Original article

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Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial

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Background: We report the first results of a randomized trial assessing a new oral aminobisphosphonate, ibandronate, in patients with bone metastases from breast cancer.

Patients and methods: Patients ($n = 435$) received placebo, or oral ibandronate 20 mg or 50 mg once-daily for 96 weeks. The primary efficacy measure was the number of 12-week periods with new bone complications [skeletal morbidity period rate (SMPR)]. Multivariate Poisson regression analysis assessed the relative risk reduction of skeletal-related events. Secondary efficacy analyses included bone pain and analgesic use. Adverse events were monitored.

Results: SMPR was significantly reduced with oral ibandronate [placebo 1.2, 20 mg group 0.97 ($P = 0.024$), 50 mg group 0.98 ($P = 0.037$)]. Ibandronate 50 mg significantly reduced the need for radiotherapy ($P = 0.005$ versus placebo). The relative risk of skeletal events was reduced by 38% (20 mg dose) and 39% (50 mg dose) versus placebo ($P = 0.009$ and $P = 0.005$). The tolerability profile of ibandronate was similar to placebo.

Conclusions: Oral ibandronate is an effective and well-tolerated treatment for metastatic bone disease. The 50 mg dose is being further evaluated in clinical trials, and this dose was recently approved in the European Union for the prevention of skeletal events in patients with breast cancer and bone metastases.

Key words: bisphosphonate, breast cancer, metastatic bone disease, oral ibandronate, skeletal events

Introduction

An estimated 65–75% of women with breast cancer will go on to develop bone metastases [1, 2], with complications including pathological fractures, spinal cord compression and hypercalcemia [3]. Two-thirds of patients with bone metastases experience severe pain and disability [4], with detrimental effects on quality of life that may persist throughout the duration of cancer therapy and beyond.

Bisphosphonates effectively reduce the risk of skeletal complications from metastatic bone disease, and are currently considered to be the standard of care for most patients [5–12]. Current treatment typically involves intravenous (i.v.) pamidronate [5], or recently approved zoledronate [10]. Yet while i.v. administration may be appropriate for certain patients, the need for regular clinic visits is a distinct disadvantage, reducing treatment convenience. For most patients, oral bisphosphonate therapy would be preferable, allowing convenient self-administration at home.

Clodronate is the only bisphosphonate currently available as an oral formulation for the treatment of metastatic bone disease. Clodronate is less effective against skeletal complications than i.v. pamidronate [7] and its use can lead to gastrointestinal side-effects such as diarrhea [13–17]. Because of the low potency of clodronate [18], 1040 or 1600 mg/day is administered over multiple doses, with a large tablet size that may be difficult for some patients to swallow [19, 20] and this may affect compliance.

Ibandronate, a highly potent, third-generation aminobisphosphonate, has been developed in both i.v. and oral formulations. The results of a placebo-controlled phase III trial have shown that i.v. ibandronate 6 mg infused every 3–4 weeks is effective at reducing skeletal complications and alleviating bone pain in patients with metastatic bone disease from breast cancer [21]. This report presents the results from a phase III trial of oral ibandronate in this indication.

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Patients and methods

Patients

This randomized, parallel-group, double-blind, placebo-controlled multicenter study was conducted at 68 centers in the USA, Australia, New Zealand, Bulgaria, Russia and South Africa. Women with histologically confirmed breast cancer and radiologically confirmed bone metastases were recruited into the study. Patients had a World Health Organization (WHO) performance status of 0–2, were at least 18 years of age, and provided written informed consent. Exclusion criteria included previous treatment with bisphosphonates or gallium nitrate within the last 6 months, life expectancy <60 weeks, hypercalcemia (serum calcium, albumin-corrected, ≥2.7 mmol/l); hypocalcemia (serum calcium, albumin-corrected, ≤2.0 mmol/l), impaired renal function (serum creatinine >3.0 mg/dl), Paget's disease of the bone, primary hyperparathyroidism, known liver/brain metastases, and treatment with aminoglycoside antibiotics within 4 weeks prior to the start of study medication.

Therapy

Subjects were randomized to receive placebo, oral ibandronate 20 mg or oral ibandronate 50 mg once daily for up to 96 weeks. Patients were instructed to take one tablet daily in the morning, 1 h before breakfast, but not to take the tablet with milk, milk products or calcium tablets. To assess compliance with therapy, patients were required to return their oral medication blister packs to the investigator every 12 weeks. Concomitant treatments were allowed during the study (except those specified as exclusion criteria). Randomization was carried out according to a pre-determined randomization list based on block randomization. Treatment was only unblinded in the case of a medical necessity for patient management.

Assessments

Patients attended clinic visits at 4-week intervals for assessment of fractures, episodes of radiotherapy, surgical interventions, bone pain and analgesic consumption. Bone scans and X-rays of the thoracic and lumbar spine were performed at baseline and weeks 24, 48, 72 and 96. Additional radiographs were performed if necessitated by clinical symptoms. Vertebral fractures were assessed morphometrically [22]. At each 4-weekly visit, a clinical assessment for fractures occurring during the previous 4 weeks was performed. Episodes of radiotherapy and surgical interventions for actual or impending fractures were recorded by the investigator. Adverse events (AEs) were recorded throughout the study. An AE was defined as any undesired, noxious or pathological change in a patient as indicated by signs, symptoms and/or laboratory changes that occurred in association with treatment, whether considered related or not. An AE was considered serious if the event was fatal or acutely life-threatening, required in-patient hospitalization (or prolonged existing-hospitalization), resulted in persistent or significant disability or incapacity, or resulted in malignancy or congenital malformation/anomaly. Non-serious AEs were not graded. Based on the recommendations of the European Committee for Proprietary Medicinal Products (CPMP), post-withdrawal follow-up (PWFU) safety and efficacy data (i.e. for the period from study withdrawal until death or last scheduled study visit) were also collected for the 181 patients (40%) who withdrew early (placebo group $n = 69$, 20 mg group $n = 56$, 50 mg group $n = 56$) to minimize the possible effects of non-random withdrawal from the different treatment groups.

Analysis of efficacy and safety

The primary efficacy parameter was the skeletal morbidity period rate (SMPR), defined as the number of 12-week periods with new skeletal complications (vertebral and non-vertebral fractures, bone radiotherapy or bone surgery), divided by the number of periods on the study. SMPR was calculated using a 'revised event ratio' method [23], as described in detail elsewhere [24]: SMPR = number of periods with new skeletal events + 1/number of 12-week periods on study + 0.5.

Supportive analyses of the SMPR included the incidence of all new bone events (mean number of events per patient, the mean number of periods with events, the total number of 12-week periods with events, and the percentage of patients with events during the study period) and time to first new bone event.

A preplanned multivariate Poisson regression analysis [25] of reductions in skeletal related events (SREs) was also conducted to determine the risk of developing a skeletal event during the study period while controlling for any differences in the baseline characteristics of the three treatment groups.

At each 4-weekly visit, patients were asked to rate their bone pain on a scale from 0 (none) to 4 (intolerable). Analgesic use was scored on a scale from 0 (none) to 6 [opiates ≥100 mg morphine (or equivalent) daily] [26]. Pain scores and analgesic use were assessed using last observation carried forward (LOCF) scores. Urinary excretion of calcium, phosphate and C-terminal crosslinking telopeptide of type I collagen (CTX) were also measured as markers of bone turnover.

Statistics

A closed-test procedure was applied on the primary end point to adjust for the multiple tests comparing the various treatments. A global null hypothesis was tested in a first step at the two-sided α-level of 5% using the non-parametric Jonckheere–Terpstra test [27, 28]. In case this trend test on placebo, lower dose and higher dose groups showed significance, all pairwise comparisons between treatments were performed using the Wilcoxon rank sum test again at two-sided α-levels of 5%. This test procedure guarantees multiple α-levels of 5%. For any test, the maximum of the *P*-values from the global test and the test itself is regarded as an overall or adjusted *P*-value. Tests on the components of the primary end point were considered exploratory and no further α-adjustment was made. A logistic regression continuation model was assumed for sample size calculations. Based on historical data and assuming a 15% increase in patients with no event period, a sample size of 68 patients per group was calculated given a two-sided test level of 5% and a power of 80%. The sample size was set to 100 randomized patients per group to allow for a drop-out rate of ~30%. The trial was designed so that the statistical analysis was powered for SMPR of the primary end point (i.e. sum of the individual SMPR components). The Poisson regression model was employed to determine the relative risk (RR) reduction for SREs. All efficacy analyses were conducted on the intent-to-treat population (all patients randomized to study groups) and included PWFU data for the primary end point SMPR. Evaluation of safety was based on all randomized patients who had received at least one dose of study drug with at least one follow-up assessment.

Ethics

The study was performed in accordance with the principles of the Declaration of Helsinki, the Guidelines on Good Clinical Practice and local medicines legislation in place at the time of study initiation. Informed consent was obtained for all subjects.

Results

Patients

A total of 435 patients were randomized to treatment and included in the intention-to-treat (ITT) analysis (Figure 1). Patient demographic and baseline characteristics are shown in Table 1. The ibandronate 50 mg group had a lower percentage of patients with a WHO status of 2 (10.8%) compared with the 20 mg (19.4%) and placebo (15.4%) groups, and the ibandronate 20 mg group had a relatively low percentage of patients with at least 2 years since

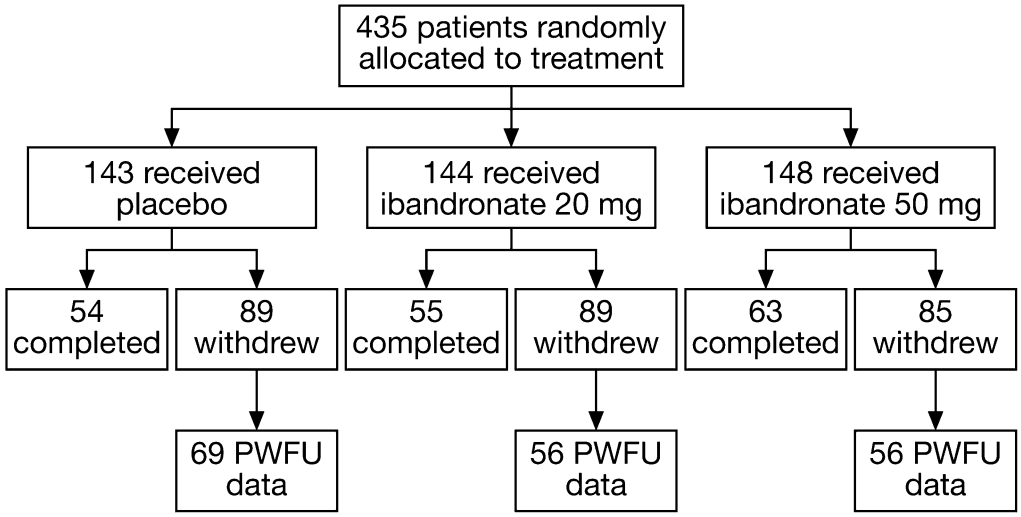

Figure 1. Flow diagram of the study population.

time of diagnosis to study initiation (17.4%) compared with the 50 mg or placebo groups (25.0% and 28.0%, respectively).

The median time on study was similar for the placebo, ibandronate 20 mg and ibandronate 50 mg groups (69.7, 72.3 and 73.3 weeks, respectively), as was the percentage of early withdrawals (62.2%, 61.8% and 57.4%). The most common reasons for early withdrawal were malignancy progression (placebo: 19.6%; ibandronate 20 mg: 18.8%, ibandronate 50 mg: 8.8%), other AEs (14.0%, 11.1% and 11.5%), death (9.8%, 11.8% and 13.5%) or personal reasons (8.4%, 12.5% and 10.1%, respectively) (Table 2). None of the patients discontinued treatment due to difficulty in swallowing the placebo or ibandronate tablets.

Efficacy

Skeletal events. Both active treatment groups achieved a statistically significant reduction in mean SMPR including PWFU data (global *P*-value versus placebo, 0.044) (Table 2). This reduction was due primarily to a decrease in the incidence of events requiring radiotherapy with ibandronate, which reached statistical significance for the 50 mg dose ($P = 0.005$ versus placebo). Other components of the SMPR (vertebral and non-vertebral fractures, bone events requiring surgery) were similar between the ibandronate and placebo groups (Table 3).

Compared with placebo, oral ibandronate significantly reduced the mean number of new bone events and the mean number of measurement periods with events per patient, the total number of periods with events, and the percentage of patients with events (Table 4). Poisson regression analysis revealed a statistically significant reduction in the RR of SREs with ibandronate compared with placebo (20 mg dose RR 0.62, $P = 0.009$; 50 mg dose RR 0.61, $P = 0.005$) (Table 4).

Time from randomization to first new bone event was delayed in the ibandronate groups (20 mg dose 76 weeks, 50 mg dose 54 weeks) compared with placebo (48 weeks), although this effect did not reach statistical significance (global comparison $P = 0.297$).

Bone pain and analgesic use. From baseline to study end point, LOCF bone pain scores increased by +0.21 in the placebo group, compared with a reduction of –0.06 with 20 mg ibandronate ($P = 0.071$) and a slight increase of +0.03 in the 50 mg group ($P = 0.201$). Mean analgesic score was higher in the placebo group than for either active treatment group (change from baseline; placebo = 0.96, ibandronate 20 mg = 0.43, ibandronate 50 mg = 0.73). The difference was statistically significant for the ibandronate 20 mg group ($P = 0.006$ versus placebo), and approached significance for the 50 mg group ($P = 0.074$ versus placebo).

Biochemical markers of bone turnover. At end point, the median urinary creatinine-corrected calcium concentration was increased by 32% in the placebo group compared with a 25% decrease with 20 mg ibandronate and a 42% decrease in the 50 mg group. Creatinine-corrected urinary phosphate concentrations increased in all three treatment groups. Patients on ibandronate had significantly lower CTX values than patients in the placebo groups (median change from baseline: –39% ibandronate 20 mg; –55% ibandronate 50 mg, +47% placebo, $P < 0.0001$). In addition, the decrease in CTX values for the 50 mg group was significantly lower than the 20 mg group ($P = 0.0006$).

Safety

Oral ibandronate was well tolerated. Overall, the incidence of AEs with oral ibandronate was similar to placebo. As expected for a population of patients with advanced cancer, most patients (95.8%) reported at least one AE during the course of the study. Over half of the patients (57.3%) experienced serious AEs, most commonly malignancy progression (placebo, 44.1% of patients; 20 mg group, 47.9%; 50 mg group, 36.1%), spontaneous bone fracture (placebo, 5.6% of patients; 20 mg group, 3.5%; 50 mg group, 2.0%) and bone pain (placebo, 3.5% of patients; 20 mg group, 1.4%; 50 mg group, 4.8%). There were no significant differences between treatment groups in frequency or type of other serious AEs.

Table 1. Baseline demographics and disease characteristics of patients

	Placebo (n = 143)	Ibandronate 20 mg (n = 144)	Ibandronate 50 mg (n = 148)
Age, years[a]			
Median	57	56	57
Range	31–83	30–82	29–92
Sex/race			
Female, n (%)	143 (100)	144 (100)	148 (100)
Caucasian, n (%)	127 (88.8)	126 (87.5)	130 (87.8)
Time from breast cancer diagnosis, years[b]			
Median	4.23	3.7	3.33
Range	0.07–23.98	0.05–19.29	0.05–24.16
Time from metastatic bone disease diagnosis, years[c]			
Median	0.59	0.35	0.4
Range	0.04–23.73	0.02–5.95	0.04–15.46
Any blastic lesions, n (%)	33 (23)	23 (16)	31 (21)
Any mixed lesions, n (%)	11 (8)	14 (10)	21 (14)
Performance status, n (%)[a]			
WHO grade 0 or 1	122 (84.6)	117 (80.5)	132 (89.2)
WHO grade 2	21 (15.4)	27 (19.4)	16 (10.8)
Ongoing use of cytotoxic drugs, n (%)	46 (32.2)	50 (34.7)	58 (39.2)
Estrogen/progesterone receptor status, n (%)[a,d]			
Positive for either or both	52 (36.4)	59 (41.0)	63 (42.6)
Negative	14 (9.8)	18 (12.5)	10 (6.8)
Unknown	75 (52.4)	66 (45.8)	74 (50.0)
Pain score[a]			
Mean	1.23	1.34	1.30
SD	0.81	0.82	0.84
Analgesic score[a]			
Mean	1.29	1.46	1.49
SD	1.61	1.66	1.69
Presence of at least one lesion			
>1 cm, n (%)[a]	41 (32)	55 (44)	47 (36)
No previous chemotherapy, n (%)[a]	95 (67)	91 (64)	94 (64)
Narcotic analgesic use, n (%)	77 (53.8)	94 (65.3)	85 (57.4)
Prior fractures at baseline, n (%)[a,e]	63 (44.1)	71 (49.3)	67 (45.3)

[a]Input variables for the Poisson multivariate analysis model.
[b]Placebo, n = 106; ibandronate 20 mg, n = 109; ibandronate 50 mg, n = 113.
[c]Placebo, n = 112; ibandronate 20 mg, n = 110; ibandronate 50 mg, n = 115.
[d]Placebo, n = 141; ibandronate 20 mg, n = 143; ibandronate 50 mg, n = 147.
[e]History of ≥1 fracture due to metastatic bone disease prior to randomization.
SD, standard deviation; WHO, World Health Organization.

Treatment-related AEs were reported slightly more frequently with ibandronate (placebo, 21.7%; ibandronate 20 mg, 26.4%; ibandronate 50 mg, 27.9%) The incidence of treatment-related nausea, hypocalcemia and abdominal pain was also slightly higher with ibandronate than with placebo. Approximately 10% of patients in each group experienced treatment-related upper gastrointestinal AEs (Table 5). Six patients withdrew due to esophagitis and dyspepsia (one from the placebo group, three from the 20 mg group and two from the 50 mg group).

The incidence of renal AEs was not significantly different across groups: 4.2% with placebo, 3.5% with ibandronate 20 mg and 6.8% with ibandronate 50 mg. Only one patient withdrew from the study due to a renal AE (a 92-year-old woman receiving ibandronate 50 mg who developed azotemia).

Table 2. Reasons for withdrawal

	Placebo (n = 143)	Ibandronate 20 mg (n = 144)	Ibandronate 50 mg (n = 148)
Malignancy progression reported as an AE, n (%)	28 (19.6)	27 (18.8)	13 (8.8)
Other AEs, n (%)	20 (14.0)	16 (11.1)	17 (11.5)
Death, n (%)	14 (9.8)	17 (11.8)	20 (13.5)
Personal reasons, n (%)	12 (8.4)	18 (12.5)	15 (10.1)
Lost to follow-up, n (%)	6 (4.2)	4 (2.8)	8 (5.4)
Non-compliance, n (%)	2 (1.4)	2 (1.4)	4 (2.8)
Total, n (%)	89 (62.2)	89 (61.8)	85 (57.4)

AE, adverse event.

Table 3. SMPR analyses (including PWFU data)

	Placebo (n = 143)	Ibandronate 20 mg (n = 144)	Ibandronate 50 mg (n = 148)	Global P-value[a]
All new bone events (SMPR)	1.20	0.97	0.98	0.044
		$P = 0.024$[b]	$P = 0.037$[b]	
Vertebral fractures	0.51	0.52	0.52	0.730
		$P = 0.315$[b]	$P = 0.739$[b]	
Non-vertebral fractures	0.52	0.54	0.54	0.887
		$P = 0.596$[b]	$P = 0.890$[b]	
Events requiring radiotherapy	0.99	0.81	0.77	0.004
		$P = 0.082$[b]	$P = 0.005$[b]	
Events requiring surgery	0.44	0.50	0.43	0.643
		$P = 0.738$[b]	$P = 0.644$[b]	

[a]Jonckheere–Terpstra method, global P-value versus placebo.
[b]Wilcoxon rank sum test, P-value versus placebo.
PWFU, post-withdrawal follow-up; SMPR, skeletal morbidity period rate.

During the course of the study, 65 patients died. The incidence of death was similar across the treatment groups (placebo 11.2%, ibandronate 20 mg 16%, ibandronate 50 mg 17.7%). In most cases (83%), death was due to malignancy progression and there were no treatment-related deaths.

Discussion

The results of this study clearly demonstrate that oral ibandronate effectively reduces the incidence of new skeletal events in women with breast cancer and bone metastases. Although the study was not powered to detect statistical significance on individual components of the SMPR, the most marked effect of ibandronate treatment was observed on the need for bone radiotherapy, which is considered to be an important sequela of bone metastases. The reduction in the need for radiotherapy was highly statistically significant for oral ibandronate 50 mg. A similar, statistically significant reduction in overall SMPR and SMPR for radiotherapy has also been demonstrated with i.v. ibandronate 6 mg infused every 3–4 weeks, in a randomized clinical trial of patients with metastatic breast cancer [21].

A pre-planned Poisson regression analysis of the SREs was conducted to reflect the impact of treatment on skeletal morbidity while controlling for differences between groups at baseline such as bone pain score and the presence of fractures. The results revealed a highly statistically significant ($P = 0.0005$) RR reduction for both ibandronate doses of 39% (20 mg) and 38% (50 mg). These RR reductions are comparable with that provided by i.v. ibandronate 6 mg (40% reduction versus placebo, $P = 0.0033$) [21].

Direct comparisons between bisphosphonates are difficult because of differences in the parameters used to assess skeletal events (SMPR versus skeletal morbidity rate). Previous studies of other bisphosphonates have assessed drug efficacy using the skeletal morbidity rate. However, this methodology involves multiple counting of events that are closely related and consequently may overestimate treatment outcomes. The use of the SMPR in our study provides a more conservative estimate of drug efficacy by

Table 4. Analyses of overall bone events

All new bone events	Placebo (n = 143)	Ibandronate 20 mg (n = 144)	Ibandronate 50 mg (n = 148)	Global P-value[a]
Mean number of events per patient	2.23	1.36	1.43	0.017
		$P = 0.001$[b]	$P = 0.014$[b]	
Relative risk reduction by Poisson model		38%	39%	
		$P = 0.009$[c]	$P = 0.005$[c]	
Mean number of measurement periods with events	1.27	0.79	0.84	0.017
		$P = 0.002$[b]	$P = 0.014$[b]	
Total number of periods with events	182	114	125	0.017
		$P = 0.002$[b]	$P = 0.014$[b]	
Percentage of patients with events	61.5	46.5	52.0	0.036
		$P = 0.011$[b]	$P = 0.102$[b]	

[a]Jonckheere–Terpstra method, global P-value versus placebo.
[b]Wilcoxon rank sum test, P-value versus placebo.
[c]Poisson regression analysis, P-value versus placebo.

Table 5. Treatment-related AEs reported by ≥2% of patients in any treatment group

AE	Placebo (n = 143)	Ibandronate 20 mg (n = 144)	Ibandronate 50 mg (n = 147)
Abdominal pain	2 (1.4%)	1 (0.7%)	5 (3.4%)
Dyspepsia	11 (7.7%)	12 (8.3%)	15 (10.2%)
Nausea	3 (2.1%)	8 (5.6%)	7 (4.8%)
Esophagitis	2 (1.4%)	2 (1.4%)	4 (2.7%)
Nausea and vomiting	3 (2.1%)	0	2 (1.4%)
Flatulence	3 (2.1)	0	1 (0.7%)
Diarrhea	2 (1.4%)	1 (0.7%)	1 (0.7%)
Hypocalcemia	6 (4.2%)	9 (6.3%)	10 (6.8%)

AEs, adverse events.

not counting an event more than once because it occurred over a number of weeks.

In this study, bone pain scores with ibandronate were lower than with placebo throughout the treatment period (approaching statistical significance for the 20 mg group, $P = 0.071$), and were accompanied by a significant reduction in analgesic use ($P = 0.006$). Although reductions in bone pain from skeletal metastases have been demonstrated in clinical studies of other bisphosphonates [10–12, 19, 30], ibandronate is the only bisphosphonate shown to maintain bone pain reductions below baseline for 2 years [24].

Oral ibandronate was well tolerated in the current study. The incidence of treatment-related AEs was only slightly higher in the active treatment groups and the pattern of events was as expected for bisphosphonates [31]. Although slightly more patients in the 50 mg group experienced treatment-related upper gastrointestinal adverse events than in the 20 mg group, the number of patients who discontinued treatment because of these adverse events was similar in all three study groups. The incidence of gastrointestinal events with ibandronate was less than that reported with oral clodronate (particularly for diarrhea) in clinical studies [13,14,17].

Approximately 60% of patients withdrew from our study before 96 weeks. Although a high proportion of drop-outs may distort the results, this drop-out rate is somewhat lower than those observed with pamidronate. In the study by Hortobagyi et al., ~75% of patients on pamidronate withdrew before 2 years [9].

Although the two oral doses of ibandronate demonstrated comparable efficacy on the primary end point in the current study, the 50 mg dose demonstrated a greater effect on the individual end points of the SMPR (particularly radiotherapy). A pooled analysis of data from this and a second multicenter study with an identical design has also shown greater effects on skeletal complications and symptoms with the 50 mg dose than with the 20 mg dose [32–34]. The superiority of the 50 mg dose is further supported by the results of a phase II dosing finding study [35] and pre-clinical

data showing that administration of ibandronate 50 mg daily given 30 min before food provides comparable bone surface exposure to a 6 mg i.v. dose administered every 28 days (F. Hoffmann-LaRoche Ltd, unpublished data). The use of the 50 mg dose helps to ensure adequate dosing of ibandronate under 'real-world' situations, where patients may not always comply with recommended fasting periods (thus minimizing the impact of food intake on drug efficacy). The 50 mg dose is being further evaluated in clinical trials, and this dose was recently approved in the European Union for the prevention of skeletal events in patients with breast cancer and bone metastases.

The availability of ibandronate as a highly effective and well-tolerated oral bisphosphonate allows flexibility in the choice of dosing regimen, so that patients may receive i.v. or oral therapy while in hospital, followed by oral therapy in the outpatient setting. Self-administration of a single daily dose of therapy might improve treatment convenience and compliance. Oral therapy eliminates the need to visit hospital solely for i.v. bisphosphonate therapy. This would be of particular benefit in patients who are not currently receiving, or have completed, i.v. chemotherapy. The convenience and compliance benefits of oral treatment may encourage patients to remain on bisphosphonate therapy for longer periods. Supporting this, 42% of patients receiving oral ibandronate 50 mg in this study completed the 96-week study period, compared with 18% for i.v. ibandronate 6 mg in another phase III trial with a similar study design [21].

Oral ibandronate may also prove to be cost-effective in the treatment of metastatic bone disease. Economic analyses have shown that existing i.v. bisphosphonates are associated with relatively high costs in relation to clinical benefit [36], with administration contributing considerably to the overall cost of treatment [37].

In conclusion, once-daily treatment with oral ibandronate is an effective treatment for metastatic bone disease from breast cancer, and offers the additional benefits of treatment tolerability and convenience. Ibandronate appears to possess equivalent efficacy to i.v. bisphosphonates and therefore represents an important clinical advance in metastatic bone disease management.

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