

# Intravenous pamidronate versus oral and intravenous clodronate in bone metastatic breast cancer: a randomized, open-label, non-inferiority Phase III trial

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**Purpose:** Patients with metastasized breast cancer often suffer from discomfort caused by metastatic bone disease. Thus, osteoprotection is an important part of therapy in breast cancer metastasized to bone, and bisphosphonates (BPs) are a major therapeutic option. In this study, our objectives were to compare the side effects of oral versus intravenous BP treatment and to assess their clinical effectiveness.

**Patients and methods:** In this prospective randomized, open-label, non-inferiority trial, we enrolled breast cancer patients with at least one bone metastasis and an Eastern Cooperative Oncology Group performance status of 0–2. Patients were randomly assigned to one of the three treatment groups: A, 60 mg pamidronate intravenously q3w; B-iv, 900 mg clodronate intravenously q3w; and B-o, 2,400 mg oral clodronate daily. Assessments were performed at baseline and every 3 months thereafter.

**Results:** Between 1995 and 1999, 321 patients with confirmed bone metastases from breast cancer were included in the study. At first follow-up, gastrointestinal (GI) tract side effects were most common, and adverse effects on the GI tract were more frequent in the oral treatment group ( $P=0.002$  and  $P<0.001$ , respectively). There were no statistically significant differences among the treatment cohorts for other documented side effects (skin, serum electrolytes, urinary tract, immune system, and others). No significant differences in clinical effectiveness of BP treatment, as assessed by pain score, were detected among the groups; however, pathologic fractures were more effectively prevented by intravenous than oral BP administration ( $P=0.03$ ). Noncompliance rates were similar among the study cohorts.

**Conclusion:** We conclude that oral BP treatment is significantly associated with higher rates of adverse GI side effects. Additionally, our data indicate that intravenous BP administration is more effective than oral treatment in prevention of pathologic fractures; hence, oral administration should be considered with caution.

**Keywords:** metastatic bone disease, bisphosphonates, adverse effects, clinical effectiveness

## Introduction

Breast cancer is the most common malignancy among women, with nearly 70,000 new cases in Germany every year.<sup>1</sup> Primary treatment options include surgery, chemotherapy, irradiation, and Her2/neu-targeted and endocrine therapies. Individual treatment depends on various factors, such as TNM status, tumor grade, and hormone receptor, and Her2/neu status, as well as the age of the patient. Approximately 10%–15% of all breast cancer patients develop early metastatic disease within 3 years

of initial diagnosis,<sup>2</sup> and >50% of patients with advanced breast cancer develop metastatic lesions of the bony matrix.<sup>3</sup> Of note, the survival of women with metastatic breast cancer exclusively in their bones is higher than that of patients with additional organs affected by metastases.<sup>4,5</sup> Patients with metastatic bone disease often suffer from a great deal of pain and functional disability. Eventually, severely debilitating consequences may occur, including pathologic fractures and spinal cord compression.<sup>3,6</sup> Metastatic cancer treatment is primarily aimed at improving the quality of life of patients, in terms of physical functioning and psychological well-being. In addition to various local and systemic therapies, including radiation and chemotherapeutics, the use of osteoprotective drugs has led to significant advances for patients.<sup>7</sup>

Osteoprotective substances comprise osteoclast inhibitors, that is, bisphosphonates (BPs) and denosumab, a fully human monoclonal antibody. Although clinical trials have shown that denosumab is superior to BPs in the prevention of skeletal-related events,<sup>8</sup> BPs are still widely used. BPs are chemically related to inorganic pyrophosphate, and are preferentially adsorbed onto hydroxyapatite crystals in the extracellular matrix of bone. From the extracellular matrix, they are taken up by osteoclasts and induce apoptotic processes.<sup>9,10</sup> Parenterally infused BPs are completely bioavailable, independent of varying individual intestinal absorption rates. Currently, three generations of approved BPs are available, which differ in their aliphatic side chains. Non-nitrogen-containing BPs, for example, clodronate, belong to the first generation. Clodronate can be administered intravenously or orally. Intravenous administration is suitable for normalization of hypercalcemia and to reduce skeletal complications, but because of a requirement for long infusion times, it is not frequently used and clodronate is usually taken as an oral medication.<sup>10</sup> Pamidronate was the first of the second-generation aminobisphosphonates to be approved for treatment of hypercalcemia and osteolytic disease due to breast cancer and multiple myeloma. Pamidronate can only be administered intravenously. Due to its strong affinity for bone surface hydroxyapatite, pamidronate is more potent than clodronate.<sup>10</sup> By contrast, third-generation nitrogen-containing BPs, such as zoledronic acid and ibandronic acid, are substantially more effective than earlier compounds. While zoledronate, with its high potency, is currently the most commonly used BP, ibandronate is also frequently prescribed, since it is suitable for both intravenous and oral administration.<sup>10</sup> Despite the overall beneficial effects of osteoclast inhibitors, these therapies are not without untoward effects.<sup>10,11</sup> In this study, we aimed to assess the adverse

effects and clinical value of two different classes of BPs, administered either intravenously or orally.

## Patients and methods

### Study design and patients

In this prospective randomized controlled trial, we enrolled patients according to the following eligibility criteria:  $\geq 18$  years of age, female sex, at least one radiologically confirmed bone metastasis from a histologically confirmed breast cancer, approximate life expectancy of  $\geq 6$  months, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and willingness to give written informed consent. Exclusion criteria were treatment with BPs within 6 months before randomization, cerebral or liver metastases, hypercalcemia or hypercalciuria, tumors other than breast cancer, insulin-dependent diabetes mellitus, chronic heart failure or myocardial infarction within 6 months before randomization, and pregnancy.

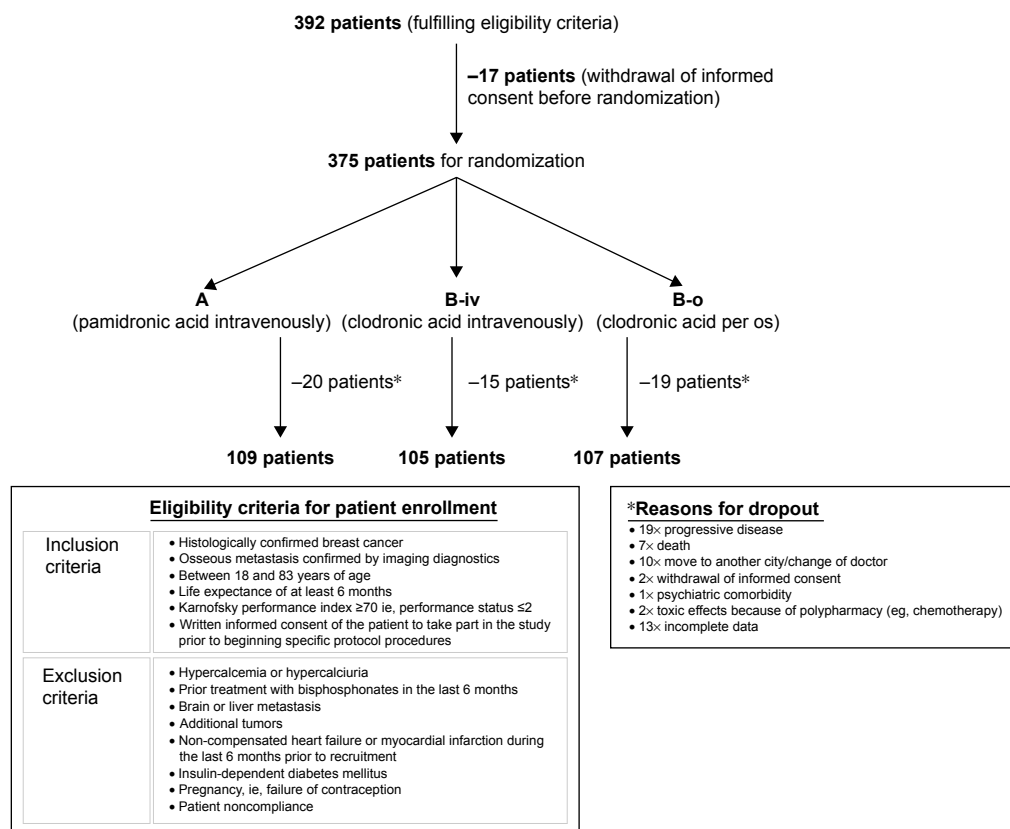
The present trial was approved by the University of Heidelberg Ethics Committee, and all patients gave written informed consent to participate in the study.

### Procedures

Patients were randomly assigned to one of three different groups: A, intravenous pamidronate (Aredia; CIBA-GEIGY GmbH CIBA Pharma, Wehr, Germany); B-o, oral clodronate (Bonefos, 800 mg tablets; Astra Chemicals GmbH, Wedel, Germany); and B-iv, intravenous clodronate (Bonefos pro infusione; Astra Chemicals GmbH).

Patients assigned to groups A, B-o, and B-iv received 60 mg of pamidronic acid intravenously every 3 weeks, 2,400 mg of clodronic acid orally daily, and 900 mg of clodronic acid intravenously every 3 weeks, respectively.<sup>12,13</sup> The planned duration of treatment was 24 months (Figure 1).

Study assessments were made at baseline and subsequently every 3 months for at least three follow-up visits, while fractures were documented throughout the follow-up period. Baseline assessment included a full medical history, details of previous breast cancer diagnosis and treatment, pain scoring (visual analog scale), hormone receptor status, distribution of metastatic disease, and laboratory results, including full-blood count and biochemistry (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets, gamma-oxalacetic transaminase, gamma-pyruvic transaminase, gamma-glutamic transpeptidase, alkaline phosphatase, sodium, potassium, calcium, creatinine, lactate dehydrogenase, uric acid, and urea). Subsequent 3-monthly assessments included medical check-up, ECOG status, pain scoring, progression of breast cancer, medication, laboratory results



**Figure 1** Flowchart of study design and eligibility criteria.

**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate.

(as described earlier), adverse effects (in terms of quality, quantity, and time of incidence), and patient compliance (attendance at appointment for intravenous BP administration or patient confirmation of taking oral BP).

Adverse effect records were evaluated three times. Dose modifications were made in each group for hypocalcemia ( $<2.2$  mmol/L), and in cases of persistent hypocalcemia ( $<1.9$  mmol/L) or hypercalcemia ( $>3$  mmol/L), participants were withdrawn from the study protocol.

## Statistical analyses

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). The primary aim of our study was to demonstrate that oral BP treatment is not inferior to intravenous BP therapy, with regard to side effects and patient compliance.

As a secondary objective, we also examined the effectiveness of treatments according to the number of pathologic fractures and the development of pain. Statistical analysis of pain development was performed by calculating the difference between the number of patients with pain increase and those with pain decrease for each treatment group and comparing these differences using the chi-squared test.

Differences between mean values were calculated using the Kruskal–Wallis test. To compare the number of side effects among the three study groups, the chi-squared test was employed. A Wilcoxon test was applied to compare effectiveness among the different treatment groups. A value of  $P < 0.05$  was considered to indicate a statistically significant difference, while a  $P$ -value of  $< 0.1$  was considered to indicate a tendency toward difference.

## Results

### Patient characteristics

Between 1995 and 1999, we enrolled 392 patients with confirmed bone metastases from breast cancer to our study, of whom 375 were randomly allocated to one of the three treatment groups (group A, 129 patients; group B-iv, 120 patients; group B-o, 126 patients). For various reasons, 20, 15, and 19 patients from groups A, B-iv, and B-o, respectively, were excluded from the study. Finally, 109 patients were allocated to receive pamidronate intravenously (group A), 105 patients received intravenous clodronate (group B-iv), and 107 patients took oral clodronate (group B-o) (Figure 1). Follow-up was planned to continue for 24 months. The average follow-up achieved was 15.6 months (standard

deviation [SD] =9.0) in group A, 15.5 months (SD =8.6) in group B-iv, and 13.4 months (SD =9.2) in group B-o, with no significant difference among the three groups ( $P=0.08$ ). The baseline characteristics of patients (age, BMI, tumor stage, and hormone, receptor, and menopausal statuses) were also similar among the cohorts, as were initial tumor stages (T and N status; Table 1).

## Patient compliance

A total of 50 out of 321 patients (15.6%) were noncompliant during BP treatment, with no significant difference among the three study groups (A =11.9%, B-iv =15.2%, B-o =19.6%;  $P=0.3$ ).

## Adverse effects of BPs

Side effects occurring during BP treatment were categorized as those of the skin, gastrointestinal (GI) tract, serum electrolytes, urinary tract, or immune system. Adverse events that could not be allocated to one of these groups (eg, cough, depression, vertigo, headache) were summarized as “other side effects”. Results are presented in Table 2.

Documented cutaneous side effects were exanthema, rash, or necrosis due to extravasation. Nine events were relatively evenly distributed among the study groups ( $P=0.682$ ) at first follow-up, while no skin side effects were noted at subsequent follow-up visits.

GI tract-associated side effects, including nausea, vomiting, heartburn, abdominal cramps/pain, and diarrhea, were the most common adverse effects experienced by participants in this study. In total, 40 patients were affected by GI tract side effects at first follow-up, with significantly more adverse effects occurring in the oral treatment group ( $P=0.002$ ; Figure 2). The significance of this finding was even more evident when oral BP treatment (group B-o) was compared with all intravenous administration (ie, groups A and B-iv together). The occurrence of GI effects diminished markedly at subsequent follow-up visits, with no significant differences among the study cohorts (Table 2).

With BP therapy, serum electrolyte analyses revealed only rare changes of calcium levels (hypocalcemia), independent of the type of treatment. Similarly, immune system effects were infrequent and mainly took the form of acute-phase reactions (ie, flu-like symptoms, including subfebrile temperatures, bone pain, arthralgias, myalgias, and abnormal fatigue), and no significant differences were observed among the study groups. In addition, few renal function or “other side effects” were recorded, and these did not differ significantly among groups (Table 2).

## Clinical effectiveness of BPs

As a secondary aim, we examined the effectiveness of the three BP treatment regimens by comparing pain

**Table 1** Clinical characteristics of patients

Characteristics	Group A	Group B-iv	Group B-o	Total	P-value
Number of patients	109	105	107	321	
Follow-up (months)	15.6	15.5	13.4	14.8	0.08
Time from diagnosis to randomization (months)	73.2	73.2	58.8	68.4	0.16
Average age (years)	53.0	52.8	52.9	52.9	0.99
Average BMI (kg/m <sup>2</sup> )	26.3	26.2	27.0	26.5	0.43
Tumor stage					
T1, n (%)	35 (35.4%)	22 (23.4%)	27 (27.3%)	84 (28.8%)	0.421
T2, n (%)	40 (40.4%)	48 (51.1%)	46 (46.5%)	134 (45.9%)	
T3, n (%)	12 (12.1%)	8 (8.5%)	8 (8.1%)	28 (9.6%)	
T4, n (%)	12 (12.1%)	16 (17%)	18 (18.2%)	46 (15.8)	
Missing, n	10	11	8	29	
N0, n (%)	33 (32.7%)	25 (27.5%)	27 (27.6%)	85 (29.3%)	0.489
N1, n (%)	61 (60.4%)	52 (57.1%)	58 (59.2%)	171 (59.0%)	
N2, n (%)	7 (6.9%)	12 (13.2%)	10 (10.2%)	29 (10%)	
N3, n (%)	0 (0%)	2 (2.2%)	3 (3.1%)	5 (1.7%)	
Missing, n	8	14	9	31	
Hormone receptor status					
ER-positive, n (%)	48 (52.2%)	50 (58.1%)	48 (53.3%)	146 (54.5%)	0.701
Missing, n	17	19	17	53	
PR-positive, n (%)	41 (47.1%)	36 (50.0%)	48 (52.7%)	125 (50%)	0.755
Missing, n	22	33	16	71	

**Notes:** P-values were calculated by chi-squared test.

**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

**Table 2** Toxic effects of bisphosphonates

Side effects	Group A (n=109)	Group B-iv (n=105)	Group B-o (n=107)	Total	P-value
Skin					
First check-up	2 (1.8%)	4 (3.8%)	3 (2.8%)	9 (2.8%)	0.682
Second check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
Third check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
GI tract					
First check-up	10 (9.2%)	7 (6.7%)	23 (21.5%)	40 (12.5%)	0.002*
Second check-up	3 (2.8%)	3 (2.9%)	0 (0%)	6 (1.9%)	0.216
Third check-up	1 (0.9%)	1 (1.0%)	1 (0.9%)	3 (0.9%)	1.000
Serum electrolyte changes					
First check-up	1 (0.9%)	0 (0%)	2 (1.9%)	3 (0.9%)	0.368
Second check-up	2 (1.8%)	0 (0%)	1 (0.9%)	3 (0.9%)	0.378
Third check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
Immune system					
First check-up	1 (0.9%)	1 (1.0%)	0 (0%)	2 (0.6%)	0.604
Second check-up	1 (0.9%)	0 (0%)	0 (0%)	1 (0.3%)	0.377
Third check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
Urinary tract					
First check-up	1 (0.9%)	2 (1.9%)	0 (0%)	3 (0.9%)	0.354
Second check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
Third check-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	nd
Other side effects					
First check-up	27 (24.8%)	21 (20.0%)	16 (15.0%)	64 (19.9%)	0.196
Second check-up	9 (8.3%)	6 (5.7%)	8 (7.5%)	23 (7.2%)	0.762
Third check-up	4 (3.7%)	0 (0%)	2 (1.9%)	6 (1.9%)	0.140

**Notes:** Number (%) of patients affected is presented. P-values were calculated by chi-squared test. \* $P < 0.05$ .

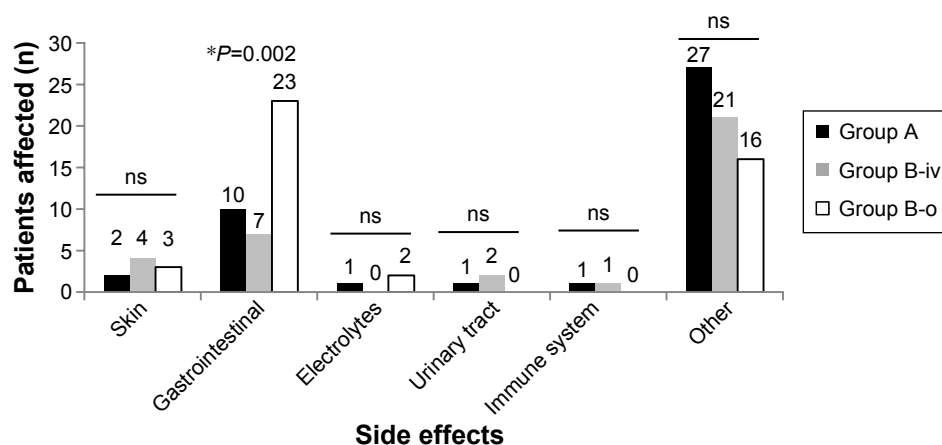
**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate; nd, not determined; GI, gastrointestinal.

development and occurrence of pathologic fractures among the study groups. The results of this analysis are summarized in Table 3.

Employing the visual analog scale, pain scores at baseline and final examinations were not significantly different among the trial cohorts (Table 3). Pain development was documented as pain increase, pain decrease, or stable pain

between check-ups. Overall, there was a slight increase in pain scores over time, with no significant difference among the three groups ( $P = 0.36$ ; Figure 3).

At baseline, 10.3% of all study patients had already presented with pathologic fractures (Table 3). At final check-up, the highest number of new pathologic fractures was recorded for group B-o with 19 incidents, compared to 15 for B-iv and



**Figure 2** Occurrence of bisphosphonate side effects at first follow-up.

**Note:** \*Significant difference,  $P < 0.05$ .

**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate; ns, not significant.

**Table 3** Clinical effectiveness of bisphosphonate treatment

Parameters	Group A (n=109)	Group B-iv (n=105)	Group B-o (n=107)	Total	P-value
<b>Pain score</b>					
Baseline examination					
No pain	32 (29.4%)	30 (28.6%)	32 (29.9%)	94 (29.3%)	0.423
Pain score 1	39 (35.8%)	32 (30.5%)	43 (40.2%)	114 (35.5%)	
Pain score 2	33 (30.3%)	36 (34.3%)	30 (28.0%)	99 (30.8%)	
Pain score 3	5 (4.6%)	7 (6.7%)	2 (1.9%)	14 (4.4%)	
Final examination					
No pain	31 (28.4%)	31 (29.5%)	25 (23.4%)	87 (27.1%)	0.602
Pain score 1	41 (37.6%)	30 (28.6%)	32 (29.9%)	103 (32.1%)	
Pain score 2	20 (18.3%)	23 (21.9%)	42 (39.3%)	85 (26.5%)	
Pain score ≥3	17 (15.6%)	21 (20.0%)	8 (7.5%)	46 (14.3%)	
<b>Pain development from baseline to final examination</b>					
Pain increase	36 (33.0%)	38 (36.2%)	41 (38.3%)	115 (35.8%)	0.547
Pain decrease	25 (22.9%)	32 (30.5%)	22 (20.6%)	79 (24.6%)	
Stable pain	48 (44.0%)	35 (33.3%)	44 (41.1%)	127 (39.6%)	0.36
Difference pain increase – pain decrease (patients, n)	11	6	19	36	
<b>Pathologic fractures</b>					
At baseline	10 (9.2%)	16 (15.2%)	7 (6.5%)	33 (10.3%)	0.1
New fractures	8 (7.3%)	15 (14.3%)	19 (17.8%)	42 (13.1%)	0.07

**Notes:** Number (%) of patients is presented. P-values calculated by Kruskal–Wallis test or chi-squared test as appropriate.

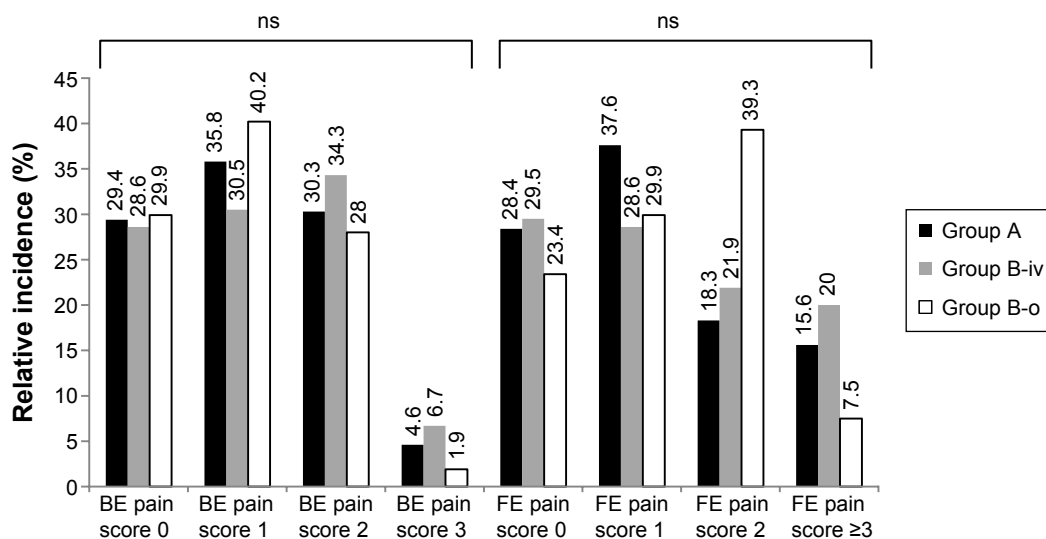
**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate.

eight for A ( $P=0.07$ ), suggesting a tendency toward higher numbers of fractures in the oral BP group. In support of this interpretation, comparison with the pooled intravenous administration groups (A and B-iv) indicates a significant excess of new fracture events in the oral BP group B-o ( $P=0.03$ ).

## Discussion

Currently, BPs are routinely used for treatment of metastatic bone disease, secondary to breast cancer, to reduce pain and

bone destruction. However, the choice of oral or intravenous drug formulations remains a matter of debate. Clearly, oral BPs are more convenient and less costly than intravenous medication. As relevant comparative data are either rare<sup>14</sup> or lacking,<sup>15</sup> in the present trial, we assessed both the occurrence of adverse effects and the clinical effectiveness of intravenous pamidronate, a second-generation nitrogen-containing BP, versus intravenous and oral clodronate, a first-generation non-nitrogenous BP.



**Figure 3** Pain scores relating to bisphosphonate treatment at baseline and final examinations.

**Abbreviations:** A, intravenous pamidronate; B-iv, intravenous clodronate; B-o, oral clodronate; BE, baseline examination; FE, final examination; ns, not significant.

In terms of our primary objective (evaluation of BP-associated side effects), this large randomized prospective Phase III study did not demonstrate non-inferiority of daily oral clodronate, compared to intravenous infusions of clodronate or pamidronate every 3 weeks. GI side effects occurred significantly more frequently with oral clodronate, which is in line with previous reports demonstrating that intravenous pamidronate is an appropriate alternative for treatment of osteoporosis in cases with contraindications for, or intolerance to, oral BPs.<sup>16</sup> The recently published results of the ZICE trial, demonstrating a higher occurrence of adverse GI effects with oral ibandronate than with intravenous zoledronate in the treatment of bone metastatic breast cancer, are also consistent with our findings.<sup>14</sup>

In the present study, nephrotoxic side effects<sup>11,17</sup> and the occurrence of hypocalcemia,<sup>18,19</sup> acute-phase reactions, and adverse cutaneous events were rare and occurred at similar frequencies in the three patient groups, thus precluding clear clinical conclusions.

The secondary aim of our trial was assessment of the clinical efficacy of BP administered by oral versus intravenous routes, in terms of pain reduction and prevention of pathologic fractures. With regard to pain development, there was a shift to an increased pain score in category 3 (visual analog scale) over time, with no significant difference among the three groups studied. The numbers of patients with “no pain” or “pain score 1” remained unchanged in all groups. These data are at variance with earlier reports that intravenous BPs are more effective in pain reduction than oral medication.<sup>10,20–22</sup> However, other recently published data demonstrate an equivalent pain-reducing capacity for oral and intravenous BPs,<sup>14</sup> in complete agreement with the present results.

New pathologic fractures occurred significantly more frequently during BP treatment in the oral clodronate group compared to the intravenous BP groups. Intriguingly, these data are perfectly concurrent with a recent report demonstrating oral ibandronate to be inferior to intravenous zoledronate in terms of reducing the frequency of skeletal-related events in patients with breast cancer metastatic to bone.<sup>14</sup> The limited overall efficacy of oral BPs might be due, at least in part, to a degree of noncompliance, which is typical of any oral therapy. In the present trial, however, compliance rates were not significantly different among the study groups.

A limitation of this study is that compliance with oral clodronate was only determined by patient reports of drug use. Another limitation is that bone imaging was not routinely

performed to diagnose asymptomatic pathologic fractures, although most skeletal-related events do present symptomatically. Finally, the trial was an open-label type, that is, pain assessments were made with patients and investigators being aware of the drug or treatment being given, and the results should therefore be interpreted with caution.

## Conclusion

Our results suggest that oral clodronate is associated with significantly more frequent adverse events affecting the GI tract than intravenous BPs. Further, our results indicate that oral clodronate is inferior to intravenous clodronate and pamidronate in preventing pathologic fractures. Thus, despite the inconvenience and costs of parenteral administration, intravenous BPs appear to be preferable for treatment of patients with breast cancer metastasized to bone.

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## Author contributions

All authors had control of the data and information submitted for publication. All authors contributed toward data analysis, drafting and revising the paper, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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