

Eldecalcitol is more effective for the prevention of osteoporotic fractures than alfacalcidol

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Abstract Eldecalcitol, a vitamin D₃ analogue, significantly reduces the risk of new vertebral fractures and increases bone mineral density (BMD) more than does alfacalcidol. To determine the effect of eldecalcitol on the incidence of all fragility fractures caused by osteoporosis, we conducted post hoc analyses of the phase III clinical trial to evaluate the incidence of the osteoporotic fractures defined in the World Health Organization (WHO) Technical Report, and, also, the incidence of the major osteoporotic fractures utilized in the WHO Fracture Risk Assessment Tool (FRAX), and compared those in the eldecalcitol group with those in the alfacalcidol group. We also analyzed the incidence of osteoporotic fractures stratified by prespecified risk factors for fractures. Eldecalcitol treatment reduced the incidence of osteoporotic fractures defined by the WHO more than alfacalcidol treatment (18.6 % vs. 25.2 %; hazard ratio, 0.70; 95 % CI, 0.54–0.93). Prevalent vertebral fractures, two or more

prevalent vertebral fractures, and total hip BMD *T* score less than -2.5 were the risk factors for new osteoporotic fractures with significant differences between the two treatments. Eldecalcitol also decreased the incidence of major osteoporotic fractures in the FRAX more than alfacalcidol (11.1 % vs. 16.3 %; hazard ratio, 0.66; 95 % CI, 0.46–0.94). In conclusion, treatment with eldecalcitol reduced the risk of fragility fractures caused by osteoporosis compared with alfacalcidol administration, which may result from a potent effect of eldecalcitol on BMD, bone structure, and bone turnover.

Keywords Eldecalcitol · Fracture · FRAX · Osteoporosis · Vitamin D

Introduction

Eldecalcitol is a new active vitamin D₃ analogue with a hydroxypropyloxy group introduced at the 2 β position of 1 α ,25-dihydroxyvitamin D₃. Alfacalcidol, 1 α -hydroxyvitamin D₃, is a prodrug of an active form of vitamin D₃. A randomized, double-blind, placebo-controlled, clinical study demonstrated that, compared to a placebo, 1-year treatment with eldecalcitol significantly increased lumbar spine and total hip bone mineral density (BMD) in a dose-dependent manner [1]. Further, in comparison to alfacalcidol treatment, eldecalcitol treatment significantly decreased the incidences of vertebral fractures (morphometric and clinical) and wrist fractures, with marked increases in lumbar spine BMD and total hip BMD, as assessed by a 3-year, randomized, double-blind, clinical trial [2]. On the basis of these results, eldecalcitol has been approved for the treatment of osteoporosis in Japan.

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A characteristic type of fracture frequently found in osteoporosis is the so-called fragility fracture. However, diagnosis of fragility fractures in patients with osteoporosis is often difficult in daily practice because of uncertainty in evaluating the degree of causative energy loaded onto the fracture site. Recently, the World Health Organization (WHO) Scientific Group [3, 4] introduced a new approach to characterizing fractures relevant to osteoporosis. These “osteoporotic fractures” are fractures whose risk of incidence is associated with low bone mass and whose incidences rise with age after the age of 50 years. Fractures pertinent to these criteria are those at the spine, distal forearm (wrist), humerus, ribs, clavicle/scapula/sternum, pelvis, tibia/fibula, hip, and other femoral fractures. Prevention of these osteoporotic fractures is of prime importance in patients with osteoporosis. We have already reported the reduction in the incidence of three major predefined nonvertebral fractures of the humerus, wrist, and hip [2]. However, we did not analyze the incidences of osteoporotic fractures including major fractures used in the WHO Fracture Risk Assessment Tool (FRAX).

In the present study, we analyzed the data derived from the phase III clinical trial of the efficacy of eldecalsitol versus alfacalcidol on fracture prevention in osteoporotic patients (Clinical Trials Gov Number NCT00144456) to determine the effect of eldecalsitol on the incidence of osteoporotic fractures in comparison to that of alfacalcidol. We also analyzed the effect of each agent on the risk of major osteoporotic fractures included in FRAX—i.e., clinical vertebral fracture and fractures of the hip, distal forearm, and humerus—without discriminating between traumatic and nontraumatic fractures. Then, we analyzed the incidences of osteoporotic fractures stratified by pre-specified risk factors for fractures at baseline.

Materials and methods

Details of the double-blind fracture prevention clinical study of eldecalsitol have been published previously [2]. Briefly, 1,054 patients with primary osteoporosis [5, 6] were divided into two groups: an eldecalsitol group ($n = 528$) and an alfacalcidol group ($n = 526$). They were given either oral eldecalsitol ($0.75 \mu\text{g}$) or oral alfacalcidol ($1.0 \mu\text{g}$) once a day for 3 years (36 months). Patients with serum 25-hydroxyvitamin D values lower than 20 ng/ml at the time of enrollment were given an oral vitamin D₃ supplement (400 IU) once a day without calcium supplementation. Patients with lumbar spine or total hip BMD T score below -1.7 were enrolled if they had one to five vertebral fractures. Patients without vertebral fractures were also enrolled if their lumbar spine or total hip BMD T score was below -2.6 and they were aged 70 years or

older, or if their T score was below -3.4 and they were aged less than 70 years. Patients with metabolic bone disease such as primary hyperparathyroidism, Cushing’s syndrome, premature menopause, poorly controlled diabetes mellitus ($\text{HbA1c} > 9\%$), or other causes of secondary osteoporosis or patients who had a history of urolithiasis were excluded from the study. Patients were also excluded if they had taken any oral bisphosphonates within 6 months before entry or for more than 2 weeks during the period 6–12 months before entry, or intravenous bisphosphonates at any time; had taken glucocorticoids, calcitonin, vitamin K₂, active vitamin D compounds, raloxifene, or hormone replacement therapy within 2 months; had serum calcium levels above 10.4 mg/dl or urinary calcium excretion greater than 0.4 mg/dl GF ; or had serum creatinine above 1.3 mg/dl .

The primary endpoint of the study was the incidence of nontraumatic new vertebral fractures, and the secondary endpoints were the percent change in lumbar spine BMD and total hip BMD, percent change of bone turnover markers, and incidence of nonvertebral fractures. The incidence of nontraumatic new vertebral fractures was evaluated by using lateral radiographs of the thoracic and lumbar spine obtained at baseline and at 6, 12, 24, and 36 months after initiation of drug administration. Incidences of nonvertebral fractures were assessed using radiographic examinations at the clinical site by investigators, and the data were reported at the time of incidence to the central facility and analyzed. In this study, we compared the two treatment groups with respect to the incidence of osteoporotic fractures as defined by the WHO Scientific Group [3, 4], their site-specific incidences, and the incidence of major osteoporotic fractures included in FRAX. We also analyzed the incidence of osteoporotic fractures based on prespecified risk factors for fractures at baseline: age, serum 25-hydroxyvitamin D value, number and degree of severity of prevalent vertebral fractures, lumbar spine BMD, and total hip BMD.

Statistical analysis

We performed the analysis for all subjects in the Full Analysis Set (eldecalsitol group, $n = 526$; alfacalcidol group, $n = 523$). First, the incidences of fractures at any of the nine osteoporotic fracture sites and their subgroup analyses were evaluated by Kaplan–Meier estimation. Then, the incidences of fractures at each respective site were assessed. The incidences of major osteoporotic fractures were also estimated by the Kaplan–Meier method. To compare the effects of eldecalsitol with those of alfacalcidol, we performed stratified log-rank tests (two-sided, 5 % significance level) and determined the hazard ratios and the 95 % confidence intervals of those incidences by

stratified Cox regression models, as described in the subgroup analyses of the previous report [2], with adjustment for the number of prevalent vertebral fractures at baseline (categories were no fracture, one fracture, or more than one fracture).

Results

There were no significant differences in the patients' background data with regard to age, percentage of male patients, body mass index, the prevalence of vertebral fractures, nonvertebral fractures, BMD, or metabolic bone markers (Table 1).

The incidence of all osteoporotic fractures for 3 years was 18.6 % in the eldecalsitol group and 25.2 % in the alfacalcidol group, according to the Kaplan–Meier estimate (Fig. 1a), and the risk of osteoporotic fracture in the eldecalsitol group was significantly lower than in the alfacalcidol group (hazard ratio, 0.70; 95 % CI, 0.54–0.93; $p = 0.013$). The incidence of nonvertebral osteoporotic fractures was 5.8 % in the eldecalsitol group and 9.7 % in the alfacalcidol group (Fig. 1b), indicating a significant

decrease in the risk in the eldecalsitol group relative to that in the alfacalcidol group (hazard ratio, 0.59; 95 % CI, 0.37–0.94, $p = 0.026$).

The incidence of the four major osteoporotic clinical fractures used in FRAX (clinical vertebral fractures, and fractures of the humerus, distal forearm, and hip) for 3 years was 11.1 % in the eldecalsitol group and 16.3 % in the alfacalcidol group. The risk of these fractures was significantly lower in the eldecalsitol group than in the alfacalcidol group (hazard ratio, 0.66; 95 % CI, 0.46–0.94; $p = 0.020$) (Fig. 2).

In the subgroup analyses of osteoporotic fractures, all the values of the point estimates for hazard ratio in the eldecalsitol group were less than 1.0 compared to the alfacalcidol group. The categories of subgroups that showed marked significant differences ($p < 0.01$) were presence of prevalent vertebral fractures (hazard ratio, 0.66; 95 % CI, 0.49–0.89; $p = 0.007$), two or more prevalent vertebral fractures (hazard ratio, 0.59; 95 % CI, 0.41–0.86; $p = 0.006$), and total hip BMD T-score of less than -2.5 (hazard ratio, 0.55; 95 % CI, 0.36–0.84; $p = 0.006$) (Fig. 3).

Site-specific numbers of osteoporotic fractures of the vertebrae, ribs, clavicle/scapula/sternum, tibia/fibula, and distal forearm that occurred during the 3-year trial were smaller in the eldecalsitol group than in the alfacalcidol group, but a statistically significant difference was observed only for vertebra and distal forearm (vertebra: hazard ratio, 0.72; 95 % CI, 0.52–0.99; distal forearm: hazard ratio, 0.28; 95 % CI, 0.11–0.69) (Table 2).

Discussion

This study clearly demonstrated that, compared with 1.0 µg daily alfacalcidol administration, daily administration of 0.75 µg eldecalsitol reduced the risk of osteoporotic fractures as defined by WHO and decreased the risk of major osteoporotic fractures included in FRAX. A significant decrease in the incidence of nonvertebral osteoporotic fractures was also observed in the eldecalsitol group.

In the subgroup analysis, eldecalsitol was found to be more effective at reducing the risk of osteoporotic fractures than alfacalcidol in patients with total hip BMD T score less than -2.5 . The hazard ratio for patients with two or more prevalent vertebral fractures was markedly smaller than the hazard ratios for patients with one or no prevalent vertebral fracture. Thus, eldecalsitol seems to be more effective than alfacalcidol in preventing osteoporotic fractures in patients with multiple prevalent vertebral fractures.

Table 1 Baseline characteristics of enrolled patients

	Eldecalsitol (<i>n</i> = 526)	Alfacalcidol (<i>n</i> = 523)
Age (years)	72.2 ± 6.59	72.1 ± 6.62
Male patients [<i>n</i> (%)]	9 (1.71)	15 (2.87)
Body mass index (kg/m ²)	22.3 ± 3.19	22.3 ± 3.20
Number of prevalent vertebral fractures	1.19 ± 1.28	1.25 ± 1.36
0 [<i>n</i> (%)]	198 (37.6)	193 (36.9)
1 [<i>n</i> (%)]	155 (29.5)	159 (30.4)
≥2 [<i>n</i> (%)]	173 (32.9)	171 (32.7)
Prevalent vertebral fracture		
Grade 0 [<i>n</i> (%)]	198 (37.6)	193 (36.9)
Grade 1 [<i>n</i> (%)]	110 (20.9)	118 (22.6)
Grade 2 [<i>n</i> (%)]	132 (25.1)	102 (19.5)
Grade 3 [<i>n</i> (%)]	86 (16.3)	110 (21.0)
History of nonvertebral fracture		
Absent [<i>n</i> (%)]	367 (69.8)	379 (72.5)
Present [<i>n</i> (%)]	159 (30.2)	144 (27.5)
Lumbar spine bone mineral density (BMD) T score	-2.70 ± 0.94	-2.72 ± 0.90
Total hip BMD T score	-2.26 ± 0.82	-2.27 ± 0.79
Bone alkaline phosphatase (BAP) (U/l)	33.4 ± 14.4	33.8 ± 12.5
Urinary NTx (nmol BCE/mmol Cr)	58.0 ± 58.7	57.0 ± 32.7

Data are mean ± SD. There were no significant differences in the patients' background data

Fig. 1 Kaplan–Meier estimates of the incidence of all osteoporotic fractures defined by the WHO Scientific Group (a), and the incidence of nonvertebral osteoporotic fractures in the eldecalcitol and alfacalcidol groups (b)

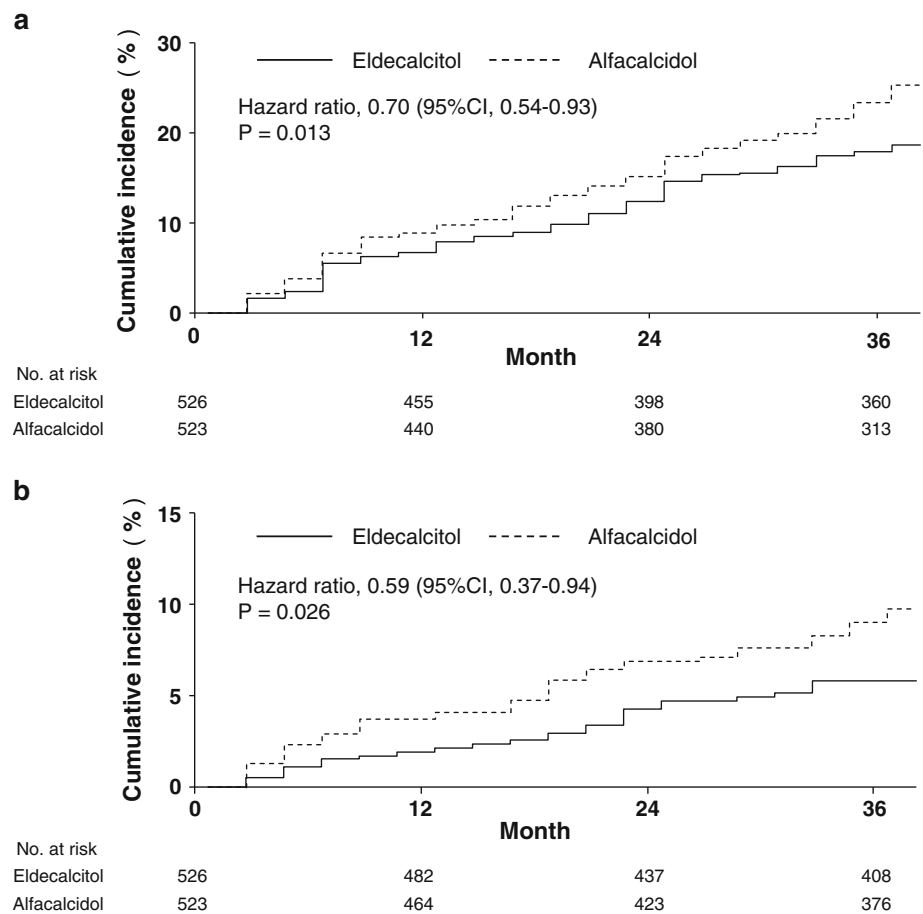
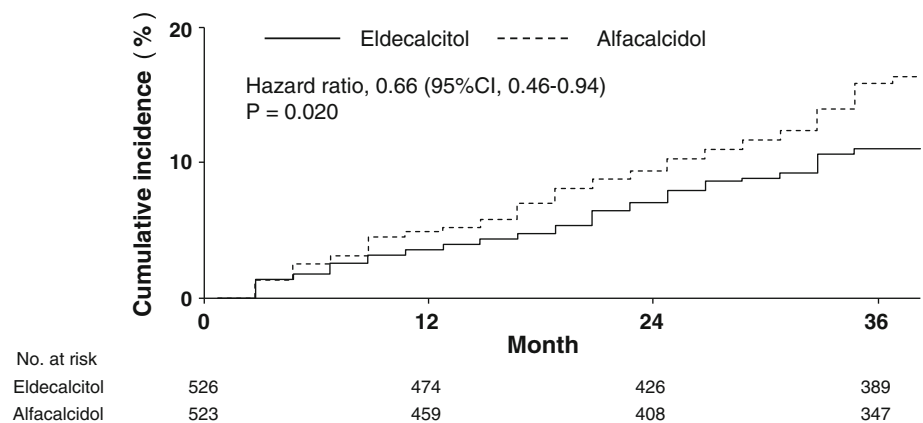


Fig. 2 Kaplan–Meier estimates of the incidence of major osteoporotic fractures included in the Fracture Risk Assessment Tool (FRAX) in the eldecalcitol and alfacalcidol groups



In the previous study, we demonstrated the efficacy of eldecalcitol in preventing morphometric vertebral fractures and nonvertebral fragility fractures at three major sites (humerus, wrist, and hip) [2]. In this study, we analyzed the incidences of all radiographically confirmed osteoporotic fractures of the vertebrae, ribs, pelvis, humerus, clavicle/scapula/sternum, hip, other femoral sites, tibia/fibula, and distal forearm. Then, we compared the incidences of the nonvertebral osteoporotic fractures. We also calculated the incidences of the four major osteoporotic fractures listed in

the FRAX [vertebrae (clinical fracture), hip, distal forearm, and humerus]. These data compatibly indicated the superior efficacy of eldecalcitol compared to that of alfacalcidol on the prevention of fractures in patients with osteoporosis. The superiority of eldecalcitol in preventing nonvertebral osteoporotic fractures appeared to be largely the result of reductions in the incidence of fractures of the ribs, clavicle/scapula/sternum, tibia/fibula, and distal forearm.

The effect of eldecalcitol on reducing the risk of osteoporotic fractures and nonvertebral osteoporotic fractures

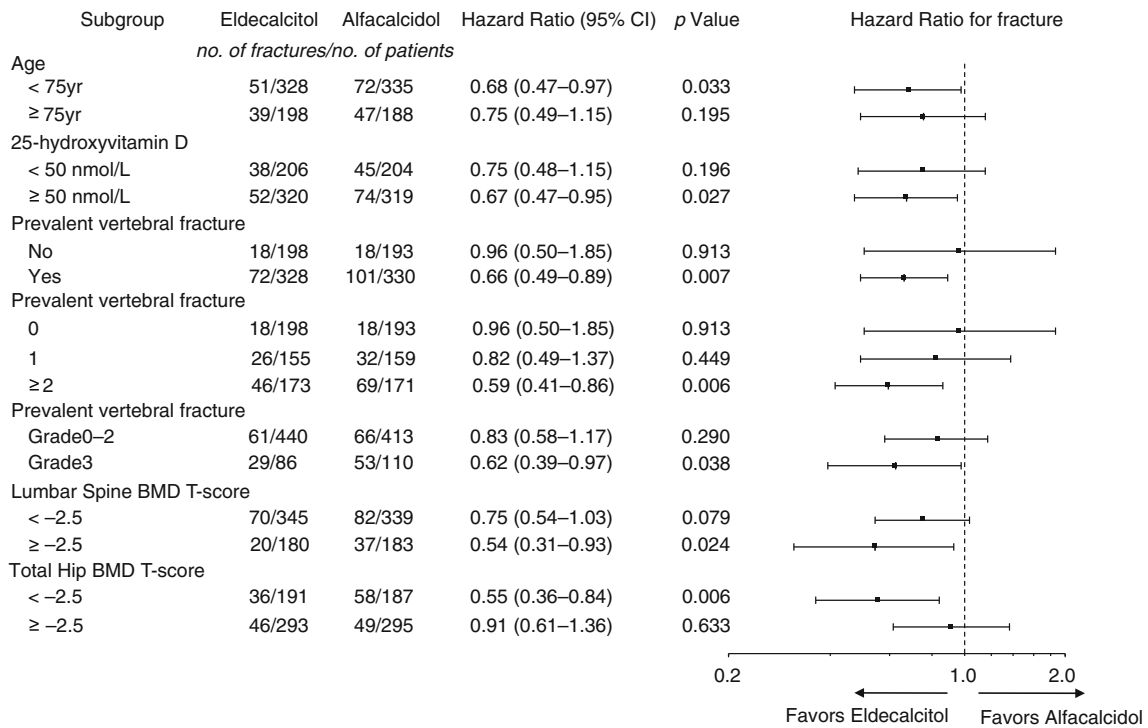


Fig. 3 Subgroup analyses of the effect of eldecalcitol in comparison with alfacalcidol on osteoporotic fractures

Table 2 Osteoporotic fractures defined by the WHO Scientific Group and their site-specific incidences

	Eldecalcitol (n = 526)	Alfacalcidol (n = 523)	Hazard ratio (95 % CI)
All osteoporotic fractures	90	119	0.70 (0.54–0.93)
Nonvertebral osteoporotic fractures	28	46	0.59 (0.37–0.94)
Osteoporotic fractures at specific sites			
Vertebra	64	83	0.72 (0.52–0.99)
Ribs	8	14	0.56 (0.23–1.33)
Pelvis	3	1	2.95 (0.31–28.34)
Humerus	2	1	1.92 (0.17–21.22)
Clavicle, scapula, sternum	1	3	0.33 (0.03–3.20)
Hip	7	5	1.41 (0.45–4.44)
Other femoral fracture	0	1	–
Tibia, fibula ^a	1	5	0.20 (0.02–1.69)
Distal forearm	6	21	0.28 (0.11–0.69)

^a Tibial and fibular fractures listed are those in women

seems to depend on the potent effect of eldecalcitol in increasing BMD and strengthening bone structure. Eldecalcitol was shown to increase lumbar BMD by 3.3 % and total hip BMD by 1.5 % in 1 year in comparison to placebo [1] and to increase lumbar BMD by 3.3 % and total hip BMD by 2.7 % in 3 years compared to alfacalcidol [2]. Subgroup analysis in this study confirmed the potent efficacy of eldecalcitol compared to alfacalcidol. With eldecalcitol treatment, urinary NTx, a bone resorption marker, was observed to decrease by 20 % in 3 months in comparison to baseline levels [1] and by 23 % in 3 years

compared to that when treated with alfacalcidol [2]. Also, femoral bone geometry assessment using clinical computed tomography (multidetector-row CT) scanning has shown that, compared with alfacalcidol, eldecalcitol more markedly increases the cross-sectional cortical bone area in patients with osteoporosis, maintains the thickness of cortical bone, and improves the bone biomechanical parameters of the femoral neck [7]. The volumetric BMD value at the femoral neck also significantly increased with eldecalcitol treatment compared to with alfacalcidol treatment. These data strongly suggest that eldecalcitol improves the

material strength of bone and also the cortical bone structure.

Preventing a chain reaction of fragility fractures in patients with osteoporosis is critically important in daily clinical practice. Meta-analysis studies suggest that a previous fracture history is associated with a significant (approximately doubled) increase in risk of any fracture compared with individuals without a prior fracture [8, 9]. Robinson et al. [10] reported that fractures of the hip, wrist, and proximal part of humerus were associated with a high risk of later re-fracture at any of the four sites they examined (hip, wrist, proximal part of the humerus, and ankle), and the relative risks were 5.76, 3.98, and 4.87, respectively. Center et al. [11] reported that absolute risk of subsequent fracture was increased in women across all age groups for most fracture types with clinical symptoms, including hip, vertebra, upper limb, ribs, and lower limb, and their relative risks were 2.79, 2.52, 1.69, 1.84, and 1.39, respectively. These data indicate that a prevalent fracture is a strong indicator of secondary fractures. This study confirmed the potent efficacy of eldecacitol in preventing subsequent osteoporotic fractures in patients with prevalent, especially multiply prevalent, vertebral fractures.

This study has several limitations. First, this was a post hoc analysis. Second, this study had no placebo group. Third, the study population was not large enough to reliably evaluate the subgroup analyses and analyses of site-specific osteoporotic fractures. Therefore, these analyses should be considered exploratory.

In conclusion, daily administration of 0.75 µg eldecacitol reduces the risk of osteoporotic fractures compared with 1.0 µg alfacalcidol administration in 3 years. Eldecacitol was also superior to alfacalcidol in reducing non-vertebral osteoporotic fractures, which could be the result of the potent effect that eldecacitol has on BMD, bone structure, and bone turnover.

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Conflict of interest T.N. has received consulting fees (Asahi Kasei Pharma, Astellas, Banyu, Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Ono, Takeda, Teijin Pharma) and belongs to the Japan

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