thereof as the active ingredient, characterized in that PTH (1-34) or salt thereof is administered once a week over a duration exceeding 48 weeks to 72 weeks or longer, which is for the inhibition of bone fractures to treat osteoporosis patients who satisfy all of the following conditions (2) and (3) below:

(2) Prevalent bone fractures

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher.

C. Differences between Invention 1 and Exhibit Ko 14 Invention

(A) Difference 4

With regard to "osteoporosis patients," the condition "(1) Age 65 years or older" is

added in Invention 1.

(B) Difference 5

The dose of "PTH (1-34) or salt thereof" is "a unit dose of 200 units" in Invention 1, whereas it is "a unit dose of 100 units" in Exhibit Ko 14 Invention.

D. Ease in conceiving of the Differences

(A) Difference 4

The presence or absence of bone fractures, bone density, and age are important factors for diagnosing the progression of osteoporosis, but they are irrelevant to the process in Exhibit Ko 14 Invention of selecting osteoporosis patients who satisfy all of the Three Conditions as the patients to whom PTH is to be applied. In addition, the prior art documents have no description or suggestion that motivates the selection of osteoporosis patients who satisfy all of the Three Conditions.

Therefore, a person skilled in the art could not have easily conceived of the matters that define Invention 1 relating to Difference 4.

(B) Difference 5

Exhibit Ko 1 Document indicates that, if the agent is administered over a duration exceeding 48 weeks in a clinical trial including administration of 200 units, a considerable number of patients are expected to drop out, and therefore 48 weeks were thought to be the limit of duration of administration in the test planning phase. As a result of the trial, as many as 22% of the patients (more than half the patients experiencing side effects) dropped out without being able to withstand the trial in the case of administration of 200 units, which means that an excessively high dropout rate was observed even with a duration of 48 weeks.

Considering the need to reduce the burden on patients, the document does not suggest that the dose of 200 units, which causes many side effects, is appropriate, and it neither clearly indicates nor suggests a motivation for trying a dose of 200 units. Therefore, a person skilled in the art could not have easily conceived of the matters that define Invention 1 relating to Difference 5.

E. Summary on Invention 1

The effect of Invention 1 is as mentioned in (1) E. above, and Invention 1 demonstrates a conspicuous pharmacological effect that cannot be predicted. Therefore, Invention 1 could not have been easily made by a person skilled in the art based on Exhibit Ko 14 Invention.

F. Regarding Invention 2

As Invention 2 is an invention that has added limitations as mentioned in (1) G. above, Invention 2 also could not have been easily made by a person skilled in the art

based on Exhibit Ko 14 Invention based on the same grounds as those for Invention 1.
(3) Regarding whether there is a violation of the support requirement (Grounds for Invalidation 1)

In Working Example 2 of the Description, a calcium agent and a vitamin agent are both used for the PTH 200 unit group as well as for the placebo group, and the RRR is calculated from the ratio between the incidence of bone fractures in the PTH 200 unit group and the incidence of bone fractures in the placebo group. Therefore, even if the calcium agent were to have some influence, the inhibitory effect on bone fractures is regarded as being evaluated while excluding such influence. Accordingly, it cannot be said that the detailed explanation of the invention of the Description fails to disclose Inventions 1 and 2 in such a manner that the problems to be solved by the inventions may be solved, on a basis that the Description does not contain an example of using 200 units of PTH alone without using a calcium agent or data of such example.

Moreover, the pharmacological actions of Teribone in Exhibit Ko 11 "Review report dated March 31, 2017" (hereinafter referred to as "Exhibit Ko 11 Document") and Exhibit Ko 30 "Re-examination report dated November 8, 2018" (hereinafter referred to as "Exhibit Ko 30 Document") indicate the same trend, and Exhibit Ko 11 Document states that "the incidences of new vertebral fractures in the respective evaluation periods of the period extension test did not show a sharply increasing trend after administration for 72 weeks" (lines 3 to 4 on page 8) with regard to Tables 7 and 8 on page 8. Considering these matters, even if Exhibit Ko 11 Document and Exhibit Ko 30 Document state that bone fractures occurred in the PTH group after 49 weeks or later, the results in the two documents do not deny the credibility of the results in [Table 35] of the Description (reducing the incidence of bone fractures to 0% in comparison to the placebo associated with continued incidence of bone fractures) or the "effect of completely inhibiting bone fractures in practice."

Due to the above, Inventions 1 and 2 are described in the detailed explanation of the invention in such a manner that a person skilled in the art is able to recognize that the problems to be solved by the inventions may be solved.
(4) Regarding whether there is a violation of the enablement requirement (Grounds for Invalidation 2)

Working Example 2 of the Description states that the agent showed an inhibitory effect on bone fractures in patients satisfying the Three Conditions to which 200 units of PTH were administered once a week ([Table 34], [Table 35], paragraphs [0132] and [0133]), and in light of the statement of the claims, Inventions 1 and 2 do not exclude combined use of calcium. Accordingly, even if the Description does not contain an

example of using 200 units of PTH alone without using a calcium agent or data of such example, it cannot be said that the detailed explanation of the invention is not stated in a manner that is clear enough and sufficient to enable a person skilled in the art to work the inventions.

Furthermore, similar to (3) above, the results in Exhibit Ko 11 Document and Exhibit Ko 30 Document do not deny the credibility of the results in [Table 35] of the Description (reducing the incidence of bone fractures to 0% in comparison to the placebo associated with continued incidence of bone fractures) or the "effect of completely inhibiting bone fractures in practice," and the contents of the two documents do not affect the abovementioned determination.

(5) Regarding a lack of novelty based on Exhibit Ko 12 Invention (Grounds for Invalidation 5)

In light of the statements in [14] and [15] in paragraph [0014], paragraphs [0032], [0034], [0131] through [0133], [Table 34], and [Table 35] of the initial description, claims, or drawings at the time of the filing (hereinafter referred to as the "initial description, etc. of the original application") of Patent Application No. 2011-530844, which is the original application of the Application (Exhibit Ko 12; hereinafter referred to as the "original application"), it can be said that a mode that does not require combined use of a calcium agent is also sufficiently described in the original application.

It follows that, as the Application is deemed to have been filed on September 8, 2010, which is the filing date of the original application, and Exhibit Ko 12 Document was published after that on March 17, 2011, it cannot be said that Inventions 1 and 2 lack novelty based on Exhibit Ko 12 Invention.

4. Grounds for rescission

(1) Error in the determination on an inventive step based on Exhibit Ko 1 Invention (Grounds for Rescission 1)

(2) Error in the determination on an inventive step based on Exhibit Ko 14 Invention (Grounds for Rescission 2)

(3) Error in the determination concerning the support requirement (Grounds for Rescission 3)

(4) Error in the determination concerning the enablement requirement (Grounds for Rescission 4)

(5) Error in the determination on novelty based on Exhibit Ko 12 Invention (Grounds for Rescission 5)

(omitted)

No. 4 Summary of the court decision

1. Regarding the Invention

(1) Matters stated in the Description

The Description (Exhibit Ko 69) contains statements as described in Attachment 1 "Matters stated in the Description (extract)." According to these statements, the following matters are found to be disclosed with regard to the Invention.

A. Technical Field

The Invention relates to a therapeutic or prophylactic agent for osteoporosis that contains PTH (parathyroid hormone) as the active ingredient, and also relates to an agent to inhibit or prevent bone fractures that contains PTH as the active ingredient (paragraphs [0001] and [0018]).

B. Background Art

Osteoporosis is a disease characterized by a decrease in bone strength that poses an increased risk of bone fractures, and PTH preparations are known as one agent for the treatment of osteoporosis (paragraph [0002]).

A prior art reference discloses a method of treating osteoporosis by subcutaneous administration of a unit dose of 100 or 200 units of PTH to the osteoporosis patient once a week over a period of 26 weeks, but it does not demonstrate whether or not the treatment method is capable of increasing the bone strength of the osteoporosis patient or decreasing the risk of bone fractures (paragraphs [0004] and [0005]).

There are also prior art references disclosing methods of treatment through daily administration of PTH, but as there were reports of instances of hypercalcemia as an adverse drug reaction and the like, and the treatment methods cannot be called adequate in terms of safety, a highly safe and effective method of treating osteoporosis by PTH was desired (paragraphs [0006] through [0009]).

C. Problems to be Solved by the Invention

The Invention provides a highly safe and effective method for treating or preventing osteoporosis by PTH, and furthermore, provides a highly safe method for inhibiting or preventing bone fractures by PTH (paragraph [0012]).

D. Means to Solve the Problems, etc.

In order to solve the above problems, it was discovered that a highly safe and effective method of treating or preventing osteoporosis and a highly safe method of inhibiting/preventing bone fractures can be achieved by limiting the PTH dose and administration interval, specifically, by administering PTH once a week in a unit dose of 100 to 200 units, and that these methods are especially effective in patients having a

high risk of bone fractures (paragraphs [0013], [0015], [0018], [0034], and [0035]).

While risk factors for bone fractures in osteoporosis include age, gender, low bone density, prevalent bone fractures, smoking, alcohol consumption, steroid use, family history of bone fractures, exercise, factors related to falls, bone metabolism markers, weight, calcium intake, and the like, osteoporosis patients who satisfy the following three conditions are defined as "high-risk patients" in the Invention: (1) age 65 years or older; (2) prevalent bone fractures; and (3) bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher (paragraph [0068]).

E. Working Example 1

Male and female patients diagnosed with primary osteoporosis, of which examples include involutional osteoporosis (postmenopausal osteoporosis and senile osteoporosis) and idiopathic osteoporosis (postpregnancy osteoporosis, juvenile osteoporosis, and the like), were classified into high-risk patients and low-risk patients (patients other than high-risk patients), and were subcutaneously administered 5 or 100 units of teriparatide acetate, which is a PTH preparation, once a week, intermittently (paragraphs [0037], [0077], and [0079]).

In the high-risk patients, a significant increase in the bone density, a significantly lower occurrence of new vertebral fractures, and a significantly lower occurrence of fractures at sites other than the vertebrae were found among the 100 unit group in comparison to the 5 unit group, and administration of 100 units of teriparatide acetate once a week was confirmed to provide a useful osteoporosis therapeutic agent and agent to inhibit or prevent bone fractures in high-risk patients; however, no significant difference could be found between the 100 unit group and the 5 unit group in the low-risk patients in terms of the bone density, the occurrence of new vertebral fractures, and the occurrence of fractures at sites other than the vertebrae (paragraphs [0083] through [0094], and [Table 4] through [Table 11]).

The administration also did not cause hypercalcemia at either dose during the administration period (paragraph [0095] and [Figure 1]).

F. Working Example 2

Teriparatide acetate "200 units" (test drug) and placebo (control) were each administered subcutaneously at a frequency of once a week over a span of 72 weeks to male and female high-risk patients diagnosed with primary osteoporosis (paragraph [0098]).

When the incidence of multiple vertebral fractures (two or more new vertebral fractures) (number of cases) was compared in the test drug group and control group after 72 weeks of administration, it was 2.1% (6 cases) in the control group and 0.8%

(2 cases) in the test drug group, and the test drug demonstrated an inhibitory or preventative effect against multiple vertebral fractures (paragraph [0109] and [Table 12]). In addition, the test drug was shown to be effective on worsening bone fractures (paragraph [0118] and [Table 20]).

The incidence of new vertebral fractures every six months was basically steady at approximately 5% in all divisions of the placebo group, but in contrast, the incidence of each division dropped as the administration period lengthened in the PTH200 unit group, and no new vertebral fractures occurred after 48 weeks; the incidence of new vertebral fractures was also lower than that of the placebo group in all divisions consisting of within 24 weeks, 24 to 48 weeks, and 48 to 72 weeks, and the relative risk reduction (RRR) in comparison to the placebo increased as administration continued; thus, weekly administration of 200 units of PTH inhibited the occurrence of new vertebral fractures from an early stage, and the risk of fractures had already dropped 53.9% versus the placebo after 24 weeks, and the inhibitory effect of this drug on bone fractures also tended to intensify as administration continued (paragraphs [0131] and [0132], [Table 34], and [Table 35]).

The incidence of vertebral fractures (new + worsening) after 72 weeks by Kaplan-Meier estimation in the FAS (Full Analysis Set) of the fracture study was 3.5% in the PTH200 unit group and 16.3% in the placebo group, and the incidence in the PTH 200 unit group was thus lower than that in the placebo group (log rank test, $p < 0.0001$); 200 units of this drug also lowered the risk of vertebral fractures (new + worsening) 78.6% in comparison to the placebo after 72 weeks; and when the six-month vertebral fracture (new + worsening) incidence was compared between groups, the incidence of the PTH200 group was lower than that of the placebo group in all divisions consisting of within 24 weeks, 24 to 48 weeks, and 48 to 72 weeks (paragraph [0133]).

(2) Regarding the statement of the Description

According to the contents of a reply (undisputed fact; Exhibit Ko 76) made by the Plaintiff that owns the Patent to the trial panel at the time of the trial of the present case, the following points are found in the contents disclosed by the Description.

A. While Working Example 1 relates to patients who were diagnosed with osteoporosis based on Exhibit Ko 5 Diagnostic Criteria ([Non-patent Reference 12] in paragraph [0011], and paragraph [0077]), they are all patients who have one or more vertebral fractures and were diagnosed with osteoporosis due to falling under the category of "I. With vertebral fracture on X-ray film" under the diagnostic criteria. They do not include patients who were diagnosed with osteoporosis due to falling under the category of "II. Without vertebral fracture on X-ray film" and "Degree of bone atrophy of II or higher

on spinal X-ray images or a bone density value of less than 70% of YAM" under the diagnostic criteria.

B. As tests relating to the Invention did not make bone density measurement a requirement, patients without no data of the lumbar spine bone mineral density are included. Therefore, the young adult mean value (YAM value) of the lumbar spine bone mineral density indicated is the mean value for patients for whom such data was obtained.

The number of patients for whom the YAM value data of the lumbar spine bone mineral density was obtained was as follows: in [Table 2] (paragraph [0081]), 35 out of the total 64 cases in the 5 unit group, and 35 out of the total 52 cases in the 100 unit group; and in [Table 3] (paragraph [0081]), 8 out of the total 10 cases in the 5 unit group, and 2 out of the total 11 cases in the 100 unit group.

Of the total numbers of cases mentioned above, those for whom the bone density was measured with regard to the changes in the lumbar spine bone mineral density situation in high-risk patients (paragraph [0084] and [Table 4]) was 33 cases in the 5 unit group and 30 cases in the 100 unit group. Those for whom the bone density was measured with regard to the changes in the lumbar spine bone mineral density situation in low-risk patients (paragraph [0085] and [Table 5]) was 7 cases in the 5 unit group and 1 case in the 100 unit group. The numbers are even smaller than the numbers of patients for whom the YAM value data of the lumbar spine bone mineral density was obtained, due to such reasons as that the lumbar spine bone mineral density at each point of time after the start of administration could not be measured for the relevant patients' own reasons, etc. and therefore the change rate of the lumbar spine bone mineral density could not be evaluated.

C. With regard to the situation of new vertebral fractures in high-risk patients (paragraph [0087] and [Table 6]), the number of cases evaluated was 64 cases in the 5 unit group and 52 cases in the 100 unit group. With regard to the situation of new vertebral fractures in low-risk patients (paragraph [0088] and [Table 7]), the number of cases made subject to evaluation was 10 cases in the 5 unit group and 11 cases in the 100 unit group. The respective total numbers of cases are the same as those in [Table 2] and [Table 3].

D. In [Table 2] (paragraph [0081]), the number of cases of high-risk patients was 64 in the 5 unit group and 52 cases in the 100 unit group, whereas in the situation of new vertebral fractures every 26 weeks in high-risk patients shown in [Table 8] (paragraph [0091]), the number was 63 cases in the 5 unit group and 51 cases in the 100 unit group. This was due to erroneous entry of the number of cases evaluated in [Table 8], the cause

of which is unknown. Even if [Table 8] is re-analyzed and the significant difference is examined, the incidence of bone fractures in the 100 unit group is significantly lower than that in the 5 unit group.

Meanwhile, in the situation of new vertebral fractures in high-risk patients shown in [Table 6] (paragraph [0087]), the number of cases of bone fractures in the 5 unit group is 13 cases, whereas in the situation of new vertebral fractures every 26 weeks in high-risk patients shown in [Table 8], the number is 18 cases in the 5 unit group. This is because, in [Table 8], the number of cases with bone fractures is aggregated for each evaluation division in the 5 unit group, whereas in [Table 6], the number of cases that experienced bone fractures throughout the entire period is aggregated (a patient that experienced fractures in multiple divisions is counted as one case).

E. In [Table 3] (paragraph [0081]), the number of cases of low-risk patients was 10 cases in the 5 unit group and 11 cases in the 100 unit group, whereas in the situation of new vertebral fractures every 26 weeks in low-risk patients shown in [Table 9] (paragraph [0091]), the number was 21 cases in the 5 unit group and 12 cases in the 100 unit group. This was due to erroneous entry of the number of cases evaluated in [Table 9], the cause of which is unknown. Even if [Table 9] is re-analyzed (shown below) and the significant difference is examined, no significant difference is found between the groups.

	5 unit group				100 unit group			
	No. evaluated	No. with fractures	Incidence (%)	No. of fractures	No. evaluated	No. with fractures	Incidence (%)	No. of fractures
After 26 W	10	0	0.0	0	11	1	9.1	2
After 52 W	10	1	10.0	1	11	0	0.0	0
After 78 W	7	0	0.0	0	11	0	0.0	0
After 104 W	2	0	0.0	0	6	0	0.0	0
After 130 W	1	0	0.0	0	3	0	0.0	0

F. In the situation of fractures of sites other than the vertebrae in high-risk patients (paragraph [0093] and [Table 10]), the number of cases evaluated is 64 cases in the 5 unit group and 52 cases in the 100 unit group, which are the same as the total numbers of patients in [Table 2].

2. Regarding whether there are Grounds for Rescission 1 (error in the determination on an inventive step based on Exhibit Ko 1 Invention)

(1) Regarding Exhibit Ko 1 Invention

Exhibit Ko 1 Document contains statements as described in Attachment 2 "Matters stated in Exhibit Ko 1 Document (extract)" (the Japanese translation of this document is based on Exhibit Otsu 2). According to these statements, Exhibit Ko 1 Invention can be found in the same manner as it was in the JPO Decision, and there is no dispute between the parties regarding this point.

Meanwhile, "the diagnostic criteria proposed by a Committee supported by the Ministry of Health and Welfare" in Exhibit Ko 1 Invention is found to be Exhibit Ko 6 Diagnostic Criteria.

(2) Regarding the common general technical knowledge as of the Base Date (September 8, 2010)

In this case, there is a dispute between the parties regarding the base time for determining the requirements for patentability of the Patent (there are explicit allegations in Grounds for Rescission 5), but this point is set aside for the moment, and an examination is first made based on the earlier date, September 8, 2010, alleged by the Defendant (the Base Date).

A. Regarding the common general technical knowledge concerning osteoporosis as of the Base Date

(A) The following documents contain the statements respectively cited below.

a. "Kotsusoshōshō no byōtai to chiryō: Kotsusoshōshō no atarashii shindan kijun to mondaiten" (Disease states and treatment of osteoporosis: a new diagnostic criteria for osteoporosis and issues) (1999; Exhibit Ko 6)

[i] "In Japan, the Ministry of Health and Welfare Silver Science Osteoporosis Research Group (Leader [A]) proposed diagnostic criteria based on a scoring system in 1988, from a standpoint that importance should be placed on both decreased bone mass and clinical conditions (Table 1)." (Line 18 of the left column to line 2 of the right column on page 38)

[ii] "Table 1. Diagnostic criteria for involutional osteoporosis

		Score		
1) With low bone mass		3		
2) With bone fracture	1 at the spine	1	Determined	
	2 or more at the spine	2	Certain	5 points or more
	At the femoral neck	3	Almost certain	4 points
	At the radius	1	Possible	3 points
3) Premenopausal woman		-1	Denied	2 points or less

4) With low back pain	1	
5) Serum calcium, phosphorus, and AL-P values		
Normal	1	
1 item abnormal	0	
2 items abnormal	-1	

" (page 38; This "Table 1. Diagnostic criteria for involutional osteoporosis" is Exhibit Ko 6 Diagnostic Criteria.)

b. "Kotsusoshōshō" (Osteoporosis) (1989; Exhibit Ko 7)

[i] "Introduction

In recent years, osteoporosis has drawn substantial interest in line with the advent of an aging society ... the Ministry of Health and Welfare Silver Science 'Comprehensive Research Group for Prevention and Treatment of Senile Osteoporosis' (Leader [A]) has proposed draft criteria for allowing anyone to easily diagnose osteoporosis, that is, a method to weigh subjective and objective findings in the form of scores, and make a diagnosis according to those scores." (Lines 1 to 13 of the upper column on page 27)

[ii] "(3) Age

Looking at the incidence of osteoporosis by age and by gender, the incidence is overwhelmingly high in women of age 60 years or older, whereas it rises sharply at age 80 years or older in men. This means that, in women, osteoporosis associated with clinical symptoms begins to develop 10 to 15 years after menopause." (Lines 6 to 11 of the upper column on page 30)

[iii] "This disease does not develop within a short term, but begins to develop over the course of a long term based on aging ..." (Lines 14 to 16 of the lower column on page 31)

c. "Diagnostic criteria for primary osteoporosis (year 1996 revision)" (1997; Exhibit Ko 5)

"Table 4. Diagnostic criteria for primary osteoporosis (year 1996 revision)

I. With vertebral fracture on X-ray film
A case with a low bone mass (degree of bone atrophy of I or higher, or bone density less than 80% of the young adult mean (YAM)) and non-traumatic vertebral fracture is determined to have osteoporosis.
II. Without vertebral fracture on X-ray film

	Spinal X-ray images	Bone density value
Normal	Without bone atrophy	
Decreased bone mass	Grade I bone atrophy	80 to 70% of YAM
Osteoporosis	Grade II bone atrophy or higher	Less than 70% of YAM

YAM: young adult mean (age 20 to 44 years)

(Note) The bone density value is that of the lumbar spine, in principle. Only when evaluation of the lumbar spine bone mineral density value is difficult, the bone density value of the radius, second metacarpal, femoral neck, or calcaneus is used.

Bone atrophy corresponds to radiographic osteopenia.

..." (page 223; This "Table 4. Diagnostic criteria for primary osteoporosis (year 1996 revision)" is Exhibit Ko 5 Diagnostic Criteria.)

d. "Diagnostic criteria for primary osteoporosis (year 2000 revision)" (2001; Exhibit Ko 9)

[i] "In 1995, the Japanese Society for Bone and Mineral Metabolism (now the Japanese Society for Bone and Mineral Research) established The Osteoporosis Diagnostic Criteria Review Committee, which consisted of representatives from the fields of orthopedics, internal medicine (geriatrics), gynecology, radiology, and sports medicine who were involved in clinical research or the medical care of patients with osteoporosis. After obtaining the consensus of its members and following discussions held at the 13th scientific meeting of the Society, the Committee created diagnostic criteria for primary osteoporosis. ... Further, the Committee reviewed the diagnostic criteria in 1996, and created the year 1996 revision of the criteria. ... This time, the Committee created the year 2000 revision by incorporating the results of osteoporosis research achieved from 1996 onward." (Lines 2 to 13 of the left column on page 76)

[ii] "Table 3. Diagnostic criteria for primary osteoporosis (draft year 2000 revision)

Primary osteoporosis is diagnosed when no disease causing low bone mineral density other than osteoporosis and no secondary osteoporosis are observed, and the results of bone assessment meet the following requirements.

I. With fragility fracture(Note 1)	
III. Without fragility fracture	
Bone mineral density (BMD)(Note 2)	Radiographic osteopenia of the spine(Note 3)

Normal	80% of YAM or higher	Absent
Decreased bone mass	70%–80% of YAM	Possible
Osteoporosis	Less than 70% of YAM	Present

YAM: young adult mean (age 20–44 years)

Note 1: Fragility fracture is a non-traumatic bone fracture that is caused by slight external force to a bone with low BMD (BMD less than 80% of YAM or presence of radiographic osteopenia of the spine). Sites of fracture include the spine, femoral neck, and the distant end of the radius.

Note 2: Bone mineral density usually refers to lumbar BMD. ...

Note 3: In the evaluation of radiographic osteopenia of the spine, existing criteria for determining the degree of bone atrophy are to be referenced.

Radiographic osteopenia of the spine	Existing criteria for determining the degree of bone atrophy
Absent	Without bone atrophy
Possible	Grade I bone atrophy
Present	Grade II bone atrophy or higher

"(page 78; the word "draft year 2000 revision" in the title is found to be a misdescription of "year 2000 revision"; this "Table 3. Diagnostic criteria for primary osteoporosis (draft year 2000 revision)" is Exhibit Ko 9 Diagnostic Criteria.)

e. "Kotsusoshōshō no yobō to chiryō gaidorain 2006 nenban" (Guidelines on prevention and treatment of osteoporosis 2006) (2006; Exhibit Ko 23)

[i] "At the National Institutes of Health (NIH) Consensus Development Conference, the definition of osteoporosis was revised to "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture." The conference also stated that "bone strength" consists of two features, bone density and bone quality, and that BMD accounts for approximately 70% of bone strength. It consolidated the explanatory factor for the remaining 30% into the term "bone quality," stating that bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization ..." (Lines 27 to 36 of the right column on page 2)

[ii] "Osteoporosis is a disease that is frequently seen in elderly people..." (Line 3 of the right column on page 30)

[iii] "Against a background of progress and diffusion of bone mass measurement

methods, at the International Conference on Osteoporosis in 1991, osteoporosis was defined to be a disease characterized by low bone mass and the microarchitectural deterioration of bone tissue, with a consequent increase in the fragility of bone and susceptibility to fracture. Diagnostic criteria compliant with this definition were developed also in Japan, and based on the diagnostic criteria created by the Japanese Society for Bone and Mineral Research in 1996, a revised version was created in 2000, which has been used to date (Table 21)." (Lines 3 to 10 of the left column on page 31)

[iv] "III. Risk factors of bone fracture associated with osteoporosis

...

The risk factors for bone fractures are factors that affect "a decrease in bone density," "a decrease in bone quality," and "external force (such as a fall)." In order to determine patients with a high risk of bone fractures, it is necessary to evaluate risk factors related to "bone quality" and "external force," in addition to measuring the bone density. The key is an understanding of what are risk factors for bone fractures that are independent of bone density.

Age and gender

... Being a woman and advanced age are important risk factors for bone fractures associated with osteoporosis. Age is a fracture risk factor that is independent of bone density, and even if the bone density is the same, the fracture risk will be higher if the age is higher...

Low bone density

Low bone density strongly predicts bone fractures. ...

Prevalent bone fractures

Presence of prevalent bone fractures approximately doubles the future fracture risk, irrespective of gender and site. ...

Smoking

...

Alcohol consumption

...

..." (Page 34)

[5] "Table 22. Risk factors for bone fractures (only indicating the results of a meta-analysis or systematic review [Evidence Level I])

Risk factor	Document	Results
Low bone density	...	...

Risk factors independent of bone density	Prevalent bone fractures*	...	...
	Smoking*	...	...
	Alcohol consumption*	...	...
	...	...	...
...	...	...	...

..." (Page 35)

[vi] "Summary

At present, osteoporosis treatment is started according to the bone density. However, even if the bone density is the same, the fracture risk will be higher if the age is higher and a larger number of risk factors* shown in Table 22 are present. By comprehensively considering the bone density, age, and risk factors, it is possible to screen people with a higher fracture risk more effectively." (Lines 1 to 7 of the right column on page 35)

[vii] "The purpose of osteoporosis treatment is to reduce the risk of bone fractures and to maintain and improve the quality of life (QOL)." (Lines 1 to 2 of the left column on page 50)

[viii] "Bone strength is defined by bone density and bone quality, and about 70% of bone strength depends on bone density. Therefore, decreased bone density is the central factor that increases the risk for bone fractures in osteoporosis. Moreover, it has become clear in recent years that there are many factors other than decreased bone density that increase the risk of bone fractures. The risk factor items mentioned by the U.S. National Osteoporosis Foundation (NOF), the WHO group, Canada guidelines, and the like slightly differ from each other. However, the commonly mentioned factors are being a woman, estrogen deficiency (menopause), age (65 years or older), low bodyweight (less than 57.8 kg), prevalent bone fracture, maternal history of femur fracture, smoking habit, excessive alcohol consumption, and hypomotility." (Lines 9 to 20 of the left column on page 50)

[ix] "Apart from low bone density, the WHO confirmed seven factors, namely, prevalent bone fractures, smoking, large alcohol consumption (two units or more per day: nearly equivalent to 2 *go* (approx. 360 ml) of Japanese sake), parental history of femoral neckbone fracture, advanced age, rheumatoid arthritis, and use of steroids, as clinical risk factors for bone fractures through a meta-analysis. ...In addition, the WHO indicated that the six clinical risk factors for bone fractures, other than low bone density and age, respectively increase the fracture risk by about 1.6 to 2 times independently. ... It also states that age is a factor that increases the fracture risk from the other seven risk factors for bone fractures.

Moreover, the WHO sets the incidence of bone fractures in the general population of each region or country as a relative fracture risk of 1, and proposes to use the absolute fracture risk, which is obtained by multiplying said fracture risk by the sum of the relative risks associated with low bone density and the other seven clinical fracture risk factors, as a criterion for starting drug treatment. ... Indeed, it is considered necessary also for Japan to introduce the "absolute fracture risk" in determining the start of treatment in the future. Currently, however, although there is evidence concerning low bone density, prevalent bone fractures, and age, there is still no sufficient data on relative risks associated with other clinical fracture risk factors and their relevance to age." (Lines 6 to 31 of the right column on page 51)

(B) According to the respective statements in (A) above, the common general technical knowledge concerning osteoporosis as of the Base Date was as follows.

Specifically, it can be said that the following were known: [i] osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, and the purpose of its treatment is to prevent bone fractures and to maintain and improve the quality of life (QOL); [ii] the incidence of osteoporosis increases with age; [iii] in Japan, there is evidence concerning low bone density, prevalent bone fractures, and age from among the several risk factors for bone fractures associated with osteoporosis; [iv] with regard to diagnostic criteria for osteoporosis, there were diagnostic criteria proposed by the Ministry of Health and Welfare Silver Science Project "Comprehensive Research Group for Prevention and Treatment of Senile Osteoporosis " (Exhibit Ko 6 Diagnostic Criteria) as of 1990, but the diagnostic criteria were revised in 1996 (Exhibit Ko 5 Diagnostic Criteria), and then further revised in 2000 (Exhibit Ko 9 Diagnostic Criteria); and [v] bone strength consists of two features, bone density and bone quality, and bone density accounts for approximately 70% of bone strength, while bone quality accounts for the remaining 30%.

B. Regarding the common general technical knowledge concerning the administration period of a PTH preparation as of the Base Date

(A) The following documents contain the statements respectively cited below.

a. "Kotsusoshōshō no yobō to chiryō gaidorain 2006 nenban" (Guidelines on prevention and treatment of osteoporosis 2006) (2006; Exhibit Ko 23)

" ■ Parathyroid hormone (PTH)

Human PTH (1-34) (teriparatide) subcutaneous injection agent

PTH, which is expected to demonstrate effects as an osteogenesis promoter, has undergone large-scale clinical trials overseas, and has already been approved in many

countries including the United States. In a large-scale clinical trial targeting osteoporosis patients with vertebral fracture who were five or more years past menopause, 20 μg of human PTH (1-34) was self-administered subcutaneously daily over an average period of 18 months. As a result, the incidence of new vertebral fractures was reduced to 5%, nearly one-third of the incidence of 14% for the control group. In addition, the incidence of new non-vertebral fractures was also reduced to 3%, half of the incidence of 6% for the control group. The bone density in the lumbar spine and the femoral neck increased by 9% and 3%, respectively, as a result of administration of 20 μg of human PTH (1-34), showing notable bone density increases in both sites. These results show that a notable decrease in the fracture rate can be achieved in the short term of 18 months through daily subcutaneous administration of human PTH (1-34), and clinically prove that, due to promotion of bone formation, bone density increases even if the bone turnover is enhanced. Based on these results, clinical trials of daily subcutaneous administration of human PTH (1-34) targeting osteoporosis patients are also under way in Japan. On the other hand, the effects of a subcutaneous injection preparation for weekly administration have also been studied in the past, and the results of its phase II clinical trial showed that weekly administration of 200 units (equivalent to approx. 60 μg) for one year increases the vertebral bone density by 8.1%." (Lines 1 to 25 of the right column on page 99)

b. "Kotsu keisei sokushin'yaku / fukukōkōsen horumon (PTH) / PTH (1-34)" (Osteogenesis promoter / parathyroid hormone (PTH) / PTH (1-34)) (2007; Exhibit Ko 34)

"3. Clinical trial: daily subcutaneous administration of PTH (1-34)

a. Effects to improve bone density and inhibit bone fractures

In a recent large-scale clinical study, PTH (1-34) was administered daily to 1,637 postmenopausal women with prevalent vertebral fracture for an average of 19 months. As a result, in the 20 μg group, the bone density increased by 9.7% at the lumbar spine and by 2.8% at the femoral neck, while the frequency of new vertebral fractures decreased by 65%, and the frequency of non-vertebral fractures was also inhibited by 53%." (Lines 11 to 23 of the left column on page 444)

c. "Review report dated April 6, 2010" attached to "Report on the deliberation results dated May 6, 2010" (April 2010; Exhibit Ko 45)

[i] "[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." (Page 2)

[ii] "2) Foreign phase III study (...)

... A placebo-controlled, randomized, double-blind, parallel-group study was conducted in foreign postmenopausal patients with osteoporosis (the target sample size of 1,476 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.

... The median treatment duration [the 25th percentile, the 75th percentile] was 576.0 [534, 624] 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).

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." (Pages 53 to 54)

[iii] Tables 17, 18, and 19

"

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

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." (Page 54)

[iv] "3) Maximum duration of treatment

... 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." (Page 96)

d. Exhibit Ko 2 Document

[i] "Abstract

...

Methods: We randomly assigned 1,637 postmenopausal women with prior vertebral fractures to receive 20 or 40 μg of parathyroid hormone (1-34) or placebo, administered subcutaneously by the women daily. ...

Results: New vertebral fractures occurred in 14 percent of the women in the placebo group and in 5 percent and 4 percent, respectively, of the women in the 20-μg and 40-μg parathyroid hormone groups; the respective relative risks of fracture in the 20-μg and 40-μg groups, as compared with the placebo group, were 0.35 and 0.31 (95 percent confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility factures occurred in 6 percent of the women in the placebo group and in 3 percent of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). As compared with placebo, the 20-μg and 40-μg doses of parathyroid hormone increased bone mineral density by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck; ... Parathyroid hormone had only minor side effects (occasional nausea and headache).

Conclusions: Treatment of postmenopausal osteoporosis with parathyroid hormone

(1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated." (Lines 1 to 42 of the left column on page 1434)

[ii] "The cumulative duration of the study treatment in the group that received placebo, the group that received 20 μg of parathyroid hormone (1-34) per day, and the group that received 40 μg per day was 798, 779, and 774 patient-years, respectively, and the mean (±SD) duration of treatment in the three groups was 18±5, 18±6, and 17±6 months, respectively." (Lines 46 to 53 of the right column on page 1435)

[iii] "Figure 1. Cumulative Proportion of Women Assigned to Receive Placebo or Parathyroid Hormone (1-34) (PTH) at a Daily Dose of 20 μg or 40 μg Who Had One or More Nonvertebral Fractures (Panel A) and the Cumulative Proportion Who Had One or More Nonvertebral Fragility Fractures (Panel B) during the Study.

For both panels, the respective numbers of women in the placebo group and in the 20-μg and 40-μg PTH groups were 544, 541, and 552 at base line; 497, 492, and 486 at 6 months; 477, 465, and 456 at 12 months; and 404, 400, and 390 at 18 months. P≤0.05 for all pairwise comparisons with placebo, by the log-rank test." (Figure 1)

[iv] "Figure 1.

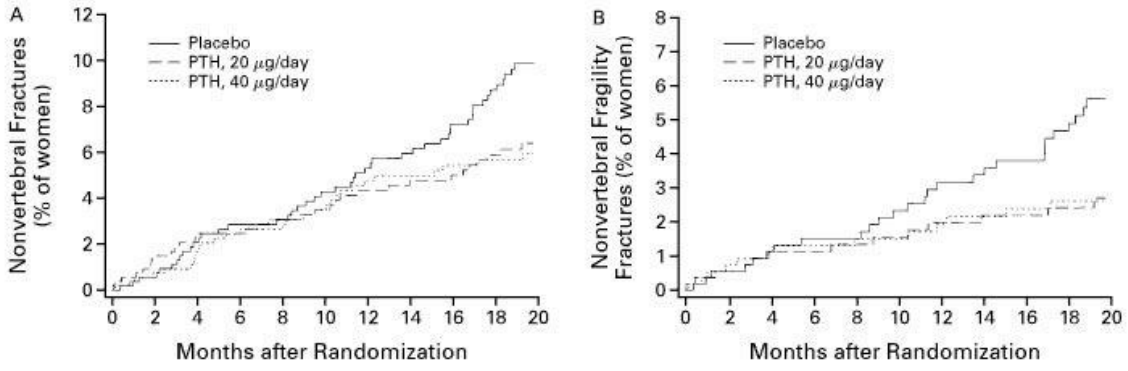


Figure 1. Cumulative Proportion of Women Assigned to Receive Placebo or Parathyroid Hormone (1-34) (PTH) at a Daily Dose of 20 μg or 40 μg Who Had One or More Nonvertebral Fractures (Panel A) and the Cumulative Proportion Who Had One or More Nonvertebral Fragility Fractures (Panel B) during the Study.

For both panels, the respective numbers of women in the placebo group and in the 20-μg and 40-μg PTH groups were 544, 541, and 552 at base line; 497, 492, and 486 at 6 months; 477, 465, and 456 at 12 months; and 404, 400, and 390 at 18 months. P≤0.05 for all pairwise comparisons with placebo, by the log-rank test." (Page 1438)

(B) According to the respective statements in (A) above, the common general technical knowledge concerning the administration period of the PTH preparation as of the Base Date was as follows.

Specifically, it is found that the following were known as the common general

technical knowledge: [i] a preparation for daily administration of 20 μg of PTH was already approved overseas for a maximum administration period of 24 months; and [ii] an increase in bone density and inhibition of new vertebral fractures can be achieved through daily administration of 20 μg or 40 μg of PTH for 18 months or longer.

(3) Regarding the ease in conceiving of Difference 1

A. Examination

(A) Exhibit Ko 1 Invention and Invention 1 are the same in terms of the dose, as they are both "characterized in that PTH (1-34) or salt thereof is administered once a week in a unit dose of 200 units," but they differ in terms of the scope of osteoporosis patients to which they are administered.

(B) As mentioned in (1) above, those selected as the subject patients for administration in Exhibit Ko 1 Invention are patients who were diagnosed with osteoporosis based on Exhibit Ko 6 Diagnostic Criteria. However, as it is a common practice for a person skilled in the art to select patients by referring to newer criteria, it can be said that if a person skilled in the art who comes across Exhibit Ko 1 Invention is to select the subjects for administration of the agent for the treatment of osteoporosis for weekly administration of 200 units of PTH in Exhibit Ko 1 Invention, the person would refer to not only Exhibit Ko 6 Diagnostic Criteria, but also to newer Exhibit Ko 5 Diagnostic Criteria or Exhibit Ko 9 Diagnostic Criteria.

As mentioned in A. (A) c. and d. above, those diagnosed with osteoporosis based on Exhibit Ko 5 Diagnostic Criteria are [i] those with a low bone mass (degree of bone atrophy of I or higher or bone density less than 80% of YAM) and non-traumatic vertebral fracture, or [ii] those without vertebral fracture on X-ray film, but with the degree of bone atrophy of II or higher or a bone density value of less than 70% of YAM. Meanwhile, those diagnosed with osteoporosis based on Exhibit Ko 9 Diagnostic Criteria are [iii] those with a non-traumatic bone fracture, etc. that is caused by slight external force to a bone with low bone density (degree of bone atrophy of II or higher or bone density less than 80% of YAM) (fragility fracture), or [iv] those without fragility fracture, but with the degree of bone atrophy of II or higher or a bone density value of less than 70% of YAM.

As Conditions (2) and (3) are the same as [i] above ("prevalent bone fractures" include "non-traumatic vertebral fractures"), it is not at all difficult for a person skilled in the art to select osteoporosis patients for administration of the agent for the treatment of osteoporosis for weekly administration of 200 units in Exhibit Ko 7 Invention based on Conditions (2) and (3).

In addition, as mentioned in (2) A. (B) above, there was the common general

technical knowledge that the incidence of osteoporosis increases with age. As it is clear that elderly people are people of advanced age, it is a commonsense practice to select those of age 65 years or older as elderly people. Also, as mentioned in (2) A. (A) e. [ix] above, the age of 65 years or older is a commonly mentioned factor from among the risk factor items mentioned by the U.S. NOF, the WHO group, Canada guidelines, and the like, and Article 32 of the Act on Assurance of Medical Care for Elderly People also defines elderly people to be those of age 65 years or older. Accordingly, it is a natural choice and not difficult at all to consider these points and to set a condition like Condition (1), in addition to Conditions (2) and (3), by selecting those of age 65 years or older as osteoporosis patients subject to administration, focusing on the fact that age is mentioned, along with low bone density and prevalent bone fractures, as multiple risk factors for bone fractures associated with osteoporosis.

Therefore, it would not have been particularly difficult for a person skilled in the art who came across Exhibit Ko 1 Invention to specify the subject patients for administration to be patients who satisfy all of the Three Conditions, even as of the Base Date.

B. Regarding the Defendant's allegations

As mentioned in No. 3, 1. (2) B. above, the Defendant alleges the following: [i] there is no reason to apply Exhibit Ko 5 Diagnostic Criteria as of the priority date of the Patent, and even if patients were diagnosed with osteoporosis based on Exhibit Ko 5 Diagnostic Criteria, there is no motivation to select those who satisfy Conditions (2) and (3) from among them; [ii] as special circumstances are needed for using 200 units of PTH that have the risk of side effects on elderly people of age 65 years or older, who generally have poor physical strength, there is no motivation to select those who satisfy Condition (1); and [iii] Exhibit Ko 1 Document states that no differences were observed in the effects even when the subjects were divided into subgroups based on viewpoints including "age" and "prevalent bone fractures," and does not motivate the combination of the Three Conditions.

As mentioned in (2) A. (A) e. above, Exhibit Ko 5 Diagnostic Criteria divide patients into those with or without bone fracture, and change the degree of bone atrophy and the bone density value. However, given that osteoporosis is a skeletal disorder with an increased risk of fracture as mentioned in (2) A. (B) above, a person skilled in the art may select, as appropriate, the diagnostic criteria for a case with prevalent bone fractures from among those criteria. Whichever diagnostic criteria are used, a person who satisfies the diagnostic criteria will be diagnosed with osteoporosis. Therefore, which diagnostic criteria to select is merely an arbitrary choice of a person skilled in

the art. Also, merely because elderly people generally have poor physical strength compared to young people, it is unlikely for a person skilled in the art to give up application of the agent for the treatment of osteoporosis, which elderly people particularly need, as the incidence increases with age as mentioned in (2) A. (B) above.

Indeed, it is found that Exhibit Ko 1 Document contains a statement that "Responses were similar among subgroups of subjects who were 64 years or younger and 65 years or older, weighed 49 kg or less and 50 kg or more, were less than 10 years, between 10 and 20 years and more than 20 years after the postmenopause, and had 0, 1 and 2 or more vertebral fractures" (line 11 of the left column to line 6 of the right column on page 300) as described in Attachment 2. However, this statement merely compares the drug effect between the subgroups that were divided based on the conditions stated above, and it cannot be said that this statement impedes the overall act of dividing the subject patients for administration in Exhibit Ko 1 Invention into subgroups.

Accordingly, all of the Defendant's allegations above are unacceptable.

(4) Regarding the ease in conceiving of Difference 2

A. Examination

As mentioned in (2) A. (B) above, there was the common general technical knowledge that osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, the purpose of its treatment is to prevent bone fractures, "bone strength" consists of two features, bone density and bone quality, and bone density accounts for approximately 70% of bone strength. Therefore, it should be said that a person skilled in the art would have understood that an increase in bone density contributes to prevention of bone fractures.

It follows that, as Exhibit Ko 1 Document states that "considerable advances have been made in the prevention of fractures through increases in bone mineral density (BMD) by using these agents" (line 10 of the right column on page 296 to line 25 of the left column on page 297), indicating that an increase in bone density contributes to prevention of bone fractures, and also discloses that bone density increased by 8.1% after 48 weeks of administration (line 11 of the left column to line 6 of the right column on page 300), a person skilled in the art could have easily conceived of using the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention for the purpose of inhibiting bone fractures, even as of the Base Date.

B. Regarding the Defendant's allegations

(A) As mentioned in No. 3, 1. (2) C. (A) above, the Defendant alleges that the inhibitory effect on bone fractures cannot be completely substituted by the bone density value alone, and therefore even if the lumbar spine BMD increased due to administration of

the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention, it is not possible to predict the inhibitory effect on bone fractures from Exhibit Ko 1 Invention, for which comparison tests with a placebo, etc. has not been conducted.

With regard to this point, PFSB/ELD Notification No. 742 dated April 15, 1999 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare "Kotsusoshōshō-yō-yaku no rinshō hyōka hōhō ni kansuru gaidorain ni tsuite" (Regarding guidelines for clinical evaluation methods for osteoporosis drugs) (Exhibit Ko 41-2) contains statements on the three items below. [i] Clinical trials are divided into the following: a phase I trial conducted based on information obtained in non-clinical trials, targeting a relatively limited number of healthy volunteers, with focus on confirmation of the safety of the test drug on humans; a phase IIa trial, targeting osteoporosis patients, conducted for making an exploratory study on the efficacy, relative safety, and dosage/dose response of the test drug, as well as differences in its effects by osteoporosis type or disease; a phase IIb trial, targeting osteoporosis patients, conducted for clarifying the dose-response relationship and determining the dosage/administration for the phase III trial; and a phase III trial conducted for confirming the efficacy and safety, the dosage/administration for the indications, and side-effects, and for investigating the state of recovery, to study the effects produced when the test drug is actually put to clinical use. [ii] In the phase III controlled trial, the clinical efficacy and safety of the test drug are evaluated by comparing the test drug with a standard drug or a placebo by a randomized, double-blind method (page 2260). [iii] For evaluating the efficacy of an osteoporosis drug, it is desirable to track changes in bone strength as the endpoint, but as it is difficult to measure bone strength in humans at present, it is necessary to indicate the effect against bone fractures associated with osteoporosis as a surrogate endpoint; and to evaluate drug efficacy by the current evaluation means, one year of observation is insufficient, and at least three years are expected to be normally required (pages 2259 to 2260). Exhibit Ko 1 Invention reports the results of the phase IIb trial.

However, "Daitai endo pointo no hyōka" (Evaluation of surrogate endpoints) (June 2009; Exhibit Otsu 14) states as follows: "The FDA changed the policy to approve drugs based on test results using bone density as a surrogate endpoint, and has come to require a clinical trial using the true endpoint, bone fracture, as the endpoint in a phase III trial (...). However, bone density has been approved as a surrogate endpoint by Japanese, U.S., and European regulatory authorities, and when filing a new-drug application, it is a common practice to use bone density as a surrogate endpoint in the phase II trial to study the dose response, and use bone fracture, the true endpoint, in the phase III trial

to conduct a placebo- or active-control trial." (Page 16) The abovementioned "Kotsusoshōshō-yō-yaku no rinshō hyōka hōhō ni kansuru gaidorain ni tsuite" (Regarding guidelines for clinical evaluation methods for osteoporosis drugs) also states as follows with regard to the endpoint for a phase IIb trial: "as proof of efficacy, it is primarily desirable to see changes in bone strength or the fracture rate, but as this requires a long period of time, it can be substituted by seeing changes in bone mass" (page 2258).

In light of these points, it is found to have been merely required, when intending to obtain approval of a drug, to confirm its inhibitory effect on bone fractures in a placebo-control trial, while taking it for granted that an increase in bone density contributes to inhibition of bone fractures, and it cannot be said that it is impossible to predict an agent's inhibitory effect on bone fractures from an increase in bone density unless the inhibitory effect is confirmed by a placebo-control trial.

Accordingly, the Defendant's allegation above is unacceptable.

(B) In addition, as mentioned in No. 3, 1. (2) C. (B) above, the Defendant alleges that Exhibit Ko 1 Document contains a statement that, with regard to the number of vertebral fractures in groups with different increases in bone density, "the difference between the groups was not significant."

However, although there are some cases in which an increase in bone density is not linked with an inhibitory effect on bone fractures, it can be said, as mentioned in A. above, that as long as a person skilled in the art understands that an increase in bone density contributes to prevention of bone fractures, the person would understand that if bone density increases, it will have an inhibitory effect on bone fractures. In addition, while Exhibit Ko 1 Document states that there was no significant difference between group L (50 unit group), group M (100 unit group), and group H (200 unit group) with regard to the number of vertebral fractures, it merely means that there was no significant difference between each group, and it does not suggest that the 200 unit administration has no prospect of having an inhibitory effect on bone fractures.

Accordingly, the Defendant's allegation above is unacceptable.

(C) As mentioned in No. 3, 1. (2) A. (C) above, the Defendant alleges that the 200 unit group in Exhibit Ko 1 Invention experienced many cases of side effects, and therefore, a dose level of 200 units is recognized to be associated with a high side-effect-related dropout rate, whereas the Three Conditions are based on a novel finding achieved for the first time through a stratified analysis that PTH's inhibitory effect on bone fractures is high when Conditions (1) through Condition (3) are combined, and this has made it possible for the first time to enjoy a benefit worth the risk.

Indeed, as described in Attachment 2, Exhibit Ko 1 Document contains information that side effects occurred in 42% of group H which received weekly administration of 200 units of PTH, with 16 out of 72 subjects (about 22%) dropping out due to side effects, and that the rate of side effects and that of dropout due to side effects in this group are higher than those in both group L to which 50 units were administered (the rate of side effects: 19%) and group M to which 100 units were administered (the rate of side effects: 19%) (Table 6). As treatment of osteoporosis takes a long time, and it is undesirable for the agent to cause side effects that directly affect the patient's symptoms or intention to continue to receive treatment when it is put to clinical use (Exhibits Ko 48, 50-1 and 2, and Exhibit Otsu 50), a person skilled in the art who comes across the abovementioned information in Exhibit Ko 1 Document may recognize that it is more appropriate to administer the agent in 100 units than in 200 units, when considering this aspect alone.

On the other hand, however, Exhibit Ko 1 Document also states that no serious adverse phenomena were noted. (Line 1 of the left column to line 4 of the right column on page 301) Furthermore, it states that administration of 200 units caused the lumbar spine bone mineral density to increase by 8.1% after 48 weeks, showing a larger increase than 3.6% for administration of 100 units and 0.6% for administration of 50 units, and evaluates that a significant dose-dependent increase in lumber BMD in a relatively short period of 48 weeks makes PTH quite promising. (Line 11 of the left column to line 6 of the right column on page 300, and line 5 of the right column on page 301 to line 23 of the right column on page 303; It would be hard to understand that administration of 200 units alone is excluded from the promising object doses.) In addition, as mentioned in (2) A. (B) above, while the purpose of osteoporosis treatment is to prevent bone fractures, there is the common general technical knowledge that low bone density is one of the fracture risk factors for which there is evidence in Japan, along with prevalent bone fractures and age, and that bone density accounts for approximately 70% of bone strength.

According to the above, when a person skilled in the art who comes across Exhibit Ko 1 Document compares weekly administration of 200 units and weekly administration of 100 units, the person is likely to determine which to choose by comprehensively considering the aspect of side effects and the aspect of the effect of the agent. On such basis, the person skilled in the art would not likely consider weekly administration of 200 units to be so inferior that it would be excluded from the choice; rather, it should be said that there is also sufficient motivation for the person to choose this dose level.

Furthermore, as indicated in (3) A. (B) above, in light of the common general technical knowledge as of the Base Date, it would not have been particularly difficult for a person skilled in the art who comes across Exhibit Ko 1 Invention to specify the subject patients for administration to be patients who satisfy all of the Three Conditions. In addition, there is no sufficient evidence to find that the combination of the Three Conditions is a special choice from an objective viewpoint, or that combining the Three Conditions has a special meaning in itself, while various combinations including other fracture risk factors as well can be assumed (as mentioned later, the stratified analysis alleged by the Defendant merely made a comparison between a group of patients who satisfy all of the Three Conditions (high-risk patients) and only a part of a group of patients who do not satisfy all or part of the Three Conditions (low-risk patients), and its result itself cannot be immediately judged to serve as a basis for finding a conspicuous effect as alleged by the Defendant).

It follows that, even by making examination anew from the viewpoints of the side effects associated with the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention and the inhibitory effect on bone fractures achieved by choosing the Three Conditions, as alleged by the Defendant, the determination mentioned in A. above is not affected.

Accordingly, the Defendant's allegation above is unacceptable.

(D) Other allegations made by the Defendant also do not affect the determination mentioned in A. above.

(5) Regarding the ease in conceiving of Difference 3

A. Examination

(A) Technical meaning of administration "over a duration exceeding 48 weeks to 72 weeks or longer"

While the structure of Invention 1 relating to Difference 3 specifies the administration period as "over a duration exceeding 48 weeks to 72 weeks or longer," this can be understood as defining administration within a specific range of period by stating "over a duration," and specifying the start of that range (the administration itself starts from week 0) as "exceeding 48 weeks" and the end of that range as "72 weeks or longer."

The Description states that, in a double-blind comparative clinical trial with the occurrence of bone fractures as the primary endpoint, the effect of the agent appeared early at after 24 or 26 weeks, and that no new vertebral fractures were found when administration went beyond 48 weeks, and presents 24 weeks or longer, 26 weeks or longer, 48 weeks or longer, 52 weeks or longer, 72 weeks or longer, and 78 weeks or

longer as examples of administration periods, with 78 weeks or longer being the most favorable (paragraph [0032]).

In addition, the Description states, as Working Example 2, that when patients who satisfy all of the Three Conditions (high-risk patients) were subcutaneously administered the test drug (PTH 200 units) or the control (placebo) once a week, intermittently, for a duration of 72 weeks (paragraph [0098]), the incidence of new vertebral fractures every six months was basically steady at approximately 5% in all divisions, consisting of within 24 weeks, 24 to 48 weeks, and 48 to 72 weeks, in the control group, but in contrast, the incidence of each division dropped as the administration period lengthened in the test drug group, and that no new vertebral fractures occurred after 48 weeks (paragraphs [0131] and [0132], [Table 34], and [Table 35]). It also states that the incidence of vertebral fractures (new + worsening) after 72 weeks by Kaplan-Meier estimation was 3.5% in the test drug group and 16.3% in the control group (paragraph [0133]).

According to these statements, it is understood that the Invention specified "exceeding 48 weeks" as the start of the range of the administration period in consideration that no new vertebral fractures occurred after 48 weeks at the latest, and specified "72 weeks or longer" (including week 72) as the end of that range in consideration that the test period lasted for 72 weeks and therefore that administration needs to be continued for at least 72 weeks.

Meanwhile, while the Description has no statements other than the above concerning the technical meaning of the numerical value "48 weeks," administration exceeding 48 weeks is premised on administration of the agent up to 48 weeks. The fact that no new bone fractures occurred after 48 weeks until 72 weeks in [Table 34] means that no further bone fracture occurred after the last bone fracture that occurred after 24 weeks until 48 weeks, and although the time of the occurrence of that last fracture is unknown, given that only two cases of bone fractures occurred during the considerably long period of 24 weeks ([Table 35] of the Description), if focus is to be simply placed on whether or not new vertebral fractures occurred, it can also be evaluated that the effect was already demonstrated in the division of 24 to 48 weeks. Furthermore, 72 weeks was indicated only because the test period was 72 weeks, and although the Description states 72 weeks "or longer," the incidence of bone fractures for the period exceeding 72 weeks is unknown from the Description.

According to the above, "48 weeks" and "72 weeks or longer" are not defined to have technical meaning in themselves, and no particular technical meaning can be found in the limitation of the Invention specifying the specific range of period of "over a

duration exceeding 48 weeks to 72 weeks or longer" to indicate the start and the end of the range. It is reasonable to regard that, in showing that the incidence of bone fractures dropped through continuous administration of PTH for the discretionary divisions of the test period that were divided for convenience, this period was merely adopted by focusing on the fact that no new vertebral fractures occurred in that period, as a fact indicating the test result.

(B) Regarding the ease of conceiving of the difference

As mentioned in (2) B. (B) above, it was known as of the Base Date that bone density increases and the occurrence of bone fractures decreases through daily administration of a PTH preparation over a duration exceeding 48 weeks.

Meanwhile, in Exhibit Ko 1 Invention, as a result of weekly administration of 200 units of PTH, the lumbar spine BMD continuously increased up to 48 weeks, significantly increasing by 8.1% after 48 weeks (line 1 of the left column to line 7 of the right column on page 296 of Exhibit Ko 1 Document), and further, no vertebral fractures occurred in group H, which is the PTH 200 unit group, during the administration period of 48 weeks (line 11 of the left column to line 6 of the right column on page 300 of Exhibit Ko 1 Document).

While it can be said that a person skilled in the art would have understood that an increase in bone density contributes to prevention of bone fractures based on the common general technical knowledge mentioned in (2) A. above, the test in Exhibit Ko 1 Document, conducted for administration for up to 48 weeks, shows a continuous increase in the lumbar spine BMD, although there is a diminishing trend in the increase rate (Figure 1 of Exhibit Ko 1 Document), and no grounds are found to indicate that the increase turns to a decrease when administration exceeds 48 weeks.

According to the above, it can be said that, even as of the Base Date, a person skilled in the art could have easily conceived of also administering the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention over a duration exceeding 48 weeks in order to increase bone density and prevent bone fractures, based on the report that daily administration of PTH was conducted over a duration exceeding 48 weeks, and that bone density increased and the occurrence of bone fractures decreased as a result. As a consequence, it should be said that a person skilled in the art could have arrived at Invention 1.

B. Regarding the Defendant's allegations

(A) As mentioned in No. 3, 1. (2) D. (A) above, the Defendant alleges as follows: [i] given the high rate of side effects and dropout rate for the weekly administration of 200 units of PTH in Exhibit Ko 1 Invention, there is no motivation to attempt long-term

administration of the agent with this dosage and administration; and [ii] in the test in Exhibit Ko 1 Invention, a duration of 48 weeks was considered to be the limit of continuous administration, and therefore, there is an obstructive factor for attempting long-term administration of the agent in Exhibit Ko 1 Invention.

However, the allegation mentioned in [i] above is unacceptable due to the following reasons: although it cannot be confirmed from the matters disclosed (Figure 1) in Exhibit Ko 1 Document that the increase rate of the lumbar spine BMD rose due to administration over a period exceeding 48 weeks, it can be confirmed that the net lumbar spine BMD increased while the increase rate diminished; thus, even if there is naturally a limit to the increase in the lumbar spine BMD due to the limits of the human body, there are no particular grounds indicating that the increase in the lumbar spine BMD immediately disappears after 48 weeks of administration; also, even if there is no significant statement concerning the inhibitory effect on bone fractures itself, the fact that an increase in bone density contributes to prevention of bone fractures was common general technical knowledge, as mentioned above; therefore, it cannot be said that a person skilled in the art would be obstructed from applying the agent to clinical use due to the high rate of side effects and dropout rate for the weekly administration of 200 units of PTH in Exhibit Ko 1 Invention, and it can be regarded that there is sufficient motivation to adopt long-term administration when making such application, in light of the effect of the agent to increase the BMD.

Moreover, Exhibit Ko 1 Document states as follows: "... the period of the study was set at 48 weeks. This was also thought to be the limit of duration for an adequately controlled multicenter study with regular bone measurement and blood and urine sampling without suffering an excessive dropout rate, in a population of osteoporotics at constant risk and anxiety for fracture." (Line 48 of the right column on page 297 to line 24 of the left column on page 298) Therefore, it is clear in Exhibit Ko 1 Document that the direct reason for setting the test period at 48 weeks was for concerns about the problem in management of the clinical trial. Also considering that the test period was to be set before knowing the results of the test in Exhibit Ko 1 Document, it should be said that when a person skilled in the art who saw the results of the test in Exhibit Ko 1 Document uses the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention in practical treatment, the person cannot be regarded to be obstructed from administering the agent for a period exceeding 48 weeks. Therefore, the allegation mentioned in [ii] above is also unacceptable.

(B) As mentioned in No. 3,1. (2) D. (B) above, the Defendant alleges that, as Exhibit Ko 2 Document is about a test with different dosage and administration from those of

Exhibit Ko 1 Invention, the matters stated in Exhibit Ko 2 Document would not serve as a motivation for administering the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention over a duration exceeding 48 weeks.

However, although the dosage and administration in the clinical trial in Exhibit Ko 2 Document differ from those in Exhibit Ko 1 Invention, and therefore it cannot be regarded that a continuation period that is completely the same can immediately be adopted, it is natural and reasonable for a person who came across information on an agent, which is also a PTH preparation, and which is also found to have an effect of increasing bone density, to conceive of administering an agent for the treatment of osteoporosis with weekly administration of 200 units of PTH, which is expected to increase bone density, over a duration exceeding 48 weeks. Accordingly, it at least cannot be said that Exhibit Ko 2 Document would not serve as a motivation.

(C) The Defendant has also made other allegations, but none of them affect the determination mentioned in A. (B) above.

(6) Regarding the effect of the invention

A. Regarding an unpredictable and outstanding effect

Whether or not the effect of an invention is unpredictable and outstanding needs to be examined from the perspectives of whether the effect is one that a person skilled in the art could not have predicted as an effect produced by the structure of the invention as of the base date for determining the patentability of the invention and whether the effect is an outstanding one that goes beyond the scope of effect that a person skilled in the art could have predicted based on that structure (see the judgment of the Third Petty Bench of the Supreme Court, 2018 (Gyo-Hi) 69, rendered on August 27, 2019, Shumin, No. 262, at 51). Indeed, as it is difficult to determine whether or the invention is found to have an unpredictable and outstanding effect solely from the structure of the invention, it is regarded to be permissible to take into consideration the effect produced by prior art that was selected as having a structure similar to that of the invention or a similar type of effect that had been achieved by the state of the art at the time. Meanwhile, the burden of proof regarding the unpredictable and outstanding effect lies on the patentee. Therefore, even if the effect produced by the structure of the invention is unknown, it cannot be immediately concluded that the invention has an unpredictable and outstanding effect.

B. Regarding the effect of the Invention

(A) Regarding the unpredictable and outstanding effects alleged by the Defendant

As mentioned above, the structure of Invention 1 could have been easily conceived of by a person skilled in the art. In contrast, however, as mentioned in No. 3, 1. (2) E.

(B) above, the Defendant alleges that the following are unpredictable and outstanding effects of the Invention: [i] a remarkable inhibitory effect on bone fractures, indicating a 79% RRR in comparison to the placebo, after 72 weeks (Effect [i]); [ii] an effect that the inhibitory effect on bone fractures is intensified through continuous administration of the agent (Effect [ii]); and [iii] an effect of completely inhibiting bone fractures in practice after 48 weeks (Effect [iii]). Therefore, these effects are examined below.

(B) Regarding unpredictable and outstanding effects of the Invention

First, the Defendant alleges that, if the question of whether or not the effect of an invention is unpredictable and outstanding should be determined based on the structure of the invention, in this case, it would be sufficient to examine the inhibitory effect on bone fractures in patients not satisfying the Three Conditions, which is a structure of Invention 1, and there is no need to compare the inhibitory effect on bone fractures in patients satisfying the Three Conditions to that in patients not satisfying the Three Conditions, and also, there is no need for such comparison to be stated in the Description.

However, Invention 1 is an invention that has discovered an inventive step in administering PTH to a group of patients from among a group administered with PTH for which an extremely high effect can be achieved, based on a premise that PTH was well-known as an agent for the treatment of osteoporosis as of the base time of this case. Therefore, in order to confirm the agent's inhibitory effect on bone fractures in patients who satisfy all of the Three Conditions, it is necessary to compare the inhibitory effect on bone fractures in high-risk patients and that in low-risk patients (patients other than high-risk patients). Merely comparing high-risk patients administered with the agent for the treatment of osteoporosis in the Invention and patients administered with the placebo and showing that the agent has an inhibitory effect on bone fractures in those high-risk patients means only showing that the agent has an extremely high inhibitory effect on bone fractures in a group of patients in the PTH group in comparison to the placebo group. It does not mean clarifying that the high-risk patient group is a patient group from among the PTH group in which the agent has a particularly high effect in comparison to other patient groups, and it merely means confirming the agent's inhibitory effect on bone fractures in the PTH group.

Accordingly, the Defendant's allegation above is unacceptable.

C. Regarding Effect [i]

(A) As mentioned in (2) A. (B) above, there was the common general technical knowledge that osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, the purpose of its treatment is to

prevent bone fractures, "bone strength" consists of two features, bone density and bone quality, and bone density accounts for approximately 70% of bone strength. Therefore, a person skilled in the art would have understood that an increase in bone density contributes to prevention of bone fractures. On such basis, Exhibit Ko 1 Document states that "considerable advances have been made in the prevention of fractures through increases in bone mineral density (BMD) by using these agents" (line 10 of the right column on page 296 to line 25 of the left column on page 297), indicating that an increase in bone density contributes to prevention of bone fractures, and discloses that bone density increased by 8.1% after 48 weeks of administration (line 11 of the left column to line 6 of the right column on page 300). It follows that a person skilled in the art would have easily understood that the agent for the treatment of osteoporosis in Exhibit Ko 1 Invention has an effect of inhibiting bone fractures.

(B) The endpoint for the inhibitory effect on bone fractures, mentioned as Effect [i], is not regarded to refer to a mere decrease in the incidence of bone fractures, but to the rate of decrease in the incidence of bone fractures in comparison to that in the placebo group. However, as mentioned in B. above, in order to confirm Effect [i], there is a need to compare the inhibitory effect on bone fractures in high-risk patients and that in low-risk patients, and merely comparing high-risk patients and the placebo patients and showing that the agent has an inhibitory effect on bone fractures in high-risk patients does not mean clarifying that the high-risk patient group is a patient group from among the PTH group in which the agent has a particularly high effect. Given these points, it cannot be understood from the statement of the Description that the agent's inhibitory effect on bone fractures in high-risk patients, who are defined as patients who satisfy all of the Three Conditions, is higher than that in low-risk patients, who are defined as patients who do not satisfy all or part of the Three Conditions.

(C) In other words, the Description only states in Working Example 1 that, among high-risk patients, a significant difference could be found between the incidence of new vertebral fractures in the group with weekly administration of 100 units and that in the group with weekly administration of 5 units, which is practically the placebo group, in all comparisons, whereas in low-risk patients, no significant difference could be found between the new vertebral fractures in the group with weekly administration of 100 units and that in the group with weekly administration of 5 units in all comparisons (paragraphs [0086] through [0096], [Table 6] through [Table 11]). Even based on the values re-analyzed after correcting erroneous entries (1. (2) E. above), with regard to new vertebral fractures in low-risk patients, there was only one case of bone fracture out of the 11 patients in the group with weekly administration of 100 units and one out

of the 10 patients in the group with weekly administration of 5 units. It is clear that, under such a small number of cases, the abovementioned rate of decrease in the incidence of bone fractures in comparison to that in the placebo group (RRR) will fluctuate substantially by a mere increase or decrease in the number of cases of bone fractures by one. In the case of administration to low-risk patients, the number of cases of bone fracture is small even in the group with weekly administration of 5 units, and therefore it is natural that the value of RRR, which is the rate of decrease of the incidence of bone fractures in the group with weekly administration of 100 units in comparison to that in the group with weekly administration of 5 units, is smaller than the value for the high-risk patients.

In this regard, the Defendant alleges that, if there is a significant difference between the inhibitory effect on bone fractures in patients satisfying the Three Conditions and that in the placebo group, and there is no significant difference between the inhibitory effect on bone fractures in patients not satisfying the Three Conditions and that in the placebo group, it can be said immediately that the agent for the treatment of osteoporosis in Invention 1 has an extremely high effect in patients satisfying the Three Conditions. However, there being no significant difference merely means that it is unknown whether there is a high effect, and it does not mean immediately that the effect is not high. Also, it cannot be denied that there being no significant difference was caused by an insufficient number of cases (Exhibit Ko 35). Therefore, it is not appropriate to derive a conclusion as mentioned above.

Accordingly, it cannot be understood from Working Example 1 that PTH's inhibitory effect on bone fractures in high-risk patients is higher than that in low-risk patients.

(D) Next, the Description states as follows with regard to Working Example 2: regarding weekly administration of 200 units of PTH to patients satisfying the Three Conditions, the incidence of bone fractures in the control (placebo) group was basically steady at approximately 5% in all of the periods of ["≤24 weeks," ">24 weeks to ≤48 weeks," and ">48 weeks to ≤72 weeks" after the start of administration, whereas in the group with weekly administration of 200 units of PTH, the incidence decreased from 2.3%, 0.9%, to 0%, and the RRR in comparison to the placebo group increased as administration continued; in the group with weekly administration of 200 units of PTH, the risk of bone fractures had dropped 53.9% versus that in the placebo group after 24 weeks; and 200 units of the drug also lowered the risk of vertebral fractures (new + worsening) 78.6% in comparison to the placebo after administration for 72 weeks (paragraphs [0131] through [0133], [Table 34], and [Table 35]).

However, these statements merely compare patients to whom the osteoporosis

therapeutic agent referred to in the Invention was administered and patients to whom a placebo was administered, among those who satisfy the Three Conditions, and does not indicate that the inhibitory effect on bone fractures is higher in patients who satisfy all of the Three Conditions than in patients who do not in the case where the agent for the treatment of osteoporosis in the Invention is administered.

(E) In addition, as mentioned in 1. (2) A. above, because all patients in Working Example 1 have one or more vertebral fractures, they are all patients who satisfy Condition (2), and because they fall under the category of "I. With vertebral fracture on X-ray film" under Exhibit Ko 5 Diagnostic Criteria, and therefore have a low bone mass with "the degree of bone atrophy of I or higher, or bone density less than 80% of the young adult mean (YAM))," they are all patients who satisfy Condition (3) (although patients with a bone density value of precisely 80% of YAM do not satisfy Condition (3), that is hard to imagine in reality). In other words, those referred to as high-risk patients (patients satisfying the Three Conditions) in the Description are, by definition, patients who satisfy Conditions (1) through (3), and even those referred to as low-risk patients (patients not satisfying the Three Conditions) in the Description satisfy Conditions (2) and (3) as mentioned above. Therefore, Working Example 1 only compares the inhibitory effect on bone fractures between those who satisfy Condition (1), which is age 65 years or older, and those who do not. Meanwhile, as mentioned above, Working Example 2 does not compare the inhibitory effect on bone fractures in patients not satisfying the Three Conditions with that in patients satisfying the Three Conditions in the case where the agent for the treatment of osteoporosis in the Invention is administered. This makes it even more difficult to compare the degree of inhibition of new vertebral fractures in high-risk patients with that in low-risk patients and conclude that the former effect is higher than the latter effect based on the Description.

(F) Furthermore, when looking at other parts of the Description, they contain statements that merely indicate a conclusion to the effect that "the agent has a higher inhibitory effect on bone fractures in high-risk patients than in low-risk patients." As these are not based on pharmacological test data, and it cannot be reasonably understood from such statements that PTH's inhibitory effect on bone fractures in high-risk patients (patients satisfying the Three Conditions) is higher than that in low-risk patients (patients not satisfying the Three Conditions), after all, it should be said that Effect [i] is not based on the statement of the Description.

(G) The Plaintiff alleges that Effect [i] is clear from Exhibit Ko 64 Certificate and Exhibit Ko 68 Certificate.

However, as long as it cannot be understood from the statement of the Description

that PTH's inhibitory effect on bone fractures in high-risk patients is higher than that in low-risk patients and as long as this also cannot be presumed from the statement of the Description, it is not reasonable to find Effect [i], which is not disclosed to the public, by adopting the respective Experiment Result Certificates mentioned above.

Even if reference were to be made to the respective Experiment Result Certificates mentioned above, these certificates, even according to the Defendant's allegations, come down to comparing the number of fracture cases in the PTH groups consisting of a group of patients who are "age 65 years or older, without prevalent bone fractures, and whose bone density is less than 80% of the young adult mean" and a group of patients who are "age 65 years or older, with prevalent bone fractures, and whose bone density is less than 80% of the young adult mean," that is, between groups in which only Condition (2)—the presence or absence of prevalent bone fractures—differs, against that in the placebo groups (control groups) for the case of administration exceeding 48 weeks and the case of administration for 72 weeks or longer, and merely making a comparison between a group of patients who satisfy all of the Three Conditions (high-risk patients) and only a part of a group of patients who do not satisfy all or part of the Three Conditions (low-risk patients); therefore, the certificates are not at all suitable for concluding that the degree of inhibition of bone fractures in patients who satisfy all of the Three Conditions is higher than that in patients who do not satisfy the Three Conditions. It follows that, even by looking at the respective Experiment Result Certificates above, it cannot be understood that PTH's inhibitory effect on bone fractures in patients who satisfy all of the Three Conditions is higher than that in patients who do not satisfy the Three Conditions.

(H) According to the above, Effect [i] cannot be found in any case. Therefore, without having to make determinations on other points, there is no room for finding that Invention 1 has an unpredictable and outstanding effect.

D. Regarding Effect [ii]

(A) As mentioned in C. above, the Description states as follows with regard to Working Example 2: regarding weekly administration of 200 units of PTH to patients satisfying the Three Conditions, the incidence of bone fractures in the control (placebo) group was basically steady at approximately 5% in all of the periods of "≤24 weeks," ">24 weeks to ≤48 weeks," and ">48 weeks to ≤72 weeks" after the start of administration, whereas in the group with weekly administration of 200 units of PTH, the incidence decreased from 2.3%, 0.9%, to 0% (paragraphs [0131] through [0133], [Table 34], and [Table 35]).

However, these statements merely compare patients to whom the osteoporosis therapeutic agent referred to in the Invention was administered and patients to whom a

placebo was administered, among those who satisfy the Three Conditions, and does not indicate that the inhibitory effect on bone fractures is higher in patients who satisfy all of the Three Conditions than in patients who do not in the case where the agent for the treatment of osteoporosis in the Invention is administered. In addition, while it can be read from Figure 1 of Exhibit Ko 1 Document that the lumbar spine BMD in group H with weekly administration of 200 units increased by about 5% at 24 weeks from the start of administration and by 8.1% at 48 weeks from the start of administration, there are no grounds indicating that the increase in the lumbar spine BMD immediately disappears after 48 weeks of administration, although the increase rate is expected to diminish, as mentioned in (5) A. (B) above. As long as bone density increases, the inhibitory effect on bone fractures can also be expected to increase. On the other hand, bone density does not increase in the placebo group. Therefore, it is clear that the inhibitory effect on bone fractures in the group with weekly administration of 200 units of PTH will increase in comparison to that in the placebo group as the administration period progresses. In addition, Exhibit Ko 2 Document contains statements relating to daily administration of 20 μg of PTH or daily administration of 40 μg of PTH that when 20 or 40 μg of PTH was administered daily for an average of 17 or 18 months for the treatment of osteoporosis in postmenopausal women, the treatment decreased the risk of vertebral and nonvertebral fractures and increased vertebral, femoral, and total-body bone mineral density (lines 1 to 42 of the left column on 1434, and lines 46 to 53 of the right column on page 1435), and that the rate of inhibition of bone fractures by the PTH administration became higher as the administration period became longer (Figure 1). Therefore, if Effect [ii] simply refers to an effect that the inhibitory effect on bone fractures achieved by weekly administration of 200 units to patients satisfying the Three Conditions would be intensified through continuous administration of the agent, it would have been sufficiently within the scope of expectation for a person skilled in the art.

(B) Furthermore, when looking at other parts of the Description, it cannot be understood that PTH's inhibitory effect on bone fractures in high-risk patients (patients satisfying the Three Conditions) will be intensified more than that in low-risk patients (patients not satisfying the Three Conditions) through continuous administration of the agent, and this also cannot be presumed from the statement of the Description; thus, after all, it should be said that Effect [ii] is not based on the statement of the Description.

(C) According to the above, Effect [ii] cannot be found in any case. Therefore, without having to make determinations on other points, there is no room for finding that Effect [ii] is an unpredictable and outstanding effect.

E. Regarding Effect [iii]

(A) As mentioned in C. (A) above, while it is understood that an increase in bone density contributes to prevention of bone fractures, Exhibit Ko 1 Invention significantly increases bone density by 8.1% in 48 weeks, and is expected to continuously increase the lumbar spine BMD if the administration exceeds 48 weeks. As a fact indicating the test result, Exhibit Ko 1 Document shows that, in the 200 unit group, no vertebral fracture occurred during the administration for 48 weeks (line 11 of the left column to line 6 of the right column on page 300). Thus, it is natural to consider that, even if the administration period exceeds 48 weeks in Exhibit Ko 1 Invention with administration of 200 units of PTH, an equivalent inhibitory effect on bone fractures as that during the administration period of 48 weeks will continue to a certain extent.

(B) The inhibitory effect on bone fractures of Effect [iii] is to reduce the incidence of bone fractures to 0% when 200 units of PTH relating to Invention 1 are administered to patients who satisfy all of the Three Conditions every week for a duration exceeding 48 weeks to at least 72 weeks. However, as mentioned in (5) A. (A) above, no particular technical meaning can be found in the numerical values "48 weeks" and "72 weeks" themselves. It only refers to a fact indicating a test result that no new vertebral fractures were found when administration went beyond 48 weeks, which can hardly be found to mean that the osteoporosis therapeutic agent referred to in the Invention is a therapeutic agent that completely inhibits bone fractures in practice after 48 weeks of administration (a complete wonder drug). The defendant also does not allege that the osteoporosis therapeutic agent referred to in the Invention has such effect (indeed, the following are found in the case of Teribone, for which there is no dispute between the parties that it is a product embodying Invention 1: the incidence of new vertebral fractures was 0.7% from 49 to 72 weeks of administration, and the incidence of bone fractures was 2.2% from 73 to 104 weeks of administration, although these are results for which the subject patients for administration are not limited to high-risk patients (Exhibit Ko 11); and the incidence of new vertebral fractures by Kaplan-Meier estimation was 1.7% at 24 weeks, 2.5% at 48 weeks, and 3.3% at 72 weeks (Exhibit Ko 30)).

Moreover, as mentioned in (A) above, while it is natural to consider that the inhibitory effect on bone fractures will continue to a certain extent even after 48 weeks in Exhibit Ko 1 Invention, given that no vertebral fractures were found during 48-week administration also in Exhibit Ko 1 Invention, even though it is merely a fact indicating a test result, it can be understood that the bone fracture incidence was originally low. Accordingly, even if the number of bone fractures during the period exceeding 48 weeks

to 72 weeks was zero in Invention 1 and thus the incidence of bone fractures was 0%, one cannot go so far as to say that this fact itself was surprising for a person skilled in the art. Rather, it can be said that this fact was within the scope of expectation for a person skilled in the art.

F. Summary

Other allegations made by the Defendant also do not affect the determination mentioned in C. through E. above. Without the need to add further examination on the degree of the effect, etc., Invention 1 is not found to have an outstanding effect which could not have been predicted by a person skilled in the art.

(7) Summary on Invention 1

According to the above, it is found to have been easy for a person skilled in the art to conceive of the structures of Invention 1 relating to Differences 1 through 3, even on a premise of making the determination based on the Base Date, and the effects of Invention 1 are also not found to be outstanding effects which could not have been predicted by a person skilled in the art. Therefore, after all, without having to make determinations on other points, it should be said that Differences 1 through 3 could have been easily conceived of by a person skilled in the art. Thus, there is an error in the determination in the JPO Decision which found that a person skilled in the art could not have easily conceived of Differences 1 through 3. It follows that, the determination in the JPO Decision which found that Invention 1 involves an inventive step is erroneous.

(8) Regarding Invention 2

As mentioned in (7) above, there is an error in the determination in the JPO Decision which found that a person skilled in the art could not have easily conceived of Differences 1 through 3 in Invention 1. It follows that there is also an error in the determination in the JPO Decision which immediately found that Invention 2 involves an inventive step, for the same reason as for Invention 1, on a basis that Invention 2 is an invention that has limited Invention 1.

3. Conclusion

As described above, Grounds for Rescission 1 are well-founded, and without having to make determinations on other points, the JPO Decision is rescinded, and the judgment is rendered as indicated in the main text.

Intellectual Property High Court, Fourth Division
Presiding Judge: KANNO Masayuki
Judge: MOTOYOSHI Hiroyuki
Judge: NAKAMURA Kyo

(Attachment 1)

Matters stated in the Description (Abstract)

(Tables are posted together at the end of the Attachment.)

[Detailed explanation of the invention]

[Technical field]

[0001]

The present invention relates to a therapeutic or prophylactic agent for osteoporosis containing PTH as the active ingredient. Further, the present invention relates to an inhibitor or prophylactic agent for fractures containing PTH as the active ingredient. In particular, the present invention relates to the aforementioned agents that are characterized by administering 100 units to 200 units of PTH per dose per week.

[Background art]

[0002]

Osteoporosis is a "disease characterized by a decrease in bone strength that poses an increased risk of fractures." Currently, PTH (Parathyroid Hormone) is known as one of the therapeutic agents for osteoporosis.

[0003]

PTH is a hormone involved in the regulation of blood calcium concentration along with calcitonin and vitamin D. For example, it is also known that PTH has the action of promoting calcium absorption in the intestinal tract by increasing active vitamin D_3 production in the kidney in vivo (Non-patent Document 1).

[0004]

Patent Document 1 discloses a therapeutic method of osteoporosis where 100 units or 200 units of PTH per dose are administered by subcutaneous injection to patients with osteoporosis at the frequency of once a week over a 26-week period so that the bone density of the cancellous bone of the patients with osteoporosis is increased and the bone density of the cortical bone of the same will not be decreased.

[0005]

Thus, Patent Document 1 discloses that the therapeutic method merely induces an increase in bone density but does not state whether it is a therapeutic method to increase the bone strength of patients with osteoporosis or to reduce the risk of fractures. In addition, PTH alone is used and no calcium agent is used in combination.

[0006]

Non-patent Document 1 discloses that in a clinical trial relating to the osteoporosis therapy with PTH, when blood was collected after 4 hours to 6 hours after administration of PTH (20 μg/day) to patients with osteoporosis, hypercalcemia was

observed in 11% of the patients, and sustained hypercalcemia was observed in 3% thereof. In addition, Non-patent Document 1 discloses that, before the following administration of PTH, serum calcium returned to normal for most of the patients; however, increases in a sustained serum calcium was observed in one of 541 patients, and therefore the treatment was discontinued for that patient.

[0007]

With respect to a daily subcutaneous administration of PTH in combination with a calcium agent, Non-patent Document 2 discloses that serum calcium after administration of the present agent is clinically not a problem, but also reports that serum calcium after administration has increased. Non-patent Document 3 is a package insert of a daily subcutaneous administration formulation disclosed in Non-patent Document 2. This document reports that transient hypercalcemia after administration of the formulation was observed in clinical trials while disclosing various adverse events after administration of the formulation. Further, Non-patent Document 3 discloses that there is a report of adverse reactions of hypercalcemia in the post-marketing surveillance of the formulation.

[0008]

As described above, Non-patent Documents 1 through 3 disclose cases of adverse reactions of hypercalcemia in the treatment of osteoporosis with PTH, and the therapeutic methods disclosed therein are regarded to be insufficient in terms of safety.

[0009]

Given the aforementioned background, an osteoporosis treatment method using PTH, which is highly safe and excellent in efficacy and effects, was required.

[Prior art document]

[Non-patent document]

[0011]

[Non-patent Document 12] Hajime Orimo et al, "Diagnostic Criteria for Primary Osteoporosis (revised version of FY1996)," 1997, Journal of Japanese Society for Bone and Mineral Metabolism Vol. 14, at 219-233

[Non-patent Document 13] Diagnostic Criteria for Primary Osteoporosis and Prevention and Treatment Guidelines for Osteoporosis (Hajime Orimo et al, "Prevention and Treatment Guidelines for Osteoporosis 2006," 2006, at 34-35)

[Outline of the invention]

[Problems to be solved by the invention]

[0012]

The problem of the present invention is to provide an osteoporosis treatment method

and prevention method using PTH, which is highly safe and excellent in efficacy and effects. In addition, the problem of the present invention is to provide an inhibiting and preventing method of fractures using highly safe PTH.

[Means of solving the problems]

[0013]

In order to solve the above problems, the present inventors have conducted extensive research and development, and as a result, surprisingly, they found an osteoporosis treatment and prevention method that is excellent in both efficacy and effects and safety by limiting the dose and administration interval of PTH. In addition, they found that specifying the dose and administration interval of PTH results in a highly safe fracture inhibition and prevention method. Furthermore, they also found that the method particularly shows effects for high-risk patients.

[0014]

In other words, the present invention relates to the following:

[1] A therapeutic or prophylactic agent for osteoporosis containing PTH as the active ingredient, which is characterized by administration in combination with a calcium agent and by 100 units to 200 units of PTH per dose per week.

[2] A therapeutic or prophylactic agent for osteoporosis stated in [1] above, which is characterized by the administration in combination with a calcium agent once per week or more often.

[3] A therapeutic or prophylactic agent for osteoporosis stated in [1] or [2] above, which is characterized by the administration in combination with a calcium agent of 200 mg to 800 mg per day as calcium.

[4] Any therapeutic or prophylactic agent for osteoporosis stated in [1] through [3] above, wherein the PTH is human PTH (1-34).

[5] A therapeutic or prophylactic agent for osteoporosis stated in any of [1] through [4] above for administration over a period exceeding 24 weeks or 48 weeks.

[6] Any therapeutic or prophylactic agent for osteoporosis stated in [1] through [5] above for patients with osteoporosis who meet all requirements in (1) through (3) below:

(1) Age 65 years or older

(2) Prevalent fractures; and

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher.

[7] A therapeutic or prophylactic agent for osteoporosis stated in any one of [1] through [6] above for treatment and prevention of secondary osteoporosis caused by steroid or

diabetic osteoporosis.

[8] A therapeutic or prophylactic agent for osteoporosis stated in any one of [1] through [6] above for treatment and prevention of osteoporosis that has a complication with at least any one of the following diseases in (1) through (8) below:

(1) diabetes;

(2) hypertension;

(3) hyperlipidemia;

(4) arthralgia;

(5) spondylosis deformans;

(6) deformans low back pain;

(7) hip osteoarthritis; and

(8) temporomandibular joint osteoarthritis.

[9] A therapeutic or prophylactic agent for osteoporosis stated in any one of [1] through [6] above for administering to patients with osteoporosis having medication history of at least any one of therapeutic agents for osteoporosis in the following (1) through (6):

(1) L-calcium aspartate;

(2) alfacalcidol;

(3) elcatonin;

(4) raloxifene hydrochloride;

(5) menatetrenone; and

(6) calcium lactate.

[10] A therapeutic or prophylactic agent for osteoporosis stated in any one of [1] through [6] above for administering to patients with osteoporosis having mild renal dysfunction or moderate renal dysfunction.

[11] A therapeutic or prophylactic agent for osteoporosis stated in any one of [6] through [10] above, wherein the PTH is human PTH (1-34).

[12] A therapeutic or prophylactic agent for osteoporosis stated in any of [6] through [11] above, wherein the therapeutic agent for osteoporosis containing the aforementioned PTH as the active ingredient is a subcutaneous injection.

[13] A drug combination or medical kit consisting of a therapeutic or prophylactic agent for osteoporosis stated in any one of [1] through [12] above and at least any one of the following agents (1) through (6):

(1) metoclopramide;

(2) domperidone;

(3) famotidine;

(4) mosapride citrate;

(5) lansoprazole; and
(6) Rokushingan.
[14] A therapeutic or prophylactic agent for osteoporosis containing PTH as the active ingredient, which is characterized by the administration of 100 units to 200 units of PTH per dose per week and is used for the treatment of patients with osteoporosis who meet all requirements in (1) through (3) below:
(1) Age 65 years or older;
(2) Prevalent fractures; and
(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher.
[15] A therapeutic or prophylactic agent for osteoporosis with high risk of fracture, which contains PTH as the active ingredient and is characterized by the administration of 100 units to 200 units of PTH per dose per week.
[16] A therapeutic or prophylactic agent for osteoporosis containing PTH as the active ingredient, which is characterized by the administration of 100 units to 200 units of PTH per dose per week and is used for treatment and prevention of secondary osteoporosis caused by steroid or diabetic osteoporosis.
[17] A therapeutic or prophylactic agent for osteoporosis containing PTH as the active ingredient, which is characterized by the administration of 100 units to 200 units of PTH per dose per week and is used for administration to patients with osteoporosis having mild renal dysfunction or moderate renal dysfunction.
[18] An inhibitor or prophylactic agent for fractures containing PTH as the active ingredient, which is characterized by the administration in combination with a calcium agent and of 100 units to 200 units of PTH per dose per week.
[19] An inhibitor or prophylactic agent for fractures stated in [18] above, which is characterized by administration in combination with a calcium agent once per week or more often.
[20] An inhibitor or prophylactic agent for fractures stated in [18] or [19] above, which is characterized by administration in combination with a calcium agent of 200 mg to 800 mg per day as calcium.
[21] Any inhibitor for fractures stated in [18] through [20] above, wherein the PTH is human PTH (1-34).
[22] Any inhibitor or prophylactic agent for fractures stated in [18] through [21] above that is used for administration to subjects who meet all requirements in (1) through (3) below:
(1) Age 65 years or older;

(2) Prevalent fractures; and
(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher.
[23] An inhibitor or prophylactic agent for fractures stated in [22] above, wherein the PTH is human PTH (1-34).
[24] An inhibitor or prophylactic agent for fractures stated in [22] or [23] above, which contains PTH as the active ingredient and is a subcutaneous injection.
[25] An inhibitor or prophylactic agent for fractures stated in any one of [18] through [24] above, which is an inhibitor or prophylactic agent for multiple bone fracture.
[26] An inhibitor or prophylactic agent for fractures stated in any one of [18] through [25] above, which is an inhibitor or prophylactic agent for worsening fractures.
[27] A therapeutic or prophylactic agent for osteoporosis stated in [14] or [15] above that is used for treatment and prevention of secondary osteoporosis caused by steroid or diabetic osteoporosis.
[28] A therapeutic or prophylactic agent for osteoporosis stated in [14] or [15] above that is used for administration to patients with osteoporosis having mild renal dysfunction or moderate renal dysfunction.
[29] A therapeutic or prophylactic agent for osteoporosis stated in [27] above that is used for administration to patients with osteoporosis having mild renal dysfunction or moderate renal dysfunction.
[30] A therapeutic or prophylactic agent for osteoporosis stated in [16] above that is used for administration to patients with osteoporosis having mild renal dysfunction or moderate renal dysfunction.
[31] A preventive or therapeutic method using a therapeutic agent, prophylactic agent, preparation, drug combination or medical kit stated in any of [1] through [30] above.
[Effects of the invention]
[0015]
The therapeutic agent for osteoporosis in the present invention is highly safe and excellent in efficacy and effect. Also, the inhibitor or prophylactic agent for fractures in the present invention is highly safe and useful.
[Brief description of the drawings]
[0016]
[FIG. 1] FIG. 1 is a graph showing the results of the serum calcium concentration changes for each administration group (high-risk subjects, low-risk subjects).
[FIG. 2] It shows the impact of administration of the test drug on time-dependent changes in incidence of new vertebral fractures. The test drug administration group is

indicated as "PTH 200 group" and the control drug administration group is indicated as "P group."

[FIG. 3] It shows the impact of administration of the test drug on time-dependent changes in incidence of new vertebral fractures. The test drug administration group is indicated as "PTH 200 group" and the control drug administration group is indicated as "P group."

[FIG. 4] It shows the results of testing for variations in urinary calcium levels when the test drug ("PTH 200 group") or the control drug ("P group") is administered to patients once a week for 72 weeks. The ratio of urinary calcium level / urinary creatine level was compared before the start of administration and during the observation weeks. Urinary calcium was measured at the start and after 12 weeks, 24 weeks, 48 weeks, and 72 weeks. Standard concomitant drugs (610 mg of calcium, 400 IU of Vitamin D_3, and 30 mg of magnesium) were administered once per day after dinner for the period from when informed consent was obtained until the end of the clinical trial.

[FIG. 5] It shows the results of testing for variations in corrected serum calcium levels when the test drug ("PTH 200 group") or the control drug ("P group") is administered to patients once a week for 72 weeks. Serum calcium was measured at the start and after 12 weeks, 24 weeks, 48 weeks, and 72 weeks. Standard serum calcium level is 8.4 mg/dL to 10.4 mg/dL. Standard concomitant drugs (610 mg of calcium, 400 IU of Vitamin D_3, and 30 mg of magnesium) were administered once per day after dinner for the period from when informed consent was obtained until the end of the clinical trial.

[Mode for working the invention]

[0017]

The present invention will be described in detail.

[0018]

The present invention provides a treatment or prevention method for osteoporosis or an inhibition or prevention method for fractures using PTH, which is characterized by administration of 100 units to 200 units of PTH per dose per week (hereinafter "per week" may be referred to as "every two weeks"). In addition, the present invention provides a therapeutic or prophylactic agent for osteoporosis or an inhibitor or prophylactic agent for fractures using PTH as the active ingredient, which is characterized by administration of 100 units to 200 units of PTH per dose every two weeks. Furthermore, the present invention provides the use of PTH for manufacturing said therapeutic or prophylactic agent for osteoporosis or inhibitor or prophylactic agent for fractures.

[0019]

I. Active ingredient

PTH, which is the active ingredient in the present invention (hereinafter it may be simply referred to as "PTH" in some cases) contains human PTH (1-84), which is human parathyroid hormone, and peptides at a molecular weight of approximately 4,000 to 10,000, which have the same or similar activity as human PTH (1-84).

[0020]

PTH includes any of natural PTH, PTH produced by the genetic engineering procedure, and PTH synthesized by chemical synthesis. PTH can be produced by genetic engineering procedures publicly known per se (Non-patent Document 8). Alternatively, PTH can be synthesized by a peptide synthesis method publicly known per se (Non-Patent Document 11), and can be synthesized, for example, by solid-phase method which extends peptide chains from the C-terminus on an insoluble polymeric carrier (Non-patented Document 4). In addition, the PTH used in the present invention may be derived from sources not limited to humans, but also from rats, bovines, pigs, etc.

[0021]

In the description of the present application, when indicating human PTH (n-m), it means a peptide shown in the partial amino acid sequence from the n-th to the m-th amino acid sequence of human PTH (1-84). For example, human PTH (1-34) means a peptide represented by a partial amino acid sequence consisting of the first to the 34th amino acid sequence of human PTH (1-84).

[0022]

PTH, which is the active ingredient in the present invention, may be a salt formed with 1, 2 or more kinds of volatile organic acids. As examples of the volatile organic acid, trifluoroacetic acid, formic acid, acetic acid, etc. are cited, among which acetic acid is preferred. The ratio of PTH in the free form and the volatile organic acid when forming a salt is not particularly limited as long as it forms salt. For example, since human PTH (1-34) has 9 molecules of basic amino acid residues and 4 molecules of acidic amino acid residues in its molecule, 5 residues of basic amino acid can be regarded as the chemical equivalent weight of acetic acid in consideration of salt formation in these molecules. For example, when the acetic acid content expressed by the formula "the weight of acetic acid × 100 (%) / the weight of the peptide of human PTH (1-34)" is used for the volume of acetic acid, as one theory, the chemical equivalent weight of acetic acid to human PTH (1-34) in the free form is approximately 7.3% (wt%). In the description of the present application, PTH (1-34) in the free form is sometimes referred to as teriparatide, and an acetate of teriparatide is referred to as

teriparatide acetate, respectively. The acetic acid content in teriparatide acetate is not particularly limited so long as the teriparatide and acetate form salt. For example, it may be 7.3% or more, which is the aforementioned theoretical chemical equivalent weight, or may be 0% to 1%. More specifically, for example, the acetic acid content in teriparatide acetate may be 1% to 7%, preferably 2% to 6%. These salts can be prepared according to methods publicly known per se (Patent Documents 4 and 5).

[0023]

As PTH, human PTH (1-84), human PTH (1-34), human PTH (1-38), hPTH (Non-patent Document 5), human PTH (1-34) NH_2, [$Nle^{8,18}$] human PTH (1-34), [$Nle^{8,18}$, Tyr^{34}] human PTH (1-34), [$Nle^{8,18}$] human PTH (1-34) NH_2, [$Nle^{8,18}$, Tyr^{34}] human PTH (1-34) NH_2, rat PTH (1-84), rat PTH (1-34), bovine PTH (1-84), bovine PTH (1-34), bovine PTH (1-34) NH_2, etc. are cited as examples. As preferred PTH, human PTH (1-84), human PTH (1-38), human PTH (1-34), and human PTH (1-34) NH_2 are cited as examples (Patent Document 3, etc.). As particularly preferred PTH, human PTH (1-34) is cited. As further preferred PTH, human PTH (1-34) obtained by chemical synthesis, and as the most preferred PTH, teriparatide acetate (Working Example 1), are cited.

[0024]

II. Combination with other agents

As a result of implementing a double-blind comparative clinical trial using the occurrence of fractures as the primary endpoint concerning PTH used in combination with a calcium agent, the present inventors found that the effect was expressed from an early stage at 24 weeks after or 26 weeks after and hypercalcemia was not confirmed as an adverse event (Working Examples 1 and 2). Accordingly, one of the features of the therapeutic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention is that it is to be used in combination with other agents. Here, the expression, "to be used in combination with other agents," refers to the use in combination with another agent (other agents) different from the therapeutic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention.

[0025]

As another agent of the present invention, calcium can be cited preferentially as an example. However, when stating "to be used in combination with other agents" in the present invention, it does not exclude cases where it is used in combination with agents other than said other agents. Therefore, as a use in combination with calcium, the following can be cited preferentially as examples:

use in combination with calcium alone; and
use in combination with calcium, vitamin D (including its derivatives) and/or magnesium alone.
Consequently, a calcium agent may be cited as a specific example of other agents; and, preferentially, the following can be cited as examples:
(1) a calcium agent containing calcium as the active ingredient; and
(2) a calcium agent containing calcium, vitamin D (including its derivatives), and magnesium respectively as the active ingredients.
[0026]

The form (administration frequency, administration route, administration site, dose, etc.) of the combination of the therapeutic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention with other agents is not particularly limited and can be determined by the prescriptions by physicians, etc. based on individual patients as necessary.
[0027]

For example, when a calcium agent is used in combination as the aforementioned other agent, the calcium agent may be administered simultaneously (which means once a week) with the therapeutic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention that contains PTH as the active ingredient or may be administered more frequently, or may be administered once or several times a day. Accordingly, said other agent may be a drug combination consisting with the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention, or the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention and said other agent may be separate agents. As an example of said calcium agent, "新カルシチュウ(Shin Karushichu) (trademark) D_3" (Distributor: Daiichi Sankyo Healthcare Co., Ltd.; Manufacturer and distributor: Nitto Pharmaceutical Industries, Ltd.) can be cited.
[0028]

Also, other agents may be administered in conjunction with or sequentially (i.e., at separate times), by the same or different administration routes with the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention. Therefore, the dosage form of other agents are not particularly limited, and such forms as tablets, capsules, fine granules, etc. can be cited as examples. In cases where said other agent is a calcium agent, it is preferred to be a calcium agent containing 100 mg to 400 mg (preferably, 150 mg to 350 mg) of calcium per single

dosage form. Thus, if a calcium tablet containing 100 mg to 400 mg of calcium per unit dosage form, e.g., 2 tablets per day, is administered according to a working example of the present invention, 200 mg to 800 mg of calcium will be administered per day, but not limited thereto.

[0029]

As specific examples of the aforementioned other agents, in cases of a calcium agent, for example, publicly known agents containing such agents as precipitated calcium carbonate, calcium lactate, calcium carbonate, calcium chloride, calcium gluconate, calcium aspartate, calcium phosphate, calcium hydrogen phosphate, calcium citrate, etc. as the active ingredients may be cited. Agents containing precipitated calcium carbonate are preferred. In addition to said other agents, fillers, binders, disintegrants, lubricants, antacids, etc. may be included as necessary.

[0030]

It is known that gastrointestinal symptoms, such as vomiting, retching, nausea, heavy stomach, stomach discomfort, pyrosis, etc., are transiently observed at a certain rate in patients with PTH administration (Patent Document 6).

[0031]

As a result of testing of various administration times and efficacies of antiemetic agents for transient retching and vomiting in association with the administration of the test drug, the present inventors confirmed that Primperan (generic name of the medicinal property is metoclopramide), Nauzelin (generic name of the medicinal property is domperidone), Gaster D (generic name of the medicinal property is famotidine), Gasmotin (generic name of the medicinal property is mosapride citrate), Takepron OD (generic name of the medicinal property is lansoprazole), and Rokushingan are effective for retching or vomiting in association with the administration of PTH (Working Example 2). Thus, as additional other agents, the aforementioned antiemetic agents can be cited preferably, and Nauzelin (generic name of the medicinal property is domperidone), Gasmotin (generic name of the medicinal property is mosapride citrate), and/or Rokushingan may be cited more preferably. The dosage and administration of these antiemetic agents can be set by physicians, etc. based on the symptoms, etc. of individual patients as necessary.

[0032]

III. Administration period

The administration period of the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention is not particularly limited but may be determined as necessary by prescriptions, etc. by

physicians, etc. depending on individual patients. The present inventors conducted a double-blind comparative clinical trial using the occurrence of fractures as the primary endpoint while setting an administration period to be 156 weeks or 72 weeks. In the present trial, a significant inhibitory effect on fractures by the administration was confirmed and the effects appeared as early as 24 weeks after or 26 weeks after (Working Examples 1 and 2). Furthermore, no new vertebral fracture was observed after 48 weeks from the administration (Working Example 2). Accordingly, as examples of the administration period, 24 weeks or more, 26 weeks or more, 48 weeks or more, 52 weeks or more, 72 weeks or more, or 78 weeks or more may be cited, and 78 weeks or more is the most preferable. Also, in the present trial, no hypercalcemia as an adverse event was found (Working Example 1).

[0033]

IV. Dosage

As a result of a double-blind comparative clinical trial using 100 units or 200 units of PTH per dose, the present inventors confirmed a significant inhibitory effect on fractures by said administration and that the effect appeared as early as 24 weeks after or 26 weeks after; however, they observed no hypercalcemia as an adverse event (Working Examples 1 and 2).

[0034]

Accordingly, one of the features of the present invention is that the dosage is 100 units to 200 units per dose. Here, one unit amount of PTH can be measured by the activity measurement method publicly known per se (Non-patented Document 9). As a dosage, 100 units or 200 units per dose is cited as an example preferably, and 200 units per dose is cited as being the most preferable.

[0035]

V. Administration interval

As a result of a double-blind comparative clinical trial wherein PTH is administered once a week, the present inventors confirmed a significant inhibitory effect on fractures by said administration and that the effect appeared as early as 24 weeks after or 26 weeks after; however, they observed no hypercalcemia as an adverse event (Working Examples 1 and 2). Accordingly, one of the features of the present invention is that the administration interval is every two weeks.

[0036]

VI. Administration route

The therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention may be administered by an

appropriate administration route based on its preparation form. For example, when the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention is an injection, they may be administered intravenously, intra-arterially, subcutaneously, intramuscularly, etc. As a result of subcutaneous injection of PTH, the present inventors have demonstrated excellent efficacy and effectiveness and safety (Working Examples 1 to 2). Thus, the present invention can cite a subcutaneous route as its preferred administration route.

[0037]

VII. Target disease

Osteoporosis related to the present invention is not particularly limited and includes both primary osteoporosis and secondary osteoporosis. As examples of the primary osteoporosis, involutional osteoporosis (post-menopausal osteoporosis and senile osteoporosis), and idiopathic osteoporosis (post-pregnancy osteoporosis, juvenile-onset osteoporosis, etc.) are cited. Secondary osteoporosis is osteoporosis induced by a specific disease, specific agents, etc. For example, specific agents, rheumatoid arthritis, diabetes, hyperthyroidism, sexual dysfunction, immobility, alibility, or other congenital disorders, etc. are cited as causes. As a specific agent, for example, steroids are cited. As an example of osteoporosis related to the present invention, osteoporosis with a high risk of fractures can be cited preferably. The application of the present invention to osteoporosis with a high risk of fractures means the application of the present invention to the following high-risk patients.

[0038]

The present inventors confirmed the effects, efficacy, and safety of the present invention in the clinical trial targeting patients with primary osteoporosis (Working Examples 1 and 2). Therefore, as osteoporosis related to the present invention, primary osteoporosis can be cited preferably, and involutional osteoporosis can be cited most preferably.

[0039]

The present inventors confirmed the effects of the present invention in a clinical trial targeting patients with primary osteoporosis who take steroids that induce secondary osteoporosis (Working Example 2). Therefore, as patients with primary osteoporosis related to the present invention, patients with primary osteoporosis who take steroids that induce secondary osteoporosis can be cited preferably.

[0040]

The present inventors confirmed the effect of the present invention in a clinical trial targeting patients with primary osteoporosis who have complications (diabetes,

hypertension, or hyperlipidemia) (Working Example 2). Accordingly, as patients with osteoporosis related to the present invention, patients with osteoporosis who have at least one of the following complications: diabetes, hypertension, and hyperlipidemia, can be cited as examples preferably, and patients with primary osteoporosis who have at least one of the following complications: diabetes, hypertension, and hyperlipidemia, can be cited as examples more preferably.

[0041]

It is known that diabetes is highly likely to be a risk factor for osteoporotic fracture (Non-patent Document 16).

[0042]

Concerning the relationship between diabetic osteoporosis and PTH, the following reports are found in animal experiments.

1) It was reported that increases are observed in 'bone mass,' 'trabecular thickness,' 'osteoid surface,' 'calcified surface,' 'bone mineralization rate,' and 'bone formation rate' in the cancellous envelope by administering hPTH to streptozotocin-administered rats that present diabetic osteopenia; and increases in 'osteoid surface,' 'calcified surface,' 'bone mineralization rate,' and 'cortical bone thickness' in the endocortical envelope (Non-patent Document 21). However, unlike rats with osteopenia due to other causes, no significant decrease in absorption surface is seen in the present rats.

2) As a result of administration of PTH to streptozotocin-administered rats for 8 weeks, it was reported that turnover and recovery of cancellous bone mass were observed (Non-patent Document 22).

3) It was reported in an experiment of cultured cells that when exposed to high concentration glucose, reaction to hPTH (1-34) decreases (effects of PTH become less) (Non-patent Document 20).

[0043]

Although the present inventors understand that there are many opinions of physicians, etc. who expect the effects of PTH administration in patients with diabetic osteoporosis (e.g., http://ww.richbone.com/kotsusoshosho/basic_shindan/tonyo.htm), there was no article proving the effects.

[0044]

Therefore, it is important knowledge that the trial in the present invention proved the fact that the risk of vertebral fractures for patients with primary osteoporosis and diabetes is reduced by the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of bone fractures related to the present invention.

[0045]

Fractures related to the present invention are not particularly limited and include both vertebral fractures and non-vertebral fractures (Working Example 1), and include both pathologic fractures due to osteoporosis, dysostosis, bone tumor, etc., and traumatic fractures due to traffic accidents, bruises, etc. Preferably, it is possible to cite, as examples, the application to fractures due to osteoporosis, and more preferably, vertebral fractures due to osteoporosis. The site of fractures is not particularly limited; however, typically, vertebral compression fractures, femoral neck fractures, femoral intertrochanteric fractures, femoral shaft fractures, humeral neck fractures, and distal radius fractures can be cited and, in particular, vertebral compression fractures can be cited as examples.

[0046]

The number of fractures related to the present invention is not particularly limited and includes both a single fracture and multiple fractures. The term "a single fracture" means a disease state where a bone is broken or cracked in only one location, and the term "multiple fractures" means a disease state where a bone is broken or cracked in 2 or more locations. The number of fractures in multiple fractures is not particularly limited; however, the application to the case where a bone is broken or cracked in 2 to 4 locations is preferred.

[0047]

Vertebral fractures related to the present invention include both new fractures and worsening fractures. For example, the degree of deformation of the entire vertebral body can be classified by Grade as follows: Grade 0 (normal), Grade 1 (vertebral body height reduced by approximately 20%-25% and vertebral body area reduced by 10%-20%), Grade 2 (vertebral body height reduced by approximately 25%-40% and vertebral body area reduced by 20%-40%), and Grade 3 (vertical body height reduced by approximately 40% or more and vertebral body area reduced by 40% or more). The classification of new and worsening can be carried out based on the Grade increase pattern according to the B]'s criteria. Specifically, when a change from Grade 0 to Grade 1, Grade 2, or Grade 3 is observed, it is diagnosed as a new fracture, and when a change from Grade 1 to Grade 2 or Grade 3, or from Grade 2 to Grade 3 is observed, it can be regarded as a worsening fracture. Further, in order to accurately determine a change in Grades, vertebral body height was measured according to the method of [C] et al. (Non-patent Document 35) and the method of [D] et al. (Non-patent Document 36).

[0048]

The present inventors confirmed the effect of inhibiting worsening fractures in a clinical trial targeting patients with a pre-existing fracture (Working Example 2).

Accordingly, in the present invention, as application targets, patients with osteoporosis, preferably patients who have a pre-existing fracture, and more preferably patients with a pre-existing fracture and the possibility of an worsening fracture can be cited.

[0049]

There are many unclear points related to PTH's mechanism of enhancing bone strength. Bone strength reflects not only bone density but also bone quality conditions. This means that not only bone density but also bone microstructure, calcification, and other bone quality factors define bone strength (Non-patent Document 17). The present inventors consider that bone quality may have an impact not only on bone strength but also on the risk of developing a disease that is different from osteoporosis and the performance of curing complications thereof. It was suggested that the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention may be dominant over previous therapeutic agents (Patent Document 2) in these points.

[0050]

Patent Document 2 discloses that, as a result of administering rhPTH (1-34) to patients with osteoporosis, not only bone mineral content (BMC) and bone mineral density (BMD) but also the bone area of the lumbar spine and femur, etc. are increased. Increases in bone area mean that bones thicken towards the outside.

[0051]

However, as a result of administering the therapeutic or prophylactic agent of osteoporosis or inhibitor or prophylactic agent of fractures related to the present invention to patients with osteoporosis, cortical bone thickness increased not towards the outside but towards the inside of the bones. That is, there was little change in the thickness of the bones overall. It is considered that this mechanism, for example, shows the following important clinical meaning.

[0052]

(1) There is no joint destruction by long bone hypertrophy.

A femur is one of the long bones (long bones comprising the extremities) and its epiphysis comes into contact with articular cartilage and forms the knee joint along with the synovial membrane and meniscus. The contact surface is referred to as an articular surface covered with cartilage that has a few millimeters in thickness. Knee osteoarthritis is cited as an example of a disease that causes knee arthralgia.

[0053]

On the other hand, it is known that Forteo (PTH for daily administration) showed stronger bone reinforcing efficacy than Fosamax for patients who have the complication

of prednisone-induced osteoporosis and arthralgia (Non-patent Documents 23 and 24).
[0054]

However, the administration of Forteo is a conventional therapeutic method substantially the same as PTH administration as stated in Patent Document 2. As mentioned above, said conventional therapeutic method is to thicken bones towards the outside of the bone. Hypertrophy of the femur towards the outside means an increase in the area of the articular surface, while the number of chondrocytes does not increase as compared to the hypertrophy of the bone. Therefore, the hypertrophy of the femur towards the outside, which is caused by the conventional therapeutic method, may facilitate joint destruction via damage to chondrocytes that are initiated or worsened by the increase in the area of the articular surface.
[0055]

However, as in the present invention, the present inventors consider that there is the possibility that the hypertrophy of the femur towards the inside may cause no increases in the area of the articular surface and may stabilize cartilage more, and that as a result, burden on cartilage may not increase and joint destruction may not be substantially promoted. This suggests that treatment of osteoporosis with the present agent may be kinder to joints than the treatment of osteoporosis by the conventional method.
[0056]

(2) There is no worsening or onset of spondylosis deformans due to vertebral body hypertrophy.

When normal vertebral body bone mass decreases due to aging and other causes, the vertebral body becomes unstable. Destabilization begins with deformation of the endplate. In concrete terms, destabilization of the vertebral body is a thinning of the endplate or the enlargement of endplate holes (Haversian canal). As the destabilization progresses, the intervertebral disc enters the endplate hole and the disc narrows. If the symptoms progress further, it will lead to the generation of osteophytes due to collisions between vertebrae. This degeneration of the spine is a disease called spondylosis deformans. When spondylosis deformans occurs, the space between vertebrae becomes stable, causing pain due to the invasion of the intervertebral disc and pain due to surrounding muscle expansion.
[0057]

However, as described in Patent Document 2, when PTH is administered daily to thicken the outside of the bone, there is a possibility that a sufficient inhibitory effect on enlargement of the endplate hole is not observed. Alternatively, an increase in the contact area between the vertebral body and the intervertebral disc reduces the distance

between the vertebral bodies, leading to instability of the vertebral body, resulting in an increased risk of developing or worsening spondylosis deformans.

[0058]

On the other hand, the administration of the therapeutic agent of osteoporosis and inhibitor or prophylactic agent of fractures in the present invention increases the cortical bone thickness not to the outside but to the inside of the bone. Therefore, it may sufficiently suppress the enlargement of the endplate hole and the invasion of the intervertebral disc into the endplate hole.

[0059]

(3) It does not promote worsening or development of hip osteoarthritis and temporomandibular joint osteoarthritis.

Hip osteoarthritis is a situation where the articular cartilage on the contact surface between acetabular, which forms the hip joint, and the femur head suffers wear and degeneration, and irreversible changes are caused due to poor blood flow to the joint, extreme weight, or overuse. The femoral cortical bone area of patients with hip osteoarthritis is significantly larger than that of healthy individuals (Non-patent Document 18). An increase in femoral cortical bone area means hypertrophy of the femur to the outside, and this may therefore be involved in the development or worsening of hip osteoarthritis. In the case of thickening towards the inside of the femur as in the present invention, the femur will not be thickened towards the outside of the bone, and thus there is the possibility that the risk of developing or worsening hip osteoarthritis is not increased. The main symptom of temporomandibular joint osteoarthritis is temporomandibular joint deformation, but cortical bone thickening is also one of the diagnostic findings (Non-patent Document 19). Thus, further outward hypertrophy of the cortical bone may worsen or develop symptoms. When the bone is thickened towards the inside of the bone as in the present invention, it is presumed that there is the possibility that the risk of developing or worsening such temporomandibular joint osteoarthritis is not increased.

[0060]

As described above, when (1) to (3) are summarized, patients with osteoporosis having at least one of the diseases of arthralgia, spondylosis deformans, deformans low back pain, hip osteoarthritis, or temporomandibular joint osteoarthritis as a complication (preferably patients with primary osteoporosis) can be preferably cited as examples of patients suited for the application of the therapeutic or prophylactic agent of osteoporosis and inhibitor or prophylactic agent of bone fractures in the present invention.

[0061]

The present inventors evaluated the influence of the medication history of other therapeutic agents for osteoporosis within one year on the efficacy of the present agent. As a result, higher efficacy of the test drug was revealed for patients with primary osteoporosis having medication history of other therapeutic agents for osteoporosis than for patients with no medication history (Working Example 2). Therefore, in the present invention, as patients with osteoporosis, the application to patients with osteoporosis having medication history of other therapeutic agents for osteoporosis can be cited as an example preferably, and the application to patients with primary osteoporosis who have a medicinal history of other therapeutic agents for osteoporosis can be more preferably cited as an example.

[0062]

Further, as other therapeutic agents for osteoporosis, L-aspartate calcium, alphacalcidol, raloxifene hydrochloride, elcatonin, menatetrenone, and calcium lactate are cited, and preferably, L-aspartate calcium, alphacalcidol, and elcatonin are cited as examples. Regarding patients with osteoporosis having medication history of other therapeutic agents for osteoporosis, said other therapeutic agents for osteoporosis are allowed to have been used alone or in combination.

[0063]

It is preferable to administer the therapeutic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention for 24 weeks to 72 weeks or longer to patients with osteoporosis having medication history of other therapeutic agents for osteoporosis. In particular, it is preferable to administer the present agent for 24 weeks or longer to patients with a high risk of lumbar spine fracture, and for 72 weeks or longer to patients with a high risk of fractures of the femoral neck or proximal region of the femur.

[0064]

The prevalence of osteoporosis and renal dysfunction increases with age. There is also a large epidemiological study report that 85% of female patients with osteoporosis have mild to moderate renal dysfunction (Non-patent Document 32). Therefore, it is important to provide an effective and safe agent for patients with osteoporosis that have renal dysfunction.

[0065]

The present inventors presented that the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention are effective to any of patients with osteoporosis having normal renal function, patients

with osteoporosis having mild renal dysfunction, and patients with osteoporosis having moderate renal dysfunction (Working Example 2). In addition, it has been found that in terms of safety related to serum calcium, the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention work equally for all patient groups.

[0066]

Normal renal function and dysfunction, and degree of dysfunction can be classified based on creatinine clearance. Specifically, when creatinine clearance is 80 mL/min. or more, renal function can be determined to be normal; when creatinine clearance is 50 mL/min. or more and less than 80 mL/min., it is determined to be mild renal dysfunction; and when creatinine clearance is 30 ml/min. or more and less than 50 mL/min., it is determined to be moderate renal dysfunction.

[0067]

In general, the normal upper limit of serum calcium concentration is 10.6 mg/mL, and 11.0 mg/mL, which exceeds the upper limit, is a slightly high value. In the conventional daily administration of PTH, after administration to patients with osteoporosis having moderate renal dysfunction, a slightly high value of serum calcium exceeding 11.0 mg/mL was observed in 11.76% thereof (Non-patent Document 32). However, in the present invention, as a result of administration of the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention to patients with osteoporosis having moderate renal dysfunction, no patients with serum calcium exceeding 11.0 mg/L were observed at all occasions of examinations from the start to the end of administration (Working Example 2). That is, it is considered that the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention are more excellent not only in terms of efficacy but also safety. Therefore, as patients subject to the application of the present invention, patients with osteoporosis having mild renal dysfunction and/or patients with osteoporosis having moderate renal dysfunction can be preferably cited as examples, and more preferably patients with primary osteoporosis having mild renal dysfunction and/or patients with primary osteoporosis having moderate renal dysfunction can be cited as examples.

[0068]

The race, age, gender, height, weight, etc. of subjects to apply the drug administration or treatment method related to the present invention are not particularly limited; however, patients with osteoporosis are cited as examples of the subjects, and it is preferable to apply the method of the present invention or to administer the

therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention to patients with osteoporosis who have risk factors of fractures in osteoporosis. Risk factors for fractures in osteoporosis include age, gender, low bone density, prevalent fractures, smoking, alcohol drinking, steroid use, family history of fractures, exercise, factors related to falls, bone metabolism markers, weight, calcium intake, and the like (Non-patent Document 10). Thus, in the present invention, patients (or subjects) with osteoporosis who meet all of the requirements (1) to (3) below are defined as "high-risk patients":

(1) Age 65 years or older;

(2) Having prevalent fractures; and

(3) Bone density less than 80% of the young adult mean and/or degree of bone atrophy of I or higher.

[0069]

Bone density as used here typically refers to bone mineral content in the lumbar spine. However, when it is difficult to evaluate the bone mineral content in the lumbar spine, the bone density can be indicated by the bone mineral content values of the radius, second metacarpal bone, femoral neck, and calcaneus. In addition, the young adult mean refers to the average value of bone density between 20 through 44 years old. The bone density can be measured by a method publicly known per se, such as dual-energy X-ray absorptiometry, photodensitometry, photon absorptiometry, quantitative CT, and quantitative ultrasonography, etc. In the present invention, the degree of bone atrophy means the degree of bone loss on X-ray. The degree of bone atrophy is classified into no bone atrophy, bone atrophy degree I, bone atrophy degree II, and bone atrophy degree III. "No bone atrophy" in the degree of bone atrophy indicates a normal state, and specifically means a state in which the trabecular structure cannot be recognized because the trabeculae in the vertical and horizontal directions are dense. Bone atrophy degree I means that the vertical trabeculae are conspicuous. Typically, the vertical trabeculae look thin but are densely arranged, and the vertebral endplates become conspicuous. Bone atrophy degree II in the degree of bone atrophy means a state in which the vertical trabeculae are rough, the vertical trabeculae look thick, the arrangement is rough, and the vertebral endplates look light. Bone atrophy degree III in the degree of bone atrophy means a state in which the vertical trabeculae are also unclear, the vertebral body shadow is obscured as a whole, and the difference from the intervertebral disc shadow decreases (Journal of osteoporotic medicine, 5/3, July 2006, "Diagnosis of osteoporosis by simple radiograph"). The degree of bone atrophy can be determined, for example, from a lumbar lateral X-ray image. The number of vertebral

fractures in the present invention can be easily measured, for example, by the method of [B] et al. (Non-patent Document 14). Bone fractures at sites other than the vertebral body can be easily confirmed, for example, by using an X-ray film.

[0070]

In the present invention, it is particularly preferable to apply the method of the present invention or administer the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention to high-risk patients (Working Example 1).

[0071]

On the other hand, generally, it is preferable to avoid applying the method in the present invention and avoid administrating the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention to patients (subjects) corresponding to at least any of the following (1) to (6):

(1) Patients who are prone to hypersensitivity, such as bronchial asthma and rash (erythema, wheals, etc.);

(2) Patients with hypercalcemia;

(3) Women who are or may be pregnant;

(4) Patients with hypothyroidism or hyperparathyroidism;

(5) Patients with drug hypersensitivity in the past; and

(6) Patients with serious complications, such as heart disease, liver disease, renal dysfunction.

Therefore, in the present invention, it is preferable to target patients with osteoporosis who are the high-risk patients and who do not correspond to all of (1) through (6) above.

[0072]

VIII. Preparation

The therapeutic or prophylactic agent for osteoporosis or inhibitor or prophylactic agent for fractures in the present invention (hereinafter simply referred to as the "present agent" in some cases) may be used in various preparation forms. In general, the present agent can be prepared as an injection or the like using PTH alone or with a conventional pharmaceutically acceptable carrier. An injection is preferred as the dosage form of the present agent.

[0073]

For example, in cases where the present agent is an injection, it can be prepared by the following procedures: after PTH is dissolved with an appropriate solvent (sterile water, buffer solution, saline, etc.), it is filtrated and/or sterilized by other appropriate

methods, and then filled into an aseptic container. At that time, it is preferred that the necessary additives (for example, excipients, stabilizers, solubilizers, antioxidants, soothing agents, tonicity agents, pH adjusters, preservatives, etc.) be added together with PTH. Examples of such additives include sugars, amino acids, sodium chloride, and the like. When sugars are used as additives, it is preferable to add one weight or more (preferably 50 weight to 1000 weight) of mannitol, glucose, sorbitol, inositol, sucrose, maltose, lactose, or trehalose as sugars per weight of PTH. When sugar and sodium chloride are used as additives, it is preferable to add 1/1000 weight to 1/5 weight (preferably 1/100 weight to 1/10 weight) of sodium chloride per weight of sugar.

[0074]

For example, when the present agent is an injection, it may be solidified by freeze drying, etc. (freeze-dried preparation or the like) and may be dissolved with an appropriate solvent before use. Alternatively, when the present agent is an injection, it may be a liquid that is dissolved in advance.

[0075]

The present agent is preferably stored in a package on which it is stated that 100 units to 200 units of human PTH (1-34) per dose should be administered every two weeks as a therapeutic agent for osteoporosis and inhibitor or prophylactic agent for fractures, or stored in a package along with a package insert stating to that effect.

[0076]

The utility of the invention in the present application can be confirmed easily by statistical processing, etc. of the results of the clinical trials presented in working examples by the usual methods. In addition, the present invention is explained more concretely below through working examples, but the scope of the present invention is not limited thereto.

[Working examples]

[0077]

(Working Example 1)

Male and female patients who are diagnosed with primary osteoporosis (Non-patent Reference 12) were subcutaneously administered 5 units or 100 units of teriparatide acetate, which were prepared using the [E]'s method (Patent Documents 4 and 5; Non-patent Document 11), intermittently once a week (each administration group is referred to as a 5-unit group or a 100-unit group). The activity of the teriparatide acetate was measured according to the article of Marcus et al. (Non-patent Document 9).

[0078]

The 5-unit group or the 100-unit group is administered with a full amount of a

solution in which freeze-dried preparation containing 5 units or 100 units of teriparatide acetate per vial is dissolved with 1 mL saline before use. Both the 5-unit group and the 100-unit group were administered with two tablets of calcium agent (containing 500 mg of precipitated calcium carbonate [200 mg as calcium] per tablet) once a day.

[0079]

Comparison was conducted by classifying patients with osteoporosis according to the conditions as shown in Table 1 based on the fracture risk factors as shown in Non-patent Document 13. High-risk patients (hereinafter simply referred to as "high-risk subjects" in some cases) were defined as having all three factors, including age, prevalent vertebral fractures, and bone density or bone atrophy; and low-risk subjects were defined as other than the above.

[0080]

[Table 1] (To be presented below.)

Patient backgrounds are as shown in Table 2 and Table 3, and no statistically significant difference was observed between the backgrounds of both groups ($p < 0.05$).

[0081]

[Table 2] (To be presented below.)

[Table 3] (To be presented below.)

[0082]

During the administration period, combination with calcitonin preparation, active vitamin D_3 preparation, vitamin K preparation, ipriflavone preparation, bisphosphonate preparation, estrogen preparation, anabolic hormone preparation, calcium preparation according to a physician's prescription (however, excluding the aforementioned calcium agents that are administered as two tablets per day) and other agents that are considered to have effects on bone metabolism was prohibited. As a bone evaluation, lumbar spine bone density and the occurrence of fractures were checked. The second through the fourth lumbar spine bone densities were measured at the start and every 6 months thereafter using dual-energy X-ray absorptiometry (DXA method). Regarding the frequency of bone fractures, in the vertebral body, X-ray imaging of the front and side from the 4th thoracic vertebra to the 5th lumbar spine was performed at the start and every 6 months thereafter; referring to the method of [B] et al. (Non-patent Document 14), new vertebral fractures were evaluated by comparing X-ray films at the start and at the following times. Parts other than the vertebral body were evaluated by confirming with X-ray film. In all cases, blood was collected at the start of administration and during the administration period, and general laboratory values including calcium concentration were measured. (DXA and new vertebral fractures were collectively

determined at the center, and non-vertebral fractures were determined by X-ray film by the physician in charge.) The administration period with high-risk patients was 85.1±20.8 weeks in the 5-unit group and 83.7 ± 19.8 weeks in the 100-unit group; and there was no significant difference between the two groups ($p < 0.05$). The administration period with low-risk subjects was 72.7 ± 19.4 weeks in the 5-unit group and 88.3 ± 21.3 weeks in the 100-unit group; and there was no significant difference between the two groups ($p < 0.05$).

[0083]

Table 4 and Table 5 show changes in lumbar spine density by administration group and by high-risk and low-risk subjects. In high-risk subjects, concerning the bone density in the 100-unit group, a significantly higher increase of bone density than at the start of administration was observed, and significantly higher values than the 5-unit group were shown ($p<0.05$). On the other hand, in the low-risk subjects, no significant difference was observed in comparison with the value at the start of administration and between the groups ($p> 0.05$).

[0084]

[Table 4] (To be presented below.)

[0085]

[Table 5] (To be presented below.)

[0086]

Table 6 and Table 7 show the results of occurrence of new vertebral fractures by administration group and by high-risk and low-risk subjects. In high-risk subjects, the 100-unit group showed significantly lower occurrence of fractures than the 5-unit group ($p <0.05$). On the other hand, there was no significant difference between groups in low-risk subjects ($p> 0.05$).

[0087]

[Table 6] (To be presented below.)

[0088]

[Table 7] (To be presented below.)

[0089]

Table 8 and Table 9 show the results of occurrence of new vertebral fractures every 26 weeks by administration group and by high-risk and low-risk subjects. In high-risk subjects, the occurrence of fractures was suppressed at 26 weeks after in the 100-unit group, compared to the 5-unit group. On the other hand, there was no difference between groups in low-risk subjects.

[0090]

[Table 8] (To be presented below.)
[0091]
[Table 9] (To be presented below.)
[0092]

Table 10 and Table 11 show the results of occurrence of fractures at sites other than the vertebral body by administration group and by high-risk and low-risk subjects. In high-risk subjects, the 100-unit group showed significantly lower occurrence of fractures than the 5-unit group. On the other hand, there was no significant difference between groups in low-risk subjects.

[0093]
[Table 10] (To be presented below.)
[0094]
[Table 11] (To be presented below.)
[0095]

FIG. 1 shows the results of changes in serum calcium concentration by administration group and by high-risk and low-risk subjects. Among the clinical laboratory test results using the collected blood samples, hypercalcemia was not observed in all cases except for one case where the value was higher than that before the start of drug administration in a low-risk subject in the 5-unit administration group. The tendency of increases in serum calcium was not observed.

[0096]

As can be seen from the above tables, in patients with primary osteoporosis who have risk factors for new fractures, significant increases in bone density of the lumbar spines and suppression of new vertebral fractures were observed as a result of subcutaneously administering teriparatide acetate once a week for 100 units intermittently. In other words, it was confirmed that 100 units of teriparatide acetate administered once a week to high-risk patients for new fractures in the present invention can be a useful therapeutic agent for osteoporosis and inhibitor or prophylactic agent for fractures.

[0097]

In addition, during the administration period, under the weekly administration of teriparatide acetate in the present invention, there was no onset of hypercalcemia with any dosage, and it is considered to be useful compared to a daily administration of teriparatide acetate, which has already been known.

[0098]
(Working Example 2)

The test drug (1 vial; injectable freeze-dried preparation containing 200 units of teriparatide acetate per vial), which is prepared by the [E]'s method (Patent Documents 4 and 5, Non-patent Document 11) or the control drug (1 vial; placebo preparation that substantially does not contain teriparatide acetate per vial) is dissolved with 1 mL of saline respectively before use and administered once a week intermittently for 72 weeks to male and female high-risk patients who were diagnosed to have primary osteoporosis.
[0099]

The aforementioned patients took two tablets of calcium agents daily after dinner in combination. The calcium agent is a soft chewable preparation containing 610 mg calcium, 3400 IU of Vitamin D_3 and 30 mg of magnesium in two tablets; it contains, as ingredients, precipitated calcium carbonate, magnesium carbonate, cholecalciferol (vitamin D_3), etc.; and it is marketed under the commercial name of "新カルシチュウ (Shin Karushichu) (trademark) D_3" (Distributor: Daiichi Sankyo Healthcare Co., Ltd.; Manufacturer and distributor: Nitto Pharmaceutical Industries, Ltd.).
[0100]

The aforementioned patients are all outpatients capable of walking independently and do not fall under any of the following criteria (1) to (19).
(1) A patient diagnosed with secondary osteoporosis due to predetermined causes. Here, the predetermined causes refer to endocrine (hyperthyroidism, gonadal dysfunction, Cushing syndrome), alibility (scurvy, other (protein deficiency, vitamin A or D excess)), drug (corticosteroid, Methotrexate (MTX), heparin, aromatase inhibitor, GnRH agonist), immobility (systemic (bed rest, paraplegia, space flight), local (after fracture, etc.)), congenital (osteogenesis imperfecta, Marfan's syndrome, etc.), and other (rheumatoid arthritis, diabetes, liver disease, gastrointestinal disease (gastrectomy), etc.).
(2) A patient having a predetermined disease that shows bone mass loss other than osteoporosis. Here, the predetermined diseases include various types of osteomalacia, primary, secondary hyperparathyroidism, bone metastasis of malignant tumors, multiple myeloma, spinal hemangioma, spinal caries, pyogenic spondylitis, etc.
(3) A patient with predetermined X-ray findings that are considered to affect vertebral body strength. Here, the term "predetermined X-ray findings" refers to the state where 6 or more consecutive vertebral bodies form cross-links; where significant ossification is observed in the ligaments around the vertebral bodies; where the spine has a significant spinal deformity; and where surgery has been performed on a vertebral body.
(4) A patient wearing a corset that covers the entire thoracolumbar body.
(5) A patient who was administered bisphosphonate preparation within 52 weeks (364 days) before obtaining informed consent.

(6) A patient who was administered with a therapeutic agent for osteoporosis on the date of informed consent (however, if drug washout of 8 weeks (56 days) or more is possible before the start of treatment, the patient can be selected as a subject). Calcitonin preparation, active vitamin D_3 preparation, vitamin K preparation, ipriflavone preparation, estrogen preparation, SERM preparation, or anabolic hormone preparation.
(7) A patient who is prone to hypersensitivity, such as bronchial asthma, rash (erythema, wheals, etc.), etc.
(8) A patient with a history of hypersensitivity to PTH preparation.
(9) A patient with Paget's disease of bone.
(10) A patient with a history of malignant bone tumor or a history of malignant tumor within 5 years.
(11) A patient with multiple exostosis.
(12) A patient with a history of radiation external-beam radiotherapy or a history of radiation brachytherapy.
(13) A patient with 11.0 mg/dL or more of serum calcium value.
(14) A patient with more than twice the standard upper value of alkaline phosphatase value.
(15) A patient with serious renal disease, liver disease, or heart disease. The criteria for each disease are as follows.

Renal disease: Serum creatinine level is 2 mg/dL or higher.

Liver disease: AST (GOT) or ALT (GPT) level is 2.5 times the upper limit of the reference value or 100 IU/L or higher.

Heart disease: To be determined in reference to Grade 2 as shown in "Severity classification criteria of adverse reactions of pharmaceuticals" (June 29, 1992; PFSB/SD Notification No. 80).

(16) A patient who was determined to have low reliability in interview (be sure to exclude at least patients who were diagnosed as having dementia).
(17) A patient who was administered other study drugs within 26 weeks (182 days) prior to obtaining informed consent.
(18) A patient who was administered a PTH preparation in a clinical trial in the past.
(19) Other patients who were determined to be non-conforming by the investigator (sub-investigator) when implementing the clinical trial.

[0101]

In addition, for the aforementioned patients, administration of any of the following drugs (1) to (6) was prohibited from the time of obtaining informed consent for the

clinical trial until the end of the clinical trial.
(1) Therapeutic agents for osteoporosis other than teriparatide acetate (specifically, bisphosphonate preparation, calcitonin preparation, active vitamin D_3 preparation, calcium preparation (however, excluding the aforementioned calcium preparation that is administered once a day after dinner), vitamin K preparation, ipriflavone preparation, estrogen preparation, SERM preparation, and anabolic hormone preparation)
(2) Corticosteroid preparation (however, in cases of intramuscular injection, intravenous injection, or oral administration in prednisolone conversion, where administration exceeds 5 mg/day on average for one week, where the daily dose exceeds 10mg/day, or where the total dose exceeds 450 mg)
(3) Aromatase inhibitor
(4) GnRH agonist
(5) Other study drugs
[0102]

The numbers of administration cases of the test drug and the control drug are 290 cases (it may be referred to as the "test drug group" in working examples) and 288 cases (it may be referred to as the "control group" in working examples), and the total number of administration cases was 578 cases. However, the number of examples in each administration group may differ depending on the types of tests, and may be expressed by, for example, (n = **) or the number of evaluation examples.
[0103]

For bone evaluation, bone density, bone geometry, and bone fracture occurrence were checked.
[0104]

Concerning lumbar spine bone density, the second spine to the fourth spine density were measured at the start and every 24 weeks thereafter using dual-energy X-ray absorptiometry (DXA method).
[0105]

Concerning femur bone density, the proximal region of the femur was rotated internally by 20 degrees and only the left side was measured at the start and every 24 weeks thereafter using dual-energy X-ray absorptiometry (DXA method).
[0106]

DXA geometry was evaluated with femur bone density data measured by the physician in charge at the start and every 24 weeks thereafter.
[0107]

CT geometry was performed by using multi-slice CT at the start of measurement of

the proximal region of the femur, and after 48 weeks and 72 weeks.

[0108]

Regarding the frequency of bone fractures, in the vertebral body, X-ray imaging of the front and side surfaces from the 4th thoracic vertebra to the 5th lumbar spine was performed at the start and every 24 weeks thereafter; referring to the method of [B] et al. (Non-patent Document 14), new and worsening vertebral fractures were evaluated by comparing X-ray films at the start and at the following times. Regarding sites other than the vertebral body, evaluation was conducted through checking with X-ray films (DXA, bone geometry, new and worsening vertebral fractures were determined collectively at the center, and non-vertebral fractures were determined by the physician in charge using the X-ray films).

[0109]

(A) Efficacy of the test drug for multiple vertebral fractures

Here, multiple vertebral fractures are defined as two or more new vertebral fractures. Comparing the incidence of multiple vertebral fractures between the test drug group (n=261) and the control group (n=281) in 72 weeks after the administration, the incidence was 2.1% for the control group (6 cases) and was 0.8% for the test drug group (2 cases). It shows that the test drug has an inhibitory or preventive effect on multiple vertebral fractures.

The number of cases by the number of bone fractures is shown in the table below.

[Table 12] (To be presented below.)

[0110]

(B) Efficacy of the test drug in patients with primary osteoporosis who are taking steroids

The efficacy of the test drug in patients with primary osteoporosis taking steroids was examined. As a result, as shown in the following tables, the test drug is effective in patients with primary osteoporosis taking steroids.

[0111]

[Table 13] (To be presented below.)

[Table 14] (To be presented below.)

[0112]

Since steroids are agents that cause secondary osteoporosis, the above results suggest that the test drug may be effective against secondary osteoporosis caused by steroidal agents that induce secondary osteoporosis.

[0113]

(C) Efficacy of the test drug in 3 sites of the femur

The efficacy of the test drug in 3 sites of the femur (femoral neck, intertrochanteric femur, and femoral shaft) were examined according to the general CT method. As a result, as shown in the following tables, the test drug is effective for each site of the femur.

[Table 15] (To be presented below.)

[Table 16] (To be presented below.)

[Table 17] (To be presented below.)

[0114]

(D) Examination of prescription for retching and vomiting in association with the administration of the test drug

The administration timing and efficacy of various treatment agents for retching and vomiting in association with the administration of the test drug was examined.

[Table 18] (To be presented below.)

[0115]

As described above, Purinperan, Nauzerin, Gaster D, Gasmotin, Takepron OD, and Rokushingan were effective. In particular, Nauselin, Gasmotin, and Rokushingan were preferred.

[0116]

(E) Assessment of the influence of the type of complication and its presence on the efficacy of the test drug

The aforementioned patients contain those with complications. Therefore, the influence of the type of complication (diabetes, hypertension, and hyperlipidemia) and its presence on the efficacy of the test drug was assessed. As a result, as shown in the following table, it became clear that the test drug suppressed the occurrence of new vertebral fractures 24 weeks after the administration, regardless of the type and presence of these complications.

[Table 19] (To be presented below.)

[0117]

Diabetic osteoporosis, for which the primary disease is diabetes, is a secondary osteoporosis; however, the fact that the effect of the test drug in patients with primary osteoporosis having diabetes as a complication was found suggests that the test drug may have a therapeutic effect on diabetic osteoporosis.

[0118]

(F) Efficacy of the test drug on worsening fractures

The efficacy of the test drug on worsening fractures was tested. As a result, as shown in the following table, the test drug is effective against worsening fractures.

[Table 20] (To be presented below.)

[0119]

(G) Assessment of the influence of the medication history of other therapeutic agents for osteoporosis on the efficacy of the test drug

As described above, it was prohibited to administer any therapeutic agents for osteoporosis other than teriparatide acetate to the aforementioned patients for the period from when informed consent for the clinical trial was obtained until the end of the clinical trial in principle. However, there were patients who were administered other therapeutic agents for osteoporosis under the predetermined conditions prior to when informed consent for the clinical trial was obtained. Therefore, the influence of the medication history with other therapeutic agents for osteoporosis on the efficacy of the test drug was assessed from the perspective of the incidence of new vertebral fractures and the rate of changes in bone density.

[0120]

The assessment results regarding the incidence of new vertebral fractures are shown in the table below. In the table, at the 72nd week after the administration of the test drug, concerning patients having a medication history with other therapeutic agents for osteoporosis, the bone fracture rate was 2.9% for the test drug group and was 16.1% for the control group; however, concerning patients without a medication history, the bone fracture rate was 3.2% for the test drug group and was 12.9% for the control group. In other words, it was revealed that the efficacy of the test drug is higher in patients with a medication history of other therapeutic agents for osteoporosis than patients without a medication history.

[Table 21] (To be presented below.)

[0121]

Next, the evaluation results for the bone density change rate are shown in the table below. In the table, regarding lumbar spine bone density, the increase in the bone density was remarkable at the 48th week after the administration of the test drug even in patients with a medication history with other therapeutic agents for osteoporosis. In particular, in patients with a medication history with any of L-calcium aspartate, elcatonin, alfacalcidol, menatetrenone, and calcitriol as other therapeutic agents for osteoporosis in the test drug group, a significant increase in lumbar spine bone density was observed as early as at the 24th week after the administration. It is further noted that when other therapeutic agents for osteoporosis are L-calcium aspartate and elcatonin, a distinctive increase in bone density of the femoral neck and proximal region of the femur was observed at the 72nd week after the administration of the test drug. In

particular, it is worthy of note that when the other therapeutic agent for osteoporosis is elcatonin, the bone density in the proximal region of the femur already increased drastically at the 24th week after the administration of the test drug.

[Table 22] (To be presented below.)

[0122]

In addition, the following table shows the results of the detailed assessment of the influence of the medication history of other therapeutic agents for osteoporosis on the efficacy of the test drug for each of said other therapeutic agents for osteoporosis from the perspective of the incidence of new vertebral fractures. As can be seen from the table, in patients with a medication history with therapeutic agents for osteoporosis other than calcitriol, significant suppression of new bone fractures by the administration of the test drug was observed.

[Table 23] (To be presented below.)

[0123]

(H) Efficacy and safety of the test drug in patients with osteoporosis having renal dysfunction

The efficacy and safety of the test drug were examined in the group of patients with osteoporosis having normal renal function, the group of patients with osteoporosis having mild renal dysfunction, and the group of patients with osteoporosis having moderate renal dysfunction.

[0124]

(H-1) Distribution of background factors in each patient group (detail)

The group of patients with osteoporosis having normal renal function is indicated as "Normal (80≤)," the group of patients with osteoporosis having mild renal dysfunction as "Mild impairment (50≤ <80)," and the group of patients with osteoporosis having moderate renal dysfunction as "Moderate impairment (<50)." In addition, the test drug administration group is indicated as "PTH 200 group" and the control drug administration group as "P group." Also, the group of patients with osteoporosis having mild renal dysfunction and the group of patients with osteoporosis having moderate renal dysfunction are collectively indicated as "Abnormal (<80)" in some cases. Each patient was classified into the above groups based on their creatinine clearance. Specifically, when creatinine clearance is 80 mL/min. or more, renal function can be determined to be normal; when creatinine clearance is 50 mL/min. or more and less than 80 mL/min., it is regarded as mild renal dysfunction; and when creatinine clearance is 30 mL/min. or more and less than 50 mL/min., it is regarded as moderate renal dysfunction.

[0125]

(H-1) Distribution of background factors in each patient group

The distribution of background factors in each patient group is as shown below.

[Table 24] (To be presented below.)

[0126]

(H-2) Efficacy of the test drug in each patient group (fracture suppression)

It was revealed that the test drug has the efficacy to inhibit new vertebral fractures in all of the groups of patients with osteoporosis having normal renal function and the groups of patients with osteoporosis with (mild and moderate) renal dysfunction.

[Table 25] (To be presented below.)

[0127]

(H-3) Efficacy of the test drug in each patient group (increases in bone density)

It was revealed that the test drug has the efficacy to increase lumbar spine bone density in all of the group of patients with osteoporosis having normal renal function, the group of patients with osteoporosis having mild renal dysfunction, and the group of patients with osteoporosis having moderate renal dysfunction.

[Table 26] (To be presented below.)

[0128]

(H-4) Safety of the test drug in each patient group (corrected serum calcium)

As a result of administering the test drug in the group of patients with osteoporosis having normal renal function, the group of patients with osteoporosis having mild renal dysfunction, and the group of patients with osteoporosis having moderate renal dysfunction, there were no significant differences between the test drug group and the control group. Thus, it was revealed that the test drug works equally for all groups in terms of safety related to serum calcium.

[Table 27] (To be presented below.)

[0129]

(H-5) Safety of the test drug in each patient group (incidence of adverse events)

The incidence of adverse events after the administration of the test drug was examined in the group of patients with osteoporosis having normal renal function, the group of patients with osteoporosis having mild renal dysfunction, and the group of patients with osteoporosis having moderate renal dysfunction, respectively.

[Table 28] (To be presented below.)

[Table 29] (To be presented below.)

[Table 30] (To be presented below.)

[0130]

(H-6) Safety of the test drug in each patient group (incidence of adverse reactions)

As a result of administering the test drug to the group of patients with osteoporosis having normal renal function, the group of patients with osteoporosis having mild renal dysfunction, and the group of patients with osteoporosis having moderate renal dysfunction, the test drug showed approximately a double incidence of adverse reactions compared to the control drug in all patient groups. Thus, it was revealed that the test drug works equally for all groups in terms of safety related to incidence of adverse reactions.

[Table 31] (To be presented below.)

[Table 32] (To be presented below.)

[Table 33] (To be presented below.)

[0131]

(I) Effect of the administration of the test drug on time-dependent changes in the incidence of new vertebral fractures

The test drug administration group is indicated as "PTH 200 group" and the control drug administration group as "P group."

[Table 34] (To be presented below.)

[Table 35] (To be presented below.)

[0132]

As shown in the above table, the incidence of new vertebral fractures every six months was almost constant at about 5% in all sections in the P group. On the other hand, in the PTH200 group, the incidence of each section decreased as the administration period became longer, and no new vertebral fractures occurred after the 48th week. The incidence of new vertebral fractures in the PTH200 group was lower than the P group in all sections of within 24 weeks, 24 weeks to 48 weeks, and 48 weeks to 72 weeks. Relative risk reduction (RRR) for the placebo increased as administration was continued. Thus, once-weekly administration of 200 units of the test drug suppressed the occurrence of new vertebral fractures from an early stage, and, after 24 weeks, the bone fracture risk was already reduced by 53.9% compared to the placebo. In addition, the effect of suppressing bone fractures by the test drug tended to increase with administration.

[0133]

In addition, in the FAS of the fracture test, the incidence of vertebral fractures (new + worsening) after 72 weeks by the Kaplan-Meier estimation method was 3.5% for the PTH200 group and 16.3% for the P group. The incidence in the group administered 200 units of the test drug was lower than in the placebo group (logrank test, $p<0.0001$). In

addition, the administration of 200 units of the test drug reduced the risk of vertebral fracture (new + worsening) by 78.6% after 72 weeks compared to the administration of the placebo. Comparing the incidence of vertebral fractures (new + worsening) every 6 months between the groups, the incidence in the PTH 200 group was lower than in the P group in all sections of within 24 weeks, 24 weeks to 48 weeks, and 48 weeks to 72 weeks.

[0134]

(J) Effect of administration of test drug on urinary calcium and serum calcium of patients with osteoporosis

The test drug administration group is indicated as "PTH 200 group" and the control drug administration group as "P group." The results of tests on changes in urinary calcium level and corrected serum calcium level when the test drug or the control drug were administered to patients once per week for 72 weeks are shown (FIG. 4 and FIG. 5).

The mean values (and median) of the change rate in urinary calcium were 3.2% (-14.7%) for the PTH 200 group and 23.6% (1.6%) for the P group after 72 weeks, when compared with the values at the start. A decreasing tendency was more notable in the PTH 200 group than in the P group.

The corrected serum calcium level changed in the range of 9.3 mg/dL to 9.6 mg/dL on average in both groups. The corrected serum calcium after administration in the PTH 200 group was 8.5 mg/dL at a minimum (after 48 weeks and 72 weeks), 11.6 mg/dL at a maximum (after 4 weeks), and in the P group, it was 8.5 mg/dL at a minimum (after 4 weeks) and 12. 1 mg/dL at a maximum (after 12 weeks). No major changes were observed in both groups.

There were no adverse events, such as increases and decreases in serum calcium in the clinical trial.

In the clinical trial, no onset of hypercalcemia or hypercalciuria was observed in the PTH 200 group compared to the P group.

[Industrial availability]

[0135]

The therapeutic agent or prophylactic agent for osteoporosis and inhibitor or prophylactic agent for fractures in the present invention have both excellent efficacy and effects and safety. The fracture suppression method in the present invention is highly safe. Both of them are innovative medical technologies that greatly contribute to the treatment of osteoporosis and the suppression and prevention of fractures. Therefore, the therapeutic or prophylactic agent for osteoporosis and inhibitor or prophylactic

agent for fractures for said purpose are very useful in the pharmaceutical industry.

(Tables)

[Table 1]

Table 1 Classification by fracture risk factors

Risk factor	High-risk subjects	Low-risk subjects
Age	65 or older	Younger than 65
Prevalent vertebral fractures	One or more	None
Evaluation of bone density or bone atrophy*	Less than 80% of the young adult mean** or atrophy grade I or higher	80% of the young adult mean or higher or normal atrophy grade

*Bone density evaluated by x-ray films

**Young adult mean: Average bone density of 20 to 44-year-olds

[Table 2]

Table 2 Patient background of the 5-unit group and 100-unit group among high-risk subjects

Mean ± standard deviation

Group	No. of subjects	Age (years)	No. of prevalent vertebral fractures	Lumbar spine bone mineral density (%*)
5-unit group	64	73.9±4.6	2.3±1.2	63.4±11.6
100-unit group	52	73.9±5.8	2.1±1.2	67.9±15.5

*Value taking the young adult mean as 100%

[Table 3]

Table 3 Patient background of the 5-unit group and the 100-unit group among low-risk patients

Mean ± standard deviation

Group	No. of subjects	Age (years)	No. of prevalent vertebral fractures	Lumbar spine bone density (%*)
5-unit group	10	57.9±5.1	1.8±0.9	68.3±8.8
100-unit group	11	61.5±2.4	2.4±1.2	59.9±1.9

*Value taking the young adult mean as 100%

[Table 4]

Table 4 Lumbar spine bone density (% change) among high-risk subjects

Mean ± standard deviation

Group	After 26 W	After 52 W	After 78 W	After 104 W	Final check
5-unit group	-0.9±4.4	-0.6±4.1	0.4±4.1	0.4±4.0	-0.1±4.8
100-unit group	3.3±4.5*#	4.3±4.5*#	4.0±4.5*#	4.9±4.2*#	4.5±4.6*#

* Difference from the start of administration $p<0.05$

Difference from the 5-unit group $p<0.05$

[Table 5]

Table 5 Lumbar spine bone density (% change) among low-risk subjects

Mean ± standard deviation

Group	After 26 W	After 52 W	After 78 W	Final check
5-unit group	-0.6±6.4	-0.7±6.2	1.9±7.5	-0.6±5.7
100-unit group$	3.2	6.1	12.0	12.0

$ The bone density was measured for only one patient and the value is shown as a reference.

[Table 6]

Table 6 New vertebral fractures among high-risk subjects

Group	No. with fractures (persons)	No. of vertebral fractures	Difference between groups
5-unit group	13	22	$p<0.05$
100-unit group	3	3	

[Table 7]

Table 7 New vertebral fractures among low-risk subjects

Group	No. with fractures (persons)	No. of vertebral fractures	Difference between groups
5-unit group	1	1	$p>0.05$
100-unit group	1	2	

[Table 8]

Table 8 New vertebral fractures every 26 weeks among high-risk subjects

	5-unit group				100-unit group			
	No. evaluated	No. with fractures	Incidence (%)	No. of fractures	No. evaluated	No. with fractures	Incidence (%)	No. of fractures
After 26 W	63	6	9.5	8	51	1	2.0	1
After 52 W	63	7	11.1	9	51	1	2.0	1
After 78 W	57	4	7.0	4	45	1	2.2	1
After 104 W	35	1	2.9	1	25	0	—	0
After 130 W	10	0	—	0	5	0	—	0

[Table 9]

Table 9 New vertebral fractures every 26 weeks among low-risk subjects

	5-unit group				100-unit group			
	No. evaluated	No. with fractures	Incidence (%)	No. of fractures	No. evaluated	No. with fractures	Incidence (%)	No. of fractures
After 26 W	21	0	—	0	12	1	8.3	2
After 52 W	21	1	4.8	1	12	0	—	0
After 78 W	16	0	—	0	12	0	—	0
After 104 W	2	0	—	0	6	0	—	0
After 130 W	2	0	—	0	2	0	—	0

[Table 10]

Table 10 Fractures of sites other than the vertebral body among high-risk subjects

Group	No. with fractures (persons)	Site	Difference between groups
5-unit group	6	Right clavicle Proximal phalanx of the 5th toe of the right foot Left 5th rib Right 10th, 11th ribs Left pubis Right 6th rib	$p<0.05$
100-unit group	1	Neck of proximal phalanx of the 2nd toe on the left	

[Table 11]

Table 11 Fractures of sites other than the vertebral body among low-risk subjects

Group	No. with fractures (persons)	Site	Difference between groups
5-unit group	1	5th toe of the right foot	p>0.05
100-unit group	0		

[Table 12]

	New vertebral fractures			
	Test drug group (n = 261)		Control group (n = 281)	
No. of fractures	No. of Subjects	Incidence (%)	No. of Subjects	Incidence (%)
None	254	97.3	244	86.8
One	5	1.9	31	11
Two	2	0.8	4	1.4
Three	0	0.0	1	0.4
Four	0	0.0	1	0.4
Five or more	0	0.0	0	0.0

[Table 13]

	Change in bone density (%)											
Steroid	Lumbar spine				Femoral neck				Proximal femur			
Time after administration	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
Test drug group (n = 14, 18, 18)	0.00	3.50	5.97	6.82	0.00	2.53	2.79	2.44	0.00	2.46	3.39	3.06
Control group (n = 17, 21, 21)	0.00	1.26	1.91	1.23	0.00	-2.51	-1.52	-1.74	0.00	-0.86	-0.8	0.81

[Table 14]

Steroid	Existence of new vertebral fractures			Total
	Discontinued	Fracture: Yes	Fracture: No	
Test drug group	4	0	29	33
Control group	3	3	24	30

[Table 15]

(C-1) Effect on the femoral neck

Femoral neck	(At the start→48 W→72 W)	Baseline	Change from the baseline after 48 weeks (%)	p value (between groups) (*P<0.05)	Change from the baseline after 72 weeks (%)	p value (between groups) (*P<0.05)
Volume bone mineral density (total) [vBMD total]	Test drug group (n = 30→28→22)	221.38	0.92	0.1155	0.15	0.1658
	Control group (n = 37→33→30)	227.98	-0.72		-1.23	
Volume bone mineral density (cortical bone) [vBMD cortical]	Test drug group (n = 30→28→22)	665.02	-0.77	0.5638	-1.14	0.6852
	Control group (n = 37→33→30)	676.84	-0.22		-0.82	
Buckling ratio	Test drug group (n = 30→28→22)	14.01	-3.48	*0.0084	-3.40	*0.012
	Control group (n = 37→33→30)	13.44	1.27		1.85	
Maximum section modulus (SM (Z min))	Test drug group (n = 30→28→22)	0.3851	3.43	0.0819	1.87	0.5837
	Control group (n = 37→33→30)	0.3793	-0.27		0.62	

[Table 16]

(C-2) Effect on the intertrochanteric femur

Intertrochanteric femur	(At the start→48 W→72 W)	Baseline	Change from the baseline after 48 weeks (%)	p value (between groups)	Change from the baseline after 72 weeks (%)	p value (between groups)
Volume bone mineral density (total) [vBMD total]	Test drug group (n = 30→28→22)	186.45	1.36	*0.0086	0.95	0.0802
	Control group (n = 36→32→30)	196.10	-1.50		-1.47	
Volume bone mineral density (cortical bone) [vBMD cortical]	Test drug group (n = 30→28→22)	638.98	-0.49	0.8300	-1.49	0.1653
	Control group (n = 36→32→30)	646.03	-0.34		-0.61	
Buckling ratio	Test drug group (n = 30→28→22)	19.64	1.59	0.3015	1.27	0.7681
	Control group (n = 36→32→30)	19.26	4.26		2.13	
Maximum section modulus (SM (Z min))	Test drug group (n = 30→28→22)	0.6989	5.19	0.4324	3.20	0.6567
	Control group (n = 36→32→30)	0.7295	2.38		1.81	

[Table 17]

(C-3) Effect on the femoral shaft

Femoral shaft	(At the start→48 W→72 W)	Baseline	Change from the baseline after 48 weeks (%)	p value (between groups)	Change from the baseline after 72 weeks (%)	p value (between groups)
Volume bone mineral density (total) [vBMD total]	Test drug group (n = 29→28→21)	463.59	1.03	0.3521	1.25	0.0613
	Control group (n = 37→33→30)	482.05	-0.22		-1.43	
Volume bone mineral density (cortical bone) [vBMD cortical]	Test drug group (n = 30→28→22)	880.91	0.59	0.7796	0.18	0.2703
	Control group (n = 36→32→30)	892.97	0.33		-0.87	
Buckling ratio	Test drug group (n = 30→28→22)	3.64	-0.66	0.3977	-3.54	*0.0008
	Control group (n = 36→32→30)	3.39	0.92		1.91	
Maximum section modulus (SM (Z min))	Test drug group (n = 30→28→22)	0.9015	1.28	0.1499	2.69	0.1604
	Control group (n = 36→32→30)	0.9343	-0.78		0.32	

[Table 19]

			No. evaluated	No. discontinued	No. with fractures	Incidence of new vertebrae fractures (%)		
						After 24 W	After 48 W	After 72 W
Complication (diabetes)	No	Test drug group	243	54	7	2.8	3.3	3.3
		Control group	257	29	35	5.8	11.0	15.0
	Yes	Test drug group	18	4	0	0.0	0.0	0.0
		Control group	24	2	2	0.0	4.3	8.9
Complication (hypertension)	No	Test drug group	117	29	3	2.1	3.1	3.1
		Control group	150	16	26	6.3	13.0	19.0
	Yes	Test drug group	144	29	4	3.1	3.1	3.1
		Control group	131	15	11	4.0	7.5	9.2
Complication (hyperlipidemia)	No	Test drug group	156	34	4	2.2	3.0	3.0
		Control group	169	17	26	5.6	10.2	16.8
	Yes	Test drug group	105	24	3	3.2	3.2	3.2
		Control group	112	14	11	4.8	10.9	10.9

[Table 20]

FAS	No. evaluated	No. discontinued	No. with fractures	Incidence of worsening vertebral fractures (%)			Difference between investigational product group and control group after 72 W (%)			log rank test
							Difference	90% confidence interval		
				After 24 W	After 48 W	After 72 W		Lower limit	Upper limit	
Test drug group	261	60	1	0.4	0.4	0.4	1.8	0.2	3.5	0.0860
Control group	281	37	6	2.3	2.3	2.3				

[Table 21]

		No. evaluated	No. discontinued	No. with fractures	Incidence of new vertebral fractures (%)		
					After 24 W	After 48 W	After 72 W
Prior therapeutic agents for osteoporosis (No)	Test drug group	139	31	4	2.4	3.2	3.2
	Control group	142	13	17	6.7	9.8	12.9
Prior therapeutic agents for osteoporosis (Yes)	Test drug group	122	27	3	2.9	2.9	2.9
	Control group	139	18	20	3.8	11.2	16.1

[Table 22]

	Percentage change in bone density (%)											
Calcium L-aspartate	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 17, 23, 23)	0.00	3.78	6.16	5.85	0.00	1.44	1.88	4.17	0.00	1.76	2.28	3.69
P group (n = 20, 24, 24)	0.00	-0.31	-1.01	-1.52	0.00	0.57	0.83	1.61	0.00	0.71	-0.18	-0.17

Alfacalcidol	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 41, 51, 51)	0.00	3.11	5.47	6.47	0.00	1.64	0.85	2.19	0.00	2.77	2.31	2.31
P group (n = 37, 46, 45)	0.00	-0.65	-1.01	-0.69	0.00	-0.28	-0.16	-0.96	0.00	0.11	-0.89	-1.05

Raloxifene hydrochloride	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 18, 21, 21)	0.00	1.77	4.96	4.59	0.00	0.21	1.03	-0.51	0.00	2.44	2.26	3.03
P group (n = 22, 24, 24)	0.00	-0.33	-1.74	-1.89	0.00	-0.61	-0.61	0.58	0.00	0.04	0.45	0.62

Elcatonin	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 22, 28, 28)	0.00	3.95	3.59	5.36	0.00	1.62	0.72	3.15	0.00	3.86	3.44	4.41
P group (n = 20, 26, 26)	0.00	-0.29	0.20	0.95	0.00	-1.35	0.95	0.29	0.00	-0.73	-0.95	0.10

	Percentage change in bone density (%)											
Menatetrenone	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 5, 5, 5)	0.00	2.70	3.04	4.32	0.00	0.72	-3.18	-0.78	0.00	0.60	-0.56	-1.40
P group (n = 4, 6, 6)	0.00	-1.03	2.47	-1.53	0.00	-1.16	1.03	-4.70	0.00	-0.34	-2.43	-3.78

Calcium lactate	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 7, 5, 5)	0.00	1.96	3.45	4.93	0.00	0.30	-4.35	-2.53	0.00	1.78	-1.68	-3.20
P group (n = 6, 9, 9)	0.00	-0.88	-0.17	0.43	0.00	-2.19	0.83	-3.00	0.00	0.39	1.15	-1.58

Calcitriol	Lumbar spine				Femoral neck				Proximal femur			
Week	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W	0 W	24 W	48 W	72 W
PTH 200 group (n = 5, 6, 6)	0.00	3.50	4.40	6.38	0.00	-0.60	-4.03	-3.53	0.00	-1.40	-1.05	-0.04
P group (n = 11, 13, 13)	0.00	0.70	0.49	-0.72	0.00	-1.26	-1.25	-3.81	0.00	0.55	-0.01	-0.43

[Table 23]

Calcium L-aspartate	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	9	1	28	38
Control group	2	5	27	34

Alfacalcidol	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	16	1	62	79
Control group	12	11	50	73

Raloxifene hydrochloride	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	9	0	20	29
Control group	8	5	24	37

Elcatonin	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	10	2	35	47
Control group	9	5	34	48

Menatetrenone	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	1	0	6	7
Control group	3	3	4	10

Calcium lactate	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	1	0	8	9
Control group	1	2	7	10

Calcitriol	New vertebral fractures: Yes or No			Total
	Discontinued	Yes	No	
Test drug group	2	1	7	10
Control group	1	2	13	16

[Table 24]

Ccr at the start	Safety analysis set	Group	No. of cases	Average value	Standard deviation	Minimum value	Median value	Maximum value
Normal (80≤)	Age	PTH 200	49	70.2	3.8	65	70.0	78
		P	49	70.4	3.9	65	70.0	82
	Height (cm)	PTH 200	49	150.56	5.65	138.5	151.50	162.5
		P	49	151.11	4.46	140.0	151.20	162.5
	Weight (kg)	PTH 200	49	57.81	5.42	47.5	57.30	70.5
		P	49	57.51	7.73	41.5	56.50	80.1
	BMI (kg/m^2)	PTH 200	49	25.57	2.77	20.5	25.70	35.5
		P	49	25.22	3.57	17.7	24.80	37.2
	Time after menopause (years)	PTH 200	49	19.7	4.8	11	19.0	30
		P	49	20.6	6.0	10	20.0	42
	Prevalent vertebral fractures at enrollment (no.)	PTH 200	49	2.0	1.2	1	1.0	5
		P	49	1.7	0.8	1	1.0	4
	Prevalent vertebral fractures before administration (no.)	PTH 200	49	1.8	1.3	0	1.0	5
		P	49	1.3	0.9	0	1.0	4
	Lumbar spine bone mineral density before administration (YAM converted) (%)	PTH 200	33	68.9	8.4	51	69.1	82
		P	38	70.6	9.0	50	70.4	91
	Femoral neck bone mineral density before administration (YAM converted) (%)	PTH 200	37	73.3	8.7	57	74.4	94
		P	37	72.6	9.3	48	73.3	92
	Proximal femur total bone mineral density before administration (YAM converted) (%)	PTH 200	37	75.4	11.4	51	76.0	96
		P	36	79.5	9.0	57	80.6	97
Mild impairment (50≤ <80)	Age	PTH 200	160	74.3	4.7	65	74.0	85
		P	151	74.5	4.6	65	74.0	90
	Height (cm)	PTH 200	160	147.57	5.14	136.2	147.35	166.0
		P	151	147.41	5.15	134.5	147.0	160.4

Ccr at the start	Safety analysis set	Group	No. of cases	Average value	Standard deviation	Minimum value	Median value	Maximum value
	Weight (kg)	PTH 200	160	50.57	6.19	37.2	50.40	69.0
		P	151	49.73	6.56	34.2	49.80	66.0
	BMI (kg/m^2)	PTH 200	160	23.26	2.85	15.9	23.20	31.3
		P	151	22.89	2.82	15.3	22.80	30.1
	Time after menopause (years)	PTH 200	160	24.9	5.6	11	24.0	39
		P	151	25.2	5.6	12	25.0	43
	Prevalent vertebral fractures at enrollment (no.)	PTH 200	160	1.9	1.1	1	1.5	5
		P	151	2.0	1.2	1	2.0	5
	Prevalent vertebral fractures before administration (no.)	PTH 200	160	1.8	1.4	0	1.0	8
		P	151	1.7	1.3	0	1.0	6
	Lumbar spine bone mineral density before administration (YAM converted) (%)	PTH 200	91	68.4	9.4	51	67.7	99
		P	84	67.2	11.4	42	67.9	98
	Femoral neckbone mineral density before administration (YAM converted) (%)	PTH 200	104	67.3	8.7	46	67.0	96
		P	95	65.6	10.0	38	66.1	91
	Proximal femur total bone mineral density before administration (YAM converted) (%)	PTH 200	103	72.2	11.3	44	70.5	102
		P	95	69.7	11.2	42	70.2	91
Moderate impairment (<50)	Age	PTH 200	68	80.5	5.5	65	80.0	93
		P	78	80.3	5.5	65	81.0	95
	Height (cm)	PTH 200	68	144.79	6.57	124.3	145.00	158.0
		P	78	143.99	6.14	133.0	143.50	159.0
	Weight (kg)	PTH 200	68	44.48	6.65	30.4	43.65	60.5
		P	78	44.59	6.74	31.0	44.25	67.0
	BMI (kg/m^2)	PTH 200	68	21.28	3.28	14.5	21.30	29.5
		P	78	21.54	3.21	16.2	21.40	32.7
	Time after menopause (years)	PTH 200	68	31.0	6.7	12	30.0	46

Ccr at the start	Safety analysis set	Group	No. of cases	Average value	Standard deviation	Minimum value	Median value	Maximum value
		P	78	30.5	6.7	12	31.0	48
	Prevalent vertebral fractures at enrollment (no.)	PTH 200	68	2.3	1.3	1	2.0	5
		P	78	2.1	1.3	1	2.0	5
	Prevalent vertebral fractures before administration (no.)	PTH 200	68	2.3	1.5	0	2.0	6
		P	78	1.8	1.3	0	1.5	5
	Lumbar spine bone mineral density before administration (YAM converted) (%)	PTH 200	30	65.9	13.5	31	64.3	102
		P	39	71.1	11.6	51	72.8	102
	Femoral neckbone mineral density before administration (YAM converted) (%)	PTH 200	40	62.8	12.1	39	62.0	91
		P	46	63.5	10.4	42	63.1	88
	Proximal femur total bone mineral density before administration (YAM converted) (%)	PTH 200	40	65.6	13.2	33	62.9	90
		P	46	67.9	12.7	43	66.8	93

[Table 25]

			No. evaluated	No. dis-continued	No. with fractures	Incidence of new vertebral fractures (%)		
						After 24 W	After 48 W	After 72 W
Creatinine clearance value at the start	Normal (80≤)	PTH 200	46	9	0	0.0	0.0	0.0
		P	48	5	4	2.2	4.4	9.1
	Abnormal (<80)	PTH 200	202	47	6	2.8	3.4	3.4
		P	223	25	31	6.2	12.2	15.3

[Table 26]

Change in lumbar spine bone density (%)		PTH 200 group						P group					
		No. of cases	Mean	SD	Min	Median	Max	No. of cases	Mean	SD	Min	Median	Max
Normal (80≤)	After 24 W	28	4.3	4.7	-5.0	5.1	13.7	36	1.2	3.2	-5.3	1.0	8.9
	After 48 W	25	5.4	3.7	-1.1	5.6	11.9	30	1.4	3.4	-4.7	0.8	6.7
	After 72 W	24	8.1	5.3	-1.0	8.0	20.2	29	1.9	4.8	-4.9	0.8	12.6
	Final	29	7.5	5.4	-1.0	5.6	20.2	36	1.4	4.6	-4.9	0.8	12.6
Mild impairment (50≤ <80)	After 24 W	66	3.9	3.8	-4.7	3.7	15.4	73	0.3	2.9	-6.6	0.6	6.8
	After 48 W	60	6.0	4.9	-7.0	5.7	18.0	72	0.1	3.5	-8.7	0.7	7.2
	After 72 W	56	6.3	5.3	-4.6	6.6	18.3	67	-0.4	4.3	-10.2	-0.9	9.3
	Final	74	5.8	5.0	-4.6	5.4	18.3	79	-0.2	4.1	-10.2	-0.5	9.3
Moderate impairment (<50)	After 24 W	24	3.7	5.8	-8.5	3.5	15.4	33	0.4	3.5	-5.6	0.7	7.5
	After 48 W	22	4.9	4.4	-4.5	3.8	14.1	31	0.7	4.2	-8.8	0.7	9.2
	After 72 W	21	6.1	5.0	-1.3	6.3	21.5	30	0.2	4.4	-9.1	0.5	8.0
	Final	27	5.6	5.3	-2.4	4.9	21.5	36	0.0	4.1	-9.1	0.1	8.0

[Table 27]

Corrected serum calcium (mg/dL)		PTH200 group						P group					
		No. of cases	Mean	SD	Min	Median	Max	No. of cases	Mean	SD	Min	Median	Max
Normal (80≤)	At the start	49	9.5	0.3	8.8	9.5	10.6	49	9.5	0.4	8.9	9.5	10.4
	After 4 W	49	9.5	0.4	8.8	9.5	10.6	48	9.6	0.3	8.9	9.6	10.5
	After 12 W	45	9.6	0.4	8.6	9.5	10.5	48	9.5	0.3	8.6	9.5	10.3
	After 24 W	43	9.5	0.4	8.9	9.5	10.7	48	9.5	0.4	8.9	9.5	10.9
	After 48 W	39	9.3	0.3	8.8	9.2	10.0	44	9.4	0.3	8.8	9.4	10.3
	After 72 W	37	9.4	0.3	8.9	9.3	10.1	43	9.3	0.3	8.6	9.3	10.2
	Final	49	9.4	0.3	8.9	9.4	10.4	48	9.3	0.3	8.6	9.3	10.2
Mild impairment (50≤ <80)	At the start	160	9.5	0.4	8.8	9.5	10.9	151	9.5	0.4	8.8	9.5	10.8
	After 4 W	155	9.5	0.4	8.6	9.5	11.6	151	9.6	0.4	8.8	9.6	11.7
	After 12 W	137	9.6	0.3	8.8	9.5	10.5	149	9.5	0.4	8.7	9.5	12.1
	After 24 W	121	9.5	0.4	8.7	9.5	10.7	143	9.5	0.3	8.7	9.4	11.6
	After 48 W	112	9.3	0.3	8.5	9.3	10.8	135	9.3	0.3	8.7	9.3	10.2
	After 72 W	107	9.3	0.3	8.5	9.3	10.7	128	9.3	0.3	8.7	9.3	10.2
	Final	157	9.4	0.3	8.5	9.4	10.7	151	9.4	0.3	8.5	9.3	10.9
Moderate impairment (<50)	At the start	68	9.6	0.4	8.6	9.5	10.6	78	9.6	0.4	8.9	9.5	10.8
	After 4 W	66	9.5	0.3	9.0	9.5	10.8	78	9.6	0.4	8.5	9.6	10.7
	After 12 W	62	9.5	0.4	8.8	9.5	10.4	75	9.6	0.4	8.9	9.6	10.7
	After 24 W	59	9.5	0.4	8.8	9.5	10.5	71	9.6	0.4	8.8	9.5	10.5
	After 48 W	51	9.3	0.3	8.7	9.3	10.2	67	9.4	0.4	8.7	9.4	10.5
	After 72 W	45	9.4	0.3	8.8	9.4	10.2	63	9.4	0.4	8.7	9.3	10.3

	Final	67	9.4	0.4	8.7	9.4	10.4	78	9.4	0.4	8.5	9.3	10.4

[Table 28]

Normal (80≤)	Adverse events				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	46	93.9	3	6.1	49	83.1	98.7	1.0000	2.0	-10.2	14.3
P group	45	91.8	4	8.2	49	80.4	97.7				

[Table 29]

Mild impairment (50≤ <80)	Adverse events				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	147	91.9	13	8.1	160	86.5	95.6	0.6689	-1.5	-7.9	4.9
P group	141	93.4	10	6.6	151	88.2	96.8				

[Table 30]

Moderate impairment (<50)	Adverse events				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	65	95.6	3	4.4	68	87.6	99.1	0.3385	4.6	-4.8	13.9
P group	71	91.0	7	9.0	78	82.4	96.3				

[Table 31]

Normal (80≤)	Side effects				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	22	44.9	27	55.1	49	30.7	59.8	0.0318	22.4	2.2	42.7
P group	11	22.4	38	77.6	49	11.8	36.6				

[Table 32]

Mild impairment (50≤ <80)	Side effects				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	72	45.0	88	55.0	160	37.1	53.1	<.00001	29.1	18.8	39.4
P group	24	15.9	127	84.1	151	10.5	22.7				

[Table 33]

Normal (<50)	Side effects				Total	95% confidence interval of each group (exact)		Fisher's exact test p value (2-way)	Point estimate of the difference	95% confidence interval of the difference (asymptote) (with continuity correction)	
	Yes		No								
	No. of cases	(%)	No. of cases	(%)		Lower limit	Upper limit			Lower limit	Upper limit
PTH 200 group	25	36.8	43	63.2	68	25.4	49.3	0.0251	17.5	1.7	33.3
P group	15	19.2	63	80.8	78	11.2	29.7				

[Table 34]

FAS	No. evaluated	No. dis-continued	No. with fractures	Incidence of new vertebral fractures (%)			Difference between PTH200 group and P group after 72 W (%)			log rank test
				After 24 W	After 48 W	After 72 W	Difference	90% confidence interval		
								Lower limit	Upper limit	
PTH 200 group	261	58	7	2.6	3.1	3.1	11.4	7.3	15.4	<.00001
P group	281	31	37	5.3	10.4	14.5				

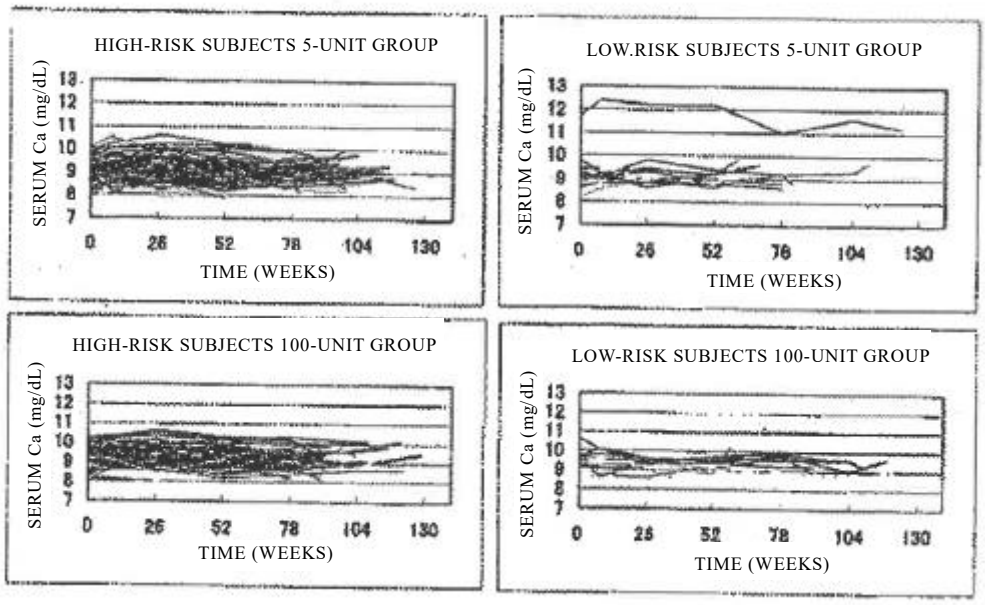
[Table 35]

	New vertebral fractures							
	PTH 200 group				P group			
Time after administration	No. evaluated	No. with fractures	Incidence of fractures (%)	No. of fractures	No. evaluated	No. with fractures	Incidence of fractures (%)	No. of fractures
≤24 W	261	6	2.3	7	281	14	5.0	18
24 W< ≤ 48 W	219	2	0.9	2	257	13	5.1	13
48 W< ≤72 W	206	0	0	0	245	13	5.3	15

(Figures)

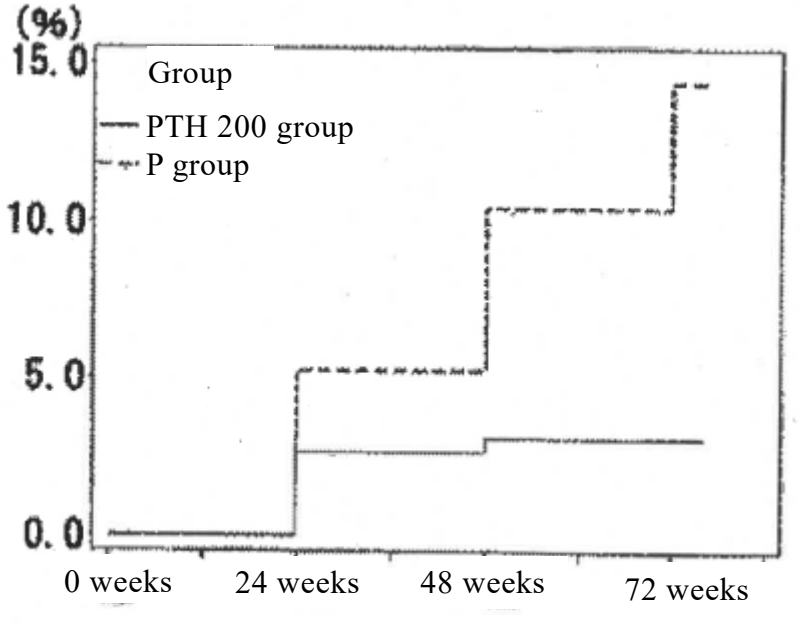
[Figure 1]

Figure 1 Changes in serum calcium concentration by risk and group



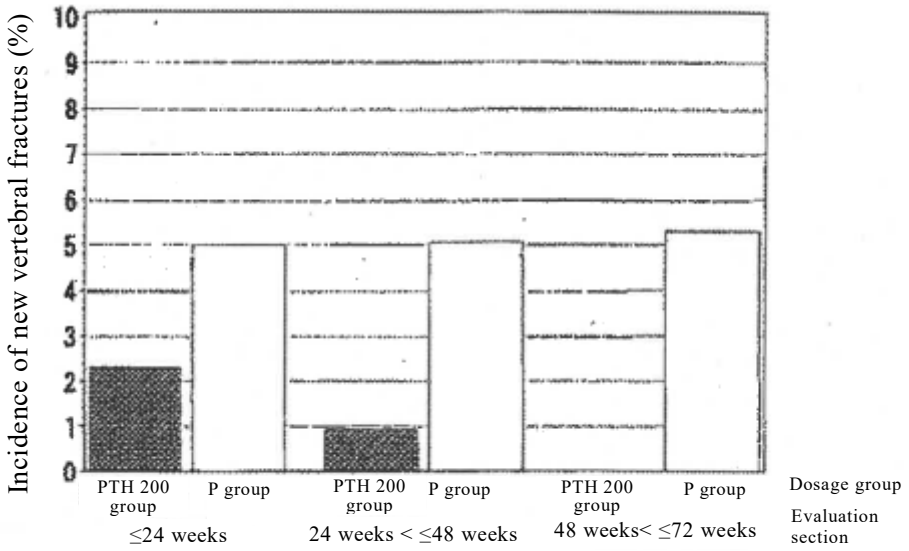
[Figure 2]

Incidence of new vertebral fractures (%)

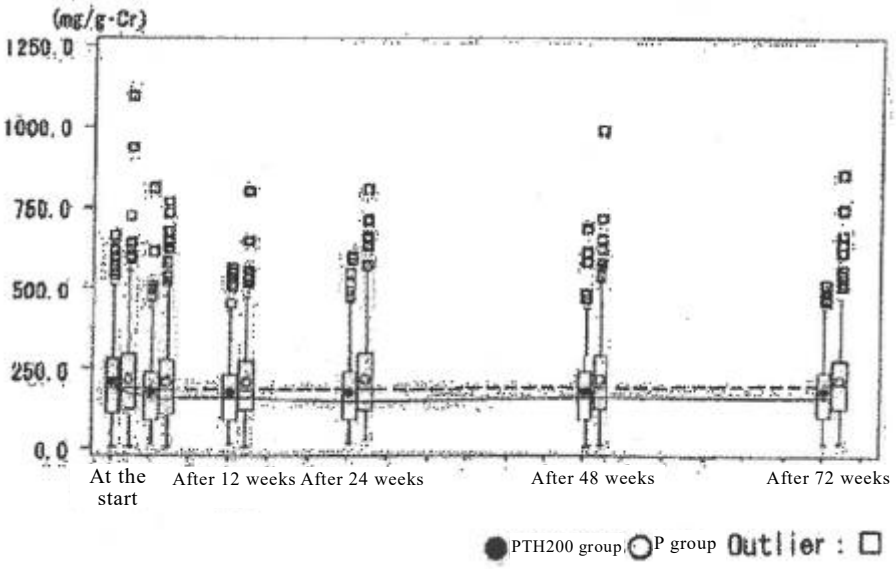


Observation day (weeks after the administration)

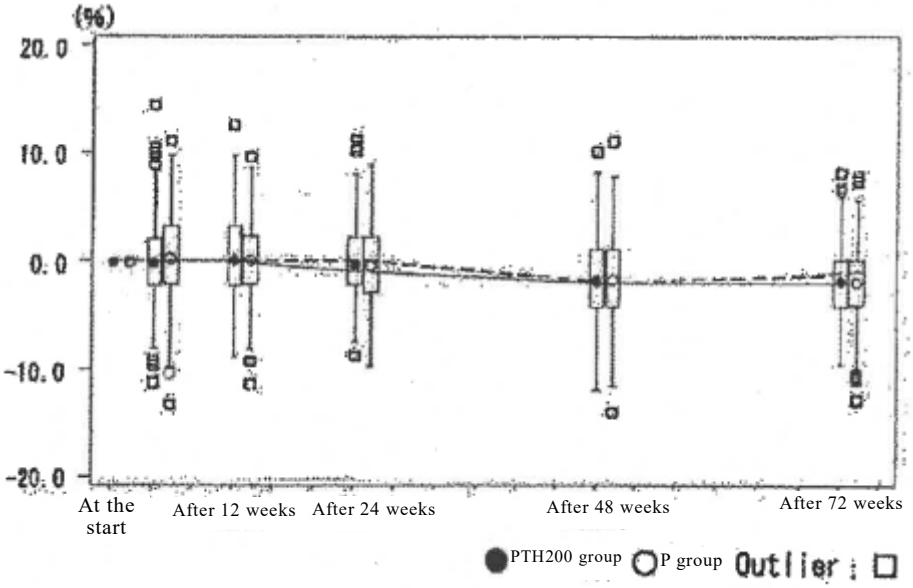
[Figure 3]


Incidence of new vertebral fractures (%)
10
9
8
7
6
5
4
3
2
1
0
PTH 200 group
P group
PTH 200 group
P group
PTH 200 group
P group
Dosage group
≤24 weeks
24 weeks < ≤48 weeks
48 weeks< ≤72 weeks
Evaluation section

[Figure 4]


(mg/g·Cr)
1250.0
1000.0
750.0
500.0
250.0
0.0
At the start
After 12 weeks
After 24 weeks
After 48 weeks
After 72 weeks
PTH200 group
P group
Outlier : □

[Figure 5]


(%)
20.0
10.0
0.0
-10.0
-20.0
At the start
After 12 weeks
After 24 weeks
After 48 weeks
After 72 weeks
PTH200 group
P group
Outlier : □

(Attachment 2)

Matters stated in Exhibit Ko 1 Document (Abstract)

(Tables and figures are posted together at the end of the Attachment.)

[Page 296, left column, line 1 through right column, line 7]

Abstract

To test the effect of amino-terminal peptide 1-34 of human parathyroid hormone (hPTH (1-34)) as a possible bone anabolic agent in the treatment of osteoporosis, weekly subcutaneous injection of 50 units (L group), 100 units (M group) or 200 units (H group) of hPTH (1-34) was started with 220 patients with osteoporosis at 71 institutions, who were randomly divided into three groups in a double-blind system. Lumbar spine bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) increased by 0.6%, 3.6% and 8.1% after 48 weeks in groups L, M and H, respectively. Responses in groups M and H were significantly higher than in L group ($p<0.05$, [F]'s U-test). Since the coefficient of variation for lumbar spine measurement stayed at 1% to 2.5%, increases of 3.6% and 8.1% appeared significant. Metacarpal BMD and cortical thickness measured by radiogrammetry did not change significantly. Serum calcium decreased in each group and serum phosphorus decreased in groups M and H. Urinary calcium/creatinine decreased at the 12th week in group H and at the 24th and 48th weeks in groups M and L. Serum 25(OH) vitamin D and $1.25(OH)_2$ vitamin D decreased in each group at the 48th week ($p<0.05$). Serum bone-specific alkaline phosphatase was increased at the fourth week in groups H and M and decreased at the 48th week in group H. Urinary hydroxyproline, pyridinoline and deoxypyridinoline declined significantly in each group. Backache improved in 30% to 40% of each group. No serious adverse reactions were found during the test period. Intermittent weekly injection of hPTH (1-34) increased lumbar spine BMD in patients with osteoporosis, suggesting usefulness in the treatment of osteoporosis.

[Page 296, right column, line 10 through page 297, left column, line 25]

Introduction

Treatment of postmenopausal and involutional osteoporosis has mainly depended on antiresorptive agents such as estrogen, bisphosphonates and calcitonins. As considerable advances have been made in the prevention of fractures through increases in bone mineral density (BMD) by using these agents, stimulators of bone formation would supplement the prompt and sometimes transient effect of antiresorbers, and given that their bone anabolic effects are of longer duration, they would be expected to be

particularly useful in the treatment of involutional osteoporosis, especially in those with low-turnover disease. Parathyroid hormone (PTH) has been shown to have bone anabolic effects in animals and humans, especially by intermittent administration. However, as seen in primary hyperparathyroidism, when bones are exposed to a large amount of PTH continuously, osteitis fibrosa may develop. According to the result of a preliminary study where 100 units or 200 units of amino-terminal peptide 1-34 of human PTH (hPTH (1-34)) was administered by subcutaneous injection for a single time, decreases in serum phosphorus, increases in serum cyclic AMP, increases in urinary calcium and cyclic AMP excretion, and other important effects on the metabolic system were observed. When 100 units or 200 units are administered weekly, lumber spine BMD significantly increased at the 26th week after the start of the treatment; however, no effects were seen under administration of 5 units weekly.

Based on these results, in this clinical trial, a randomized, prospective, double-blind, and multicenter study was conducted with 220 patients with osteoporosis in order to observe the effects when 50 units, 100 units, or 200 units of hPTH (1-34) are administered weekly. Primary endpoint is an assessment of lumbar spine BMD using a dual-energy X-ray absorptiometry (DXA). Secondary endpoints are metacarpal cortex BMD by radiogrammetry and biochemical marker of bone turnover. The clinical trial examined whether once-weekly administration of hPTH (1-34) at the concentrations listed here - meaning an intermittent administration plan at low concentrations that has never been examined - is beneficial to the treatment of osteoporosis.

[Page 297, left column, line 27 through right column, line 42]
Subject of the clinical trial

A multicenter clinical trial with the participation of 71 institutions was conducted. The clinical trial was conducted with 220 subjects between the ages of 45 and 95 years who were diagnosed as having osteoporosis based on the diagnostic criteria proposed by a committee supported by the Ministry of Health and Welfare. This system does not simply define osteoporosis as the presence of a non-traumatic fracture or the presence of spine fractures at 2 sites but defines osteoporosis by evaluating multiple factors as scores. The case where patients' total score is more than 4 (defined as osteoporosis) is used as a criterion for enrollment in the clinical trial. In most areas in Japan, the method that healthcare personnel can use for diagnosing osteoporosis is still limited to X-ray imaging of spines. Therefore, X-ray imaging had to be implemented as a diagnostic criterion of osteoporosis. Bone loss on X-ray film is determined to be found when trabecular thinning is observed on an X-ray film of the side of the lumbar spine; in other

words, (1) vertical trabeculae become conspicuous due to horizontal trabeculae defect; (2) vertical trabeculae become rough; and (3) vertical trabeculae loss is observed. Bone loss on X-ray film corresponds to loss by 20% or 2.5 SD in BMD from the young adult mean value. In this clinical trial, for example, the following persons were included in the subjects: those whose lumbar spine BMD mean value is 0.736 g/cm^2 when measured using a DPX densitometer manufactured by Luna Innovations Inc.; 0.694 g/cm^2 when measured using a QDR densitometer manufactured by Hologic, Inc.; or 0.624 g/cm^2 when measured using an XR densitometer manufactured by Norland, respectively. These criteria conform to other criteria that are used at present. When the degree of bone loss on X-ray film is Grade 1 to Grade 3 or when BMD is less than 2.5 SD from the young adult mean, the score is 3. If a vertebral fracture occurred at one site, the score is 1 and if a vertebral fracture occurred at two or more sites, the score is 2. If there is a femoral neck fracture, the score is 3 and if there is a distal radius fracture, the score is 1. In order to eliminate osteomalacia, primary hyperparathyroidism, and renal osteodystrophy, etc. that cause decreases in bone mass, as a factor to support the diagnosis of osteoporosis, the score of normal serum calcium, phosphorus, and alkaline phosphatase value is determined to be 1. However, if there are one or more abnormalities, the score is reduced by 1. In the same way, if a subject is in premenopause, the score is reduced by 1.

Subjects whose serum creatinine level is 2 mg/dL or higher, or BUN is 30 mg/dL or higher and who are suspected of having reduced renal function, subjects who have pre-existing hypersensitivity, or subjects for whom the reliability of their self-evaluation of subjective symptoms is questionable, were eliminated. Intradermal test with 0.003 units of hPTH (1-34) was conducted with each person scheduled to participate in the clinical trial. Subjects who presented a positive result with a diameter of erythematous area exceeding 10 mm after 15 minutes were also excluded.

In order to avoid any mixture of the effects of other agents with the effects of hPTH (1-34), the use of agents that are considered to have impact on bone turnover and the progress of osteoporosis was withheld voluntarily for three months prior to the start of the clinical trial and the administration of these agents was also withheld during the clinical trial period. Such agents include estrogen, calcitonin, active vitamin D, Vitamin K_2, ipriflavone, bisphosphonate, and anabolic steroids.

Analgesics and muscle relaxants were administered when the physician in charge found it to be necessary. Physical therapies and agents for complications continued to be provided and administered without making any changes before and after the study as long as the patient's symptoms allowed it.

Prior to the start, the importance of the clinical trial, including the characteristics and possible adverse reactions of hPTH (1-34), was explained in detail to the persons scheduled to participate in the clinical trial and the informed consent of the subjects was obtained orally or in writing. This clinical trial was approved by the institutional review board of each participating facility.

[Page 297, right column, line 43 through page 298, left column, line 24]
Preparation and administration method of hPTH (1-34) (teriparatide acetate)

The purity and biological effects of hPTH(1-34) synthesized by Asahi Chemical Industry Co., Ltd. were assessed by using the generation of cyclic AMP of bovine PTH (1-84) by the cortical membrane of rat kidney, which is an international standard, and the result was 3,300 units/mg. Each vial was determined to contain 50 units, 100 units, and 200 units of teriparatide acetate. They correspond to approximately 15 μg, 30 μg, and 60 μg of peptide, respectively. 3 lots were prepared from one batch, and vials containing 50 units, 100 units, and 200 units were created. Based on the aforementioned preparation, 5,000 vials containing one type of concentration were always prepared from one lot. Preparations were stable at 25°C for 3 years. The content of the vial was measured with randomly extracted samples by a neutral institution. Controllers (physician [G] and physician [H]) confirmed that 3 vials were indistinguishable. The content of the vial was dissolved with 1 mL of saline immediately before use and subcutaneously injected once a week for 48 weeks.

102 sets of 50 units, 100 units, and 200 units of samples were prepared as controllers for the clinical trial. They were assigned randomly within the set (numbers were assigned, such as 1, 2, and 3), and then each set was sent to participating facilities on a first-come-first-served basis. Each set was opened at each facility and sample numbers 1, 2, and 3 were administered to patients sequentially over time. In order to ensure the double-blind nature of the clinical trial, codes were locked and maintained until the end of the clinical trial.

According to the preliminary study results, when 100 units or 200 units of hPTH (1-34) were administered once a week for 26 weeks, lumbar spine BMD increased. Then, the clinical trial period was set for 48 weeks. This period was considered to be the upper limit where even if regular bone measurement and blood and urine sampling are implemented with patients who always have a risk and concern of fractures, dropouts will not be excessive and a multicenter test can be implemented under sufficient control. [I] et al. also reported safety in the administration of 5 μg/kg of PTH (1-84) to human beings.

[Page 298, left column, line 25 through page 299, left column, line 9]
Accumulated data
Data before the start of the treatment: The following items were recorded: age, gender, age of menopause, body height, body weight, experience of hospitalization or ambulatory status, general medical record, intradermal test results of hPTH (1-34) antigenicity, score for osteoporosis diagnosis, pre-existing disease(s), treatment of osteoporosis and complications of osteoporosis before the clinical trial, agents other than the test drug that were administered during the clinical trial period, nonprescription calcium preparations and dairy products.

Subjective symptoms: Pain due to osteoporosis is classified into spontaneous pain at rest and pain on motion and evaluated in accordance with the following grades at the 0th week, 2nd week, 4th week, 12th week, 24th week, and 48th week after the start of the treatment or at the end of the clinical trial. The pain at rest was shown as the following grades: 1: No pain; 2: Moderate pain; 3: Pain that cannot be ignored but acceptable; and 4: Serious and severe pain. The pain on motion was shown as the following grades: 1: No pain; 2: Moderate pain; 3: Pain that hinders motion and cannot be ignored; and 4: Serious disabling pain. Patients voluntarily evaluated degree of their pain using an analog scale.

Bone findings: (a) Measurement of lumbar spine BMD: Bone mineral content, bone area of lumbar spines (L2-L4), and BMD were measured using a DXA (QDA (Hologic), DPX (Lunar), or XR (Norland)) by imaging anteroposteriorly at the 0th week, 12th week, 24th week, and 48th week after the start of the treatment or at the end of the clinical trial. It was difficult to maintain appropriate accuracy management at many participating facilities. Each facility measured BMD every day using a phantom on a routine basis in accordance with the recommendation attached to the device. As a result, the coefficient of variation (CV) was maintained between 1% to 2.5%.

Since the age of patients was high, when anteroposteriorly measuring spine BMD, degenerative changes of the spine was a major problem in addition to compression fractures and changes in association thereto. Based on the aforementioned reasons, all subjects who had degenerative changes of the spine, such as osteophyte in L2, L3, or L4, compression, deformation, etc., were eliminated from the data that serves as the basis for efficacy of the test drug. For this reason, the dropout rate at spine BMD measurement before enrollment was high.

(b) Measurement of metacarpal BMD: In order to implement radiogrammetry of the second metacarpal bone of a non-dominant hand, anteroposterior X-rays of the hand were taken along with a phantom at 0th week, 12th week, 24th week, and 48th week after the start of the treatment or at the end of the clinical trial. At the end of the clinical trial, all films taken at 71 facilities were measured at Toyo Kensa Center Co., Ltd. using computerized digital image processing. Concerning the accuracy of digital image processing when an observer measured metacarpal BMD (ΣGS/D) 10 consecutive times using the same film, CV was 0.59. When the same process was conducted by 3 observers, it was 1.47. If the hand of the same subject was filmed 4 times, measurement was conducted separately and CV was 1.72.
(c) Assessment of vertebral fractures: X-ray films of lateral lumbar spines and thoracic spines focused on L3 and T8 respectively, and one radiologist assessed compression fractures and deformations of vertebral bodies. If the anterior border height/posterior border height ratio decreased by 25% or more and if the center height/posterior border height ratio decreased by 20% or more, it was defined as a significant deformation.

Biochemical parameters: Before the start of the treatment and the 2nd week, 4th week, 12th week, and 48th week after the start of the treatment or at the end of the clinical trial, the following parameters were measured by the largest laboratory testing company in Japan, SRL, Inc.: Calcium (Ca), phosphorus (P), 25(OH) vitamin D (measured by competitive protein binding analysis), $1.25(OH)_2$ vitamin D (measured by radio-receptor assay), osteocalcin, intermediate PTH (measured by radio-receptor assay), total alkaline phosphatase and bone-specific alkaline phosphatase, and albumin in serum, and Ca, P, hydroxyproline, pyridinoline, deoxypyridinoline (measured by HPLC), and creatinine in urine. The following processes were conducted at each facility at the 0th week, 12th week, 24th week, 36th week, and 48th week after the start of the treatment or at the end of the clinical trial: cytometry (RBC, WBC and differential hemocyte count, hematocrit, hemoglobin, and blood platelet), serum biochemical test (GOT, GPT, A/G, BUN, creatinine, total cholesterol, CPK, Na, K, Cl, and glucose), and urine test (occult blood, protein, sugar, urobilinogen, bilirubin, and pH).

Investigation of adverse reactions and adverse events: Adverse events during the clinical trial period were recorded and examined in detail. Adverse events were classified into the following grades based on a comprehensive process assessment, the severity, treatment, and outcome: (1) adverse event caused by the test drug; (2) adverse event considered to be caused by the test drug; (3) adverse event for which it is difficult

to consider that the test drug was the cause; and (4) adverse event for which the test drug was not the cause. Adverse reactions are determined to include (1) through (3) tentatively.

Statistical analysis

Patient group backgrounds were assessed with a chi-square test with a risk rate of 10% for two-sided tests. Measured values were assayed with U test of [F] and exact test of [J] with a risk rate of 5% for two-sided tests.

[Page 299, left column, line 10 through page 300, left column, line 3]

Results

Table 1 is a summary of the details of the clinical trial enrollment criteria for subjects who were permitted to participate in the clinical trial.

220 subjects who were originally registered to the clinical trial were assigned randomly in a double-blind system [73 subjects were assigned to 50-unit group (L), 75 subjects to 100-unit group (M), and 72 subjects to 200-unit group (H)]. 41 subjects from them were determined to be non-conforming since they did not conform to the diagnosis criteria of osteoporosis and the washout period of the drug that was administered before the clinical trial was insufficient.

When subjects who have degenerative changes and compression changes of the lumbar spine that hinder accurate BMD measurement and patients who were measured during non-specified times were eliminated, an additional 64 persons were non-conforming. Therefore, the analysis of the effects on lumbar spine BMD was conducted with 115 subjects. The details were 39 subjects in L group, 38 subjects in M group, and 38 subjects in H group (Table 2). 61 subjects could not complete the study due to an adverse reaction, rejection of the clinical trial due to a change of mind halfway through, worsening complications, etc. However, they were determined to be included in the analysis group if they did not drop out within the first 3 months.

Characteristics of subjects at the start of the clinical trial were compared by the group in Table 3. It was confirmed that subjects were distributed evenly in all 3 groups.

[Page 300, left column, lines 4 through 10]

Subjective symptoms

Subjective symptoms mainly comprised of backache were moderately or slightly improved for 21 subjects out of 52 (40%) in L group, 18 subjects out of 60 (30%) in M group, and 17 subjects out of 47 (36%) in H group. There was no significant difference

between groups (Table 4).

[Page 300, left column, line 11 through right column, line 6]
Bone measurement

Changes in lumbar spine BMD for 48 weeks during the clinical trial period were shown in FIG. 1. Lumbar spine BMD increased in a dose-dependent manner at the 24th week and 48th week after the start of the treatment compared to the start of the clinical trial, and changes were 0.6%, 3.6%, and 8.1% for L group, M group, and H group, respectively. The degree of increase in M group and H group was larger than in L group at the 24th week and 48th week and it was larger in H group than M group at the 48th week ($p<0.05$). Responses to drugs were similar among subgroups of subjects who were 64 years or younger and 65 years or older, who weighed 49 kg or less and 50 kg or more, for whom it was less than 10 years, between 10 years to 20 years, and more than 20 years after the postmenopause, and who had 0, 1 and 2 or more vertebral fractures. There was no significant difference in the bone density of the second metacarpal bone (consisting of cortical bone) on X-ray film. It showed that cortical bone and the degree of bone loss on X-ray film in each group did not change and was kept constant. Vertebral fracture occurred in 3 subjects in L group, 5 subjects in M group, and 0 subjects in H group; however, there was no significant difference between groups.

[Page 301, left column, line 1 through right column, line 4]
Biochemical parameters

As shown in FIG. 2, serum calcium started to decrease from the 2nd week after the start of the treatment and it was significantly lower at the 4th week and after than the standard value before the start of the treatment. Serum P also started to decrease at the 2nd week after the start of the treatment. Urine calcium started to decrease at the 2nd week and it remained lower than the standard value throughout the clinical trial period. Urine P also decreased. As shown in FIG. 3, serum 25(OH) vitamin D and $1.25(OH)_2$ vitamin D levels slightly decreased in each group at the 48th week from the start of the treatment. As shown in FIG. 4, bone-specific alkaline phosphatase was higher at the 4th week after the start of the treatment than the level at the start of the treatment and it was low only in H group at the 24th week and 48th week. As shown in FIG. 5, excretions of pyridinoline, deoxypyridinoline, and hydroxyproline into urine decreased in L group and H group at the 24th week and 48th week from the level at the start of the treatment.

As shown in FIG. 5, abnormal test results appeared in each group during the clinical trial period; however, not all of them were obvious or were transient and it could not be

defined that the test drug was the cause. Table 6 is a summary of adverse reactions that occurred during the treatment. In 29 cases, subjects dropped out due to several symptoms. The total number of adverse reactions increased in conjunction with increases in the dose of hPTH (1-34); however, no serious adverse event was observed.

[Page 301, right column, line 5 through page 303, right column, line 23]
Consideration

In primary hyperparathyroidism, an excess amount of PTH is continuously secreted and it is characterized by significant bone defect, in particular, the cortical bone defect; however, based on the results of histomorphometry, the cancellous bone is well preserved comparatively. PTH probably stimulates both osteoblast activity and osteogenesis and may have an anabolic effect on bone.

In animal testing, the anabolic effect of PTH was often observed and it was reported that it physically improves bone quality. Since the anabolic effect almost disappears only by eliminating one amino acid from N terminal, it is considered to depend on the full-length of amino acid at the N terminal.

It has been constantly reported that cancellous bone increases; however, the response of cortical bone was defective. Intermittent administration is considered to be more effective in the bone anabolism of PTH. In the past, for the treatment of osteoporosis, an antiresorptive agent, such as estrogen, calcitonin, bisphosphonate, etc., was mainly administered and osteogenesis promoters that stimulate bone resorption are considered to be effective for low-turnover osteoporosis. Despite activity to induce increases in BMD to an extent far exceeding expectations, fluoride has problems. In other words, fluoride cannot reduce fracture incident, but causes adverse reactions, such as bone pain, etc. However, PTH still has a great expectation as a candidate osteogenesis promoter. If PTH is administered in high doses, increases in BMD were seen also in human beings; however, an intermittent administration method, which shows preferable effects in human beings, is an unsolved problem. [K] et al. implemented a multicenter test with 12 patients with osteoporosis. It was reported that through intermittent administration, wherein hPTH (1-34) was administered for 7 days and then withdrawn for 21 days and this cycle was repeated 16 times, whole-body Ca slightly increased, but no significant increase in BMD at various sites was observed. Daily administration is intermittent when compared to continuous infusion and a preferable impact was observed. According to [K] et al., when approximately 250 units of hPTH (1-34) were administered daily to 21 patients for 6 months to 24 months, no serious adverse reaction was observed, while serum alkaline phosphatase increased by 15% and significant

increases in bones were observed. [L] et al. conducted a 3-year randomized double-blind controlled study, wherein 25 μg of hPTH (1-34) was subcutaneously injected daily to 17 women after menopause who were receiving hormone replacement therapy, and the results were compared with 17 other women to whom hormone replacement therapy alone was provided as a control. Spine BMD increased by 13.0% in the PTH group; however, no significant increase was observed in the control group. In other studies, PTH was effective when it was administered with estrogen.

It is also considered to enhance the effects of PTH by using it in combination with vitamin D derivative. Actually, when 400 units to 500 units of hPTH (1-34) were administered along with 0.25 μg of $1.25(OH)_2$ vitamin D_3, an increase in cancellous bone was observed. Administration in combination with calcitonin was also conducted. [M] et al. administered 720 units to 750 units of hPTH (1-34) daily for 8 weeks and, simultaneously, intranasally administered calcitonin on the 2nd day to the 4th day, the 6th day to the 8th day, and the 8th day to the 10th day. This cycle was repeated 4 times. [N] et al. repeated an administration cycle for 2 years, wherein 800 units of PTH were administered daily for one month with an interval of 2 months, and found that lumbar spine BMD increased by 8% to 10%.

Biological activity per unit weight of hPTH (1-34) seems to have variety between studies. In the study of [L] et al., for example, 400 units (25 μg) of hPTH (1-34) were used. Since the preparation method used for the study is different, it is not easy to compare the results of the clinical trial concerning the dose of hPTH (1-34) with the results of other studies. However, when they were compared with many past studies, the weekly intermittent administration, which was used in the clinical trial, can clearly reduce the total dose of hPTH (1-34). Since hPTH (1-34) dominantly increased lumbar spine BMD (mainly consisting of cancellous bone) in a dose-dependent manner over a relatively short period, such as 48 weeks, etc., without reducing bone density of metacarpal bone (consisting mostly of cortical bone), treatment of osteoporosis using hPTH (1-34) is considered to be very promising.

Table 1 Details of enrollment criteria for participants in the clinical trial

Enrollment criteria		L group (50 units)	M group (100 units)	H group (200 units)
Decreases in bone density				
Bone atrophy				
Grade 1		31	26	18
Grade 2		19	29	26
Grade 3		21	19	27
Unknown		2	1	1
DXA				
DPX	≥0.831	5	7	3
	<0.831	17	14	18
QDR	≥0.711	25	17	11
	<0.711	15	23	27
	Unknown	1	0	0
XR	≥0.701	2	4	1
	<0.701	7	10	12
	Unknown	1	0	0
Number of vertebral fractures				
0		32	30	29
1		14	18	15
≥2		27	26	28
Unknown		0	1	0
Number of femoral fractures				
0		65	72	69
≥1		8	3	3
Number of distal radius fracture				
0		72	71	69
≥1		1	4	3
Total score				
=<2		0	2	0
3		2	2	1
4		14	13	13
≥5		57	58	58

Table 2 Number of cases by endpoint in the clinical trial

Group	Total number of cases	Dropouts (due to adverse reaction)	Symptom assessment	Lumbar spine BMD assessment	Metacarpal bone BMD assessment
L (50 units)	73	12 (3)	62	39	60
M (100 units)	75	25 (10)	65	38	58
H (200 units)	72	24 (16)	56	38	50
Total	220	61 (29)	183	115	168

Table 3 Comparison of backgrounds at the start of treatment by group

	L group (50 units)	M group (100 units)	H group (200 units)	x^2 test
Age (years)	70.2±9.84 (73)	70.1±9.64 (75)	71.7±10.78 (72)	NS
Body weight (kg)	47.7±7.49 (73)	49.2±7.54 (75)	45.8±8.21 (72)	NS
Body height (cm)	148.2±8.01 (73)	148.9±7.77 (75)	147.3±6.97 (72)	NS
Years elapsed after menopause	19.0±8.52 (73)	18.8±8.35 (75)	20.6±9.43 (72)	NS
Number of vertebral fractures	1.86±2.65 (62)	1.62±1.89 (61)	1.82±2.65 (55)	NS
Lumbar spine BMD (g/cm^2)				
DPX	0.746±0.123 (13)	0.753±0.089 (10)	0.711±0.159 (11)	NS
QDR	0.719±0.103 (19)	0.723±0.140 (17)	0.640±0.132 (19)	NS
XR	0.637±0.115 (7)	0.680±0.130 (11)	0.556±0.064 (8)	NS
Metacarpal BMD (ΣGS/D)				
	1.875±0.350 (60)	1.917±0.404 (58)	1.850±0.446 (50)	NS

Data is mean value ± standard variation; figures in parentheses are the number of cases.

Table 4 Subjective symptoms

Group	Number of cases	Moderate or more improvement	Mild improvement	Unchanged	Worsening	U-test	[redacted]'s test; moderate or higher
L group (50 units)	52	21 (40)	16 (31)	14 (27)	1 (2)		
M group (100 units)	60	18 (30)	28 (47)	14 (23)	0 (0)	NS	NS
H group (200 units)	47	17 (36)	21 (45)	9 (19)	0 (0)		

Units for the figures in parentheses are percentages.

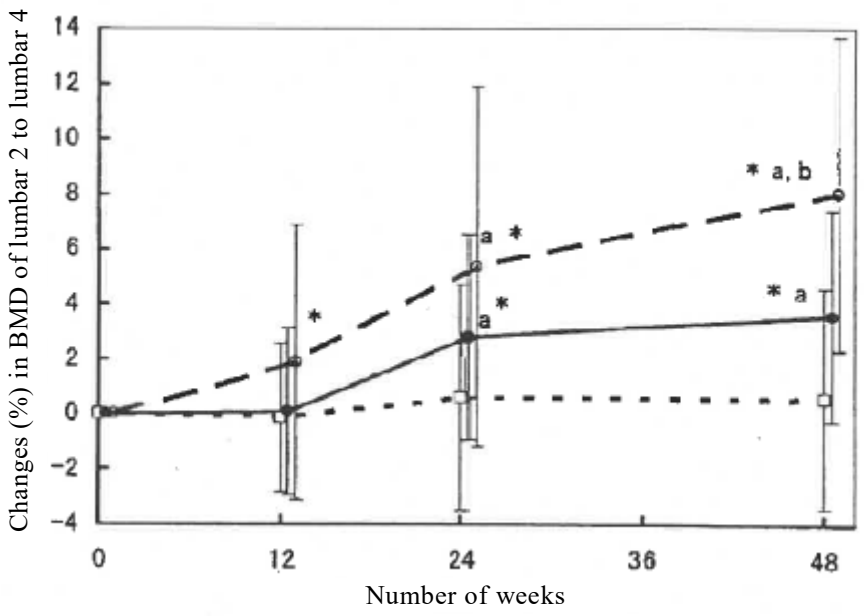


FIG. 1 Number of treatment weeks and change rate of lumbar spine BMD (mean ± standard variation)

□ refers to data of L group (50 units), ● refers to data of M group (100 units), and ○ refers to data of H group (200 units).

Significant difference of $p<0.005$ in comparison with the value of [a]L group; significant difference of $p<0.005$ in comparison with the value of [b]M group; by U-test of [redacted].

* Significant increase with significant difference of $p<0.05$ in comparison with the start of the treatment; by U-test of [redacted].

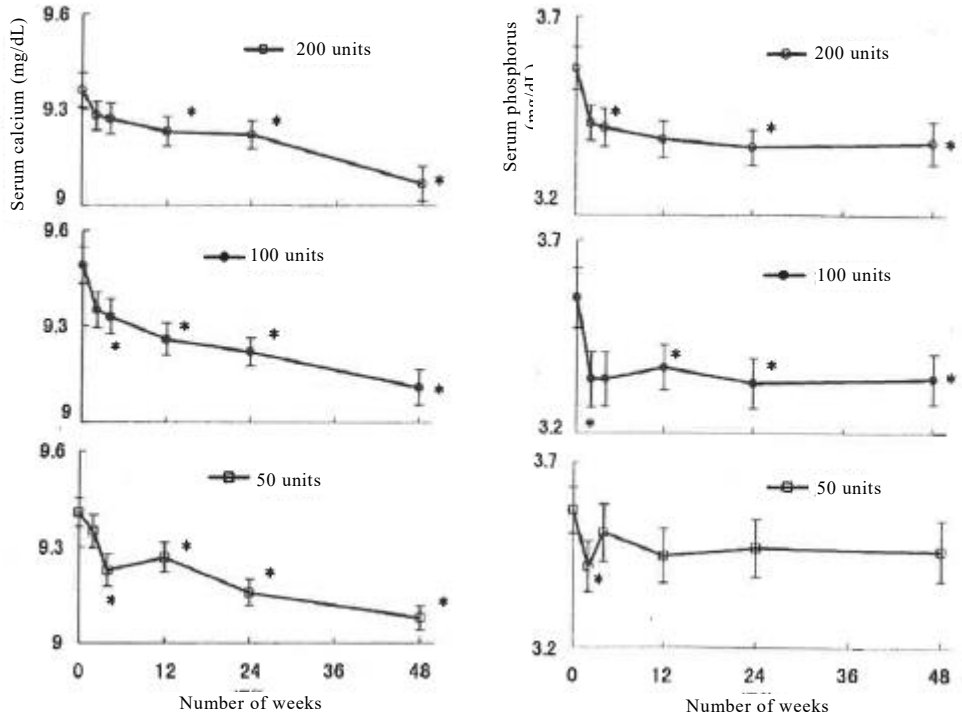


FIG. 2 Number of weeks and serum calcium (left) and serum phosphorus (right) (mean ± standard variation)

□ refers to data of PTH 50 units (L group), ● refers to data of PTH 100 units (M group), and ○ refers to data of PTH 200 units (H group).

* Significant difference of $p<0.05$ in comparison with the start of the treatment; by U-test of [redacted].

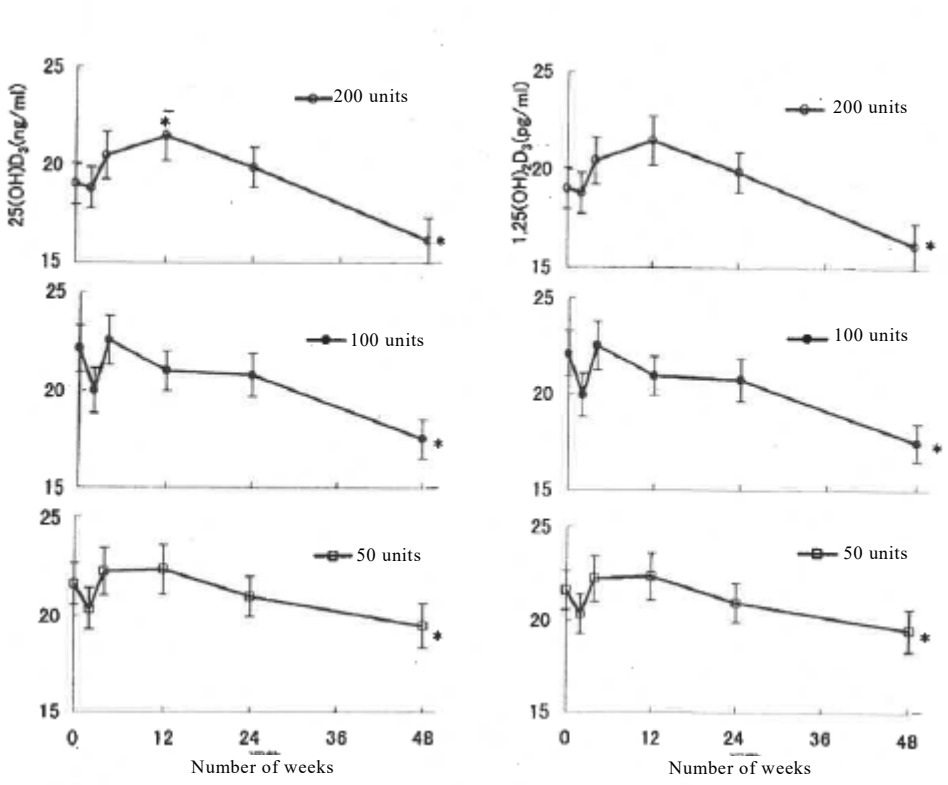


FIG. 3 Number of weeks and 25(OH) vitamin D (left) and 1.25$(OH)_2$ vitamin D (right) in the blood (mean ± standard variation)

Symbols refer to the same as FIG. 2.

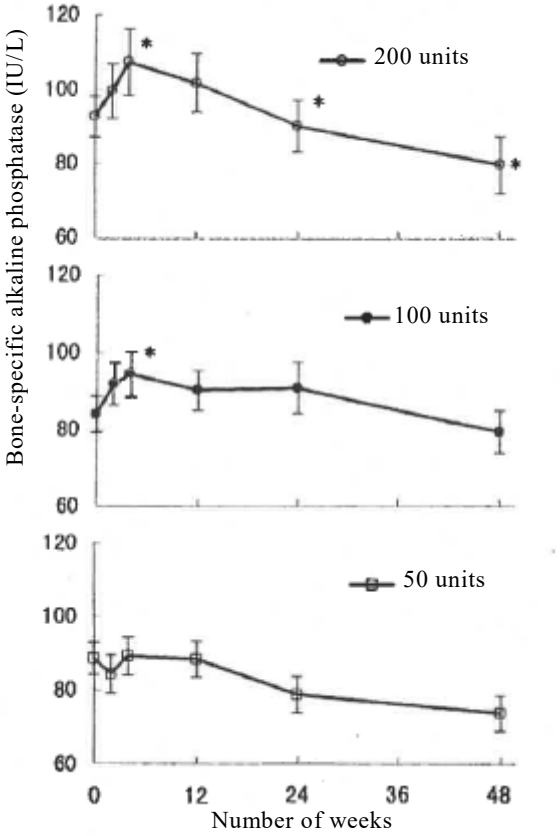


FIG. 4 Number of weeks and bone-specific alkaline phosphatase (mean ± standard variation) Symbols refer to the same as FIG. 2.

Table 5 Abnormal laboratory values of subjects during the treatment period

	L group (50 units)	M group (100 units)	H group (200 units)
Total number of cases	73	75	72
Number of abnormal laboratory values (%)	8 (11%)	4 (5%)	12 (17%)
Number of abnormal data	16	7	22
Decreases in red blood cell count	1	1	
Increases in segmental karyosphere	1	1	
Lymphopenia	1		2
Eosinopenia			1
Basopenia			1
Decreases in hematocrit	2	1	
Decreases in hemoglobin	2	1	
Decreases in platelet count			1
Increases in GOT	1		1
Increases in GPT	1		
Decreases in A/G	1		
Increases in BUN			2
Increases in total cholesterol	2	1	2
Increases in CPK	1	2	2
Decreases in Na			2
Increases in K			2
Decreases in K			1
Increases in Cl			1
Decreases in Cl			1
Increases in blood glucose		1	
Blood in urine	1		2
Urinary protein	1		
Urinary bilirubin	1		

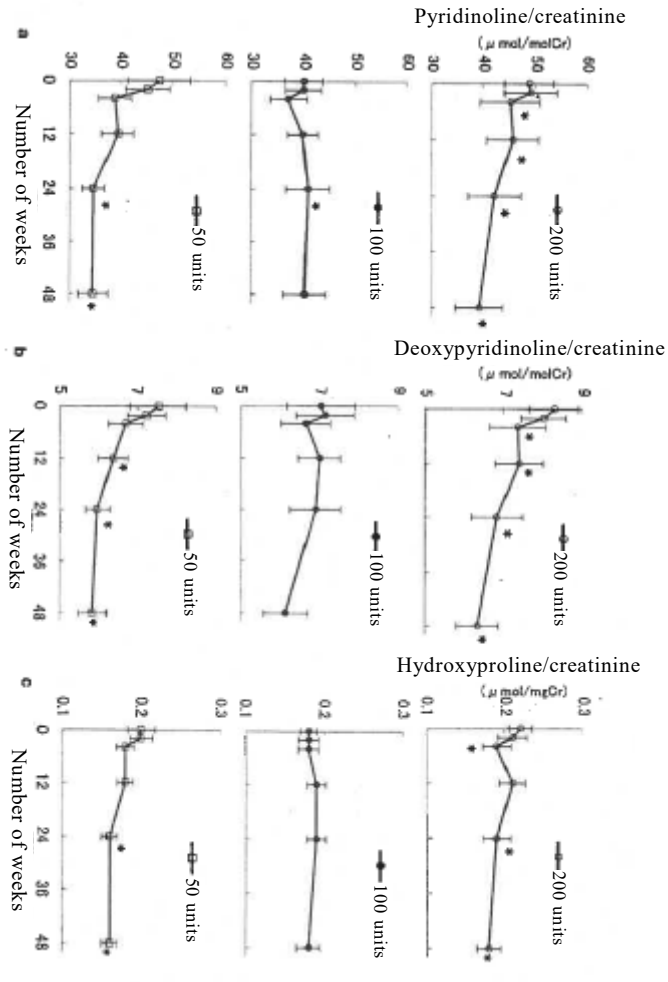


FIG. 5 Number of weeks and pyridinoline (a), deoxypyridinoline (b), hydroxyproline (c), blood bone-specific alkaline phosphatase in the urine (mean ± standard variation)
Symbols refer to the same as FIG. 2.

Table 6 Adverse reactions of subjects during the treatment period

	L group (50 units)			M group (100 units)			H group (200 units)		
Total number of cases	73			75			72		
Number of cases with development of adverse reactions[a] (%)	14 (3[b]) (19%)			14 (10[b]) (19%)			30 (16[b]) (42%)		
Severity and number of cases	Mild 8	Moderate 6	Total 14	Mild 13	Moderate 10	Total 23	Mild 19	Moderate 18	Total 37
Subcutaneous hemorrhage	1		1						
Whole-body flush					1	1			
Facial flush								1	1
Eczema	1		1						
Itching	1		1						
Lumber pain					1	1		1	1
Headache	1	1	2	3		3	2	2	4
Dizziness		1	1	1	1	2		1	1
Retching	3	1	4	5	2	7	9	6	15
Vomiting				1		1	2	2	4
Stomachache		1	1					1	1
Belching					1	1			
Yawning					1	1			
Dry mouth	1		1						
Anorexia								1	1
Heat sensation		1	1	1	1	2	1		1
Fever					1	1	3		3
Weakness				1		1	1		1
General malaise		1	1		1	1	1	2	3
Chill								1	1
Sleepiness				1		1			

[a.] Including abnormal laboratory values

[b.] Number of dropouts due to adverse reactions

(Attachment 3)

Exhibit Ko 64 (excluding cover page)

<Outline>

Inhibitory effect on bone fractures was compared between patients satisfying conditions and patients not satisfying conditions using the following data set* (Analysis [i] through Analysis [iii]). Data analysis was outsourced to CMIC Co., Ltd.

■ Data set (*)

- PTH group: Group of patients with primary osteoporosis with whom the following 3 conditions can be judged and fracture inhibition rate can be calculated, in the post-marketing data for the application for re-examination of Teribone® (teriparatide (human PTH 1-34) acetate; dose and administration of 200 units per week), which is the product of the invention in the application in question (1321 cases).
- Control group: Group of patients with primary osteoporosis with whom the following 3 conditions can be judged and fracture inhibition rate can be calculated, in the data that integrated the placebo group in clinical trials of our products (Teribone®, Elcitonin®) related to osteoporosis (365 cases).

■ Fractures subject to calculation of fracture incidence

Clinical fractures

<Analysis [i]: Comparison of inhibitory effect on bone fractures in patients satisfying the three conditions and patients not satisfying the three conditions>

■ Data analysis date: September 1, 2018 to October 12, 2018

■ Grouping of patients in the data used for analysis

・Patients satisfying the three conditions

Patients who satisfy all of the following 1) through 3)

・Patients not satisfying the three conditions

Patients who satisfy 1) below, but do not satisfy at least one of 2) or 3)

<u>3 conditions</u>

1) Age 65 years or older

2) Prevalent bone fractures

3) Bone density less than 80% of the young adult mean

* Bone density was measured at the lumbar spine or femur (neck, proximal region).

* Degree of bone atrophy is not yet measured. However, if bone density is YAM 80% or more, the degree of bone atrophy is usually considered to be less than 1. Therefore, condition 3) is deemed to be equivalent to "Bone density less than 80% of the young adult mean and/or degree of bone atrophy of 1 or higher."

■ Analysis results

(Table 1)

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the three conditions	PTH	825	40 (4.8)	8.6	p<0.0001	p<0.0001
	Control	304	41 (13.5)			
Patients not satisfying the three conditions	PTH	496	18 (3.6)	4.6	p=0.0906	p=0.0950
	Control	61	5 (8.2)			

Fracture incidence was suppressed in the PTH group, even in patients not satisfying the three conditions, more than the control group; however, fracture incidence was significantly suppressed in patients satisfying the three conditions in the PTH group more than the control group.

<Analysis [ii]: Comparison of inhibitory effect on bone fractures when PTH is administered for the period in excess of 48 weeks>

■ Data analysis date: August 28, 2019 to October 4, 2019

■ Patients in the data used for analysis

・Patients satisfying the four conditions [i]

Patients who satisfy all of the following 1) through 4) among the aforementioned data set (*)

・Patients not satisfying the four conditions [i]

Patients who satisfy 1) and 4) below, but do not satisfy at least one of 2) or 3), in the aforementioned data set (*).

<u>4 conditions</u>

1) Age 65 years or older

2) Prevalent bone fractures

3) Bone density less than 80% of the young adult mean

4) Administration over a duration in excess of 48 weeks

* Bone density was measured at the lumbar spine or femur (neck, proximal region).

* Degree of bone atrophy is not yet measured. However, if bone density is YAM 80% or more, the degree of bone atrophy is usually considered to be less than 1. Therefore, condition 3) is deemed to be equivalent to "Bone density less than 80% of the young adult mean and/or degree of bone atrophy of 1 or higher."

■ Analysis results

(Table 2) Administration over a duration in excess of 48 weeks

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the four conditions [i]	PTH	428	26 (6.1)	6.3	p=0.0036	p=0.0049
	Control	266	33 (12.4)			
Patients not satisfying the four conditions [i]	PTH	261	13 (5.0)	3.8	p=0.2618	p=0.3370
	Control	57	5 (8.8)			

* Difference: Fracture rate (%) in the control group - Fracture rate (%) in the Teribone group

Fracture incidence was suppressed in the PTH group, even in patients not satisfying the four conditions [i], more than the control group; however, fracture incidence was significantly suppressed in patients satisfying the four conditions [i] in the PTH group more than the control group.

<Analysis [iii]: Comparison of inhibitory effect on bone fractures when PTH is administered for the period in excess of 72 weeks>

■ Data analysis date: August 28, 2019 to October 4, 2019

■ Patients in the data used for analysis

・Patients satisfying the four conditions [ii]

Patients who satisfy all of the following 1) through 5) among the aforementioned data set (*)

・Patients not satisfying the four conditions [ii]

Patients who satisfy 1) and 5) below, but do not satisfy at least one of 2) or 3), in the aforementioned data set (*).

4 conditions

1) Age 65 years or older

2) Prevalent bone fractures

3) Bone density than 80% of the young adult mean

5) Administration over a duration in excess of 72 weeks

* Bone density was measured at the lumbar spine or femur (neck, proximal region).

* Degree of bone atrophy is not yet measured. However, if bone density is YAM 80% or more, the degree of bone atrophy is usually considered to be less than 1. Therefore, condition 3) is deemed to be equivalent to "Bone density less than 80% of the young adult mean and/or degree of bone atrophy of 1 or higher."

■ Analysis results

(Table 3) Administration over a duration in excess of 72 weeks

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the four conditions [ii]	PTH	348	19 (5.5)	7.8	p=0.0011	p=0.0017
	Control	218	29 (13.3)			
Patients not satisfying the four conditions	PTH	206	9 (4.4)	2.3	p=0.5128	p=0.4554
	Control	45	3 (6.7)			

[ii]						

* Difference: Fracture rate (%) in the control group - Fracture rate (%) in the Teribone group

Fracture incidence was suppressed in the PTH group, even in patients not satisfying the four conditions [ii], more than the control group; however, fracture incidence was significantly suppressed in patients satisfying the four conditions [ii] in the PTH group more than the control group.

(Attachment 4)

Exhibit Ko 68 (excluding cover page)

<Outline>

The following Analysis [i] to Analysis [iv] were conducted using the data set* that was used for the analysis of laboratory performance certificate I (Exhibit Otsu 24) submitted as of January 29, 2021.

Data analysis was outsourced to CMIC Co., Ltd.

■ Data set (*)

- PTH group: Group of patients with primary osteoporosis with whom the following 3 conditions can be judged and fracture inhibition rate can be calculated, in the post-marketing data for the application for re-examination of Teribone® (teriparatide (human PTH 1-34) acetate; dose and administration of 200 units per week), which is the product of the invention in the application in question (1321 cases).
- Control group: Group of patients with primary osteoporosis with whom the following 3 conditions can be judged and fracture inhibition rate can be calculated, in the data that integrated the placebo group in clinical trials of our products (Teribone®, Elcitonin®) related to osteoporosis (365 cases).

■ Fractures subject to calculation of fracture incidence

Clinical fracture

■ Grouping of patients in the data used for analysis

・Patients satisfying the three conditions

Patients who satisfy all of the following 1) through 3)

・Patients not satisfying the three conditions

Patients who satisfy 1) below, but do not satisfy at least one of 2) or 3)

<u>3 conditions</u>

1) Age 65 years or older

2) Prevalent bone fractures

3) Bone density less than 80% of the young adult mean

* Bone density was measured at the lumbar spine or femur (neck, proximal region).

* Degree of bone atrophy is not yet measured. However, if bone density is YAM 80% or more, the degree of bone atrophy is usually considered to be less than 1. Therefore, condition 3) is deemed to be equivalent to "Bone density less than 80% of the young adult mean and/or degree of bone

atrophy of 1 or higher."

■ Data analysis date: October 26, 2020 to December 21, 2020

<Analysis [i]: Comparison of patient backgrounds before and after the revision of the Diagnostic Criteria for Primary Osteoporosis (FY2012 revised version)>

Concerning the PTH group in the aforementioned data set (* above), patients who were diagnosed based on the Diagnostic Criteria for Primary Osteoporosis (FY2000 revised version) or the Diagnostic criteria for Primary Osteoporosis (FY2012 revised version) were mixed. Then, whether there were differences in the backgrounds of patients between both diagnostic criteria was compared.

The Diagnostic Criteria for Primary Osteoporosis (FY2012 revised version) were estimated to be published on January 31, 2013. Therefore, patients who started administration of PTH before January 31, 2013 are defined as patients diagnosed based on the FY2000 revised version and other patients are defined as patients diagnosed based on the FY2012 revised version.

Analysis results are shown below; however, specific difference in the backgrounds of patients between both diagnostic criteria was not observed.

(Table 1) Patient backgrounds by diagnosis criteria in Exhibit Otsu 24 Table 1

	Patients diagnosed by the FY2000 revised version	Patients diagnosed by the FY2012 revised version
Age (mean value)	78.8 years old	78.7 years old
Prevalent fractures (case rate)	75.3%	71.4%
YAM value (mean value)	64.4%	67.7%

In addition, the same analysis was conducted for Table 2 and Table 3 in Exhibit Otsu 24 and the same results were obtained.

(Table 2): Patient backgrounds by the diagnosis criteria in Exhibit Otsu 24 Table 2

	Patients diagnosed by the FY2000 revised version	Patients diagnosed by the FY2012 revised version
Age (mean value)	78.6 years old	78.3 years old
Prevalent fractures (case rate)	74.7%	70.8%

YAM value (mean value)	64.5%	66.5%

(Table 3): Patient backgrounds by the diagnosis criteria in Exhibit Otsu 24 Table 3

	Patients diagnosed by the FY2000 revised version	Patients diagnosed by the FY2012 revised version
Age (mean value)	78.6 years old	78.3 years old
Prevalent fractures (case rate)	73.5%	74.8%
YAM value (mean value)	64.2%	66.6%

<Analysis [ii]: Comparison of satisfaction/non-satisfaction of the three conditions in patients who were diagnosed by year 2000 revision>

All control groups in the aforementioned data set (* above) were patients diagnosed by the FY2000 revised version. Concerning the PTH group, the inhibitory effect on bone fractures was compared between patients satisfying the three conditions and patients not satisfying the three conditions by limiting to patients who were diagnosed by the FY2000 revised version and conditions were arranged to be the same as the control group.

Fracture incidence of the PTH group and control group is shown below.

(Table 4): Fractures in patients who were diagnosed by the FY2000 revised version in Exhibit Otsu 24 Table 1

	Group	Cases evaluated	Cases of fractures (%)	Difference *	p-value (x^2)	p-value (Fisher)
Patients satisfying the three conditions	PTH	484	25 (5.2)	8.3	p<0.0001	p<0.0001
	Control	304	41 (13.5)			
Patients not satisfying the three conditions	PTH	250	10 (4.0)	4.2	p=0.1702	p=0.1839
	Control	61	5 (8.2)			

Fracture incidence was suppressed in the PTH group, even in patients not satisfying the three conditions, more than the control group; however, fracture incidence was significantly suppressed in patients satisfying the three conditions in the PTH group more than the control group.

In addition, the same analysis was conducted for Table 2 and Table 3 in Exhibit Otsu 24 and the same results were obtained.

(Table 5): Fractures in patients who were diagnosed by the FY2000 revised version in Exhibit Otsu 24 Table 2

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the four conditions [i]	PTH	268	18 (6.7)	5.7	p=0.0253	p=0.0275
	Control	266	33 (12.4)			
Patients not satisfying the four conditions [i]	PTH	147	8 (5.4)	3.3	p=0.3823	p=0.3589
	Control	57	5 (8.8)			

(Table 6): Fractures in patients who were diagnosed by the FY2000 revised version in Exhibit Otsu 24 Table 3

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the four conditions [ii]	PTH	218	13 (6.0)	7.3	p=0.0094	p=0.0141
	Control	218	29 (13.3)			
Patients not satisfying the four conditions [ii]	PTH	126	5 (4.0)	2.7	p=0.4619	p=0.4350
	Control	45	3 (6.7)			

<Analysis [iii]: Mean administration period>

Mean administration period of each group in the aforementioned data set (*) is shown below.

(Table 7): Mean administration period of each group in Exhibit Otsu 24 Table 1

	Group	Mean administration period (week)
Patients satisfying the three conditions	PTH	46
	Control	69
Patients not satisfying the three conditions	PTH	46
	Control	70

In addition, the mean administration period of each group in Exhibit Otsu 24, Table 2 and Table 3 is shown below.

(Table 8): Mean administration period of each group in Exhibit Otsu 24 Table 2

	Group	Mean administration period (week)
Patients satisfying the four conditions [i]	PTH	74
	Control	75
Patients not satisfying the four conditions [i]	PTH	73
	Control	74

(Table 9): Mean administration period of each group in Exhibit Otsu 24 Table 3

	Group	Mean administration period (week)
Patients satisfying the four conditions [ii]	PTH	77
	Control	77
Patients not satisfying the four conditions [ii]	PTH	77
	Control	75

<Analysis [iv]: Analysis excluding cases where administration was discontinued at an early stage>

Concerning the aforementioned data set (*), the inhibitory effect on fractures was compared between patients satisfying the three conditions and patients not satisfying the three conditions, excluding cases where administration was discontinued at an early stage (cases where

administration was discontinued after less than 12 weeks or less than 24 weeks).

Fracture incidence of the PTH group and control group is shown below.

(Table 10) Excluding cases where administration was discontinued after less than 12 weeks

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the three conditions	PTH	626	30 (4.8)	8.7	p<0.0001	p<0.0001
	Control	297	40 (13.5)			
Patients not satisfying the three conditions	PTH	391	17 (4.3)	4.1	p=0.1706	p=0.1892
	Control	59	5 (8.5)			

(Table 11) Excluding cases where administration was discontinued after less than 24 weeks

	Group	Cases evaluated	Cases of fractures (%)	Difference*	p-value (x^2)	p-value (Fisher)
Patients satisfying the three conditions	PTH	547	29 (5.3)	8.0	p<0.0001	p<0.0001
	Control	285	38 (13.3)			
Patients not satisfying the three conditions	PTH	336	16 (4.8)	3.7	p=0.2411	p=0.2203
	Control	59	5 (8.5)			

Fracture incidence was suppressed in the PTH group, even in patients not satisfying the three conditions, more than the control group; however, fracture incidence was significantly suppressed in patients satisfying the three conditions in the PTH group more than the control group.

In addition, mean administration period of each group in Table 10 and Table 11 is shown below.

(Table 12): Mean administration period of each group in Table 10

	Group	Mean administration period (week)
Patients satisfying the three conditions	PTH	69
	Control	70
Patients not satisfying the three conditions	PTH	58
	Control	72

(Table 13): Mean administration period of each group in Table 11

	Group	Mean administration period (week)
Patients satisfying the three conditions	PTH	65
	Control	72
Patients not satisfying the three conditions	PTH	64
	Control	72