Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial

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Summary

Background Previous bisphosphonate treatment attenuates the bone-forming effect of teriparatide. We compared the effects of 12 months of romosozumab (AMG 785), a sclerostin monoclonal antibody, versus teriparatide on bone mineral density (BMD) in women with postmenopausal osteoporosis transitioning from bisphosphonate therapy.

Methods This randomised, phase 3, open-label, active-controlled study was done at 46 sites in North America, Latin America, and Europe. We enrolled women (aged ≥55 to ≤90 years) with postmenopausal osteoporosis who had taken an oral bisphosphonate for at least 3 years before screening and alendronate the year before screening; an areal BMD T score of –2·5 or lower at the total hip, femoral neck, or lumbar spine; and a history of fracture. Patients were randomly assigned (1:1) via an interactive voice response system to receive subcutaneous romosozumab (210 mg once monthly) or subcutaneous teriparatide (20 µg once daily). The primary endpoint was percentage change from baseline in areal BMD by dual-energy x-ray absorptiometry at the total hip through month 12 (mean of months 6 and 12), which used a linear mixed effects model for repeated measures and represented the mean treatment effect at months 6 and 12. All randomised patients with a baseline measurement and at least one post-baseline measurement were included in the efficacy analysis. This trial is registered with ClinicalTrials.gov, number NCT01796301.

Findings Between Jan 31, 2013, and April 29, 2014, 436 patients were randomly assigned to romosozumab (n=218) or teriparatide (n=218). 206 patients in the romosozumab group and 209 in the teriparatide group were included in the primary efficacy analysis. Through 12 months, the mean percentage change from baseline in total hip areal BMD was 2·6% (95% CI 2·2 to 3·0) in the romosozumab group and –0·6% (–1·0 to –0·2) in the teriparatide group; difference 3·2% (95% CI 2·7 to 3·8; p<0·0001). The frequency of adverse events was generally balanced between treatment groups. The most frequently reported adverse events were nasopharyngitis (28 [13%] of 218 in the romosozumab group *vs* 22 [10%] of 214 in the teriparatide group), hypercalcaemia (two [<1%] *vs* 22 [10%]), and arthralgia (22 [10%] *vs* 13 [6%]). Serious adverse events were reported in 17 (8%) patients on romosozumab and in 23 (11%) on teriparatide; none were judged treatment related. There were six (3%) patients in the romosozumab group compared with 12 (6%) in the teriparatide group with adverse events leading to investigational product withdrawal.

Interpretation Transition to a bone-forming agent is common practice in patients treated with bisphosphonates, such as those who fracture while on therapy. In such patients, romosozumab led to gains in hip BMD that were not observed with teriparatide. These data could inform clinical decisions for patients at high risk of fracture.

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Introduction

Patients with osteoporosis are usually treated with bisphosphonates as first-line therapy because of medium to high effectiveness, long-term experience, and price considerations. For patients who do not respond sufficiently, such as those who have persistently low bone mineral density (BMD) or those who develop fractures on therapy, switching to a bone-forming agent is common clinical practice.

Bone-forming agents are important in the management of patients with osteoporosis at high risk for fracture because they are associated with large BMD gains that can address both the bone mass and microarchitectural deficits responsible for the increased fracture risk. In practice, the use of bone-forming agents such as teriparatide is often reserved for patients with a very high fracture risk (eg, two or more prevalent fractures) or those who have been previously exposed to

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Research in context

Evidence before this study

We searched PubMed for papers in any language published up to May 30, 2016 with the terms "bone anabolic", "bisphosphonate", "osteoporosis", "romosozumab", and "teriparatide". We restricted the search to papers published in peer-reviewed journals only. We reviewed all publications that reported the results of randomised clinical trials and relevant preclinical studies. Although randomised controlled trials have investigated the effects of sequential bisphosphonate and bone-forming osteoporosis therapy, none have addressed the sequential use of alendronate and a sclerostin monoclonal antibody.

Added value of this study

Bone-forming agents are important for the treatment of patients at high risk of fracture because they can improve deficits in both mass and microstructure that contribute to fracture risk. Teriparatide, a parathyroid hormone analogue, is a bone-forming agent, approved for human use by the US Food and Drug Administration. Teriparatide is often prescribed to patients who have been previously exposed to bisphosphonates. However, the use of parathyroid hormone therapy after bisphosphonate might have limitations; a blunting of the bone-forming effect of teriparatide on bone mineral density (BMD) has been reported in women with previous bisphosphonate use compared with bisphosphonate-naive patients. The reduced effect of teriparatide during sequential administration is most notable at the hip, where losses in areal bone density have been documented in patients transitioning from bisphosphonate to teriparatide, particularly in the year following transition. Thus, it is important to understand the effects of the bone-forming agent romosozumab compared with teriparatide on bone density and estimated strength in patients with osteoporosis who were previously treated with antiresorptive agents, such as bisphosphonates, in routine clinical practice. To our knowledge, STRUCTURE is the first large, randomised, phase 3 trial to directly compare the effects of romosozumab and teriparatide on BMD, bone turnover, and estimated bone strength in postmenopausal women with osteoporosis who were previously treated with oral bisphosphonates. Our findings showed that 12 months of treatment with romosozumab in patients transitioning from oral bisphosphonate therapy resulted in BMD gains and improved estimated hip strength compared with teriparatide, and that romosozumab was well tolerated in this population.

Implications of all the available evidence

These findings are clinically relevant because many patients are considered candidates for bone-forming agents after bisphosphonate therapy. Our findings suggest that romosozumab might be an effective treatment option for patients at increased risk for fracture who are transitioning from oral bisphosphonate therapy.

bisphosphonate therapy; however, data suggest that the clinical benefit of teriparatide might be reduced in patients transitioning from bisphosphonates compared with bisphosphonate-naive patients. Indeed, the use of teriparatide in patients who were previously exposed to antiresorptives, such as oral bisphosphonates, results in a blunting of BMD gains compared with treatment-naive patients, particularly at the hip, with decreases in areal BMD seen in the first year.[1–5] Thus, transitioning patients at high risk for fracture from a bisphosphonate to teriparatide poses a clinical challenge.

Romosozumab (AMG 785) is a bone-forming agent that inhibits sclerostin with a dual effect on bone, increasing bone formation and decreasing bone resorption.[6,7] In a 12-month, phase 2, placebo-controlled study of postmenopausal women with low bone mass treated with romosozumab, alendronate, or teriparatide, romosozumab treatment significantly increased mean areal BMD from baseline (11·3% at the lumbar spine and 4·1% at the total hip) and was well tolerated.[7] In this treatment-naive population, areal BMD gains were larger in patients treated with romosozumab than in those treated with teriparatide. Additionally, findings from a pivotal fracture study in women with postmenopausal osteoporosis showed that the rapid and large gains in BMD associated with romosozumab treatment reduced the risk of new vertebral fractures and clinical fractures at 12 months compared with placebo.[8]

Here, we report the results of a phase 3 study comparing the effects of romosozumab versus teriparatide treatment for 12 months in women with postmenopausal osteoporosis transitioning from bisphosphonate therapy.

Methods

Study design and participants

STRUCTURE is a phase 3b, randomised, open-label, active-controlled, parallel-group trial. The study was done at 46 sites (clinical practices, hospitals, and research centres) in North America, Latin America, and Europe.

Patients were ambulatory, postmenopausal women (aged ≥55 to ≤90 years at randomisation) who had received oral bisphosphonate therapy at a dose approved for postmenopausal osteoporosis for at least 3 years before screening, and alendronate (70 mg weekly or equivalent) the year immediately before screening. Patients had a history of non-vertebral fracture after age 50 years or vertebral fracture; osteoporosis as documented by an areal BMD T score of –2·5 or lower at the total hip, femoral neck, or lumbar spine on dual-energy x-ray absorptiometry (DXA) scans; and at least one hip and at least two vertebrae in the L1–L4 region

evaluable by DXA. Patients were excluded from the study if they had recently used other agents affecting bone metabolism, had a serum 25-hydroxyvitamin D concentration of less than 50 nmol/L, or had a history of metabolic or bone disease, or other disease or condition known to affect bone mass. Full inclusion and exclusion criteria are detailed in the summary protocol, which is available online. An amendment to the protocol is summarised in the appendix (p 2).

This study was done in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. An independent ethics committee or institutional review board at each site approved the protocol, informed consent form, and all protocol amendments. Patients gave written informed consent before any study-specific procedures were done.

Randomisation and masking

Within 35 days after screening, eligible patients were randomly assigned (1:1) in an open-label manner to receive either romosozumab or teriparatide for the 12-month treatment period (appendix p 5). Randomisation was done via a central interactive voice response system according to a computer-generated schedule prepared by the sponsor before the study. Treatment was open label, but investigators assessing efficacy endpoints were masked to treatment assignment.

Procedures

Romosozumab (Amgen, Thousand Oaks, CA, USA) 210 mg was supplied by the sponsor in single-use prefilled syringes and was given subcutaneously as three injections of 70 mg each by a health-care professional at clinic visits on day 1 and monthly for a total of 12 doses. Teriparatide 20 µg was delivered by a pre-assembled commercially available pen device (Forteo, USA; Forsteo, Europe); patients self-administered teriparatide 20 µg subcutaneously daily for 12 months. Patients were asked to return all used and unused pen devices to facilitate assessment of compliance. Throughout the study, all patients were provided with calcium (500–1000 mg/day) and vitamin D (600–800 IU/day) supplementation. Patients in the romosozumab group with a serum 25-hydroxyvitamin D concentration of between 50 nmol/L and 100 nmol/L at screening received 50 000–60 000 IU vitamin D after randomisation, which was optional for patients with higher concentrations at screening and for patients in the teriparatide group.

Areal BMD was measured by DXA (Lunar, Madison, WI, USA, or Hologic, Waltham, MA, USA) at the proximal femur and lumbar spine (L1–L4) at baseline and at months 6 and 12. Integral, cortical, and trabecular volumetric BMD and bone mineral content (BMC) at the total hip were measured by quantitative CT at baseline and at months 6 and 12 with Medical Image Analysis Framework software (MIAF-Femur version 6.2.0; University of Erlangen, Germany). The quantitative CT analysis[9] and details of the segmentation of the hip data and precision results[10] have been described elsewhere. For BMD by DXA and quantitative CT, analysis of the scans and quality control of the scanners and individual scans were done, masked to treatment assignment, by a central facility (Bioclinica, Portland, OR, USA, and Hamburg, Germany).

For the **protocol** see https://www.clinicaltrialsregister.eu/ctr-search/search?query=20080289

See **Online** for appendix

Hip strength for a simulated sideways fall was estimated by finite element analysis, with the VirtuOst software (ON Diagnostics, Berkeley, CA, USA), which is approved by the US Food and Drug Administration for identifying patients at high risk of fracture and for monitoring treatment. By use of previously described methods,[11] hip strength was assessed from the quantitative CT images obtained at baseline and at months 6 and 12, and all image processing and assessments for the finite element analysis were done masked to treatment assignment (ON Diagnostics, Berkeley, CA, USA).

Blood biochemistry and haematology were assessed at baseline, day 1, and months 1, 6, and 12. Bone turnover markers procollagen type 1 N-terminal propeptide (P1NP) and C-telopeptide of type 1 collagen (CTX; Quintiles, Marietta, GA, USA) were assessed in fasting serum samples obtained at baseline, day 14, and months 1, 3, 3+14 days, 6, 6+14 days, 9, and 12. Romosozumab immunogenicity (PPD, Richmond, VA, USA) was assessed in romosozumab-treated patients at day 1 and at months 1, 3, 6, and 12 with a validated electrochemiluminescent immunoassay, and samples that tested positive for binding antibodies were also tested for neutralising antibodies as previously described by McClung and colleagues.[7] In both treatment groups, blood samples were taken before administration of the drug.

Data for adverse events and concomitant medications were obtained throughout the study. Potential cases of osteonecrosis of the jaw and atypical femoral fracture were externally adjudicated by independent committees.

Outcomes

The primary endpoint was the percentage change from baseline in areal BMD by DXA at the total hip through month 12 (mean of months 6 and 12). Secondary endpoints were percentage change from baseline in areal BMD by DXA at the total hip, femoral neck, and lumbar spine at months 6 and 12; percentage change from baseline in hip strength estimated by finite element analysis at months 6 and 12; and percentage change from baseline in cortical and integral volumetric BMD and integral volumetric BMC by quantitative CT at the hip at months 6 and 12. The percentage change from baseline in bone turnover markers (P1NP and CTX) was an exploratory endpoint. Other quantitative CT measurements (eg, trabecular volumetric BMD, cortical

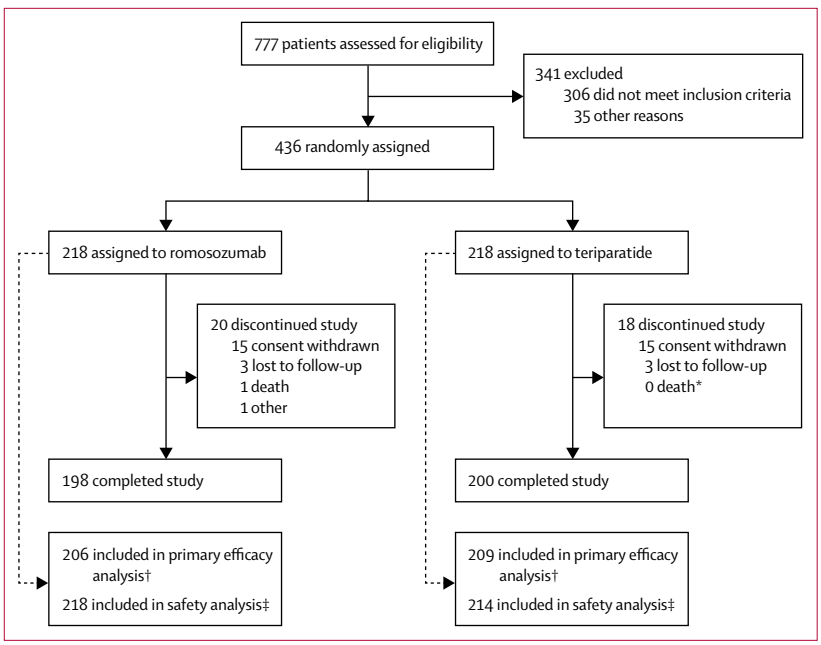

Figure 1: **Trial profile**
*One death occurred 3 days after the end of the study. †Primary efficacy analysis population included all randomly assigned patients with a non-missing baseline measurement and at least one post-baseline measurement for the endpoint of interest. ‡Safety analysis population included all randomised patients who received at least one dose of investigational product. Four patients in the teriparatide group never received teriparatide per the patients' request, so they were excluded from the safety analysis set.

and trabecular volumetric BMC) were also assessed. Safety was assessed on the basis of the frequency of adverse events, changes from baseline in laboratory measurements and vital signs, and the presence of anti-romosozumab antibodies.

Statistical analysis

A key consideration in power calculations for the study was the expected total hip areal BMD changes at month 12 with romosozumab and teriparatide. We assumed that the mean percentage changes in total hip areal BMD by DXA from baseline to month 12 would be 0·8% (SD 1·5) in the romosozumab group (estimating a lower increase than that seen in treatment-naive patients[7]) and –1·2 % (4·5) in the teriparatide group, on the basis of findings from previous studies.[1–3,12] A sample size of 200 patients per group was determined, on the basis of a two-sided two-sample *t* test with a 5% significance level, to provide 99% power to detect a difference between treatment groups with respect to the primary endpoint and about 90% power for the comparison of romosozumab with teriparatide with respect to the percentage change from baseline in total hip, femoral neck, and lumbar spine areal BMD by DXA, total hip volumetric BMD by quantitative CT, and cortical volumetric BMD by quantitative CT at months 6 and 12, assuming an annual 5% dropout rate.

A planned two-step, step-down, fixed-sequential testing procedure was used for the primary and key secondary efficacy endpoints for the comparison of romosozumab with teriparatide for multiplicity adjustment to maintain the overall significance level at 0·05, as described in the appendix (p 2).

All patients with a baseline measurement and at least one post-baseline measurement were included in the analyses of primary and secondary efficacy endpoints. The analysis of the primary endpoint, the treatment difference in the percentage change from baseline in DXA BMD at the total hip up to month 12, used a linear mixed effects model for repeated measures and represented the average treatment effect at months 6 and 12. The model included main effects for treatment group, visit (categorical), baseline serum CTX, baseline hip DXA areal BMD value, DXA machine type (categorical), and machine type by baseline value interaction (to adjust for the effect of machine type on baseline DXA areal BMD value) as fixed effects with an unstructured within-subject variance-covariance structure. Analyses were not adjusted for geographical region because BMD response would not be expected to vary by region; we assessed the primary endpoint by region with a repeated measures model to confirm this assumption. The denominator degrees of freedom were determined by the Kenward-Roger approach. Least-squares mean of the treatment difference (romosozumab–teriparatide) and the corresponding two-sided 95% CI are reported. The assumptions of the mixed effects model were assessed and there was no evidence that the assumptions were violated.

The percentage change from baseline in the secondary DXA areal BMD endpoints (including total hip, lumbar spine, and femoral neck) at each timepoint of interest used the same linear mixed effects model for repeated measures as did the analysis of the primary endpoint, apart from the addition of the treatment-by-visit interaction. The analysis of the percentage change from baseline in secondary quantitative CT endpoints used the same model as the secondary DXA areal BMD endpoints model, apart from the replacement of the baseline DXA areal BMD by the baseline quantitative CT parameter value and the removal of the DXA machine type variable. For bone turnover markers, the significance of the treatment difference for the percentage change from baseline at each timepoint of interest was assessed with a Wilcoxon rank-sum test. Statistical analyses were done with SAS version 9.2.

Safety endpoints are summarised descriptively for all patients who received at least one dose of investigational product. Patients in this subset were analysed according to the actual treatment received. This study is registered with ClinicalTrials.gov, number NCT01796301.

Role of the funding source

Amgen and UCB Pharma representatives designed the study in collaboration with external investigators, and Amgen was responsible for study monitoring and

oversight. Amgen statisticians did the statistical analyses according to a prespecified statistical analysis plan. The first author (BLL) wrote the initial manuscript draft with assistance from professional medical writers who were funded by Amgen and UCB Pharma. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 31, 2013, and April 29, 2014, 436 patients were randomly assigned to receive romosozumab (n=218) or teriparatide (n=218). Of these patients, 198 (91%) in the romosozumab group and 200 (92%) in the teriparatide group completed the study. Reasons for discontinuation were similar in the two groups (figure 1).

Baseline demographics and disease characteristics were similar in the treatment groups (table 1). Women were enrolled from western Europe (209 [48%]), central and eastern Europe (116 [27%]), Latin America (79 [18%]), and North America (32 [7%]). All patients received oral bisphosphonate therapy in the 3 years immediately before screening and all except two in the teriparatide group received alendronate in the year before screening (protocol deviation). Most patients had received alendronate in the 3 years before the study, with a mean duration of previous alendronate use of 5·6 years (SD 3·15; table 1). Baseline serum concentrations of P1NP and CTX were low, indicating the use of antiresorptive therapy, and were similar in the two groups.

	Romosozumab (n=218)	Teriparatide (n=218)
Age (years)	71·8 (7·4)	71·2 (7·7)
Race		
White	191 (88%)	196 (90%)
Other	23 (11%)	18 (8%)
American Indian or Alaska native	4 (2%)	1 (<1%)
Asian	0	2 (1%)
Multiple	0	1 (<1%)
Oral bisphosphonate use in the 3 years before screening	218 (100%)	218 (100%)
Alendronate in the year before screening	218 (100%)	216 (99%)
Duration of previous bisphosphonate use (years)	6·2 (2·9)	6·2 (2·9)
Duration of previous alendronate use (years)	5·5 (3·2)	5·8 (3·1)
Alendronate use in the 3 years before the study	192 (88%)	202 (93%)
BMD T score		
Total hip	−2·27 (0·75)	−2·21 (0·72)
Femoral neck	−2·49 (0·67)	−2·43 (0·66)
Lumbar spine	−2·83 (1·10)	−2·87 (1·04)
Serum CTX (pmol/L)*	982 (654–1348)	1012 (732–1378)
Serum P1NP (µmol/L)†	0·33 (0·24–0·45)	0·33 (0·27–0·44)
Previous fracture	218 (100%)	217 (<100%)
Total hip cortical volumetric BMD by QCT (mg/cm^3)	472·8 (64·3)	475·8 (57·5)
Total hip integral volumetric BMD by QCT (mg/cm^3)	194·9 (38·9)	194·5 (34·4)
Hip strength under fall loading conditions (N)	2892 (494)	2923 (506)

Data are mean (SD), n (%), or median (IQR). BMD=bone mineral density. CTX=C-telopeptide of type 1 collagen. P1NP=procollagen type 1 N-terminal propeptide. QCT=quantitative CT. *Premenopausal reference range for serum CTX 861–3875 pmol/L. †Premenopausal reference range for serum P1NP 0·23–0·82 µmol/L.

Table 1: **Baseline characteristics**

206 patients in the romosozumab group and 209 in the teriparatide group were included in the primary efficacy analysis. The mean percentage change from baseline in areal BMD by DXA at the total hip up to month 12 (ie, the mean of month 6 and month 12) was 2·6% (95% CI 2·2 to 3·0) in the romosozumab group and –0·6% (–1·0 to –0·2) in the teriparatide group; mean difference between groups was 3·2% (95% CI 2·7 to 3·8; p<0·0001). Similar results were obtained in the per-protocol analysis: 2·5% (95% CI 2·1 to 2·9) in the romosozumab group and –0·8% (–1·2 to –0·3) in the teriparatide group; mean difference between groups 3·3% (95% CI 2·7 to 3·9; p<0·0001). The mean differences between treatment groups were similar across geographical regions (data not shown).

For the secondary efficacy endpoints, the mean percentage changes from baseline in DXA areal BMD at the total hip, femoral neck, and lumbar spine were significantly greater in the romosozumab group than in the teriparatide group at month 6 and at month 12 (figure 2; appendix p 3). Significantly greater gains in integral and cortical volumetric BMD and volumetric BMC at the hip were also noted in the romosozumab group than in the teriparatide group at months 6 and 12 (figure 3; appendix p 3), whereas trabecular volumetric BMD increased significantly from baseline in both treatment groups (figure 3; appendix p 3). On an absolute scale, integral volumetric BMC was unchanged with teriparatide; romosozumab treatment resulted in significant gains compared with teriparatide, with increases in volumetric BMC roughly twice as high in cortical (+290 mg) versus trabecular (+148 mg) compartments (appendix p 4).

Greater gains in the percentage change from baseline in hip strength (estimated by finite element analysis) were seen in the romosozumab group than in the teriparatide group at month 6 (2·1% *vs* –1·0%, respectively) and month 12 (2·5% *vs* –0·7%, respectively; p<0·0001 between treatment groups; figure 4, appendix p 3).

Concentrations of the bone formation marker P1NP rose rapidly after the first dose in the romosozumab group, with an initial increase that was significantly greater than in the teriparatide group (figure 5). In the romosozumab group, P1NP concentrations peaked in the first month and then gradually returned towards baseline values during the 12 months of treatment. The bone resorption marker CTX declined rapidly after the first dose of romosozumab and returned to baseline by month 3, with concentrations remaining near baseline up to month 12. Transient increases in P1NP and reductions in CTX were also noted in the romosozumab group when

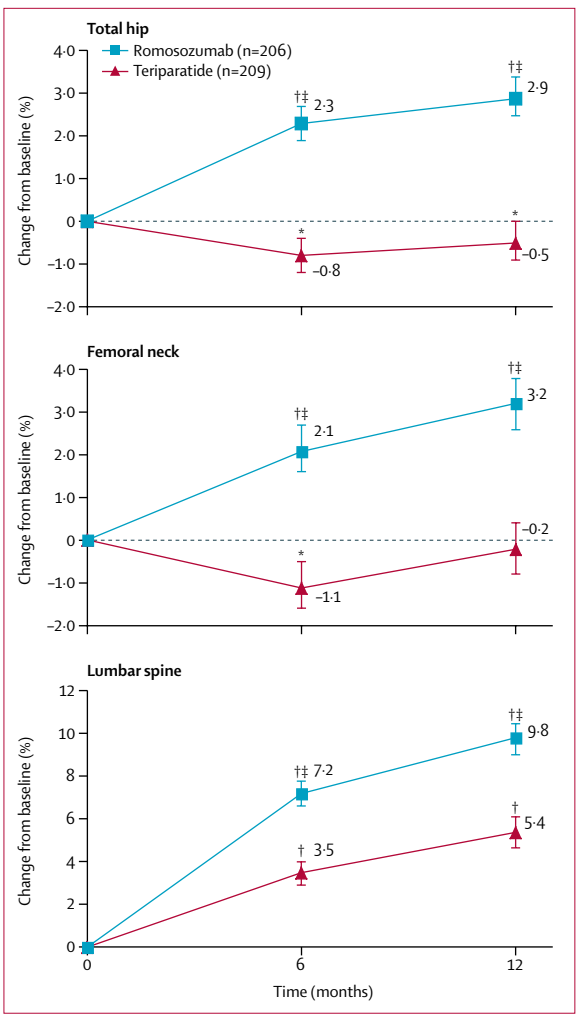

Figure 2: **Percentage change from baseline in areal bone mineral density at the total hip, femoral neck, and lumbar spine by dual energy x-ray absorptiometry**
Data are least-squares means and 95% CI. *p<0·05 versus baseline. †p<0·0001 versus baseline. ‡p<0·0001 versus teriparatide.

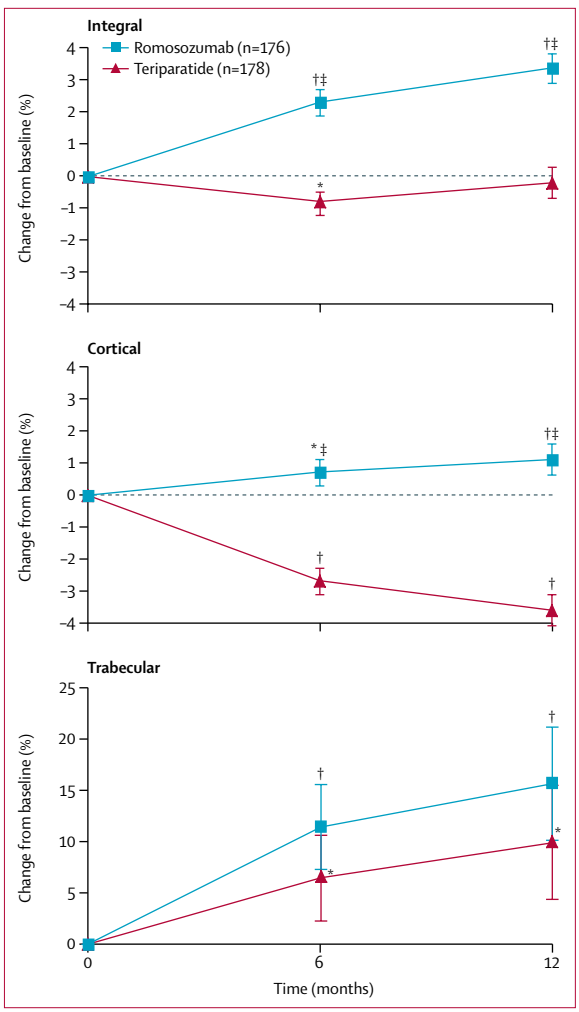

Figure 3: **Percentage change from baseline in integral, cortical, and trabecular volumetric bone mineral density at the hip by quantitative CT**
Data are least-squares means and 95% CI. *p<0·05 versus baseline. †p<0·0001 versus baseline. ‡p<0·0001 versus teriparatide.

concentrations were assessed 2 weeks post dose at months 3 and 6 (figure 5). In the teriparatide group, P1NP and CTX concentrations increased during the first 6 months of treatment and either stabilised (P1NP) or decreased (CTX) during the course of therapy, and remained significantly higher than baseline values for the subsequent 6 months of treatment. Concentrations of P1NP and CTX were significantly higher in patients in the teriparatide group than in the romosozumab group at all timepoints measured between months 3 and 12.

432 patients (218 on romosozumab and 214 on teriparatide) received at least one dose of investigational product and were included in the safety analysis. Overall, the percentages of patients reporting adverse events were generally balanced between the treatment groups (table 2), and the types of adverse events reported were those that would be expected in the population studied. Six (3%) patients in the romosozumab group and 12 (6%) patients in the teriparatide group had adverse events leading to discontinuation of study therapy. Serious adverse events were reported in 17 (8%) patients on romosozumab and in 23 (11%) on teriparatide; none were judged by the investigator to be treatment related. Serious adverse events reported by more than one participant in either treatment group were atrial fibrillation (two [<1%] patients in the romosozumab group) and pneumonia and abdominal pain (each reported by two [<1%] patients in the teriparatide group). Fractures were reported in 15 patients; seven (3%) had seven fractures in the romosozumab group (femoral neck, foot [two], rib [two], sternum, and ulna) and eight (4%) had nine fractures in the teriparatide group (humerus, foot, forearm, pubis [two], radius [three], and tibia). There was one death in each treatment group, neither of which was thought to be related to the investigational product.

Injection-site reactions were reported by 17 (8%) patients in the romosozumab group and six (3%) in the teriparatide group. Most were mild and none were judged serious. One patient discontinued romosozumab on study day 180 because of injection-site erythema, pruritus, and swelling that was reported as severe and judged related to romosozumab by the investigator. Three (1%) non-serious adverse events of hypocalcaemia were reported in the romosozumab group, two of which were asymptomatic (detected only biochemically) and one in association with complaints of constipation and asthenia after the second dose of romosozumab; six other patients were reported to have mild decreases in calcium detected via laboratory assessments (grade 1 abnormalities defined as below the normal reference range but no lower than 2·0 mmol/L), which were not reported as adverse events. In the teriparatide group, there were no reports of hypocalcaemia and 22 (10%) patients had reports of hypercalcaemia, which were reported as grade 1 (mild) in severity. No cases of osteonecrosis of the jaw or atypical femoral fracture were reported in either group.

All patients in the romosozumab group tested negative for pre-existing antibodies against romosozumab. Of the 210 patients with post-baseline results, 37 (17%) were positive for binding antibodies post baseline at least at one visit; 16 (43%) of these cases were transient (ie, results were negative at the last on-study determination). No neutralising antibodies were detected during the 12-month study period. The presence of antibodies did not seem to affect the efficacy or safety of romosozumab (data not shown).

Discussion

In women transitioning from bisphosphonate therapy, romosozumab treatment significantly increased areal BMD by DXA at the hip and spine compared with teriparatide in 1 year of therapy. At the hip, the gains in areal BMD remained significant despite previous use of bisphosphonate, which is known to result in decreased bone turnover; at the spine, the gains with romosozumab approached those previously reported in treatment-naive patients.[7,8] Although a small study, romosozumab therapy was overall well tolerated in this patient population and no new safety findings were seen.

In this high-risk population, areal BMD at the hip declined at 6 months with teriparatide, in accordance with findings from previous studies.[2,3] Quantitative CT results extended the hip DXA areal BMD results and provided insight into the compartment changes seen with romosozumab and teriparatide at this anatomical site. The changes in the cortical compartment with each treatment are of interest for two reasons. First, there are directionally opposed changes (ie, increases with romosozumab and decreases with teriparatide), which mirror the bone-forming effect of romosozumab on the cortex and a catabolic effect of teriparatide,

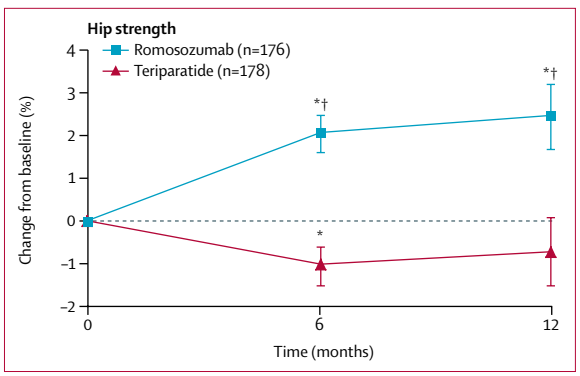

Figure 4: **Percentage change from baseline in estimated hip strength by finite element analysis**
Data are least-squares means and 95% CI. *p<0·0001 versus baseline. †p<0·0001 versus teriparatide.

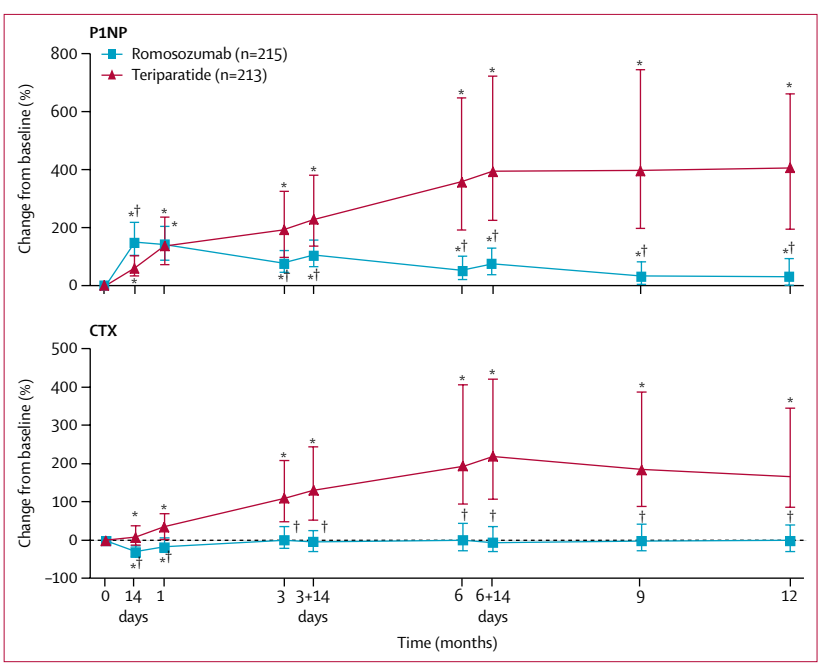

Figure 5: **Percentage change from baseline in serum procollagen type 1 N-terminal propeptide (P1NP) and serum C-telopeptide of type 1 collagen (CTX)**
Data are median (IQR). *p<0·0001 versus baseline. †p<0·0001 versus teriparatide.

which is thought to be a result of increased cortical porosity.[13–16] Second, although the percentage changes in volumetric BMD suggest greater change in the trabecular versus cortical compartment, assessment of the absolute changes in volumetric BMC shows that the contributions to the integral changes in terms of added or subtracted bone matrix are larger from the cortical versus trabecular compartment.

These changes translated into estimated hip strength alterations, which showed declines with teriparatide early in treatment and significant gains with romosozumab from baseline and over teriparatide at month 6 and continuing at month 12. The finite element analysis technique uses engineering

	Romosozumab (n=218)	Teriparatide (n=214)
All adverse events	164 (75%)	148 (69%)
Adverse events		
Nasopharyngitis*	28 (13%)	22 (10%)
Arthralgia*	22 (10%)	13 (6%)
Hypercalcaemia*	2 (<1%)	22 (10%)
Injection-site reaction†	17 (8%)	6 (3%)
Hypocalcaemia‡	3 (1%)	0
Serious adverse events	17 (8%)	23 (11%)
Leading to discontinuation of investigational product§	6 (3%)	12 (6%)
Death¶	1 (<1%)	1 (<1%)

Data are number of patients (%). Denominator is number of patients who received at least one dose of investigational product. *Events reported as 10% or higher in either treatment group; †Reported as different types of injection-site reactions with the most frequent as injection-site pain in the romosozumab group. ‡Includes events reported as hypocalcaemia and decreased blood calcium concentration. §Adverse events leading to study discontinuation in each treatment group were single event types with no particular pattern. ¶There were two deaths during the trial, unrelated to investigational product; one participant with leukaemia in the romosozumab group had a haemorrhage and one participant in the teriparatide group had a gastrointestinal haemorrhage.

Table 2: **Adverse events**

computational mechanics principles to simulate a virtual stress test, in which a patient-specific model of the proximal femur is virtually loaded to its failure point under forces typical of a sideways fall. Taken together, these results suggest that, despite a large percentage increase in trabecular BMD with teriparatide treatment, the concomitant decrease in cortical BMD was sufficiently large that no significant gain in hip strength from baseline was seen during the 12 months after treatment initiation.

The reasons for the larger gains in BMD and estimated strength with romosozumab might relate to its mechanism of action, because romosozumab has a dual effect, increasing bone formation and decreasing bone resorption.[7] In the setting of transition from bisphosphonates, P1NP concentrations increased early with romosozumab, peaking at 2 weeks and falling back towards baseline during the 12-month treatment period, remaining higher than baseline concentrations at month 12. Serum CTX declined early with romosozumab and rose back to baseline values by month 3. Overall, this pattern is similar to that seen in patients not previously exposed to other osteoporosis treatment,[7,8] although it also might indicate some offset of the antiresorptive therapy with overlying effects of romosozumab treatment to prevent escalations in bone resorption expected to occur after discontinuation of bisphosphonates. The larger increase in density and mass, denoting a larger bone-forming net effect with romosozumab, arose in the context of a smaller rise in P1NP with romosozumab than with teriparatide. If P1NP is a marker of the amount of new bone being formed, the profile of bone turnover markers suggests that the pro-remodelling effect of teriparatide to increase bone resorption is likely to partly counteract the apparently larger bone formation response. Indeed, the increase in remodelling associated with teriparatide might be responsible for the deterioration of cortical mass seen with teriparatide, as shown by the cortical volumetric BMD effects detected in this study.

In primate studies, romosozumab increased bone formation predominantly on modelling surfaces,[17] thus not depending on ongoing remodelling. If the same process occurred in people, it could account for the significant improvement in bone mass after treatment in patients transitioning from a bisphosphonate; by contrast, teriparatide, which improves bone formation mainly on remodelling surfaces, might have had less of a bone accretion action in patients previously treated with a bisphosphonate because of less continuous remodelling, as shown in this study. A consequence of these differences is an increased improvement in BMC, BMD, and estimated bone strength, which is desirable for patients at risk for fracture. These data are clinically important because bone-forming agents in practice are commonly used after a patient has received a bisphosphonate and had a fracture.

A limitation of this study was the open-label study design, which was necessary because of the inability to mask the teriparatide pen; however, although the treatment assignments were open label, the efficacy endpoints were objective measurements and assessed by investigators who were masked to treatment allocation. Also, this study was not powered to assess the difference in fracture incidence between treatment groups, and fracture events were not adjudicated or confirmed, although finite element analysis showed significant gains in strength from baseline. Another limitation derives from our not being able to measure any changes in the degree of mineralisation. Ettinger and colleagues[1] proposed that early declines in areal BMD and volumetric BMD seen with teriparatide could result from the replacement of highly mineralised bone with less mineralised bone, which would become more mineralised over time. However, recent work suggests that the bone mineralisation density distribution does not differ in biopsy samples obtained at 6 months and 24 months in patients given teriparatide.[18] Although our study could not distinguish between highly mineralised bone with some porosity versus less mineralised bone with less porosity, the finite element-based measurements of estimated strength and the associated biomechanics depend only on the net amount of mineral in the bone tissue. Thus, our simulations suggest that, irrespective of the exact cause of the decrease in BMD in the teriparatide group, overall bone strength was not increased over the course of 12 months.

Finally, because the duration of the study was 12 months, and teriparatide is approved for up to

24 months of treatment, our results cannot address whether a longer duration of teriparatide treatment would have resulted in increased mass and strength over a longer exposure term. However, in an 18-month study of teriparatide-treated patients who had previously been on alendronate,[1] mean BMD gains at the total hip remained at or below baseline up to month 12, with mean gains from baseline of 0·3% at month 18. Notably, if the reason to transition a patient from a bisphosphonate to a bone-forming agent is to achieve an increase in strength to reduce fracture risk, the first year of therapy is of clinical relevance. Indeed, it is well documented that after a fracture, the risk of a subsequent fracture is highest in the next year,[19] and other clinical characteristics of patients have been identified as putting patients at high risk for fracture over a 1-year time horizon.[20] Such patients at high risk for fracture over the near term might particularly benefit from a treatment that improves bone strength during this period.

Strengths of this study include the various complementary imaging modalities used to assess the effects of romosozumab treatment, which showed consistent and complementary results. The data obtained by finite element analysis provided a mechanistic basis for interpreting the noted changes in BMD in terms of more clinically relevant biomechanical outcomes—namely, the estimated strength of the proximal femur under typical loading conditions associated with a sideways fall. Finally, the analyses in this study controlled for baseline variables.

Our findings showed that in patients at high risk for fracture transitioning from bisphosphonates, romosozumab increased hip and spine BMD and estimated hip strength compared with teriparatide through a dual effect, increasing bone formation and decreasing bone resorption. Integral BMD at the hip and estimated hip strength declined with teriparatide use at 6 months in this population. These results suggest that romosozumab might offer a unique benefit to patients with postmenopausal osteoporosis who are transitioning from bisphosphonate therapy.

Contributors

BLL, MAB, JPB, ED, JSF, SG, LH, EJ-G, DK, PL, JMal, FEM, JFM, and MRU were involved in data acquisition. KE and TMK performed image analysis. NSD was the study statistician. All authors participated in the interpretation of the data, and in the critical review and revision of the manuscript. All authors approved the final manuscript for publication.

Declaration of interests

BLL reports fees (to her institution), during the conduct of the study; she reports personal fees from Amgen, Eli Lilly, Merck, and UCB; non-financial support from Eli Lilly and Orkla Health; and grants and non-financial support from Novo Nordisk, outside the submitted work. CL is an employee of UCB Pharma and reports UCB Pharma stock and stock options. DBC, NSD, JMad, and AG are employees of Amgen and report Amgen stock or stock options. JPB reports research grants from Amgen (paid to institution), during the conduct of the study; and grants (paid to institution) and personal fees from Amgen and Eli Lilly and personal fees from Merck and Radius, outside of the submitted work. KE reports personal fees from Amgen Bone Academy Germany, outside the submitted work. HKG reports consulting fees from Amgen, Lilly, Merck, Novartis, Pfizer, Janssen, Daiichi, Medtronic, AgNovos Healthcare, BioMarin, Clementia, and BioClinica, outside the submitted work. SG reports grants, personal fees, and non-financial support from Amgen, during the conduct of the study; and grants from MSD, Novartis, UCB, and Eli Lilly, outside the submitted work. EJ-G reports personal fees for consulting from UCB Pharma, personal fees for consulting and speaking from Eli Lilly, and personal fees and other fees for clinical trials, consulting, and speaking from Merck and Amgen, outside the submitted work. TMK reports consulting fees from and equity ownership in ON Diagnostics and consulting fees from Amgen and AgNovos Healthcare, outside the submitted work. In addition, he has a patent US Application 11/241,627 pending to UC Berkeley, a patent US Application 14/311,242 pending to ON Diagnostics, and a patent US Application 14/455,867 pending to ON Diagnostics, and he serves as consulting Chief Science Officer for ON Diagnostics, which was paid to perform some of the technical services for this study. DK reports research grants and honoraria from Amgen and Eli Lilly, research grants from AstraZeneca and Astellas, and consulting fees from Merck, during the conduct of the study. PL reports personal fees from Amgen, Merck, Sanofi, Fresenius-Kabi, and Servier, outside the submitted work. JFM reports research funding from Amgen. All other authors declare no competing interests.

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