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ORIGINAL ARTICLE

The safety and effectiveness profile of eldecalcitol in a prospective, post-marketing observational study in Japanese male patients with osteoporosis

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Abstract
We conducted a post-marketing observational study to investigate the safety and effectiveness of eldecalcitol for the treatment of osteoporosis in a Japanese clinical setting. The observation period was 12 months for women and 36 months for men. The final results for the female patients have already been published. In this article, the final results for the male patients are reported. A total of 470 male osteoporosis patients were enrolled. The safety analysis set included 431 patients (mean age, 76.8 years; mean ± SD follow-up period, 631.0 ± 450.3 days), and 175 patients continued treatment throughout the 3-year observational period. Adverse drug reactions (ADRs) were reported in 28 patients (6.49%); the most common ADRs were hypercalcemia (1.16%) and renal impairment (1.16%). Serious ADRs were reported in 5 patients (1.16%). Mean serum calcium was within the normal range throughout the observation period. The cumulative incidence of new vertebral and nonvertebral fractures at 36 months, estimated by Kaplan–Meier analysis, was 10.23 and 4.06%, respectively. At the last observation, mean lumbar spine bone mineral density was 3.49% higher ($P < 0.0001$) than at baseline, and levels of the bone turnover markers BAP and TRACP-5b were reduced (–14.64%; $P = 0.0009$, and − 29.51%; $P < 0.0001$, respectively). In conclusion, the safety and effectiveness of eldecalcitol for the treatment of Japanese male osteoporosis patients was confirmed in clinical practice. Careful monitoring of serum calcium and estimated glomerular filtration rate, both before and during treatment, is necessary to minimize the risk of hypercalcemia and renal impairment while maximizing the effectiveness of eldecalcitol.

Keywords Eldecalcitol · Japanese · Male patients · Osteoporosis · Post-marketing surveillance

Introduction

Osteoporosis is often thought of as women's disease. Women are particularly at risk owing to the marked decrease in bone mineral density (BMD) after menopause. In addition, osteoporotic fractures (i.e., fractures associated with low BMD) are more common in women than in men of the same age, because the age-related increase in the incidence of such fractures occurs 5–10 years earlier in women. However, the aging of the world's population means that osteoporotic fractures are expected to affect an increasing proportion of men. Globally, the incidence of hip fractures in men is predicted

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to be 3.1-fold higher in 2050 than in 1990, compared with a 2.4-fold increase in women over the same period [1]. In Japan, around a quarter (3 million) of the 12.8 million people with osteoporosis are men [2], and men made up around a fifth (37,600) of the estimated 175,700 new hip fracture patients in 2012, based on the results of a nationwide survey conducted by the Japanese Ministry of Health, Labour and Welfare [3]. Therefore, osteoporosis in men is an increasing important public health problem, particularly in countries, such as Japan, with a rapidly aging population.

Eldecalcitol is an active vitamin D_3 analog bearing a hydroxypropyloxy substituent at the 2β position. It was developed in Japan for the treatment of osteoporosis, and approved for this indication in 2011. Eldecalcitol is now widely used in Japanese general clinical practice. The safety profile of eldecalcitol and its beneficial effect on calcium metabolism are similar to those of active vitamin D, but it has a stronger therapeutic effect on bone [4]. It has a grade A rating (confirmed by well-designed, randomized, controlled trials) for increasing bone density and preventing vertebral fractures, according to the most recent Japanese guidelines for the prevention and treatment of osteoporosis [2].

Several randomized clinical studies have been conducted in Japan to evaluate the safety and effectiveness of eldecalcitol, and the major adverse drug reactions (ADRs) related to eldecalcitol were increased blood calcium and increased urinary calcium [5–7]. However, out of the total of 1492 patients enrolled in these studies, there were only 33 male patients. Therefore, we conducted a prospective, post-marketing observational study to investigate the safety and effectiveness of eldecalcitol, under conditions of actual clinical use, with an extended observation period for men (36 months, versus 12 months for women). The 12-month results for both sexes have been published in an interim report [8]; eldecalcitol was shown to be effective, consistent with the findings of a phase III study in Japan [6], and no major safety concerns were identified. Here, we report the final 36-month results of the safety and effectiveness of eldecalcitol in male patients in our study.

Materials and methods

Study design

This was a prospective, multicenter, observational study conducted in Japan as part of post-marketing surveillance for eldecalcitol, and in accordance with Good Post-marketing Study Practice. Male and female patients with a diagnosis of osteoporosis, based on diagnostic criteria established by the Japanese Society for Bone and Mineral Research [9] were eligible. The observation period was 12 months for women and 36 months for men.

Details of the study design, including how the target number of patients of either sex ($n = 2903$) was calculated, are described in the interim report [8]. All male patients who received at least one dose of eldecalcitol were included in the safety analysis set in the present analysis. Included in the effectiveness analysis set in this analysis were male patients for whom baseline data on BMD, bone turnover markers (BTMs), or fracture incidence were available, and who had visited their physician at least once after administration of eldecalcitol.

Treatment protocol

The male patients received eldecalcitol (Edirol; Chugai Pharmaceutical, Tokyo, Japan) daily, by oral administration, for up to 36 months. The dose was 0.75 μg, with the option to reduce the dose to 0.5 μg depending on the condition of individual patients. Participating physicians provided medical care according to their clinical judgment and usual practice. Data were recorded at baseline and at regular intervals until the end of the observation period (i.e., 36 months).

Safety profile

Adverse drug reactions were defined as adverse events (AEs) for which a causal relationship with eldecalcitol could not be excluded, and included abnormal laboratory test values. Participating physicians provided reports of spontaneous ADRs. Data from these reports were then collated, using the preferred terms listed in the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) version 18.1.

Effectiveness

Assessment of the effectiveness of eldecalcitol treatment was based on percent change from baseline in BMD and levels of BTMs, and on changes in fracture incidence from baseline.

Bone mineral density was measured at lumbar vertebrae 2–4 (L2–L4), total hip, and/or distal radius by dual-energy X-ray absorptiometry. The BTM bone-specific alkaline phosphatase (BAP), serum collagen type 1 cross-linked N telopeptide (serum NTX), urinary collagen type 1 cross-linked N telopeptide (urinary NTX), and tartrate-resistant acid phosphatase 5b (TRACP-5b) were measured at the discretion of participating physicians. BMD and BTMs were measured in accordance with testing methods at each study center, and data were recorded at baseline, 6, 12, 36 months, and at discontinuation.

New fragility fractures reported at any hospital visit from baseline onwards were subsequently recorded as new clinical fractures on the basis of radiographic evidence and the judgment of individual investigators, in accordance with the

usual procedure at each study center. The incidence of clinical fractures was summarized every 6 months throughout the observation period.

Data relating to treatment adherence were collected, including the number of patients who continued treatment throughout the observation period and dosing periods, and the number of patients who discontinued treatment and the reasons for their discontinuation.

Statistical analysis

In the safety analysis, percentages were calculated by dividing the number of patients with an ADR by the number of patients in the safety analysis set. An individual patient in whom multiple occurrences of the same ADR were reported was counted only once.

In the effectiveness analysis, data from patients with baseline values and at least one post-dose value were used. For BMD and BTM levels, mean and 95% confidence interval (CI) were used to calculate percent changes between baseline and last observation. The last-observation-carried-forward method was used to impute missing data at 36 months. The paired *t* test was used to compare BMD and BTM levels at baseline and last observation. The Kaplan–Meier method was used to estimate cumulative incidence (and 95% CI) of vertebral and nonvertebral fractures.

P values < 0.05 were considered statistically significant. All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

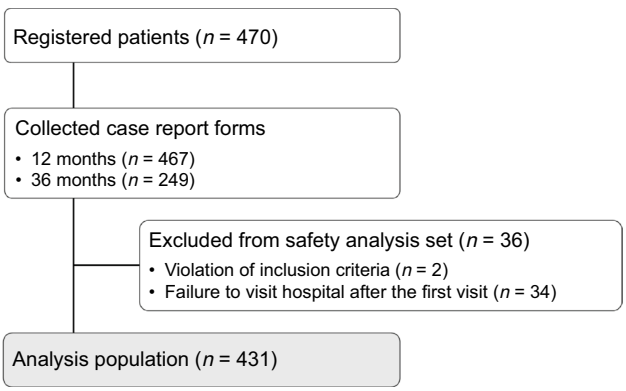


Fig. 1 Patient enrollment and outcomes

Results

From July 1, 2011 to March 31, 2012, 3567 patients (470 men and 3097 women) were registered at 426 medical institutions throughout Japan. As of October 2015, case report forms had been collected for 3532 patients, including the 467 registered male patients. After exclusion of 36 of these male patients, 431 were included in the safety and effective analysis sets (Fig. 1).

Baseline characteristics

Table 1 shows the baseline characteristics of the 431 patients included in the safety analysis. Mean age was 76.8 years, and 136 patients (31.55%) had sustained one or more prevalent vertebral fractures. Mean values of the BTMs (BAP, serum NTX, urinary NTX, and TRACP-5b) were above the upper limit of the normal range. Estimated glomerular filtration rate (eGFR) was < 30 mL/min/1.73 m^2 in 1.16% of patients (5/431), ≥ 30 mL/min/1.73 m^2 in 43.62% (188/431), and unknown in 55.22% (238/431). A total of 235 patients (54.52%) received only eldecalcitol throughout the observation period. The data on baseline characteristics have been updated since the interim report was published [8] because additional information was collected and some definitions were reviewed.

Safety profile

Adverse drug reactions were reported in 28 of the 431 patients in the safety analysis set (6.49%). The frequency of ADRs according to the length of treatment (period between the start of administration of eldecalcitol and the onset of ADR) is as follows: < 90 days, 10 patients; ≥ 90 days and < 180 days, 5 patients; ≥ 180 days and < 270 days, 2 patients; ≥ 270 days and < 360 days, 1 patient; ≥ 360 days and < 540 days, 3 patients; ≥ 540 days and < 720 days, 3 patients; ≥ 720 days and < 900 days, 1 patient; ≥ 900 days and < 1080 days, 2 patients; unknown, 1 patient.

The most common ADRs were hypercalcemia and renal impairment, each of which were reported in 5 patients (1.16%) (Table 2). In all 5 patients with hypercalcemia, the severity was not serious; 4 of the patients recovered, and the outcome was unknown for 1 patient. Of the patients whose blood calcium was measured both at baseline and during the follow-up period, 2.42% (4/165) had hypercalcemia.

Serious ADRs were reported in 5 patients (1.16%) (Table 3). Death was reported in 2 patients (0.46%). The reporting physician commented that there was no causal relationship between these deaths and eldecalcitol treatment; however, we decided not to rule out a possible relationship [8].

Table 1 Patient characteristics

Characteristic	Category	Mean ± SD or *n* (%)[a]
Age (years)		76.8 ± 9.0
Body height		161.03 ± 7.16 (*n* = 262)
Body weight		56.74 ± 10.02 (*n* = 262)
Prevalent vertebral fractures	0	194 (45.01)
	1	91 (21.11)
	≥ 2	45 (10.44)
	Unknown	101 (23.43)
Concomitant use of anti-osteoporosis drug	Yes	196 (45.47)
	Calcium	20 (4.64)
	Estrogen	1 (0.23)
	Parathyroid hormone	9 (2.08)
	Calcitonin	59 (13.68)
	Active vitamin D3	8 (1.85)
	Calcium/native vitamin D3/magnesium combination	1 (0.23)
	Vitamin K2	8 (1.85)
	Bisphosphonates	139 (32.25)
	Denosumab	1 (0.23)
	No	235 (54.52)
Concomitant use of oral corticosteroid	Yes	7 (1.62)
Complications	Yes	274 (63.57)
	Renal impairment	12 (2.78)
	Urinary lithiasis	2 (0.46)
	Hepatic impairment	8 (1.85)
eGFR (mL/min/1.73 m^2)	eGFR < 30	5 (1.16)
	30 ≤ eGFR < 45	10 (2.32)
	45 ≤ eGFR < 60	38 (8.81)
	60 ≤ eGFR < 90	110 (25.52)
	eGFR ≥ 90	30 (6.96)
	Unknown	238 (55.22)
Bone turnover markers	BAP (μg/L)	17.27 ± 8.37 (*n* = 71)
	Serum NTX (nmol BCE/L)	17.86 ± 8.57 (*n* = 83)
	Urinary NTX (nmol BCE/mmol Cr)	65.73 ± 211.87 (*n* = 66)
	TRACP-5b (mU/dL)	495.48 ± 216.42 (*n* = 44)

BAP bone-specific alkaline phosphatase, *BCE* bone collagen equivalent, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *NTX* collagen type 1 cross-linked N telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b

[a]Total *n* = 431 unless otherwise specified

Table 2 Adverse drug reactions (ADRs) reported in ≥ 2 patients

ADR (s)	No. of patients (%)[a]
All ADRs	28 (6.49)
Hypercalcemia	5 (1.16)
Renal impairment	5 (1.16)
Constipation	2 (0.46)
Death	2 (0.46)

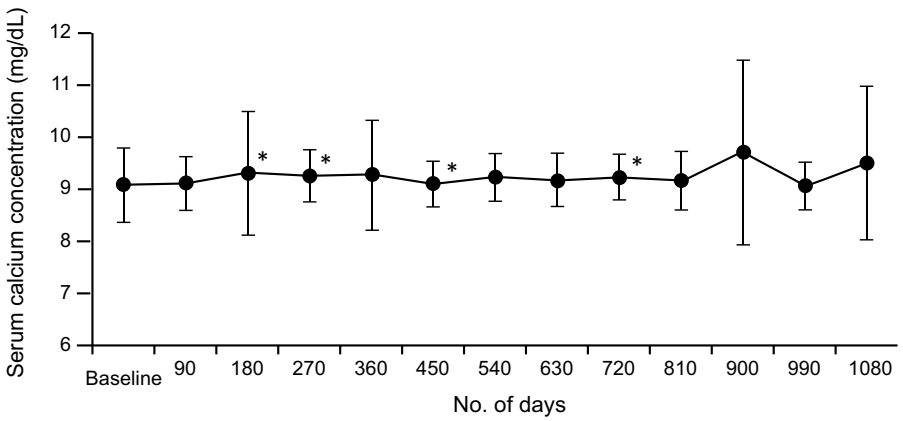
[a]Percentage of the 431 patients in the safety analysis set

Table 3 Serious and non-serious adverse drug reactions (ADRs)

ADR(s)	No. of patients (%)[a]	
	Serious	Not serious
All ADRs	5 (1.16)	24 (5.56)[b]
Death	2 (0.46)	0
Cardio-respiratory arrest	1 (0.23)	0
Nephrolithiasis	1 (0.23)	0
Renal impairment	1 (0.23)	4 (0.92)

[a]Percentage of the 431 patients in the safety analysis set

[b]One patient had both serious and non-serious ADRs



No. of patients	214	73	78	40	84	25	38	22	36	24	27	14	38
Mean ± SD	9.10 ± 0.72	9.13 ± 0.52	9.33 ± 1.19	9.28 ± 0.51	9.29 ± 1.06	9.12 ± 0.44	9.25 ± 0.46	9.20 ± 0.51	9.25 ± 0.44	9.19 ± 0.57	9.73 ± 1.78	9.08 ± 0.46	9.52 ± 1.48
P	–	0.680	0.006*	0.019*	0.102	0.042*	0.055	0.185	0.002*	0.133	0.134	0.170	0.097

Fig. 2 Changes in blood calcium concentration. Data represent mean ± SD. Differences between values at baseline and at each time point were assessed by *t* test. *$P < 0.05$

Table 4 Treatment adherence

Category	No. of patients (%)
Continued treatment throughout the observation period[a]	175 (40.60)[b]
Dosing period (days)	
< 91	67 (15.54)[b]
91 ≤, < 182	48 (11.13)[b]
182 ≤, < 273	21 (4.87)[b]
273 ≤, < 364	17 (3.94)[b]
364 ≤, < 728	82 (19.02)[b]
728 ≤, < 1092	46 (10.67)[b]
1092 ≤	150 (34.80)[b]
Discontinued treatment	256 (59.39)[b]
Failure to visit hospital	151 (58.98)[c]
Change of hospital	38 (14.84)[c]
Adverse event	31 (12.10)[c]
Other reason	36 (14.06)[c]

[a]Total dosing period (mean ± SD), 631.0 ± 450.3 days

[b]Percentage of the 431 patients in the safety analysis set

[c]Percentage of the 256 patients who discontinued treatment

In the 214 patients for whom baseline data for serum calcium concentration were available, serum calcium was significantly increased from baseline values at several time points; however, serum calcium remained within the normal range throughout the observation period (Fig. 2).

Data for treatment adherence are summarized in Table 4. The proportion of patients who continued eldecalcitol treatment throughout the 36-month observation period was 40.6% (175/431 patients); 59.3% (256/431 patients) discontinued treatment. The main reason for discontinuation was failure to visit the hospital (58.9%, 151/256 patients).

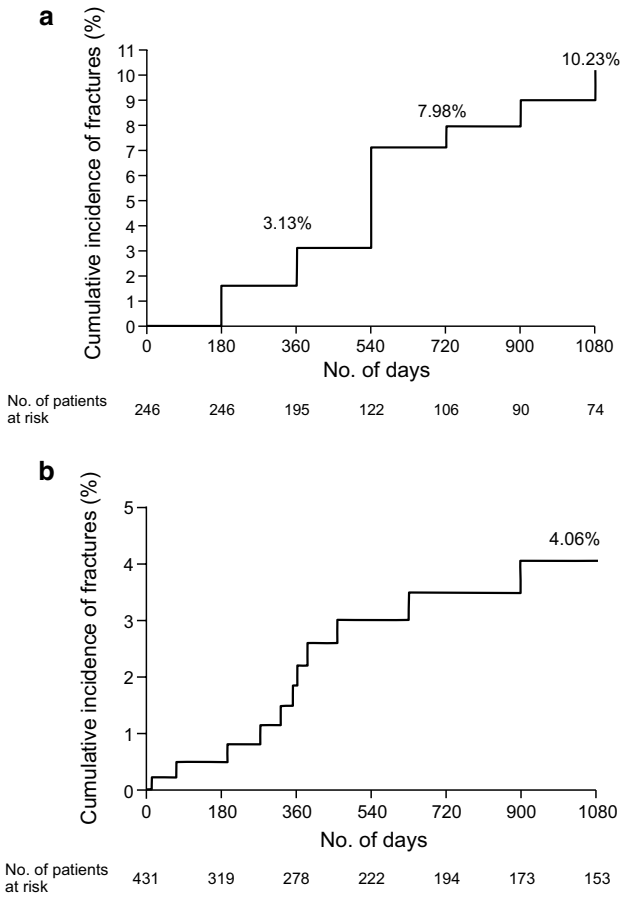
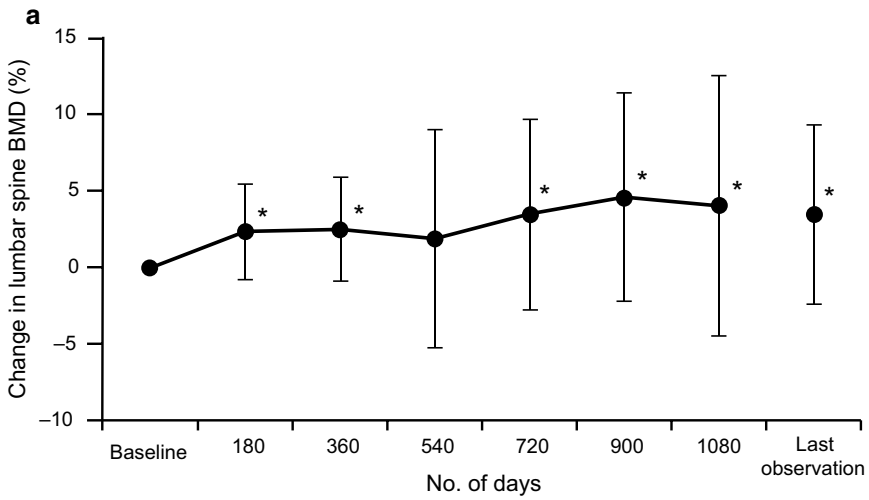
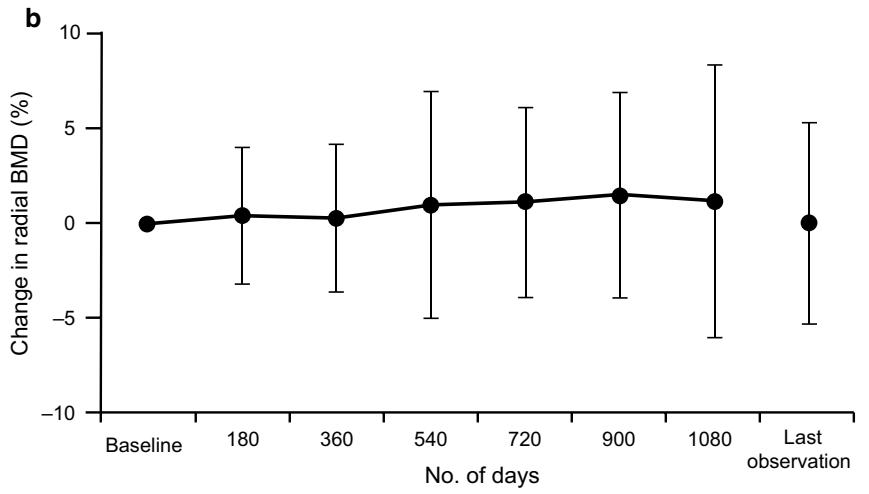


Fig. 3 Cumulative incidence of vertebral fractures (**a**) and nonvertebral fractures (**b**) at 36 months. Data represent Kaplan–Meier estimates



No. of patients	65	44	45	30	24	21	25	65
Mean ± SD	–	2.36 ± 3.09	2.51 ± 3.36	1.90 ± 7.07	3.47 ± 6.18	4.56 ± 6.76	4.04 ± 8.45	3.49 ± 5.81
P	–	< 0.0001*	< 0.0001*	0.151	0.011*	0.006*	0.025*	< 0.0001*



No. of patients	107	70	83	43	41	35	27	107
Mean ± SD	–	0.44 ± 3.58	0.31 ± 3.88	0.99 ± 5.93	1.13 ± 4.97	1.51 ± 5.40	1.20 ± 7.16	0.03 ± 5.28
P	–	0.304	0.466	0.278	0.153	0.106	0.390	0.939

Fig. 4 Percent changes from baseline in bone mineral density (BMD) at the lumbar spine (**a**) and the distal radius (**b**), as assessed by dual-energy X-ray absorptiometry. Data represent mean ± SD. Differences between values at baseline and at each time point were assessed by *t* test. *$P < 0.05$

In addition, 12.1% (31/256 patients) discontinued treatment because of AEs; of them, 4 patients had hypercalcemia.

Fracture incidence

Figure 3 shows the cumulative incidence of new fractures over the 36-month observation period. The incidence of vertebral fractures and nonvertebral fractures at 36 months, as estimated by Kaplan–Meier analysis, was 10.23 and 4.06%, respectively.

Bone mineral density

Figure 4 shows percent changes from baseline in lumbar spine and radial BMD over the 36-month observation period and at last observation. Between baseline and last observation, lumbar spine BMD increased by 3.49% ($P < 0.0001$) and radial BMD increased by 0.03%.

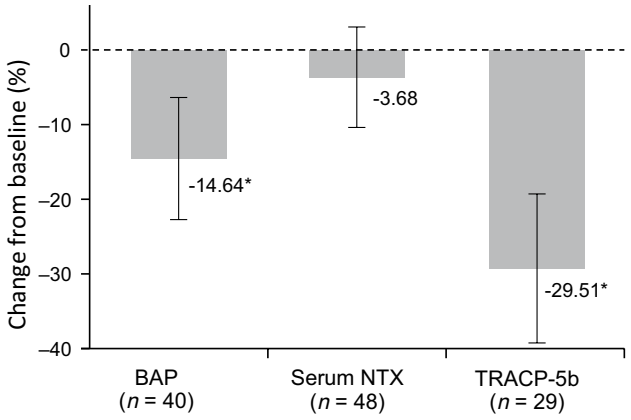


Fig. 5 Percent changes in levels of bone turnover markers from baseline to last observation. Data represent mean ± 95% CI. Differences between values at baseline and at last observation were assessed by *t* test. *$P < 0.05$. *BAP* bone-specific alkaline phosphatase, *serum NTX* serum collagen type 1 cross-linked N telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b

Bone turnover markers

At baseline, mean levels of each BTM were above the upper limit of the normal range. Between baseline and the last observation, levels of BAP, serum NTX, and TRACP-5b decreased (Fig. 5). The percent changes were − 14.64% for BAP ($P = 0.0009$), − 3.68% for serum NTX ($P = 0.28$), and −29.51% for TRACP-5b ($P < 0.0001$).

Discussion

Information on the safety and effectiveness of pharmaceutical treatments for osteoporosis in Japanese male patients is limited. The results of studies of alendronate [10, 11], risedronate [12, 13], ibandronate [14], zoledronic acid [15–17], denosumab [18, 19], and teriparatide [20, 21] have shown that these drugs have similar safety and efficacy in men compared with those in post-menopausal women with osteoporosis; however, these studies were conducted outside Japan. We previously reported the safety and effectiveness of up to 12 months of eldecalcitol treatment in both male and female Japanese patients with osteoporosis in the clinical setting [8]. In this article, we report the safety and effectiveness of eldecalcitol, as well as adherence to eldecalcitol treatment, in Japanese men with osteoporosis over a longer period (up to 36 months), also in the clinical setting.

Based on the results of the present study, no new safety concerns were found as compared with the safety information obtained up to the time of drug approval. The most commonly reported ADRs were hypercalcemia and renal impairment. Eldecalcitol increases intestinal calcium absorption, thereby increasing serum calcium concentration after administration.

Although the mechanism of renal impairment is unknown, in a phase III study, eGFR was reduced by both alfacalcidol and eldecalcitol treatment especially in patients with higher eGFR but it recovered after the end of treatment and neither treatment causes a sustained reduction in eGFR [22]. Thus, renal impairment may be a temporary change during eldecalcitol treatment.

In the 431 patients included in the safety analysis set, up to 36 months of treatment, the incidence of all ADRs was 6.49%, and the incidence of hypercalcemia was 1.16%; neither exceeds the equivalent incidences reported for clinical trials of eldecalcitol [23]. Mean serum calcium concentration showed transient increases at some time points; however, all values remained within the normal range, and no continuous increase in serum calcium accompanying an increase in the length of the dosing period was found.

There was no major increase in ADR incidence, and there were no new serious ADRs, compared with the 12-month results reported previously, in which the incidence of all ADRs and hypercalcemia in male patients was 5.10 and 0.46%, respectively [8]. Therefore, no new safety concerns arose when eldecalcitol was used by male patients in the clinical setting when treatment was extended for up to 3 years.

Eldecalcitol treatment was well tolerated. Of 256 patients who discontinued treatment, the major reasons for discontinuation were failure to attend follow-up (no hospital visit or change of hospital by patients, 189 patients). Out of the remaining 67 patients who discontinued treatment but attended follow-up, 31 patients discontinued because of AEs. AEs were reported as the reason for discontinuation in some patients who had pain as the primary complaint and discontinued hospital visits following improvement of the symptom. In addition, patients with osteoporosis often have few subjective or objective symptoms, so their adherence to treatment is considered to be poor [24]. Therefore, it was suggested that the safety and effectiveness of eldecalcitol had little negative influence on treatment adherence. The adherence to eldecalcitol treatment (40.6% at 36 months) was similar to that reported for other osteoporosis therapies [25].

Eldecalcitol treatment resulted in significantly increased BMD at the lumbar spine, consistent with the findings of clinical trials of eldecalcitol in Japanese patients with osteoporosis [5, 6]. This finding suggests that eldecalcitol treatment is effective in increasing BMD in the clinical setting, despite the concurrent use of bisphosphonates or selective estrogen receptor modulators by nearly half the patients in this study.

The cumulative incidence of vertebral fractures over the 36-month observation period (< 11% at 36 months) was

lower in the present analysis than in the phase III clinical trial of eldecalcitol [6]. This may be partly because fractures were diagnosed based on radiographic assessments carried out by individual investigators in the present study, whereas quantitative assessments were conducted by two or more radiologists in clinical trials. In addition, since the present study was conducted in the real-world clinical practice setting, some patients did not undergo regular clinical examination, whereas in the phase III study, regular clinical examinations were carried out for all patients. Furthermore, in the phase III trial, use of other anti-osteoporosis drugs, including bisphosphonates and selective estrogen receptor modulators, was not allowed, whereas in the present study, some patients received concomitant treatment with other anti-osteoporosis drugs.

The study design allowed assessment of the safety and effectiveness of eldecalcitol treatment in patients with osteoporosis who might not normally be eligible for participation in randomized clinical trials, for example, because of complications, concomitant use of other medications, and previous use of other osteoporosis treatments. Since complications such as rheumatoid arthritis [26, 27] and diabetes mellitus [28–30] are known risk factors for fracture, appropriate treatment strategies for such patients need to be explored [31]. The results of the present study showed that eldecalcitol was an effective osteoporosis treatment option in a population in which 63.57% of patients had ≥ 1 complication, including rheumatoid arthritis (2.78%) and diabetes mellitus (6.03%).

The present study has several limitations. First, there is the potential for bias and confounding that is inherent with an observational study design; the study involved a single cohort without a comparator or control arm. Second, in the present study, not all patients underwent radiography of the spine, so the possibility of subclinical vertebral fractures cannot be excluded. Third, BTM and BMD data were not available for every study time point. Finally, some patients received concomitant treatment with other anti-osteoporosis agents. For some, eldecalcitol was started at the same time as these agents, whereas for others it was added to treatment. Because the present study was not an interventional study, but done in a real-world clinical setting, we analyzed data from the entire analysis population.

In conclusion, this report provides clinicians with useful information on the use of eldecalcitol in male Japanese patients with osteoporosis. The safety profile of eldecalcitol reported here is similar to that described in reports of the results of clinical trials of eldecalcitol, and no new safety concerns were found as compared with the safety information obtained up to the time of drug approval. Eldecalcitol appears to be an effective treatment for osteoporosis in male Japanese osteoporosis patients in the clinical setting, as shown by the improvement in BMD, the suppression of BTM levels, and the low cumulative incidence of vertebral fractures. These results suggest that clinical trial findings regarding the safety profile and efficacy of eldecalcitol extend to real-world clinical practice in Japan. They provide further evidence that eldecalcitol can be used safely and effectively in Japanese patients with osteoporosis, provided that serum calcium concentration and eGFR are measured before and during treatment.

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Compliance with ethical standards

Conflict of interest All authors except YK are employees of Chugai Pharmaceutical Co., Ltd. YK is an employee of Taisho Toyama Pharmaceutical Co., Ltd.

References

1. Gullberg B, Johnell O, Kanis JA (1997) World-wide projections for hip fracture. Osteoporos Int 7:407–413
2. Editorial Committee on Guidelines for Prevention and Treatment of Osteoporosis (2015) Guidelines for prevention and treatment of osteoporosis. Japan Osteoporosis Society, Tokyo, Japan **(in Japanese)**
3. Orimo H, Yaegashi Y, Hosoi T, Fukushima Y, Onoda T, Hashimoto T, Sakata K (2016) Hip fracture incidence in Japan: estimates of new patients in 2012 and 25-year trends. Osteoporos Int 27:1777–1784
4. Xu Z, Fan C, Zhao X, Tao H (2016) Treatment of osteoporosis with eldecalcitol, a new vitamin D analog: a comprehensive review and meta-analysis of randomized clinical trials. Drug Des Devel Ther 10:509–517
5. Matsumoto T, Miki T, Hagino H, Sugimoto T, Okamoto S, Hirota T, Tanigawara Y, Hayashi Y, Fukunaga M, Shiraki M, Nakamura T (2005) A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 90:5031–5036
6. Matsumoto T, Ito M, Hayashi Y, Hirota T, Tanigawara Y, Sone T, Fukunaga M, Shiraki M, Nakamura T (2011) A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures—a randomized, active comparator, double-blind study. Bone 49:605–612
7. Sakai A, Ito M, Tomomitsu T, Tsurukami H, Ikeda S, Fukuda F, Mizunuma H, Inoue T, Saito H, Nakamura T, e-ADVANCED Study Group (2015) Efficacy of combined treatment with alendronate (ALN) and eldecalcitol, a new active vitamin D analog, compared to that of concomitant ALN, vitamin D plus calcium treatment in Japanese patients with primary osteoporosis. Osteoporos Int 26:1193–1202
8. Saito H, Kakihata H, Nishida Y, Yatomi S, Nihojima S, Kobayashi Y, Tabata H, Nomura M (2017) The safety and effectiveness

profile of eldecalcitol in a prospective, post-marketing observational study in Japanese patients with osteoporosis: interim report. J Bone Miner Metab 35:456–463
9. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H, Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
10. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A (2000) Alendronate for the treatment of osteoporosis in men. N Engl J Med 343:604–610
11. Ringe JD, Dorst A, Faber H, Ibach K (2004) Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int 24:110–113
12. Ringe JD, Farahmand P, Faber H, Dorst A (2009) Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int 29:311–315
13. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD (2009) Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res 24:719–725
14. Orwoll ES, Binkley NC, Lewiecki EM, Gruntmanis U, Fries MA, Dasic G (2010) Efficacy and safety of monthly ibandronate in men with low bone density. Bone 46:970–976
15. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S, HORIZON Recurrent Fracture Trial (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809
16. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J et al (2012) Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med 367:1714–1723
17. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, Bucci-Rechtweg C, Readie A, Mesenbrink P, Weinstein RS (2010) Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res 25:2239–2350
18. Orwoll E, Teglbjærg CS, Langdahl BL, Chapurlat R, Czerwinski E et al (2012) A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 97:3161–3169
19. Langdahl BL, Teglbjærg CS, Ho PR, Chapurlat R, Czerwinski E et al (2015) A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab 100:1335–1342
20. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA (2003) The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17
21. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, Lindsay R, Mitlak BH (2005) Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 16:510–516
22. Kondo S, Takano T, Ono Y, Saito H, Matsumoto T (2015) Eldecalcitol reduces osteoporotic fractures by unique mechanisms. J Steroid Biochem Mol Biol 148:232–238
23. Japanese package insert for Edirol® Capsule. 2016. Online. Available: https://chugai-pharm.jp/hc/ss/pr/drug/edr_cap0075/pi/PDF/edr_pi.pdf. Accessed May, 2017 **(in Japanese)**
24. Tomková S, Telepková D, Vanuga P, Killinger Z, Sulková I, Celec P, Payer J (2014) Therapeutic adherence to osteoporosis treatment. Int J Clin Pharmacol Ther 52:663–668
25. Weycker D, Macarios D, Edelsberg J, Oster G (2006) Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int 17:1645–1652
26. Kim SY, Schneeweiss S, Liu J, Daniel GW, Chang CL, Garneau K, Solomon DH (2010) Risk of osteoporotic fracture in a large population-based cohort of patients with rheumatoid arthritis. Arthritis Res Ther 12:R154
27. Weiss RJ, Wick MC, Ackermann PW, Montgomery SM (2010) Increased fracture risk in patients with rheumatic disorders and other inflammatory diseases: a case-control study with 53,108 patients with fracture. J Rheumatol 37:2247–2250
28. Fan Y, Wei F, Lang Y, Liu Y (2016) Diabetes mellitus and risk of hip fractures: a meta-analysis. Osteoporos Int 27:219–228
29. Janghorbani M, Van Dam RM, Willett WC, Hu FB (2007) Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 166:495–505
30. Vestergaard P (2007) Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a metaanalysis. Osteoporos Int 18:427–444
31. Gregson CL, Dennison EM, Compston JE, Adami S, Adachi JD et al (2014) Disease-specific perception of fracture risk and incident fracture rates: GLOW cohort study. Osteoporos Int 25:85–95