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Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer

I.J. Diel [a,*], J.-J. Body [b], M.R. Lichinitser [c], E.D. Kreuser [d], W. Dornoff [e], V.A. Gorbunova [f], M. Budde [g], B. Bergström [h], the MF 4265 Study Group

[a] *CGG-Klinik GmbH, Quadrat P7, 16–18, Mannheim 68161, Germany*
[b] *Université Libre de Bruxelles, Institut Jules Bordet, Bruxelles, Belgium*
[c] *Department of Clinical Chemotherapy, Cancer Research Center, Moscow, Russia*
[d] *Krankenhaus der Barmherzigen Brueder, Onkologische Ambulanz, Regensburg, Germany*
[e] *Mutterhaus der Borromaeerinnen, Trier, Germany*
[f] *Department of Chemotherapy, Cancer Research Center, Moscow, Russia*
[g] *F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[h] *Hoffmann-La Roche Inc., Nutley, NJ, USA*

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Abstract

Bone metastases occur in most women with advanced breast cancer and can lead to considerable morbidity and a rapid deterioration in the patient's quality of life. It was the aim of the present study to assess changes in quality of life and bone pain due to intravenous (i.v.) ibandronate, a potent third-generation bisphosphonate. In a phase III randomised, double-blind, placebo-controlled trial in patients with bone metastases due to breast cancer, 466 women were randomised to receive placebo, 2 mg ibandronate or 6 mg ibandronate for up to 96 weeks. Treatment was administered i.v. at 3- or 4-weekly intervals. Clinical endpoints included the incidence of adverse events, quality of life (assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Scale – Core 30 questionnaire (QLQ-C30)), and bone pain (assessed on a 5-point scale from 0 = none to 4 = intolerable). Ibandronate was generally well tolerated. Compared with baseline measurements, the bone pain score was increased at the last assessment in both the placebo and 2 mg ibandronate groups, but was significantly reduced in the patients receiving 6 mg ibandronate (-0.28 ± 1.11, $P < 0.001$). A significant improvement in quality of life was demonstrated for patients treated with ibandronate ($P < 0.05$) for all global health status. Overall, at the last assessment, the 6 mg ibandronate group showed significantly better functioning compared with placebo ($P = 0.004$), and had significantly better scores on the domains of physical, emotional, and social functioning, and in global health status ($P < 0.05$). Significant improvements in the symptoms of fatigue and pain were also observed in the 6 mg ibandronate group. I.v. ibandronate treatment leads to significant improvements in quality of life, and is an effective and well-tolerated palliative treatment in patients with bone metastases due to breast cancer.

Keywords: Metastatic bone disease; Quality of life; Bone pain; Ibandronate; Breast cancer; Bisphosphonate; Intravenous

1. Introduction

Bone metastases occur in up to 80% of women with advanced breast cancer [1,2]. This leads to major skeletal complications including bone pain, fractures and hypercalcaemia. Combined, these manifestations can cause significant morbidity and deterioration in the patient's quality of life. The management of the secondary complications of metastatic breast cancer is therefore important from patient welfare and societal care perspectives [3–5].

* Corresponding author. Tel.: +49-621-125-06420.
E-mail address: diel@cgg-mannheim.de (I.J. Diel).

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Treatment options in metastatic bone disease can be divided into local (irradiation and surgery) or systemic (hormone therapy, chemotherapy and bisphosphonates) treatments. The primary goal of antiosteolytic treatment with bisphosphonates is the reduction of skeletal-related complications such as hypercalcaemia, pathological fractures and spinal cord compression [6]. These effects are mainly achieved by the osteoclast-inhibiting property of bisphosphonates, and possibly by a direct antitumour action. Bisphosphonates are a class of pyrophosphate analogues characterised by a central PCP backbone. Bisphosphonates bind strongly on bone surface, particularly in zones with activated turnover. Incorporated into osteoclasts (or other cells), bisphosphonates may induce apoptotic or necrotic cell death [7,8].

Oral (p.o.) (e.g. clodronate) and intravenous (i.v.) (e.g. pamidronate) bisphosphonates are currently the standard treatment for metastatic bone disease due to breast cancer. Bisphosphonates are known to delay skeletal-related events and improve bone pain, and may also be expected to improve overall quality of life [9–13]. However, there is limited data on this latter point as few studies have directly measured the effects of bisphosphonate treatment on quality of life. Furthermore, previous studies that incorporated these measurements, have generally failed to show a direct correlation between reduction in skeletal events and improved quality of life [11,13]. Therefore, to improve overall quality of life in patients with metastatic bone disease, additional issues may be important. These could include improvement of other disease symptoms, overall functioning, and ease of therapy administration.

Ibandronate is a potent, third-generation bisphosphonate that is effective in the treatment of hypercalcaemia of malignancy [14–16]. Ibandronate has also been evaluated in patients with metastatic bone disease due to breast cancer. A phase II dose-finding study indicated that i.v. doses of 2 and 6 mg, once every 4 weeks, were effective and sufficiently well tolerated for further evaluation [15,17]. A subsequent phase III study was initiated to evaluate the tolerability and efficacy of i.v. ibandronate administered at 2 and 6 mg, once every 3 or 4 weeks, for at least 60 weeks. Primary efficacy results from this study have recently been reported [18]. Treatment with 6 mg ibandronate was associated with significant clinical benefits. In addition to reducing the rate of skeletal complications, the 6 mg dose extended the time to the first skeletal event by more than 4 months.

Since reducing the incidence of skeletal events and minimising bone pain would be expected to lower disease burden, we report secondary efficacy results from the phase III study to assess the effect of ibandronate on the patient's quality of life.

2. Patients and methods

2.1. Study design

This was a randomised, double-blind, placebo-controlled, parallel group, phase III study. Patients were enrolled at 75 centres in Europe, Kuwait, Russia, South Africa and the United States.

2.2. Patients

Patients with histologically confirmed breast cancer and bone metastases, confirmed by X-ray and/or nuclear magnetic resonance (NMR) imaging, with World Health Organisation (WHO) performance status $\leqslant 2$ and aged $\geqslant 18$ years, were included in the study. Patients were excluded if they had a life expectancy <60 weeks, were pregnant or lactating, or had received bisphosphonate or gallium nitrate treatment within the last 6 months. Patients receiving any investigational drug or aminoglycoside antibiotic within the last 30 days or previous high-dose chemotherapy (dose intensity >3 times standard therapy) were also excluded from the trial. Other exclusions were patients with hypercalcaemia (serum calcium >2.7 mmol/l) or hypocalcaemia (serum calcium <2.0 mmol/l), Paget's disease of the bone, primary hyperparathyroidism, aspirin-sensitive asthma, or known liver or brain metastases. Informed consent was obtained from all patients. This study was conducted in compliance with the institutional review board regulations of the United States, and, in European centres, it was reviewed by ethics committees in accordance with the Declaration of Helsinki.

2.3. Sample size estimate

At the time of planned patient recruitment, the logistic regression continuation ratio model was considered to be the primary method of data analysis. Data from comparable breast cancer studies were used to define the median study duration and probable distribution of complications over time [9–11,19]. Using a 5% two-sided alpha test and a power of 90%, a total of 92 evaluable patients per treatment group was estimated to demonstrate that patients on ibandronate 6 mg would experience no complications in a 12-week period ($P = 0.4$). Allowing for dropouts during the study, it was recommended that a minimum of 120 patients were randomised per treatment arm.

2.4. Treatment

Patients were randomised in a 0.5:1:0.5:1 ratio to receive either placebo or 2 mg ibandronate by i.v. bolus injection, or placebo or 6 mg ibandronate by i.v. infusion over 1–2 h. Therefore, the study was blinded with respect

to placebo or ibandronate treatment, but the dose was open-label due to differences in the mode of delivery. Each study 'arm' received either injection or infusion of ibandronate or placebo on day 0. Subsequent treatments were administered at 3- or 4-weekly intervals for a minimum of 60 weeks and a maximum of 96 weeks. Patients were limited to a maximum of 24 treatments during the study. Concomitant medication (including chemotherapy, hormone therapy and localised radiotherapy) was allowed due to the severe nature of the underlying disease in the patients included in this study.

2.5. Assessments

Because of patient dropouts, efficacy variables were evaluated using last-observation-carried-forward (LOCF) assessments.

2.6. Clinical efficacy assessments

Clinical efficacy assessments (fractures, radiotherapy and surgery) were performed at each 3- or 4-weekly visit.

2.7. Bone pain and analgesic consumption

The assessment of bone pain was carried out at each study visit using the patient-rated scoring system for pain and analgesic use previously described [20]. Patients were asked to describe, on average, how severe their bone pain had been over the last week and to score it on the scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe) or 4 (intolerable). Similarly, analgesic use was scored on a scale of 0 (none), 1 (mild analgesic [aspirin or paracetamol/acetaminophen] or non-steroidal anti-inflammatory drug [NSAID]), 2 (mild analgesic and NSAID), 3 (moderate analgesic: e.g., propoxyphene, codeine or tramadole), 4 (opiates <40 mg morphine [or equivalent] daily), 5 (opiates $\geqslant 40$ mg, but <100 mg morphine [or equivalent] daily), or 6 (opiates $\geqslant 100$ mg morphine [or equivalent] daily).

2.8. Quality of life

Quality of life was assessed using a validated Quality of Life Scale (QLQ-C30) produced for the European Organisation for Research and Treatment of Cancer (EORTC) [21]. This is a 30-item questionnaire incorporating five functional scales (physical functioning, role functioning [work and household], cognitive functioning, emotional functioning and social functioning), three symptom scales (fatigue, pain and nausea and vomiting), and a global health scale. The remaining items assess additional symptoms commonly reported by cancer patients (dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea), as well as the perceived financial difficulties underlying the disease and its treatment. The EORTC QLQ-C30 was completed at baseline and one day before each of the appropriate study visits (visits 2–5, 8, 11, 14, 17, 20, 23 and 26). The effect of treatment was determined by calculating the mean change in global quality of life score from baseline to last study visit and the mean change in the five individual functional domains, global health status and symptoms scores.

2.9. Survival

Patient survival in the different treatment groups was compared using Kaplan–Meier estimates and the proportional hazards model (Cox regression). In these analyses, the day of death (rather than the day of onset of an adverse event leading to death) was used as event definition to study all-cause mortality.

2.10. Other assessments

Efficacy assessments including bone scans, X-rays and laboratory tests were also performed at baseline and at 4-weekly intervals throughout the study. Concomitant medication and adverse events were documented continuously throughout the study. Adverse events were graded according to WHO criteria. Serious adverse events were defined as adverse events that were fatal or acute life-threatening, required hospitalisation, resulted in persistent or significant disability or incapacity, or resulted in malignancy or congenital abnormality/anomaly.

2.11. Statistics

The analyses were performed on the intent-to-treat (ITT) data-set, which included patients who had received at least one dose of study medication and had at least one postbaseline efficacy measurement. In the efficacy analyses, the two placebo groups were combined. Global comparisons between treatments were conducted using the Jonckheere–Terpstra test, based on the sum of the ranks of all five functional parameters (O'Brien's rank test with multiple endpoints) [22] on the absolute change from baseline to last assessment. Differences between placebo and the ibandronate 2 mg and ibandronate 6 mg treatment groups were analysed by pairwise comparison using the Wilcoxon rank-sum test (again using O'Brien's rank test with multiple endpoints) [22]. The quality of life score was analysed according to the evaluation procedure described by the authors of this score (EORTC QLQ-C30) [21]. Briefly, all subscale scores are transformed to a 0–100 scale. Higher scores on the functional scales represent better functioning; higher scores on the symptom scales represent worsening symptoms. One-way analysis of variance (ANOVA) was used to assess the statistical significance of group differences (unadjusted for multiple comparisons).

The statistical analysis of the QLQ-C30 data gave prioritisation to the assessment of the global health status score, followed by the assessment of the individual domains. Conducting the treatment comparisons in sequence for as long as 5% significance was achieved guaranteed the multiple significance level of 5%, according to the closed-test-principle.

3. Results

3.1. Patient demographics

A total of 469 patients with bone metastases as a result of histologically confirmed breast cancer were enrolled, 466 of whom received trial medication and comprised the ITT population (158 patients received placebo, 154 received 2 mg ibandronate, 154 patients received 6 mg ibandronate). Although patients were limited to a maximum of 24 treatments, 4 patients in the placebo group, 9 patients in the 2 mg group and 6 patients in the 6 mg group received 25 treatments.

The mean age of the patients was 55 years and these had an average WHO performance score of 1. Baseline characteristics were similar between the treatment groups (Table 1).

The mean time from cancer diagnosis to study drug treatment was slightly longer in the ibandronate treatment groups compared with placebo. However, mean

Table 1
Patient characteristics at baseline

	Placebo ($n = 158$)	Ibandronate 2 mg ($n = 154$)	Ibandronate 6 mg ($n = 154$)
Mean age, years (SD)	54.5 (11.5)	55.3 (10.9)	56.1 (11.4)
Median age (range)	53.0 (27–82)	55.5 (32–77)	57.0 (34–97)
Mean time from breast cancer diagnosis to bone metastases, months (SD)	46.0 (59.0)[c]	54.7 (50.2)[d]	48.7 (56.9)[e]
Mean time from breast cancer diagnosis to bone metastases, months (range)	43.8 (0.8–390.6)	61.1 (0.8–230.3)	47.6 (0.4–413.8)
Mean time from bone metastases to study entry, months (SD)	17.4 (21.6)	17.3 (21.8)	15.4 (19.0)
Median time from bone metastases to study entry, months (range)	8.0 (0.4–122.8)	8.7 (0.4–113.2)	8.3 (0.4–101.4)
Bone metastases only, *n* (%)	105 (66.5)	101 (65.6)	106 (68.8)
Lung metastases, *n* (%)	18 (11.4)	23 (14.9)	9 (5.8)
Other metastases[a], *n* (%)	35 (22.2)	36 (23.4)	26 (16.9)
Vertebral fractures, *n* (%)	46 (29.1)	49 (31.8)	49 (31.8)
Non-vertebral fractures, *n* (%)	28 (17.7)	31 (20.1)	33 (21.4)
Line of tumour treatment[b,f], *n* (%)			
1st	25 (15.8)	31 (20.1)	34 (22.1)
2nd	49 (31.0)	38 (24.7)	36 (23.4)
3rd	34 (21.5)	36 (23.4)	33 (21.4)
4th	40 (25.3)	44 (28.6)	43 (27.9)
Radiotherapy, *n* (%)	53 (33.5)	48 (31.2)	43 (27.9)
Bone pain score[f], *n* (%)			
Median bone pain score (range)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)
None	26 (16.5)	30 (19.5)	21 (13.6)
Mild	51 (32.3)	60 (39.0)	51 (33.1)
Moderate	51 (32.3)	42 (27.3)	49 (31.8)
Severe	23 (14.6)	16 (10.4)	22 (14.3)
Intolerable	0 (0.0)	1 (0.7)	2 (1.3)
WHO performance status[f], *n* (%)			
Median WHO performance status (range)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)
0	27 (17.1)	41 (26.6)	32 (20.8)
1	91 (57.6)	89 (57.8)	84 (54.5)
2	36 (22.8)	23 (14.9)	36 (23.4)
3	3 (1.9)	1 (0.6)	2 (1.3)
4	1 (0.6)	0 (0.0)	0 (0.0)

n = number of patients.
SD, standard deviation; WHO, World Health Organisation.
[a] Except liver and brain metastases (exclusion criteria).
[b] Includes chemotherapy and hormonal therapy.
[c] $n = 149$.
[d] $n = 146$.
[e] $n = 145$.
[f] Some data are missing in some of the subgroups.

time since diagnosis of bone metastases to study drug treatment was similar for the three treatment groups (Table 1). Most patients ($n = 283$) received concomitant hormone therapy at baseline, 110 patients received chemotherapy and 69 received neither hormone nor chemotherapy. There were no marked differences between the groups in the type and number of concomitant medications taken throughout the study.

3.2. Treatment administration

A total of 249 patients completed 60 weeks of treatment (53% of those randomised to the study). Of the 466 randomised patients, 279 patients withdrew prematurely (i.e., prior to week 96) including 64 patients who died before the end of the study. Fewer patients in the 2 mg (53.2%) and 6 mg (57.1%) groups withdrew from the study compared with patients in the placebo group (69.0%). This was reflected in the median time on study medication, which was greater for the 2 and 6 mg ibandronate groups (18.1 months) than the placebo group (13.1 months).

Adverse events, death and personal reasons were the main reasons for withdrawal from treatment (Table 2).

Ibandronate treatment was generally well-tolerated. The incidence of adverse events was comparable between study groups. Flu-like syndrome and arthralgia occurred slightly more frequently in the ibandronate groups than in the placebo group (placebo 1.9%, 2 mg ibandronate 6.5%, 6 mg ibandronate 6.6%; placebo 7.6%, ibandronate 2 mg 13.1%, ibandronate 6 mg 11.2%, respectively).

The most common serious adverse events were disease progression (locally or metastatic: placebo 39.5%, 2 mg ibandronate 30.1%, 6 mg ibandronate 29.6%), bone pain (placebo 7.6%, 2 mg ibandronate 7.2%, 6 mg ibandronate 2.0%) and spontaneous bone fracture (placebo 4.5%, 2 mg ibandronate 5.9%, 6 mg ibandronate 3.9%).

3.3. Bone pain and analgesic consumption

The 2 mg ibandronate and placebo groups both recorded a mean increase in the bone pain score between baseline and last assessment (0.21 ± 0.09 and 0.19 ± 0.11, respectively). In contrast, the 6 mg ibandronate group demonstrated a lower mean bone pain score at the last assessment than at baseline (mean change -0.28 ± 1.11). The mean change in bone pain score was significantly different ($P < 0.001$) between the 6 mg ibandronate and placebo groups, indicating that ibandronate treatment had a beneficial effect on bone pain (Fig. 1).

Baseline analgesic scores were lower in the ibandronate groups (2 mg ibandronate 0.65 ± 1.25, 6 mg ibandronate 0.90 ± 1.48) compared with placebo (1.16 ± 1.78), and analgesic requirement increased throughout the study in all treatment groups. However, the mean absolute change in analgesic requirement was lower in the 6 mg ibandronate group (0.51 ± 1.54) compared with placebo (0.90 ± 1.64). This difference did not reach statistical significance (Fig. 1).

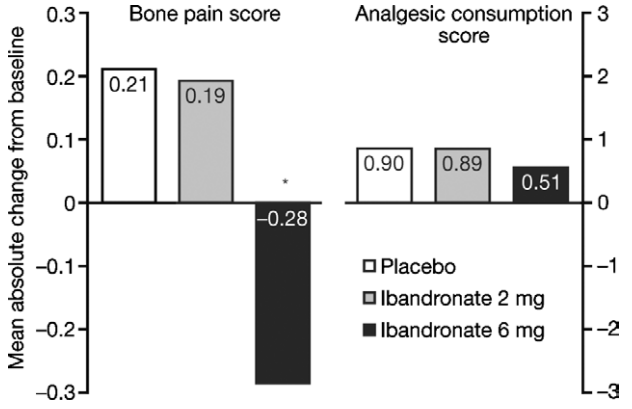

Fig. 1. Mean absolute change in bone pain score and analgesic consumption score from baseline to last study assessment. *$P < 0.001$ versus placebo. For standard deviations, please see results text.

Table 2
Primary reason for premature withdrawal from the study

	Placebo ($n = 158$) n (%)	Ibandronate 2 mg ($n = 154$) n (%)	Ibandronate 6 mg ($n = 154$) n (%)
Death	25 (15.8)	16 (10.4)	23 (14.9)
Adverse event	46 (29.1)	41 (26.6)	38 (24.7)
Lost to follow-up	5 (3.2)	5 (3.2)	3 (1.9)
Personal reasons	21 (13.3)	12 (7.8)	14 (9.1)
Non-compliance with protocol	3 (1.9)	4 (2.6)	1 (0.6)
Non-compliance with drug	0 (0.0)	1 (0.6)	0 (0.0)
Inappropriate enrolment	1 (0.6)	0 (0.0)	1 (0.6)
Other reasons	8 (5.1)	3 (1.9)	8 (5.2)
Total	109 (69.0)	82 (53.2)	88 (57.1)

3.4. Quality of life

3.4.1. Functioning

Of the 466 randomised patients, 419 patients were assessed for changes in quality of life score from baseline to endpoint using the LOCF method (placebo, $n = 143$; 2 mg ibandronate, $n = 139$; 6 mg ibandronate, $n = 137$). On the basis of the five functional domains, mean overall quality of life scores decreased to a lesser extent between baseline and last assessment, for patients receiving 2 mg ibandronate (−18.1) and 6 mg ibandronate (−10.3), compared with patients receiving placebo (−45.4). The overall difference in functioning between placebo and ibandronate treatment was statistically significant ($P = 0.005$). Pairwise comparisons versus placebo using the Wilcoxon rank-sum test also revealed a statistically significant difference in global functioning between the 6 mg ibandronate group and placebo ($P = 0.004$). The pairwise comparison between the 2 mg ibandronate group and placebo in global functioning approached statistical significance at the 5% level ($P = 0.067$).

A similar number of patients within each study group returned scores for global health status and the individual functioning domains at weeks 24, 48, 72 and 96 (variance ±2 between domains). As a guide, physical functioning scores in the placebo group were returned by 102 patients at week 24, 72 patients at week 48, 46 patients at week 72, and 20 patients at week 96. The corresponding values for the active treatment groups were as follows: ibandronate 2 mg, $n = 112$, $n = 91$, $n = 58$ and $n = 32$, and ibandronate 6 mg $n = 112$, $n = 90$, $n = 63$ and $n = 26$. Taking each of the five categories measuring function individually, patients receiving 2 or 6 mg ibandronate had higher mean quality of life scores than patients receiving placebo treatment (Fig. 2). These differences were statistically significant ($P < 0.05$) in the physical, emotional and social functioning categories as well as global health status for 6 mg ibandronate treatment compared with placebo (Fig. 2).

3.5. Symptoms

For patients receiving 6 mg ibandronate, fatigue and pain had improved significantly ($P < 0.05$) at the last assessment compared with placebo (Table 3). Other symptoms including nausea and vomiting, dyspnoea, insomnia, appetite loss and constipation, showed a greater improvement in the 6 mg ibandronate group compared with placebo, but these differences were not

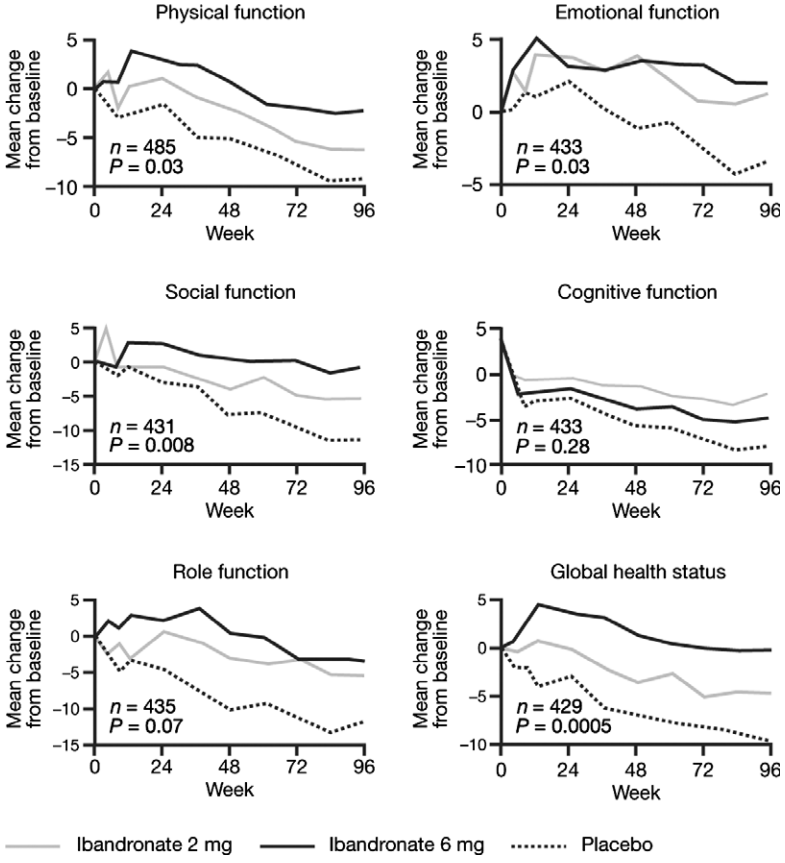

Fig. 2. Mean absolute change (from baseline) in quality of life function scores and global health status, throughout the 96-week treatment period (*P*-values show global comparison between treatments: Jonckheere–Terpstra test).

Table 3
Mean absolute change in quality of life symptoms score from baseline to last assessment

Symptoms	Placebo ($n = 143$) (S.D.)	Ibandronate 2 mg ($n = 139$) (S.D.)	Ibandronate 6 mg ($n = 137$) (S.D.)
Fatigue	10.41 (2.3)	4.58 (2.3)	4.84* (2.2)
Nausea/vomiting	3.73 (2.2)	2.70 (2.2)	2.52 (2.0)
Pain	2.78 (2.8)	4.46 (3.0)	−6.35* (2.8)
Dyspnoea	6.34 (2.2)	3.76 (2.1)	3.19 (2.1)
Insomnia	0.23 (2.9)	−4.93 (2.4)	−1.70 (2.6)
Appetite loss	12.91 (3.3)	2.84* (2.7)	6.28 (2.8)
Constipation	2.78 (2.3)	−0.96 (2.8)	1.70 (2.7)
Diarrhoea	−1.39 (1.7)	−0.48 (1.6)	2.43 (1.9)
Financial difficulties	5.36 (2.3)	1.44 (2.1)	−2.24* (2.1)

n-values = last-observation-carried-forward (LOCF) assesments.
* $P < 0.05$ in comparison with placebo (adjusted).

statistically significant (Table 3). For patients receiving 2 mg ibandronate, improvements were observed in all symptoms except pain when compared with placebo. However, this was only significant ($P < 0.05$) for appetite loss. Overall, the quality of life was significantly increased ($P = 0.002$) for patients treated with 6 mg ibandronate compared with patients treated with placebo.

3.6. Survival

The median overall survival was slightly longer in the 2 mg (116.4 weeks; 95% CI 104–133) and 6 mg ibandronate (113.3 weeks; 95% CI 97–129) groups compared with placebo (106.7 weeks; 95% CI 95–124), but this difference did not reach statistical significance.

4. Discussion

Our data show that overall quality of life, as assessed by the EORTC QLQ-C30 quality of life scale, showed significantly less deterioration in patients treated with 6 mg ibandronate compared with placebo. The 2 mg dose was less effective than 6 mg ibandronate, but did improve some aspects of quality of life relative to placebo. Furthermore, ibandronate treatment improved all aspects of functioning as assessed by the EORTC QLQ-C30 quality of life scale. Significant improvements were observed in the 6 mg ibandronate group compared with placebo in physical, emotional and social functioning, as well as global health status and in the symptoms of fatigue and pain. Significant improvements in the 'financial difficulties' symptom score in this group may also reflect overall improvements in patient functioning.

The estimated differences in treatment effect between the placebo group and the ibandronate groups were based on the change from baseline to last assessment, using the LOCF method. This method is likely to provide a conservative measure of efficacy because patients with more serious disease (and therefore poorer quality of life) are more likely to withdraw early from the study, and early withdrawal affected more patients in the placebo group than in the ibandronate groups. This is shown by the number of patients contributing to the quality of life scores at each assessment point in Fig. 2.

In addition to assessing quality of life in terms of a mean change from baseline, it is common to evaluate the percentage of patients experiencing a clinically meaningful improvement, defined as a greater than 10-point change in global quality of life score [21,23]. It is difficult to quantify whether ibandronate provided clinically meaningful improvements in quality of life in this trial, as mean quality of life score deteriorated in all three treatment groups during the 96-week study period. However, the deterioration in global quality of life score in the placebo group was approximately 35 points greater than with ibandronate 6 mg, and 27 points greater than with ibandronate 2 mg. Using a 10-point change as a guide, these results suggest that ibandronate did provide a clinically meaningful benefit for patient quality of life, in terms of less deterioration over time compared with placebo.

Treatment with 6 mg ibandronate was also associated with a significant improvement in bone pain score, which was reflected in a trend towards a lower requirement for analgesic medication in this treatment group. This specific improvement in bone pain would almost certainly have contributed to the significant improvement in pain overall, identified in the EORTC QLQ-C30. Overall, the trial results show that ibandronate 6 mg has greater efficacy on primary and secondary endpoints than the 2 mg dose (see Body et al. [18]).

Guidelines on the use of bisphosphonates from the American Society of Clinical Oncology recommend that breast cancer patients be initiated on bisphosphonates at the first detection of bone metastases [6]. Consequently, a potential source of bias in our study was the fact that patients had been diagnosed with bone metastases for approximately 17 months before study entry. Another potential source of bias was the use of LOCF analysis. However, patient discontinuations were

linear for all treatment groups throughout the 96-week study period.

Clinical decision-making about treatment alternatives in breast cancer cannot be made solely on the basis of quality of life data [24]. Nevertheless, improving quality of life is an important consideration for the effective management of metastatic bone disease. Bisphosphonates do not improve overall survival, but decrease disease burden by lowering the rate of skeletal complications and reducing bone pain. Consequently, quality of life measurements should be one of the components in making a treatment choice for patients with skeletal metastases.

Previous research has indicated that bisphosphonate therapy reduces skeletal morbidity in breast cancer patients and this may be expected to result in improvements in quality of life [9–13]. However, few previous studies have included specific quality of life measurements in their efficacy endpoints. In one study, pamidronate treatment was shown to significantly improve selected aspects of quality of life (bone pain and mobility impairment) in breast cancer patients with bone metastases, but did not improve fatigue [19]. Two other trials that included quality of life measures failed to show a statistically significant, overall quality of life benefit for bisphosphonate-treated patients [11,13].

In two randomised, placebo-controlled trials, pamidronate (given as a 90 mg i.v. infusion) significantly reduced the number of skeletal complications, prolonged the time to first complication and reduced bone pain in patients with advanced breast cancer and lytic bone lesions [11,12]. However, Spritzer quality of life scores deteriorated between baseline and end of study measurements in both placebo and pamidronate treatment groups. Furthermore, the deterioration of quality of life scores was not significantly different between the two treatment groups [11].

Similarly, oral clodronate (1600 mg) has been shown to significantly reduce the number of skeletal-related events and prolong the time to first event compared with no additional therapy. Improvement was observed in several quality of life aspects, but there was no statistically significant difference between control and clodronate groups [13]. These data along with the results of the present paper suggest that significant improvements in overall quality of life are not generated by reductions in skeletal-related events and bone pain alone. Other aspects such as improvements in other disease symptoms, overall functioning, and patient convenience may also be important.

In conclusion, the data presented in this paper demonstrate that ibandronate treatment significantly improves quality of life in patients with metastatic bone disease due to breast cancer, and significantly reduces pain scores.

Conflict of Interest statement

The clinical trial and data analysis were conducted by Roche, the manufacturers of ibandronate. All authors (except M. Budde and B. Bergström from Roche clinical) were principal investigators in the trial. The authors would like to thank Thomson Gardiner-Caldwell US for their editorial support.

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