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Denosumab Versus Risedronate in Glucocorticoid-Induced Osteoporosis: Final Results of a Twenty-Four–Month Randomized, Double-Blind, Double-Dummy Trial

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Objective. Clinical trial results have shown that, in glucocorticoid-treated patients, treatment with denosumab 60 mg subcutaneously once every 6 months (Q6M) increased spine and hip bone mineral density (BMD) at month 12 significantly more than treatment with risedronate 5 mg orally once daily (QD). The present analysis was performed to compare efficacy and characterize safety through month 24.

Methods. This phase III study enrolled men and women ≥18 years old who had received ≥7.5 mg daily prednisone or equivalent for <3 months (glucocorticoid-initiating) or for ≥3 months (glucocorticoid-continuing) before screening. All patients <50 years old had a history of osteoporotic fracture. Glucocorticoid-continuing patients ≥50 years old had T scores of −2.0 or less (or −1.0 or less with fracture history). Patients were randomized (1:1) to receive denosumab 60 mg subcutaneously Q6M or risedronate 5 mg orally QD for 24 months, with daily calcium and vitamin D.

Results. Of 795 patients, 590 (74.2%) completed the study (in the glucocorticoid-initiating group, 109 of 145 patients treated with denosumab and 117 of 145 patients treated with risedronate; in the glucocorticoid-continuing group, 186 of 253 patients treated with denosumab and 178 of 252 patients treated with risedronate). Denosumab was superior to risedronate in increasing lumbar spine and total hip BMD at all time points assessed, among glucocorticoid-initiating patients (24-month lumbar spine: BMD increase of 6.2% versus 1.7%, respectively [$P < 0.001$]; 24-month total hip: BMD increase of 3.1% versus 0.0% [$P < 0.001$]) and among glucocorticoid-continuing patients (24-month lumbar spine: BMD increase of 6.4% versus 3.2% [$P < 0.001$]; 24-month total hip: BMD increase of 2.9% versus 0.5% [$P < 0.001$]). Adverse events, serious adverse events (including infections), and fractures were similar between treatment groups.

Conclusion. Denosumab was superior to risedronate in terms of increases in spine and hip BMD through month 24, and the safety profile was similar between treatment groups. Denosumab may offer a new osteoporosis treatment option for glucocorticoid-treated patients.

INTRODUCTION

Long-term glucocorticoid use is highly prevalent (1) and associated with an increased risk of fracture, even at low daily doses (2). Calcium and vitamin D supplementation is recommended with oral glucocorticoid therapy, and the addition of a bisphosphonate or other osteoporosis treatment is recommended for patients at moderate-to-high risk of fracture who are taking oral glucocorticoids (3,4). These recommendations are supported by several randomized, controlled clinical trials showing that bisphosphonates such as alendronate (5–7), risedronate (7–10), or zoledronic acid (11,12) effectively prevent bone loss in patients receiving oral glucocorticoid therapy. Based on extensions to these studies (13) and meta-analyses, bisphosphonates may reduce the risk of vertebral fractures associated with glucocorticoid use (5,7,9,10,13–16). However, inconvenient dosing regimens and potential side effects of bisphosphonates can lead to low adherence in patients with osteoporosis (17,18). Furthermore, the increase in bone mineral density (BMD) with bisphosphonate therapy plateaus after 3–4 years (19–22). Teriparatide may also reduce fracture risk in those taking glucocorticoids (23), but daily injections and restriction to a 2-year lifetime for treatment limit its use. Therefore, there is great interest in other therapeutic options for patients receiving oral glucocorticoid therapy.

Denosumab is a fully human monoclonal antibody that binds to and neutralizes the activity of human RANKL. In postmenopausal women with osteoporosis, long-term denosumab treatment for up to 10 years was well tolerated, continued to increase BMD without therapeutic plateau, and was associated with a sustained low incidence of fracture (24). The primary analysis, conducted at month 12 of a 24-month study of glucocorticoid-treated patients, has demonstrated that subcutaneous denosumab 60 mg once every 6 months (Q6M) increased BMD at the spine and hip significantly more than oral risedronate 5 mg once daily (QD) (25). However, glucocorticoid treatment often extends beyond 1 year in the clinical setting due to the chronic nature of the inflammatory diseases for which it is taken (26,27). Therefore, it is important to assess the continued efficacy and safety of denosumab, compared with risedronate, during the second year of treatment. Our report extends the findings of this double-blind, active-controlled trial to month 24. The objectives of this final analysis were to compare the effects of denosumab versus risedronate on BMD through month 24 and further characterize the safety profile of continued denosumab treatment in this population.

PATIENTS AND METHODS

Patients. Participants in the study were men and women ≥18 years old who were receiving glucocorticoid therapy (prednisone or its equivalent) at a dose of ≥7.5 mg for <3 months (glucocorticoid-initiating) or ≥3 months (glucocorticoid-continuing) before screening. Patients <50 years old in either subpopulation were required to have a history of osteoporosis-related fracture. Patients ≥50 years old in the glucocorticoid-continuing subpopulation were required to have a lumbar spine, total hip, or femoral neck BMD T score of –2.0 or less, or a T score of –1.0 or less with a history of osteoporosis-related fracture. Women of childbearing potential were required to use 2 highly effective forms of contraception through 7 months after the last injection of study medication.

Study design. This was a phase III, international, randomized, double-blind, double-dummy, active-controlled, parallel-group study (ClinicalTrials.gov identifier: NCT01575873). Patients were randomized 1:1 within each subpopulation to receive subcutaneous denosumab 60 mg Q6M and oral placebo (for risedronate) QD for 24 months, or oral risedronate 5 mg QD (the dosing regimen approved for the treatment and prevention of glucocorticoid-induced osteoporosis) and subcutaneous placebo (for denosumab) Q6M for 24 months, stratified by sex within each subpopulation using an interactive voice-response system. The sponsor's Global Randomization and Blinding Group, which was independent of the study team, prepared the randomization before study initiation using a computer-generated schedule. All patients were to receive daily supplementation with calcium (≥1,000 mg) and vitamin D (≥800 IU). Enrollment of men was restricted to 30–40% in each subpopulation. The patients' primary or specialist physicians managed their glucocorticoid therapy.

This study was conducted in accordance with the Declaration of Helsinki and followed the International Conference for Harmonisation Guidelines for Good Clinical Practice. An independent review board approved the study design for each center. Written informed consent was obtained from each patient before study participation.

Assessments. At the 12-month and 24-month screenings, BMD of the lumbar spine, total hip, femoral neck, and 1/3 radius was measured by dual x-ray absorptiometry (Lunar or Hologic) and analyzed centrally (BioClinica). At months 6 and 18, only BMD of the lumbar spine was measured and analyzed.

In a bone turnover marker substudy, markers of bone resorption (C-telopeptide of type I collagen [CTX]) and bone formation (N-propeptide of type I collagen [PINP]) were measured on days 1 and 10, and at months 3, 4, 5, 6, 12, and 24. CTX was assessed centrally (Esoterix Laboratory Services) using IDS-iSYS based on chemiluminescence technology, and PINP was analyzed centrally (Covance Central Laboratory Services) using UniQ PINP radioimmunoassay.

To identify prevalent and incident vertebral fractures, a central facility (BioClinica) provided Genant semiquantitative grading of lateral thoracic and lumbar spine radiographs obtained on day 1 and at months 12 and 24 or at early termination. Data on clinical and nonvertebral fractures were collected based on adverse event reporting. Clinical fractures were defined as all fractures excluding skull, facial bones, mandible, metacarpus, finger phalanges, toe phalanges, and cervical vertebrae, and were not associated with

known high-trauma severity or pathologic fractures. Participants were queried about adverse events and concomitant medications at each study visit. Potential cases of osteonecrosis of the jaw and atypical femoral fracture, identified based on prespecified search criteria, were reviewed by independent, blinded, external adjudication committees using published case definitions (28,29).

The final analysis described herein examined secondary end points for the percentage change from baseline through month 24 in lumbar spine and total hip BMD, in both subpopulations separately. Exploratory efficacy end points were the percentage change from baseline through month 24 in femoral neck and 1/3 radius BMD in both subpopulations separately, and in bone turnover markers (CTX and PINP) in the combined subpopulations. Safety objectives compared denosumab with risedronate in the combined subpopulations.

Statistical analysis. Percentage changes from baseline in BMD were assessed using an analysis of covariance (ANCOVA) model with main effects for treatment, sex, baseline BMD, and machine type, and an interaction effect for baseline BMD and machine type. For the glucocorticoid-continuing subpopulation, duration of prior glucocorticoid use (<12 months versus ≥12 months) was an additional covariate in the model. Because missing BMD values were not imputed, only patients with observed BMD data at baseline and at the time point of interest (e.g., month 12, month 24) were included in the efficacy analysis at each postbaseline visit.

A sensitivity analysis for BMD results was done for the per-protocol analysis set of patients who did not have important protocol deviations and received all planned denosumab doses (or matching placebo) and at least 80% of the planned risedronate doses (or matching placebo). Additional sensitivity analyses for missing data for BMD results included a repeated-measures model without imputation, an ANCOVA model with baseline values carried forward, and an ANCOVA model with multiple imputation. Diagnostic plots were generated to examine model assumptions.

Percentage changes from baseline for bone turnover markers were analyzed using nonparametric methodology in the combined subpopulations. Wilcoxon's rank sum test was used to compare treatment groups. Analyses included patients in the bone turnover marker substudy who had values observed at the time points of interest. Undetectable values were imputed using the lower limit of detection value.

Safety analyses included patients who received ≥1 dose of risedronate or denosumab. Patient incidence rates of treatment-emergent adverse events were summarized in the combined subpopulations, and the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used. Serious infections were assessed in subgroups of patients receiving concomitant biologic and/or nonbiologic immunosuppressants. Statistical comparisons were not conducted for analyses of adverse events.

New and worsening vertebral fractures were assessed in the combined subpopulations for patients who had a baseline spine radiograph and ≥1 postbaseline spine radiograph. Low-trauma nonvertebral fractures were assessed in the combined subpopulation in patients who received ≥1 dose of risedronate or denosumab. Chi-square tests were used to compare fracture incidence rates between the treatment groups.

RESULTS

Patient characteristics. This study was conducted at 79 centers in Europe, North America, Latin America, and Korea. Of the 795 patients who were enrolled, 590 (74.2%) completed the 24-month study, including 226 glucocorticoid-initiating patients (109 of 145 treated with denosumab and 117 of 145 treated with risedronate) and 364 glucocorticoid-continuing patients (186 of 253 treated with denosumab and 178 of 252 treated with risedronate) (Figure 1). The leading causes of study discontinuation overall were withdrawal of consent (13.6% denosumab, 12.3% risedronate) and adverse events (4.8% denosumab, 4.0% risedronate). The baseline characteristics of the treatment groups were balanced within each subpopulation (Table 1). Overall, 45.3% of patients
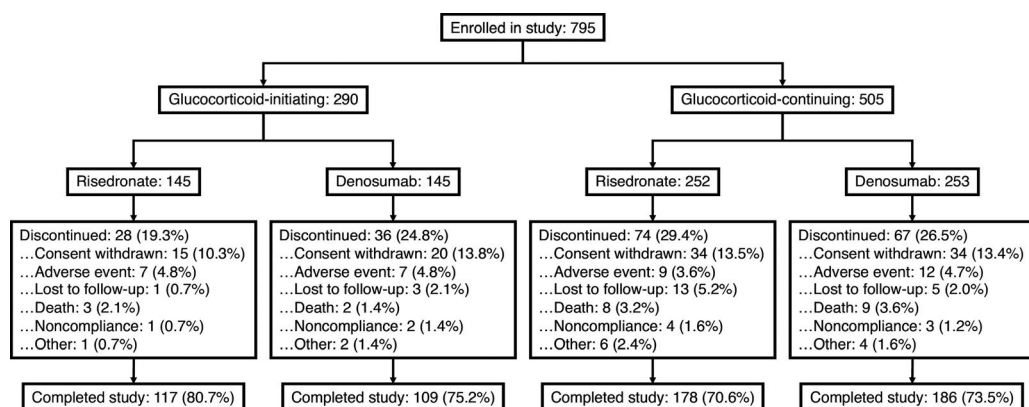
Figure 1. Disposition of the patients enrolled in the study.

Table 1. Demographic and disease characteristics of the patients at baseline*

	Glucocorticoid-initiating		Glucocorticoid-continuing	
	Risedronate (n = 145)	Denosumab (n = 145)	Risedronate (n = 252)	Denosumab (n = 253)
Female sex, no. (%)	93 (64.1)	93 (64.1)	185 (73.4)	185 (73.1)
Premenopause	7 (7.5)	10 (10.8)	25 (13.5)	24 (13.0)
Postmenopause	83 (89.2)	82 (88.2)	157 (84.9)	159 (85.9)
Unknown	3 (3.2)	1 (1.1)	3 (1.6)	2 (1.1)
Race, no. (%)				
White	123 (84.8)	122 (84.1)	223 (88.5)	230 (90.9)
Asian	9 (6.2)	9 (6.2)	12 (4.8)	6 (2.4)
Black or African American	2 (1.4)	2 (1.4)	4 (1.6)	4 (1.6)
Other	11 (7.6)	12 (8.3)	13 (5.2)	13 (5.1)
Age, mean ± SD years	64.4 ± 10.0	67.5 ± 10.1	61.3 ± 11.1	61.5 ± 11.6
Condition requiring glucocorticoid, no. (%)†				
Rheumatologic disorders	129 (89.0)	129 (89.0)	184 (73.0)	173 (68.4)
Rheumatoid arthritis	46 (31.7)	49 (33.8)	119 (47.2)	96 (37.9)
Polymyalgia rheumatica	52 (35.9)	51 (35.2)	18 (7.1)	21 (8.3)
Systemic lupus erythematosus	4 (2.8)	2 (1.4)	16 (6.3)	15 (5.9)
Vasculitis	10 (6.9)	7 (4.8)	9 (3.6)	15 (5.9)
Other	34 (23.4)	32 (22.1)	30 (11.9)	38 (15.0)
Respiratory disorders	11 (7.6)	12 (8.3)	37 (14.7)	46 (18.2)
COPD	1 (0.7)	1 (0.7)	5 (2.0)	7 (2.8)
Asthma	2 (1.4)	3 (2.1)	17 (6.7)	20 (7.9)
Other	8 (5.5)	8 (5.5)	16 (6.3)	20 (7.9)
Inflammatory bowel disease	0 (0.0)	1 (0.7)	5 (2.0)	3 (1.2)
Sarcoidosis	0 (0.0)	0 (0.0)	5 (2.0)	4 (1.6)
Neurologic disorders	2 (1.4)	1 (0.7)	15 (6.0)	11 (4.3)
Dermatologic disorders	5 (3.4)	6 (4.1)	8 (3.2)	9 (3.6)
Other	11 (7.6)	12 (8.3)	37 (14.7)	46 (18.2)
Glucocorticoid dose, mg/day‡				
Mean ± SD	15.6 ± 10.25	16.6 ± 13.01	11.1 ± 7.69	12.3 ± 8.09
Median (IQR)	12.5 (9.0–20.0)	12.5 (10.0–20.0)	10.0 (7.5–10.0)	10.0 (7.5–12.5)
Prior glucocorticoid use, no. (%)§				
0 to <3 months	129 (89.0)	133 (91.7)	8 (3.2)	13 (5.1)
≥3 months	16 (11.0)	10 (6.9)	242 (96.0)	239 (94.5)
3 to <12 months	8 (5.5)	7 (4.8)	75 (29.8)	81 (32.0)
≥12 months	8 (5.5)	3 (2.1)	167 (66.3)	158 (62.5)
Missing data	0 (0.0)	2 (1.4)	2 (0.8)	1 (0.4)
Immunosuppressant therapy at baseline, no. (%)	51 (35.2)	52 (35.9)	135 (53.6)	122 (48.2)
Biologic medication	6 (4.1)	5 (3.4)	12 (4.8)	7 (2.8)
Nonbiologic immunosuppressant	48 (33.1)	50 (34.5)	133 (52.8)	120 (47.4)
25(OH)D, median (IQR) ng/ml	28.6 (24.2–36.4)	28.8 (23.6–36.0)	28.0 (23.6–36.3)	29.2 (24.2–37.6)
BMD T score, mean ± SD				
Lumbar spine	−1.06 ± 1.57	−0.92 ± 1.86	−1.96 ± 1.38	−1.92 ± 1.38
Total hip	−0.98 ± 1.07	−1.14 ± 1.00	−1.56 ± 0.96	−1.66 ± 0.96

(Continued)

Table 1. *(Cont'd)*

	Glucocorticoid-initiating		Glucocorticoid-continuing	
	Risedronate (n = 145)	Denosumab (n = 145)	Risedronate (n = 252)	Denosumab (n = 253)
Osteoporotic fracture after age ≥18 years, no. (%)	51 (35.2)	49 (33.8)	135 (53.6)	136 (53.8)
Prevalent vertebral fracture, no. (%)	26 (17.9)	21 (14.5)	81 (32.1)	67 (26.5)
Serum CTX, median (IQR) ng/liter	230 (115–321)	259 (150–375)	140 (85–264)	205 (111–344)
Fracture risk, median (IQR)¶				
Major osteoporotic fracture	11.3 (7.3–17.2)	11.5 (7.6–17.9)	14.0 (8.1–23.1)	14.5 (7.8–24.5)
Hip fracture	2.7 (0.9–5.8)	3.1 (1.4–6.0)	4.2 (1.5–8.1)	4.4 (1.8–8.2)

* COPD = chronic obstructive pulmonary disease; IQR = interquartile range; 25(OH)D = 25-hydroxyvitamin D; BMD = bone mineral density; CTX = C-telopeptide of type I collagen.
† Patients could have >1 medical condition requiring glucocorticoid therapy.
‡ Dose in prednisone equivalents.
§ Investigators assigned each patient to a subpopulation (glucocorticoid-initiating or glucocorticoid-continuing) and recorded the start date of glucocorticoid use separately. The start date was used to calculate the duration of glucocorticoid use for each patient. Thus, in some instances (<10%), there was a mismatch.
¶ Determined using Fracture Risk Assessment Tool.

were receiving ≥1 immunosuppressant therapy at baseline, including biologic medications in 3.8% of patients and nonbiologic immunosuppressants in 44.2%. Immunosuppressant therapies that at least 5% of patients were using at baseline were methotrexate (33.2%), azathioprine (5.3%), and leflunomide (5.0%).

Bone mineral density. Denosumab was superior to risedronate with regard to the percentage change from baseline in lumbar spine BMD and total hip BMD at each assessment through month 24 in each subpopulation (Figure 2). Denosumab was also superior to risedronate with regard to the percentage change from baseline to month 24 in BMD at the femoral neck and 1/3 radius (Figure 2). The difference between denosumab and risedronate treatment groups in mean percentage change in BMD from baseline to month 24 was 4.5% (95% confidence interval [95% CI] 3.2–5.8%) for the lumbar spine, 3.1% (95% CI 2.2–3.9%) for the total hip, 2.5% (95% CI 1.3–3.6%) for the femoral neck, and 1.5% (95% CI 0.5–2.5%) for the 1/3 radius in the glucocorticoid-initiating subpopulation. In the glucocorticoid-continuing subpopulation, the difference in the mean percentage change was 3.2% (95% CI 2.0–4.3%) for the lumbar spine, 2.5% (95% CI 1.7–3.2%) for the total hip, 1.8% (95% CI 0.7–2.9%) for the femoral neck, and 1.6% (95% CI 0.7–2.4%) for the 1/3 radius. Results of the sensitivity analyses for BMD were consistent with those of the planned analysis.

Bone turnover markers. The bone turnover marker substudy included 269 patients (140 treated with denosumab and 129 treated with risedronate). In both treatment groups, bone turnover markers for resorption (CTX) and formation (PINP) decreased from baseline throughout the study (Figure 3). The reduction in levels from baseline were significantly greater

in the denosumab group than in the risedronate group for both CTX (from day 10 to month 12) and PINP (from month 3 to month 12). By month 24, the reductions from baseline were not significantly different between the denosumab and risedronate groups.

Adverse events. Incidence rates of adverse events, serious adverse events, and adverse events leading to discontinuation of study treatment or discontinuation from study were similar between treatment groups (Table 2). The incidence of any infection in the denosumab and risedronate groups was 36.3% (143 of 394) and 36.4% (140 of 385), respectively, and the incidence of any serious infection was 5.8% (23 of 394) and 6.5% (25 of 385). Incidence rates of serious infections in high-risk subgroups were as follows for those receiving a concomitant biologic: 0% (0 of 23) in the denosumab group and 12.1% (4 of 33) in the risedronate group. In patients receiving a concomitant biologic, or any biologic or nonbiologic immunosuppressant, the rates were as follows: 3.6% (7 of 195) in the denosumab group and 6.8% (14 of 207) in the risedronate group. There was no fatal infection in the denosumab group and 1 fatal infection (septic shock) in the risedronate group. Study treatment was discontinued due to an infection in 1 patient in the denosumab group and 4 patients in the risedronate group.

As reported previously (25), 1 instance of positively adjudicated atypical femoral fracture in the denosumab group occurred in a 60-year-old man with a >30-year history of glucocorticoid use for asthma, ~2 months after his second dose of denosumab. This event was treated with surgical fixation and resolved within ~7 months. There were no cases of positively adjudicated osteonecrosis of the jaw.

Fractures were a safety end point. Osteoporosis-related fractures through month 24 were reported in 8.8% of patients
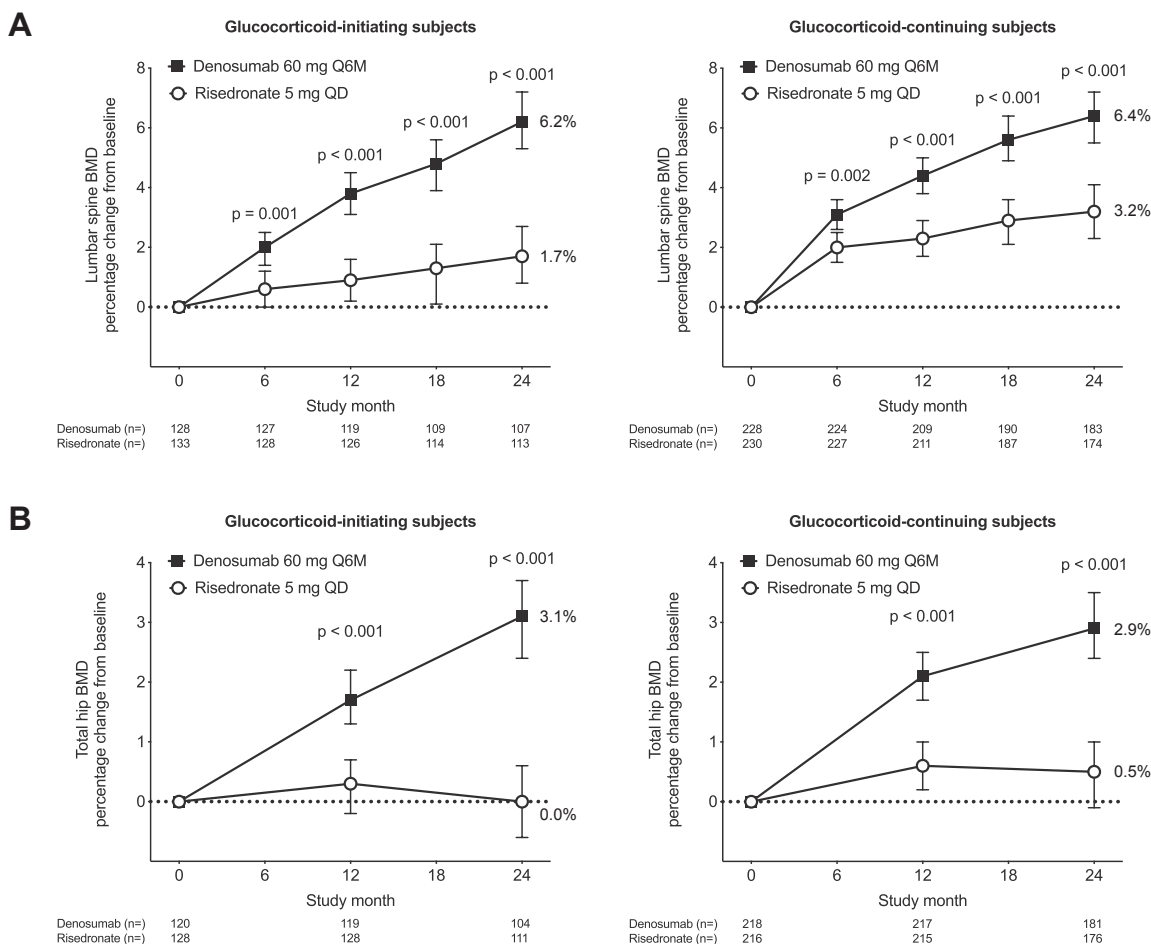
Figure 2. Percentage change from baseline in bone mineral density (BMD) at the lumbar spine (**A**), total hip (**B**), femoral neck (**C**), and 1/3 radius (**D**) for each subpopulation. Between-group comparisons are based on analysis of covariance models with adjustment for treatment, baseline BMD, sex, machine type, and baseline BMD × machine type interaction. For the glucocorticoid-continuing subpopulation, duration of prior glucocorticoid use (<12 months versus ≥12 months) was included as an additional covariate. Values are the least squares means and 95% confidence intervals. Q6M = once every 6 months; QD = once daily.

in the denosumab group and 9.1% of patients in the risedronate group (Table 3). New and worsening vertebral fractures were reported in 4.4% of patients in the denosumab group and 6.9% of patients in the risedronate group. Low-trauma nonvertebral fractures occurred in 5.3% of patients in the denosumab group and 3.8% of patients in the risedronate group. None of the above differences in fracture end points between the 2 treatment groups were statistically significant.

DISCUSSION

This final analysis of a 24-month, prospective, randomized, double-blind, double-dummy trial provided additional evidence of the efficacy and safety of denosumab, compared with risedronate, an established therapy, in glucocorticoid-treated individuals at high risk of fracture. The superior effect of denosumab versus risedronate on spine and hip BMD that was observed in the primary analysis at month 12 (25) continued

through month 24 in each subpopulation: the glucocorticoid-initiating subpopulation, in which patients had recently initiated glucocorticoid treatment, and the glucocorticoid-continuing subpopulation, in which patients had been using a glucocorticoid for ≥3 months before study entry. Increases in BMD at the femoral neck were also significantly greater with denosumab, compared with risedronate, in each subpopulation at month 12 and at month 24. In the glucocorticoid-initiating subpopulation, BMD at the femoral neck declined ~1% by month 24 with risedronate, compared with an increase of ~1% with denosumab. Changes in BMD at the 1/3 radius have been shown to be limited with many antiresorptives (30,31); however, a statistically significant increase in BMD of the 1/3 radius was observed with denosumab treatment, compared with risedronate treatment, at month 24. The treatment difference for BMD at each skeletal site was larger at month 24 than at month 12, reflecting the progressive increase for most measures of BMD in the denosumab group versus the plateau in the risedronate
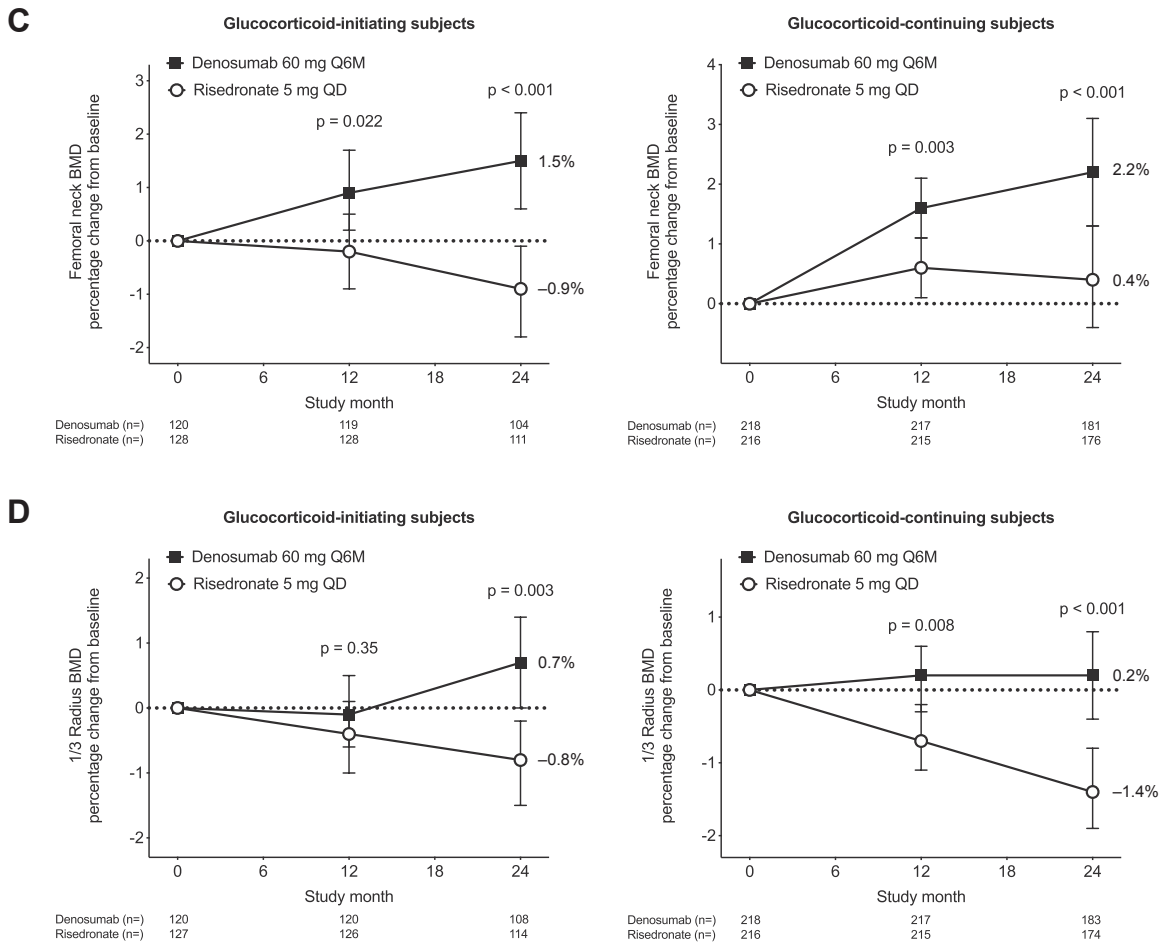
C

Glucocorticoid-initiating subjects

Femoral neck BMD percentage change from baseline

p = 0.022
p < 0.001
1.5%
−0.9%

Study month: 0 6 12 18 24

Denosumab (n=)	120	119	104
Risedronate (n=)	128	128	111

Glucocorticoid-continuing subjects

Femoral neck BMD percentage change from baseline

p = 0.003
p < 0.001
2.2%
0.4%

Study month: 0 6 12 18 24

Denosumab (n=)	218	217	181
Risedronate (n=)	216	215	176

D

Glucocorticoid-initiating subjects

1/3 Radius BMD percentage change from baseline

p = 0.35
p = 0.003
0.7%
−0.8%

Study month: 0 6 12 18 24

Denosumab (n=)	120	120	108
Risedronate (n=)	127	126	114

Glucocorticoid-continuing subjects

1/3 Radius BMD percentage change from baseline

p = 0.008
p < 0.001
0.2%
−1.4%

Study month: 0 6 12 18 24

Denosumab (n=)	218	217	183
Risedronate (n=)	216	215	174

Figure 2. *(Cont'd)*

group beyond 12 months, which has also been shown in other studies (19–22).

Reductions in serum concentrations of bone turnover markers were significantly greater with denosumab versus risedronate through month 12 but were not significantly different between the treatment groups at month 24 in this analysis. In contrast to the FREEDOM study, in which >7,000 postmenopausal women with osteoporosis were enrolled and followed up for >3 years, and in which a placebo group and not a bisphosphonate group was used as comparator (32), the present study was not designed with adequate statistical power to detect fracture differences between treatment
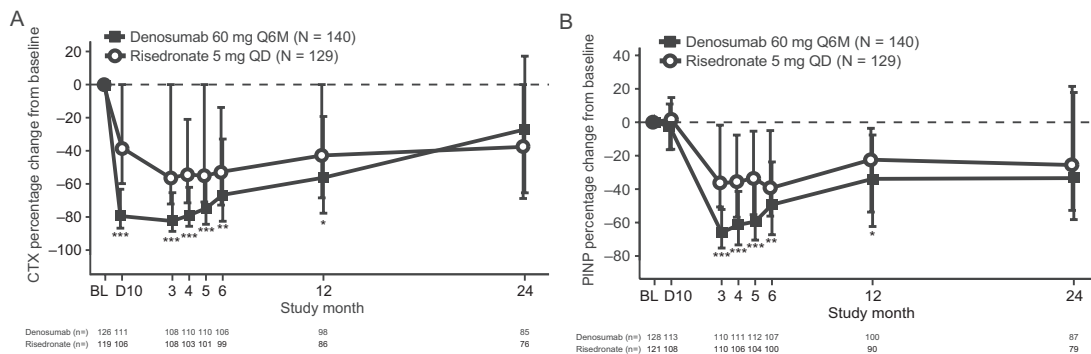
A

CTX percentage change from baseline

Denosumab 60 mg Q6M (N = 140)
Risedronate 5 mg QD (N = 129)

***   *** *** *** ***   *

Study month: BL D10 3 4 5 6 12 24

Denosumab (n=)	126 111	108 110 110 106	98	85
Risedronate (n=)	119 106	108 103 101 99	86	76

B

PINP percentage change from baseline

Denosumab 60 mg Q6M (N = 140)
Risedronate 5 mg QD (N = 129)

***   *** *** **   *

Study month: BL D10 3 4 5 6 12 24

Denosumab (n=)	128 113	110 111 112 107	100	87
Risedronate (n=)	121 108	110 106 104 100	90	79

Figure 3. Percentage change from baseline (BL) in serum concentrations of C-telopeptide of type I collagen (CTX) (**A**), a marker of bone resorption, and of N-propeptide of type I collagen (PINP) (**B**), a marker of bone formation, in the combined subpopulations of the bone turnover marker substudy. Values are the median and interquartile range.* = $P \leq 0.05$; ** = $P \leq 0.025$; *** = $P \leq 0.001$, by Wilcoxon's rank sum test. D10 = day 10; Q6M = once every 6 months; QD = once daily.

Table 2. Incidence of clinically relevant treatment-emergent adverse events through month 24*

	Risedronate (n = 385)	Denosumab (n = 394)
Total adverse events	300 (77.9)	324 (82.2)
Leading to discontinuation of study drug	37 (9.6)	31 (7.9)
Leading to discontinuation from study	15 (3.9)	18 (4.6)
Fatal	9 (2.3)†	13 (3.3)
Most frequently reported		
Back pain	23 (6.0)	25 (6.3)
Arthralgia	34 (8.8)	23 (5.8)
Hypertension	15 (3.9)	21 (5.3)
Viral upper respiratory tract infection	19 (4.9)	20 (5.1)
Upper respiratory tract infection	12 (3.1)	20 (5.1)
Bronchitis	17 (4.4)	19 (4.8)
Urinary tract infection	13 (3.4)	18 (4.6)
Headache	9 (2.3)	16 (4.1)
Nausea	17 (4.4)	15 (3.8)
Cataract	20 (5.2)	10 (2.5)
Osteoarthritis	16 (4.2)	10 (2.5)
Selected adverse events of interest		
Atypical femoral fracture‡	0 (0.0)	1 (0.3)
Osteonecrosis of the jaw‡	0 (0.0)	0 (0.0)
Malignancy	7 (1.8)	12 (3.0)
Any serious infection	25 (6.5)	23 (5.8)
Serious infections reported for >1 patient		
Pneumonia	8 (2.1)	7 (1.8)
Diverticulitis	1 (0.3)	2 (0.5)
Erysipelas	1 (0.3)	2 (0.5)
Bronchitis	2 (0.5)	0 (0.0)
Sepsis	2 (0.5)	0 (0.0)

* Patient count indicates number of patients who received ≥1 dose of investigational product; categories include data based on patients reporting ≥1 event. There were no significant differences between treatment groups. Values are the number (%).
† Two additional deaths (due to pneumonia bacterial and polymyositis) were reported in patients randomized to receive risedronate. These patients were not included in the safety analysis set, because it was not possible to confirm that they had taken ≥1 dose of oral investigational product. The 2 patients died prior to the 6-month visit and oral investigational product accountability verification.
‡ Osteonecrosis of the jaw and atypical femoral fracture were positively adjudicated by independent, blinded, external adjudication committees using published case definitions.

groups: ~700 patients were followed up for >2 years. Moreover, only 1 clinical trial in glucocorticoid-induced osteoporosis demonstrated a significant risk reduction for fractures in the primary analysis, with fewer vertebral fractures in the teriparatide group than in the alendronate group (23). In that study, there was a greater proportion of postmenopausal women compared with other similarly designed studies. Significant fracture risk reduction with bisphosphonates, compared with placebo, was seen in extensions to the original alendronate clinical trials (5,13) or when 2 risedronate trials were combined (9). In the present study, consistent with the results of the primary analysis at month 12, the cumulative

incidence of fracture at month 24 was low in both groups and similar between treatment groups.

It is notable that the relationship between BMD and fracture risk may differ between patients with glucocorticoid-induced osteoporosis and postmenopausal women with osteoporosis, and patients receiving glucocorticoids may have a different BMD threshold for fracture from those not receiving such medications (33). Thus, it is important to examine both BMD and fracture in studies of patients with glucocorticoid-induced osteoporosis. Denosumab treatment in this active-controlled study was associated with greater BMD gains at all skeletal sites measured compared with a treatment (risedronate) that has shown trends

Table 3. Incidence of fractures through month 24*

	Risedronate	Denosumab
Any osteoporosis-related fracture†	36/397 (9.1)	35/398 (8.8)
New and worsening vertebral fracture‡	24/346 (6.9)	15/338 (4.4)
Men	5/101 (5.0)	1/100 (1.0)
Women	19/245 (7.8)	14/238 (5.9)
Premenopause	2/29 (6.9)	2/33 (6.1)
Postmenopause	16/211 (7.6)	12/202 (5.9)
Unknown	1/5 (20.0)	0/3 (0.0)
Nonvertebral fracture (low-trauma)	15/397 (3.8)	21/398 (5.3)

* Values are the number/total (%).
† Includes new and worsening vertebral fracture and low-trauma nonvertebral fracture.
‡ Defined as an increase of ≥1 grade from baseline; evaluated in patients with a baseline assessment and ≥1 postbaseline assessment of vertebral fracture.

toward fracture risk reduction relative to placebo in previous trials in glucocorticoid-induced osteoporosis (9). Furthermore, denosumab has demonstrated antifracture effects in both primary (postmenopausal) and secondary (androgen deprivation therapy or aromatase inhibitor therapy) osteoporosis settings (32,34,35). A meta-analysis of bisphosphonate studies showed that the effects on the incidence of vertebral and, to a lesser degree, nonvertebral fractures in glucocorticoid-induced osteoporosis were comparable to those observed in postmenopausal osteoporosis (16).

The overall incidences of adverse events, serious adverse events, and adverse events leading to discontinuation of study drug were similar between the denosumab and risedronate groups in the combined subpopulations. Consistent with the results of the primary analysis at month 12, rates of infection, including serious infections, were similar between treatment groups through month 24 in this study of patients with an inflammatory disease who were taking glucocorticoids, with or without biologics and other immunomodulatory agents. However, the study was not powered for this exploratory safety end point in a small subset of patients at higher risk of infection. Atypical femoral fracture and osteonecrosis of the jaw have been identified as risks with antiresorptive treatment, including denosumab (24,36). As previously reported in the analysis at month 12 of this study, there was 1 case of positively adjudicated atypical femoral fracture in the denosumab group. No additional cases of atypical femoral fracture, or any cases of osteonecrosis of the jaw, were reported in either group with continued treatment beyond month 12.

Strengths of this study include the large sample size, long-term follow-up with study completion by 74% of patients in each treatment group, and use of an active treatment control group instead of a placebo control group. A potential limitation of the study is that it was neither designed nor powered to evaluate

fracture as an efficacy end point; fracture data were collected as a safety end point. However, it would be difficult to show efficacy for fracture prevention in this setting due to the very large number of patients that would be needed in order to show superiority with respect to a fracture end point, especially compared with patients receiving active treatment. This study compared denosumab with only one drug—risedronate. Thus, how denosumab compares with other bisphosphonates or other bone-specific agents is unknown. We did not stratify randomization by the underlying glucocorticoid-requiring illness because of the difficulty of recruiting for such a study. This could introduce heterogeneity, but this issue should be adequately addressed by randomizations. Another potential limitation was a lack of data on treatment patterns or outcomes after completion of denosumab dosing. It is established that the effects of denosumab are reversible when discontinued without follow-on therapy. In the setting of denosumab discontinuation in postmenopausal osteoporosis, a transient rise in bone turnover above baseline and a decline in BMD toward baseline have been shown (37–39). This is associated with a return of fracture risk to that of an untreated patient and an increased risk of multiple vertebral fracture (40). Similar consideration of the need to either continue denosumab or transition to another antiresorptive agent is warranted in patients with glucocorticoid-induced osteoporosis.

In conclusion, denosumab continued to be superior to risedronate with regard to increases in spine and hip BMD through month 24. The overall safety profile was similar between treatment groups. Denosumab may offer a new option for treatment of at least 24 months for patients with glucocorticoid-induced osteoporosis.

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