Effects of denosumab in Japanese rheumatoid arthritis patients treated with conventional anti-rheumatic drugs: 36-month extension of a phase 3 study

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Short Running Head: Denosumab for csDMARD-treated patients

ABSTRACT

Objective: To evaluate safety and efficacy of long-term denosumab 60 mg every 6 (Q6M) or 3 months (Q3M) in rheumatoid arthritis (RA) patients.

Methods: This 12-month, randomised, double-blind, placebo-controlled, multicentre phase 3 trial with an open-label extension period from 12 to 36 months (DESIRABLE) enrolled Japanese RA patients treated with placebo for 12 months then denosumab Q6M (P/Q6M) or denosumab Q3M (P/Q3M); denosumab Q6M for 36 months (Q6M/Q6M); or denosumab Q3M for 36 months (Q3M/Q3M). Efficacy was assessed by van der Heijde modified total Sharp (mTSS), bone erosion (ES), and joint space narrowing (JSN) scores.

Results: Long-term treatment better maintained mTSS and ES suppression in the P/Q3M and Q3M/Q3M versus P/Q6M and Q6M/Q6M groups; changes from baseline in total mTSS at 36 months were 2.8 (standard error 0.4), 1.7 (0.3), 3.0 (0.4), and 2.4 (0.3), respectively; corresponding changes in ES were 1.3 (0.2), 0.4 (0.2), 1.4 (0.2), and 1.1 (0.2). No JSN effect was observed. Bone mineral density consistently increased in all groups after denosumab initiation, regardless of concomitant glucocorticoid administration. Serum C-telopeptide of type I collagen decreased rapidly at 1-month post-denosumab administration (both in the initial 12-month [Q3M, Q6M groups] and long-term treatment [P/Q3M, P/Q6M groups] phases). Adverse event incidence leading to study drug discontinuation was similar across treatment groups.

Conclusion: Denosumab treatment maintained inhibition of progression of joint destruction up to 36 months. Based on effects on ES progression, higher dosing frequency at an earlier treatment stage may be needed to optimise treatment. Denosumab was generally well tolerated.

Trial Registration Number: ClinicalTrials.gov (NCT01973569).

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown aetiology characterised by persistent synovitis, systemic inflammation, and irreversible localised joint destruction. The development of biological disease-modifying anti-rheumatic drugs (bDMARDs) has improved RA outcomes, particularly in controlling disease activity and preventing local joint destruction (1). However, alternatives are needed for patients who cannot use these drugs because of immune suppression, side effects, contraindications, or cost. Furthermore, some patients may need additional consideration of systemic bone destruction, including glucocorticoid-mediated osteoporosis, which may not be sufficiently prevented by bDMARDs (1). Denosumab, a fully human monoclonal antibody (IgG2 subclass), inhibits the receptor activator of nuclear factor κ-B ligand (RANKL), a key mediator of osteoclast formation, function, and survival, thus blocking bone resorption, and potentially joint destruction progression (1,2).

Joint destruction and systemic osteoporosis are bone-related consequences of RA, and RA patients have double the osteoporosis risk, even without glucocorticoid use (1,3). Although joint destruction in RA and systemic osteoporosis occur via different mechanisms, activation of osteoclasts via RANKL is necessary for both (1). The RANKL inhibitor, denosumab, has potential significance in preventing local and systemic RA bone destruction.

Two phase 2 studies investigated the treatment effects and dose-response of denosumab on bone and joint destruction in RA patients, but differed in treatment doses and duration. In a US and Canadian study, patients receiving methotrexate (MTX) were administered denosumab 60 or 180 mg every 6 months (4), whereas in a Japanese study, patients receiving MTX were administered denosumab 60 mg every 2, 3, or 6 months (5).

Denosumab significantly increased bone mineral density (BMD) in post-menopausal women (6), supporting its use for bone resorption. Denosumab also prevents bone loss and increases BMD in RA patients (4,7).

The phase 3 DESIRABLE study investigated the safety and efficacy of denosumab in a 12-month, double-blind phase (8), and then in a 24-month, open-label extension period. Progression of joint destruction in Japanese patients with RA receiving conventional synthetic DMARDs (csDMARDs) was assessed using the van der Heijde modified total Sharp score (mTSS). We investigated the safety and efficacy of long-term denosumab 60-mg treatment in patients with RA by analysing the results of the open-label period (<24 months), which evaluated safety and efficacy every 6 months (Q6M) or every 3 months (Q3M).

MATERIALS AND METHODS

Study design and patients

This was a 12-month, randomised, double-blind, placebo-controlled, multicentre phase 3 trial with an open-label extension period (DESIRABLE; ClinicalTrials.gov #NCT01973569) (8). Japanese patients fulfilling the American College of Rheumatology (ACR) 1987 criteria and ACR/European League Against Rheumatism (ACR/EULAR) classification criteria for RA and being treated with csDMARDs, were enrolled at 94 Japanese sites. Results of the 12-month double-blind period were published previously (8). Patients were randomised (1:1:2:2) to receive: placebo for 12 months (double-blind period) followed by denosumab Q6M (P/Q6M) (open-label extension period); placebo for 12 months followed by denosumab Q3M (P/Q3M); denosumab Q6M for 12 months followed by denosumab Q6M (Q6M/Q6M); or denosumab Q3M for 12 months followed by denosumab Q3M (Q3M/Q3M) (Supplementary Figure 1). Treatment was a 60-mg subcutaneous injection of denosumab or matching placebo. Randomisation was stratified by baseline glucocorticoid use. Because the study period was defined as continuation until drug approval in Japan, the follow-up period differed for each patient and not all reached the full 36-month follow-up period. Ethical approval was gained from institutional review boards of all sites (principal trial site: University of Occupational and Environmental Health, approval number: 10312) and the study was conducted in accordance

with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Eligibility criteria

Patients fulfilled the ACR 1987 and ACR/EULAR criteria (9,10) for a diagnosis of RA and included men or women aged ≥20 years at the time of informed consent, and with a RA duration of 0.5–<5 years and ≥6 swollen joints among 66 joints at screening.

The main exclusion criteria were presence or history of inflammatory joint disease other than RA; history of RA treatment with any biological product or administration of tofacitinib or use of glucocorticoids (≥10 mg/day prednisone equivalent) ≤4 weeks before enrolment; use of parathyroid hormone or its derivatives within 1 year of enrolment; history of, or scheduled for, surgery for joint replacement of the hands or feet; and severe, progressive, or uncontrolled disease (e.g., congestive heart failure, or chronic obstructive pulmonary disease) as judged by the investigator.

The main prohibited medications during the study were any bDMARD for RA treatment, tofacitinib, bisphosphonate, oral corticosteroids (≥10 mg/day prednisone equivalent), parathyroid hormone or its derivatives, and other investigational drugs. Injectable corticosteroids or oral/injectable hyaluronic acid to joints assessed by the modified Sharp method were not permitted during the study. However, patients who received injectable

corticosteroids or oral/injectable hyaluronic acid >2 weeks prior to enrolment and had ≤3 uses/year of each drug type for reasons other than the modified Sharp assessment of an evaluable joint remained eligible.

Concomitant use of csDMARDs (including MTX), and calcium (600 mg/day) and vitamin D (400 IU/day) supplements were allowed; such treatments could be added, discontinued, or the dose modified.

Radiographic analysis

Hand and feet radiographs at baseline and at 12, 24, and 36 months were re-read in blinded time order to assess mTSS. For the current analysis, radiographs were assessed Q6M in the double-blind phase and either Q6M for 18 months or Q12M for 36 months in the open-label extension phase (Supplementary Table 1). Radiographs obtained at baseline and <12 months (scored in campaign 1) were scored again with additional radiographs from the open-label phase, up to 18 months (campaign 2) or 36 months (campaign 3). Two readers with no knowledge of the double-blind treatment assignments or mTSS score from previous analyses assessed each set of images, independent of the initial 12-month double-blind analysis (8). Therefore, radiographic results reported previously at 12 months may differ from those in the current analysis. The mean score of the two readers at each time point was used.

BMD analysis

BMD of the lumbar spine (L1–L4) was assessed with dual energy x-ray absorptiometry (DXA) at screening and at 12, 24, and 36 months. DXA was performed at each study site with masked scans sent for analysis by Bioclinica Inc.

Efficacy endpoints

The efficacy endpoints were: a) changes in total mTSS, bone erosion score (ES) and joint space narrowing (JSN) score assessed by the modified Sharp-van der Heijde method from baseline to 36 months (11); b) changes in Disease Activity Score using 28 joints and C-reactive protein (DAS28-CRP) and health assessment questionnaire disability index (HAQ-DI) from baseline to 36 months; c) changes in lumbar spine (L1–L4) BMD from baseline; and d) changes in bone turnover and cartilage markers including serum C-telopeptide of type I collagen (CTX-I), cartilage oligomeric matrix protein (COMP), and urine C-telopeptide of type II collagen (CTX-II). CTX-II was adjusted for creatinine (CTX-II/Cre). Serum, plasma, and urine samples were analysed by LSI Medience Corporation.

Safety analysis

Safety was assessed by the frequency of adverse events (AEs) in person-years (PY), summarised using the Medical Dictionary for Regulatory Activities, ver. 19.0. The presence of

binding or neutralising antibodies to denosumab was assessed at screening, every 12 months after visit 12, and at study completion/discontinuation. Serum samples for measurement of anti-denosumab antibodies were analysed by LSI Medience Corporation.

Statistics

The long-term radiographic analysis set included all randomised patients who were administered the investigational product and had available baseline and ≥1 post-administration mTSS data, and mTSS data after the initial 12-month double-blind period. The mean and standard deviation (SD) of percent changes from baseline in lumbar spine BMD were presented by glucocorticoid use (absence or presence) at 12, 24, and 36 months. Median and interquartile ranges of percent changes from baseline in CTX-I, COMP, and CTX-II/Cre were determined at the time point of interest. Mean changes from baseline in DAS28-CRP and HAQ-DI were assessed each year. Missing data were not imputed.

As this was a post hoc analysis of the change from baseline in mTSS, an integrated approach (12) was applied using all available data at each time point (i.e., at baseline and 12 months, campaign 1–3 data were available for analysis; at 6 months, only campaign 1 and 2 data were available; Supplementary Table 1). Changes from baseline in mTSS for all campaigns were analysed using a multilevel linear mixed model with a compound symmetry correlation structure. Treatment, time point, baseline value, and treatment-by-time point

interaction were fixed effects; campaign was a random effect. The least-squares means of the change from baseline in mTSS were calculated at each time point. Campaign 1 (i.e., double-blind period) analysis was performed using data from patients who were administered the investigational product and had available baseline data and ≥1 mTSS assessment post-administration during the initial 12-month double-blind period.

For AEs, exposure-adjusted incidence rates were calculated, and events classified according to system organ class and preferred term. Exposure adjustments were made to account for patients who switched from placebo in the double-blind period to denosumab in the open-label period: the analysis period for AEs only included the open-label period for patients in the switching group whereas the analysis period included both double-blind and open-label periods for patients who received denosumab continuously throughout the entire study. Statistical analysis was performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition

A total of 679 patients were randomised; 12 did not receive the study drug, and the remaining patients were allocated as follows: P/Q6M, n=113; P/Q3M, n=110; Q6M/Q6M, n=222; and Q3M/Q3M, n=222 (Figure 1). Of these, 607 patients completed the double-blind

period and entered the long-term extension phase (P/Q6M, n=105; P/Q3M, n=103; Q6M/Q6M, n=199; and Q3M/Q3M, n=200).

The main reasons for discontinuation before the end of the 12-month period and before entry to the long-term extension phase included AEs (n=15), consent withdrawal (n=14), invasive dental procedure (n=14), prohibited concomitant drug (n=6), protocol deviation (n=6), and disease progression (n=3) (Figure 1). The main reasons for discontinuation during the open-label extension phase included consent withdrawal (n=42), invasive dental procedure (n=37), AEs (n=26), prohibited concomitant drug (n=13), and disease progression (n=6).

Baseline patient characteristics in the long-term radiographic analysis set were similar among all treatment groups with no notable differences in age or sex (Table 1). Mean disease duration was 2.3, 1.9, 2.3, and 2.2 years in each group, respectively. Rheumatoid factor was positive in 60.3% of patients and was similar among treatment groups.

Efficacy

In the continuous administration and crossover groups, mTSS and ES suppression were maintained in the P/Q3M and Q3M/Q3M groups during the long-term treatment phase compared with P/Q6M and Q6M/Q6M groups (Figure 2A, B). At 36 months, changes (standard error [SE]) from baseline in total mTSS for P/Q3M, Q3M/Q3M, P/Q6M, and Q6M/Q6M groups were 2.8 (0.4), 1.7 (0.3), 3.0 (0.4), and 2.4 (0.3), respectively. Corresponding values for

changes (SE) in ES were 1.3 (0.2), 0.4 (0.2), 1.4 (0.2), and 1.1 (0.2). Changes (SE) from 12 to 24 months and 24 to 36 months in total mTSS were 0.55 (0.22), 0.52 (0.16), 1.02 (0.21;), 0.81 (0.16;) and 0.54 (0.30), 0.39 (0.22), 0.71 (0.29), 0.52 (0.22), respectively. Changes in mTSS after 12 months during campaigns 1 (double-blind period) and 3 (current open-label extension) are compared in Supplementary Table 2.

For ES, changes (SE) from 12 to 24 months and 24 to 36 months were 0.16 (0.10), 0.10 (0.07), 0.36 (0.10), 0.34 (0.07) and 0.11 (0.15), 0.02 (0.11), 0.16 (0.14), 0.15 (0.11), respectively. No effect on JSN was observed in any group (Figure 2C). Changes (SE) from 12 to 24 months in JSN score were 0.38 (0.14, 0.41 (0.10), 0.65 (0.13), and 0.46 (0.10) for the P/Q3M, Q3M/Q3M, P/Q6M, and Q6M/Q6M groups, respectively. Corresponding changes (SE) from 24 to 36 months were 0.42 (0.2), 0.36 (0.15), 0.54 (0.20), and 0.36 (0.15). Similar changes in DAS28-CRP and HAQ-DI scores were observed across all groups during the long-term treatment phase, with the largest changes seen in the Q3M/Q3M group (Supplementary Figures 2 and 3).

Increases in BMD from baseline to 36 months were observed in the continuous administration groups; 8.9% and 9.9% in the Q6M and Q3M groups, respectively. In the crossover groups, BMD changes at 36 months (24 months after first denosumab dose) were 6.7% and 7.8% in the P/Q6M and P/Q3M groups, respectively (Figure 3A). Similar increases in BMD were observed regardless of glucocorticoid use (Figure 3B, C).

Serum CTX-I decreased 1 month after the first denosumab dose with relatively sustained reductions (Figure 4). A substantial decrease in CTX-I was observed at 1-month post-administration in the initial 12-month phase (Q3M and Q6M groups) and long-term treatment phase (after 12 months in P/Q3M and P/Q6M groups) and was sustained throughout the study (Figure 4). However, although a substantial decrease in CTX-II/Cre was observed 1 month following denosumab initiation in the initial 12-month phase and long-term treatment phase (after 12 months), CTX-II/Cre began to increase after 3 months of denosumab treatment and returned to baseline by 6 months in the Q6M groups (Supplementary Figure 4A). COMP levels were unaffected by denosumab treatment (Supplementary Figure 4B).

Safety

The exposure-adjusted incidence rate of serious AEs (SAEs) and AEs leading to discontinuation of the study drug were similar across treatment groups (Table 2), ranging from 4.6/100 subject-years in the Q6M/Q6M group to 5.8/100 subject-years in the P/Q3M group. The incidence of SAEs tended to be higher in the Q6M/Q6M (6.9/100 subject-years) and Q3M/Q3M (8.6/100 subject-years) groups than the P/Q6M (4.7/100 subject-years) and P/Q3M (7.2/100 subject-years) groups.

Three deaths occurred in the Q3M/Q3M group during the study period: interstitial pneumonia (judged as related to the study drug), and pneumocystis pneumonia and acute heart

failure (both judged as not related to the study drug). No atypical femoral fracture events were observed in any group in the double-blind or long-term analyses (Table 2).

Neutralising antibodies to denosumab were not detected in any treatment group during the long-term phase.

DISCUSSION

Here we report the results of the long-term, open-label extension of the DESIRABLE phase 3 trial, the only study to have verified the long-term effects of denosumab in RA patients. During the long-term treatment phase of this study, denosumab sustained the inhibition of mTSS and ES progression.

In the 12-month double-blind phase of the DESIRABLE study, inhibition of worsening mTSS (primary endpoint) was maintained for <12 months of treatment in the denosumab groups and was superior to that of placebo (8). In the current analysis, this trend was maintained for <36 months after treatment initiation. Additionally, a notable reduction in the mTSS progression rate was observed in the placebo/denosumab groups starting at 12 months of treatment, when patients were switched to denosumab from placebo, with a similar trend in ES. Furthermore, comparing the denosumab/denosumab 60 mg Q6M and Q3M groups shows that inhibition of mTSS and ES progression was slowed more by Q3M administration at 12 months, and this trend continued until 36 months. Similarly, when comparing the P/Q6M

and P/Q3M groups, increased inhibition was also observed in the Q3M group. These findings suggest that long-term denosumab treatment may be more effective with Q3M than with Q6M administration.

Marked inhibition of ES progression was observed in the patient groups receiving denosumab treatment from the start of the double-blind period and was more pronounced in the Q3M group than in the Q6M group. Furthermore, the change in ES from baseline remained lower in the Q3M/Q3M group than the Q6M/Q6M group and the crossover groups at all time points. This suggests that earlier intervention with denosumab may be more effective for inhibition of erosion progression, and that bone destruction by erosion is irreversible.

No effects on JSN scores were observed for any of the groups. Additionally, the changes in DAS28-CRP and HAQ-DI, indicators of disease activity, were similar across all groups, as previously reported (4,5).

The 3-year long-term study showed an approximately 4% increase in BMD after 12 months of denosumab treatment in the Q6M and Q3M groups that started denosumab treatment in the initial 12-month phase, with a slight decrease in BMD in the placebo groups during this phase. This further supports the efficacy of denosumab in terms of increasing BMD, as previously reported (1). Importantly, BMD subsequently increased in the crossover groups after switching from placebo to denosumab treatment at 12 months.

Regarding the influence of glucocorticoid treatment, an increase in BMD with denosumab treatment was observed across all groups, suggesting that denosumab increases BMD regardless of concomitant glucocorticoid use. In placebo groups receiving glucocorticoid treatment, a slight decrease in BMD was observed at 12 months. As reported to date, this was considered attributable to the BMD-reducing effect of glucocorticoids (1,13,14). However, even in patients using glucocorticoids, denosumab increased BMD. Hence, the positive effects of denosumab on BMD, which have been demonstrated in patients with osteoporosis, are confirmed in RA patients (2,6). Furthermore, these results suggest that denosumab may be effective in patients with RA who have concurrent osteoporosis, and the use of denosumab should be considered for patients likely to develop osteoporosis associated with glucocorticoid therapy. Moreover, our study demonstrates that denosumab improves BMD over long time periods.

In terms of markers of bone turnover and cartilage destruction, a substantial decrease in CTX-I was observed 1 month after starting denosumab treatment in the initial 12-month phase and the long-term treatment phase (after 12 months), and was sustained for 3 years. The decrease in CTX-I, a bone resorption marker, indicated sustained inhibition of bone resorption by long-term denosumab treatment. Notably, in the Q6M groups, CTX-I slightly increased before the next dose, whereas sustained inhibition was observed in the Q3M groups. There have been concerns that sustained inhibition of bone resorption (represented by reduced CTX-I)

may be associated with an increased incidence of atypical bone fractures (15,16). However, no such increase was observed in this study in the Q3M groups over the 3-year study period, in agreement with osteoporosis studies (6,17).

Serum and urinary levels of CTX-II typically exceed normal ranges in RA and osteoarthritis patients (18). To date, studies conducted in patients with RA have clarified that denosumab has no effect on cartilage destruction, demonstrated by no improvement in JSN (2,4). Our study shows that CTX-II decreased over the first 3 months of denosumab treatment, suggesting that CTX-II is not necessarily a marker of only cartilage destruction, which is corroborated by a recent report (18). In contrast, COMP is a marker of cartilage turnover found in peripheral blood. In this study, changes over time were similar, with no significant difference between the denosumab and placebo groups at 12 months, showing that denosumab does not affect cartilage.

Denosumab was well tolerated in Japanese patients with RA over 36 months of treatment, and the safety profiles of denosumab were generally consistent with previous studies (4–6,17). The effects of denosumab were not attenuated during the 3-year long-term treatment period. To date, a clinical study on osteoporosis reported that neutralising antibodies against denosumab were not induced (19), consistent with the present study. This suggests that neutralising antibodies were not induced in patients with RA, resulting in the maintenance of the effects of denosumab, which may mean it has advantages over other bDMARDs.

In recent years, treatment with bDMARDs has become more common and has dramatically improved outcomes of patients with RA; however, it is not recommended in all patients owing to concerns regarding adverse drug reactions or economic burden (1). Because of economic reasons or safety concerns, only about 20% of patients in Japan with RA are treated with bDMARDs (1,20), with 80% treated with csDMARDS; however, prevention of joint destruction is limited (1). While denosumab does not control disease activity, our study indicates that, in patients treated with csDMARDS, denosumab has the therapeutic potential to prevent joint destruction. Moreover, denosumab also increased BMD regardless of glucocorticoid use, an advantage over bDMARDs, which do not prevent osteoporosis associated with RA or glucocorticoid use (1).

A subgroup analysis by patient demographic characteristics is currently in progress, based on the pooled phase 2/3 study data (5,8). It is hoped that the results of the subgroup analysis will help identify patients who might receive greater benefit from denosumab. It will also be necessary to verify the long-term benefits of denosumab in such patients.

The main study limitation is that the open-label design of the extension phase does not allow for comparisons with placebo or an active comparator. In addition, the results may not be generalisable to all patients with RA, because the study enrolled patients being treated with csDMARDs and steroids, but prohibited the concomitant use of bDMARDs and tofacitinib during the study period.

In conclusion, this study demonstrated that denosumab can maintain the trend of mTSS and ES suppression during long-term treatment. Additionally, denosumab better suppresses ES progression with Q3M versus Q6M administration, indicating that a higher dosing frequency at an earlier treatment stage may be necessary to achieve an optimal treatment regimen. Denosumab also improved BMD regardless of glucocorticoid use, and was generally well tolerated in Japanese patients with RA on current csDMARD therapy. Denosumab is a potential new therapeutic option to inhibit progression of structural joint damage and systemic osteoporosis in patients with RA.

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http://ard.bmj.com/content/77/Suppl_2/947.share

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DATA SHARING STATEMENT

De-identified individual participant data and applicable supporting clinical trial documents (protocol, statistical analysis plan, and clinical study report) may be available upon request, to qualified scientific and medical researchers for the purpose of conducting legitimate research, by applying to https://vivli.org/. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/

AUTHOR CONTRIBUTIONS

YT, TT, SS, and HY provided substantial contributions to the study conception and design. TY diagnosed the oral adverse events. ST diagnosed the atypical femoral fracture events. TN was involved in the design and conduct of the study and in collecting data. NO was involved in the

design of the study and data analysis. DvdH supervised scoring of the radiographs. All authors interpreted the data. All authors discussed and agreed on the content of the manuscript before submission.

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FIGURE LEGENDS

Figure 1. Patient disposition in the DESIRABLE study.

*The long-term radiographic analysis set includes patients in the full analysis set who had mTSS scores available after the initial 12-month double-blind period.

P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

Figure 2. Mean change in mTSS (A), bone ES (B), and JSN score (C) from baseline.

ES, erosion score; JSN, joint space narrowing; mTSS, modified total Sharp score; P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

Figure 3. Percent change in lumbar spine (L1–L4) BMD from baseline (A), and stratified by glucocorticoid use (B), and non-use (C).

BMD, bone mineral density; P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

Mean (± 95% confidence interval). Long-term radiographic analysis set, observed data.

Figure 4. Percent change in serum C-telopeptide of type I collagen from baseline to each visit.

CTX-I, C-telopeptide of type I collagen; P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

Median (interquartile range). Long-term radiographic analysis set.

Table 1. Baseline patient demographics and characteristics

	P/Q6M N=105	P/Q3M N=101	Q6M/Q6M N=191	Q3M/Q3M N=193	Total N=590
Female, n (%)	81 (77.1)	80 (79.2)	150 (78.5)	137 (71.0)	448 (75.9)
Age (years)	54.5 ± 12.6	56.8 ± 10.5	57.2 ± 12.1	57.6 ± 11.3	56.8 ± 11.7
Body weight (kg)	56.7 ± 10.4	57.4 ± 11.2	56.0 ± 11.0	57.2 ± 11.2	56.7 ± 11.0
Disease duration (years)	2.3 ± 1.4	1.9 ± 1.2	2.3 ± 1.3	2.2 ± 1.3	2.2 ± 1.3
Rheumatoid factor positive, n (%)	62 (59.0)	66 (65.3)	121(63.4)	107 (55.4)	356 (60.3)
Anti-CCP antibody positive, n (%)	71 (67.6)	64 (63.4)	136 (71.2)	130 (67.4)	401 (68.0)
Swollen joint count (0–66)	9.3 ± 4.9	9.7 ± 3.9	9.5 ± 4.9	8.9 ± 4.4	9.3 ± 4.6
Tender joint count (0–68)	6.7 ± 6.7	6.5 ± 6.2	7.4 ± 8.2	7.0 ± 7.8	7.0 ± 7.5
Bone erosion score (0–280)	5.2 ± 8.1	6.2 ± 12.0	6.3 ± 8.0	6.2 ± 9.9	6.1 ± 9.4
Joint space narrowing score (0–168)	8.8 ± 12.4	9.2 ± 15.7	10.1 ± 14.4	10.1 ± 12.8	9.7 ± 13.8
Modified total Sharp score (0–448)	14.0 ± 19.5	15.4 ± 26.6	16.5 ± 20.3	16.3 ± 21.0	15.8 ± 21.6
C-reactive protein (mg/dL)	0.4 ± 0.6	0.4 ± 0.6	0.6 ± 1.3	0.4 ± 0.8	0.5 ± 0.9
DAS28-CRP	3.4 ± 1.0	3.4 ± 0.9	3.6 ± 1.1	3.5 ± 1.0	3.5 ± 1.0
Baseline concomitant drugs, n (%)					

Glucocorticoid	32 (30.5)	28 (27.7)	61 (31.9)	58 (30.1)	179 (30.3)
NSAID	78 (74.3)	59 (58.4)	133 (69.6)	132 (68.4)	402 (68.1)
MTX only	69 (65.7)	60 (59.4)	108 (56.5)	129 (66.8)	366 (62.0)
MTX dose (mg/week)	9.8 ± 3.3	9.5 ± 3.0	9.3 ± 3.0	9.6 ± 3.0	9.5 ± 3.1

Values are shown as mean ± standard deviation unless otherwise indicated.

N = Number of patients who received at least one dose of investigational product and had a baseline value, at least one post-baseline radiograph, and one radiograph after 12 months of dosing.

CCP, cyclic citrullinated peptide; DAS28-CRP, Disease Activity Score using 28 joints and C-reactive protein; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

Table 2. Summary of AEs

	Long-term treatment phase		Double-blind + long-term treatment phase	
	P/Q6M	P/Q3M	Q6M/Q6M	Q3M/Q3M
All AEs	98 (245.6)	97 (196.4)	215 (211.4)	213 (183.3)
Serious AEs	9 (4.7)	13 (7.2)	37 (6.9)	46 (8.6)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
AEs leading to IP discontinuation	10 (5.1)	11 (5.8)	26 (4.6)	30 (5.2)
AEs of interest				
Hypocalcaemia	2 (1.0)	4 (2.1)	11 (2.0)	5 (0.9)
Bacterial cellulitis	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.9)
Infection	66 (63.0)	65 (61.4)	167 (71.3)	173 (69.9)
Eczema	14 (7.7)	8 (4.4)	32 (6.2)	24 (4.4)
Hypersensitivity	16 (8.9)	16 (9.2)	55 (11.4)	55 (11.0)
Cardiovascular disorder	8 (4.2)	4 (2.1)	22 (4.1)	24 (4.4)
Malignant or unspecified tumours	1 (0.5)	3 (1.6)	13 (2.3)	11 (1.9)
Cataract	0 (0.0)	1 (0.5)	5 (0.9)	3 (0.5)
Atypical femoral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal pain	11 (6.0)	11 (5.9)	36 (7.1)	34 (6.5)

AE data are listed as n (incidence rate per 100 subject-years), where n = number of patients who experienced an AE and incidence rate = n / total exposure time (years) × 100. A patient

who experienced repeated episodes of the same AE within the interval of interest was counted only once for that interval.

For the P/Q6M and P/Q3M groups, patients who received at least one dose of the study drug during the open-label extension phase were included.

For the Q6M/Q6M and Q3M/Q3M groups, patients who received at least one dose of the study drug during the double-blind phase and the long-term treatment phase were included.

AE, adverse event; IP, investigational product; P, placebo; Q3M, denosumab 60 mg every 3 months; Q6M, denosumab 60 mg every 6 months.

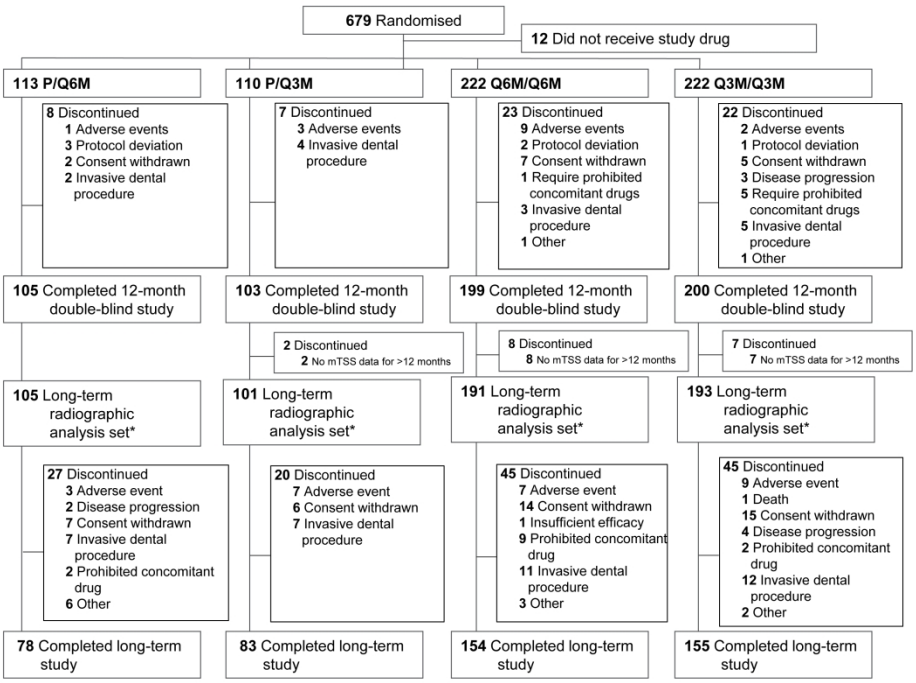

Figure 1

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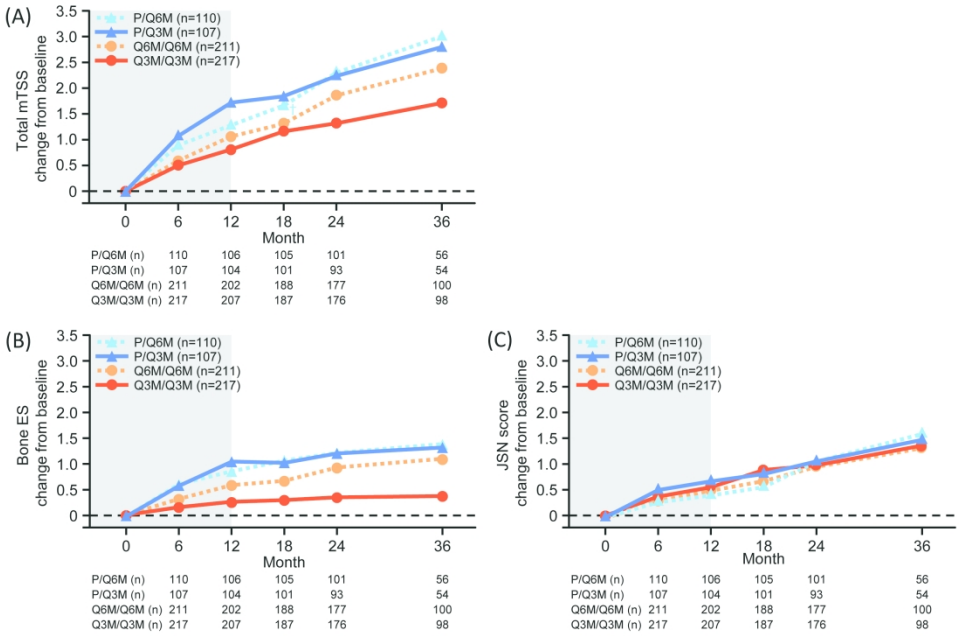

Figure 2

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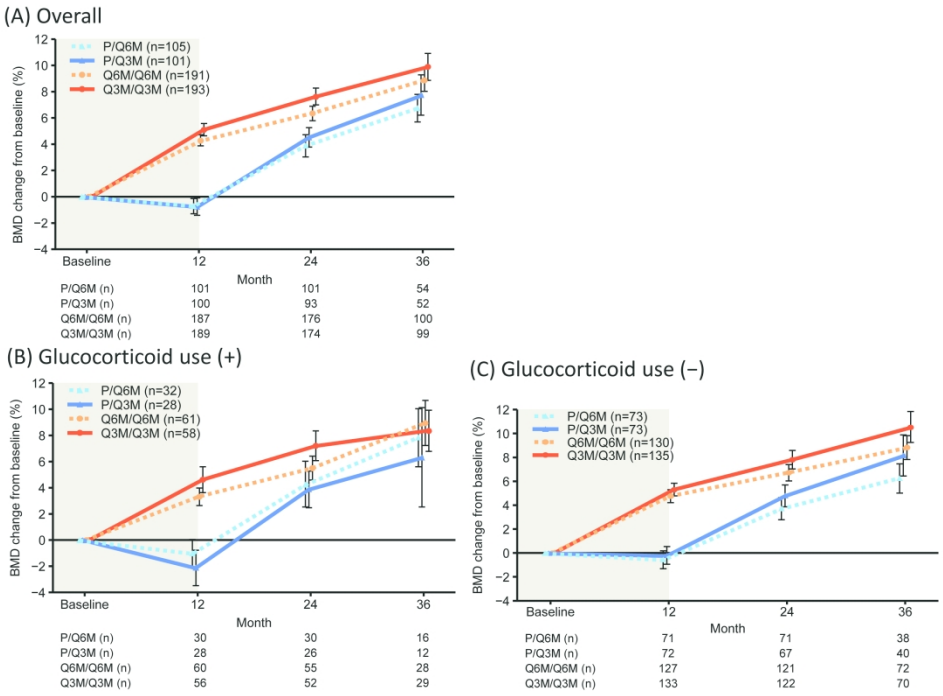

Figure 3

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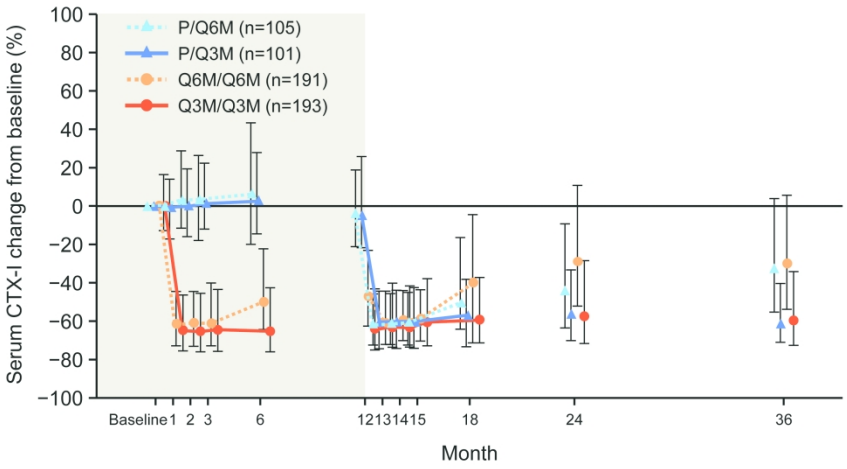

Figure 4

275x190mm (300 x 300 DPI)