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ORIGINAL ARTICLE

Monthly oral ibandronate 100 mg is as effective as monthly intravenous ibandronate 1 mg in patients with various pathologies in the MOVEST study

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Abstract The non-inferiority of oral ibandronate 100 mg to intravenous (i.v.) ibandronate 1 mg in increasing lumbar spine (LS) bone mineral density (BMD) after 12 months of treatment was demonstrated in the randomized, phase III MOVEST study. We conducted subgroup analyses in the per-protocol set of the study ($n = 183$ oral ibandronate; $n = 189$ i.v. ibandronate). In patients with LS BMD T score ≥ -3.0 or < -3.0 at screening, LS BMD gains from baseline were 4.42 and 5.79%, respectively, with oral ibandronate, and 4.60 and 5.83%, respectively, with i.v. ibandronate. LS BMD gains in patients with or without prevalent vertebral fractures were 5.21 and 5.23%, respectively, with oral ibandronate, and 5.01 and 5.49%, respectively, with i.v. ibandronate. In patients aged <75 or ≥75 years, LS BMD gains were 5.46 and 4.51%, respectively, with oral ibandronate, and 5.25 and 5.77%, respectively, with i.v. ibandronate. LS BMD gains in patients with baseline 25-hydroxyvitamin D levels ≥20 or <20 ng/mL were 5.35 and 4.76%, respectively, with oral ibandronate, and 5.05 and 6.57%, respectively, with i.v. ibandronate. Similar results were obtained in patients with or without prior bisphosphonate (BP) treatment, and in those receiving osteoporosis drug treatment other than BPs. In conclusion, oral ibandronate 100 mg demonstrated comparable BMD gains with monthly i.v. ibandronate, and thus shows high utility in the lifestyle and disease conditions associated with osteoporosis in Japanese patients.

Keywords Ibandronate · Intravenous · MOVEST study · Oral

Introduction

As first-line treatment for osteoporosis, once-monthly intermittent dosing regimens of bisphosphonates (BPs) have been widely preferred by patients to more frequent administration [1, 2]. The availability of monthly intravenous (i.v.) ibandronate 1 mg in Japan, as well as the recent addition of monthly oral ibandronate 100 mg, has also increased patient adherence in daily practice.

In Western countries, two formulations of ibandronate are commercially available—monthly oral 150 mg and quarterly i.v. 3 mg/3 months. These ibandronate regimens, with an annual cumulative exposure (ACE) ≥10.8 mg, significantly reduced the risk of vertebral and non-vertebral fractures compared with ibandronate regimens with low ACE or placebo in the Monthly Oral iBandronate In LadiEs (MOBILE) and Dosing IntraVenous Administration (DIVA) studies, which showed superior bone mineral density (BMD) increases to the daily oral regimen [3, 4]. Increases in BMD at all sites were maintained in long-term extensions of these two studies [5, 6]. The significant efficacy of monthly oral and quarterly i.v. regimens of ibandronate in risk reduction of vertebral, non-vertebral and clinical fractures was also confirmed in meta-analyses of

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these registration trials [7, 8]. Furthermore, a significantly longer time to fracture with intermittent regimens of ibandronate versus placebo over 5 years was reported in a post hoc analysis of individual patient data from the MOBILE and DIVA studies, plus the long-term extensions [9].

Two formulations of ibandronate were developed in Japan, based on the ACE concept. The MOnthly intraVenous ibandronatE versus daily oral Risedronate (MOVER) study demonstrated the non-inferiority of monthly i.v. ibandronate 1 mg (ACE of 12.0 mg) to oral risedronate in vertebral fracture risk reduction [10, 11]. Monthly i.v. ibandronate 1 mg consistently reduced the incidence of not only vertebral fractures, but also non-vertebral fractures, compared with risedronate [12]. The efficacy and safety of monthly oral ibandronate 100 mg was compared with monthly i.v. ibandronate 1 mg in the Monthly Oral VErsus intravenouS ibandronaTe (MOVEST) study in Japanese patients with osteoporosis [13]. The non-inferiority of monthly oral ibandronate 100 mg to i.v. ibandronate 1 mg was demonstrated in terms of the mean relative change from baseline in lumbar spine (LS) BMD after 12 months of treatment. Subsequently, both formulations of ibandronate were made commercially available in Japan.

Osteoporosis is a skeletal disorder which has various pathologies requiring long-term treatment duration. To accumulate further evidence for the efficacy of monthly oral ibandronate 100 mg in patients with osteoporosis, and to determine whether the two monthly formulations of ibandronate would have comparable efficacy in various osteoporotic-related disease conditions, we performed subgroup analyses of the MOVEST study.

Materials and methods

Study design and population

Patient subgroups used in this analysis originated from the MOVEST study [13], where monthly oral ibandronate 100 mg was compared with monthly i.v. ibandronate 1 mg in Japanese women and men with osteoporosis (Clinical trial number JapicCTI-121982). Ambulatory patients aged ≥55 years with primary osteoporosis were randomized to receive monthly oral ibandronate 100 mg plus monthly i.v. placebo, or monthly i.v. ibandronate 1 mg plus monthly oral placebo. All patients received supplementary calcium 610 mg and vitamin D 400 IU/day during the study. Study drug administration was recorded by the investigator at the time of dosing. Prior continuous treatment with other BPs within 1 year of the start of the study, or with teriparatides, was not permitted. Informed consent was obtained from all patients prior to any study-related procedures.

The primary endpoint of the study was to prove the non-inferiority of oral versus i.v. ibandronate with respect to LS BMD gains after 12 months of treatment. The primary analysis was performed on the per-protocol set (PPS). BMD was evaluated by the relative change from baseline. Missing data were imputed by the last observation carried forward method.

Subgroup analysis

LS BMD gains were compared in the following pre-defined subgroups—LS BMD *T* score at screening (≥ −3.0 or < −3.0), prevalent vertebral fracture (yes or no), age (<75 or ≥75 years), baseline vitamin D (25-hydroxyvitamin D [25(OH)D] levels ≥20 or <20 ng/mL), BPs as a prior treatment (yes or no), and prior osteoporosis drug treatment other than BPs within 1 year of the start of the study (yes or no). Patients eligible for the MOVEST study had LS BMD <70% of the young adult mean (YAM) or <80% of the YAM with fragile bone fracture. The cut-off value for randomization was based on a *T* score of −3.0 [13], which is <70% of the YAM in Japan. The age categories of <75 or ≥75 years were chosen due to the overall health status of elderly Japanese people. The 25(OH)D level was set at 20 ng/mL for subgroup analysis, as levels <20 ng/mL are reported as vitamin D deficiency in Japan [14].

Schedule of assessments

All BMD measurements were performed centrally (BioClinica, Newark, CA, USA) at screening, baseline, and at 4, 6, and 12 months using dual energy X-ray absorptiometry (DXA) of Hologic bone densitometers. Measurements of a quality control phantom were collected and analyzed by BioClinica to monitor the stability of each DXA scanner. Each study site received the cross-calibration phantom results and cross-calibration scans were sent to BioClinica for processing and statistical analysis.

Results

Patient disposition and baseline characteristics

A total of 422 patients were enrolled, with 205 and 203 patients (198 and 199 women) randomized to receive monthly oral ibandronate 100 mg and i.v. ibandronate 1 mg, respectively. Overall, 177 and 184 patients in the oral and i.v. ibandronate groups, respectively, completed the study. The PPS for the primary endpoint analysis comprised 183 and 189 patients in the oral and i.v. ibandronate groups,

respectively. Baseline patient characteristics between the two treatment groups were well balanced (Table 1).

Bone mineral density in subgroups

The mean relative change in LS BMD values from baseline to 12 months for oral 100 mg and i.v. 1 mg ibandronate, respectively, was 5.22% [95% confidence interval (CI) 4.65–5.80%] and 5.34% (95% CI 4.78–5.90%) [13].

In patients with LS BMD *T* score ≥ −3 or < −3 at screening, LS BMD gains at 12 months were 4.42% (95% CI 3.64–5.21%) and 5.79% (95% CI 4.99–6.59%), respectively, with oral ibandronate, and 4.60% (95% CI 3.77–5.44%) and 5.83% (95% CI 5.07–6.58%), respectively, with i.v. ibandronate (Fig. 1a, b). LS BMD gains in patients with or without prevalent vertebral fractures were 5.21% (95% CI 4.11–6.31%) and 5.23% (95% CI 4.55–5.91%), respectively, with oral ibandronate, and 5.01% (95% CI 3.83–6.19%) and 5.49% (95% CI 4.86–6.12%), respectively, with i.v. ibandronate at 12 months (Fig. 1c, d).

In patients aged <75 or ≥75 years, LS BMD gains at 12 months were 5.46% (95% CI 4.83–6.09%) and 4.51% (95% CI 3.17–5.85%), respectively, with oral

Table 1 Baseline patient characteristics

Characteristic	Ibandronate	
	Oral 100 mg/month ($n = 183$)	i.v. 1 mg/month ($n = 189$)
Women, *n* (%)	177 (96.7)	186 (98.4)
BMD *T* score at screening, *n* (%)		
Lumbar spine (L2–L4) ≥ −3.0	76 (41.5)	75 (39.7)
Lumbar spine (L2–L4) < −3.0	107 (58.5)	114 (60.3)
Prevalent vertebral fractures, *n* (%)		
0	124 (67.8)	130 (68.8)
≥1	59 (32.2)	59 (31.2)
Age, years, *n* (%)		
55–74 years	138 (75.4)	156 (82.5)
≥75 years	45 (24.6)	33 (17.5)
25(OH)D, ng/mL, *n* (%)		
≥20 ng/mL	145 (79.2)	153 (81.0)
<20 ng/mL	38 (20.8)	36 (19.0)
BPs as a prior treatment, *n* (%)		
Yes	39 (21.3)	46 (24.3)
No	144 (78.7)	143 (75.7)
Prior osteoporosis drug treatment other than BPs or teriparatide, *n* (%)		
Yes	51 (27.9)	61 (32.3)
No	132 (72.1)	128 (67.7)
BMD value at baseline by subgroup, g/cm^2, mean (SD)		
Lumbar spine (L2–L4) ≥ −3.0	0.705 (0.047)	0.702 (0.045)
Lumbar spine (L2–L4) < −3.0	0.599 (0.045)	0.594 (0.049)
Prevalent vertebral fractures 0	0.633 (0.061)	0.636 (0.065)
Prevalent vertebral fractures ≥1	0.665 (0.081)	0.640 (0.082)
Age 55−74 years	0.646 (0.066)	0.638 (0.070)
Age ≥75 years	0.635 (0.080)	0.632 (0.078)
25(OH)D ≥20 ng/mL	0.641 (0.068)	0.640 (0.073)
25(OH)D <20 ng/mL	0.651 (0.075)	0.627 (0.062)
BPs as a prior treatment: yes	0.656 (0.058)	0.643 (0.066)
BPs as a prior treatment: no	0.640 (0.072)	0.636 (0.072)
Prior osteoporosis drug treatment other than BPs or teriparatide: yes	0.645 (0.068)	0.628 (0.075)
Prior osteoporosis drug treatment other than BPs or teriparatide: no	0.643 (0.070)	0.642 (0.069)

Values are the mean, except where indicated

BMD bone mineral density, *25(OH)D* 25-hydroxyvitamin D

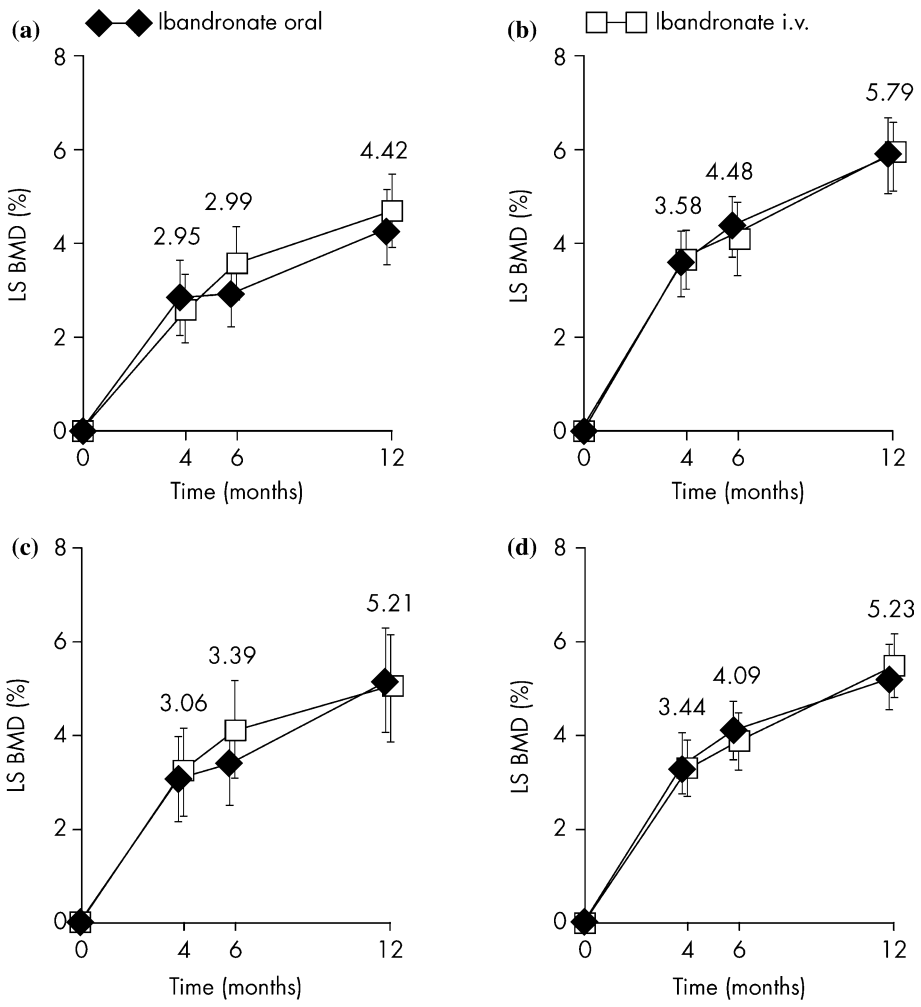

Fig. 1 Mean relative change from baseline to 12 months (with 95% CI) in LS BMD in patients with LS BMD *T* scores **a** ≥ −3.0 or **b** < −3.0 at screening, and **c** with or **d** without prevalent vertebral fractures. Patient numbers **a** oral ($n = 76$), i.v. ($n = 75$), **b** oral ($n = 107$), i.v. ($n = 114$), **c** oral ($n = 59$), i.v. ($n = 59$), **d** oral ($n = 124$), i.v. ($n = 130$)

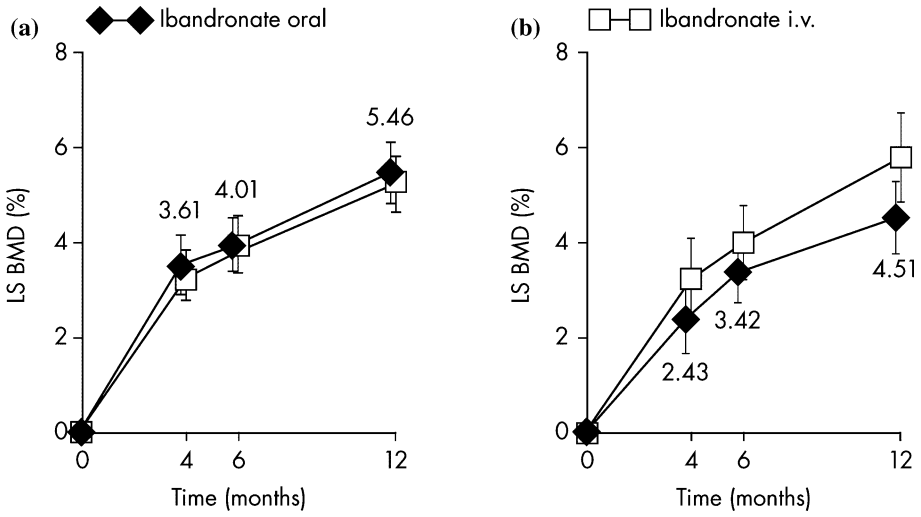

Fig. 2 Mean relative change from baseline to 12 months (with 95% CI) in LS BMD in patients aged **a** <75 years or **b** ≥75 years. Patient numbers **a** oral ($n = 138$), i.v. ($n = 156$), **b** oral ($n = 45$), i.v. ($n = 33$)

ibandronate, and 5.25% (95% CI 4.64–5.86%) and 5.77% (95% CI 4.24–7.31%), respectively, with i.v. ibandronate (Fig. 2).

LS BMD gains in patients with baseline 25(OH)D levels ≥20 or <20 ng/mL, were 5.35% (95% CI 4.67–6.02%) and 4.76% (95% CI 3.68–5.83%), respectively,

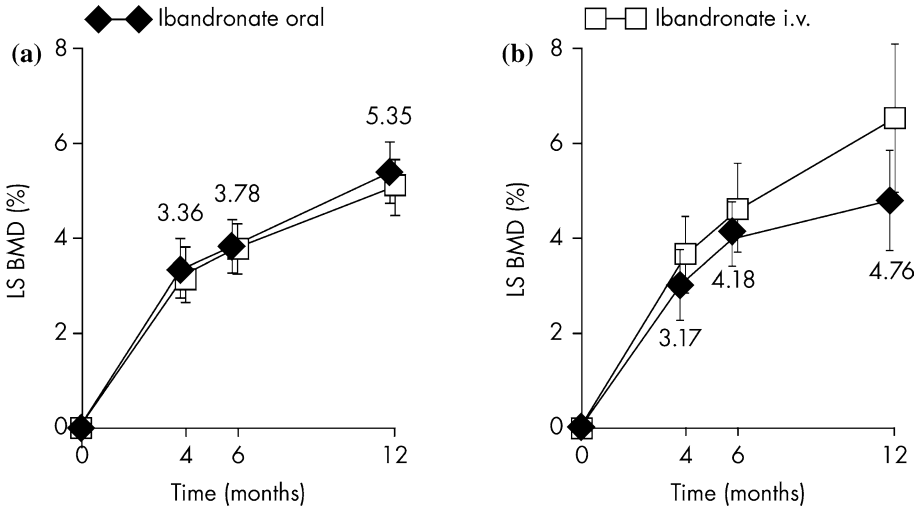

Fig. 3 Mean relative change from baseline to 12 months (with 95% CI) in LS BMD in patients with baseline 25(OH)D levels **a** ≥20 ng/mL or **b** <20 ng/mL. Patient numbers **a** oral ($n = 145$), i.v. ($n = 153$), **b** oral ($n = 38$), i.v. ($n = 36$)

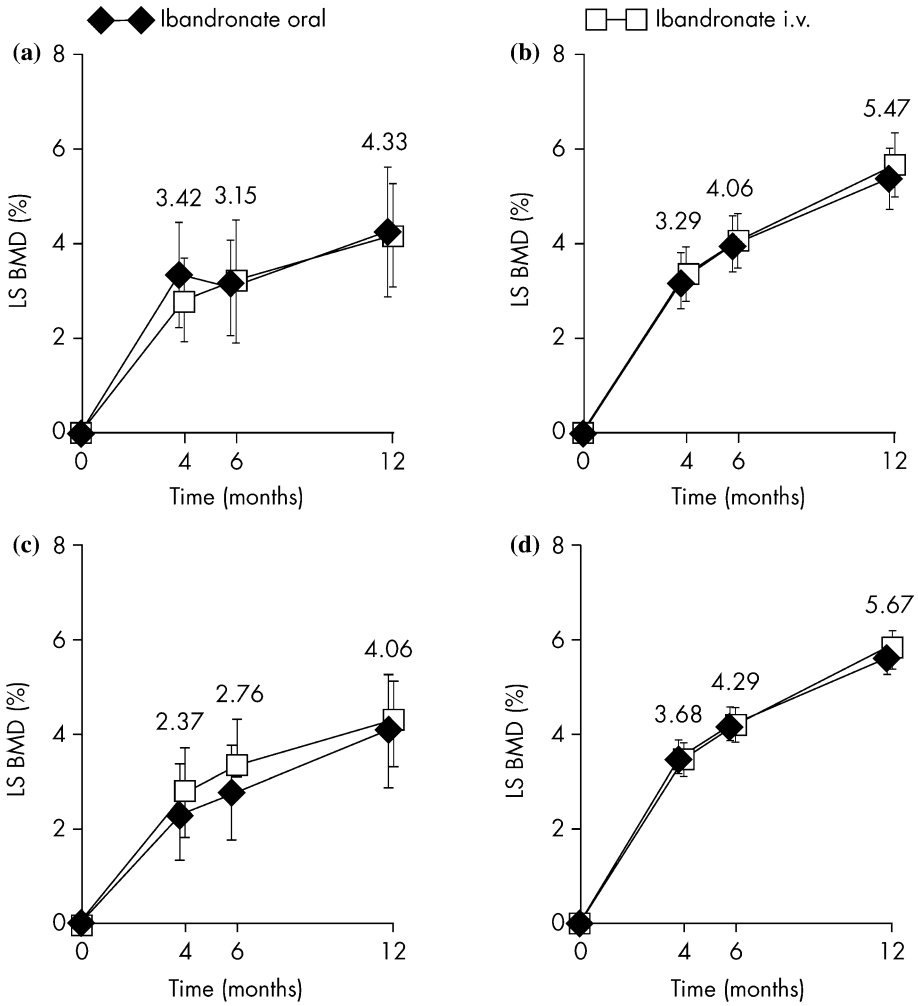

Fig. 4 Mean relative change from baseline to 12 months (with 95% CI) in LS BMD in patients **a** with or **b** without BPs as a prior treatment, and **c** with or **d** without prior osteoporosis drug treatment other than BP. Patient numbers **a** oral ($n = 39$), i.v. ($n = 46$), **b** oral ($n = 144$), i.v. ($n = 143$), **c** oral ($n = 51$), i.v. ($n = 61$), **d** oral ($n = 132$), i.v. ($n = 128$)

with oral ibandronate, and 5.05% (95% CI 4.47–5.63%) and 6.57% (95% CI 4.91–8.22%), respectively, with i.v. ibandronate (Fig. 3).

In patients with or without BP pretreatment, LS BMD gains at 12 months were 4.33% (95% CI 2.96–5.70%) and 5.47% (95% CI 4.83–6.10%), respectively, with oral

ibandronate, and 4.22% (95% CI 3.17–5.27%) and 5.70% (95% CI 5.04–6.36%), respectively, with i.v. ibandronate (Fig. 4a, b). LS BMD gains in patients with or without prior osteoporosis drug treatment other than BPs were 4.06% (95% CI 2.87–5.26%) and 5.67% (95% CI 5.03–6.32%), respectively, with oral ibandronate, and 4.23% (95% CI 3.32–5.13%) and 5.87% (95% CI 5.17–6.57%), respectively, with i.v. ibandronate (Fig. 4c, d). The two formulations of ibandronate demonstrated BMD gains throughout the study and increased BMD levels to the same extent in all of the patient subgroups described.

Discussion

We performed subgroup analyses of patients from the phase III MOVEST study to examine the efficacy of monthly oral ibandronate 100 mg compared with monthly i.v. ibandronate 1 mg in patients with various pathologies of osteoporosis. Oral and i.v. ibandronate demonstrated comparable LS BMD gains in all of the subgroups assessed.

The relationship between BMD gains and fracture risk reduction with ibandronate at high ACE (10.8–12.0 mg) has previously been established [15, 16]. In addition, monthly i.v. ibandronate 1 mg (ACE 12.0 mg) showed anti-fracture efficacy in the MOVER study in Japanese osteoporotic patients [10]. Monthly oral ibandronate 100 mg (ACE 11.0 mg), having demonstrated non-inferiority in BMD gains to monthly i.v. ibandronate 1 mg in the MOVEST study, would also be expected to show efficacy in fracture risk reduction [13, 17]. In the current subgroup analysis of the MOVEST study, oral and i.v. ibandronate increased BMD levels to the same extent in patient subgroups defined by different disease parameters, which would support the hypothesized fracture risk reduction with oral ibandronate 100 mg.

We first examined the efficacy of oral ibandronate 100 mg in high-risk patients, such as those with low LS BMD *T* score at screening (< −3.0) or with prevalent vertebral fractures. In the MOVER study, the incidences of vertebral fractures over 3 years in patients with femoral neck BMD *T* scores < –2.5 were numerically lower with i.v. ibandronate 1 mg than with risedronate [12]. The current analysis showed that increases in LS BMD with oral ibandronate 100 mg were comparable with i.v. ibandronate 1 mg in patients with LS BMD *T* scores at screening < −3.0. Thus, monthly oral ibandronate 100 mg is expected to be efficacious in fracture risk reduction in patients with low BMD *T* score at the start of treatment. Subgroup analysis of the MOVER study also indicated that monthly i.v. ibandronate 1 mg is effective for high-risk osteoporotic patients with multiple prevalent vertebral fractures [12]. In the current analysis, BMD gains with monthly oral ibandronate 100 mg were comparable with those of i.v. ibandronate 1 mg, irrespective of prevalent fracture. Since the MOVEST study enrolled patients diagnosed with osteoporosis according to the Japanese Osteoporosis Guideline [18], some patients had low BMD *T* scores without fracture, meaning that approximately 30% of patients had prevalent fractures, while around 70% of patients were without prevalent fractures. However, results of this subgroup analysis indicated that monthly oral ibandronate 100 mg was efficacious in patients with or without prevalent vertebral fractures.

We also examined patient age as an independent parameter that could impact disease stage [19]. When we divided patients into two age groups, only around 20% of patients were in the older age group (≥75 years). Higher BMD gains were observed in the i.v. ibandronate group in patients aged ≥75 years versus <75 years. Oral ibandronate showed the same range of BMD gains as i.v. ibandronate in this patient subgroup. It is noteworthy that older patients might have comorbid risk factors other than osteoporosis, and therefore further absorptive variation of the oral tablet compared with the i.v. injection might have occurred in the most elderly patient subgroup.

Nakano et al. reported that a small number of non-responders in the monthly i.v. ibandronate 1 mg-treated group in the MOVER study, supplemented with 305 mg of calcium and 200 IU of vitamin D daily, had lower 25(OH) D baseline levels than responders, suggesting that 25(OH) D levels could be a useful indicator of BMD response to therapy [20, 21]. The current subgroup analysis in the MOVEST study, supplemented with 610 mg of calcium and 400 IU of vitamin D daily, showed comparable increases in LS BMD with oral and i.v. ibandronate in patients with low versus high 25(OH)D levels; although LS BMD gains were higher with i.v. versus oral ibandronate in patients with low 25(OH)D levels (<20 ng/mL) at 12 months. The baseline 25(OH)D level of both treatment groups was 25.3 ng/mL. After 1 year of treatment, 25(OH)D levels were 29.0 ng/mL in the oral ibandronate group and 28.2 ng/mL in the i.v. ibandronate group following calcium and vitamin D supplementation. Compliance not only with study drugs, but also supplementation, was well-controlled. However, the reason for this differing result between the treatment groups in the MOVEST study remains unclear. Intravenous administration could lead to better absorption of the agent than oral administration. It is preferable to know the patient's condition, including vitamin D status, when starting ibandronate therapy. If the decision to use i.v. or oral administration was determined according to patient data, rather than just patient preference, this may lead to more efficient outcomes.

BPs are an established first-line therapy for osteoporosis in Japan. Therefore, the influence of BP treatment history and prior osteoporosis drug treatment history other than BPs on subsequent medications are of interest. In

the current analysis, comparable LS BMD increases were observed with oral and i.v. ibandronate in patients with or without prior BP history. There is a possibility that future BMD increases may be attributed not only to ibandronate but also to vitamin D status during prior osteoporosis treatments [22]. It is suggested that treatment history and the necessity for supplementation of sufficient calcium and vitamin D are considered carefully.

There are some limitations to this subgroup analysis. Due to the small sample size of some subgroups, the results should be interpreted with caution. According to the inclusion criteria of the MOVEST study, fewer patients had LS BMD T scores ≥ -3.0 versus <-3.0 at screening. Similarly, the number of patients with prevalent vertebral fractures was less than those without fractures. According to the expansion and penetration of BP therapy in Japan, the number of patients with BP pretreatment was one-third of the overall population.

In conclusion, oral and i.v. ibandronate increased BMD levels to the same extent in patient subgroups defined by LS BMD T score at screening, prevalent vertebral fracture, age, 25(OH)D levels, BP treatment history, and prior osteoporosis drug treatment other than BPs. Monthly ibandronate injections have been widely accepted by patients in Japan and have resulted in improved adherence to medication. Monthly ibandronate tablets could also offer clinical benefit to patients, which may help to maintain adherence in the management of this long-term disease. These data suggest that the availability of two types of formulation of one compound, ibandronate, may enhance treatment compliance for Japanese patients with osteoporosis.

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Compliance with ethical standards

Conflict of interest Hiroshi Hagino has received consulting fees from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Banyu Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corp., Ono Pharmaceutical Co., Ltd., Pfizer Inc., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. Masako Ito has received consulting fees from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Inc., and Ono Pharmaceutical Co., Ltd. Junko Hashimoto, Masao Yamamoto, Koichi Endo, Kyoko Katsumata, and Yoshihiro Asao are employees of Chugai Pharmaceutical Co., Ltd. Rumiko Matsumoto is an employee of Taisho Pharmaceutical Co., Ltd. Tetsuo Nakano has received consulting fees from Asahi Kasei Pharma Corp., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Inc., and Teijin Pharma Ltd. Hideki Mizunuma has received consulting fees from Chugai Pharmaceutical Co., Ltd. and Serono Japan Co., Ltd. Toshitaka Nakamura has received research grants and/or consulting fees from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Banyu Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Inc., Eisai Co., Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd.

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