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ORIGINAL ARTICLE

# Efficacy and safety of once-monthly risedronate in osteoporosis subjects with mild-to-moderate chronic kidney disease: a post hoc subgroup analysis of a phase III trial in Japan

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## Abstract

Limited data are available on the safety and efficacy of anti-resorptive agents, particularly once-monthly bisphosphonates, for use in osteoporotic patients with chronic kidney disease (CKD). We conducted a post hoc analysis of data from a 12-month, randomized, double-blind, phase III study to evaluate the safety and efficacy of once-monthly risedronate (RIS-OM) 75 mg tablets in Japanese osteoporosis patients with mild-to-moderate CKD. Patients who received RIS-OM 75 mg were stratified by baseline estimated glomerular filtration rate (eGFR; ≥ 90, ≥ 60 to < 90, or ≥ 30 to < 60 mL/min/1.73 $m^2$). Safety endpoints were incidence of adverse events (AEs) and percent change from baseline in eGFR, serum creatinine, calcium, and phosphorus. Efficacy endpoints were percent change from baseline in lumbar spine bone mineral density (BMD) and bone turnover markers (BTMs). In 420 patients included (age 67.7 ± 6.7 years, women 98.8%), the incidence of all AEs, gastrointestinal disorders, acute phase reaction, non-vertebral fractures, and renal and urinary disorders was not significantly different among subgroups. Interaction between subgroups and time was significant for eGFR ($p = 0.010$) and serum creatinine ($p = 0.001$) but considered to be regression to the mean and clinically insignificant. BMD significantly increased while BTMs significantly decreased from baseline with a similar degree of change among the subgroups. In conclusion, RIS-OM 75 mg showed consistent safety and efficacy in suppressing bone turnover and increasing BMD in Japanese primary osteoporosis patients with mild-to-moderate CKD. These results should, however, be interpreted with caution because the number of patients with moderate CKD was limited.

**Keywords** Bisphosphonate · Chronic kidney disease · eGFR · Once-monthly risedronate · Renal safety

## Introduction

Globally, bisphosphonates are widely prescribed for the prevention and treatment of osteoporosis. Guidelines from the American College of Physicians [1], UK National Osteoporosis Guideline Group [2], Japan Osteoporosis Society

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[3], American Association of Clinical Endocrinologists and American College of Endocrinology [4] recommend bisphosphonates as pharmacological interventions for osteoporosis patients. However, one major problem with oral bisphosphonates is poor adherence attributable to their complex dosing procedures [5, 6]. Once-monthly bisphosphonates were, therefore, developed to improve persistence and adherence compared to once-weekly or once-daily formulations [7, 8]. In Japan, where both risedronate and alendronate are recommended for the first-line treatment of osteoporosis, risedronate is available in daily, once-weekly, and once-monthly oral formulations, while once-monthly alendronate is available only in intravenous formulation [9]. According to the prescription data from 13 university hospitals in Japan, once-monthly bisphosphonates were prescribed to about half [45.3% (2281/5039)] of the patients who newly started bisphosphonates between November 2011 and January 2013 [8].

Another problem associated with bisphosphonates is safety concerns, specifically nephrotoxicity. Since aging is associated with decreases both in bone strength and in glomerular filtration, chronic kidney disease (CKD) is a common comorbid condition with osteoporosis in the elderly. Further, CKD itself is associated with an increased risk of fracture [10, 11]. Although Japanese guidelines recommend bisphosphonates for the treatment of elderly osteoporotic patients with CKD [3, 12], bisphosphonates carry labeled warnings or a contraindication for use in patients with reduced renal function in view of the mechanism of excretion via the kidney and the lack of clinical data in patients with severe renal impairment [13]. In addition, data on intravenous pamidronate and zoledronate have suggested that renal adverse events (AEs) may be related to the maximum blood concentration and rapid (< 5 min) infusion rather than the area under the curve; dosage should thus be adjusted accordingly in patients with reduced renal function [14]. Bisphosphonates are also associated with acute phase reactions (APRs), usually characterized by influenza-like symptoms, which have a rapid onset [15]. The literature suggests that 42% of postmenopausal women with osteoporosis who received intravenous zoledronate had an APR after the first infusion compared with 12% of the placebo group [16]. Notably, several studies have reported that APRs are more common with once-monthly than once-daily bisphosphonates [17–19]. Other known safety concerns associated with bisphosphonates include gastrointestinal disorders, osteonecrosis of the jaw (ONJ), and atypical femoral fractures (AFF) [1–4].

Attempts have been made to assess the safety and efficacy of bisphosphonates in patients with CKD. A recent systematic review attempted to clarify the benefits and harm of osteoporosis medications, including bisphosphonates, in patients with CKD; however, their effects on bone mineral density (BMD), fracture risk, and safety were not clearly established [20]. Although the safety of once-daily (RIS-OD) and once-weekly risedronate (RIS-OW) and alendronate in patients with reduced renal function has been analyzed in several studies [21–23], the number of assessed cases remains limited. Furthermore, the safety of once-monthly bisphosphonates in patients with CKD has yet to be evaluated, despite the higher dosages used. It thus remains to be determined whether the safety profile of a once-monthly bisphosphonate formulation is comparable to that of a once-daily formulation. In addition, the difference in approved risedronate doses between Japan and other countries (once-daily, 2.5 mg vs. 5 mg; once-weekly, 17.5 mg vs. 35 mg; once-monthly, 75 mg vs. 150 mg), due to pharmacokinetic differences, is another factor that needs to be taken into consideration [24, 25]. Taken together, these findings highlight a lack of evidence regarding the safety and efficacy of once-monthly risedronate (RIS-OM) in CKD patients, especially for the Japanese-approved dose of 75 mg.

Results from a phase III study conducted in Japan reported that RIS-OM 75 mg had non-inferior efficacy in terms of BMD, and was similarly well tolerated, compared to RIS-OD 2.5 mg in Japanese patients with involutional osteoporosis [19]. The aim of this post hoc analysis was to assess the safety and efficacy of RIS-OM 75 mg utilizing data from the phase III study in Japanese patients with involutional osteoporosis who had mild-to-moderate CKD and were stratified by renal function.

## Materials and methods

### Brief explanation of the objective of the post hoc study and the study design, patient population and treatment of the phase III study utilized as data source for this analysis

This study is a post hoc analysis of patients with mild-to-moderate CKD from a 12-month, randomized, double-blind, multicenter, phase III study conducted at 60 study sites in Japan between February 2010 and August 2011 [19]. The post hoc analysis is using data from a phase III study which was conducted to compare the efficacy and tolerability of RIS-OM 75 mg with RIS-OD 2.5 mg in Japanese patients with involutional osteoporosis [19]. The design of the phase III study has been described previously [19]. In brief, the study consisted of a screening phase followed by a 12-month, double-blind treatment phase; each patient was required to visit the study site on day 15 after the first dose of study drug (day 1 being the first treatment day) and then monthly for a total of 12 months.

Japanese male and female patients, aged ≥ 50 years, with a diagnosis of primary osteoporosis, as per the guidelines

of the Japanese Society for Bone and Mineral Research [26] were included. In female patients, ≥ 2 years must have passed since menopause. Key exclusion criteria were secondary osteoporosis and any other diseases causing decreased bone mass or affecting lumbar spine BMD, bisphosphonate use within 24 weeks before the first study drug dose, and use of any drug affecting bone metabolism within 8 weeks before the first study drug dose [19]. With regard to renal function, patients with serum creatinine levels ≥ 2 mg/dL were regarded as having severe renal impairment, and therefore, excluded from the study.

Patients were randomized (1:1) to receive RIS-OM 75 mg or RIS-OD 2.5 mg. Matching placebo tablets were also administered to maintain the double-blind status. All patients received oral calcium lactate 1.54 g (containing 200 mg $Ca^{2+}$) once daily until the end of the study. Any concomitant drug that might affect bone metabolism, e.g., vitamin D, was prohibited during the study [19].

## Post hoc analysis

### Study population

All patients who received RIS-OM 75 mg ($n = 422$) in above described phase III study were assessed for eligibility in this post hoc analysis based on baseline renal function. As a result, 420 patients out of the 422 patients were included in the analysis and two patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 $m^2$ (CKD stage G4) were excluded, which resulted in 420 patients being considered for analysis. For the post hoc analysis, eGFRs were calculated based on serum creatinine levels at baseline obtained from the phase III study using the formula recommended by the Japanese Society of Nephrology [27]. Based on the eGFR, the CKD stage for each patient was determined in accordance with the criteria in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) [28] and the Japanese CKD guidelines [12] for CKD.

### Incidence of AEs and change in eGFR, serum creatinine, calcium, and phosphorus

In this post hoc analysis, the overall incidence of AEs, gastrointestinal disorders, APRs, non-vertebral fractures, renal and urinary disorders, ONJ, and AFF was assessed using the data of the phase III study [19]. AEs were defined as all undesirable or unintended medical events experienced during the study regardless of the causal relationship with the drug; among the AEs, those having a causal relationship with the study drug (determined by the investigator) were regarded as drug related. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. Gastrointestinal disorders were AEs classified as MedDRA system organ class "gastrointestinal disorders." AEs potentially associated with APR were defined as symptoms of influenza-like illness or pyrexia that started within the first 3 days after the first dose of study drug with duration of ≤ 7 days. Serum creatinine, calcium, and phosphorus were measured at baseline and months 0.5, 3, 6, 9, and 12. eGFR was calculated at baseline and months 0.5, 3, 6, 9, and 12.

### Effect of risedronate on lumbar spine BMD and bone turnover markers (BTMs)

In the present study, the effect of risedronate on lumbar spine BMD, bone resorption markers [urinary N-terminal telopeptide of type 1 collagen (NTX), C-terminal telopeptide of type 1 collagen (CTX), and serum tartrate-resistant acid phosphatase 5b (TRACP-5b)], and a bone formation marker (serum bone-specific alkaline phosphatase [BAP]) was evaluated using the data of the phase III study [19]. Lumbar spine BMD obtained in the phase III study were measured at baseline and months 6 and 12 by dual-energy X-ray absorptiometry using a quantitative digital radiography system (model: Hologic QDR-4500 or higher). Additionally, BTMs were measured at baseline and months 1, 3, 6, 9, and 12. NTX and CTX were corrected for urine creatinine level.

## Statistical analysis

Patients were divided into three subgroups by baseline eGFR [≥ 90 mL/min/1.73 $m^2$ (CKD stage G1: renal function, normal or high), ≥ 60 to < 90 mL/min/1.73 $m^2$ (G2: mildly decreased), and ≥30 to < 60 mL/min/1.73 $m^2$ (G3a + G3b: mildly to severely decreased)]. Patients with eGFR ≥ 45 to < 60 mL/min/1.73 $m^2$ [G3a (mildly to moderately decreased), $n = 38$] and ≥ 30 to < 45 mL/min/1.73 $m^2$ [G3b (moderately to severely decreased), $n = 3$] were integrated into one subgroup in consideration of the small number of G3b patients. Patients with eGFR < 30 mL/min/1.73 $m^2$ [G4 (severely decreased), $n = 2$] were excluded from the analysis in view of their small numbers.

Further, to assess baseline factors possibly affecting APR onset, another set ofsubgroups was developed to divide patients into those who experienced and did not experience APR.

Continuous variables were calculated as mean ± standard deviation, and categorical variables were calculated as number of subjects and percentage. Tests for significance among subgroups at baseline eGFR were conducted using one-way analysis of variance for numerical variables, Chi-square test for nominal variables, and the Fisher's exact test for the presence of diabetes mellitus, hypertension, or dyslipidemia. Differences among the subgroups in age, body mass index (BMI), years since menopause, serum creatinine,

**Table 1** Baseline patient demographics and clinical characteristics

| Variable | Overall ($n=420$) | eGFR (mL/min/1.73 $m^2$) | | | $p$ value |
|---|---|---|---|---|---|
| | | ≥ 90 ($n=69$) | ≥ 60 to < 90 ($n=310$) | ≥ 30 to < 60 ($n=41$) | |
| Age, years, mean (SD) | 67.7 (6.7) | 64.2 (6.7) | 67.9 (6.5) | 71.8 (5.7) | < 0.001[d] |
| Sex, female, *n* (%) | 415 (98.8) | 69 (100.0) | 305 (98.4) | 41 (100.0) | 0.408[e] |
| Height, cm, mean (SD) | 151.3 (5.4) | 151.5 (5.8) | 151.4 (5.3) | 150.4 (5.4) | 0.537[d] |
| Weight, kg, mean (SD) | 50.1 (7.3) | 48.6 (6.5) | 50.2 (7.3) | 51.3 (8.1) | 0.126[d] |
| BMI, kg/$m^2$, mean (SD) | 21.9 (3.1) | 21.2 (2.8) | 21.9 (3.1) | 22.7 (3.3) | 0.049[d] |
| Comorbidities associated with lifestyle disease, *n* (%) | | | | | |
| Diabetes mellitus | 15 (3.6) | 3 (4.3) | 11 (3.5) | 1 (2.4) | 0.904[f] |
| Hypertension | 137 (32.6) | 19 (27.5) | 97 (31.3) | 21 (51.2) | 0.028[f] |
| Dyslipidemia | 178 (42.4) | 28 (40.6) | 131 (42.3) | 19 (46.3) | 0.844[f] |
| Years since menopause, mean (SD)[a] | 17.4 (7.5) | 14.6 (7.5) | 17.3 (7.1) | 22.7 (7.2) | < 0.001[d] |
| Lumbar spine BMD[b], g/$cm^2$, mean (SD) | 0.64 (0.07) | 0.64 (0.06) | 0.64 (0.07) | 0.64 (0.07) | 0.843[d] |
| T score, mean (SD) | –3.12 (0.55) | –3.09 (0.51) | –3.13 (0.56) | –3.15 (0.56) | 0.843[d] |
| Number of prevalent fractures[c], *n* (%) | | | | | 0.462[e] |
| 0 | 317 (75.5) | 57 (82.6) | 231 (74.5) | 29 (70.7) | |
| 1 | 78 (18.6) | 10 (15.0) | 60 (19.4) | 8 (19.5) | |
| 2 | 20 (4.8) | 1 (1.4) | 15 (4.8) | 4 (9.8) | |
| ≥ 3 | 5 (1.2) | 1 (1.4) | 4 (1.3) | 0 (0.0) | |
| History of fragility fracture, *n* (%) | 130 (31.0) | 18 (26.1) | 97 (31.3) | 15 (36.6) | 0.499[e] |
| History of bisphosphonate use, *n* (%) | 33 (7.9) | 4 (5.8) | 26 (8.4) | 3 (7.3) | 0.763[e] |
| Serum Ca, mg/dL, mean (SD) | 9.33 (0.35) | 9.27 (0.34) | 9.33 (0.35) | 9.42 (0.32) | 0.068[d] |
| Serum P, mg/dL, mean (SD) | 3.67 (0.38) | 3.64 (0.35) | 3.67 (0.37) | 3.78 (0.44) | 0.160[d] |
| Serum Cre, mg/dL, mean (SD) | 0.61 (0.10) | 0.48 (0.03) | 0.61 (0.06) | 0.79 (0.09) | < 0.001[d] |
| Urinary Cre, mg/dL, mean (SD) | 68.6 (44.2) | 70.7 (55.7) | 67.7 (41.2) | 71.6 (45.1) | 0.793[d] |
| eGFR, mL/min/1.73 $m^2$, mean (SD) | 76.6 (14.0) | 98.7 (8.6) | 74.5 (8.4) | 54.8 (5.2) | < 0.001[d] |
| Serum 25-OH-D, ng/mL, mean (SD) | 20.6 (6.9) | 20.3 (6.5) | 20.6 (6.9) | 21.5 (7.2) | 0.640[d] |
| Serum BAP, U/L, mean (SD) | 26.4 (8.9) | 27.3 (7.4) | 26.4 (9.5) | 24.8 (6.7) | 0.345[d] |
| Serum TRACP-5b, mU/dL, mean (SD) | 457 (170) | 469 (183) | 458 (171) | 421 (138) | 0.338[d] |
| Urinary DPD/Cre, nmol/mmolCre, mean (SD) | 7.64 (2.65) | 7.98 (2.62) | 7.64 (2.73) | 7.14 (2.07) | 0.279[d] |
| Urinary NTX/Cre, nmolBCE/mmolCre, mean (SD) | 55.6 (22.8) | 63.0 (23.7) | 55.1 (22.3) | 47.0 (21.9) | 0.001[d] |
| Urinary CTX/Cre, μg/mmolCre, mean (SD) | 307 (142) | 343 (150) | 304 (137) | 270 (152) | 0.026[d] |

*25-OH-D* 25-hydroxyvitamin D, *ANOVA* analysis of variance, *BAP* bone alkaline phosphatase, *BMD* bone mineral density, *BMI* body mass index, *Ca* calcium, *Cre* creatinine, *CTX* C-terminal telopeptide of type 1 collagen, *DPD* deoxypyridinoline, *eGFR* estimated glomerular filtration rate, *NTX* N-terminal telopeptide of type 1 collagen, *P* phosphorus, *SD* standard deviation, *TRACP-5b* tartrate-resistant acid phosphatase 5b

[a]Overall, $n=351$; eGFR ≥ 90 mL/min/1.73 $m^2$, $n=59$; eGFR ≥ 60 to < 90 mL/min/1.73 $m^2$, $n=257$; eGFR ≥ 30 to < 60 mL/min/1.73 $m^2$, $n=35$

[b]L2–L4

[c]Th4–L4

[d]One-way ANOVA

[e]Chi-square test

[f]Fisher's exact test

calcium, eGFR, urinary NTX, and CTX were also analyzed by the trend test. Incidence of AEs was compared among subgroups using the Fisher's and Cochran–Armitage tests. Differences between subgroups of patients with or without APR were analyzed using a two-sample *t* test for numerical variables, a Chi-square test for nominal variables, and the Fisher's exact test for the presence of diabetes mellitus, hypertension, or dyslipidemia. Interaction between subgroup and time was analyzed using a linear mixed effect model for eGFR, serum creatinine, calcium, phosphorus, BMD, and BTMs. The individuals were included as a random effect, and CKD stages, time, and interaction between CKD stages and time were included as fixed effects in this model. The degrees of freedom to calculate *F*-statistics were estimated

**Table 2** Summary of adverse events

| Number of patients with events, *n* (%) | Overall (*n* = 420) | eGFR (mL/min/1.73 $m^2$) | | | *p* value | |
|---|---|---|---|---|---|---|
| | | ≥ 90 (*n* = 69) | ≥ 60 to < 90 (*n* = 310) | ≥ 30 to < 60 (*n* = 41) | Fisher's test | Cochran–Armitage test |
| All AEs | 363 (86.4) | 63 (91.3) | 265 (85.5) | 35 (85.4) | 0.439 | 0.286 |
| Gastrointestinal disorders | 160 (38.1) | 32 (46.4) | 111 (35.8) | 17 (41.5) | 0.233 | 0.391 |
| Diarrhoea | 35 (8.3) | 5 (7.2) | 26 (8.4) | 4 (9.8) | NT | NT |
| Abdominal discomfort | 28 (6.7) | 3 (4.3) | 22 (7.1) | 3 (7.3) | NT | NT |
| Constipation | 18 (4.3) | 7 (10.1) | 10 (3.2) | 1 (2.4) | NT | NT |
| Abdominal pain upper | 17 (4.0) | 1 (1.4) | 13 (4.2) | 3 (7.3) | NT | NT |
| Gastritis | 14 (3.3) | 4 (5.8) | 9 (2.9) | 1 (2.4) | NT | NT |
| Dental caries | 13 (3.1) | 3 (4.3) | 8 (2.6) | 2 (4.9) | NT | NT |
| Acute phase reaction[a] | 24 (5.7) | 3 (4.3) | 18 (5.8) | 3 (7.3) | 0.780 | 0.507 |
| Non-vertebral fractures[b] | 9 (2.1) | 2 (2.9) | 7 (2.3) | 0 (0.0) | 0.473 | 0.141 |
| Renal and urinary disorders[c] | 9 (2.1) | 2 (2.9) | 5 (1.6) | 2 (4.9) | 0.191 | 0.690 |
| Osteonecrosis of the jaw | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NT | NT |
| Atypical femoral fractures | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NT | NT |

AEs with ≥3% incidence are listed for gastrointestinal disorders

*AEs* adverse events, *eGFR* estimated glomerular filtration rate, *NT* not tested

[a]Sum of pyrexia, back pain, headache, malaise, vomiting, nausea, arthralgia, asthenia, influenza-like illness, myalgia, and pain in extremity that started within the first 3 days after the first dose of study drug with a duration of ≤ 7 days

[b]Sum of fractures in the rib, ankle, foot, hand, humerus, patella, radius, and wrist

[c]Sum of hypertonic bladder, pollakiuria, renal impairment, chromaturia, haematuria, and stress urinary incontinence

using the Satterthwaite method [29]. The change from baseline in BMD, BTMs, eGFR, serum creatinine, calcium, and phosphorus was expressed as a percentage, and a one-sample *t* test was conducted to test its significance. Missing values were not imputed in any of the analyzes. Statistical significance was evaluated at a significance level of 0.05. SAS version 9.3 (Cary, NC, USA) was used for analysis.

## Results

### Baseline demographics and characteristics

Of the 422 patients who received RIS-OM 75 mg in the phase III study, 420 patients with CKD stage 1–3 were included in this post hoc analysis. Two patients with eGFR < 30 mL/min/1.73 $m^2$ (CKD stage G4) were excluded. Of the 420 patients included the majority of the patients [310 (73.8%)] were in CKD stage G2 (eGFR ≥ 60 to < 90 mL/min/1.73 $m^2$), followed by G1 [≥ 90 mL/min/1.73 $m^2$, 69 (16.4%)] and G3a or G3b [≥ 30 to < 60 mL/min/1.73 $m^2$, 41 (9.8%)]. Age ($p < 0.001$), BMI ($p = 0.049$), years since menopause ($p < 0.001$), and serum creatinine ($p < 0.001$) significantly increased with advanced CKD stage, whereas urinary NTX ($p = 0.001$) and urinary CTX ($p = 0.026$) significantly decreased with advanced CKD stage. The trend test also showed significant differences (age, $p < 0.001$; BMI, $p = 0.014$; years since menopause, $p < 0.001$; serum creatinine, $p < 0.001$; serum calcium, $p = 0.022$; eGFR, $p < 0.001$; urinary NTX, $p < 0.001$; urinary CTX, $p = 0.007$) among subgroups according to the CKD stage. Other baseline patient demographic and clinical characteristics were comparable among the three subgroups (Table 1).

### AEs

Overall, no significant differences were observed in the incidence of all AEs (85.4–91.3%), gastrointestinal disorders (35.8–46.4%), APRs (4.3–7.3%), non-vertebral fractures (0–2.9%), and renal and urinary disorders (1.6–4.9%) among the three subgroups. No patients reported ONJ or AFF (Table 2). Likewise, no significant differences were reported in the incidence of drug-related AEs among the subgroups (data not shown).

Approximately, 6% (24/420) of the patients experienced APRs. Patients who experienced an APR tended to have lower baseline serum phosphorus levels than those who did not (3.54 ± 0.25 mg/dL vs. 3.68 ± 0.38 mg/dL, $p = 0.015$). However, the clinical relevance of this observation is not known. No significant differences were observed in other baseline factors, including age, serum 25-hydroxyvitamin D (25-OH-D), and prior bisphosphonate use (Table 3).

**Table 3** Background factors possibly affecting the onset of acute phase reaction

| Variable | Acute phase reaction | | *p* value |
|---|---|---|---|
| | Yes (*n* = 24) | No (*n* = 396) | |
| Age, years, mean (SD) | 66.6 (5.7) | 67.8 (6.8) | 0.401[d] |
| Sex, female, *n* (%) | 24 (100.0) | 391 (98.7) | 0.580[e] |
| Height, cm, mean (SD) | 153.2 (4.1) | 151.2 (5.4) | 0.081[d] |
| Weight, kg, mean (SD) | 49.7 (7.5) | 50.1 (7.3) | 0.778[d] |
| BMI, kg/m$^2$, mean (SD) | 21.2 (3.4) | 21.9 (3.1) | 0.271[d] |
| Comorbidities associated with lifestyle disease, *n* (%) | | | |
| Diabetes mellitus | 0 (0.0) | 15 (3.8) | 1.000[f] |
| Hypertension | 5 (20.8) | 132 (33.3) | 0.264[f] |
| Dyslipidemia | 9 (37.5) | 169 (42.7) | 0.676[f] |
| Years since menopause, mean (SD)[a] | 15.0 (6.0) | 17.5 (7.5) | 0.152[d] |
| Lumbar spine BMD[b], g/cm$^2$, mean (SD) | 0.62 (0.08) | 0.64 (0.06) | 0.075[d] |
| T score, mean (SD) | − 3.32 (0.68) | − 3.11(0.54) | 0.075[d] |
| Number of prevalent fractures[c], *n* (%) | | | 0.793[e] |
| 0 | 18 (75.0) | 299 (75.5) | |
| 1 | 4 (16.7) | 74 (18.7) | |
| 2 | 2 (8.3) | 18 (4.6) | |
| ≥ 3 | 0 (0.0) | 5 (1.3) | |
| History of fragility fracture, *n* (%) | 7 (29.2) | 123 (31.1) | 0.846[e] |
| History of bisphosphonate use, *n* (%) | 0 (0.0) | 33 (8.3) | 0.141[e] |
| Serum Ca, mg/dL, mean (SD) | 9.40 (0.25) | 9.32 (0.35) | 0.328[d] |
| Serum P, mg/dL, mean (SD) | 3.54 (0.25) | 3.68 (0.38) | 0.015[d] |
| Serum Cre, mg/dL, mean (SD) | 0.61 (0.10) | 0.61 (0.10) | 0.900[d] |
| eGFR, mL/min/1.73 m$^2$, mean (SD) | 76.7 (17.7) | 76.6 (13.8) | 0.961[d] |
| ≥ 90, *n* (%) | 3 (12.5) | 66 (16.7) | 0.803[e] |
| ≥ 60 to < 90, *n* (%) | 18 (75.0) | 292 (73.7) | |
| ≥ 30 to < 60, *n* (%) | 3 (12.5) | 38 (9.6) | |
| Serum 25-OH-D, ng/mL, mean (SD) | 20.1 (6.6) | 20.6 (6.9) | 0.695[d] |
| Serum BAP, U/L, mean (SD) | 25.3 (5.3) | 26.5 (9.1) | 0.332[d] |
| Serum TRACP-5b, mU/dL, mean (SD) | 425 (132) | 459 (172) | 0.354[d] |
| Urinary DPD/Cre, nmol/mmolCre, mean (SD) | 7.01 (2.49) | 7.68 (2.66) | 0.231[d] |
| Urinary NTX/Cre, nmolBCE/mmolCre, mean (SD) | 49.4 (21.4) | 56.0 (22.8) | 0.169[d] |
| Urinary CTX/Cre, μg/mmolCre, mean (SD) | 276 (121) | 309 (143) | 0.262[d] |

*25-OH-D* 25-hydroxyvitamin D, *BAP* bone alkaline phosphatase, *BMD* bone mineral density, *BMI* body mass index, *Ca* calcium, *Cre* creatinine, *CTX* C-terminal telopeptide of type 1 collagen, *DPD* deoxypyridinoline, *eGFR* estimated glomerular filtration rate, *NTX* N-terminal telopeptide of type 1 collagen, *P* phosphorus, *SD* standard deviation, *TRACP-5b* tartrate-resistant acid phosphatase 5b

[a]Yes, *n* = 19, No, *n* = 332

[b]L2–L4

[c]Th4–L4

[d]Two-sample *t* test

[e]Chi-square test

[f]Fisher's exact test

## Change from baseline in eGFR, serum creatinine, calcium, and phosphorus

In the overall population, serum calcium and phosphorus significantly decreased from baseline at month 0.5, with this trend continuing until month 12. There was a significant decrease in eGFR and increase in creatinine from baseline at months 3 and 12, but the changes were not significant at months 0.5, 6, and 9 (Electronic supplementary file 1). The interaction between the subgroups and time was significant for eGFR ($p = 0.010$) and serum creatinine ($p = 0.001$), but not with serum calcium ($p = 0.585$) and phosphorus

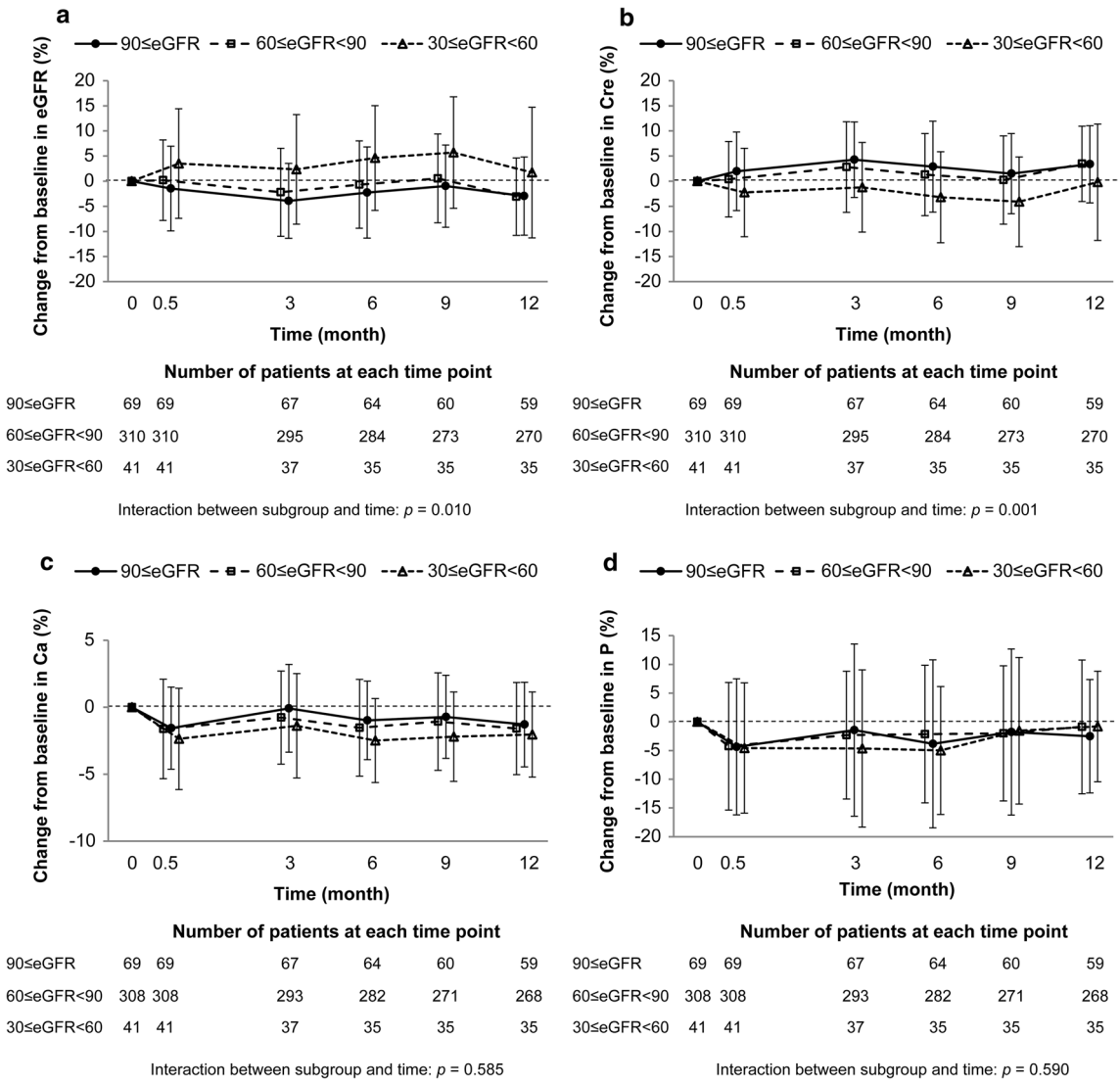


**Fig. 1** Percent change from baseline in **a** eGFR, **b** serum creatinine, **c** serum calcium, **d** serum phosphorus in three eGFR subgroups (mean ± SD). *Ca* calcium, *Cre* creatinine, *eGFR* estimated glomerular filtration rate, *P* phosphorus, *SD*standard deviation

($p = 0.590$), indicating that changes in eGFR and serum creatinine over time differed among the subgroups (Fig. 1). The mean eGFR and serum creatinine increased from baseline in CKD stage G3 patients (i.e., with lower baseline eGFR), while they declined in stage G1 patients (i.e., with higher baseline eGFR).

## Change from baseline in lumbar spine BMD

Lumbar spine BMD significantly increased from baseline in all three subgroups at months 6 and 12. No significant interaction was observed between the three subgroups and time ($p = 0.078$; Fig. 2). Although urinary NTX and CTX at baseline were significantly lower in patients with advanced CKD stage (Table 1), percent change in lumbar spine BMD was similar among the three subgroups, indicating that treatment response was comparable irrespective of CKD stage (Fig. 2).

## Change from baseline in BTMs

All four BTMs significantly decreased from baseline in all three subgroups at months 1–12, with similar changes among the subgroups. No significant interaction was observed between the three subgroups and time (urinary NTX, $p = 0.851$; urinary CTX, $p = 0.901$; serum TRACP-5b, $p = 0.840$; serum BAP, $p = 0.998$; Fig. 3). As with lumbar spine BMD, percent change in BTMs was similar among the subgroups, indicating that treatment response was comparable irrespective of CKD stage (Table 1, Fig. 3).

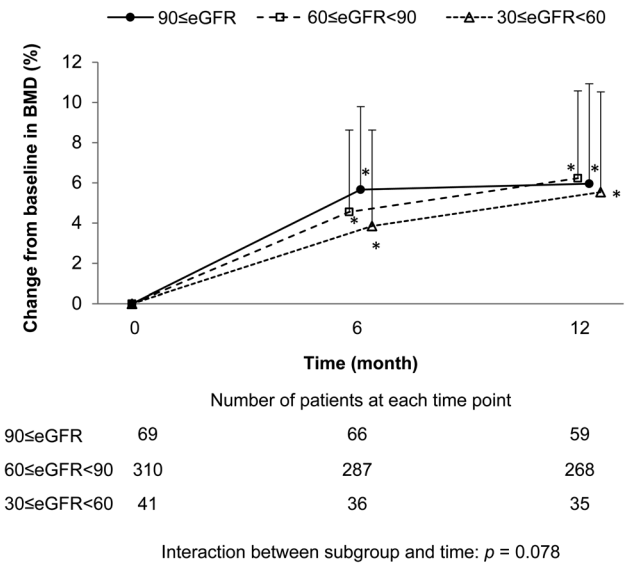


**Fig. 2** Percent change from baseline in lumbar spine bone mineral density in three eGFR subgroups (mean ± SD). *Significantly ($p < 0.05$) different from baseline. *BMD* bone mineral density, *eGFR* estimated glomerular filtration rate, *SD* standard deviation

## Discussion

The use of oral once-monthly bisphosphonates in patients with CKD is of general concern since they may elicit severe nephrotoxicity in patients with reduced renal function compared with once-daily formulations due to the higher dosages used. However, limited data are available on the safety of once-monthly bisphosphonates in patients with CKD. To our knowledge, this is the first analysis to assess the safety and efficacy of RIS-OM 75 mg in osteoporotic patients stratified by eGFR. The analysis population included osteoporotic patients with mildly decreased (CKD stage G2, 74%) and mildly–moderately (G3a) or moderately–severely (G3b) decreased kidney function (10%), which enabled us to compare them with patients having normal or high kidney function (G1, 16%).

Overall, no significant differences were observed in the incidence of both AEs and drug-related AEs among the three eGFR subgroups, suggesting that RIS-OM 75 mg is generally well tolerated in osteoporotic patients with CKD stage G3. Results from clinical studies suggest that APRs are more common with once-monthly bisphosphonates than once-daily formulations due to their higher dosage: in the MOBILE study, the proportion of patients reporting influenza-like symptoms within 3 days of monthly oral ibandronate (6.6%–8.3%) was slightly higher compared with the daily regimen (2.8%) [17]. In a randomized, double-blind, multicenter study with risedronate, APR incidence was slightly higher in postmenopausal osteoporosis patients receiving RIS-OM 150 mg (1.4%) than those receiving RIS-OD 5 mg (0.2%) [18]. In the original phase III study with Japanese osteoporosis patients, AEs potentially associated with APR (symptoms of influenza-like illness or pyrexia with a starting date within the first 3 days after the first dose of study drug and a duration of ≤ 7 days) occurred in the RIS-OM 75 mg group (2.1%, 9/422 patients) but not in the RIS-OD 2.5 mg group (428 patients) [19]. Since the pharmacokinetics of risedronate is affected by renal function on account of the drug being excreted primarily via the kidney [13, 30], caution is advised when administering risedronate in patients with renal dysfunction. However, the results of our study indicated that there was no statistically significant difference in the incidence of APR among the subgroups receiving RIS-OM 75 mg, although the incidence in those with CKD stage G3a or G3b was marginally higher than the incidence in those with CKD stage G1 or G2 (7.3% vs. 4.3–5.8%). Comparison of RIS-OM and RIS-OD could not be made due to the lack of APR incidence data with either RIS-OD 2.5 mg or RIS-OW 17.5 mg in the study by Shigematsu et al. [23].

A number of known risk factors for APR following bisphosphonate administration have been established, including advanced age, vitamin D insufficiency, and no prior history of bisphosphonate use [16, 31]. However, our results did not show any significant difference in APR incidence with age or serum 25-OH-D. As for prior history of bisphosphonate use, none of the 33 patients with prior bisphosphonate use developed APR, which is expected and consistent with previous findings [16]. It should, however, be noted that the difference between patients with and without APR was not statistically significant in our analysis ($p = 0.141$; Table 3). Interestingly, serum phosphorus levels were found to be marginally but significantly lower in patients who developed APR. To our knowledge, this relationship has not been previously discussed in the literature, and further investigation is, therefore, warranted.

The interaction between the subgroups and time was significant for eGFR and serum creatinine. Additionally, there was a significant decrease in eGFR and increase in creatinine from baseline in the overall group. However, we suggest that these findings were attributable to the regression to the mean effect (a statistical phenomenon where natural variation in repeated data appears to be a real change) [32] and are not, therefore, clinically meaningful, as with previous findings [23]. Of note, eGFR was not decreased from baseline in CKD stage G3 patients in this subgroup analysis (Fig. 1a); similarly, no decrease in eGFR was observed in Japanese osteoporosis patients with CKD stage G3 who received RIS-OD 2.5 mg or RIS-OW 17.5 mg [23].

Serum calcium and phosphorus significantly decreased from baseline at month 0.5, with this trend continuing until month 12. These changes were attributed to the therapeutic effect of risedronate (changes in calcium homeostasis caused

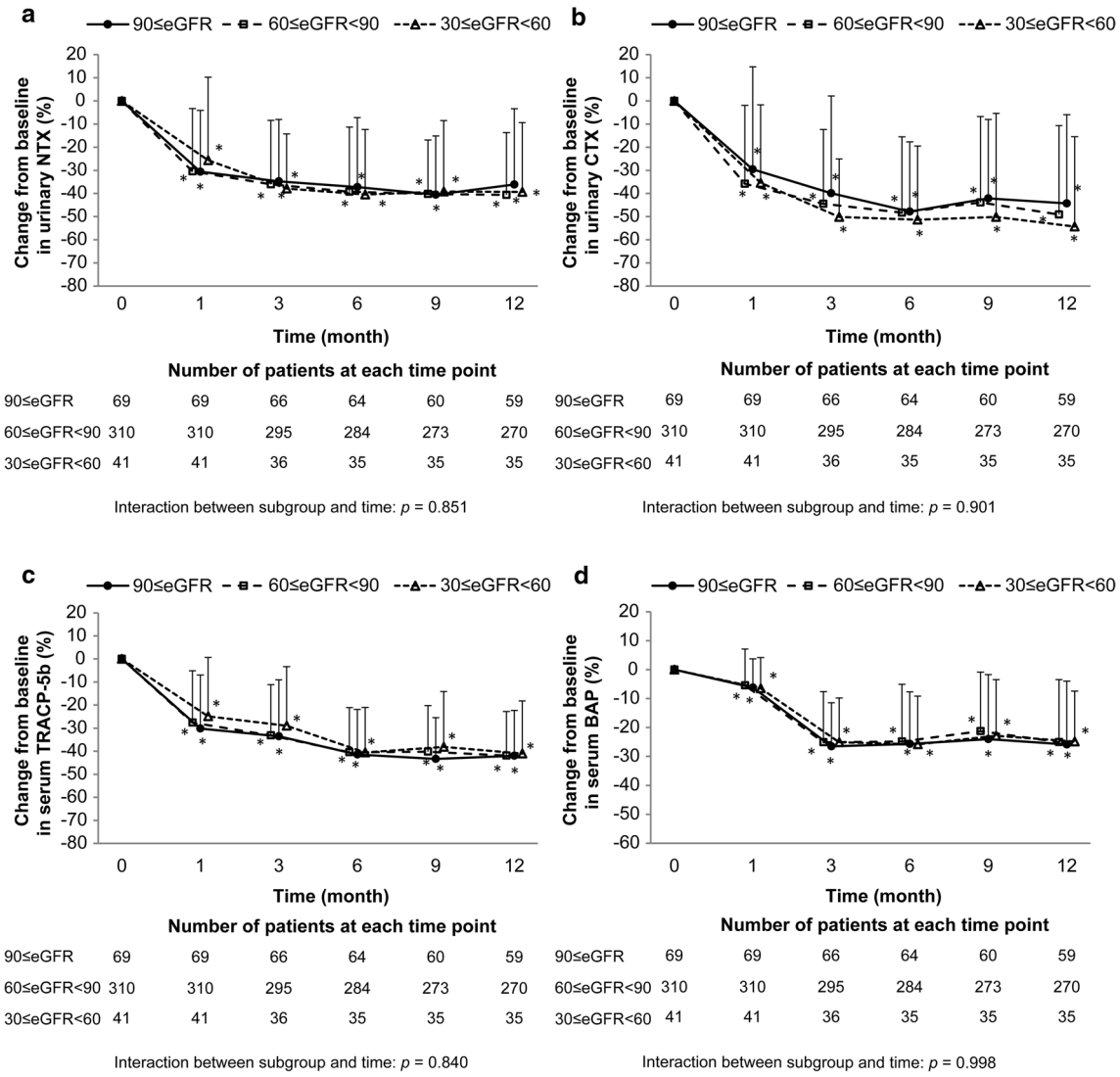


**Fig. 3** Percent change from baseline in **a** urinary NTX, **b** urinary CTX, **c** serum TRACP-5b, **d** serum BAP in three eGFR subgroups (mean ± SD). *Significantly ($p < 0.05$) different from baseline. *BAP* bone alkaline phosphatase, *CTX* C-terminal telopeptide of type 1 collagen, *eGFR* estimated glomerular filtration rate, *NTX* N-terminal telopeptide of type 1 collagen, *SD* standard deviation, *TRACP-5b* tartrate-resistant acid phosphatase 5b

by bone resorption inhibition) and thus clinically insignificant, which was in line with previous research for RIS-OD 5 mg [22] or RIS-OD 2.5 mg and RIS-OW 17.5 mg [23] in patients with renal dysfunction. Change from baseline in serum calcium was numerically greater in patients with advanced CKD stage (G1, − 0.1% to − 1.6%; G2, − 0.8% to − 1.6%; G3a or G3b, − 1.4% to − 2.5%; Fig. 1), but the differences among the subgroups were small.

Lumbar spine BMD significantly increased from baseline, and the increase was similar among the three subgroups. This is consistent with findings from previous studies that have reported comparable or modestly increased lumbar spine BMD in patients with renal dysfunction compared with those with less severe renal dysfunction [21, 22].

Although previous research has suggested that NTX and CTX are affected by renal function, while BAP and TRACP-5b are not[33–35], research on changes in BTMs in patients with renal dysfunction remains limited. In this study, all the assessed BTMs significantly decreased from baseline irrespective of patients' renal function; notably, these results lend further support to the validity of other studies that have reported that neither BAP nor TRACP-5b are affected by renal dysfunction. At month 12, the levels of BAP (CKD stage G1, 20.2 U/L; G2, 19.8 U/L; G3, 18.6 U/L) and TRACP-5b (G1, 272 mU/dL; G2, 266 mU/dL; G3, 248 mU/dL) were within the reference range set in the 2015 Japanese osteoporosis guidelines (BAP, 7.9–29.0 U/L; TRACP-5b, 120–420 mU/dL [3]) in all the CKD stages investigated.

Moreover, the decrease in BAP and TRACP-5b reached a plateau at month 3. These results indicate that these BTMs were not excessively suppressed even in patients with moderate CKD.

Overall, results reported for RIS-OM in this study were consistent with results from a post hoc analysis of data from risedronate phase III clinical trials [23]. In the previous post hoc analysis, patients who received RIS-OD (2.5 mg) or RIS-OW (17.5 mg) were also divided into the same subgroups according to eGFR levels (CKD stage G1, $n=99$; G2, $n=525$; G3a or G3b, $n=228$) and evaluated at 48 weeks [23]. As with the present study, in the previous post hoc analysis [23], the incidence of AEs was similar among the three subgroups (83–88%). Furthermore, administration of RIS-OD and RIS-OW resulted in a significant increase in lumbar spine BMD and a significant decrease in BTMs (urinary NTX, urinary CTX, and serum BAP) from baseline in the three subgroups (all $p<0.001$). Finally, the interactions between time and subgroups were not significant on inhibition of BTMs (urinary NTX, $p=0.076$; urinary CTX, $p=0.318$; serum BAP, $p=0.706$). These consistent data, when compared with results from the previous post hoc analysis, support the integrity of our results, as well as the safety and efficacy of RIS-OM in patients with kidney dysfunction despite its higher dosage and heightened safety concerns.

This study has some limitations. First, the results may not be representative of the real-world situation due to the low percentage of CKD stage G3a or G3b patients (9.8%), especially given that the numbers of patients with CKD stages 1, 2, and 3 are predicted to be 0.6, 1.7, and 10.7 million, respectively, in Japan [36]. Additionally, the imbalance in patient numbers among the subgroups (CKD stage G1, 69; G2, 310; G3a or G3b, 41) hindered us from conducting statistical analyses with sufficient power. Second, there were only five male patients included in the RIS-OM 75 mg group in the original phase III study [19], thereby limiting the generalizability of the results. Third, the efficacy outcomes did not assess femoral BMD or the risk of vertebral fracture in this subgroup analysis. Moreover, the assessment of AFF or ONJ, which requires a long-term observation period, was limited by the short study period of 12 months. Last, the post hoc approach itself should be considered a limitation of this analysis.

In conclusion, RIS-OM 75 mg showed consistent safety and efficacy, independent of renal function, in suppressing bone turnover and increasing BMD in Japanese primary osteoporosis patients with mild-to-moderate CKD, although the analysis on patients with moderate CKD was not sufficient to draw a definitive conclusion. Our results suggest that RIS-OM 75 mg is applicable to this patient population, despite its higher dosage, without new or clinically significant safety concerns and with comparable efficacy. Further research in the real-world setting is warranted.

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**Author contributions** TSu, DI (guarantor), TSh, and YN designed the study. MM designed the study and contributed to the conduct of the study and data acquisition and interpretation. IO was responsible for statistical analysis and data interpretation. All authors critically reviewed the paper for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions related to the accuracy and integrity of the paper will be investigated and properly resolved.

## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** Dr. Toshitsugu Sugimoto has received research grants from Eli Lilly Japan, Taisho Toyama Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo Co., Astellas Pharma, and Eisai, as well as consulting fee from Asahi-Kasei Pharma Co. Dr. Daisuke Inoue reports personal fees from EA Pharma and grants from Astellas Pharma, Asahi-Kasei Pharma, Chugai Pharmaceutical, Daiichi-Sankyo Co., EA Pharma, Eli Lilly Japan, Eisai, Pfizer, Ono Pharmaceutical, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Teijin Pharma, outside the submitted work. Mr. Masayuki Maehara and Mr. Ichiro Oikawa are full-time employees of EA Pharma. Dr. Takashi Shigematsu has received consultant fees from EA pharma and Takeda pharmaceutical. Dr. Yoshiki Nishizawa has no conflicts of interest to disclose.

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