10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension

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Summary

Background Long-term safety and efficacy of osteoporosis treatment are important because of the chronic nature of the disease. We aimed to assess the long-term safety and efficacy of denosumab, which is widely used for the treatment of postmenopausal women with osteoporosis.

Methods In the multicentre, randomised, double-blind, placebo-controlled, phase 3 FREEDOM trial, postmenopausal women aged 60–90 years with osteoporosis were enrolled in 214 centres in North America, Europe, Latin America, and Australasia and were randomly assigned (1:1) to receive 60 mg subcutaneous denosumab or placebo every 6 months for 3 years. All participants who completed the FREEDOM trial without discontinuing treatment or missing more than one dose of investigational product were eligible to enrol in the open-label, 7-year extension, in which all participants received denosumab. The data represent up to 10 years of denosumab exposure for women who received 3 years of denosumab in FREEDOM and continued in the extension (long-term group), and up to 7 years for women who received 3 years of placebo and transitioned to denosumab in the extension (crossover group). The primary outcome was safety monitoring, comprising assessments of adverse event incidence and serious adverse event incidence, changes in safety laboratory analytes (ie, serum chemistry and haematology), and participant incidence of denosumab antibody formation. Secondary outcomes included new vertebral, hip, and non-vertebral fractures as well as bone mineral density (BMD) at the lumbar spine, total hip, femoral neck, and one-third radius. Analyses were done according to the randomised FREEDOM treatment assignments. All participants who received at least one dose of investigational product in FREEDOM or the extension were included in the combined safety analyses. All participants who enrolled in the extension with observed data were included in the efficacy analyses. The FREEDOM trial (NCT00089791) and its extension (NCT00523341) are both registered with ClinicalTrials.gov.

Findings Between Aug 3, 2004, and June 1, 2005, 7808 women were enrolled in the FREEDOM study. 5928 (76%) women were eligible for enrolment in the extension, and of these, 4550 (77%) were enrolled (2343 long-term, 2207 crossover) between Aug 7, 2007, and June 20, 2008. 2626 women (1343 long-term; 1283 crossover) completed the extension. The yearly exposure-adjusted participant incidence of adverse events for all individuals receiving denosumab decreased from 165·3 to 95·9 per 100 participant-years over the course of 10 years. Serious adverse event rates were generally stable over time, varying between 11·5 and 14·4 per 100 participant-years. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the crossover group. The yearly incidence of new vertebral fractures (ranging from 0·90% to 1·86%) and non-vertebral fractures (ranging from 0·84% to 2·55%) remained low during the extension, similar to rates observed in the denosumab group during the first three years of the FREEDOM study, and lower than rates projected for a virtual long-term placebo cohort. In the long-term group, BMD increased from FREEDOM baseline by 21·7% at the lumbar spine, 9·2% at total hip, 9·0% at femoral neck, and 2·7% at the one-third radius. In the crossover group, BMD increased from extension baseline by 16·5% at the lumbar spine, 7·4% at total hip, 7·1% at femoral neck, and 2·3% at one-third radius.

Interpretation Denosumab treatment for up to 10 years was associated with low rates of adverse events, low fracture incidence compared with that observed during the original trial, and continued increases in BMD without plateau.

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Introduction

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue leading to bone fragility, which results in increased fracture risk.[1,2] After menopause, oestrogen deficiency increases tissue exposure to RANK ligand, resulting in increased bone resorption and bone loss, which can lead to osteoporosis.[3] Denosumab is a fully human monoclonal antibody that binds with high specificity to human RANK ligand,[4,5] thereby reducing osteoclast number and activity and

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Research in context

Evidence before this study

Osteoporosis is a chronic disease requiring long-term treatment. Therefore, evaluation of the long-term safety and efficacy of medications for osteoporosis is essential. However, limited information is available from long-term clinical trials of such medications. We searched the PubMed database up to Sept 26, 2016, for long-term trials of anti-osteoporotic medications using the terms "postmenopausal", "osteoporosis", "10 years", and "randomised", with a filter for clinical trials and no restrictions on language. Our search identified only three publications reporting the results of randomised clinical trials with long-term extensions totaling 10 years. Two trials used daily oral bisphosphonate (alendronate) and one trial used daily strontium ranelate.

Added value of this study

In a population of osteoporosis patients similar to those previously studied with bisphosphonates, this long-term study showed that RANK-ligand inhibition with denosumab produced progressive increases in bone mineral density and a sustained decrease in fracture risk, with a favourable safety profile, despite ageing of the study population. These findings distinguish denosumab among medications for long-term management of this chronic disease.

Implications of all the evidence

The results of our study support the use of denosumab as primary long-term therapy in patients with postmenopausal osteoporosis similar to our study population. Unlike bisphosphonates, routine interruption of treatment is not recommended.

resulting in decreased bone resorption. During the 3-year FREEDOM trial[6] in postmenopausal women with osteoporosis, denosumab significantly reduced bone turnover markers, increased bone mineral density (BMD), and reduced new vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20% compared with placebo.

Long-term safety and efficacy of treatment are particularly important because of the chronicity of osteoporosis. The 3-year FREEDOM trial[6] was followed by a 7-year extension during which all participants received open-label denosumab. The primary objective of this extension was to evaluate the safety and tolerability of denosumab administration for up to 7 or 10 years. We also report effects on fracture rates and BMD, as well as bone histology and remodelling.

Methods

Study design and participants

See Online for appendix

Designs of the FREEDOM trial and open-label extension have previously been described[6–9] (appendix p 19). FREEDOM was a phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-year trial done at 214 centres worldwide. Postmenopausal women aged 60–90 years old with lumbar spine or total hip BMD T-score of less than –2·5 at either location but greater than –4·0 at both locations were enrolled. Participants were randomly assigned to receive placebo or 60 mg denosumab (Prolia; Amgen, Thousand Oaks, CA, USA) subcutaneously every 6 months for 3 years, and were instructed to take daily calcium (≥1·0 g) and vitamin D (≥400 IU) supplements. All participants from either treatment group who completed the FREEDOM trial (ie, completed their 3-year visit), did not discontinue treatment with investigational product, and did not miss more than one dose of investigational product were eligible to enter the extension. Participants were excluded from the extension if they were permanently non-ambulatory (use of an assistive device was permitted), if they had developed sensitivity to mammalian cell-derived drug products during the FREEDOM study, if they had been unable to tolerate calcium supplementation during the last 6 months of the FREEDOM study, if they were receiving—or had received during the FREEDOM study—any investigational products other than denosumab, or if they were using any of the following osteoporosis agents: bisphosphonates, calcitonin, fluoride, parathyroid hormone, selective oestrogen receptor modulators, systemic oral or transdermal oestrogen (except vaginal preparations and oestrogen creams), strontium, or tibolone. The study protocol was approved by the local or central ethics committee or institutional review board for each centre, and each participant provided written informed consent.

Randomisation and masking

In FREEDOM, eligible participants were randomly assigned (1:1) to placebo or denosumab by means of an interactive voice-response system according to a schedule prepared by the sponsor before initiation of the study. The randomisation schedule was stratified by age at entry (60–64 years, 65–69 years, 70–74 years, and ≥75 years). Denosumab was provided as a sterile, clear, colourless, preservative-free liquid. Placebo was provided in identical containers; the formulation was identical to that of denosumab with the exception of protein content. Participants, investigators, and those evaluating study assessments were masked to group assignment during FREEDOM. During the extension, denosumab was provided open label. All central laboratories remained blinded to the FREEDOM treatment assignments during the extension.

Procedures

During the 7-year extension, all participants received denosumab (60 mg) subcutaneously every 6 months (±1 month) and were instructed to take daily calcium (≥1·0 g) and vitamin D (≥400 IU). Therefore, extension

data represent up to 10 years of denosumab exposure for women who also received 3 years of denosumab in FREEDOM (long-term group), and up to 7 years of denosumab exposure for women who received 3 years of placebo in FREEDOM (crossover group). Study visits were scheduled at baseline (end of the FREEDOM trial), at 10 days after baseline, and every 6 months thereafter for 7 years. Participants were queried about adverse events, clinical fracture information, and concomitant medications by study coordinators at the various sites at 10 days after baseline, and then every 3 months (in person at each clinical visit and by telephone mid-timepoint between clinical visits). In the third year of the extension, two procedural changes were instituted on a programme-wide basis to enhance safety monitoring. Specific inquiries were incorporated to better characterise possible cases of osteonecrosis of the jaw. Also, an adjudication process was initiated to review potential cases of atypical femoral fracture. Each potential case of osteonecrosis of the jaw was reviewed by an independent, external adjudication committee with prespecified criteria.[10] For cases of osteonecrosis of the jaw, temporary denosumab interruption was not mandated but was left to physician discretion. Available x-ray images of femoral fractures that occurred at any time between baseline and year 3 of the extension were retrospectively reviewed by a panel at the central radiographic vendor (BioClinica [formerly Synarc]; Newark, CA, USA). Subsequent fractures were assessed prospectively using the same criteria. The criteria established by the American Society for Bone and Mineral Research (ASBMR) 2010 Task Force for Atypical Subtrochanteric and Diaphyseal Femoral Fractures[11] were used for adjudication by this panel until Oct 30, 2013, after which the updated criteria established by the ASBMR 2013 Task Force for Atypical Subtrochanteric and Diaphyseal Femoral Fractures[12] were applied to any new potential events. A finding of indeterminate was not allowed.

Vertebral fractures were identified by a central facility (BioClinica; formerly Synarc) on the basis of the Genant semiquantitative grading scale[13] using lateral thoracic and lumbar spine radiographs obtained at extension baseline, and extension years 2, 3, 5, and 7. Vertebral fractures present at the extension baseline and new vertebral fractures were defined as described previously.[8] Clinical and non-vertebral fractures required confirmation by diagnostic imaging or a radiologist's report. High-force trauma or pathological clinical vertebral and non-vertebral fractures due to infection or tumour were excluded, as described previously.[6] Consistent with the report[9] of 8-year data from FREEDOM, hip fractures were defined as those at the femoral neck or intertrochanteric region, whereas in previous analyses of FREEDOM, subtrochanteric fractures had been also included.[6–8]

A subset of participants underwent transiliac bone biopsies in FREEDOM (at 2 years or 3 years of placebo or denosumab exposure[14]), the extension (at 5 years,[15] 10 years, or both, of denosumab exposure), or both. Participants underwent a double-labelling procedure with tetracycline or demeclocycline before their biopsy visit (6 months after their previous denosumab dose); samples were prepared and analysed by the Mayo Clinic Laboratory as previously described.[14] Additional post-hoc assessment of the degree and heterogeneity of bone mineralisation was done at the INSERM UMR 1033 (Lyon, France). Bone matrix mineralisation was assessed by digitised quantitative microradiography and analysed using Matlab version R2012b.[16] The mean degree of bone mineralisation and the heterogeneity index of the distribution of degree of bone mineralisation were calculated for cancellous and cortical bone, the endocortical and periosteal cortical sub-compartments, and total bone (cancellous plus cortical).

Measurements of the serum bone turnover markers C-terminal telopeptide of type 1 collagen (CTx; Nordic Bioscience Diagnostics A/S, Herlev, Denmark), procollagen type 1 N-terminal propeptide (P1NP; Orion Diagnostica Oy, Espoo, Finland), and bone-specific alkaline phosphatase (Beckman Coulter, Chaska, MN, USA) were done on samples collected after an overnight fast from a subset of women who had participated in the FREEDOM bone-turnover-marker substudy and continued in the extension, as well as from additional participants as previously described.[7–9] Undetectable bone-turnover-marker values were imputed using the corresponding assay's established lower limit of detection value (CTx 0·049 ng/mL; P1NP 10 µg/L; bone-specific alkaline phosphatase 9·5 µg/L).

BMD measurements were done by dual-energy x-ray absorptiometry of the lumbar spine and proximal femur (all participants) and at the one-third radius (subset) during FREEDOM and at extension baseline and extension years 1, 2, 3, 5, and 7. All scans were centrally read by BioClinica (formerly Synarc).

Outcomes

The primary objective of the extension was safety monitoring, comprising assessments of adverse event incidence and serious adverse event incidence, changes in safety laboratory analytes (ie, serum chemistry, haematology), and participant incidence of denosumab antibody formation. The main secondary endpoints were actual values, changes, and percent changes in BMD of the lumbar spine, total hip, femoral neck, and one-third radius from FREEDOM baseline and extension baseline at all timepoints when BMD was collected; incidence of vertebral fractures at months 24, 36, 60, and 84; incidence of any non-vertebral fractures and hip fractures during the study. Other secondary endpoints were actual values, changes, and percent changes in bone turnover markers (CTx, P1NP, and bone-specific alkaline phosphatase), intact parathyroid hormone, and osteoprotegerin from FREEDOM baseline and extension baseline at prespecified timepoints in a subset of participants (day 10 and months 6, 12, 24, 36, 48, 60, 72, and 84 for CTx and P1NP; day 10 and months 6, 12, and 24 for bone-specific alkaline

phosphatase, intact parathyroid hormone, and osteoprotegerin); actual values, changes, and percent changes from extension baseline at day 10 for albumin-adjusted serum calcium; serum denosumab concentrations at prespecified timepoints (day 10 and months 3, 4, and 6) in a subset of participants; and bone biopsy findings (including bone histology and actual values of histomorphometric parameters) at months 24 and 84 of the extension in a subset. For consistency with previous reports,[7–9] the Medical Dictionary for Regulatory Activities version 13.0 was used to code and report adverse events for this publication. Adverse events continuing at the month 36 visit of the FREEDOM trial were carried over to the extension.

Statistical analysis

The 10-year safety and efficacy analyses reported in this manuscript are analysed according to their original randomised FREEDOM treatment assignments, consistent with previous reports of extension data.[7–9] In the original 3-year FREEDOM trial, seven participants originally assigned to receive placebo inadvertently received one dose each of denosumab and were reported with the denosumab group for the safety analyses.[6] Review of the safety data for these seven participants provides no indication that their inclusion in the denosumab group for the FREEDOM analyses and in the crossover group during the extension affected the conclusions. We did a combined analysis of all participants who received at least one dose of denosumab or placebo in FREEDOM, or denosumab in the extension, according to their actual years of exposure to placebo or denosumab. Descriptive analyses of adverse events and serious adverse events included exposure-adjusted participant incidence. Within each yearly or cumulative interval, we calculated exposure-adjusted participant incidence as the number of participants who experienced at least one occurrence of a particular adverse event divided by the total exposure time within the interval. A participant who experienced repeated episodes of the same adverse event within the yearly or cumulative interval of interest was counted only once for that interval. For example, a participant who experienced a common cold during years 1 and 3 was counted once in year 1 and once in year 3 for those yearly intervals, but only once for the cumulative interval.

Analyses of fractures included cumulative and yearly crude participant incidence of new vertebral fracture rates and Kaplan-Meier estimates of cumulative and yearly participant incidence of non-vertebral fracture and hip fracture rates. We also analysed data for those participants who completed the year-10 visit and missed no more than one dose of investigational product in FREEDOM and no more than one dose of denosumab in the extension. To calculate the Kaplan-Meier estimates for non-vertebral and hip fractures during each yearly interval, we included participants who were still enrolled at the beginning of the interval, reset their time-to-fracture variable from the beginning of the yearly interval, and censored participants who had not had a fracture at the end of the yearly interval (ie, at day 366). The yearly incidence shown in the figures reflects the Kaplan-Meier estimate at day 366.

Because we did not have a placebo group in the extension, we used a simulation method developed for such an extension study design[17] to estimate expected fracture rates had the denosumab participants who enrolled in the extension received placebo throughout (hypothetical cohort of placebo controls or so-called virtual twins), as described previously.[8] Briefly, the virtual twins were Monte Carlo simulations of placebo participants matched on baseline characteristics to the actual long-term treatment group participants, and based on the actual placebo group data from FREEDOM. We did protocol-specified exploratory analyses to compare the fracture rates estimated for the virtual twins with those observed in the long-term treatment group. We calculated estimates of the relative risks (RRs) and their respective bootstrap 95% CIs.

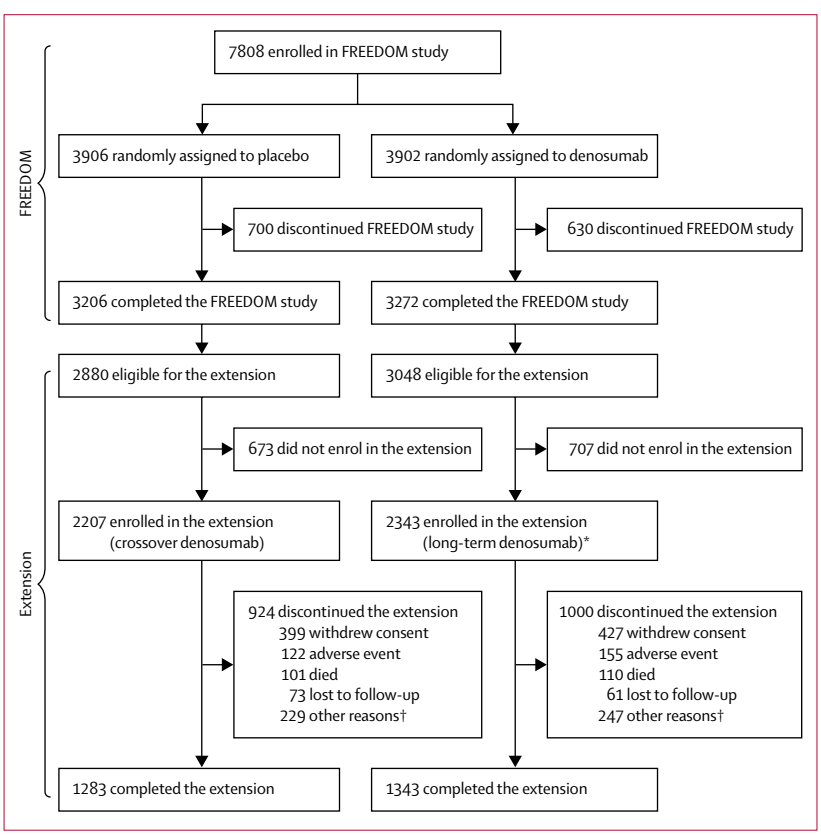

Figure 1: **Trial profile**

*Two women who discontinued denosumab also entered the extension in the long-term group. †Other reasons were declining to participate in the last 5 years of the extension (129 crossover, 139 long-term), non-compliance (20 crossover, 13 long-term), administrative decision (14 crossover, 13 long-term), requirement for alternative therapy (4 crossover, 14 long-term), protocol deviation (6 crossover, 5 long-term), ineligibility determined (3 crossover, 4 long-term), disease progression (1 crossover), and various reasons such as transportation issues, family considerations, relocation, and closure of site during the extension, totalling 52 crossover and 59 long-term participants.

We used standard nomenclature and calculations for bone histology, histomorphometry, degree of bone mineralisation, and heterogeneity index.[16,18] We calculated mean degree of bone mineralisation and the heterogeneity index of the distribution of degree of bone mineralisation for cancellous and cortical bone, the endocortical and periosteal cortical sub-compartments, and total bone (cancellous plus cortical). We summarised continuous and categorical variables using descriptive statistics. We used the 2-sided Wilcoxon rank-sum test to assess the difference between selected treatment groups (2 or 3 years of placebo treatment; 2 or 3, 5, and 10 years of denosumab treatment) in mean degree of bone mineralisation and heterogeneity index, without adjustment for multiple comparisons.

Analyses of bone turnover markers included substudy participants who received at least one dose of denosumab in the extension and had observed values at the timepoints of interest; we present results as medians (IQRs).

Analyses of percentage change in BMD measured by dual-energy x-ray absorptiometry from either FREEDOM or extension baseline required observed values at the respective baseline and the timepoints of interest, and

	Long-term denosumab (n=2343)		Crossover denosumab (n=2207)	
	FREEDOM baseline	Extension baseline	FREEDOM baseline	Extension baseline
Age (years)	71·9 (5·0)	74·9 (5·0)	71·8 (5·1)	74·8 (5·1)
Age groups, n (%)				
≥65 years	2209 (94%)	2294 (98%)	2067 (94%)	2149 (97%)
≥75 years	662 (28%)	1258 (54%)	624 (28%)	1151 (52%)
Years since menopause	23·7 (7·3)	26·7 (7·3)	23·7 (7·4)	26·7 (7·4)
Prevalent vertebral fractures, n (%)	559 (24%)	573 (24%)	485 (22%)	551 (25%)
Lumbar spine BMD T-score	−2·83 (0·67)	−2·14 (0·80)	−2·84 (0·68)	−2·81 (0·75)
Total hip BMD T-score	−1·85 (0·79)	−1·50 (0·79)	−1·85 (0·79)	−1·93 (0·80)
CTx (ng/mL), median (IQR)*	0·505 (0·357–0·700)	0·182 (0·086–0·555)	0·555 (0·420–0·661)	0·568 (0·426–0·728)
P1NP (µg/L), median (IQR)*	46·17 (31·45–56·79)	17·25 (10·31–25·98)	55·81 (42·52–65·60)	48·80 (35·04–67·58)

Data are mean (SD) unless otherwise noted. BMD=bone mineral density. CTx=C-terminal telopeptide of type 1 collagen. P1NP=procollagen type 1 N-terminal propeptide. *Data are from women who enrolled in the bone turnover marker substudy at FREEDOM baseline (35 crossover and 60 long-term) and FREEDOM extension baseline (38 crossover and 76 long-term).

Table 1: **Baseline characteristics of FREEDOM extension participants**

	Placebo			Combined denosumab groups									
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Number of participants	3883	3687	3454	6085	5787	5452	4099	3890	3582	3261	1743	1585	1451
All adverse events	189·5	156·3	132·8	165·3	137·8	124·6	129·9	110·9	110·0	108·4	107·6	109·5	95·9
Infections	38·6	33·9	31·7	35·1	30·3	29·5	29·1	26·0	27·2	26·5	27·0	27·0	23·0
Malignancies	1·8	1·6	1·5	1·9	1·5	2·2	2·3	2·4	2·2	2·7	1·7	2·6	1·6
Eczema	0·8	0·5	0·6	1·4	1·1	1·0	1·1	1·2	0·9	0·7	0·8	0·9	1·3
Hypocalcaemia	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	0	<0·1	<0·1	0	0·1
Pancreatitis	<0·1	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	<0·1	0·1	<0·1	0
Serious adverse events	11·7	11·9	10·8	12·0	11·5	12·3	11·5	12·9	12·6	14·4	11·5	13·1	12·3
Infections	1·1	1·4	1·4	1·5	1·6	1·4	1·4	1·3	1·9	2·3	1·2	1·5	2·6
Cellulitis or erysipelas	0	0	<0·1	<0·1	<0·1	0·2	<0·1	<0·1	0·1	<0·1	0·2	<0·1	0·1
Fatal adverse events	0·8	0·8	1·0	0·7	0·6	0·7	0·5	0·8	0·9	1·5	0·7	1·0	0·9
Osteonecrosis of the jaw	0	0	0	0	<0·1	0	<0·1	0	0·2	<0·1	0	<0·1	<0·1
Atypical femoral fracture	0	0	0	0	0	<0·1	0	0	0	<0·1	0	0	0

Analyses were based on the original randomised treatment groups in FREEDOM. Data include all participants who received at least one dose of investigational product in FREEDOM or the extension. Placebo data are for all participants who received at least one dose of placebo during FREEDOM. Denosumab data are for all participants who received at least one dose of denosumab during FREEDOM or the extension. Data are shown for each year of exposure; thus a long-term participant could have up to 10 years of exposure and a crossover participant could have up to 7 years of exposure to denosumab. All adverse and serious adverse events were coded using Medical Dictionary for Regulatory Activities version 13.0.

Table 2: **Yearly exposure-adjusted participant incidence of adverse events per 100 participant-years of follow-up for placebo and for the combined FREEDOM, long-term, and crossover denosumab participants, up to 10 years**

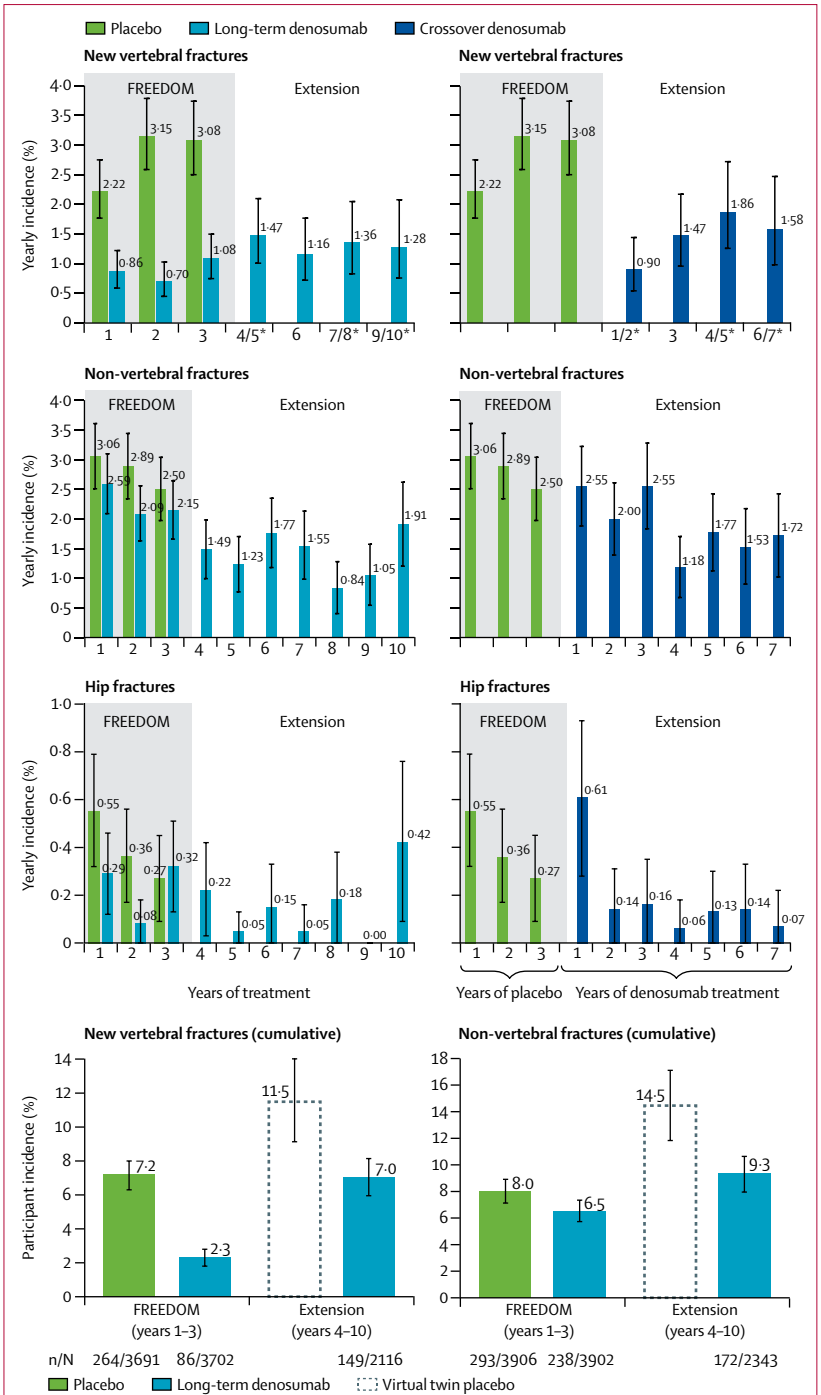

Figure 2: **Yearly incidence of new vertebral, non-vertebral, and hip fractures and cumulative incidence of new vertebral and non-vertebral fractures during FREEDOM and the FREEDOM extension**
For new vertebral fractures, percentages are crude incidence (95% CI); lateral radiographs (lumbar and thoracic) were not obtained at extension years 1, 4, and 6 (long-term denosumab treatment years 4, 7, and 9). For non-vertebral and hip fractures, percentages are Kaplan-Meier estimates (95% CI). For incidence of cumulative new vertebral fractures and non-vertebral fractures, solid bars represent actual data collected and dashed bars represent virtual placebo data. Percentages for new vertebral fractures are crude incidence (95% CI) and percentages for non-vertebral fractures are Kaplan-Meier estimates (95% CI). *Annualised incidence (2-year incidence/2).

were done using a linear mixed effects model for repeated measures, as described previously.[8] We generated diagnostic plots to examine model assumptions. Residuals were normally distributed, and the variance of the residuals appears constant over the range of the predicted values without apparent outliers. We calculated estimates of least-squares means with 95% CIs and assessed differences between consecutive BMD percent changes. We reported nominal p values to describe differences from baseline at each visit or between visits without adjusting for multiplicity. We also analysed data for those participants who completed the year-10 visit and missed no more than one dose of investigational product in FREEDOM and no more than one dose of denosumab in the extension. The FREEDOM trial (NCT00089791) and its extension (NCT00523341) are both registered with ClinicalTrials.gov.

Role of the funding source

This study was funded by Amgen. Representatives of Amgen designed the study in collaboration with study investigators and performed the analyses according to a prespecified statistical analysis plan. HGB had full access to the data and developed the initial draft of the manuscript in collaboration with a coauthor from Amgen (MNB). All authors contributed to the interpretation of the results, wrote or revised the manuscript, and approved the decision to submit the manuscript for publication.

Results

Between Aug 3, 2004, and June 1, 2005, 7808 women were enrolled in the FREEDOM study with a mean age of 72·3 years (SD 5·2). 5928 (76%) women were eligible for enrolment in the extension; of these, 4550 (77%) were enrolled (2343 long-term, 2207 crossover; figure 1) between Aug 7, 2007, and June 20, 2008, at 178 centres. 2626 women (1343 long-term; 1283 crossover) completed the extension. The proportion of women who discontinued the study and the reasons for discontinuation were similar between the long-term and crossover groups. The demographics of the two groups seemed balanced at the start of the extension (table 1). The mean age at the end of the extension for women who completed the year-10 visit was 80·8 years (SD 4·6). FREEDOM baseline characteristics for participants who completed the year-10 visit are shown in the appendix (p 1).

The yearly exposure-adjusted incidence for all adverse events was stable throughout the study for the long-term and crossover groups separately (appendix pp 2, 4) and combined (table 2). The yearly incidence for adverse events of interest including hypocalcaemia, pancreatitis, serious cellulitis or erysipelas, osteonecrosis of the jaw, and atypical femoral fracture remained similar throughout the extension. For adverse events and serious adverse events less frequent than 0·1 per 100 participant-years, yearly incidence is expressed per 10 000 participant-years (appendix pp 3, 5, 6).

During the extension, five subtrochanteric or diaphyseal femoral fractures occurred in the long-term group and four occurred in the crossover group. Of these fractures, two were adjudicated as atypical (0·8 per 10 000 participant-years): one in the long-term group during year 4 of the extension (year 7 of denosumab treatment) and one in the crossover group during year 3 of the extension (year 3 of denosumab treatment), as previously reported.[7,9] No atypical femoral fractures were reported during years 5–7 of the extension in either group.

During the extension, we observed a total of 13 positively adjudicated cases of osteonecrosis of the jaw: seven in the long-term group and six in the crossover group (5·2 per 10 000 participant-years). Eight of these cases have previously been reported.[7–9] Of the 13 cases, one affected participant discontinued the study (long-term group) and one withdrew consent (crossover group) and their outcomes are not reported. All of the other cases have resolved. Of these, four achieved complete resolution while on denosumab treatment (three while on uninterrupted treatment and one after intentional omission of one scheduled dose, with resolution occurring within 3 months after resuming treatment).

Consistent with the results of the original FREEDOM trial,[6] neutralising antibodies to denosumab did not develop in any participants. Regarding changes in safety laboratory analytes, shifts in laboratory values from grade 0 or 1 at extension baseline to grade 3 or 4 post baseline were generally rare (appendix pp 7–8). Reductions in albumin-corrected serum calcium concentration at day 10 were small and not clinically significant in either group (appendix p 9). Mean and median serum denosumab concentrations were similar at all timepoints assessed between the long-term and crossover groups. As expected, serum denosumab concentrations at month 6 were near the lower limit of quantification (0·8 ng/mL) for both groups, and were also similar (appendix p 10).

In the long-term group, the annualised participant incidence of new vertebral fractures, non-vertebral fractures, and hip fractures during the extension remained similar to the incidence observed during the FREEDOM trial (figure 2). The cumulative incidence of new vertebral fractures and of non-vertebral fractures in the extension was lower than the estimated incidence for the virtual twins placebo group (figure 2). Based on the virtual twins model, the estimated relative risk for new vertebral fractures was 0·62 (95% CI 0·47–0·80) and the relative risk for non-vertebral fractures was 0·54 (95% CI 0·43–0·68).

In the extension, the most common non-vertebral fracture sites in the long-term group were wrist (72 women), rib (23), hip (femoral neck or intertrochanteric; 22), ankle (17), and humerus (12).

In the crossover group, the annualised participant incidence of new vertebral fractures, non-vertebral fractures, and hip fractures was similar to that observed during the first 7 years of denosumab treatment in the long-term group (figure 2). In the extension, the most common non-vertebral fracture sites in the crossover group were wrist (93 women), hip (femoral neck or intertrochanteric; 26), ankle (24), humerus (23), and rib (20). For both groups, we obtained similar annualised results for participants who completed the year-10 visit and missed no more than one dose of investigational product in FREEDOM and no more than one dose of denosumab in the extension (appendix p 20).

22 biopsy samples were evaluable for qualitative histology in participants with 10 years of denosumab exposure; all samples showed normally mineralised lamellar bone and no pathological findings (eg, osteomalacia, woven bone, or marrow fibrosis).[19] 21 biopsy samples were evaluable for histomorphometry; these samples showed that the antiresorptive effects of denosumab were maintained over time. Remodelling activation frequency with 10 years of denosumab treatment (median 0·001 per year [IQR 0·001–0·012]) was low and did not differ from that after 5 years (0·031 per year [0·001–0·071]) and 2 or 3 years (0·002 per year [0·001–0·004]) of denosumab treatment.[19]

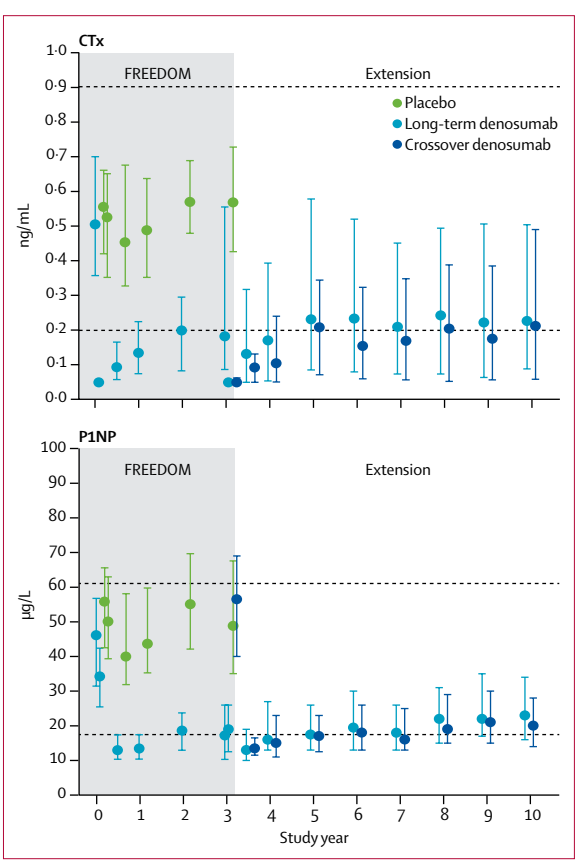

Figure 3: **Serum bone turnover markers during FREEDOM and the FREEDOM extension**

Serum concentrations of predose C-telopeptide of type I collagen (CTx) and procollagen type 1 N-terminal propeptide (P1NP) are shown. Dashed lines represent the premenopausal reference ranges: 0·20–0·90 ng/mL for CTx and 17·4–61·6 µg/L for P1NP. Data are median (IQR).

After 5 years of denosumab treatment, the degree of bone mineralisation for total bone (median 1·132 g/cm³ [IQR 1·110–1·150]) was greater than that after 2 or 3 years of denosumab treatment in FREEDOM (1·081 g/cm³ [1·059–1·107]; p<0·0001).[20] Conversely, the heterogeneity index after 5 years (0·116 g/cm³ [0·110–0·122]) was lower than that after 2 or 3 years of denosumab treatment (0·128 g/cm³ [0·116–0·134]; p=0·0056).[20] Notably, the mean degree of mineralisation at 10 years (1·135 g/cm³ [1·122–1·152]) was not different from that at 5 years and the heterogeneity index at 10 years (0·114 g/cm³ [0·106–0·124]) was also not different from that at 5 years.[20] We observed similar results in all bone compartments assessed (data not shown). Detailed analyses of the complete histomorphometric and mineralisation data will be published separately.

Median serum concentrations of CTx and P1NP were reduced throughout the 7 years of the extension, totalling up to 10 years of therapy in the long-term group (figure 3). In the crossover group, median concentrations of serum CTx and P1NP reduced rapidly after the initial administration of denosumab, a finding similar to the effect of treatment observed in those who received denosumab during FREEDOM. Reductions in the crossover group were sustained throughout 7 years of treatment and were consistent with the results for the long-term group during the first 7 years of denosumab exposure (figure 3). We observed similar results for bone-specific alkaline phosphatase up to and including the last measurement at month 24 (appendix p 21). Serum concentrations of intact parathyroid hormone and osteoprotegerin remained similar between the long-term and crossover groups up to and including the last measurements at month 24 of the extension (appendix p 21).

Mean percentage changes in BMD from FREEDOM baseline (long-term group) and extension baseline (crossover group) to extension year 7 were significant (all p<0·05; appendix pp 11–18]; figure 4). The values observed in the crossover group at extension year 7 largely replicated those observed in the long-term group after 7 years of treatment with denosumab. For both

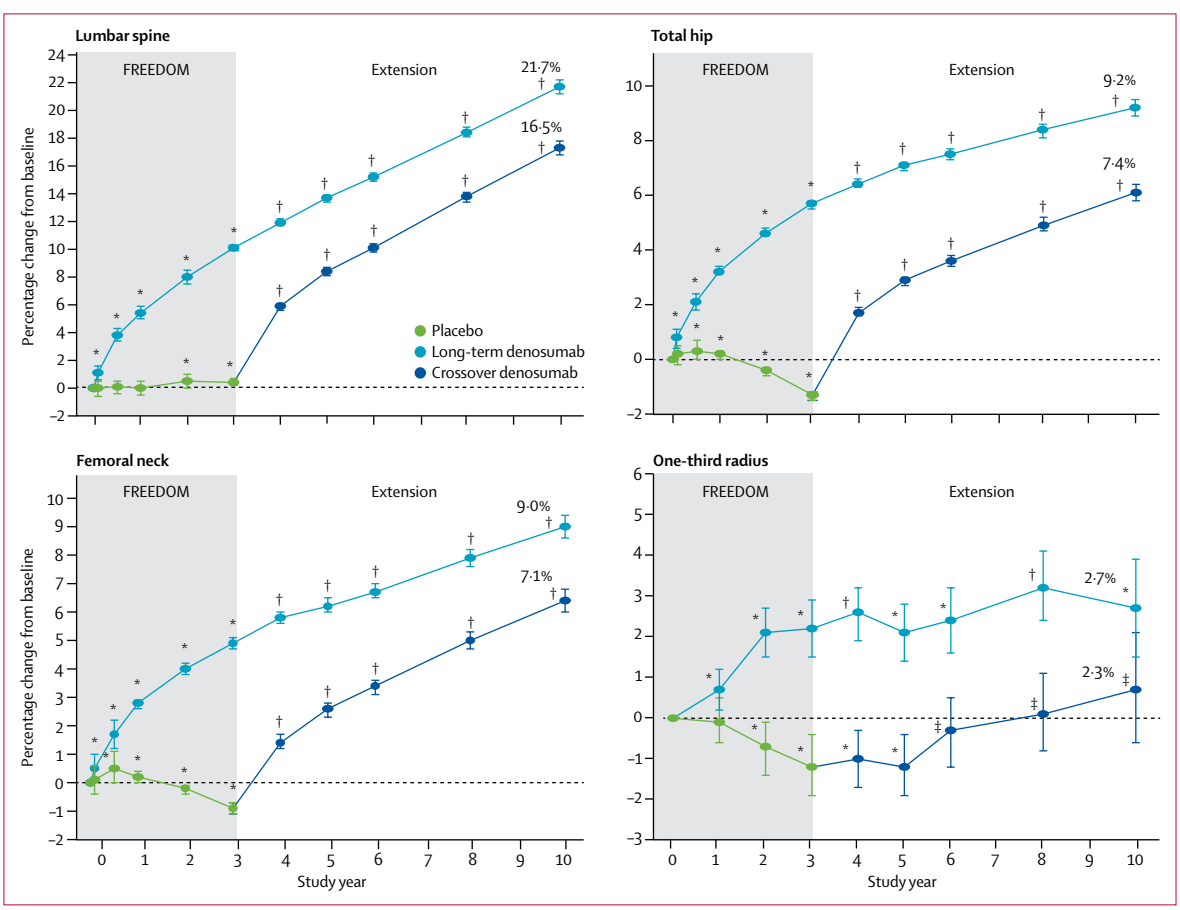

Figure 4: **BMD during FREEDOM and the FREEDOM extension**
Percentage changes from FREEDOM baseline in BMD are shown for the lumbar spine, total hip, femoral neck, and one-third radius. Final number listed at year 10 represents BMD percentage change while on denosumab treatment (from FREEDOM baseline for the long-term group and from extension baseline for the crossover group). Data are least-squares means (95% CI). BMD=bone mineral density. *p<0·05 compared with FREEDOM baseline. †p<0·05 compared with FREEDOM and extension baselines. ‡p<0·05 compared with extension baseline.

groups, mean percentage changes from baseline in BMD at the lumbar spine, total hip, and femoral neck were greater at each timepoint than those observed at the previous timepoint. Results were also consistent for long-term and crossover participants who completed the year-10 visit and missed no more than one dose of investigational product in FREEDOM and no more than one dose of denosumab in the extension (appendix p 22).

Discussion

The FREEDOM extension trial was designed to characterise the safety and efficacy of up to 10 years of exposure to denosumab. Relatively few other long-term clinical trials have investigated drugs for osteoporosis, three of which have reported extensions for up to 10 years of treatment with daily oral bisphosphonate (alendronate)[21,22] and daily strontium ranelate.[23] In the FREEDOM extension trial, postmenopausal women with osteoporosis who were treated with denosumab for up to 10 years had an overall safety profile that remained consistent over time, with low fracture incidence (similar to rates observed during the FREEDOM trial and lower than that of a virtual long-term placebo cohort), sustained reduction of bone turnover, and continued gains in BMD. These findings suggest a continued favourable balance between benefit and risk through 10 years of treatment with denosumab. These data address important considerations in interpretation of the safety and efficacy of a new and different therapeutic class of treatment for long-term use against osteoporosis in an ageing population.

The primary purpose of this study was to evaluate the long-term safety of denosumab. The year-by-year results show that the safety profile of denosumab remained consistent and favourable over 10 years of treatment. In this ageing population, the participant incidence of adverse events—such as serious infection, cellulitis, eczema, and malignancy—remained low. We observed two cases meeting the predefined criteria for atypical femoral fracture, but the cumulative exposure-adjusted participant incidence—including both the long-term and crossover groups—remained very low (0·8 per 10 000 participant-years). Thus, many of the questions that were initially raised about long-term safety with denosumab's unique mechanism of action have largely been addressed.

Cases of osteonecrosis of the jaw occurred throughout the extension; the exposure-adjusted participant incidence in both groups combined was 5·2 per 10 000 participant-years. Although a relation exists between denosumab treatment and osteonecrosis of the jaw, the pathophysiological mechanism of osteonecrosis of the jaw remains unclear. The number of cases we observed per year in this study was small; however, the sponsor has revised the prescribing information to state that the risk of osteonecrosis of the jaw might increase with the duration of exposure. An international task force commented that "Other risk factors for [osteonecrosis of the jaw] include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, as well as other drugs, including antiangiogenic agents".[24] At the time of this report, only two cases have not been reported to be resolved; one participant discontinued the study and one participant withdrew consent, so the outcomes of those cases remain unknown. All other cases are known to have resolved; of these, four achieved complete resolution during continued treatment with denosumab.

Phase 3 trials of drugs for the treatment of osteoporosis generally have placebo control arms, but placebo assignment cannot be continued long term in consideration of the wellbeing of the participants. The first attempt to address this problem used projections based on the fracture rate of the placebo group, adjusted for age, as a referent.[21] Subsequently, a more sophisticated model was validated[17] and has been used to estimate expected fracture rates in a hypothetical cohort of placebo controls (virtual twin) in the FREEDOM extension, both in previous reports[7,8] and in this report. We note that even studies in which a very long-term placebo group is feasible might have limitations due to the development of group characteristics that no longer closely match those of the active treatment arm. For example, if the dropout pattern in the placebo group differed from that in the group continuing with treatment, then an ongoing placebo group might actually create a distortion. Comparison of a Monte Carlo-simulated control participant with similar characteristics to each actual active treatment participant provides a way to match the relevant characteristics of the two groups.

Limitations of our study include absence of a placebo treatment assignment over the long-term and participants who discontinued treatment or were lost to follow-up. These limitations were addressed through several separate analyses that reflect the robustness of fracture outcomes, including development of the virtual twin comparison and an evaluation that showed that depletion of susceptible participants[25] cannot explain the observed fracture incidence in the FREEDOM extension study. A per-protocol analysis showed a further significant decrease in the incidence of non-vertebral fracture in both treatment groups beyond the first 3 years of denosumab treatment.[26] In this report, a completer analysis of all participants who missed no more than one dose of investigational product in FREEDOM and no more than one dose of denosumab in the extension showed similar fracture results compared with the primary analyses, which included participants who were lost to follow-up.

FREEDOM transiliac biopsy results from women with 2 or 3 years of denosumab treatment showed low dynamic parameters of remodelling.[14] In the FREEDOM extension, bone biopsies were done in participants with 5 years of denosumab treatment, and findings were similar to those in participants with 2 or 3 years of denosumab treatment in FREEDOM.[15] As reported here, bone biopsies also were done in participants with 10 years of denosumab treatment.[20] Overall, histology showed normal bone

microarchitecture, and histomorphometry was consistent with denosumab's antiresorptive mechanism of action. The remodelling activation frequency with 10 years of denosumab treatment was low and similar to that with 5 years and 2 or 3 years of denosumab. Similar to previous observations in people treated with bisphosphonates,[22] we found no evidence of further decrease in remodelling with long-term exposure to denosumab. However—unlike with bisphosphonates—the action of denosumab on bone metabolism is reversible and cessation of treatment is associated with transient increases in bone remodelling and rapid decreases of BMD.[27,28] This mechanism needs to be considered in patients who stop denosumab treatment, as recent reports have described cases with multiple vertebral fractures after discontinuation of denosumab.[29–31] An analysis of participants who discontinued study drug during the 3-year FREEDOM trial or 7-year extension[32] showed that discontinuation of denosumab is associated with an increased vertebral fracture rate that is comparable with those who discontinued placebo. Furthermore, among participants who sustained vertebral fractures after discontinuation of denosumab, the frequency of multiple vertebral fractures was somewhat greater than in those who discontinued placebo (3·4% *vs* 2·1%).[32] Individuals with prior vertebral fractures are at increased risk for new vertebral fractures after treatment cessation and should continue osteoporosis therapy.[28,32] Consequently, those who discontinue denosumab should transition to another therapy promptly after the 6-month dosing interval.

Over 10 years, treatment with denosumab was associated with a sustained reduction of bone resorption and formation markers and a low remodelling rate, as shown by bone histomorphometry. This low turnover pattern was associated with a continued and progressive increase in BMD across anatomical sites—a finding that differs from those of other antiresorptive therapies.[22,33] The crossover groups' gain in BMD followed the pattern observed during the first 7 years of the long-term group, but the long-term group achieved greater cumulative density gains over the 10 years, confirming the advantageous effect of timely intervention and ongoing treatment on BMD. Prolonged reduction of bone remodelling did not result in increased fragility. In fact, fracture rates remained consistently low throughout the study, similar to rates observed in the active treatment group during FREEDOM and lower than in a virtual long-term placebo cohort. To understand the contribution of mineralisation to the continued gains in BMD and low fracture incidence observed with 10 years of denosumab treatment, we examined bone matrix mineralisation indices at years 2 and 7 of the FREEDOM extension, representing 5 and 10 years of denosumab treatment, respectively. Our findings suggest that the mean degree of mineralisation reaches a maximum by year 5 of treatment. This result provides reassurance that excessive mineralisation has not been observed and should therefore not be a hazard of prolonged denosumab treatment.

We propose that gains in BMD seen over 5 years of denosumab treatment largely reflect closing of the remodelling space and increases in secondary mineralisation of bone matrix. However, given the absence of further increases in mean degree of mineralisation of bone between years 5 and 10 of denosumab treatment, these factors do not fully explain the sustained gains in BMD through the entire 10 years. Therefore, additional mechanisms might contribute to long-term clinical outcomes, including modelling-based bone formation (as reported in animal studies)[34] and reductions in cortical porosity.[35]

Long-term treatment with denosumab resulted in progressive increases in BMD and a low incidence of fracture in comparison with the placebo group in FREEDOM and a virtual long-term placebo cohort. These findings were obtained with a larger number of study participants than in previous osteoporosis trials of similar duration.[21–23] Our results support the skeletal safety of long-term treatment with denosumab. In this study, denosumab was employed as primary therapy in a population generally similar to those of other major clinical trials for postmenopausal osteoporosis.[36–38] Over 10 years of treatment, we found that denosumab was efficacious, generally well tolerated, and had a favourable benefit–risk profile.

Contributors

HGB had full access to the data and developed the initial and subsequent drafts of the manuscript in collaboration with MNB. All authors contributed to the interpretation of the results, wrote or revised the manuscript, and approved the decision to submit the manuscript for publication. SRC was an investigator for the FREEDOM study; HGB, MLB, JPB, RC, EC, AF-P, DLK, KL, J-YR, CR, and JM were investigators for the FREEDOM and extension studies. RBW and PD had responsibility for sponsor clinical and medical oversight and execution of the study. NP was involved in data analyses. NSD and AW provided statistical analysis of the data. DWD interpreted the bone histology, histomorphometry, and matrix mineralisation findings.

Declaration of interests

HGB reports research support from Amgen, Merck, and Shire; consulting fees from Amgen, Merck, Grünenthal, Alexion, Shire, and Radius; and speakers' honoraria from Amgen and Shire. RBW, MNB, AW, and NP are Amgen employees and report Amgen stock and stock options. MLB reports research support and consulting fees from Abiogen, Alexion, Amgen, Bruno Farmaceutici, Eli Lilly, MSD, NPS, Servier, Shire, and SPA. JPB reports research support from Amgen and Eli Lilly; consulting fees from Amgen, Eli Lilly, and Merck; and is on the speakers' bureau for Amgen and Eli Lilly. RC reports research support from Chugai-Roche, Merck, and Pfizer; consulting fees from Amgen, UCB, Bioiberica, Pfizer, Sandoz, and Janssen; and other support from Eli Lilly, BMS, and Abbvie. SRC and KL report consulting fees from Amgen. EC reports research support and other support from Amgen. AF-P reports research support from Roche; consulting fees from Eli Lilly; and is on the speakers' bureau for Amgen, Eli Lilly, MSD, and Pfizer. DLK reports research support from Amgen, Astellas, AstraZeneca, and Eli Lilly; consulting fees from Amgen, Eli Lilly, Merck, and Pfizer; and is on the speakers' bureau for Amgen, Eli Lilly, and GSK. J-YR reports research support from Amgen, Eli Lilly, Servier, Meda, Cniel, and IBSA-Genevrier; consulting fees from Servier, IBSA-Genevrier, Radius Health, and Meda; and lecture fees from IBSA-Genevrier, Servier, Cniel, Meda, Pierre Fabre, and Dairy Research Council. CR reports research support from Ultragenyx; and consulting fees or honoraria from Alexion, Amgen, Eli Lilly, MSD, and UCB. JM reports research support from Lilly España and Amgen; and lecture fees from Gruenenthal. NSD was an Amgen employee at the time of the

manuscript preparation and reports Amgen stock; she is now a Sanofi employee. PD is a former Amgen employee and reports Amgen stock. DWD reports research support from Amgen and Eli Lilly; consulting fees from Amgen, Eli Lilly, Merck, Radius, and Ultragenyx; and is on the speakers' bureau for Amgen and Eli Lilly. SP reports consulting fees from Amgen, Axsome, Gador, Merck, Mereo Pharma, and UCB; and speaking fees from Amgen, Merck, Teva, and UCB.

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