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Efficacy, tolerability and safety of once-monthly administration of 75 mg risedronate in Japanese patients with involutional osteoporosis: A comparison with a 2.5 mg once-daily dosage regimen

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ABSTRACT

Oral risedronate has been shown to be effective in the treatment of osteoporosis when administered once-daily or once-weekly in Japan. This randomized, double-blind, multicenter 12-month study was conducted to compare the efficacy and tolerability of oral risedronate 75 mg once-monthly with 2.5 mg once-daily in Japanese patients with involutional osteoporosis. Bone mineral density (BMD), biochemical markers of bone metabolism, fractures, and adverse events (AEs) were evaluated. At the end of the study (Month 12, last observation carried forward [M12, LOCF]), mean percent change (SD) from baseline in lumbar spine (L_2–L_4) BMD, measured by dual energy X-ray absorptiometry (primary endpoint), was increased by 5.69 (4.00)% in the 2.5 mg once-daily group ($n = 428$), and 5.98 (4.54)% in the 75 mg once-monthly group ($n = 422$). In the non-inferiority t-test (non-inferiority margin $\Delta = 1.5\%$), the 75 mg once-monthly group was non-inferior to the 2.5 mg once-daily group ($p < 0.0001$). The difference between treatment groups was 0.28% (95% CI, −0.31% to 0.88%). Changes in biochemical markers of bone metabolism were generally comparable in the two groups, although decreases in the percent change from baseline in urinary NTX/CRN and CTX/CRN were statistically greater in the 2.5 mg once-daily group than the 75 mg once-monthly group. The frequency of new vertebral fractures (including aggravation of prevalent fractures) at the end of the study (M12, LOCF) was also similar in the two groups: 1.2% in the 2.5 mg once-daily group and 1.3% in the 75 mg once-monthly group.

The incidence of mild/moderate/severe AEs was 75.5%/6.3%/0.5% in the 2.5 mg once-daily group and 77.7%/8.1%/0.7% in the 75 mg once-monthly group. AEs associated with gastrointestinal symptoms occurred in approximately 30% of subjects in each group but with no severe cases. AEs potentially associated with acute phase reaction (including symptoms of influenza-like illness or pyrexia starting within 3 days of the first dose of the study drug and with a duration of 7 days or less) only occurred in the 75 mg once-monthly group (2.1%, 9/422 subjects; influenza-like symptoms in 1 subject and pyrexia in 8 subjects), although the incidence was low without any severe cases.

In conclusion, risedronate 75 mg once-monthly (a dosage which is 30 times higher than risedronate 2.5 mg once-daily) had non-inferior efficacy in terms of BMD and was similarly well tolerated compared to the once-daily regimen in Japanese patients with involutional osteoporosis. Consistent with the once-daily and once-weekly dosage, the once-monthly dosage of risedronate 75 mg was half that used outside Japan (150 mg).

Introduction

Globally, the antiresorptive bisphosphonates have been used extensively for the treatment of osteoporosis. In Japan, for example, alendronate and risedronate are frequently used as strongly recommended pharmacotherapy in the treatment of osteoporosis [1], and minodronate has also been approved for this indication [1]. Risedronate 2.5 mg once-daily was shown to be effective in preventing vertebral fractures in patients with involutional osteoporosis in Japan [2]. Numerous clinical studies have shown that most oral bisphosphonates that were originally developed for once-daily administration demonstrate equivalent, or non-inferior, efficacy and tolerability with once-weekly and/or monthly dosing regimens [3–7]. In these studies, the dosages used in Japan (alendronate 5 mg daily/35 mg weekly; risedronate 2.5 mg daily/17.5 mg weekly) were half the dosage used outside

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Japan (alendronate 10 mg daily/70 mg weekly; risedronate 5 mg daily/35 mg weekly) [2–6]. The difference in oral bisphosphonate dosages between Japanese and subjects outside Japan suggested a difference in bioavailability between Japanese and non-Japanese individuals, although the reasons for this difference remain unknown [8].

Adherence to the treatment regimen is important for osteoporosis but there are a number of obstacles to adherence. Since osteoporosis is a chronic disease requiring long-term clinical management, some patients may have problems complying with medication instructions consistently and find them burdensome. Indeed, it has been reported that patients who are poorly adherent to bisphosphonate therapy do not maintain the same level of improvement in bone mineral density (BMD) [9–11]. Moreover, non-adherence with antiresorptive therapy has been reported frequently and it has been reported to result in a 16–50% increased risk of fracture [9–12].

In Japan, a once-weekly regimen improved treatment adherence to bisphosphonates, which was a problem associated with once-daily products. Nevertheless, 20% or more patients stopped taking the drug after 6 months of treatment [13].

From the results of online surveys of Japanese patients and patients outside Japan taking bisphosphonates, it was shown that patients tended to prefer once-monthly products to once-daily or once-weekly products because of the lower frequency of administration [13–17]. Furthermore, treatment adherence with once-monthly and once-weekly dosage regimens has also been evaluated in clinical studies outside Japan, and once-monthly products provided improved treatment adherence compared with once-weekly products [14]. Monthly administration is expected to improve treatment adherence in Japanese patients receiving long-term bisphosphonate therapy who are having difficulty complying with daily or weekly dosage regimens [15,18,19].

The aim of this randomized, double-blind study was to compare, in patients with involutional osteoporosis, the efficacy and tolerability of oral risedronate 2.5 mg once-daily with that of 75 mg once-monthly, which is 30 times larger than the recommended daily dose and half the monthly dose (150 mg) used outside Japan [7]. This is consistent with the daily and weekly doses (2.5 mg and 17.5 mg, respectively) used in Japan, being half the daily and weekly doses (5 mg and 35 mg, respectively) used outside Japan. Risedronate 75 mg once-monthly has been approved in Japan since 25 December 2012.

Methods

Study design

This was a 12-month, phase III, multicenter, randomized, double-blind, parallel group, active comparator controlled study in Japanese patients with involutional osteoporosis.

Diagnosis of osteoporosis was based on the presence or absence of fragility fracture and BMD measurements specified in the "Guideline for the Diagnosis of Primary Osteoporosis (2000 Revised Version)" established by the Japanese Society for Bone and Mineral Research [20,21].

Patients

Individuals eligible for this study were ambulatory Japanese male and female subjects aged ≥50 years who were diagnosed with osteoporosis, based on the criteria for primary osteoporosis of the Japanese Society for Bone and Mineral Research [20,21]. Primary osteoporosis was defined by the presence of a fragility fracture and BMD <80% of the 'young adult mean' (20 to 44 years of age), or BMD <70% of the 'young adult mean' in the absence of a detectable fragility fracture [21]. In the case of female subjects, ≥2 years must have passed since menopause.

The main exclusion criteria were factors which affect efficacy evaluation; secondary osteoporosis and any other disease causing decreased bone mass or affecting lumbar spine BMD (including severe scoliosis of the spine, fracture or severe deformation in any of the L_2–L_4 lumbar vertebrae, or a spinal X-ray image suggesting severe bone sclerosis [calcification] in any of the L_2–L_4 lumbar vertebrae); administration of bisphosphonate within 24 weeks before the first dose of the study drug; administration of any drug affecting bone metabolism such as SERMs, vitamin D_3 and vitamin K_2 preparations, and calcitonin analogs, etc. within 8 weeks before the first dose of the study drug. In addition, any subject judged by the attending physician to be unsuitable to participate in the study was also excluded.

Procedures

The study was performed at 60 study sites in Japan between February 2010 and August 2011 in accordance with the ethical principles set out in the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice, and was approved by the Institutional Review Boards at each study site in line with local regulations. Prior to study registration, all subjects were given a full explanation of the study procedures and provided written informed consent.

Subjects fulfilling the inclusion/exclusion criteria were eligible for the study and were randomized (in a ratio of 1:1) to receive risedronate 75 mg once-monthly or risedronate 2.5 mg once-daily. Matching 2.5 mg and 75 mg placebo tablets were administered to maintain double blindness throughout the study. Subjects were instructed to take a single 75 mg risedronate tablet or 75 mg placebo tablet on the same calendar day each month and a single 2.5 mg risedronate tablet or 2.5 mg placebo tablet at the designated time on every day. The subjects were instructed to take the medication with water immediately upon waking in the morning and not to lie down for at least 30 min after swallowing the tablet. During this 30-min period, the subjects were required to avoid eating, drinking (other than water for taking risedronate) or taking any other medications. Supplementary calcium lactate (containing 200 mg Ca^{2+}) was administered orally once daily after dinner from the registration date until the end of the study. Concomitant use of any drug considered to affect bone metabolism, including vitamin D, was prohibited during the study.

The study comprised a screening phase followed by a 12-month double-blind treatment phase, and each subject was required to visit the study site on Day 15 after the first dose of the study drug (with Day 1 being the first treatment day) and then monthly for a total of 12 months.

Measurements

Efficacy

Lumbar spine (L_2–L_4) BMD was measured at baseline, and after 6 and 12 months (or upon discontinuation) by dual energy X-ray absorptiometry (DXA) using a QDR system (model: Hologic QDR-4500 or higher). At each study site, investigators carried out "accuracy control calibration" using a lumbar standard phantom attached to the equipment before the first measurement on the subjects at each measurement date, and checked that BMD was within acceptable limits (±1.5% of phantom values). X-ray images of thoracic vertebra and lumbar spine were taken at baseline and after 12 months (or upon discontinuation).

Two central independent committees were established for DXA assessment and for X-ray assessment. The central committee for DXA assessment confirmed whether subjects fulfilled inclusion/exclusion criteria and whether BMD measurement results were eligible. The central committee for X-ray assessment confirmed fragility fracture and evaluated vertebral fracture.

The assessment of prevalent fracture was made if the ratio of the central vertebral height to the anterior (C/A) or posterior vertebral body height (C/P) was less than 0.8, or the ratio of the anterior to posterior vertebral body height (A/P) was less than 0.75, or if the anterior, central, and posterior vertebral heights were decreased by more than

20% compared with those of the adjacent vertebral body in Th_4 to L_4. A new or worsening vertebral fracture was judged if any one of the three vertebral heights (A, C, or P), had decreased by at least 20% and by 4 mm in a vertebra diagnosed grade progression by semiquantitative assessment [22].

Compliance with treatment was determined by returned tablet counts and interviews with subjects at each clinic visit. DXA and X-ray were not required in subjects who discontinued treatment within 84 days after the first dose of the study drug.

Biochemical markers of bone metabolism were measured at baseline, and after 1, 3, 6, 9, and 12 months (or upon study discontinuation). Biochemical markers of bone metabolism included serum BAP (bone alkaline phosphatase), serum TRACP-5b (tartrate-resistant acid phosphatase 5b), urinary DPD/CRN (deoxypyridinoline, adjusted for creatinine), urinary NTX/CRN (cross-linked N-telopeptides of type 1 collagen, adjusted for creatinine), and urinary CTX/CRN (cross-linked C-telopeptide of collagen type 1, adjusted for creatinine). Serum BAP was measured by chemiluminescent enzyme immunoassay on an automatic analyzer (UniCel DxI 800, Beckman Coulter, LaBrea, CA) using Access Ostase reagent. Urinary NTX was measured by enzyme-linked immunosorbent assay on an automated machine (NIPPON ADVANCED TECHNOLOGY, Ibaraki, Japan) using Osteomark (Alere Health, Tilburg, The Netherlands); the intra- and inter-assay coefficients of variation were below 7% and 6%, respectively. Urinary CTX was measured using an enzyme immunoassay kit (Urine BETA CrossLaps® ELISA, Nordic Bioscience Diagnostics, Herlev, Denmark). The results of the biochemical markers of bone metabolism assays were measured at SRL, a central laboratory in Hachioji-shi, Tokyo, Japan, using standard methods.

Safety

Safety was evaluated by the records of all adverse events (AEs), vital signs, and clinical laboratory test values (hematology, biochemistry and urinalysis). Investigators asked the subjects questions about subjective symptoms at each visit and took vital signs, and clinical laboratory test values at baseline, and after 0.5, 3, 6, 9, and 12 months. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. The incidence of AEs was calculated in each treatment group. AEs counted as non-vertebral fractures included all fractures except those occurring in vertebra. Gastrointestinal symptoms included events that were classified in accordance with the MedDRA system organ class (SOC) as "gastrointestinal disorders", excluding the preferred terms referring to oral and anal conditions, but including the preferred terms "gastroenteritis". Adverse events potentially associated with acute phase reaction (APR) included 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 or less.

Statistical analysis

Three types of analysis sets were used. The full analysis set (FAS) was defined as all subjects who were randomized and received at least one dose of the study drug. The per-protocol set (PPS) was defined as all FAS subjects who had no major protocol deviation, fulfilled minimum protocol requirements, and whose primary endpoint was evaluable. The safety analysis set was defined as all subjects who received at least one dose of the study drug.

The primary endpoint was mean percent change from baseline in lumbar vertebrae (L_2–L_4) BMD measured using DXA at the end of the study (Month 12 with the last observation carried forward, hereafter referred to as M12, LOCF). A non-inferiority t-test (non-inferiority margin $\Delta = 1.5\%$, one-sided type I error $= 2.5\%$) was performed as the primary analysis, to compare the primary endpoint between the 75 mg once-monthly group and the 2.5 mg once-daily group in FAS.

Secondary analysis consisted of the same analysis as the primary using PPS to ensure the robustness of the results. Summary statistics using FAS were also calculated for mean percent change from baseline in (L_2–L_4) BMD at 6 and 12 months.

Secondary endpoints were analyzed using FAS. Mean percent change from baseline was calculated for biochemical markers of bone metabolism at 1, 3, 6, 9, 12 months, and at the end of the study (M12, LOCF). Vertebral fractures were also examined at 12 months and at the end of the study (M12, LOCF) by calculating the frequency, as well as the difference between the treatment groups and the 95% confidence intervals (CI).

Subgroup analysis on the primary endpoint was performed using the baseline values of the biochemical markers.

Results

Baseline patient characteristics

A total of 1251 individuals provided written informed consent and, of these, 852 subjects (429 subjects in the 2.5 mg once-daily group and 423 subjects in the 75 mg once-monthly group) were enrolled into the study and randomized (Fig. 1). A subject who had registered twice was excluded from all analyses, and the FAS comprised 850 subjects (428 subjects in the 2.5 mg once-daily group and 422 subjects in the 75 mg once-monthly group). The PPS group included 711 subjects (368 subjects in the 2.5 mg once-daily group, and 343 subjects in the 75 mg once-monthly group). Study discontinuation or withdrawal occurred in 48 and 58 subjects, respectively, in the 2.5 mg once-daily and 75 mg once-monthly groups. Pretreatment events, which were defined as any untoward medical occurrence in a subject who had signed

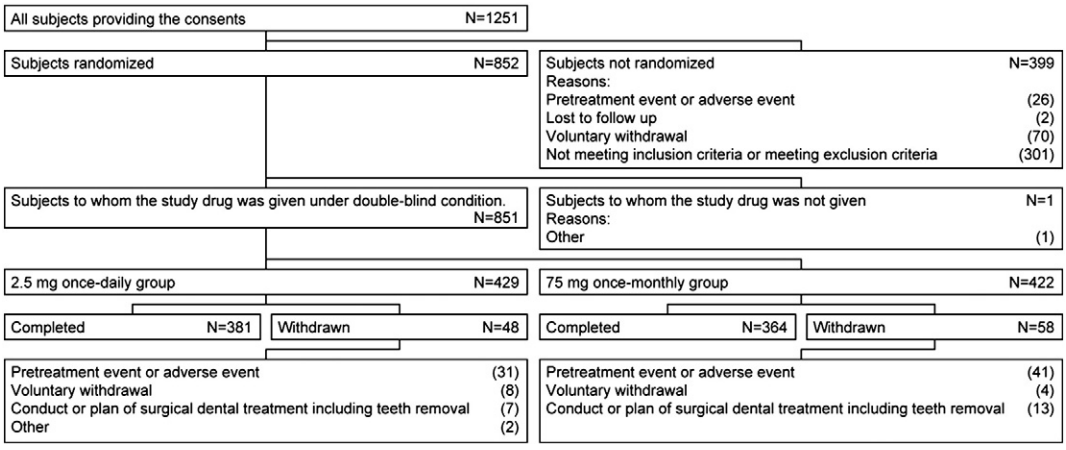


Fig. 1. Disposition of subjects.

informed consent to participate in the current study but prior to administration of any study medication, and adverse events were the most common reasons for discontinuation or withdrawal in both groups through the treatment period.

A summary of baseline demographics and characteristics of randomized subjects is presented in Table 1. With the exception of CTX/CRN levels, which were slightly higher in the 2.5 mg once-daily group compared with the 75 mg once-monthly group, all key baseline demographics and primary disease characteristics were similar in the two treatment groups. Patient characteristics at baseline in the PPS were similar to those of the randomized set.

Efficacy

Bone mineral density

Mean percent change (SD) from baseline in (L_2–L_4) BMD at the end of the study (M12, LOCF) in the FAS was 5.69 (4.00)% in the 2.5 mg once-daily group and 5.98 (4.54)% in the 75 mg once-monthly group. In the non-inferiority t-test, the 75 mg once-monthly group proved to be non-inferior to the 2.5 mg once-daily group ($p < 0.0001$). The difference between treatment groups was 0.28% (95% CI, −0.31% to 0.88%). Mean percent change from baseline in (L_2–L_4) BMD at the end of the study (M12, LOCF) in the PPS was similar to that in the FAS.

Mean percent change (SD) from baseline in (L_2–L_4) BMD in the FAS at 6 months in the 2.5 mg once-daily and 75 mg once-monthly treatment groups was 5.01 (3.62)% and 4.67 (4.16)%, respectively, and at 12 months it was 5.81 (4.02)% and 6.11 (4.50)%, respectively (Fig. 2). These data suggest that mean percent change from baseline in (L_2–L_4) BMD was increased by similar amounts in the two treatment groups over the course of this 12-month study.

Biochemical markers of bone metabolism

Mean percent changes from baseline in biochemical markers of the bone formation marker serum BAP, and the bone resorption markers serum TRACP-5b, urinary DPD/CRN, urinary NTX/CRN, and urinary CTX/CRN were generally comparable in the two treatment groups. Bone resorption markers started to decrease from 1 month after the first treatment of study drug while the bone formation marker started to decrease from 3 months after the first treatment of study drug. The reductions were maintained to the 12-month time point in both treatment groups (Fig. 3). The mean percent change from baseline in urinary NTX/CRN and urinary CTX/CRN levels showed a statistically significant decrease in the 2.5 mg once-daily group compared with the 75 mg once-monthly group throughout the treatment period (at 1, 3, 6, 9, 12 months, and at the end of the study [M12, LOCF]).

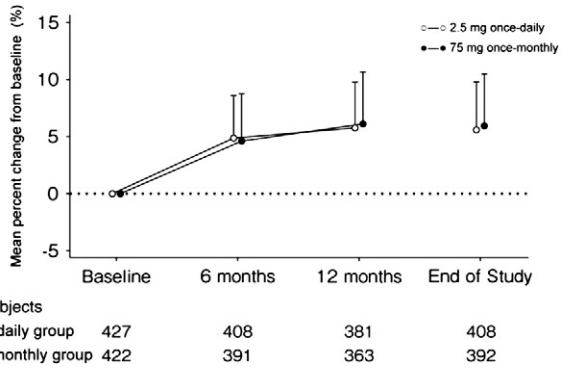


Fig. 2. Mean percent change from baseline in lumbar spine (L_2–L_4) BMD (FAS). End of study refers to the value calculation using the last observation carried forward at Month 12. There were no statistically significant differences between groups at any measurement time points. Non-inferiority validation at the end of treatment ($\Delta = 1.5\%$): $t = 5.90$ ($p < 0.0001$); intergroup difference 0.28, two-sided 95% CI −0.31 to 0.88.

The results of the subgroup analysis showed that the mean percent changes from baseline in (L_2–L_4) BMD at the end of the study (M12, LOCF) were similar between treatment groups in each subgroup of the biochemical markers (Table 2). The mean percent changes from baseline in (L_2–L_4) BMD at the end of the study (M12, LOCF) were generally higher in both treatment groups for the subgroup of subjects with higher baseline values of biochemical markers.

Frequency of vertebral fractures

Thoracic vertebra and lumbar spine X-ray images were taken at baseline and at the end of the study. The frequency of new vertebral fractures (including aggravation of prevalent fractures) at the end of the study (M12, LOCF) was 1.2% (5/410 subjects) in the 2.5 mg once-daily group and 1.3% (5/393 subjects) in the 75 mg once-monthly group. The difference between treatment groups was 0.1% (95% CI, −1.48% to 1.59%) and, thus, the effects of both treatment regimens were similar.

Safety and tolerability

Safety and tolerability were evaluated using the safety analysis set. The frequency of AEs was similar between the two groups: 82.2% (352/428 subjects) in the 2.5 mg once-daily group and 86.5% (365/422 subjects) in the 75 mg once-monthly group. In both groups, the majority of AEs were mild to moderate and the most common AE was nasopharyngitis (Table 3). The incidence of mild/moderate/severe AEs was 75.5%/6.3%/0.5% in the 2.5 mg once-daily group and 77.7%/8.1%/0.7% in the 75 mg once-monthly group.

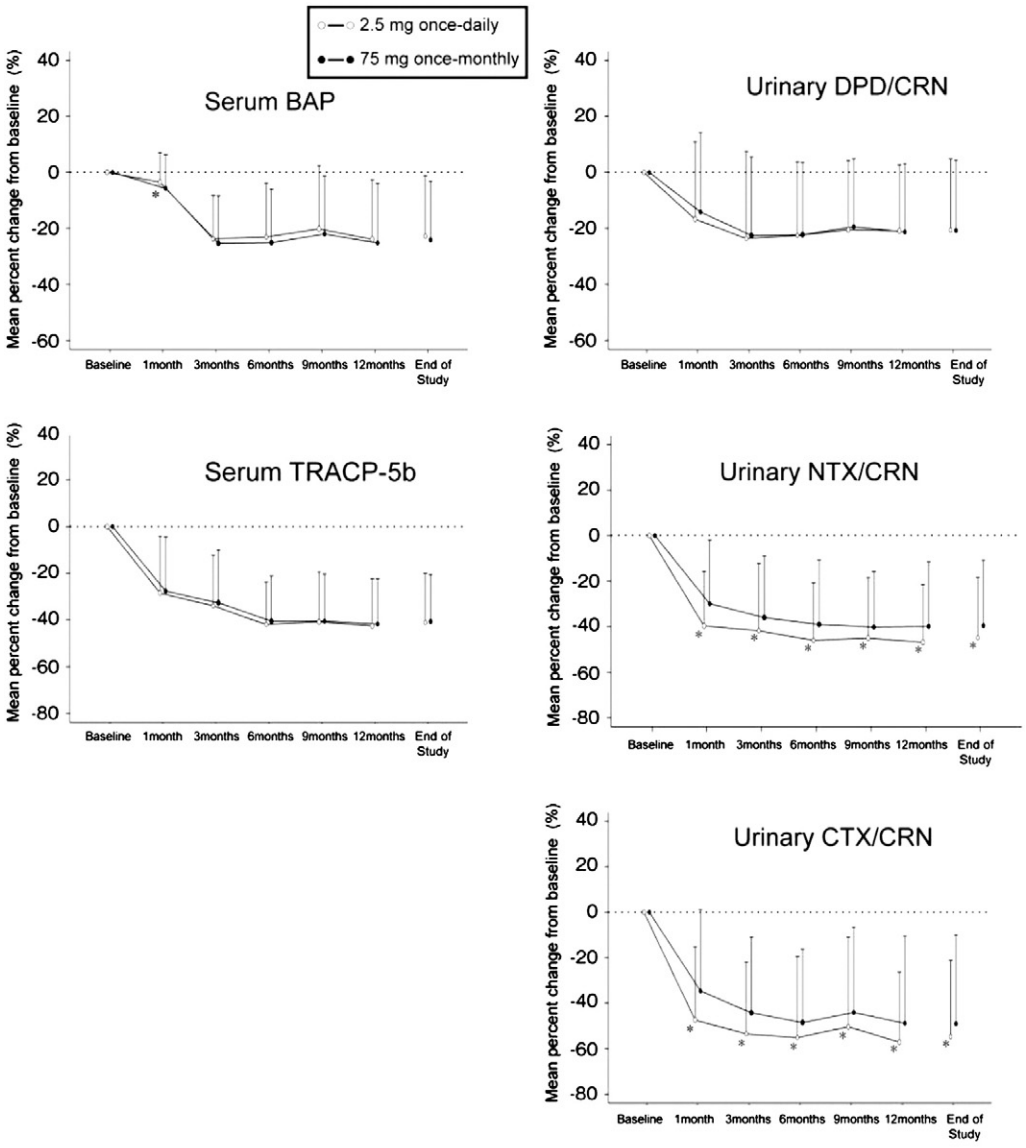
The incidence of AEs counted as non-vertebral fractures was 3.0% (13/428 subjects) in the 2.5 mg once-daily group and 2.1% (9/422 subjects) in the 75 mg once-monthly group, but these were considered to be unrelated to the study drug. Furthermore, no cases of AEs associated with non-traumatic atypical fracture of the subtrochanteric or midshaft of the femur were observed.

The frequency of AEs associated with gastrointestinal symptoms was 26.2% (112/428 subjects) in the 2.5 mg once-daily group and 30.8% (130/422 subjects) in the 75 mg once-monthly group; all of these AEs were mild to moderate and no severe events were observed. Among AEs associated with gastrointestinal symptoms, diarrhea was remarkable as its frequency was higher in the 75 mg once-monthly group

Table 1
Summary of baseline demographics and characteristics of randomized subjects.

Parameters	Risedronate dosage	
	2.5 mg once-daily	75 mg once-monthly
Number of subjects	429	423
Age (years)	68.2 ± 6.85	67.7 ± 6.73
Gender (male/female)	8/421	5/418
BMI (kg/m^2)	21.4 ± 2.8	21.9 ± 3.1
Number of years since menopause (years)	N = 346 18.1 ± 7.5	N = 353 17.4 ± 7.5
Mean lumbar spine BMD (L_2–L_4 BMD) measured by DXA		
(g/cm^2)	0.64 ± 0.06	0.64 ± 0.07
T-score	−3.11 ± 0.54	−3.12 ± 0.55
Number of prevalent fractures (Th_4-L_4), n (%)		
0	338 (79.0)	317 (75.1)
1	61 (14.3)	79 (18.7)
2	19 (4.4)	21 (5.0)
3 or more	10 (2.3)	5 (1.2)
Fragility fracture, n (%) Present	121 (28.2)	132 (31.2)
Absent	308 (71.8)	291 (68.8)
History of bisphosphonate administration	36 (8.4%)	33 (7.8%)
Serum 25-OH-D (ng/mL)	21.3 ± 6.9	20.7 ± 6.9
Serum BAP (U/L)	26.1 ± 8.4	26.4 ± 8.9
Serum TRACP-5b (mU/dL)	473 ± 163	457 ± 170
Urinary DPD/CRN (nmol/mmolCRE)	7.65 ± 2.71	7.64 ± 2.65
Urinary NTX/CRN (nmolBCE/mmolCRE)	57.8 ± 22.8	55.6 ± 22.8
Urinary CTX/CRN (μg/mmolCRE)	328 ± 151	307 ± 142

Values are mean ± SD unless specified otherwise.



Number of subjects at each measurement time point

	Baseline	1 month	3 months	6 months	9 months	12 months	End of Study
2.5 mg once-daily	428	428	415	405 **	394	382	428
75 mg once-monthly	422	422	399	385	369	365	422

Fig. 3. Mean percent change from baseline in biochemical markers of bone metabolism (FAS) (BAP = bone alkaline phosphatase; DPD, deoxypyridinoline; CRN, creatinine; NTX, collagen type 1 cross-linked N-telopeptide; CTX, collagen type 1 cross-linked C-telopeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b). End of study refers to the value calculation using the last observation carried forward at Month 12. *Statistically significant difference between treatment groups (unadjusted for multiple comparisons). **Number of subjects for serum BAP and TRACP-5b; corresponding number of subjects for urinary DPD/CRN, NTX/CRN and CTX/CRN = 404.

(8.3%, 35/422 subjects) than in the 2.5 mg once-daily group (4.2%, 18/428 subjects). AEs potentially associated with APR only occurred in the 75 mg once-monthly group (2.1%, 9/422 subjects; influenza-like symptoms in 1 subject and pyrexia in 8 subjects). The incidence was low, 8 events were mild and 1 event was moderate (pyrexia).

The frequency of serious AEs (including death) was 4.4% (19/428 subjects) in the 2.5 mg once-daily group and 5.7% (24/422 subjects) in the 75 mg once-monthly group. Serious AEs that were "related" to the study drug occurred in one subject in each group: adjustment disorder in one subject (2.5 mg once-daily group) and cerebrovascular disorder in the other subject (75 mg once-monthly group). One subject (75 mg once-monthly group) died during the study (due to drowning), but it was considered to be unrelated to the study drug. Treatment was discontinued due to AEs in 7.2% of subjects (31/428 subjects) in the 2.5 mg once-daily group and 9.7% of subjects (41/422 subjects) in the 75 mg once-monthly group.

There were no clinically significant changes in the mean values of vital signs and laboratory tests, compared with baseline, in the two groups.

Table 2
Subgroup analysis stratified on mean percent change from baseline in lumbar spine (L_2–L_4) BMD at the end of treatment period as measured by DXA (FAS).

Stratification factors	Treatment groups		Percent change (%)		
			N	Mean	SD
Serum BAP (U/L)	Min≤–≤21.1	2.5 mg once-daily	115	4.687	3.8147
		75 mg once-monthly	107	3.934	4.1973
	21.2≤–≤29.0	2.5 mg once-daily	171	5.515	3.7700
		75 mg once-monthly	151	6.290	4.2701
	29.1≤–≤Max	2.5 mg once-daily	122	6.893	4.2048
		75 mg once-monthly	134	7.256	4.5687
Serum TRACP-5b (mU/dL)	Min≤–≤119	2.5 mg once-daily	1	1.760	
		75 mg once-monthly	1	5.260	
	120≤–≤420	2.5 mg once-daily	177	4.984	3.6938
		75 mg once-monthly	174	5.206	4.3975
	421≤−≤Max	2.5 mg once-daily	230	6.257	4.1442
		75 mg once-monthly	217	6.599	4.5774
Urinary DPD/CRN (nmol/mmolCRE)	Min≤–≤5.9	2.5 mg once-daily	106	5.055	3.7247
		75 mg once-monthly	111	4.827	3.9250
	6.0≤–≤7.6	2.5 mg once-daily	142	5.742	4.1414
		75 mg once-monthly	119	6.802	4.7337
	7.7≤–≤Max	2.5 mg once-daily	160	6.074	4.0205
		75 mg once-monthly	162	6.160	4.6541
Urinary NTX/CRN (nmolBCE/mmolCRE)	Min≤–≤35.3	2.5 mg once-daily	56	3.934	3.4550
		75 mg once-monthly	71	4.429	4.1685
	35.4≤–≤54.3	2.5 mg once-daily	149	5.325	4.1529
		75 mg once-monthly	133	5.467	4.7575
	54.4 ≤–≤ Max	2.5 mg once-daily	203	6.450	3.8492
		75 mg once-monthly	188	6.923	4.3151
Urinary CTX/CRN (μg/mmolCRE)	Min≤–≤184.1	2.5 mg once-daily	62	4.328	3.8913
		75 mg once-monthly	68	4.190	4.0522
	184.2≤–≤301.4	2.5 mg once-daily	140	5.358	4.0775
		75 mg once-monthly	145	5.771	4.3580
	301.5≤–≤Max	2.5 mg once-daily	206	6.333	3.8646
		75 mg once-monthly	179	6.823	4.6643

Discussion

The primary endpoint in this Japanese phase III study (mean percent change in lumbar spine (L_2–L_4) BMD from baseline to the end of the study [M12, LOCF]) demonstrated that risedronate 75 mg once-monthly, a 30 times higher dosage compared to risedronate 2.5 mg once-daily, had non-inferior efficacy to the once-daily regimen in Japanese patients with involutional osteoporosis. In the multinational phase III study, excluding Japan (ex-Japan), the efficacy of risedronate 150 mg once-monthly, which is twice the dose used in this Japanese phase III study, was non-inferior to risedronate 5 mg once-daily in patients with involutional osteoporosis [7,23].

Doses of risedronate administered daily, weekly, and monthly in Japan are different from those used outside Japan. It has been reported that the result of the Japanese risedronate once-daily phase I study suggested differences in risedronate bioavailability between Japanese and non-Japanese subjects, although the reasons for this difference remain unknown [8].

With regard to biochemical markers of bone metabolism, the bone resorption markers (serum TRACP-5b, urinary DPD/CRN, urinary NTX/CRN and urinary CTX/CRN) started to decrease from 1 month after the first dose of the study drug and the bone formation marker (serum BAP) started to decline from 3 months after the first dose of the study drug. In both groups, the low levels achieved for these markers were maintained for the 12-month duration of the study, with only small fluctuations.

Both treatment groups showed clinically significant decreases in urinary NTX/CRN and CTX/CRN levels from baseline to the end of the study (M12, LOCF), but the reduction was statistically larger in the 2.5 mg once-daily group compared with the 75 mg once-monthly group throughout the treatment period. However, the between-group differences for these markers do not appear to be clinically significant, because the mean percent change in lumbar spine (L_2–L_4) BMD was similar in both groups from baseline to the end of the study (M12, LOCF). With regard to the between-group differences in NTX/CRN and CTX/CRN, a possible reason may be that the measurement time points were different in both treatment groups. For the 2.5 mg once-daily group, the sample for biochemical markers of bone metabolism was taken after administration of risedronate on the morning of the visit. However, for the 75 mg once-monthly group, the sample was taken

Table 3
Summary of adverse events (AEs).

Parameters	2.5 mg once-daily	75 mg once-monthly
Number of subjects	428	422
Total number of subjects with AE	352 (82.2%)	365 (86.5%)
Serious AEs	19 (4.4%)	24 (5.7%)
Number of subjects in whom treatment was discontinued due to AE	31 (7.2%)	41 (9.7%)
AEs occurring in ≥5% of subjects		
Nasopharyngitis	108 (25.2%)	119 (28.2%)
Upper respiratory tract inflammation	14 (3.3%)	21 (5.0%)
Abdominal discomfort	27 (6.3%)	28 (6.6%)
Diarrhea	18 (4.2%)	35 (8.3%)
Constipation	28 (6.5%)	19 (4.5%)
Eczema	20 (4.7%)	24 (5.7%)
Back pain	26 (6.1%)	35 (8.3%)
Osteoarthritis	23 (5.4%)	24 (5.7%)
Fall	27 (6.3%)	39 (9.2%)
Contusion	26 (6.1%)	32 (7.6%)
Adverse events of special interest		
Non-vertebral fracture[a]	13 (3.0%)	9 (2.1%)
Adverse events associated with gastrointestinal symptoms[b]	112 (26.2%)	130 (30.8%)
Adverse events potentially associated with acute phase reaction[c]	0	9 (2.1%)

[a] Includes all fractures except those occurring in vertebra.
[b] Includes events that are classified in accordance with the MedDRA SOC as "Gastrointestinal disorders", excluding the preferred terms referring to oral and anal conditions and including the preferred terms "Gastroenteritis" (SOC "Infections and infestations").
[c] Includes 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 or less.

before the next administration (the 75 mg group received risedronate in the morning on at least a day after the visit). In a multinational phase II study (ex-Japan), the reduction in serum CTX levels was larger in the 5 mg once-daily group compared with the 150 mg once-monthly group on Day 30 of Month 5 but the reduction was larger in the 150 mg once-monthly group compared with the 5 mg once-daily group on Day 4 and 14 of Month 6 after administration of Month 6. Following a gradual recovery of the serum CTX levels in the 150 mg once-monthly group, CTX levels in the 5 mg once-daily group were larger than those in the 150 mg once-monthly group on Day 30 of Month 6. The pattern of change in urinary NTX levels was similar to that in serum CTX levels [24]. In a phase I study in Japan (not published), after single administration of risedronate 75 mg, both urinary NTX/CRN and CTX/CRN decreased markedly, reaching the maximum decrease after 48 h (−63% and −76%, respectively) and, then, gradually recovering (−8% and −29% after 720 h, respectively). In our study, we believe that the marked short-term (within a short period of time after each administration) reduction in urinary CTX/CRN and NTX/CRN levels in the once-monthly group (75 mg) concurs with the reductions observed in the multinational phase II study (ex-Japan) and the phase I study in Japan. Therefore, it is thought that the effects of risedronate once-monthly (75 mg) and once-daily (2.5 mg) on these bone resorption markers are similar when comparing the area under the effect–time curve for urinary CTX/CRN and urinary NTX/CRN. Furthermore, in a multinational phase III (ex-Japan) study of risedronate at Month 12 (2-year randomized, double-blind, multicenter study comparing once-monthly risedronate 150 mg with a 5 mg once-daily regimen) [7], a similar pattern to that observed in the current phase III study in Japan was reported, such that the reduction in urinary NTX/CRN and serum CTX levels from baseline to the end of the study was slightly larger in the once-daily compared with the once-monthly group.

In the current study, the percent changes in other biochemical markers (serum TRACP-5b, urinary DPD/CRN, serum BAP) were similar in the two treatment groups. Among the biochemical markers, serum TRACP-5b is a marker that has become available recently. The result of the subgroup analysis for serum TRACP-5b was in line with the results of other biochemical markers, showing higher mean percent changes from baseline in (L_2–L_4) BMD at the end of the study (M12, LOCF) in the subgroup of subjects with higher baseline values. Additionally, all biochemical markers showed a clinically significant change from baseline at the end of the study (M12, LOCF), including the percent change for serum TRACP-5b of approximately −40%, where 12.4% is the minimum significant change previously reported for serum TRACP-5b [25]. In order to further explore the relationship between BMD and the biochemical markers, Spearman correlation coefficients were calculated. The correlation coefficients between the primary endpoint and the percent change at the end of the study (M12, LOCF) for the biochemical markers, serum BAP, urinary DPD/CRN, urinary NTX/CRN, urinary CTX/CRN, and serum TRACP-5b, were −0.378, −0.196, −0.341, −0.248, and −0.378, respectively. Serum TRACP-5b had a correlation coefficient similar to that of other biochemical markers, demonstrating it to be as useful a marker as the other biochemical markers in monitoring risedronate treatment.

The frequency of new vertebral fractures (including aggravation of prevalent vertebral fractures) at the end of the study (M12, LOCF) was shown to be similar in the two treatment groups. The incidence of non-vertebral fractures was numerically smaller in the 75 mg once-monthly group than in the 2.5 mg once-daily group [2.1% (9/422) vs. 3.0% (13/428), respectively]. The vertebral antifracture efficacy of once-daily regimens has been verified in clinical trials. The clinical literature advocates BMD as a surrogate marker for vertebral antifracture efficacy [26]. In the current study, 75 mg once-monthly was non-inferior to 2.5 mg once-daily in mean percent change from baseline in BMD, suggesting that once-monthly risedronate could be expected to possess antifracture efficacy similar to that observed with the once-daily regimen.

Similar to other bisphosphonates, risedronate is absorbed rapidly into bone tissue after administration but it is not readily degraded in vivo, resulting in an extremely long half-life in bone. Intermittent administration of risedronate is considered to have the same effect as daily administration where appropriate dose and dosing intervals have been established. In the current study, subjects in the 75 mg once-monthly group received a larger amount of drug per administration than did those in the 2.5 mg once-daily group, which results in the same total dose in a month. Stepensky and colleagues reported that lower amounts of alendronate were found in the bone of thyroidparathyroidectomy (TPTX) rats 1 day after the administration of alendronate as a 2-week continuous input from a subcutaneously implanted osmotic pump as compared with intermittent bolus administration of the same dose in total [27]. Therefore, it was considered that the amount of accumulation of bisphosphonate within bone after each single intermittent dose was more than that obtained with continuous administration. It was considerable that the amount of risedronate accumulation is higher in the 75 mg once-monthly group than in the 2.5 mg once-daily group after each single 75 mg once-monthly group treatment. Therefore, each administration of risedronate 75 mg once-monthly, which has a larger accumulation in bone, is possibly associated with more diffusion in bone than 2.5 mg once-daily administration. Therefore, it may be possible that this difference of distribution in bone between daily and monthly risedronate administration causes the difference in the prevention of bone fracture, but further research is required to obtain more data.

With regard to safety, the frequency of overall AEs, gastrointestinal AEs (which are typical AEs during bisphosphonate therapy), serious AEs, and the number of subjects for whom treatment was discontinued due to AEs, were comparable in the two treatment groups.

The frequency of AEs associated with gastrointestinal symptoms was similar between treatment groups. There was no notable difference in baseline demographics, complications, and medical history between subjects who had developed AEs associated with gastrointestinal symptoms and those who had not. AEs associated with gastrointestinal symptoms developed most frequently during the period from the initial administration to Day 30; the frequency of new onset of gastrointestinal symptoms tended to decrease thereafter in each of the treatment groups (data not presented). One of the AEs, diarrhea, was remarkable as its frequency was higher in the 75 mg once-monthly group than in the 2.5 mg once-daily group. However, the number of subjects who discontinued due to diarrhea did not differ significantly between the two treatment groups (4 and 5 subjects in the 2.5 mg once-daily and 75 mg once-monthly groups, respectively) and its severity was mild or moderate.

Influenza-like illness associated with both IV and oral bisphosphonates is transitory and self-limiting and usually does not recur after subsequent drug administration. This influenza-like illness is referred to as APR [28]. In the current study, AEs potentially associated with APRs only occurred in the 75 mg once-monthly group; the incidence was low, severity was mild or moderate, and these events were not considered to be clinically important. In the multinational (ex-Japan) phase III study, AEs potentially associated with APRs occurred at a similarly low rate as in our study; 1.4% (9/650) of subjects treated with risedronate 150 mg once-monthly and 0.2% (1/642) of subjects treated with 5 mg once-daily [7]. It is considered that the treatment of APRs with analgesics such as paracetamol is generally sufficient to manage them [29]. Overall, with regard to safety, risedronate 75 mg once-monthly was similarly well tolerated compared with 2.5 mg once-daily in Japanese patients with involutional osteoporosis.

A potential limitation of the current study, in terms of generalizability of results, relates to the fact that there were only 5 male participants in the 75 mg once-monthly group. Consequently, we need to accumulate clinical experience in males with osteoporosis through post-marketing surveillance, etc., to fully assess the efficacy and tolerability of monthly risedronate in this population. It is also important to note that the current study is of primary interest to the Japanese population;

although there were differences between the current study and the multinational (ex-Japan) phase III study in, for example, the study environment and study design, the results of the multinational (ex-Japan) phase III study [7] are mentioned here briefly, for reference. The mean percent change in lumbar spine (L_1–L_4) BMD (primary endpoint) at 12 months (LOCF) was 3.4% (95% CI, 3.03% to 3.82%) in the 5 mg once-daily group and 3.5% (95% CI, 3.15% to 3.93%) in the 150 mg once-monthly group. The once-monthly regimen was determined to be non-inferior to the daily regimen with respect to changes in lumbar spine BMD by analysis using an ANOVA model with treatment and pooled centers as fixed effects. Mean lumbar spine (L_1–L_4) BMD T-score (SD) at baseline was −3.18 (0.56) in the 5 mg once-daily group and −3.21 (0.57) in the 150 mg once-monthly. With regard to safety, the overall frequency of AEs was 78.5% (504/642) in the 5 mg once-daily group and 79.2% (515/650) in the 150 mg once-monthly group at 12 months [7]. Risedronate 150 mg once-monthly has been approved in the US since April 2008.

In conclusion, in Japanese patients with involutional osteoporosis, once-monthly risedronate 75 mg, which is 30 times the dose of once-daily risedronate, was shown to be non-inferior in efficacy to risedronate 2.5 mg once-daily. With regard to safety, risedronate 75 mg once-monthly was similarly well tolerated compared with 2.5 mg once-daily. Clinical benefit with once-monthly risedronate 75 mg in Japanese patients was achieved using half the dose (150 mg) administered in studies conducted outside Japan. This is consistent with the daily and weekly doses (2.5 mg and 17.5 mg, respectively) used in Japan being half the daily and weekly doses (5 mg and 35 mg, respectively) used outside Japan. Monthly risedronate offers patients with osteoporosis a new dosage option which may improve convenience, as well as improving treatment adherence, for those who are having difficulty complying with the daily and weekly regimens.

Conflict of interest

HH has received research grants and consulting fees (Ajinomoto Pharmaceuticals, Asahi Kasei Pharma, Astellas, Chugai Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Ono, Taisho Toyama, Takeda, Teijin Pharma, and MSD). HK has received consulting fees (Ajinomoto Pharmaceuticals, Asahi Kasei Pharma, Ono, and Takeda). HO is an employee of Ajinomoto Pharmaceuticals Company Limited. SH is an employee of Takeda Pharmaceutical Company Limited. TN has received consulting fees (Ajinomoto Pharmaceuticals, Asahi Kasei Pharma, Astellas, Banyu, Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Ono, Takeda, and Teijin Pharma) and belongs to the Japan Ministry of Health, Welfare and Labour as a councilor for hospital administration and social medical insurance.

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Appendix A

Other members of the current study

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Yokohama Minoru Clinic, Shintoukai Medical Corporation	Internal Medicine	Hyeteok Kim
Kanazawa Hospital	Orthopedics	Yoshiharu Ohtake
Keyaki Street Orthopedic Clinic	Orthopedics	Motoaki Fujimori
Nirasaki Mutual Hospital	Orthopedics	Mamoru Takimori
Yamabeonsen Hanaoka Orthopedic Clinic	Orthopedics	Toru Hanaoka
Sakudaira Orthopedic Clinic	Orthopedics	Masato Shibukawa
Nanko Hospital	Surgery	Yasuaki Miki
Takayama Medical Clinic	Internal Medicine	Junko Tachi
Aizenbashi Hospital	Orthopedics	Harukazu Tanaka
Shinsuma General Hospital	Gynecology	Hidenobu Fukunishi
Katsuga Orthopedic Clinic	Orthopedics	Tohru Nishiyama
Kinashi Obayashi Hospital	Orthopedics	Takeshi Manabe
Kochi Rehabilitation Hospital	Orthopedics	Mitsuru Kajitani
Susaki Kuroshio Hospital	Orthopedics	Norio Yamanaka
Kouhoku Kokuminkenkouhoken Hospital	Orthopedics	Akihiro Myojin
Nago Orthopedic Clinic	Orthopedics	Masaru Nago
Nagata Orthopedic Hospital	Orthopedics	Katsuya Kanesaki
Shinto Orthopedic Clinic	Orthopedics	Takayasu Shinto
Suga Orthopedic Hospital	Orthopedics	Takayoshi Suga
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Tsukide Orthopedic Clinic	Orthopedics	Kazuki Miyazono
Kikuno Hospital	Orthopedics	Ryuichiro Kikuno
Itou Orthopedic Clinic	Orthopedics	Hiroshi Ito
Kirishima Sugiyasu Hospital	Orthopedics	Kouichiro Sugiyasu
Sakura Clinic	Orthopedics	Satoshi Masuda
Sadamatsu Hospital	Orthopedics	Kanji Akiyama
Mori Orthopedic Clinic	Orthopedics	Shigeru Mori
Oyumino Orthopedic Clinic	Orthopedics	Hidenori Honda
Gyotoku Flower Street Clinic	Internal Medicine	Shin Totokawa
Shiraishi Orthopaedic Pain Clinic	Orthopaedics	Masaharu Shiraishi
Sato Orthopedic Clinic	Orthopedics	Kimihito Sato
Sumida Chuou Hospital	Surgery	Kuniaki Kojima
Otakibashi Orthopedic Clinic	Orthopedics	Hisayuki Izaki

Appendix A (*continued*)

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Murakami Karindoh Hospital	Orthopedics	Mitsuyoshi Kambara
Kataoka Orthopedic Clinic	Orthopedics	Yasufumi Kataoka
Goto Orthopedic Clinic	Orthopedics	Masataka Goto
Hashimoto Clinic	Orthopedics	Sanshiro Hashimoto
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Miyazaki Orthopedic Clinic	Orthopedics	Yu Miyazaki
Nishikamata Orthopedic Clinic	Orthopedics	Keizo Sakamoto
Inoue Orthopedic Surgery	Orthopedics	Yutaka Suzuki
Shinnihonbashi Ishii Clinic	Internal Medicine	Hikaru Ishii
Kouwa Clinic	Internal Medicine	Tsuyoshi Yamato
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