

# Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study

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## Abstract

**Summary** The long-term efficacy and safety of once-monthly ibandronate were studied in this extension to the 2-year Monthly Oral Ibandronate in Ladies (MOBILE) trial. Over 5 years, lumbar spine bone mineral density (BMD) increased from baseline with monthly ibandronate 150 mg (8.4%). Long-term monthly ibandronate is effective and well tolerated for up to 5 years in women with postmenopausal osteoporosis.

**Introduction** Once-monthly therapy with ibandronate has been studied for up to 5 years in a long-term extension (LTE) to the 2 year MOBILE trial.

**Methods** This multicenter, double-blind extension study of monthly ibandronate involved postmenopausal women who

had completed 2 years of the MOBILE core study, with  $\geq 75\%$  adherence. Patients were reallocated, or were randomized from daily therapy, to ibandronate 100 mg monthly or 150 mg monthly for a further 3 years.

**Results** A pooled intent-to-treat (ITT) analysis of 344 patients receiving monthly ibandronate from the core MOBILE baseline showed increases over 5 years in lumbar spine BMD (8.2% with 100 mg and 8.4% with 150 mg). Three-year data relative to MOBILE LTE baseline in the full ITT population of all 698 patients randomized or reallocated from MOBILE (including those previously on daily treatment) showed, on average, maintenance of proximal femur BMD gains achieved in the core 2-year study, with further small

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gains in lumbar spine BMD. In general, maintenance of efficacy was also indicated by markers of bone metabolism. **Conclusions** There were no tolerability concerns or new safety signals. Monthly treatment with ibandronate 100 and 150 mg is effective and well tolerated for up to 5 years in women with postmenopausal osteoporosis.

**Keywords** Bisphosphonate · Clinical study · Ibandronate · Long-term treatment · Postmenopausal osteoporosis

## Introduction

Postmenopausal osteoporosis is a chronic condition associated with low bone mass and deterioration in bone microarchitecture. These lead to increased risk of fractures and associated morbidity, impairment of quality of life, and mortality [1, 2]. Vertebral fractures, in particular, are associated with chronic disabling pain, and 20% of patients who sustain an osteoporotic hip fracture die within 1 year [1].

The primary goal of postmenopausal osteoporosis treatment is reduction of fracture risk, starting with lifestyle modification and followed by pharmacologic intervention [3]. Among such interventions, the bisphosphonates are considered first-line treatment [3]. Of all the agents approved by the US Food and Drug Administration and European Medicines Agency (EMA) for this condition, the bisphosphonates are considered among the most effective at reducing the risk of fracture [4].

Oral nitrogen-containing bisphosphonates, including ibandronate, alendronate, and risedronate, have become the mainstay of treatment for postmenopausal osteoporosis. Most of the pivotal fracture trials of these agents in women with postmenopausal osteoporosis have been of 3 to 4 years' duration [5–9]. Therefore, long-term efficacy and safety data from randomized controlled trials are limited. Results are available to show sustained benefit over periods of up to 10 years with alendronate and 7 years with risedronate [10–14], but similar data for ibandronate are currently lacking.

A substantial body of evidence has demonstrated the efficacy and safety of ibandronate for up to 3 years. This includes the oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) in 2,946 postmenopausal women [5, 15], the Dosing Intravenous Administration (DIVA) study in 1,395 women [16], and the Monthly Oral Ibandronate in Ladies (MOBILE) study in 1,609 women [17, 18]. The antifracture efficacy of ibandronate was sustained in the BONE study over 3 years as shown by reductions in the risk of vertebral fracture relative to placebo of 62% ( $P < 0.001$ ) with ibandronate 2.5 mg daily and 50% ( $P = 0.0006$ ) with 20 mg every other day for 12 doses every 3 months [5]. In DIVA, 2-year results showed statistically non-inferior and superior increases in lumbar

spine bone mineral density (BMD) with intravenous ibandronate (2 mg every 2 months or 3 mg every 3 months) compared with 2.5 mg daily oral ibandronate [16].

BMD and bone turnover markers are established predictors of vertebral [19] and non-vertebral [20] fracture risk. The threshold for osteoporosis is defined as a T-score of  $< -2.5$ , i.e., BMD of 2.5 or more standard deviations below the average value for healthy young women [21]. The use of surrogate endpoints for the approval of new dosing regimens or routes of administration in so-called “bridging” studies is suggested by authorities such as the EMA for drugs that have already demonstrated antifracture efficacy in randomized and controlled trials [22].

MOBILE was a multinational, phase III, non-inferiority study designed to compare the efficacy and safety of monthly oral ibandronate with the established once-daily ibandronate regimen. In this trial, once-monthly oral ibandronate (taken as two 50 mg doses on two consecutive days [50+50 mg], or as a single 100 or 150 mg dose) was at least as effective in increasing BMD and as well tolerated as ibandronate 2.5 mg daily [17, 23]. Over 2 years of treatment, lumbar spine and total hip BMD increased significantly more with ibandronate 150 mg monthly than with daily ibandronate ( $P < 0.05$ ), and pronounced reductions in the biochemical marker of bone resorption, C-telopeptide of the  $\alpha$ -chain of type I collagen (CTX), seen after 3 months in all arms were generally maintained throughout the study [18].

Extension studies have shown the therapeutic effects of once-daily alendronate to be sustained with good tolerability over 10 years [11] and BMD to be significantly ( $P < 0.05$ ) increased with no indication of loss of antifracture efficacy after 7 years of continuous treatment with once-daily risedronate [14]. In order to obtain longer-term safety and efficacy data with ibandronate, the 2-year MOBILE core study was extended for a further 3 years. Here, we present data from this long-term extension (LTE) of MOBILE, which is the first randomized trial to report 5-year safety and efficacy data for a once-monthly oral bisphosphonate, ibandronate.

## Patients and methods

### Study design and participants

This multinational, multicenter, extension study was conducted in 31 of the 65 centers originally participating in MOBILE in North America, Europe, Mexico, and Brazil. Participants were postmenopausal women who had completed 2 years of the MOBILE core study and had been at least 75% compliant with the monthly regimen.

Inclusion and exclusion criteria for the MOBILE core study have been published previously [17, 18]. Briefly, participants were ambulatory patients aged 55–80 years with at least 5 years since menopause and with osteoporosis defined as mean lumbar spine T-score between  $<-2.5$  and  $\geq-5.0$ . All patients provided written and informed consent, ethical approval was obtained from the institutional review boards of the participating institutions, and the study was carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Original randomization in the MOBILE core study was to one of four oral ibandronate treatments: 2.5 mg daily, 50+50 mg once monthly (single doses on consecutive days), 100 mg once monthly, or 150 mg once monthly.

Eligible patients for the extension study, MOBILE LTE, were allocated to one of two treatment groups with a partial randomization procedure using an interactive voice response system: patients previously treated with ibandronate 100 or 150 mg monthly continued on the same dosage, while those previously treated with ibandronate 2.5 mg daily or 50+50 mg monthly were randomized to either 100 or 150 mg monthly. To maintain the double-blind, all patients took an appropriately sized placebo with their active medication. Patients also received vitamin D 400 IU/day and elemental calcium at a dosage of at least 500 mg/day, preferably as oral calcium carbonate, in the form of a dietary supplement for the full duration of the study. Study medication was taken after an overnight fast ( $\geq 6$  h) with 240 ml of water, after which patients maintained an upright posture and fasted for at least another 60 min.

## Methods and assessments

The primary efficacy variable was the change in mean lumbar spine (L2–L4) BMD, described in relative (percent) as well as absolute (grams per square centimeter) terms, by centrally evaluated dual energy absorptiometry from the end of the 2-year MOBILE core study (month 24, baseline for MOBILE LTE) to completion of the MOBILE LTE at month 60. However, the focus of the present report is the pooled analysis of the relative change (percent change from MOBILE baseline) in mean lumbar spine BMD in patients who received continuous monthly (100 or 150 mg) treatment for up to 5 years (i.e., pooled data from patients who received monthly treatment in both the original 2-year MOBILE study and the present MOBILE LTE trial). Clinic visits were scheduled every 6 months from baseline.

A secondary efficacy endpoint was the change in mean total hip BMD from the end of the 2-year MOBILE core study (month 24) to completion of the MOBILE LTE at month 60, described in both relative (percent) and absolute (grams per square centimeters) terms. Exploratory endpoints included (1) the relative (percent) and absolute (grams per square

centimeters) change in mean femoral neck and trochanter BMD from the end of the 2-year MOBILE study (month 24) to completion of the MOBILE LTE at month 60, (2) the relative (percent) and absolute (grams per square centimeters) change in mean lumbar spine (L2–L4), total hip, femoral neck, and trochanter BMD from the start of the MOBILE core study to completion of the MOBILE LTE in a pooled analysis of patients who received continuous monthly (100 or 150 mg) treatment for up to 60 months (5 years), and (3) the relative change in median serum levels of CTX and the marker of bone formation procollagen type 1 amino-terminal propeptide (P1NP) were assessed from blood samples taken at the end of the dosing interval (immediately before dose) and measured annually from the start of the MOBILE core study to completion of the MOBILE LTE at month 60, in the pooled population of patients who received continuous monthly treatment (100 or 150 mg). For MOBILE core, serum CTX levels were analyzed centrally using the Elecsys S-CTX-I assay (an electrochemiluminescence immunoassay technique). For MOBILE LTE, serum CTX levels were originally analyzed centrally with an enzyme-linked immunosorbent assay (ELISA). For comparability of results with the MOBILE core study, the serum CTX samples in MOBILE LTE were reanalyzed using the Elecsys method after the study was unblinded and the original reporting of the data had taken place. Results from the analysis carried out using the Elecsys method are presented. Serum P1NP was not included in the original reporting but was analyzed post hoc, using frozen serum samples used for measuring serum CTX. The decision to analyze serum P1NP, in addition to serum CTX, was based on the fact that serum P1NP demonstrates greater sample stability and lower inpatient variability than serum CTX.

Adverse events (AEs) and laboratory safety parameters were monitored throughout. AEs were graded as mild, moderate, severe, or life threatening; a serious AE (SAE) was any experience that resulted in death or was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, or consisted of a congenital anomaly or birth defect.

Patients were asked to record the dates when tablets were taken on the relevant blister cards, and adherence to treatment was assessed by checking all used and unused medication containers and by periodic telephone interviews.

## Analysis populations

The primary analysis population for all efficacy endpoints was the modified intent-to-treat (mITT) population. Patients were included in the mITT population for the individual analysis of the LTE study if they were randomized, received at least one dose of trial medication, and had a valid baseline and at least one follow-up efficacy, BMD, or serum CTX measurement. Patients were included in the mITT population for the pooled

analyses if they met the above criteria and were randomized to ibandronate 100 or 150 mg monthly in MOBILE.

The safety population comprised all patients who received at least one dose of study medication and attended at least one safety follow-up visit. Patients were included in the safety population for the pooled analyses if they met these criteria and received ibandronate 100 or 150 mg monthly in MOBILE.

The per-protocol population was used to summarize serum CTX and P1NP for the pooled analysis because the protocol violators in an mITT analysis can affect the serum CTX results greatly, i.e., not fasting before dosing. The per-protocol population was not predefined for MOBILE LTE; the population was defined after the study was unblinded and the original data reporting had taken place.

No formal statistical testing was carried out in MOBILE LTE. Results are presented as descriptive, statistical summaries which include 95% confidence intervals (CIs) for relative changes from baseline in each treatment arm.

## Results

### Patient disposition and baseline characteristics

A total of 719 women with postmenopausal osteoporosis were enrolled and received monthly treatment in MOBILE LTE (100 mg,  $n=358$ ; 150 mg,  $n=361$ ). Of these, 698 formed the full ITT population (Table 1). A total of 21 patients were excluded from the mITT analysis because no

**Table 1** Baseline demographics of patients entering MOBILE LTE (mean values  $\pm$  standard deviation) in the complete ITT population, including all patients entering MOBILE LTE and the pooled analysis mITT population, those patients receiving continuous monthly ibandronate only

	Ibandronate 100 mg	Ibandronate 150 mg
Complete ITT population, including all patients entering MOBILE LTE		
	( $n=348$ )	( $n=350$ )
Age (years)	67.6 $\pm$ 6.5	67.6 $\pm$ 6.8
Weight (kg)	64.6 $\pm$ 12.2	64.6 $\pm$ 10.5
Height (cm)	158.0 $\pm$ 6.2	157.8 $\pm$ 6.5
Body mass index (kg/m <sup>2</sup> )	25.9 $\pm$ 5.0	26.0 $\pm$ 4.0
Lumbar spine (L2–L4) BMD (g/cm <sup>2</sup> )	0.79 $\pm$ 0.08	0.80 $\pm$ 0.08
	$n=347$	$n=346$
Lumbar spine (L2–L4) BMD (T-score)	-2.61 $\pm$ 0.74	-2.56 $\pm$ 0.72
	$n=347$	$n=346$
Total hip BMD (g/cm <sup>2</sup> )	0.77 $\pm$ 0.11	0.79 $\pm$ 0.11
	$n=345$	$n=348$
Serum CTX (ng/ml) <sup>a</sup>	0.21 (0.04, 0.83)	0.19 (0.03, 1.05)
	$n=57$	$n=68$
Serum P1NP (ng/ml) <sup>b</sup>	20.75 (9.27, 69.05)	18.49 (7.80, 76.57)
	$n=57$	$n=68$
Pooled analysis mITT population, those patients receiving continuous monthly ibandronate only		
	( $n=173$ )	( $n=171$ )
Age (years)	65.6 $\pm$ 6.4	65.8 $\pm$ 6.7
Weight (kg)	64.8 $\pm$ 11.9	64.0 $\pm$ 9.6
Height (cm)	158.0 $\pm$ 6.1	158.2 $\pm$ 5.9
Body mass index (kg/m <sup>2</sup> )	26.0 $\pm$ 4.8	25.6 $\pm$ 3.7
Lumbar spine (L2–L4) BMD (g/cm <sup>2</sup> )	0.76 $\pm$ 0.07	0.75 $\pm$ 0.07
	$n=173$	$n=171$
Lumbar spine (L2–L4) BMD (T-score)	-2.92 $\pm$ 0.65	-2.95 $\pm$ 0.65
	$n=173$	$n=171$
Total hip BMD (g/cm <sup>2</sup> )	0.75 $\pm$ 0.11	0.76 $\pm$ 0.11
	$n=172$	$n=169$
Serum CTX (ng/ml) <sup>a</sup>	0.54 (0.04, 1.61)	0.51 (0.08, 1.49)
	$n=173$	$n=171$
Serum P1NP (ng/ml) <sup>b</sup>	58.74 (10.56, 110.0)	60.57 (12.46, 110.3)
	$n=27$	$n=31$

Values for serum CTX and P1NP are medians (ranges)

<sup>a</sup>Baseline serum CTX levels are reanalyzed ELISA results from the MOBILE 2-year samples, where a different assay method was used

<sup>b</sup>Serum P1NP was not included in the original reporting but was analyzed post hoc

follow-up BMD or serum CTX measurement was available. The full 3-year extension study was completed by similar proportions of patients in the 100 and 150 mg groups (87% and 90%, respectively; Fig. 1). Women previously treated with ibandronate 100 mg ( $n=176$ ) or 150 mg monthly ( $n=176$ ) in the 2-year core study continued treatment in these dose groups in MOBILE LTE (i.e., up to 5 years of continuous monthly treatment) and were included in the pooled analysis, for which the mITT population included 344 patients (Table 1).

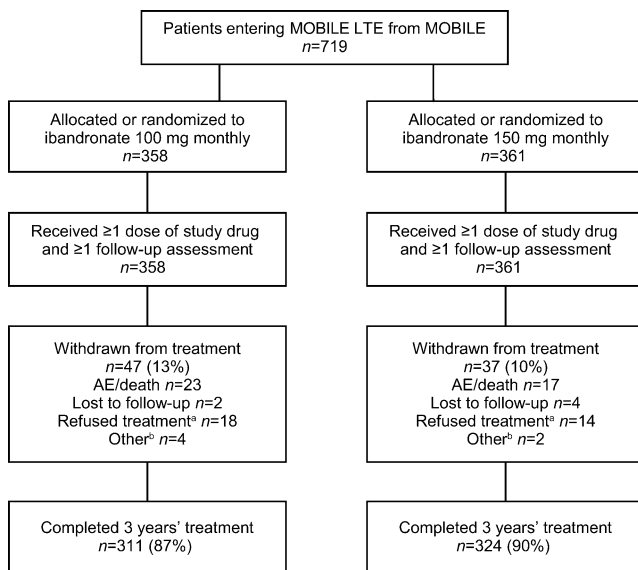
Baseline patient characteristics for the overall mITT population were well balanced across treatment arms (Table 1). Adherence to treatment over 3 years was high, with 76% of patients in the 100 mg group and 77% in the 150 mg group taking 100% of their prescribed treatment. Over the 3 years of MOBILE LTE, 89.4% and 92.2% of patients in the 100 and 150 mg groups, respectively, were  $\geq 75\%$  compliant with study medication.

### Efficacy

This is the first randomized trial to report 5-year safety and efficacy data for monthly oral ibandronate; therefore, we have focused on efficacy at 60 months.

### Pooled 5-year analysis

The pooled analysis showed a sustained response to treatment. At month 60, there were substantial mean increases in lumbar spine BMD in both monthly treatment



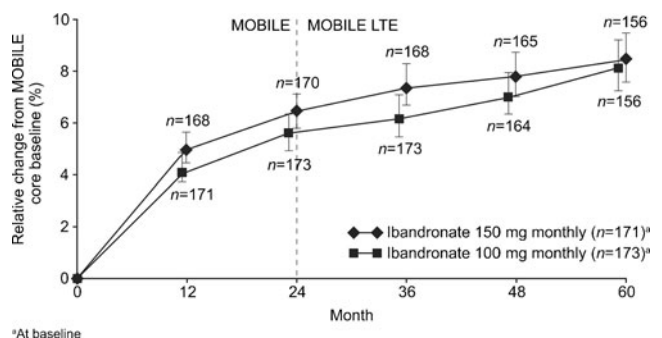
**Fig. 1** Patient disposition (3-year safety population from MOBILE LTE baseline). <sup>a</sup>Refused treatment includes “did not co-operate” and “withdrew consent,” <sup>b</sup>“Other” includes “low BMD” (one patient), “bone loss” (two patients), and “patient leaving the country” (one patient). <sup>c</sup>“Other” includes “loss of bone mass” (two patients)

arms relative to the original MOBILE core baseline values: 8.2% (95% CI 7.2, 9.2) in the 100-mg arm and 8.4% (95% CI 7.5, 9.4) in the 150-mg arm (Fig. 2).

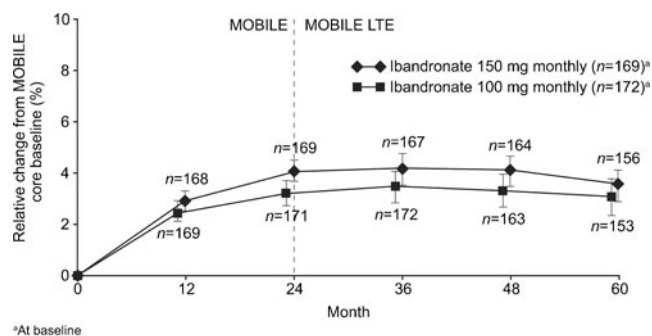
At 12, 24, and 36 months, increases in mean total hip BMD relative to MOBILE baseline were reported in both treatment groups (Fig. 3). A plateau was reached between 24 and 36 months with no further increases in total hip BMD. Mean increases at 36 months were 3.4% (95% CI 2.8, 4.0) in the 100-mg group and 4.1% (95% CI 3.5, 4.7) in the 150-mg group. After 60 months (5 years), mean increases in total hip BMD from baseline were 3.0% (95% CI 2.3, 3.7) and 3.5% (95% CI 2.8, 4.1) in the 100- and 150-mg groups, respectively.

In both treatment groups, mean BMD gains over 60 months (5 years) at the femoral neck and trochanter followed a similar pattern to those at the total hip, reaching a plateau that was generally sustained at year 5. Femoral neck BMD at month 36 increased by a mean of 2.5% (95% CI 1.9, 3.2) over the core MOBILE baseline in the 100-mg group and by 3.5% (95% CI 2.7, 4.3) in the 150-mg group. These gains were maintained to 60 months (Table 2). Mean trochanteric BMD increases at month 36 were 5.5% (95% CI 4.7, 6.3) in the 100-mg group and 6.3% (95% CI 5.6, 7.0) with 150 mg, with maintenance of similar values to month 60 (Table 2).

A small number only (37 at month 60) of the original 325 patients (per-protocol [PP] population) in the pooled analysis supplied serum CTX samples for MOBILE LTE at selected times, which limited interpretation of these data. However, the available results showed a rapid and pronounced decrease in median serum CTX values from MOBILE core baseline during the first 3 months of ibandronate treatment (to 50% (95% CI -57, -45) of baseline with ibandronate 100 mg and 66% (95% CI -70, -60) of baseline with ibandronate 150 mg; Fig. 4). Median serum CTX levels continued to decline thereafter and approached steady state with ibandronate 100 mg at month 24, after which suppression was generally sustained to year 5 (Fig. 4). Similarly, pronounced decreases in median serum levels of P1NP from baseline were seen at month 12: -69% (95% CI -74%, -65%) with ibandronate 100 mg (23 patients)



**Fig. 2** Mean relative change (percent) with 95% CIs in lumbar spine (L2–L4) BMD from MOBILE core baseline over 5 years with monthly ibandronate (mITT population; pooled analysis)



**Fig. 3** Mean relative change (percent) with 95% CIs in total hip BMD from MOBILE core baseline over 5 years with monthly ibandronate (mITT population; pooled analysis)

and  $-72\%$  (95% CI  $-79\%$ ,  $-67\%$ ) with ibandronate 150 mg (23 patients). These reductions were generally sustained at year 5 (Table 2).

### MOBILE LTE 3-year analysis

Mean lumbar spine BMD increased over the 3-year extension period that followed the MOBILE core study. Mean increases in the 100- and 150-mg groups were 0.8% (95% CI 0.4, 1.2) and 1.3% (95% CI 0.9, 1.6), respectively, after 1 year and 1.7% (95% CI 1.2, 2.2) and 1.8% (95% CI 1.3, 2.3), respectively, after 2 years, and over 2% (100 mg 95% CI 1.6, 2.7; 150 mg 95% CI 1.9, 3.0) in both groups after 3 years (Table 2). Mean total hip BMD decreased over this period but to a small and clinically non-relevant extent (Table 2). Very small changes only were also seen at the femoral neck and trochanter (Table 2).

The decreases obtained in median serum CTX and P1NP levels during the first 2 years in the MOBILE core study were essentially stable over the following 3 years (Table 2).

### Safety

#### Pooled 5-year analysis

Over the 5-year period, the majority of patients in each group (92% in the 100-mg group and 90% in the 150-mg group) reported AEs (Table 3). Of these, 29.0% and 32.4% were considered by the blinded site investigator to be probably related to treatment in the 100- and 150-mg groups, respectively (Table 3). The most frequent events in both treatment groups were hypertension, nasopharyngitis, back pain, and arthralgia (Table 3). Influenza-like symptoms were reported in 5.1% of patients in the 100-mg group and 2.8% of patients in the 150-mg group.

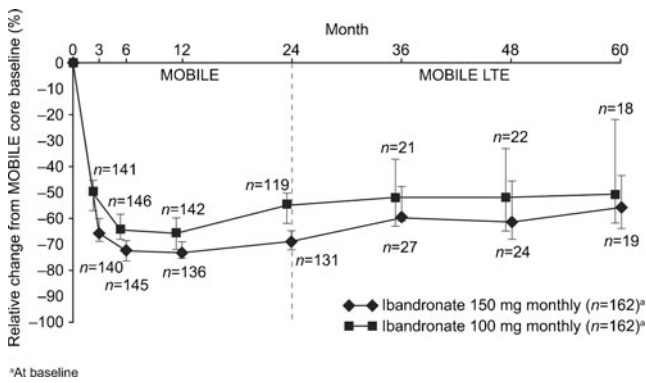
The most common AEs considered to be at least remotely related to study treatment were related to the gastrointestinal system and included dyspepsia (7.4% in each treatment group), upper abdominal pain (2.8% with

**Table 2** At 60 months, relative (percent) changes (mean values  $\pm$  standard deviation with 95% CIs) from MOBILE core baseline for the pooled analysis mITT population (those patients receiving continuous monthly ibandronate only) and MOBILE LTE baseline for the complete mITT population

	Ibandronate 100 mg	Ibandronate 150 mg
MOBILE core baseline for the pooled analysis mITT population		
	(n=173)	(n=171)
Lumbar spine (L2–L4) BMD	8.2 $\pm$ 6.2 (7.2, 9.2)	8.4 $\pm$ 6.0 (7.5, 9.4)
Total hip BMD	3.0 $\pm$ 4.4 (2.3, 3.7)	3.5 $\pm$ 4.1 (2.8, 4.1)
Femoral neck BMD	2.4 $\pm$ 5.1 (1.6, 3.2)	3.2 $\pm$ 6.8 (2.1, 4.3)
Trochanter BMD	5.6 $\pm$ 6.5 (4.5, 6.6)	6.0 $\pm$ 5.5 (5.1, 6.8)
Serum CTX <sup>a</sup>	-51.7 <sup>b</sup> (-69.1, -19.5)	-56.6 <sup>b</sup> (-64.7, -30.4)
Serum P1NP <sup>a</sup>	-51.6 <sup>b</sup> (-66.3, -27.5)	-61.3 <sup>b</sup> (-75.1, -56.4)
MOBILE LTE baseline for the complete mITT population		
	(n=348)	(n=350)
Lumbar spine (L2–L4) BMD	2.2 $\pm$ 4.9 (1.6, 2.7)	2.4 $\pm$ 4.8 (1.9, 3.0)
Total hip BMD	-0.8 $\pm$ 3.3 (-1.2, -0.4)	-0.3 $\pm$ 3.3 (-0.7, 0.02)
Femoral neck BMD	-0.4 $\pm$ 4.3 (-0.9, 0.1)	0.4 $\pm$ 4.8 (-0.2, 0.9)
Trochanter BMD	0.1 $\pm$ 4.6 (-0.5, 0.6)	0.4 $\pm$ 4.5 (-0.1, 0.9)
Serum CTX <sup>a</sup>	43.6 <sup>b</sup> (18.1, 65.6)	36.1 <sup>b</sup> (8.2, 68.0)
Serum P1NP <sup>a</sup>	22.9 <sup>b</sup> (-0.3, 39.1)	16.8 <sup>b</sup> (1.3, 27.9)

<sup>a</sup> Median values with 95% CIs

<sup>b</sup> PP population



**Fig. 4** Median relative change (percent) with 95% CIs in serum CTX levels from MOBILE core baseline to year 5 with monthly ibandronate (PP population; pooled analysis). Numbers of patients available for evaluation at each visit are shown for each data point

100 mg and 4.0% with 150 mg), nausea (3.4% in each treatment group), diarrhea (2.3% with 100 mg and 1.7% with 150 mg), and gastritis (1.7% with 100 mg and 2.3% with 150 mg). Arthralgia was reported in 4.0% of patients receiving ibandronate 150 mg only. AEs considered related to treatment that led to withdrawal were reported in seven patients (one each with esophagitis, duodenitis, esophageal ulcer, skin ulcer, myalgia, dyspepsia, or diarrhea).

Of the patients receiving ibandronate 100 mg and those receiving 150 mg, 24.4% and 29.5% reported SAEs, respectively, most of which were single occurrences. Of the SAEs reported by more than one patient in either treatment group, the most common were osteoarthritis, which was a worsening of a pre-existing condition that required surgery but was not related to study treatment (three patients with 150 mg and two with 100 mg); ankle fracture (four patients with ibandronate 150 mg); angina pectoris (three patients with 150 mg); cholelithiasis (three patients with 100 mg); myocardial ischemia (two patients with 150 mg and one with 100 mg); hypertension (two patients with 150 mg and one with 100 mg); cataract (one patient with 150 mg and two with 100 mg); nephrolithiasis (one patient with 150 mg and two with 100 mg); and cystocele (two patients with 150 mg and one with 100 mg).

There were no clinically relevant changes over 5 years in hematology or clinical chemistry values during treatment in either ibandronate group. Creatinine clearance values overall showed no detrimental effect of treatment on renal function, and no cases of osteonecrosis of the jaw were reported.

#### MOBILE LTE 3-year analysis

Similar safety profiles were reported for the monthly regimens over the 3-year extension for the mITT safety population of 719 patients. At least one AE was reported in 291/358 patients (81.3%) receiving ibandronate 100 mg

and in 285/361 (78.9%) patients receiving 150 mg. A total of 6.7% and 8.0%, respectively, were considered related to treatment.

There were generally higher incidences of gastrointestinal disorders in the 150-mg group versus the 100-mg group, the most notable events being dyspepsia (5.0% versus 3.9%), diarrhea (3.9% versus 2.8%), upper abdominal pain (3.3% versus 2.0%), and nausea (2.5% versus 1.1%).

Most AEs were of mild to moderate severity, and all 13 deaths reported were unrelated to treatment. The 3-year incidences of SAEs were 19.0% (100 mg) and 19.4% (150 mg). Most SAEs (4.7% and 3.9%, respectively) were in the MEDra system organ category injury, poisoning and procedural complications, which includes fractures. No SAEs were considered related to study treatment. Overall rates of clinical fractures (all severities) were 10.3% (100 mg) and 9.1% (150 mg).

#### Discussion

In the core MOBILE study, 1- and 2-year treatment with oral ibandronate 150 mg monthly produced substantial increases in lumbar spine and proximal femur BMD ( $P < 0.05$ ) [17, 18]. The monthly ibandronate regimens used in MOBILE were at least as effective as daily treatment, as shown by non-inferiority testing after both 1 and 2 years. The increases in lumbar spine BMD after 1 year were shown to be superior to those with the daily regimen ( $P < 0.001$ ) [17]. Moreover, the once-monthly regimens produced significant improvements in BMD of the proximal femur by the end of year 2, with the greatest gains being obtained with the 150-mg dose. Indeed, the 150-mg regimen consistently produced greater improvement in proximal femur BMD than was seen with the daily regimen.

In MOBILE LTE, further clinically meaningful increases in mean lumbar spine BMD were reported in both treatment groups, relative to baseline. The pooled analysis of patients who received monthly treatment up to 5 years showed increases in mean lumbar spine BMD relative to the original MOBILE baseline. The smaller gains relative to MOBILE LTE baseline indicated in the larger group of patients that included those originally on daily therapy in MOBILE suggest that the substantial increases in lumbar spine BMD seen in the 2-year MOBILE core study were maintained, with a further gradual increase up to the end of year 5.

Although results for proximal femoral BMD values were not as marked, a similar overall pattern was noted. The pooled analysis of patients receiving monthly ibandronate up to 5 years showed overall increases for both dosages

**Table 3** Number of patients (percent) reporting AEs during mobile core and mobile LTE with 5 years continuous treatment with monthly ibandronate (safety population; pooled analysis, 5-year safety population)

Body system/AE	Ibandronate 100 mg ( <i>n</i> =176)		Ibandronate 150 mg ( <i>n</i> =176)	
	Total AEs	Treatment-related AEs	Total AEs	Treatment-related AEs
Total patients with $\geq 1$ AE	162 (92.0)	51 (29.0)	159 (90.3)	57 (32.4)
Hypertension	44 (25.0)	2 (1.1)	44 (25.0)	
Nasopharyngitis	35 (19.9)		34 (19.3)	
Back pain	35 (19.9)		25 (14.2)	
Arthralgia	27 (15.3)		27 (15.3)	7 (4.0)
Hypercholesterolemia	20 (11.4)		20 (11.4)	
Dyspepsia	20 (11.4)	13 (7.4)	19 (10.8)	13 (7.4)
Influenza	17 (9.7)		18 (10.2)	
Urinary tract infection	16 (9.1)		19 (10.8)	
Bronchitis	19 (10.8)		15 (8.5)	
Osteoarthritis	16 (9.1)		18 (10.2)	
Cataract	17 (9.7)		15 (8.5)	
Pain in extremity	14 (8.0)		14 (8.0)	
Diarrhea	15 (8.5)	4 (2.3)	12 (6.8)	3 (1.7)
Depression	12 (6.8)		11 (6.3)	
Headache	7 (4.0)	3 (1.7)	14 (8.0)	2 (1.1)
Vertigo	9 (5.1)		11 (6.3)	
Upper abdominal pain	8 (4.5)	5 (2.8)	12 (6.8)	7 (4.0)
Cystitis	6 (3.4)		13 (7.4)	
Cough	11 (6.3)		7 (4.0)	
Constipation	8 (4.5)	1 (0.6)	10 (5.7)	2 (1.1)
Nausea	6 (3.4)	6 (3.4)	11 (6.3)	6 (3.4)
Upper respiratory tract infection	9 (5.1)		8 (4.5)	
Pneumonia	6 (3.4)		10 (5.7)	
Sinusitis	10 (5.7)		6 (3.4)	
Sciatica	7 (4.0)		9 (5.1)	
Insomnia	6 (3.4)		10 (5.7)	
Musculoskeletal pain	10 (5.7)		5 (2.8)	
Gastroenteritis	9 (5.1)	3 (1.7) <sup>a</sup>	5 (2.8)	4 (2.3) <sup>a</sup>
Influenza-like symptoms	9 (5.1)	4 (2.3)	5 (2.8)	2 (1.1)

Rates are shown for all AEs reported by  $\geq 5\%$  of patients in either group and for all AEs judged treatment related reported by  $\geq 1\%$  of patients

<sup>a</sup>Listed as “gastritis”

relative to the original MOBILE core study baseline. The results for the larger ITT population of all patients followed from the end of the 2-year core study showed that the BMD gains at the end of MOBILE core were generally maintained over the 3 years of MOBILE LTE.

The pooled results of biochemical markers of bone turnover (serum CTX and P1NP levels) showed overall decreases in patients who received monthly ibandronate consistently for 5 years. Following rapid and pronounced decreases in the initial months of the study, serum CTX and P1NP levels decreased more slowly and reached levels around 24 months that were generally sustained throughout the remainder of the 5-year period. In the MOBILE core study, around 90% of the total response was achieved after 1 year [17]. As such, we expected that maximal inhibition

of markers of bone turnover in the pooled analysis population would be achieved early in the study and that further clinically relevant decreases thereafter were not expected. These pooled analysis results should be viewed in light of the relatively small numbers of patients for whom data were available.

The safety profile of monthly ibandronate showed no noteworthy changes relative to previous experience [17, 18] after administration for up to 5 years. After 3 years of long-term extension treatment, the overall incidence of AEs was similar in the 100- and 150-mg groups, with slightly higher rates of reporting of gastrointestinal effects with ibandronate 150 mg. Rates of treatment-related gastrointestinal AEs were similar between groups. However, it is worth remembering that all comparisons between the two groups

in MOBILE LTE are confounded by the lack of a real control arm. Incidences of AEs considered to be related to study treatment were very low in the 3-year safety population of all patients enrolled in MOBILE LTE (including those previously on daily therapy) relative to the MOBILE core study and the pooled analysis safety population of patients who received monthly therapy for a full 5 years. This may be related to the selection criteria for MOBILE LTE, as only patients who had reported good compliance with the monthly regimen in the first 2 years of MOBILE were eligible. MOBILE LTE likely included patients who had already experienced good tolerability during the core study and who would, therefore, be likely to continue to tolerate ibandronate well over the longer term.

Of note, no SAEs and no deaths were attributed to ibandronate therapy in MOBILE LTE. Reports of influenza-like symptoms were infrequent and were not related to study treatment. This concurs with previous observations showing influenza-like symptoms to be a problem chiefly associated with intravenous nitrogen-containing bisphosphonates and to be linked to first exposure in patients who have previously not received these agents [24]. Renal function was monitored in this study by assessing creatinine clearance, as there have been reports of renal toxicity with pamidronate and zoledronate [24], but there were no indications of impairment of renal function in MOBILE LTE with ibandronate. Symptoms suggestive of osteonecrosis of the jaw were also not observed. This was not unexpected as this AE is more commonly associated with high, intravenous doses of nitrogen-containing bisphosphonates as used in patients with cancer [25]. Overall, MOBILE LTE showed no new safety signals and continued to demonstrate that monthly regimens of ibandronate are as well tolerated as daily treatment (as shown in the MOBILE core study) [18].

We note that published data from the first 2 years of MOBILE (i.e., the core study) referred to the PP population, as this is the type of analysis required for non-inferiority studies [17, 18]. Thus, the data from the mITT populations referred to in MOBILE LTE data are, strictly speaking, not directly comparable. However, as the ITT population in the MOBILE core study confirmed the findings of the primary PP analysis, it is reasonable to assume that the change in analysis populations will have had no relevant effect on our overall findings. We also note that statistical analysis, comparing the monthly dosing regimens in MOBILE LTE, was not incorporated into the study design, and inspection of the data gives no indication that the efficacy of the unmarketed 100-mg dosage form would be preferable to that of the marketed form. We also reiterate that patients entering the LTE had previously demonstrated compliance with monthly therapy and were likely to have a perceived positive experience of monthly ibandronate from the original study.

## Conclusion

The results of MOBILE LTE support the original findings of the MOBILE core study and show overall optimization of BMD and bone turnover outcomes with ibandronate 150 mg over 100 mg monthly. Therefore, ibandronate 150 mg once a month remains the dosage that yields an optimally sustained effect on BMD and bone turnover, together with a good tolerability profile that remains unchanged with no new safety signals over 5 years of treatment. At the licensed dose of 150 mg, once-monthly oral ibandronate is an effective and well-tolerated long-term treatment option for postmenopausal osteoporosis.

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