

Safety of daily teriparatide treatment: a post hoc analysis of a Phase III study to investigate the possible association of teriparatide treatment with calcium homeostasis in patients with serum procollagen type I N-terminal propeptide elevation

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Objective: Serum procollagen type I N-terminal propeptide (PINP), a representative marker of bone anabolic action, is strongly related to bone mineral density during teriparatide therapy. This post hoc study analyzed data from a Phase III study (ClinicalTrials.gov identifier NCT00433160) to determine if there was an association between serum PINP elevation and serum calcium concentration or calcium metabolism-related disorders.

Research design and methods: Japanese subjects with osteoporosis at high risk of fracture were randomized 2:1 to teriparatide 20 µg/day (n=137) or placebo (n=70) for a 12-month double-blind treatment period, followed by 12 months of open-label teriparatide treatment of all subjects.

Main outcome measures: Serum PINP levels were measured at baseline, and after 1, 3, 6, 12, 18, and 24 months of treatment. Serum calcium levels were measured at baseline, and after 1, 3, 6, 9, 12, 15, 18, 21, and 24 months of treatment.

Results: Serum PINP increased from baseline to 1 month of treatment and then remained high through 24 months. Twenty-eight of 195 subjects experienced PINP elevations >200 µg/L during teriparatide treatment. Serum calcium concentration in both the teriparatide and placebo groups remained within the normal range. There was no clinically relevant difference in serum calcium concentration between subjects with PINP >200 µg/L and subjects with PINP ≤200 µg/L. Two subjects experienced hypercalcemia and recovered without altering teriparatide treatment. Adverse events possibly related to calcium metabolism disorders included periartthritis calcarea (one subject) and chondrocalcinosis pyrophosphate (two subjects), but neither was accompanied with a significant increase in PINP or serum calcium concentration.

Conclusion: Although the moderate size of this study prevented statistical analysis of any potential association between calcium metabolism-related disorders and elevated PINP, this analysis suggests that there was no association between serum PINP elevation during daily teriparatide treatment and serum calcium concentration or calcium metabolism-related disorders in Japanese subjects.

Keywords: teriparatide, osteoporosis, hypercalcemia, procollagen type I N-terminal propeptide, bone metabolism markers

Introduction

The average age of the population in Japan is increasing and, as a consequence, the burden of osteoporosis and the impact of fractures are major public health concerns.

Commonly used therapies, such as bisphosphonates, selective estrogen receptor modulators, and anti-RANKL antibodies, have contributed to reducing osteoporotic fractures. However, these therapies are thought to act by reducing bone resorption only.

Teriparatide is the recombinant N-terminal fragment (residues 1–34) of human parathyroid hormone (rhPTH[1–34]). In contrast to bisphosphonates, selective estrogen receptor modulators, and anti-RANKL antibodies, teriparatide 20 µg/day increases bone formation, largely through stimulating the overall anabolic activity of osteoblasts.^{1–3}

Serum procollagen type I N-terminal propeptide (PINP) is a marker of bone formation that is cleaved off during the processing of type I procollagen to mature type I collagen.⁴ Serum PINP is relatively insensitive to the circadian rhythm or the effects of food intake and has a high signal-to-noise ratio, making it particularly clinically useful.⁵ Serum PINP increases with the increasing anabolic action of teriparatide treatment.³ There is a strong relationship between early change in PINP and later change in lumbar spine bone mineral density (BMD) during teriparatide therapy.⁴ Furthermore, monitoring with PINP and lumbar spine BMD can identify positive responses in most patients taking teriparatide and negative responses in most patients not taking teriparatide.⁴ Monitoring of PINP may therefore be a useful aid in the management of patients with osteoporosis during teriparatide treatment,⁴ and in the clinical setting in Japan, many prescribers use PINP as a marker for drug monitoring of teriparatide.⁶

The effects of teriparatide 20 µg/day on BMD, serum markers of bone turnover, incidence of fracture, and safety have been assessed in a Phase III randomized, multicenter, double-blind, placebo-controlled study in Japanese subjects (men and women) at high risk of fracture.³ The study included 12 months of placebo-controlled, blinded therapy followed by 12 months of open-label treatment during which all subjects received teriparatide.³ The data showed that teriparatide 20 µg/day was well tolerated and stimulated bone formation during 12 and 24 months of treatment in Japanese subjects with osteoporosis at high risk of fracture.³ The study data were also used to confirm the strong relationship between PINP and BMD.⁴

In the clinical setting, the PINP biomarker is the most popular assessment of bone metabolism during treatment with daily teriparatide, which provides a bone anabolic effect.⁶ Besides, serum calcium is tightly regulated by PTH through the kidneys and osteoclasts.⁷ Factors such as vitamin D₃^{8,9} have been shown to influence calcium blood

levels. Therefore, increased serum PINP³ and blood calcium homeostasis may be indirectly connected consequences of teriparatide action, while PTH activates vitamin D in the kidney via 1 alpha hydroxylase.⁷

Elevation of bone metabolism markers, including PINP, above reference values may indicate the presence of metastatic bone tumors, other bone metabolism disorders, or calcium metabolism abnormalities when stratified by sex and menopause.¹⁰ So, there has been a concern among health care providers regarding the safety of daily teriparatide treatment in patients with highly elevated PINP levels. To address this unanswered clinical question, we planned to evaluate safety of teriparatide in patients with high PINP values. Since PINP is not always measured during treatment of patients with osteoporosis, it was difficult to conduct such an evaluation in an observational, post-marketing surveillance study. We therefore performed a post hoc exploratory analysis of this Phase III study to determine if there was an association between serum PINP elevation and serum calcium concentration or calcium metabolism-related disorders.

Patients and methods

Study design

This post hoc analysis was conducted with data from a previously published, multicenter, Phase III study that assessed the safety and efficacy of teriparatide 20 µg/day in Japanese men and women with osteoporosis at high risk of fracture during a 12-month treatment period followed by an open-label treatment period (up to 24 months) in which all subjects received teriparatide.³ The study design of this Phase III study has been previously reported.³ The objectives of this post hoc analysis were to assess: 1) changes in serum calcium in patients with high serum PINP (>200 µg/L) at any time point during the study; and 2) changes in serum PINP and serum calcium in patients with calcium metabolism-related adverse events (AEs) during the study.

As previously reported, serum PINP concentrations significantly increased after teriparatide treatment in this study.³ A preliminary analysis showed that PINP exceeded the upper limit of the normal range (79.1 µg/L) at least one time point during teriparatide treatment in >80% of subjects and at every time point in >20% of subjects. A serum PINP value of 200 µg/L is approximately 2.5-fold that of the upper limit of the normal range and was between the 90th and 95th percentile (90th percentile: 180 µg/L; 95th percentile: 218 µg/L) of all measurements (all subjects at all time points; 844 points) during teriparatide treatment in this study. Since the 95th percentile is normally used to establish

the reference range for laboratory tests, we used 200 µg/L as the threshold of “abnormal” values during teriparatide treatment. As a result, the upper 5% of patients with the highest serum PINP concentrations was judged to have abnormally high values of serum PINP.

This original study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00433160) identifier NCT00433160) was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects provided written informed consent before starting any study procedure according to Good Clinical Practice.

Study population

The study population has been previously reported.³ Inclusion criteria included Japanese women (≥ 5 years post-menopause) and men who were ambulatory, ≥ 55 years old, able to use the pen injection device correctly, and at high risk of fracture defined as at least one of the following criteria: 1) BMD at lumbar spine L2–L4 $< 80\%$ of young adult mean (YAM) (based on the Japanese Normative Female Database)¹¹ with a minimum of one prevalent vertebral fragility fracture; 2) BMD at L2–L4 $< 70\%$ of YAM and age ≥ 65 ; or 3) BMD at L2–L4 $< 65\%$ of YAM and age ≥ 55 .

Treatment protocol

The treatment protocol has been previously reported.³ Subjects received teriparatide 20 µg/day (Forteo [a registered trade name of Eli Lilly and Company], Indianapolis, IN, USA), or placebo, administered subcutaneously, for a maximum of 24 months. All subjects received 610 mg calcium and 400 IU vitamin D supplementation daily (a dosage chosen to meet dietary reference values recommended by the Japanese health authorities) from the start of the screening phase and throughout the study. Male subjects were randomized at a 2:1 ratio to receive teriparatide or placebo, while female subjects were stratified based on BMD at the lumbar spine $< 65\%$, 65%–70%, or 70%– $< 80\%$ of YAM, and were then randomized at a 2:1 ratio using dynamic allocation within each stratum. Upon completing the 12-month double-blind treatment period, all subjects received teriparatide during a 12-month open-label treatment period. Thus, responses in the teriparatide 20 µg/day and placebo groups were compared through 12 months. In addition, the response through 24 months of teriparatide 20 µg/day dosing was assessed for subjects randomized to teriparatide who continued in the open-label period, as well as for subjects originally randomized to placebo who entered the open-label teriparatide treatment period (placebo-teriparatide group).³

Laboratory assessments

Serum PINP levels were measured prior to treatment (baseline), and after 1, 3, 6, 12, 18, and 24 months of treatment using samples obtained in a fasting state prior to dosing. Serum PINP was measured using a radioimmunoassay (Orion Diagnostica, Espoo, Finland). Serum calcium levels were measured prior to treatment (baseline), and after 1, 3, 6, 9, 12, 15, 18, 21, and 24 months of treatment.

Safety profile

For each treatment-emergent AE (TEAE), the severity level was recorded according to the investigator’s perceived severity of the event (mild, moderate, or severe). The incidence of TEAEs was summarized according to their maximum severity. Abnormally high values for bone metabolism markers may indicate the presence of calcium metabolism disorders, metastatic bone neoplasms, and metabolic bone disorders.¹⁰ These particular AEs were therefore analyzed, based on coding in the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0, as previously reported.³

Statistical analysis

Descriptive statistics for change from baseline were presented as medians and interquartile ranges (Q1–Q3) for serum PINP and serum calcium. Kaplan–Meier estimates were calculated to determine time-to-onset for TEAEs, in particular nausea, headache, leg cramp, and dizziness, which have been previously reported to be associated with teriparatide dosing³ and may have been related to teriparatide treatment and any change in serum PINP or serum calcium levels. Days from the first dose to the first event date were used for the time-to-onset. If a subject completed the study schedule, or discontinued the study without the subject experiencing the event, the subject was treated as a censored case at the subject’s last observed date. A comparison of the frequency of specific TEAEs between randomized treatment groups using a Fisher’s exact test has been previously published.³

Results

Baseline characteristics

Table 1 shows the baseline characteristics by treatment groups, as previously reported.³ No statistically significant differences in baseline population characteristics were seen between the treatment groups. Of the 333 subjects screened, 207 met all entry criteria and were randomized (137 to the teriparatide group and 70 to the placebo group). Three subjects were randomized but never received study drug, and one subject received incorrect study drug; these subjects

Table 1 Demographics and baseline characteristics

	Placebo-teriparatide (N=67)	Teriparatide (N=136)
Age, years (SD)	70.4 (5.4)	69.2 (6.3)
Female, n (%)	62 (92.5)	127 (93.4)
Years since natural menopause (SD) ^a	20.5 (6.1)	19.7 (7.1)
No previous vertebral fracture, n (%)	38 (56.7)	82 (60.3)
BMI, kg/m ² (SD)	22.2 (3.3)	21.6 (3.0)
BMD (L2–L4), g/cm ² (SD)	0.638 (0.079)	0.639 (0.069)
Markers of bone turnover		
PINP, µg/L (SD)	55.6 (21.9)	55.7 (21.0)

Notes: ^aFemale subjects with natural menopause: 56 (placebo-teriparatide group); 119 (teriparatide group). Data are mean (SD) or n (%).

Abbreviations: BMD, bone mineral density; BMI, body mass index; PINP, procollagen type I N-terminal propeptide; SD, standard deviation; L, lumbar spine.

were excluded from the analysis. Of the 207 randomized subjects, 120 in the teriparatide group and 60 in the placebo-teriparatide group completed the initial 12-month double-blind treatment period. Of these, 119 teriparatide and 59 placebo-teriparatide subjects entered the open-label treatment period.

Serum PINP

Teriparatide treatment was associated with a rapid increase in PINP from baseline to 1 month (Figure 1). In the teriparatide group, the increase in median PINP observed in the double-blind treatment period was sustained throughout the open-label treatment period, but with a gradual decrease after 12 months. An increase in PINP was observed in the placebo-teriparatide group at 24 months, after starting teriparatide treatment at 12 months. In the placebo-teriparatide group, the median PINP at 24 months was comparable to that of the teriparatide group at 12 months.

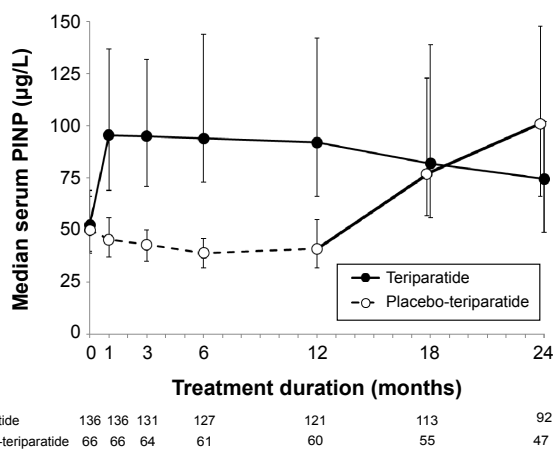


Figure 1 Change in median serum procollagen type I N-terminal propeptide (PINP) from baseline to specific time points.

Notes: During the open-label phase from 12 to 24 months, all subjects received teriparatide 20 µg/day. Values are medians and error bars indicate the interquartile ranges (Q1–Q3). The dashed line denotes the placebo component of the study. The number of subjects at each time point is indicated below the x-axis.

Comparison of serum PINP concentration at baseline to that at 1, 3, 6, and 12 months demonstrated that teriparatide was associated with increased PINP concentration compared to placebo (Figure 2). Twenty-eight of 195 subjects treated with teriparatide (136 subjects in the teriparatide group plus 59 subjects in the placebo-teriparatide group who began treatment after 12 months) experienced PINP elevations higher than 200 µg/L during the study period (n=19 and n=9 in the teriparatide and placebo-teriparatide group, respectively).

Safety

In Figure 3, nausea, headache, leg cramp (muscle spasm), and dizziness are shown as reported events related to calcium metabolism disorders in this study. The overall incidence of nausea, headache, leg cramp (muscle spasm), and dizziness was low. The time-to-onset of these events did not tend to increase in a time-dependent manner in either treatment group (Figure 3). A rapid decline in the Kaplan–Meier curves for dizziness was observed for each treatment group at the end of the observation period, caused by two subjects (one in each treatment group) whose first occurrence of dizziness occurred after most subjects had completed or discontinued the study.

There were very few cases of calcium abnormalities in this study, so we investigated potential relationships between calcium-related AEs, serum PINP concentrations, and serum calcium concentrations. Laboratory test results showed that the median corrected serum calcium concentrations for both the teriparatide and placebo-teriparatide groups remained within the normal range at all measured time points during the study (Figure 4). The corrected serum calcium concentration in subjects with low PINP levels (≤ 200 µg/L) was similar to that in subjects with high PINP levels (> 200 µg/L) in both treatment groups.

AEs related to abnormal bone metabolism, metastatic bone tumors, or other metabolic bone disease are shown

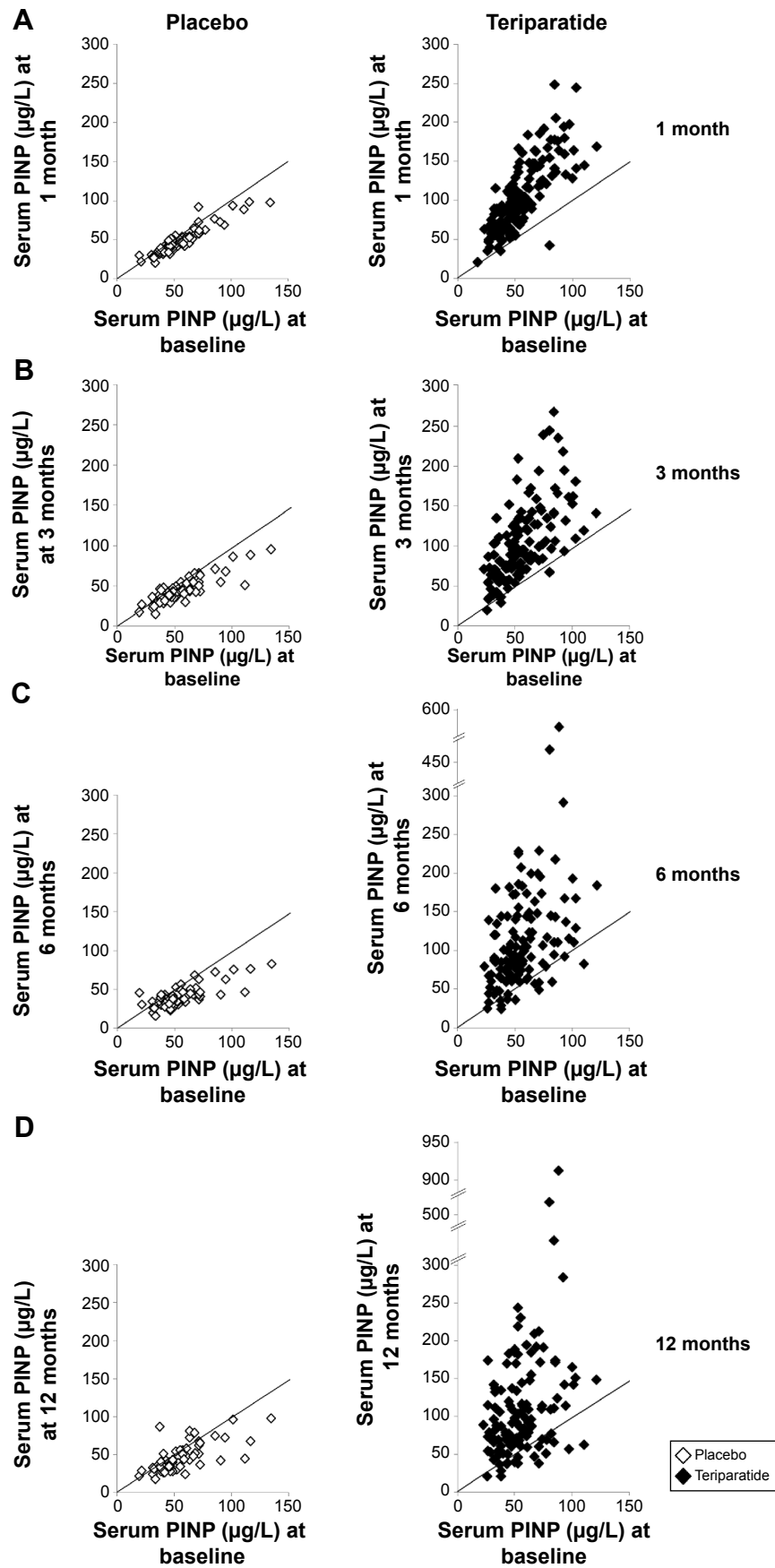


Figure 2 Comparison of distribution of serum procollagen type I N-terminal propeptide (PINP) concentration at baseline to that at 1, 3, 6, and 12 months (A, B, C, and D, respectively) in the placebo (open markers) and teriparatide (shaded markers) groups.

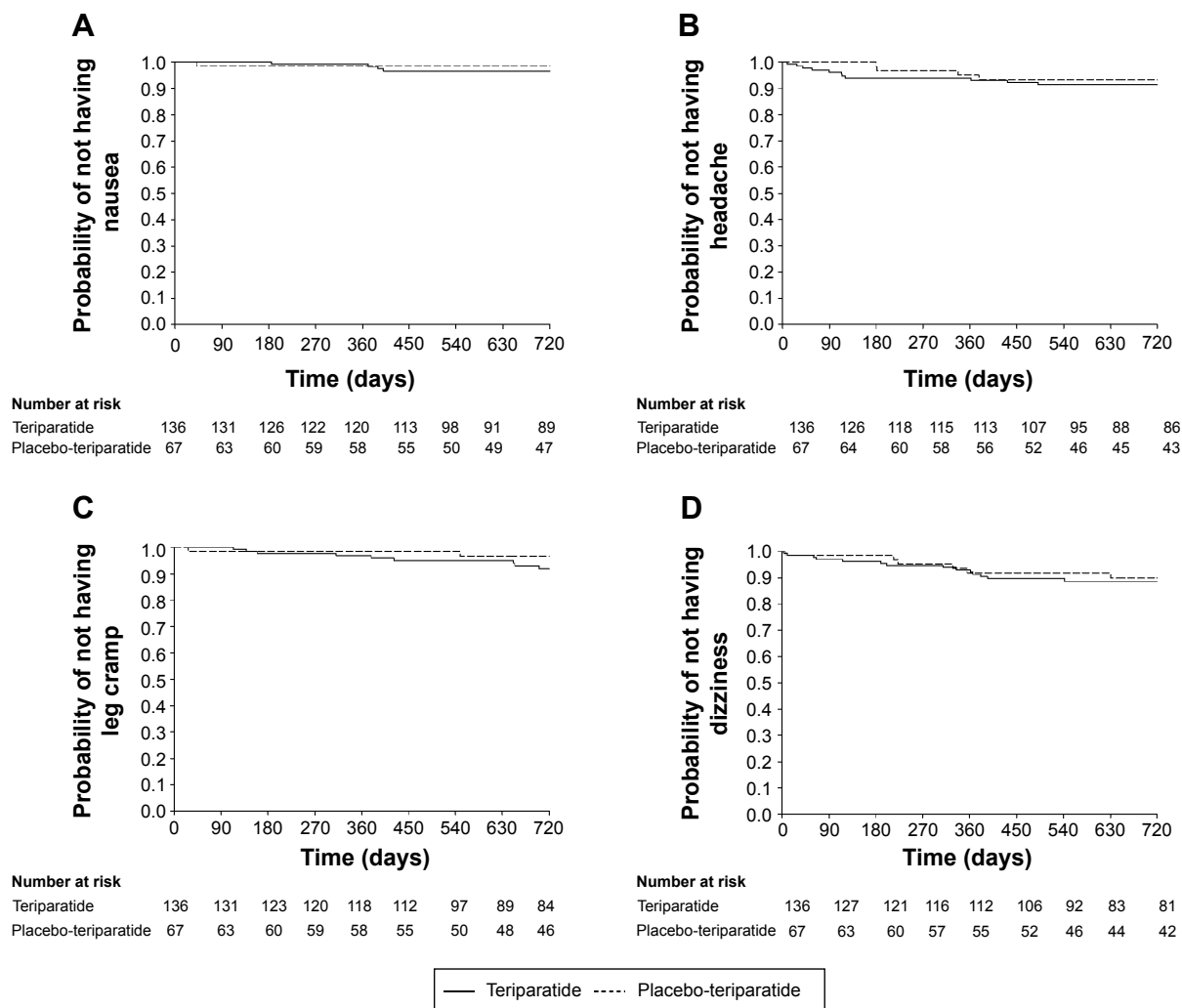


Figure 3 Kaplan–Meier plot of time-to-onset of nausea (A), headache (B), leg cramp (C), and dizziness (D) in the placebo-teriparatide and teriparatide groups. **Note:** The number of subjects at risk is indicated below the x-axis of each plot.

in Table 2. Although median serum calcium levels in both treatment groups remained within normal range, two subjects experienced hypercalcemia and recovered without altering teriparatide treatment. AEs possibly related to calcium metabolism disorders included periartthritis calcarea (one subject) and chondrocalcinosis pyrophosphate (two subjects), but neither was accompanied with a significant increase in serum PINP or serum calcium concentration. No subjects discontinued due to an elevation in serum calcium concentration.

Discussion

This exploratory post hoc analysis revealed that, in a previous Phase III study investigating daily subcutaneous administration of teriparatide in Japanese subjects with osteoporosis, there was no difference in serum calcium concentration between subjects with serum PINP higher than 200 µg/L and these with serum PINP lower than or equal to 200 µg/L.

Furthermore, typical calcium metabolism-related AEs were not observed to be accompanied with significant increases in PINP or calcium concentration.

Median serum PINP increased rapidly during teriparatide treatment and remained significantly elevated through 24 months. This finding is consistent with previous reports that PINP may serve as a primary bone formation marker for response to teriparatide.⁵ There is a strong relationship between early change in PINP and later change in lumbar spine BMD during teriparatide therapy.⁴ Furthermore, monitoring with PINP and lumbar spine BMD successfully identifies positive responses in most subjects taking teriparatide and negative responses in most subjects not taking teriparatide.⁴ Our study supports previous studies that indicate PINP monitoring may be a useful aid from a safety perspective in the management of subjects with osteoporosis during teriparatide treatment.

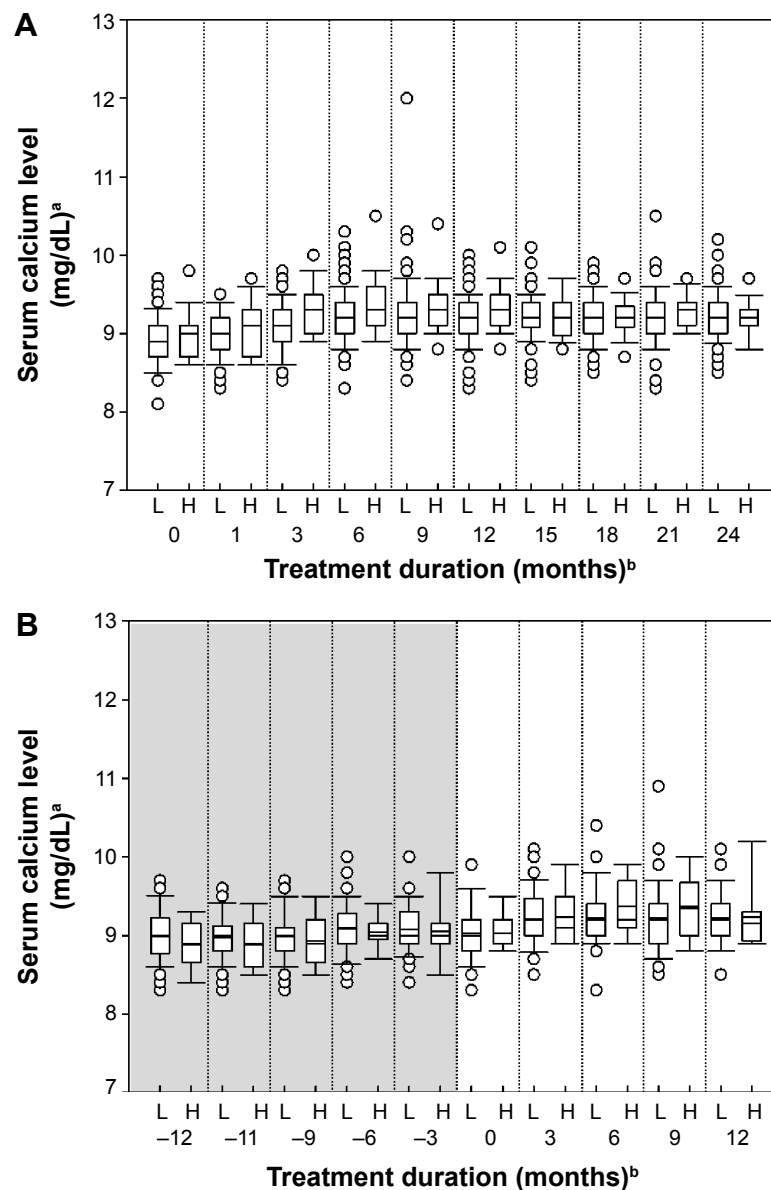


Figure 4 Median serum calcium concentration over time in the teriparatide (A) and placebo-teriparatide (B) groups.

Notes: L: subjects with serum procollagen type I N-terminal propeptide (PINP) levels ≤ 200 $\mu\text{g/L}$ during the study period ($n=117$ and $n=58$ in the teriparatide and placebo-teriparatide groups, respectively). H: subjects with serum PINP levels >200 $\mu\text{g/L}$ at any time point during the study period ($n=19$ and $n=9$ in the teriparatide and placebo-teriparatide groups, respectively). ^aAll measurements were corrected by albumin. ^bTime after starting teriparatide administration. The gray shaded component of the plot in (B) denotes the placebo component of the study. The horizontal line in the middle of each box represents the median, and the upper and lower edges of each box represent the interquartile range. The whiskers denote the largest and smallest values, and the open circles denote the outlying values.

To date, the association between an increase in PINP and a transient increase in serum calcium without AEs has been reported. Schafer et al have identified consistent correlations of bone turnover marker, PINP, and calcium responses to 3 months of PTH (1-84) therapy in postmenopausal osteoporosis.¹² We found that teriparatide was associated with a transient, rapid increase in PINP in the first month which was maintained for 12 months. Transient serum calcium elevations without AEs were consistent with reports from Miller et al.¹³ In our study, the corrected serum calcium

concentration in subjects with low PINP levels (≤ 200 $\mu\text{g/L}$) was similar to that in subjects with high PINP levels (>200 $\mu\text{g/L}$) in both treatment groups. Furthermore, subjects with calcium metabolism-related AEs did not have remarkable or constant changes in serum PINP or serum calcium concentrations. Two subjects experienced hypercalcemia and recovered without altering teriparatide treatment, although we were unable to identify any specific characteristics that were different in these two subjects compared to the other subjects in the study. In addition, no subjects discontinued

Table 2 Adverse events related to abnormal bone metabolism, metastatic bone tumors, or other metabolic bone diseases

Time of onset after first dose, weeks	Adverse event		Serum PINP, $\mu\text{g/L}$		Serum calcium, mg/dL			
	Reported term	MedDRA term	At baseline	At nearest visit (week)	At baseline		At nearest visit (week)	
					Total	Corrected	Total	Corrected
36	Hypercalcemia	Hypercalcemia	32	120 (24) 96 (52)	9.1	8.7	12.3 (36)	12.0 (36)
88 ^a	Hypercalcemia	Hypercalcemia	38	190 (76) 301 (104)	9.0	8.6	10.3 (88)	10.0 (88)
4	Periarthritis calcarea	Periarthritis calcarea	62	148 (4)	8.8	8.4	9.1 (4)	8.9 (4)
16	Polyarticular pseudogout	Chondrocalcinosis pyrophosphate	28	73 (12)	9.5	9.2	9.1 (12)	8.9 (12)
83	Pseudogout of right knee ^b	Chondrocalcinosis pyrophosphate	65	76 (76)	9.3	9.1	9.4 (76)	9.3 (76)
86	Pseudogout of bilateral ankles ^b	Chondrocalcinosis pyrophosphate	65	76 (76)	9.3	9.1	9.4 (76)	9.3 (76)

Notes: ^aPlacebo was administered during the double-blind period. ^bPseudogout of the right knee and bilateral pseudogout of the ankles occurred in the same patient.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PINP, procollagen type I N-terminal propeptide.

due to an elevation in serum calcium, despite the fact that the study protocol allowed this as a discontinuation criterion, and no increase in the incidence of potentially study drug-related AEs was observed. According to a recent report, peak PINP levels after the start of teriparatide treatment are approximately 150 $\mu\text{g/L}$, irrespective of previous history of bisphosphonate treatment.^{6,14} In this study, there were no safety signals with respect to hypercalcemia or calcium metabolism-related AEs. Given that our current findings and the outcomes of previous randomized clinical trials,^{3,4,15} a post-marketing surveillance study,⁶ and an observational real-world study in a clinical setting¹⁴ are consistent, the results shown in this report may be applicable to the real-world clinical setting.

Serum PINP increases with teriparatide treatment. Nishizawa et al indicated that the following PINP values should prompt concern for serious bone disease, such as metastatic bone tumors, or bone/calcium metabolic disorders, other than osteoporosis: >66.8 $\mu\text{g/L}$ in men; >64.7 $\mu\text{g/L}$ in premenopausal women; and >79.1 $\mu\text{g/L}$ in postmenopausal women.¹⁰ In the present study, no safety concerns relating to calcium metabolism-related AEs for subjects with serum PINP higher than 200 $\mu\text{g/L}$ were observed.

PINP is considered a bone marker of choice to monitor early skeletal response to teriparatide treatment.^{4,5,12,13} PINP is essentially a byproduct of collagen synthesis released during bone formation¹⁶ and can be conveniently measured in the clinic via a blood sample with no special precautions. A limitation to using PINP as a barometer for clinical response is the reported variability among patients.¹⁷ In addition, Eastell et al found that lesser PINP increases may be due to variations

in patient adherence, teriparatide injection and storage technique, or the presence of medical conditions to limit response to therapy.⁵ Study-specific limitations included the relatively short duration of the placebo-controlled phase (1 year) and the moderate size of the study population, which prevented statistical analysis of any potential association between calcium metabolism-related disorders and elevated serum PINP.

Conclusion

In conclusion, increases in PINP, a marker of bone formation, were rapid and sustained. There was no apparent association between serum PINP elevation after daily teriparatide treatment and serum calcium concentration or calcium metabolism-related AEs in Japanese subjects. These data suggest that teriparatide therapy may be safe and effective for treating Japanese subjects with osteoporosis at high risk of fracture.

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Author contributions

The authors are solely responsible for the opinions and research findings published in this article. TY, MT, and HS conceived and designed the study, collected the data, analyzed and interpreted the data, and prepared the first draft. All authors were involved in the drafting, review, and approval of the manuscript and the decision to submit for publication.

Disclosure

All authors are employees of Eli Lilly Japan K.K. The authors have no other conflicts of interest to disclose.

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