Abaloparatide Increases Lumbar Spine and Hip BMD in Japanese Patients With Osteoporosis: The Phase 3 ACTIVE-J Study

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Abstract

Context: Abaloparatide reduced fracture risk in postmenopausal women with osteoporosis in the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE). Its effect in Japanese patients remains unexamined.

Objective: This work aimed to determine the efficacy and safety of abaloparatide in increasing bone mineral density (BMD) in Japanese patients with osteoporosis at high fracture risk.

Methods: This was a randomized, double-blind, placebo-controlled study conducted in Japan. Postmenopausal women and men with osteoporosis with high fracture risk were given daily subcutaneous 80 µg abaloparatide or placebo for 78 weeks (18 months). The primary end point was percentage change in lumbar spine (LS) BMD from baseline at the last visit. Secondary end points included time-course changes in LS, total hip (TH), and femoral neck (FN) BMDs and bone turnover markers, and cumulative number of fractures.

Results: Abaloparatide increased LS, TH, and FN BMDs (mean [95% CI]) by 12.5% [10.3%-14.8%; P < .001], 4.3% (3.3%-5.3%), and 4.3% (2.9%-5.6%), respectively, vs placebo. Serum procollagen type I N-terminal propeptide increased rapidly to ~140% above baseline at 6 weeks and gradually decreased but was approximately 25% higher than baseline at 78 weeks. Serum carboxy-terminal cross-linking telopeptide of type I collagen gradually increased to 50% above baseline at 24 weeks and decreased gradually to the placebo-group level from 60 weeks. Four vertebrae of 3 participants in the placebo group, but none in the abaloparatide group, developed new vertebral fractures. The safety profile was similar to that in the ACTIVE study.

Conclusion: In Japanese patients with postmenopausal and male osteoporosis with high fracture risk, abaloparatide for 78 weeks robustly increased LS, TH, and FN BMDs, suggesting a similar efficacy in Japanese patients vs the ACTIVE study population.

Key Words: abaloparatide, bone formation, bone mineral density, vertebral fracture, fracture risk

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ACTIVE-J, Abaloparatide Comparator Trial In Vertebral Endpoints in Japan; BMD, bone mineral density; cAMP, 3',5'-cyclic adenosine monophosphate; CTX, carboxy-terminal cross-linking telopeptide of type I collagen; FAS, full analysis set; FN, femoral neck; LS, lumbar spine; MedDRA, Medical Dictionary for Regulatory Activities; OCN, osteocalcin; PINP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone; PTH1R, PTH receptor type 1; PTHrP, parathyroid hormone–related peptide; TH, total hip; TRACP-5b, tartrate-resistant acid phosphatase 5b.

Abaloparatide is a synthetic parathyroid hormone–related peptide (PTHrP) analog with amino acid substitutions between positions 22 and 31 of PTHrP(1-34) (1, 2). In vitro studies have shown the existence of at least 2 PTH receptor type 1 (PTH1R) conformations, R0 and RG. On binding of ligands to the RG conformation of PTH1R, Gs protein is recruited, which enhances the release of ligands, causing a transient increase in cellular 3',5'-cyclic adenosine monophosphate (cAMP). In contrast, when ligands bind to the R0 conformation of PTH1R, the cAMP response is prolonged. Abaloparatide binds with a lower affinity to the R0 conformation of PTH1R, while it binds to the RG conformation with a similar affinity as PTH(1-34) (2). Consequently, abaloparatide promotes a more transient signaling, leading to a higher anabolic effect with lesser enhancement of bone resorption compared with PTH(1-34) (2).

Teriparatide has been widely used as an anabolic agent for preventing fractures in patients with severe osteoporosis with imminent fracture risk, which has been an unmet medical need (3, 4). However, teriparatide increases not only bone formation but also bone resorption, and enhanced bone resorption was shown to have a negative effect on bone microarchitecture, especially in long bones with higher proportions of cortical bone. Indeed, cortical bone volume and

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thickness are reduced and cortical porosity is increased by teriparatide treatment (5).

In the global phase 3 Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), abaloparatide also showed stimulatory effects on bone formation and resorption, with a more pronounced anabolic action on bones compared with placebo and teriparatide (6), but few Asian patients were included. In a phase 2 dose-response study with abaloparatide involving Japanese postmenopausal women with high fracture risk, daily injection of 80 μg abaloparatide was well tolerated and resulted in dose-related increases in bone mineral density (BMD) (submitted for publication). Therefore, the primary objective of the present study was to determine the efficacy and safety of subcutaneous self-injection of abaloparatide vs placebo for increasing BMD in elderly Japanese patients with osteoporosis at high risk of fracture.

Materials and Methods

Study Design

The Abaloparatide Comparator Trial In Vertebral Endpoints in Japan (ACTIVE-J) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted at 21 sites in Japan from April 2017 to August 2019. Women with postmenopausal osteoporosis (n = 186) and men with osteoporosis (n = 20) were randomly assigned 2:1 to receive daily subcutaneous injections of abaloparatide 80 μg or a matching placebo for 78 weeks (18 months).

Study Participants

Japanese patients with osteoporosis aged 55 to 85 years at high risk of fracture were enrolled if 3 or more of their lumbar spine (LS) vertebrae 1 to 4 (L1-L4) were suitable for BMD measurement by dual energy x-ray absorptiometry. Women were required to be postmenopausal for at least 3 years at the time of informed consent. Patients aged 55 years or older who had an LS BMD T score less than –1.8 with one or more fragility vertebral fractures or an LS BMD T score less than –3.0 were eligible. Patients aged 65 years or older with an LS BMD T score ≤ –2.5 or lower were also eligible. Other eligibility criteria included normal serum calcium and estimated glomerular filtration rate greater than or equal to 30 mL/min/1.73 m².

Randomization and Blinding

Because this study involved high fracture-risk patients with osteoporosis, the number of participants allocated to the placebo group was kept as small as possible from an ethical perspective. Dynamic allocation was carried out using LS (L1-L4) BMD at the prescreening visit and sex as allocation factors. Participants were randomly assigned 2:1 to receive daily subcutaneous self-injections of abaloparatide 80 μg or matching placebo. Randomized distribution of participants to treatment groups was double blinded. Abaloparatide and placebo were administered using identical electrically operated injection devices under identical storage and dispensing conditions. An administration diary was given to each participant, and the status of abaloparatide treatment as well as daily calcium and vitamin D supplementation were recorded. At each visit to the study site, information such as the date, time, and condition of administration was entered into the medical records and case report forms, and each participant self-injected abaloparatide at the study site. For participants who missed an administration of abaloparatide or calcium/vitamin D supplementation, reinstruction was given to prevent a decline in adherence. All participants underwent self-injection training with the same electrically operated device during the run-in period.

The treatment period was 78 weeks (18 months).

Efficacy End Points

The primary efficacy end point of this study was percentage change from baseline to the last visit in LS (L1-L4) BMD using QDR, DELPHI, Explorer, Discovery, and Horizon systems (Hologic Inc). The secondary efficacy end points were percentage changes in BMD of the total hip (TH) and femoral neck (FN) from baseline at the last visit and the time-course changes in LS (L1-L4), TH, and FN BMDs at 12, 24, 48, and 78 weeks. All evaluations were conducted by independent central review.

The incidence of new vertebral fractures was assessed by anteroposterior and lateral spine radiographs, and nonvertebral fractures were assessed by radiographs as clinically indicated at 24, 48, and 78 weeks and at the last visit. Vertebral fractures were assessed using a semiquantitative technique that defines the severity of vertebral fractures (7). All assessments were performed by independent central review. Nonvertebral fractures were fragility fractures excluding those of the skull, facial bones, cervical spine, thoracic spine, LS, sternum, patella, and phalanges of the fingers and toes and those with high trauma. The nonvertebral fractures were initially self-reported, and if a fracture was suspected, radiographic assessment was performed as needed.

Serum markers of bone turnover were measured at 1, 2, 6, 12, 24, 36, 48, 60, 72, and 78 weeks at the laboratory testing site (BML Inc) according to the manufacturer’s instructions. These included procollagen type I N-terminal propeptide (PINP) assessed by radioimmunoassay (AIDIAN, catalog No. 67034, RRID: AB_2910641), carboxy-terminal cross-linking telopeptide of type I collagen (CTX) by enzyme-linked immunosorbent assay (Fuji Rebio, catalog No. 290644, RRID: AB_2910642), osteocalcin (OCN) by electrochemiluminescence immunosay assay (Roche, catalog No. 12149133122, RRID: AB_2915903), and tartrate-resistant acid phosphatase 5b (TRACP-5b) by enzyme immunoassay.
Corrected serum calcium was calculated using the following formula if serum albumin was less than 4.0 g/dL:

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\text{Corrected serum calcium} = \frac{\text{measured total calcium (mg/dL)}}{1 + \left(0.8 \times \text{serum albumin (g/dL)}\right)}
\]

Safety

Safety was assessed by monitoring physical examinations, assessing vital signs, conducting clinical laboratory tests, and reporting adverse events at each study visit. Adverse events and serious adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; ver. 21.1). The protocol specified that the participants would be withdrawn from the study if they had confirmed significant deterioration (≥ 5%) in the LS BMD from the baseline at 24 and 27 or 48 and 51 weeks or were lost to follow-up.

Results

A total of 414 participants underwent screening for the trial, of whom 201 failed to meet the eligibility criteria (Fig. 1). After randomization, one participant in the abaloparatide group did not receive the drug. Therefore, a total of 212 participants across 21 study centers in Japan received abaloparatide (n = 140, 66.0%) or placebo (n = 72, 34.0%) for the safety analysis. Among them, 136 (122 postmenopausal women, 14 men) in the abaloparatide group and 70 (64 postmenopausal women, 6 men) in the placebo group were included in the primary outcome analysis, and 101 (72.1%) in the abaloparatide group and 57 (79.2%) in the placebo group completed all
study visits (n = 158, 74.5%). Baseline demographics and clinical characteristics are shown in Table 1. Baseline demographics were similar between the 2 groups. Mean adherence to the study medication was greater than 90% in each group. Mean adherence to the combined tablets of 400 IU vitamin D and 610 mg calcium was also greater than 97% in each group. At the screening examination before entry, 60.2% of participants showed serum 25(OH)D levels at or above 15 and below 20 ng/mL. After screening, all participants received combined tablets of 610 mg/day calcium and 400 IU/day vitamin D3, and the percentage of participants with serum 25(OH)D below 20 ng/mL decreased to 25.2% in the FAS population at the start of the study. As shown in Table 2, serum 25(OH)D decreased slightly and serum 1,25(OH)2D increased after the start of abaloparatide treatment, while 25(OH)D increased and serum 1,25(OH)2D remained almost unchanged in the placebo group. Serum corrected calcium increased gradually after the start of abaloparatide treatment but remained almost unchanged in the placebo group throughout the study. In parallel with the slight increase in serum corrected calcium, serum whole PTH decreased slightly in the abaloparatide group.

Primary Outcome
The least square means of percentage changes from baseline in LS BMD at the last visit (primary end point, least square mean ± SE) were 16.3 ± 1.0% in the abaloparatide group and 3.8 ± 1.2% in the placebo group, with a treatment difference of 12.5% (95% CI, 10.3%-14.8%; P < .001). Among postmenopausal women (abaloparatide group, n = 122; placebo group, n = 64), the least square means of percentage changes from baseline in LS BMD were 14.1 ± 0.6% in the abaloparatide group and 1.9 ± 0.9% in the placebo group, with a treatment difference of 12.2% (95% CI, 10.1%-14.4%; P < .001).

Secondary Outcomes
Percentage changes from baseline in TH BMD at the last visit (mean ± SD) were 4.0 ± 3.6% in the abaloparatide group and −0.2 ± 3.0% in the placebo group, with a treatment difference of 4.3% (95% CI, 3.3%-5.3%; P < .001). For FN BMD, percentage changes from baseline at the last visit (mean ± SD) were 4.4 ± 4.9% in the abaloparatide group and 0.2 ± 4.2% in the placebo group, with a treatment difference of 4.3% (95% CI, 2.9%-5.6%; P < .001).

Percentage changes in LS, TH, and FN BMDs at 12, 24, 48, and 78 weeks are shown in Fig. 2. BMDs at all the measured sites increased with the duration of treatment in the abaloparatide group, whereas only a small increase in LS BMD and almost no changes in TH and FN BMDs were observed in the placebo group. There were statistically significant differences between the abaloparatide and placebo groups at all the measured sites after 12 weeks or longer treatment with abaloparatide compared with placebo (see Fig. 2). These results also demonstrate that BMDs at all the measured sites continued to increase steadily with abaloparatide until the end of the study period.

To examine the effect of low serum 25(OH)D on the effect of abaloparatide on BMD, changes in LS, TH, and FN BMDs at the last visit were compared between 35 participants (25.7%)...
Table 1. Baseline demographics and clinical characteristics

|                  | FAS                  |                   | Postmenopausal women |                   | Men<sup>a</sup> |                   |
|------------------|----------------------|-------------------|-----------------------|-------------------|-----------------|-------------------|
|                  | Abaloparatide (n = 136) | Placebo (n = 70)  | Abaloparatide (n = 122) | Placebo (n = 64)  | Abaloparatide (n = 14) | Placebo (n = 6)   |
| Age, mean (SD), y | 68.6 (6.0)           | 68.8 (5.6)        | 68.2 (6.0)            | 68.6 (5.2)        | 71.7 (4.4)       | 70.8 (9.0)        |
| Sex, No. of women (%) | 122 (89.7)       | 64 (91.4)        | 122 (100.0)           | 64 (100.0)        | –                | –                |
| Time since menopause or total hysterectomy, mean (SD), y | 17.3 (7.3) | 17.4 (6.8)       | 17.3 (7.3)            | 17.4 (6.8)        | –                | –                |
| Height, mean (SD), cm | 153.99 (6.96)  | 153.89 (5.77)     | 152.78 (6.05)         | 152.91 (4.62)     | 164.55 (5.41)    | 164.32 (6.96)     |
| Weight, mean (SD), kg | 51.15 (7.51)   | 50.90 (5.86)      | 50.70 (7.59)           | 50.39 (5.72)      | 55.11 (5.54)     | 56.32 (4.79)      |
| Body mass index, mean (SD), kg/m² | 21.54 (3.02)   | 21.47 (2.46)      | 21.68 (3.08)           | 21.52 (2.44)      | 20.34 (2.21)     | 20.93 (2.76)      |
| eGFR, mean (SD), mL/min/1.73 m² | 71.56 (12.60) | 68.69 (11.70)     | 71.39 (12.49)          | 69.08 (11.54)     | 73.06 (13.92)    | 64.48 (13.79)     |
| Alkaline phosphatase, mean (SD), U/L | 231.0 (58.4)    | 237.5 (67.3)      | 231.7 (56.3)           | 241.8 (67.7)      | 224.9 (75.2)     | 191.7 (42.9)      |
| No history of prior fragility fractures, No. (%) | 73 (53.7)       | 49 (70.0)         | 67 (54.9)              | 48 (75.0)         | 6 (42.9)         | 1 (16.7)          |
| No. of vertebral fractures, No. (%) | 0 | 75 (55.1)        | 51 (72.9)              | 69 (56.6)         | 50 (78.1)        | 6 (42.9)          |
|                  | 1                    | 46 (33.8)        | 13 (18.6)              | 39 (32.0)         | 11 (17.2)        | 7 (50.0)          |
|                  | ≥ 2                   | 15 (11.0)        | 6 (8.6)                | 14 (11.5)         | 3 (4.7)          | 1 (7.1)           |
| Bone mineral density, mean (SD), g/cm² |                      |                   |                       |                   |                 |                   |
| Lumbar spine (L1-L4) | 0.649 (0.073) | 0.646 (0.062)    | 0.644 (0.073)          | 0.643 (0.063)     | 0.691 (0.070)    | 0.677 (0.045)     |
| Total hip | 0.662 (0.085) | 0.660 (0.074)    | 0.654 (0.082)          | 0.659 (0.074)     | 0.734 (0.084)    | 0.674 (0.089)     |
| Femoral neck | 0.536 (0.077) | 0.535 (0.088)    | 0.527 (0.072)          | 0.531 (0.057)     | 0.614 (0.079)    | 0.569 (0.058)     |
| T score, mean (SD) |                      |                   |                       |                   |                 |                   |
| Lumbar spine (L1-L4) | –3.6 (0.6)       | –3.7 (0.6)        | –3.7 (0.6)             | –3.7 (0.6)        | –3.6 (0.6)       | –3.6 (0.3)        |
| Total hip | –2.3 (0.7)  | –2.3 (0.6)        | –2.4 (0.7)             | –2.3 (0.6)        | –2.0 (0.6)       | –2.4 (0.6)        |
| Femoral neck | –2.8 (0.7)  | –2.8 (0.5)        | –2.9 (0.6)             | –2.9 (0.5)        | –2.3 (0.6)       | –2.7 (0.4)        |
| Procollagen type I N-terminal propeptide, mean (SD), ng/mL | 48.54 (14.47) | 56.91 (20.01) | 48.83 (14.44)          | 58.71 (19.96)     | 46.04 (14.98)    | 37.75 (4.71)      |
| Osteocalcin, mean (SD), ng/mL | 20.22 (6.08) | 22.05 (5.83)    | 20.54 (6.05)           | 22.49 (5.76)      | 17.45 (5.85)     | 17.30 (4.67)      |
| Carboxy-terminal cross-linking telopeptide, mean (SD), μg/L | 0.22 (0.09) | 0.28 (0.15)     | 0.22 (0.10)            | 0.29 (0.16)       | 0.21 (0.08)      | 0.18 (0.04)       |
| Tartrate-resistant acid phosphatase, mean (SD), mU/dL | 343.8 (99.6) | 391.0 (124.0) | 343.9 (101.3)          | 394.1 (122.4)     | 343.4 (87.4)     | 358.0 (148.1)     |
| 25-(OH) vitamin D, mean (SD), ng/mL | 23.55 (4.88) | 23.74 (6.28)    | 23.38 (4.93)           | 23.14 (4.93)      | 25.07 (4.33)     | 30.13 (13.59)     |
| Whole PTH, mean (SD), pg/mL | 24.9 (5.3) | 25.1 (5.7)       | 24.7 (5.3)             | 25.1 (5.7)        | 26.7 (5.2)       | 25.3 (6.0)        |

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; PTH, parathyroid hormone.

<sup>a</sup>Male population included in the FAS.
with serum 25(OH)D levels less than 20 ng/mL and 101 participants (74.3%) with serum 25(OH)D levels greater than or equal to 20 ng/mL at week 0 in the abaloparatide group of the FAS. There were no statistically significant differences in the increase in BMD from baseline between these 2 groups (mean ± SD: LS BMD, 13.8 ± 6.3% and 14.9 ± 10.1%; TH BMD, 3.7 ± 2.7% and 4.2 ± 3.9%; and FN BMD, 4.2 ± 4.0% and 4.5 ± 5.2% in participants with serum 25(OH)D < 20 ng/mL and ≥ 20 ng/mL, respectively).

New vertebral fractures occurred in 4 vertebrae of 3 participants (4.3%) in the placebo group, whereas no vertebral fracture was observed in the abaloparatide group during the treatment duration, with a statistically significant absolute risk reduction of −4.3% (P = .038). New nonvertebral fractures occurred in 3 participants (2.2%) in the abaloparatide group and 2 participants (2.9%) in the placebo group (Table 3).

The time-profile median changes from baseline in bone turnover markers are shown in Fig. 3. Bone formation markers rapidly increased during the first 6 weeks in the abaloparatide group (approximately 140% increase in PINP and 90% increase in OCN) and gradually decreased thereafter. These bone formation markers remained elevated compared with baseline until 78 weeks, when serum PINP and OCN were approximately 25% and 15% higher than

### Table 2. Changes in serum 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; corrected calcium; and parathyroid hormone (full analysis set)

|                      | Baseline | 24 wk | 48 wk | 78 wk |
|----------------------|----------|-------|-------|-------|
| Serum 25(OH)D, mean (SD), ng/mL |          |       |       |       |
| Abaloparatide        | 23.55 (4.88) | 20.77 (5.34) | 21.22 (5.16) | 21.01 (5.09) |
| Placebo              | 23.74 (6.28) | 28.37 (7.90) | 28.33 (8.50) | 27.51 (8.35) |
| Serum 1,25(OH)2D, mean (SD), pg/mL |          |       |       |       |
| Abaloparatide        | 62.9 (22.6)  | 88.2 (31.6)  | 86.7 (34.3)  | 84.0 (31.8)  |
| Placebo              | 63.8 (24.5)  | 58.9 (18.8)  | 60.7 (24.7)  | 65.3 (22.7)  |
| Corrected serum calcium, mean (SD), mg/dL |          |       |       |       |
| Abaloparatide        | 9.33 (0.35)  | 9.53 (0.36)  | 9.65 (0.39)  | 9.68 (0.38)  |
| Placebo              | 9.34 (0.41)  | 9.35 (0.37)  | 9.49 (0.33)  | 9.44 (0.34)  |
| Serum whole PTH, mean (SD), pg/mL |          |       |       |       |
| Abaloparatide        | 24.9 (5.3)   | 21.9 (4.9)   | 20.4 (4.9)   | 21.4 (7.3)   |
| Placebo              | 25.1 (5.7)   | 26.4 (6.2)   | 23.2 (4.5)   | 25.4 (5.6)   |

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

*Reference range for serum whole PTH, 9-39 pg/mL.

Figure 2. Percentage changes from baseline in bone mineral density at the lumbar spine, total hip, and femoral neck. Mean percentage changes from baseline in bone mineral density at a, lumbar spine; b, total hip; and c, femoral neck. The descriptive statistics for the observed values and the percentage changes from baseline at each evaluation time point in each treatment group were analyzed without imputation of missing data in the full analysis set. Data are presented as means with SD. Comparisons were performed using Student’s t test. These analyses were exploratory, with no adjustments for multiplicity. *P < .001 for abaloparatide vs placebo. BMD, bone mineral density.
New nonvertebral fracture: 3/136 (2.2) vs 2/70 (2.9), β = −0.7 (−7.78 to 3.92), p ≤ .999

New vertebral fracture: 0/136 (0.0) vs 3/70 (4.3), β = −4.3 (−11.86 to −0.35), p = 0.038

The abaloparatide group (5.0%) had a greater incidence of blood calcium increase compared to the placebo group (1.4%). These adverse events were generally moderate in severity, and the participants recovered shortly after drug discontinuation.

Myocardial infarction, angina pectoris, and atrial fibrillation were observed in both groups, but none of these events were serious. However, none of these events were serious, and a causal relationship with the administration of abaloparatide was excluded for a rash in one participant in the abaloparatide group. No anaphylaxis-like events were observed. More adverse cardiovascular events were observed in the abaloparatide group than in the placebo group, including palpitations (5.0% vs 1.4%, respectively), supraventricular extrasystoles (2.9% vs 1.4%, respectively), and orthostatic hypotension (0.7% vs 0.0%, respectively). However, the severity of these events was mild or moderate. No difference was observed in the incidence of serious adverse cardiovascular events such as myocardial infarction, angina pectoris, and atrial fibrillation.

Among clinical laboratory parameters, blood uric acid increased with abaloparatide, but the increase was mild or moderate. Alkaline phosphatase increased transiently in the early stages of abaloparatide administration and gradually decreased to the baseline level. Because other laboratory data related to the hepatobiliary system did not show any changes, the transient increase in the alkaline phosphatase level could be attributed to the stimulation of bone formation by abaloparatide. No problems were found in the safety and dosing accuracy of the electrically operated injector used for drug/placebo administration. Thus, the safety profile of abaloparatide in the present study was similar to that in the global ACTIVE study (6), and no new safety concerns were identified.

### Discussion

In the present study involving Japanese patients with postmenopausal and male osteoporosis with high fracture risk, daily subcutaneous self-injection of abaloparatide for 78 weeks (18 months) robustly increased LS, TH, and FN BMDs compared with placebo. The increase in LS BMD in postmenopausal women was similar to that in the overall population. Although the number of participants with incident vertebral fracture was small, all 3 participants with vertebral fracture were in the placebo group. Treatment differences between the abaloparatide and placebo groups in LS BMD were larger than those in the ACTIVE study, while treatment differences in TH and FN BMDs between the abaloparatide and placebo groups were very similar to those in the ACTIVE study (6). The ACTIVE study reported that more participants in the abaloparatide group than in the teriparatide group met the definition of responders, defined as those who experienced more than 3% or 6% increases in BMD at all 3 anatomic sites—LS, TH, and FN (9). Taken together, the present results suggest that abaloparatide has a similar efficacy in Japanese patients with osteoporosis to that in the ACTIVE study population (6).

The rapid and robust increase in bone formation markers with a small increase in resorption markers with abaloparatide was consistent with the marked increase in BMD. Notably, the degree of increase in bone formation markers in the present study was larger than that in the ACTIVE study, and they remained elevated until the end of the study (~ 60% and 35% higher than baseline in PINP and OCN, respectively) as in the ACTIVE study (6). In contrast, the increase in bone resorption markers was slower and less prominent and decreased to the level seen in the placebo group from 60 weeks (13.8 months) until the end of the study. As mentioned earlier, abaloparatide preferentially binds to the RG conformation of PTH1R, with a shorter time course of receptor-mediated signaling compared with teriparatide, which is expected to enhance bone formation.
more than bone resorption signals (2). In the ACTIVE study, although abaloparatide stimulated bone formation less than teriparatide, the stimulation of bone resorption was also lower than that by teriparatide (6), similar to the results in the present study. This could possibly explain the stronger anabolic effect and larger increase in BMD with abaloparatide compared with teriparatide. A later analysis of the ACTIVE study to examine the relationship between serum PINP and BMD changes after abaloparatide and teriparatide treatments demonstrated that early changes

Figure 3. Median change from baseline in serum bone metabolism markers over time by treatment group. Median percentage changes from baseline in a, serum procollagen type I N-terminal propeptide; b, serum carboxy-terminal cross-linking telopeptide of type I collagen; c, serum osteocalcin; and d, serum tartrate-resistant acid phosphatase 5b. Error bars indicate median interquartile ranges. Comparisons were performed using Wilcoxon rank sum test. These analyses were exploratory, with no adjustments for multiplicity. *P < .001 for abaloparatide vs placebo; #P < .05 for abaloparatide vs placebo.

CTX, carboxy-terminal cross-linking telopeptide of type I collagen; OCN, osteocalcin; PINP, procollagen type I N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b.
Table 4. Safety profile and adverse events

|                          | Abaloparatide (n = 140) n (%) | Placebo (n = 72) n (%) |
|--------------------------|------------------------------|------------------------|
| All treatment-emergent adverse events | 128 (91.4) | 58 (80.6) |
| Any treatment-emergent adverse drug reaction | 45 (32.1) | 10 (13.9) |
| Serious treatment-emergent adverse events | 7 (5.0) | 10 (13.9) |
| Deaths | 0 (0.0) | 0 (0.0) |
| Adverse events leading to discontinuation | 4 (2.9) | 4 (5.6) |

Most frequently observed adverse events (≥ 5% in the abaloparatide treatment arm)

- Nasopharyngitis: 81 (57.9) vs. 36 (50.0)
- Headache: 19 (13.6) vs. 8 (11.1)
- Injection site bruising: 11 (7.9) vs. 7 (9.7)
- Contusion: 11 (7.9) vs. 4 (5.6)
- Abdominal discomfort: 9 (6.4) vs. 3 (4.2)
- Nausea: 9 (6.4) vs. 6 (8.3)
- Blood uric acid increased: 8 (5.7) vs. 0 (0.0)
- Blood calcium increased: 7 (5.0) vs. 1 (1.4)
- Dizziness: 7 (5.0) vs. 3 (4.2)
- Vertigo: 7 (5.0) vs. 2 (2.8)
- Back pain: 7 (5.0) vs. 6 (8.3)
- Osteoarthritis: 7 (5.0) vs. 3 (4.2)

Adverse events of special interest

- Hypersensitivity: 20 (14.3) vs. 6 (8.3)
- Eczema*: 7 (5.0) vs. 4 (5.6)
- Rash: 4 (2.9) vs. 1 (1.4)
- Urticaria: 4 (2.9) vs. 0 (0.0)
- Cardiovascular events: 23 (16.4) vs. 7 (9.7)
- Palpitation*: 7 (5.0) vs. 1 (1.4)
- Supraventricular extrasystoles: 4 (2.9) vs. 1 (1.4)
- Orthostatic hypotension: 1 (0.7) vs. 0 (0.0)

A participant with more than one event within the same level of the Medical Dictionary for Regulatory Activities terms was counted as one.

*Most frequently observed adverse events (≥ 5%).

in PINP correlated with the percentage change in LS BMD at 18 months, with a greater correlation observed with abaloparatide than teriparatide (10). Because the increase in bone formation markers and BMD was more robust in the present study than in the ACTIVE study, it is plausible that abaloparatide has similar or even greater efficacy in the Japanese population than that seen in the ACTIVE study (6).

Although this study included participants with serum 25(OH)D less than 20 ng/mL at study entry, the effect of abaloparatide is expected to be maximized under sufficient vitamin D levels.

In the present study, no safety concerns other than those reported in the ACTIVE study were identified (6). In a detailed analysis of cardiovascular adverse events associated with abaloparatide, Cosman et al (11) reported that no increased risks of serious cardiac adverse events were observed, while a transient increase in heart rate was observed immediately after injection of abaloparatide compared with placebo and resolved within 4 hours after administration. This increase in heart rate after abaloparatide injection was weakly associated with small but significant decreases in mean supine and standing systolic and diastolic blood pressures. In the present study, although heart rate was not monitored during the observation period after injection, 7 participants had palpitations and 1 participant had orthostatic hypotension in the abaloparatide group compared with 1 participant with palpitations and none with orthostatic hypotension in the placebo group. These symptoms appear to be related to the vasodilator activity of abaloparatide and possibly a direct effect on the sinoatrial node, which is known to be slightly stronger for abaloparatide than teriparatide (11, 12). Nevertheless, none of those events were serious, and as a recent meta-analysis suggested (13), both teriparatide and abaloparatide have no effect on cardiovascular risk and overall mortality.

The present study has some limitations. First, the number of participants was too small to demonstrate the antifracture efficacy of abaloparatide. However, the number of participants was enough to estimate increases in BMD at various target sites, especially LS BMD as a primary outcome, as well as to evaluate the safety of abaloparatide treatment. Second, this study included a small number of men with osteoporosis at high risk of fracture. Although the assessment of the primary outcome in the overall population was positive, further analysis is needed to evaluate the efficacy of abaloparatide in men with osteoporosis.

In conclusion, among Japanese patients with postmenopausal and male osteoporosis with high fracture risk, daily subcutaneous self-injection of abaloparatide for 78 weeks (18 months) led to statistically significant increases in BMD, in bone formation markers and with small and transient increases in bone resorption markers. These results suggest that in the Japanese population, abaloparatide has a similar efficacy to that demonstrated in the ACTIVE study.

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Teijin Pharma Ltd, in conjunction with the Clinical Development Administration Department and outside consultants, developed the study protocol and statistical analysis plan and analyzed the data. Data were collected by the investigators at the study sites listed here.

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Data Availability
Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license.

Clinical Trial Information
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