Denosumab Compared With Ibandronate in Postmenopausal Women Previously Treated With Bisphosphonate Therapy

A Randomized Open-Label Trial

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OBJECTIVE: To compare the efficacy and safety of denosumab to ibandronate in postmenopausal women with low bone mineral density (BMD) previously treated with a bisphosphonate.

METHODS: In a randomized, open-label study, postmenopausal women received 60 mg denosumab subcutaneously every 6 months (n=417) or 150 mg ibandronate orally every month (n=416) for 12 months. End points included percentage change from baseline in total hip, femoral neck, and lumbar spine BMD at month 12 and percentage change from baseline in serum C-telopeptide at months 1 and 6 in a substudy.

RESULTS: At month 12, significantly greater BMD gains from baseline were observed with denosumab compared with ibandronate at the total hip (2.3% compared with 1.1%), femoral neck (1.7% compared with 0.7%), and lumbar spine (4.1% compared with 2.0%; treatment difference P<.001 at all sites). At month 1, median change in serum C-telopeptide from baseline was –81.1% with denosumab and –35.0% with ibandronate (P<.001); the treatment difference remained significant at month 6 (P<.001).

Adverse events occurred in 245 (59.6%) denosumab-treated women and 230 (56.1%) ibandronate-treated women (P=.635). The incidence of serious adverse events was 9.5% for denosumab-treated women and 5.4% for ibandronate-treated women (P=.046). No clustering of events in any organ system accounted for the preponderance of these reports. The incidence rates of serious adverse events involving infection and malignancy were similar between treatment groups.

CONCLUSION: In postmenopausal women previously treated with a bisphosphonate and low BMD, denosumab treatment resulted in greater BMD increases than ibandronate at all measured sites. No new safety risks with denosumab treatment were identified.
Osteoporosis is a common condition, resulting in bone fragility and increased fracture risk. Clinical studies have demonstrated the efficacy of bisphosphonates in reducing the risk of osteoporosis-related fractures. Currently, bisphosphonates are the most commonly used osteoporosis treatment, but inconvenient dosing regimens or medication side effects often lead to medication nonadherence. Poor adherence to bisphosphonate therapy is common and associated with poor outcomes and increased treatment costs. Most patients who discontinue therapy do so within the first year of treatment. Although oral bisphosphonates can be given daily, weekly, or monthly, less frequent bisphosphonate dosing is considered for patients intolerant to more frequently administered oral bisphosphonate treatment or in whom treatment failed. However, there is no evidence that switching these patients from a more to less frequently administered bisphosphonate regimen provides greater benefit.

Prolia (denosumab) is a fully human monoclonal antibody that inhibits bone resorption by targeting RANKL, an essential mediator of osteoclast formation, function, and survival. Denosumab is administered every 6 months as a subcutaneous injection and has been shown to reduce the risk of new vertebral, hip, and nonvertebral fractures in postmenopausal women with osteoporosis. Previous studies have reported that denosumab treatment resulted in significantly greater increases in bone density than the oral bisphosphonate alendronate, but randomized studies compared with ibandronate, a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption, have not previously been conducted.

The objective of this open-label study was to compare the efficacy and safety of denosumab with ibandronate over 12 months in postmenopausal women with low bone density who had discontinued or poor adherence to bisphosphonate therapy.

MATERIALS AND METHODS
This was a randomized, open-label, parallel-group study in postmenopausal women with low bone density who had been treated previously with oral bisphosphonate therapy. The study enrolled women from 74 centers in the United States and Europe.

Ambulatory, postmenopausal women aged 55 years or older were eligible if they had received their first prescription of daily or weekly bisphosphonate therapy 1 month or more before screening but had either discontinued bisphosphonate treatment or remained on treatment but had insufficient adherence assessed by a score of less than 6 on the Osteoporosis Specific Morisky Medication Adherence Scale. Women with a bone mineral density (BMD) T-score of −2 or less and −4 or greater at the total hip or lumbar spine determined at the local site and had one or more proximal femur (hip) and two or more vertebrae between L1 and L4 evaluable by dual-energy x-ray absorptiometry were included.

Exclusion criteria included the current or prior use of osteoporosis medication, except daily or weekly oral bisphosphonate therapy, raloxifene, calcitonin, and hormone replacement therapy; use of medications affecting bone metabolism 3 or fewer months before screening; current enrollment in or less than 1 month since completion of other investigational drug trials; malignancy within the last 5 years, except fully resected basal or squamous cell carcinoma, cervical, or breast carcinoma in situ; impaired renal function (estimated glomerular filtration rate less than 30 mL/min/1.73 m²); or contraindications for ibandronate therapy. Study participants with screening 25-hydroxy vitamin D level less than 20 ng/mL were ineligible but could undergo vitamin D repletion and be rescreened. There was no exclusion based on fracture history.

Between July 29, 2010, and November 5, 2010, participants were randomized 1:1 using an interactive voice response system to receive 60 mg denosumab subcutaneously every 6 months or 150 mg oral ibandronate once monthly for 12 months. Treatment assignment randomization was prepared by the sponsor and supplied to the interactive voice response system before study commencement. All women received daily calcium (500 mg or more) and vitamin D (800 international units or more) supplements. This study was approved by the institutional review board or ethics committee for each study site. Study participants provided written informed consent before enrollment.

Bone mineral density at the proximal femur (for total hip and femoral neck) and lumbar spine was measured by dual-energy x-ray absorptiometry according to manufacturers’ instructions at screening and month 12 or early termination visit. Scans were analyzed by a central laboratory (Synarc, Portland, Oregon). A bone turnover marker study was conducted in a subset of women in which the percentage...
change from baseline in serum C-telopeptide was assessed at month 1 (secondary end point) and month 6 (exploratory end point). In these women, fasting serum samples for measurement of serum C-telopeptide were collected at day 1 (baseline), month 1, and month 6.

Safety was assessed over the 12-month study. Adverse events and serious adverse events were assessed throughout the study. In women in whom multiple events occurred, each event was counted as an independent event rather than assigning a single primary event.

The primary study hypothesis was that treatment with denosumab would be superior to treatment with ibandronate with respect to mean percentage change from baseline in total hip BMD at month 12. The primary end point was the percentage change from baseline in BMD at the total hip at month 12. Secondary end points included percentage change from baseline in femoral neck and lumbar spine BMD at month 12.

The superiority margin for the difference of percentage change from baseline in BMD between treatment groups was greater than 1% for the total hip. A sample size of 362 women per treatment group provided greater than 90% power to detect a difference greater than 1% for total hip BMD at month 12 using a two-sided \( t \) test at the 5% significant level and assuming a common standard deviation of 2.65%. The planned enrolment was 400 women in each treatment group to account for a dropout rate of 10% in the 12 months.

The efficacy analyses presented are based on women who had observed data at baseline and month 12 or early termination visit. Additionally, a number of prespecified analyses including all randomized women was conducted with imputation of missing data to assess possible bias resulting from different dropout reasons and rates between treatment groups related to outcomes in active-controlled open-label trials. Results from these analyses were in agreement with the analyses based on women who had observed data at baseline and month 12 or early termination visit.

The analysis of the percentage change from baseline in BMD at a given skeletal site was performed using an analysis of covariance model adjusted for treatment, timing of BMD assessment in days, treatment-by-BMD assessment day interaction, baseline BMD value, dual-energy x-ray absorptiometry machine type, and baseline BMD value-by-dual-energy x-ray absorptiometry machine type interaction. The results included least-squares mean point estimates of the percentage change from baseline at month 12 for each treatment group. The two-sided 95% confidence intervals (CIs) and associated \( P \) value were calculated for the treatment difference between treatment groups (denosumab–ibandronate). Exploratory analyses assessing the mean percentage change from baseline in total hip, femoral neck, and lumbar spine BMD at month 12 were performed by subgroups. The Gail and Simon test for assessing qualitative interactions was used when the quantitative treatment-by-subgroup interaction \( P \) value was \( \geq .05, 22 \)

The least significant change in BMD measurements for the total hip, femoral neck, and lumbar spine was calculated and compared with the measured change after 12 months of treatment with denosumab or ibandronate. The least significant change is the smallest change in BMD that, when equaled or exceeded, allows the physician to conclude that there has been a real biological change in BMD. The formula for calculating the least significant change incorporates the precision error of the BMD testing, the number of measurements performed at baseline and follow-up, and a value determined by the desired level of statistical confidence.\(^{23}\) Precision error is the mathematical result of precision assessment, in which precision is a measure of the variability in BMD measurement. The proportions of women with a BMD response less than the least significant change and greater or equal to the least significant change at each skeletal site were evaluated using a logistic model with treatment as the only explanatory variable. The Wald \( \chi^2 \) \( P \) value was reported.

For serum C-telopeptide, descriptive statistics were performed on actual serum C-telopeptide data without applying the lower limit of quantification, which was set by the central laboratory at .2 ng/mL. Differences in serum C-telopeptide percentage change from baseline between treatment groups were assessed at month 1 and as an exploratory analysis at month 6 using a Wilcoxon rank-sum test.

The safety analyses included all randomized women who had one or more dose of investigational product. Incidences of adverse events and serious adverse events were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities 14.1. Differences between the treatment groups were assessed using a log-rank test. All analyses were conducted using SAS 9.2.

**RESULTS**

In total, 833 women were enrolled and randomized to receive either denosumab (\( n=417 \)) or ibandronate...
of these, 821 (98.6%) received one or more dose of investigational product (411 denosumab, 410 ibandronate; Fig. 1). Seventy-nine women (19 [4.6%] denosumab, 60 [14.4%] ibandronate) discontinued the study. Overall, 754 (90.5%) women completed the study (398 [95.4%] denosumab, 356 [85.6%] ibandronate; \( P < .001 \)). Of the women randomized, 96.2% in the denosumab-treated group and 84.9% in the ibandronate-treated group were compliant with the treatment regimen (\( P < .001 \)), defined as having received 80% or more of the ibandronate tablets or both denosumab injections at baseline and at month 6.

Baseline demographics and characteristics were balanced between treatment groups (Table 1). Mean age was 67.2 years in the denosumab-treated women and 66.2 years in the ibandronate-treated women. The mean BMD T-scores were \(-1.8\) at the total hip and \(-2.5\) at the lumbar spine, and the median duration of prior bisphosphonate use was 17 months in both treatment groups. The proportion of women at baseline with a history of any fracture (based on patient-reported fracture history) was 43.3% in both treatment groups. Most women (86.8%) reported no parental hip fracture. The majority (55.2%) of women reported that their prior bisphosphonate use was discontinued less than 6 months before their enrollment in the study.

The mean percentage change from baseline in total hip BMD was \(2.3\%\) (95% CI 2.0–2.5) in denosumab-treated women and it was \(1.1\%\) (95% CI 0.9–1.4) in ibandronate-treated women, resulting in a treatment difference of \(1.1\%\) (95% CI 0.8–1.5, \( P < .001 \); Fig. 2) at month 12. Superior BMD gains from baseline with denosumab compared with ibandronate were also observed at the femoral neck (\(1.7\%\) compared with \(0.7\%\); treatment difference \(1.0\%\), \( P < .001 \)) and lumbar spine (\(4.1\%\) compared with \(2.0\%\); treatment difference \(2.1\%\), \( P < .001 \); Fig. 2).

To further characterize the magnitude of the change in BMD after 12 months of treatment with

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**Fig. 1.** Participant disposition. Efficacy analysis sets for the primary end point shown.

Denosumab Efficacy Compared With Ibandronate

Table 1. Baseline Demographics and Clinical Characteristics of Randomized Women

<table>
<thead>
<tr>
<th></th>
<th>Ibandronate (n=416)</th>
<th>Denosumab (n=417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>361 (86.8)</td>
<td>348 (83.5)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>66.2±7.8</td>
<td>67.2±8.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1±4.7</td>
<td>25.5±4.4</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>19.7±10.2</td>
<td>20.4±10.6</td>
</tr>
<tr>
<td>History of fracture</td>
<td>180 (43.3)</td>
<td>181 (43.4)</td>
</tr>
<tr>
<td>Osteoporotic*</td>
<td>121 (29.1)</td>
<td>132 (31.7)</td>
</tr>
<tr>
<td>Nonvertebral</td>
<td>105 (25.2)</td>
<td>121 (29.0)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>23 (5.5)</td>
<td>23 (5.5)</td>
</tr>
<tr>
<td>BMD T-score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>−1.8±0.7</td>
<td>−1.8±0.7</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−2.1±0.7</td>
<td>−2.1±0.7</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>−2.5±0.8</td>
<td>−2.5±0.9</td>
</tr>
<tr>
<td>Prior bisphosphonate use</td>
<td>374 (89.9)</td>
<td>377 (90.4)</td>
</tr>
<tr>
<td>Alendronate</td>
<td>284 (68.3)</td>
<td>277 (66.4)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>104 (25.0)</td>
<td>115 (27.6)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>12 (2.9)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Bisphosphonate (unspecified)*</td>
<td>2 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Duration of prior bisphosphonate use (mo)</td>
<td>16.8 (4.0, 57.4)</td>
<td>16.7 (4.8, 51.7)</td>
</tr>
<tr>
<td>Duration of prior bisphosphonate use (mo)</td>
<td>0 to less than 12</td>
<td>168 (40.4)</td>
</tr>
<tr>
<td>12 or more</td>
<td>247 (59.4)</td>
<td>250 (60.0)</td>
</tr>
<tr>
<td>48 or more</td>
<td>126 (30.3)</td>
<td>110 (26.4)</td>
</tr>
<tr>
<td>Serum C-telopeptide-I, ng/mL¹</td>
<td>0.4 (0.3, 0.6)</td>
<td>0.4 (0.3, 0.5)</td>
</tr>
</tbody>
</table>

BMD, bone mineral density. Data are n (%), mean±standard deviation, or median (quartile 1, quartile 3) unless otherwise specified.

* Any fracture recorded on the case report form, not including skull, facial bones, fingers, and toes and not associated with known high trauma severity or pathologic fractures.

¹ Women reporting medication name as bisphosphonates are displayed in this category.

Denosumab or ibandronate, changes at each skeletal site were compared with the least significant change for that site. The calculated least significant change was 2.12% at the total hip, 3.64% at the femoral neck, and 2.55% at the lumbar spine. At month 12, a greater number of women treated with denosumab compared with ibandronate had BMD gains that were met or exceeded the least significant change at the total hip (49% compared with 30%, P<.001), femoral neck (26% compared with 14%, P<.001), and lumbar spine (65% compared with 41%, P<.001).

When primary and secondary end points were analyzed by subgroups, including by age group, minimum baseline T-score at total hip or lumbar spine, time since initial bisphosphonate prescription, time since bisphosphonate discontinuation, previous osteoporotic fractures (data not shown), and duration of bisphosphonate treatment (Fig. 3), the results demonstrated that the effect of denosumab on total hip, femoral neck, and lumbar spine BMD remained both consistent and greater than ibandronate at month 12, whereas ibandronate treatment did not show significantly greater increases in BMD compared with denosumab at any site or any subgroup. Treatment-by-subgroup interactions were not significant. Results based on the primary imputation method or any other prespecified sensitivity methods were similar (data not shown).

At month 1, denosumab-treated women had a significantly greater reduction from baseline in serum C-telopeptide (median [quartile 1, quartile 3] percentage change from baseline −81.1% [−88.0%, −70.9%]) than ibandronate-treated women (−35.0% [−51.9%, −15.3%], P<.001). At the end of the denosumab dosing interval at month 6, significant treatment differences persisted with greater median (quartile 1, quartile 3) reductions in serum C-telopeptide from study baseline in the denosumab group (−60.5%; −77.2%, −42.1%) compared with the ibandronate group (−45.4%; −62.9%, −17.6%; P<.001). Reductions from baseline also were observed in actual serum C-telopeptide values (Fig. 4).

A total of 245 women (59.6%) in the denosumab group and 230 women (56.1%) in the ibandronate group experienced one or more adverse event during the study (P=0.35) with the most frequently experienced adverse events (4% or more in either treatment group) being arthralgia (6.1% denosumab, 5.6% ibandronate), upper respiratory tract infection...
denosumab 5.1%, ibandronate 2.2%), and urinary tract infection (3.4% denosumab, 4.6% ibandronate). Most of the adverse events in both treatment groups were categorized as being either mild or moderate in severity.

The incidence of serious adverse events was 9.5% (39 of 411) for denosumab-treated women and 5.4% (22 of 410) for ibandronate-treated women ($P = .046$; Table 2). No clustering of events in any organ system accounted for the preponderance of these reports. The incidence of serious adverse events involving infection and malignancy was similar between groups. One patient died during the study (ibandronate group) as a result of a gunshot wound. Adverse events of interest, including hypocalcemia, infection, malignancy, cardiac disorders, vascular disorders, acute pancreatitis, and adverse events potentially associated with hypersensitivity, were similar between treatment groups. There were no adverse events of osteonecrosis of the jaw, delayed fracture healing, or atypical femoral fractures. No women developed antibodies to denosumab.

This study was not designed with adequate statistical power to compare fracture rates between treatment groups. Fractures were reported as adverse events and were not adjudicated. A similar number of women in each treatment group reported one or more on-study fracture: 15 (3.6%) denosumab and 13 (3.2%) ibandronate. The most commonly reported fractures (1% or more of women in either treatment group) were wrist fractures, four (1.0%) for denosumab and one (0.2%) ibandronate; and foot fractures three (0.7%) for denosumab and five (1.2%) for ibandronate. Two women in each treatment group reported vertebral fractures, and one ibandronate-treated participant reported a hip fracture.

**DISCUSSION**

In this study, the efficacy and safety of denosumab was compared with ibandronate in postmenopausal women with low bone density who were treated with prior bisphosphonate therapy. Denosumab treatment resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate therapy, including women who had received long-term (4 or more years) prior bisphosphonate treatment, and BMD gains were observed regardless of baseline BMD. Furthermore, the gains in BMD were clinically meaningful with a higher proportion of women treated with denosumab who met or exceeded the least significant change in BMD at all skeletal sites assessed.

Low BMD is an important modifiable risk factor for fracture in postmenopausal women. Bone mineral density has been used in previous studies to compare the efficacy of different antiresorptive therapies because it has shown to be a reliable surrogate for fracture in phase 3 osteoporosis studies of those agents.\(^2,3,6,24\) The antifracture efficacy of denosumab has been previously reported,\(^18\) and a considerable relationship between BMD gains and fracture risk reductions at the individual patient level has been observed,\(^25\) thereby making BMD a clinically useful marker.
measurement of pharmacologic treatment effect in clinical practice.

The findings of the current study are consistent with previous study results, in which denosumab was compared with alendronate in postmenopausal women with low BMD who were either treatment-naïve or previously treated with alendronate (6 or more months). Few other trials have been published that assess efficacy and safety of transitioning from one bisphosphonate to another. One study assessed the use of transitioning from oral alendronate to intravenous zoledronic acid, which did not result in additional BMD gains for study participants. In a head-to-head study of men with osteoporosis given oral alendronate or intravenous zoledronic acid, similar gains in BMD were reported in both treatment groups. In long-term studies, progressive increases in BMD have been observed with denosumab over 5 years.

<table>
<thead>
<tr>
<th>Event</th>
<th>Ibandronate (n=410)*</th>
<th>Denosumab (n=411)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>230 (56.1)</td>
<td>245 (59.6)</td>
<td>.635</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Eczema</td>
<td>2 (0.5)</td>
<td>7 (1.7)</td>
<td>.122</td>
</tr>
<tr>
<td>Fractures</td>
<td>13 (3.2)</td>
<td>15 (3.6)</td>
<td>.792</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10 (2.4)</td>
<td>15 (3.6)</td>
<td>.402</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>22 (5.4)</td>
<td>39 (9.5)</td>
<td>.046</td>
</tr>
<tr>
<td>Infections</td>
<td>6 (1.5)</td>
<td>7 (1.7)</td>
<td>.903</td>
</tr>
<tr>
<td>Malignancies</td>
<td>6 (1.5)</td>
<td>5 (1.2)</td>
<td>.712</td>
</tr>
<tr>
<td>Cardiac disorders†</td>
<td>3 (0.7)</td>
<td>7 (1.7)</td>
<td>.237</td>
</tr>
<tr>
<td>Gastrointestinal disorders‡</td>
<td>1 (0.2)</td>
<td>7 (1.7)</td>
<td>.043</td>
</tr>
<tr>
<td>Respiratory disorders§</td>
<td>0 (0)</td>
<td>5 (1.2)</td>
<td>.030</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>.299</td>
</tr>
</tbody>
</table>

Data are n (%) for women reporting one or more adverse event unless otherwise specified.

*All women who received one or more dose of investigational product.
†Includes one denosumab-treated woman with three events occurring on the same day (atrial fibrillation, congestive cardiac failure, and sick sinus syndrome) and a subsequent event of congestive cardiac failure, two denosumab-treated women each with one event of congestive cardiac failure, two denosumab-treated women each with one event of atrial fibrillation or sick sinus syndrome, one ibandronate-treated woman with sick sinus syndrome and Wolff--Parkinson-White syndrome, and two ibandronate-treated women each with one event of complete atrioventricular block.
‡Includes one denosumab-treated woman with femoral hernia and inguinal hernia and six denosumab-treated women each with one event of internal hernia, intestinal ischemia, irritable bowel syndrome, dysphagia, small intestinal obstruction, or upper gastrointestinal hemorrhage; and one ibandronate-treated woman with hemmorhoids.
§Includes one denosumab-treated woman with chronic obstructive pulmonary disease and chronic respiratory failure and four denosumab-treated women each with one event of dyspnea, hypoxia, obstructive airways disorder, or pleural effusion.


Fig. 4. Median serum C-telopeptide values over time. Values are actual data, median (Q1, Q3).

*P<.001 for denosumab compared with ibandronate. n=women included in the bone turnover marker study.
years in a large cohort of the pivotal phase 3 fracture study extension of the FREEDOM study.\(^{26}\) In contrast, BMD gains have been observed to plateau over the long term (3–10 years) after initial increase with bisphosphonates, particularly at the hip.\(^{27–30}\)

Treatment with denosumab in this study was associated with significant reductions in serum C-telopeptide compared with ibandronate with maximal reduction of serum C-telopeptide by month 1 and partial release of inhibition at the end of the dosing interval, an observation consistent with other denosumab clinical trials.\(^{31,32}\) This observation contrasts with serum C-telopeptide reduction for the ibandronate group, which was stable after reaching a nadir by month 1. The differences in serum C-telopeptide profile may reflect differences in mechanism of action between denosumab and ibandronate in reducing osteoclast-mediated bone resorption. Ibandronate has affinity for hydroxyapatite and incorporates into bone matrix from which it can be gradually released; as a result, its effects may be sustained for some period after treatment cessation, as observed with alendronate.\(^{33}\) Denosumab as a RANKL inhibitor produces more complete reduction in bone resorption throughout the skeleton, but because it is not incorporated into bone matrix, the effect is reversible with treatment cessation. Our results are consistent with previous studies, which reported an association between denosumab treatment and larger reductions in serum C-telopeptide and greater gains in BMD compared with alendronate in treatment-naïve or previously alendronate-treated women.\(^{20}\)

Denosumab and ibandronate were both well tolerated in this study. Overall adverse event rates were similar between groups, although more ibandronate-treated women withdrew from the study as a result of adverse events. A greater number of serious adverse events were reported in denosumab-treated women, although no clustering of events in any organ system accounted for the preponderance of these reports. Because gastrointestinal serious adverse events were diverse in nature, it was felt that they were not suggestive of an effect as a result of mechanism of action. Serious adverse events involving infection and malignancy were similar to ibandronate. This study was not designed with adequate statistical power to evaluate antifracture efficacy of denosumab and ibandronate.

The main limitation of this study is the open-label design; however, the design reflects a situation, ie, relevant to clinical practice. Approximately half of patients stop taking osteoporosis medication within the first year and may require a switch to a different therapy.\(^{34,35}\) The results of this study imply that transitioning to a therapy with a different mechanism of action and less frequent administration provides greater BMD improvement than switching to another bisphosphonate. In this open-label study, more denosumab-treated women completed the study and were compliant compared with ibandronate-treated women, suggesting better compliance with twice-yearly injections than a monthly oral medication. The importance of less frequent dosing and patient preference of denosumab has been demonstrated previously in a 2-year randomized crossover study, suggesting that this is an appealing proposition for patients who require long-term treatment for a chronic condition.\(^{36}\)

In conclusion, these results demonstrate that women previously treated with a bisphosphonate showed greater increases in BMD at all measured skeletal sites and a larger reduction in bone turnover when they transitioned to denosumab as compared with ibandronate. No new safety risks with denosumab treatment were identified in this open-label study.

**REFERENCES**


