J Bone Miner Metab (2012) 30:439–446
DOI 10.1007/s00774-011-0332-2

ORIGINAL ARTICLE

Three years of treatment with minodronate in patients with postmenopausal osteoporosis

Hiroshi Hagino · Masataka Shiraki · Masao Fukunaga · Tetsuo Nakano · Kunio Takaoka · Yasuo Ohashi · Toshitaka Nakamura · Toshio Matsumoto

Received: 17 June 2011 / Accepted: 23 October 2011 / Published online: 2 December 2011

Abstract The objective of this study was to determine the safety and efficacy of long-term minodronate treatment in women with postmenopausal osteoporosis based on re-analysis of a phase III 2-year clinical trial with a 1-year extension. Women aged 55–80 years old with fragility fractures were enrolled and randomized to take 1 mg minodronate or placebo once a day in the original 2-year study. The subjects who completed the 2-year study were invited to participate in an additional 1-year extension in which all subjects were to receive minodronate. Finally, a total 380 subjects completed the extension study (186 from the placebo group and 194 from the minodronate group). Fracture results observed in the extension study were consistent with those observed in the first 2 years in minodronate group. In contrast, the placebo/minodronate group showed a decreased incidence of new vertebral fractures during year 3 compared to that in year 2. In the patients who received minodronate in the original 2-year study, lumbar bone mineral density (BMD) increased consistently during year 3 and bone turnover markers decreased within the first 6 months and remained constant thereafter over 3 years. Similar positive effects of minodronate on BMD and bone turnover markers occurred when therapy was initiated in the placebo/minodronate group. No new safety concerns observed during the extension period compared to the safety observations made during the 2-year study. It was concluded that daily administration of 1 mg oral minodronate is safe and well tolerated, and that the efficacy of this dose in reducing vertebral fracture risk in postmenopausal women over 2 years is sustained with continuing treatment.

Keywords Osteoporosis · Bisphosphonate · Minodronate · Fracture prevention

H. Hagino (✉)
School of Health Science, Tottori University
Faculty of Medicine, Tottori, Japan
e-mail: hagino@med.tottori-u.ac.jp

M. Shiraki
Research Institute and Practice for Involutional Diseases, Nagano, Japan

M. Fukunaga
Kawasaki Medical School, Okayama, Japan

T. Nakano
Tamana Central Hospital, Kumamoto, Japan

K. Takaoka
Hanwa Joint Reconstruction Center Hospital, Osaka, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan

T. Nakamura
Department of Orthopedic Surgery, University of Occupational and Environmental Health, Fukuoka, Japan

T. Matsumoto
Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medical Science, Tokushima, Japan

Introduction

Osteoporosis and osteoporosis-related fractures are major concerns in many countries due to the rapid increase in the elderly population. This has led to development of drugs for prevention of fragility fractures. Among anti-osteoporosis agents, nitrogen-containing bisphosphonates are the most commonly prescribed for prevention and treatment of

postmenopausal osteoporosis. This class of drugs includes minodronate (ONO-5920/YM529), which is currently marketed in Japan for treatment of osteoporosis [1, 2]. Preclinical studies have shown that minodronate is at least 10 times more potent than alendronate in inhibiting bone resorption in vivo and in vitro [3] with intermediate mineral-binding affinity [4]. A double-blind head-to-head trial of minodronate and alendronate in women with postmenopausal osteoporosis showed that treatment with each drug for 12 months increased bone mineral density (BMD) at the lumbar spine and the hip in a similar manner [1]. A phase III trial conducted to examine the effect of daily oral 1 mg minodronate for 2 years showed a significant reduction of 59% in the risk of vertebral fracture [2].

Since bisphosphonates are likely to be prescribed for more than 3 years, it is important to determine if the antifracture effect is sustained in long-term treatment. Therefore, the objective of this study was to determine the safety and efficacy of long-term minodronate treatment in women with postmenopausal osteoporosis, based on re-analysis of a phase III 2-year clinical trial with a 1-year extension.

Materials and methods

Study design

A 3-year prospective multicenter intervention study, including a 2-year randomized, double-blind, placebo-controlled study and a 1-year extension study were performed. A full description of the original 2-year study has been published elsewhere [2]. Data for the patients who participated in the extension study were re-analyzed in the current work.

Patients

The subjects in the original 2-year study [2] were women aged 55–80 years old with 1–5 fragility fractures between the T4 and L4 vertebrae, and a lumbar BMD <80% (*T* score −1.7 at the lumbar spine) of the young adult mean (YAM) [5]. In the 2-year study, subjects who met all the entry criteria were sequentially assigned an allocation number independent of the study site. Subjects were randomized to take 1 mg minodronate (Astellas Pharma, Tokyo, Japan) or placebo once a day and were treated for 24 months. The subjects were instructed to take their tablet on rising and 30 min before breakfast with water. All subjects received daily calcium (600 mg) and vitamin D (200 IU) supplementation once a day after the evening meal.

The subjects who completed the 2-year study were invited to participate in an additional 1-year extension, in which all subjects were to receive minodronate (1 mg daily). As in the original 2-year study, all subjects also received 600 mg daily of supplemental calcium and vitamin D_3 (200 IU). Adherence with the study treatment was assessed using medication diaries and counts of residual drug supplies.

This study was conducted with protection of patient rights, as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects gave written informed consent before undergoing any examination or procedure, and all study protocols were conducted in compliance with Good Clinical Practice.

Assessment of fractures

Vertebral fractures were determined based on lateral radiographs of the thoracic and lumbar spine, as described in the report of the original 2-year study [2]. Briefly, prevalent fractures were judged to be present based on a ratio of anterior or middle vertebral body height to posterior vertebral body height <0.8 [6]. Quantitative and semiquantitative techniques [7, 8] were used to identify incident vertebral fractures for the purpose of efficacy determination. Lateral and anterior-posterior radiographs of the thoracic and lumbar spine were taken at 6, 12, 18, 24, 30, and 36 months for assessment of incident fractures. An incidence of new vertebral fracture was diagnosed if the anterior, posterior, or middle vertebral height decreased by at least 15% and by 4 mm in a vertebra that was normal at baseline, or semiquantitatively as a progression in grades [6]. The assessment was performed in a blinded fashion.

All non-vertebral fractures were identified symptomatically as clinical fractures, and only non-traumatic fractures assessed by investigators were recorded. Suspected clinical fractures at six non-vertebral sites (humerus, radius/ulna, clavicle, pelvis, femur, and tibia/fibula) were only listed if confirmed radiographically.

Assessment of bone mineral density

Bone mineral density of the lumbar spine (L2-4) in posteroanterior projections was measured by dual-energy X-ray absorptiometry (DXA) at baseline and 6, 12, 18, 24, 30, and 36 months. BMD measurements were performed in centers in which DXA for the lumbar region and hip was available. Of the centers involved in the study, 19 were equipped with QDR series machines (Hologic, Waltham, MA, USA), 6 with DPX series (General Electric Company, Fairfield, CT, USA), 2 with XR series (CooperSurgical, Inc., Trumbull, CT, USA), and 1 with a BMD 1X series (Hitachi Medical Corporation, Tokyo, Japan) machine for BMD measurements. A central facility (Department of Nuclear Medicine, Kawasaki Medical School, Okayama,

Japan) performed quality assurance. The DXA machines were calibrated with standardized phantoms.

Assessment of bone turnover

Serum and urine samples were collected at baseline and 6, 12, 18, 24, and 36 months for measurement of bone turnover markers, including urinary total deoxypyridinoline (DPD) measured by high-performance liquid chromatography (SRL, Tokyo, Japan) after acid hydrolysis, urinary type I collagen N-telopeptide (NTX) (Osteomark; Ostex International, Seattle, WA, USA), serum bone-specific alkaline phosphatase (BALP) (Osteolinks BAP; Quidel, San Diego, CA, USA), serum osteocalcin (BGP-IRMA kit; Mitsubishi Kagaku Iatron, Tokyo, Japan), and serum 25-hydroxyvitamin D [25(OH)D] (^{125}I RIA kit; DiaSorin Inc., Saluggia, Italy). For these tests, subjects were asked to visit study sites in the morning, but were not required to visit in a fasted state.

Assessment of adverse events

All subjects were questioned about adverse events at each visit, and all reported adverse events were analyzed, regardless of the assessment of causality by investigators. The Medical Dictionary for Regulatory Activities (MedDRA, Version 8.1J) was used to categorize reported adverse events.

Statistical analysis

All data analyses were performed by statisticians from Ono Pharmaceuticals under the supervision of one of the authors (Y.O.), who also confirmed the validity of these analyses. The safety analysis population comprised all patients who received at least one dose in either treatment group. A full analysis set (FAS) was used for primary analysis of bone turnover markers because these data can change rapidly due to protocol violations, interruption of therapy, or concurrent illness. Statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA).

We evaluated the cumulative incidence of vertebral fractures for 3 years using an actuarial method (the life-table method). Lumbar spine BMD was expressed as a percentage relative to 100% at baseline. Differences in BMD between baseline and each measurement point were tested by paired *t* test. Those between the minodronate and placebo/minodronate groups were tested by unpaired *t* test. Data for bone turnover markers were expressed as a percentage relative to 100% at baseline, and differences between the minodronate and placebo/minodronate groups were tested by unpaired *t* test. Differences were considered to be significant if the *p* value was <0.05.

Results

Patient characteristics and disposition

Of the 492 subjects who completed 2 years of treatment, 444 agreed to participate in the 1-year extension study (218 from the placebo group and 226 from the minodronate group). A total of 380 (186 from the placebo group and 194 from the minodronate group) completed the extension study (Fig. 1). The characteristics of the extension study population at the time of enrollment into the original study (Table 1) were similar to those of the original cohort [2].

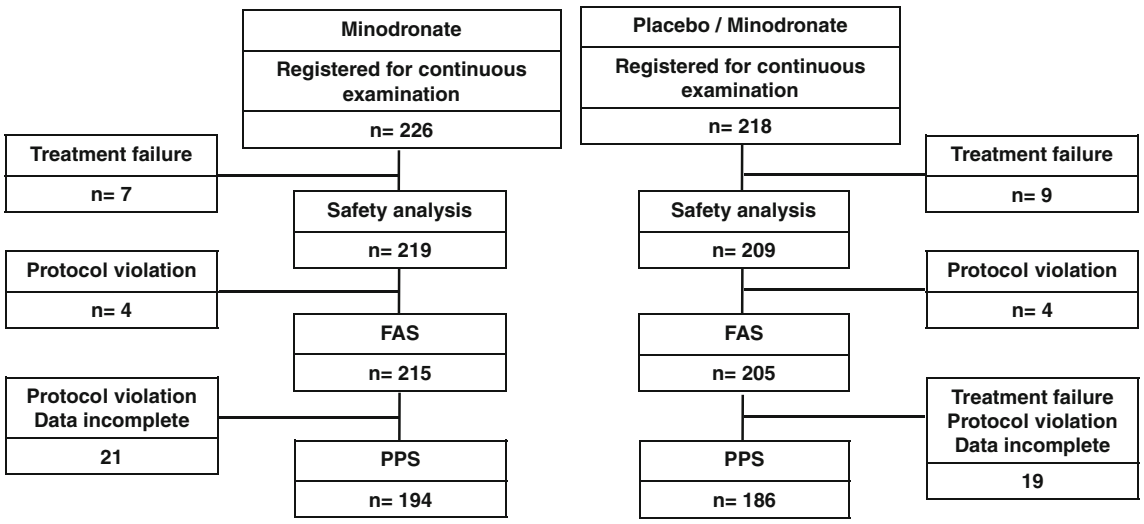

Fig. 1 Enrollment and outcomes. Of the 492 patients who completed 2 years of treatment, 444 agreed to participate in the extension study (218 from the placebo group and 226 from the minodronate group). A total of 380 patients (186 from the placebo group and 194 from the minodronate group) completed the extension study. *FAS* full analysis set, *PPS* per-protocol set

Table 1 Demographics and baseline characteristics of subjects

Characteristic	Minodronate ($n = 215$)	Placebo/ minodronate ($n = 205$)
Age (years)	71.1 (0.4)	71.1 (0.4)
Height (cm)	147.66 (0.41)	147.39 (0.40)
Body mass index (kg/m^2)	23.26 (0.21)	23.54 (0.23)
Time since menopause (years)	21.3 (0.5)	21.4 (0.5)
Number of prevalent vertebral fractures	1.9 (0.1)	1.9 (0.1)
With one fracture [*n* (%)]	106 (49.3)	103 (50.2)
With two fractures [*n* (%)]	52 (24.2)	47 (22.9)
With three or more fractures [*n* (%)]	57 (26.5)	55 (26.8)
Lumbar BMD (% of YAM)	64.77 (0.65)	64.74 (0.65)
Serum 25(OH)D (ng/mL)	24.96 (0.42)	26.17 (0.42)
Serum BALP (U/L)	32.62 (0.66)	33.23 (0.90)
Serum osteocalcin (ng/mL)	9.21 (0.19)	9.12 (0.20)
Urine total DPD (pmol/μmol Cr)	8.66 (0.25)	8.89 (0.23)
Urine NTX (nmol BCE/mmol Cr)	49.49 (1.47)	51.76 (1.60)

Data are means [SE] for the indicated number of subjects in each group

Fractures

Four subjects in the placebo/minodronate group and 6 in the minodronate group had at least one new morphometric vertebral fracture during the extension study. The Kaplan–Meier estimates of the incidence of new vertebral fractures after 36 months of treatment were 13.6% in the minodronate group and 23.5% in the placebo/minodronate group in the FAS population (Fig. 2). The incidence of new vertebral fractures during year 3 was 2.0%/year for the placebo/minodronate group and 2.9%/year for the minodronate group. In the minodronate group, the incidence of new vertebral fractures during year 3 was similar to that during year 2 (4.2%/year). In contrast, the placebo/minodronate group showed a decreased incidence of new vertebral fractures during year 3 compared to that in year 2 (10.3%/year).

Non-vertebral fractures that occurred during the 1-year extension study were determined from reports of clinical fractures and confirmed by radiographs. The rate of non-vertebral fractures of 3.9% (8 subjects) in the placebo/minodronate did not differ significantly from that of 3.3% (7 subjects) in the minodronate group.

Bone mineral density

Lumbar spine BMD was measured in 125 patients (64 in the minodronate group and 61 in the placebo/minodronate group). Over 3 years, minodronate treatment produced a significant increase in lumbar spine BMD of 10.4% from baseline, with a steady increase from 6 to 36 months (Fig. 3). The changes in the minodronate group were significant compared with baseline and with placebo at 24 months. Lumbar spine BMD increased steadily in a linear manner from 24 months until the end of the extension study. In the placebo/minodronate group, lumbar spine BMD did not increase in the first 2 years, but was significantly increased by 6.1% by minodronate administration during year 3.

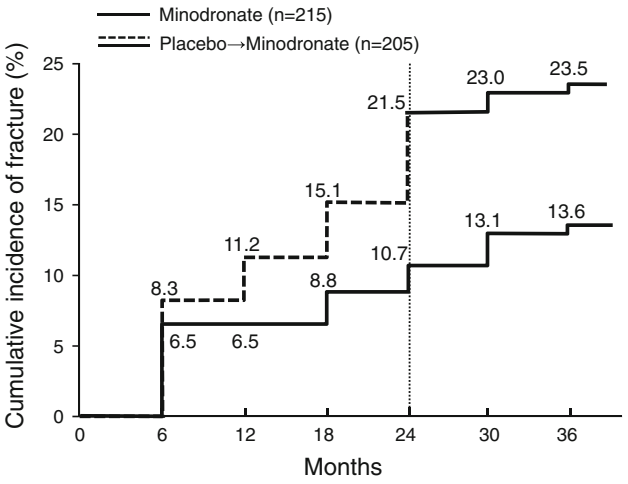

Fig. 2 Kaplan–Meier estimates of the effect of daily oral minodronate (1 mg) for 3 years on the risk of vertebral fractures in osteoporotic subjects

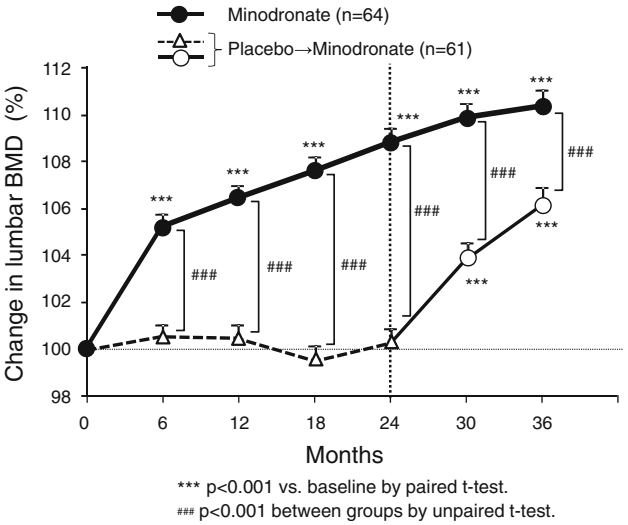

Fig. 3 Changes in lumbar spine BMD after treatment with daily oral minodronate (1 mg). Values are means ± SE. ***$p < 0.001$ versus baseline by paired *t* test. ###$p < 0.001$ between the groups by unpaired *t* test

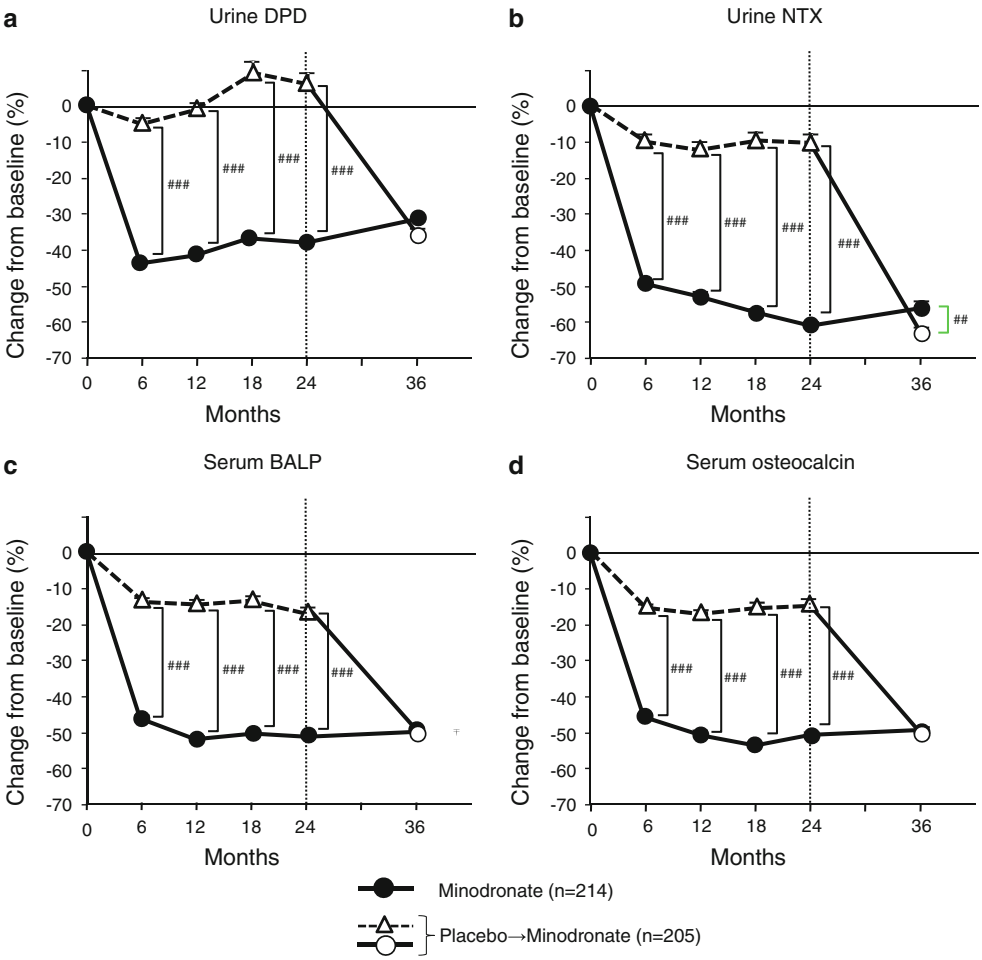

Fig. 4 Changes in bone turnover markers after treatment with daily oral minodronate (1 mg). **a** Urine total deoxypyridinoline (DPD), **b** urine type I collagen N-telopeptide (NTX), **c** serum bone-specific alkaline phosphatase (BALP), **d** serum osteocalcin (OC). Values are means ± SE. $^{###}p < 0.001$ between the groups by unpaired *t* test

Bone turnover markers

Bone resorption markers

In the minodronate group, urine DPD and NTX were rapidly reduced by 42.87% and 49.83% within 6 months, respectively, and remained relatively constant thereafter (Fig. 4a, b). In the placebo/minodronate group, these markers were reduced by 4.37 and 9.65%, respectively, within 6 months, and there were significant differences between the two groups until 2 years. After initiation of minodronate treatment in year 3, the markers in the placebo/minodronate group showed substantial reductions. At the end of the 3-year study period, there was no significant difference between the two groups in urine DPD and urine NTX in the placebo/minodronate group was lower than that in the minodronate group.

Bone formation markers

In the minodronate group, serum bone-specific alkaline phosphatase (BALP) and osteocalcin (OC) showed reductions of 46.44% and 45.73% from baseline, respectively, within the first 6 months and remained constant thereafter (Fig. 4c, d). In the placebo/minodronate group, small reductions of these respective markers by 13.66% and 15.20% from baseline were observed within the first 6 months, but there were significant differences in both markers between the two groups after 2 years. After initiation of minodronate treatment in year 3, substantial reductions in both markers were observed in the placebo/minodronate group, and the differences with the minodronate group had disappeared at the end of the 3-year study period.

Serum calcium and 25(OH)D

No significant change was observed in serum calcium and 25(OH)D during the 3-year study period.

Safety

The proportion of subjects reporting serious adverse events or withdrawing due to an adverse event during the

Table 2 Summary of adverse events

	Minodronate	Placebo/minodronate
Drug-related adverse events		
No. of patients	219	209
Total	26 (11.9)	–
First year	14 (6.4)	11 (5.3)
Second year	8 (3.7)	10 (4.8)
Third year	9 (4.1)	12 (5.7)
Drug-related gastrointestinal adverse events		
No. of patients	219	209
Total	17 (7.8)	–
First year	12 (5.5)	5 (2.4)
Second year	2 (0.9)	1 (0.5)
Third year	4 (1.8)	1 (0.5)

extension study was similar in the minodronate and minodronate/placebo groups (Table 2). The incidence of gastrointestinal tract adverse events also was similar in the two groups (Table 2). Neither osteonecrosis of the jaw nor atypical subtrochanteric or diaphyseal femoral fracture [9] was observed in either group. Overall, minodronate was well tolerated during the extension study, with no new safety concerns observed during the extension period compared to the safety observations made during the 2-year study.

Discussion

This study was designed to determine the long-term efficacy and safety of minodronate in women with postmenopausal osteoporosis, based on re-analysis of a 2-year prospective double-blinded randomized study with a 1-year extension. Although the extension study did not have a placebo arm, the data showed no indication of any loss of anti-fracture efficacy after 2 years of minodronate treatment. In addition, those patients who had been on calcium and vitamin D supplementation for 2 years and then received treatment with minodronate showed a substantial reduction in the incidence of vertebral fracture after 6 months of minodronate administration. In the patients who received minodronate in the original 2-year study, lumbar BMD changes were consistent and bone turnover markers decreased within the first 6 months and remained constant thereafter over 3 years. Similar positive effects of minodronate on BMD and bone turnover markers occurred when therapy was initiated in the placebo/minodronate group, which is consistent with previous extension studies of bisphosphonates [10].

In the original 2-year study [2], a large number of vertebral fractures occurred during the first 6 months in both the minodronate and placebo groups. We speculated that some of these vertebral fractures might actually have occurred before drug administration was started, since the assessment of vertebral fractures at baseline was performed within 2 months of the start of minodronate administration [2]. On the contrary, in the extension study, minodronate treatment reduced the incidence of vertebral fracture to 1.5% in the placebo/minodronate group during the first 6 months, compared to 6.4% during the last 6 months of placebo treatment. This preventive effect might reflect the fundamental potential of minodronate under conditions in which calcium and vitamin D levels are sufficient. In the original 2-year study, when fractures during the first 6 months were eliminated, the risk of vertebral fractures from 6 to 24 months was reduced by 74% in the minodronate group, which is very similar to the reduction observed during the first 6 months in the extension study in the placebo/minodronate group. In previous fracture prevention studies of bisphosphonates and selective estrogen receptor modulators, relative risk reductions for 3 years of 47% [11], 41% [6], and 30% [12] were found with alendronate, risedronate, and raloxifene, respectively. Therefore, the relative risk reduction due to minodronate in the current study is comparable to or greater than those produced by other drugs, although we note that this comparison is not based on a head-to-head trial.

The changes in lumbar spine BMD and bone turnover markers were consistent with continuing efficacy over 3 years, and over-suppression of bone turnover markers was not observed. These results are reassuring regarding both the long-term efficacy and safety of minodronate treatment. The findings of continuing benefits with long-term minodronate treatment are important, given the chronic nature of osteoporosis. The increase in BMD changes in the current study is similar to those in previous studies with alendronate [13, 14] and risedronate [6], which demonstrated sustained increases in BMD for up to 3 years. The increases in lumbar spine BMD were largely due to an increased degree of secondary mineralization [15]. It is also possible that part of the increase in lumbar spine BMD was artifactual due to progressive osteoarthritic changes with aging.

With regard to the safety profile of minodronate, the drug appeared to be well tolerated during this 3-year study. Safety assessment is difficult due to the lack of a placebo arm, but the overall incidence of adverse events in year 3 was similar to that in the first 2 years of the study [2], especially with regard to gastrointestinal adverse events. Osteonecrosis of the jaw and atypical subtrochanteric or diaphyseal femoral fracture are major concerns in patients with longer term administration of bisphosphonates. We did not observe these adverse events in either group, but the risks for these events are low in patients receiving

bisphosphonates for less than 3 years [16, 17]. Therefore, observation of patients treated with minodronate for a longer period is needed to clarify the longer term risk of these adverse events.

The present study has several limitations. The number of patients was relatively small and the extension study did not have a placebo arm. It is also possible that patients who elected to enter the extension study were not representative of the original cohort and may differ from patients who elected not to participate in this part of the study. Therefore, we did not perform a statistical comparison of the two groups or periods in the fracture risk incidence. However, the baseline characteristics of the extension cohort were similar to the original study cohort, which indicates that the results of the study are likely to be reflective of the entire cohort. A strength of the study is that spinal radiographs were obtained for all patients at entry and at the conclusion of the study, which allowed an accurate assessment of the incidence of radiographic vertebral fractures.

In conclusion, a 1-year extension study in postmenopausal osteoporotic women showed that daily administration of 1 mg oral minodronate is safe and well tolerated, and that the efficacy of this dose in reducing vertebral fracture risk in postmenopausal women over 2 years is sustained with continuing treatment. The study also demonstrated that initiating minodronate therapy after 2 years of calcium and vitamin D treatment had the expected positive effects on fractures, bone turnover markers, and BMD.

Acknowledgments We thank Dr. H. Morii, Osaka City University Medical School, Osaka, Japan, and clinical sites in Japan that participated in this study: T. Ota, Ota Orthopedic Clinic; M. Kokaji, M. Tsuji, S. Kawamura, Kobayashi Hospital; T. Hashimoto, Hakodate Koseiin Hakodate Central General Hospital; S. Sato, Eniwa Hospital; G. Katahira, Sapporo Kiyota Orthopaedic Hospital; Y. Saito, Hokuei Orthopedics; T. Fukunaga, Ainosato Orthopedics; T. Ando, Morioka Hospital; S. Tsukikawa, Tsukikawa Lady's Clinic; S. Harada, Tsukuba Gakuen Hospital; N. Tajima, Tajima Geka Ichouka; K. Ogata, Seiwakai Shoda Hospital; T. Michimata, Uchibori Seikeigeka Iin; H. Inoue, Inoue Hospital; M. Inuzuka, Chousei Hospital; S. Ichikawa, Cardiovascular Hospital of Central Japan; K. Toba, Toba Orthopedic Clinic; Y. Kaneda, Kaneda Orthopedics; S. Yamada, Kyoai Clinic; K. Fukuda, Shiratori Clinic; A. Yamaguchi, Yamaguchi Hospital; T. Nakamura, Abe Clinic; K. Maruyama, Gate Town Hospital; T. Nakagawa, Senpo Tokyo Takanawa Hospital; T. Takemoto, Misyuku Hospital; K. Kamada, Kumegawa Hospital; S. Yamaguchi, Gonohashi Clinic; C. Nokubo, Nokubo Orthopedic Clinic; M. Takemoto, Takemoto Orthopedics; T. Ishihara, Shirahigebashi Hospital; Y. Tsuruta, Tsuruta Clinic; S. Yamazaki, Sengoku Hospital; T. Ishibashi, T. Okubo, Oguchi East Hospital; Y. Mikami, Yokohama Rosai Hospital; I. Miyata, Aoba Orthopedics Clinic; M. Kasuga, Kasuga Orthopedics; N. Nagata, Nagata Orthopedics; Y. Murai, Murai Orthopedic Iin; S. Noto, Noto Orthopedics; M. Katsumi, Katsumi Orthopedics; H. Morishita, T. Takino, Kanazawa Social Insurance Hospital; N. Hachisuka, Hachisuka Orthopedics; M. Takimori, Nirasaki Mutual Hospital; Y. Nagasaka, Nagasaka Orthopedics; M. Suzuki, Suzuki Orthopedic Iin; S. Kumaki, Hokushin General Hospital; T. Hanaoka, Yamabe Spa Hanaoka Orthopedics; H. Misawa, Yodakubo Hospital; M. Shiraki, Research Institute and Practice for Involutional Diseases; S. Tsuboi, Shizuoka Kosei Hospital; K. Yamazaki, Hamamatsu University School of Medicine University Hospital; M. Taniguchi, Taniguchi Orthopedic Iin; M. Fukuchi, Aobadai Fukuchi Orthopedics and Gastroenterology Clinic; M. Denda, Denda Orthopedics; Y. Nishijima, Nishijima Hospital; Y. Osaka, Minamiosaka Hospital; A. Tei, Kishiwada Tokushukai Hospital; N. Sha, Kanebo Memorial Hospital; C. Terada, Ako Central Hospital; J. Sako, Irie Hospital; Y. Higashi, Himeji Central Hospital; T. Onishi, Onishi Orthopedics; T. Matsubara, Matsubara Clinic; Y. Koyama, K. Atsui, Matsubara Mayflower Hospital; M. Ozaki, Kitade Hospital; M. Ohama, Yonago East Hospital; H. Sanada, Sanada Hospital; K. Sanuki, Sanuki Orthopedic and Rheumatic Clinic; T. Taguchi, Yamaguchi University Hospital; S. Yamagata, Yamagata Iin; K. Nobutani, Sea Side Hospital; H. Yamazaki, H. Ueno, H. Murata, Y. Tanigawa, Mine City Hospital; S. Ono, Marugame Ono Clinic; T. Ogata, Ogata Orthopedic Hospital; H. Ikematsu, Haradoi Hospital; A. Iwaki, K. Domen, Okabe Hospital; Y. Ishibashi, Ishibashi Orthopedics; T. Tsuruta, Tsuruta Orthopaedic Clinic; H. Shibata, Shibata Chokodo Hospital; T. Segata, Kumamoto Saishunso National Hospital; T. Naono, Oita Oka Hospital; E. Nakamura, Nakamura Hospital; S. Okamoto, Sanyo Osteoporosis Research Foundation Okamoto Naika Clinic. The present study was sponsored by Ono Pharmaceutical Co., Ltd. and Astellas Pharma Inc.

Conflict of interest None of the authors are or were employed by Astellas Pharmaceutical or Ono Pharmaceutical.

References

1. Hagino H, Nishizawa Y, Sone T, Morii H, Taketani Y, Nakamura T, Itabashi A, Mizunuma H, Ohashi Y, Shiraki M, Minamide T, Matsumoto T (2009) A double-blinded head-to-head trial of minodronate and alendronate in women with postmenopausal osteoporosis. Bone 44:1078–1084
2. Matsumoto T, Hagino H, Shiraki M, Fukunaga M, Nakano T, Takaoka K, Morii H, Ohashi Y, Nakamura T (2009) Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: a randomized placebo-controlled double-blind study. Osteoporos Int 20:1429–1437
3. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, Rogers MJ (2001) Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. J Pharmacol Exp Ther 296:235–242
4. Ebetino FH, Hogan AM, Sun S, Tsoumpra MK, Duan X, Triffitt JT, Kwaasi AA, Dunford JE, Barnett BL, Oppermann U, Lundy MW, Boyde A, Kashemirov BA, McKenna CE, Russell RG (2011) The relationship between the chemistry and biological activity of the bisphosphonates. Bone 49:20–33
5. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
6. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral

Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 282:1344–1352
7. Wu CY, Li J, Jergas M, Genant HK (1995) Comparison of semiquantitative and quantitative techniques for the assessment of prevalent and incident vertebral fractures. Osteoporos Int 5:354–370
8. Genant HK, Wu CY, van Kuijk C, Nevitt MC (1993) Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 8:1137–1148
9. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA et al (2010) Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 25:2267–2294
10. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA (2004) Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 75:462–468
11. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348:1535–1541
12. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
13. Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora AC 2nd (1996) Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 101:488–501
14. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199
15. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ (2000) Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone 27:687–694
16. Park-Wyllie LY, Mamdani MM, Juurlink DN, Hawker GA, Gunraj N, Austin PC, Whelan DB, Weiler PJ, Laupacis A (2011) Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA 305:783–789
17. Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, Taguchi A, Toyosawa S, Nagata T, Urade M (2010) Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab 28:365–383