Report on the Deliberation Results

June 7, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Pralia Subcutaneous Injection 60 mg Syringe
Non-proprietary Name	Denosumab (Genetical Recombination) (JAN*)
Applicant	Daiichi Sankyo Co., Ltd.
Date of Application	September 23, 2016

Results of Deliberation

In its meeting held on May 30, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

May 12, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Pralia Subcutaneous Injection 60 mg Syringe
Non-proprietary Name	Denosumab (Genetical Recombination)
Applicant	Daiichi Sankyo Co., Ltd.
Date of Application	September 23, 2016
Dosage Form/Strength	Solution for injection: Each syringe (1 mL) contains 60 mg of Denosumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the inhibition of progression of bone erosion associated with rheumatoid arthritis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The safety and other aspects of the product in clinical settings should be further evaluated in post-marketing surveillance.

Indications

1. Osteoporosis
2. Inhibition of progression of bone erosion associated with rheumatoid arthritis

(Underline denotes additions.)

Dosage and Administration

1. Osteoporosis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months.

2. Inhibition of progression of bone erosion associated with rheumatoid arthritis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months. If progression of bone erosion is still observed when denosumab is injected once every 6 months, denosumab may be administered as a subcutaneous injection once every 3 months.

(Underline denotes additions.)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

April 6, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Pralia Subcutaneous Injection 60 mg Syringe
Non-proprietary Name	Denosumab (Genetical Recombination)
Applicant	Daiichi Sankyo Co., Ltd.
Date of Application	September 23, 2016
Dosage Form/Strength	Solution for injection: Each syringe (1 mL) contains 60 mg of Denosumab (Genetical Recombination).
Proposed Indications	1. Osteoporosis 2. Prevention of structural joint damage associated with rheumatoid arthritis (Underline denotes additions.)

Proposed Dosage and Administration

1. Osteoporosis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months.

2. Prevention of structural joint damage associated with rheumatoid arthritis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months. Depending on the patient's condition, denosumab may be administered as a subcutaneous injection once every 3 months.

(Underline denotes additions.)

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List of Abbreviations

ACR20 ACR50 ACR70	American College of Rheumatology 20, 50, 70 responder index
AUC	Area under the serum concentration-time curve
CI	Confidence interval
C_{max}	Maximum serum concentration
CRP	C-reactive protein
CTX-I	C-telopeptide type I
Denosumab	Denosumab (Genetical Recombination)
DMARDs	Disease modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
JAK	Janus kinase
JSN	Joint space narrowing
mTSS	Modified total sharp score
MTX	Methotrexate
PMDA	Pharmaceuticals and Medical Devices Agency
Pralia	Pralia Subcutaneous Injection 60 mg Syringe
Q2M	Quaque 2 months
Q3M	Quaque 3 months
Q6M	Quaque 6 months
RA	Rheumatoid arthritis
RANK	Receptor activator for nuclear factor-κB
RANKL	RANK ligand
t_{max}	Time to reach maximum serum concentration
TNF	Tumor necrosis factor
Japanese guidelines for the management of RA	Japan College of Rheumatology, ed. Guidelines for the Management of Rheumatoid Arthritis 2014

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Denosumab (Genetical Recombination) (hereinafter referred to as "denosumab"), an active ingredient of "Pralia Subcutaneous Injection 60 mg Syringe" and "Ranmark Subcutaneous Injection 120 mg," is a human IgG2 monoclonal antibody against receptor activator for nuclear factor-κB (RANK) ligand (RANKL). Denosumab was developed by the US-based Amgen Inc. "Pralia Subcutaneous Injection 60 mg Syringe" has been approved for the treatment of "osteoporosis," and "Ranmark Subcutaneous Injection 120 mg" has been approved for the treatment of "bone lesions due to multiple myeloma and bone metastases from solid tumors" and "giant cell tumor of bone."

Rheumatoid arthritis (RA) is an autoimmune disease of unknown cause, characterized by pain, swelling, and functional disorders associated with inflammation of the joints, and further, by systemic symptoms such as slight fever and malaise. Progression of structural joint damage adversely affects the patient's physical functions. Progression of bone erosion and narrowing of the joint space are known to lead to structural joint damage. Denosumab was developed as a therapy that would inhibit the progression of these conditions.

The development program for denosumab for prevention of structural joint damage associated with RA began in [redacted]. A partial change application has been filed based on the results of Japanese clinical studies.

As of September 2016, denosumab has been approved for indications relating to osteoporosis in 80 or more countries.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application is intended for approval of a new indication and a new dosage. No new data related to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Denosumab does not bind to the RANKL of rodents. Osteoprotegerin-Fc fusion protein (OPG-Fc), which consists of osteoprotegerin, an endogenous inhibitor of the RANKL of rats, fused to the fragment crystalized (Fc) region of immunoglobulins, was used to study the effects on the animal model of arthritis, and the study results were submitted.

3.1 Effects on rat model of collagen-induced arthritis (CTD 4.2.1.1-2)

An emulsifier consisting of bovine type II collagen and incomplete Freund's adjuvant was administered to female rats as 2 subcutaneous injections 1 week apart to generate a rat model of arthritis. OPG-Fc 3 mg/kg was administered to the rat model as 5 subcutaneous injections every other day. Decreased bone resorption and a decrease in the number of osteoclasts in the hindlimbs, and an increase in bone density in the lumbar vertebra and tarsal joint were observed in animals treated with OPG-Fc. In contrast, there

were no effects on the joint symptom score, hindlimb volume, inflammation score, cartilage damage score, and pannus score.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of denosumab on RA:

Serum RANKL concentrations are higher in patients with RA than in healthy adults (*Arthritis Rheum*. 2002;46:1744-53). Increased RANKL expression was observed in activated synovial fibroblasts, T-cells, and B-cells in patients with RA (*Nature*. 2003;423:337-42). The RANKL/RANK signaling pathway is involved in the induction of differentiation, maturation, and activation of osteoclasts, leading to bone destruction near the joint (*Nat Rev Rheumatol*. 2012;8:656-64). Blockade of the RANKL/RANK signaling pathway in the rat model of arthritis resulted in reduced progression of bone tissue damage, an increase in bone density, a decrease in the number of osteoclasts, and decreased bone resorption in inflammatory joints. Therefore, denosumab can be expected to be effective in the inhibition of progression of bone destruction in the joints of patients with RA.

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application is intended for approval of a new indication and a new dosage. Because "non-clinical pharmacokinetic data" had already been evaluated for the initial approval of Ranmark Subcutaneous Injection 120 mg, no new data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for approval of a new indication and a new dosage. No new data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum denosumab concentrations and serum C-telopeptide type I (CTX-I) concentrations were measured by enzyme immunoassay (lower limits of quantitation, 20 ng/mL for denosumab, and 0.075 ng/mL for CTX-I). Serum anti-denosumab antibodies were measured by electro-chemiluminescence bridging immunoassay.

6.2 Clinical pharmacology

Evaluation data submitted by the applicant consisted of data from Japanese clinical studies (CTD 5.3.5.1-1 and 5.3.5.1-2) in patients with RA. Unless otherwise specified, the dose levels of denosumab are expressed as Denosumab (Genetical Recombination).

6.2.1 Studies in patients with RA

6.2.1.1 Phase II study (CTD 5.3.5.1-2, Study AMG162-D-J201 [[redacted] to [redacted]])

Denosumab 60 mg was administered subcutaneously to patients with RA every 6 months (Q6M), every 3 months (Q3M), or every 2 months (Q2M) for 12 months. Table 1 shows the pharmacokinetic parameters, and Table 2 shows the change in serum CTX-I concentrations, a bone resorption marker. No anti-denosumab antibodies were detected in any of the subjects.

Table 1. Pharmacokinetic parameters following multiple subcutaneous administration of denosumab to patients with RA

Treatment group	AUC_{tau} (ng·day/mL)[a)]	C_{max} (ng/mL)	t_{max} (day)
After the first dose			
60 mg Q6M (N = 85)	230,000 ± 110,000[b)]	4350 ± 1500	28.0 [19.0, 41.0]
60 mg Q3M (N = 81)	211,000 ± 84,100[c)]	4480 ± 1510	28.0 [16.9, 38.0]
60 mg Q2M (N = 84)	150,000 ± 48,300	4060 ± 1240	28.0 [16.0, 35.8]
Month 6			
60 mg Q6M (N = 81)	251,000 ± 123,000[d)]	4660 ± 1550	28.1 [16.0, 56.0]
60 mg Q3M (N = 74)	276,000 ± 129,000[e)]	5390 ± 2220	28.0 [19.0, 63.0]
60 mg Q2M (N = 78)	255,000 ± 106,000	5780 ± 2130	28.0 [6.0, 48.9]

Mean ± standard deviation; median [range] for t_{max}

a) AUC_{183day}, AUC_{91day}, and AUC_{61day} for Q6M, Q3M, and Q2M, respectively

b) N = 84, c) N = 80, d) N = 78, and e) N = 72

Table 2. Change in serum CTX-I concentrations following multiple subcutaneous administration of denosumab to patients with RA

Treatment group	Baseline	Month 1	Month 2 (trough)[a)]	Month 3 (trough)[a)]	Month 6 (trough)	Month 12 (trough)
Placebo group (N = 88)	0.42 ± 0.26	0.39 ± 0.22	0.40 ± 0.22	0.39 ± 0.20	0.42 ± 0.23[b)]	0.46 ± 0.25[c)]
60 mg Q6M (N = 85)	0.41 ± 0.25	0.14 ± 0.02	0.14 ± 0.01	0.14 ± 0.06[d)]	0.21 ± 0.13[e)]	0.24 ± 0.18[f)]
60 mg Q3M (N = 82)	0.40 ± 0.21	0.14 ± 0.04[c)]	0.14 ± 0.03	0.14 ± 0.02	0.15 ± 0.03[g)]	0.15 ± 0.01[h)]
60 mg Q2M (N = 85)	0.47 ± 0.30	0.15 ± 0.12	0.14 ± 0.01[d)]	0.14 ± 0.01	0.14 ± 0.01[e)]	0.15 ± 0.01[g)]

Mean ± standard deviation (ng/mL)

a) Subjects in the Q3M group received placebo at Month 2, and subjects in the Q6M group received placebo at Months 2 and 3. The concentrations before receiving placebo are shown.

b) N = 86, c) N = 81, d) N = 84, e) N = 83, f) N =78, g) N = 79, and h) N = 72

6.2.1.2 Phase III study (CTD 5.3.5.1-1, Study AMG162-D-J301 [from October 2013 until the data cut-off of [redacted]])

Denosumab 60 mg was administered Q6M or Q3M subcutaneously to patients with RA for 12 months. Table 3 shows the change in serum CTX-I concentrations. No anti-denosumab antibodies were detected in any of the subjects.

Table 3. Change in serum CTX-I concentrations following multiple subcutaneous administration of denosumab to patients with RA

Treatment group	Baseline	Month 1	Month 3 (trough)[a)]	Month 6 (trough)	Month 12 (trough)
Placebo group (N = 218)	0.46 ± 0.23	0.46 ± 0.22	0.48 ± 0.24	0.49 ± 0.27[b)]	0.45 ± 0.24[c)]
60 mg Q6M (N = 217)	0.45 ± 0.25[b)]	0.15 ± 0.02[d)]	0.16 ± 0.06[e)]	0.24 ± 0.15[f)]	0.25 ± 0.16[g)]
60 mg Q3M (N = 219)	0.48 ± 0.28[h)]	0.15 ± 0.03[h)]	0.16 ± 0.07[h)]	0.15 ± 0.03[b)]	0.15 ± 0.02[i)]

Mean ± standard deviation (ng/mL)

a) Subjects in the Q6M group received placebo at Month 3. The concentrations before receiving placebo are shown.

b) N = 216, c) N = 210, d) N = 214, e) N = 213, f) N = 205, g) N = 199, h) N = 218, and i) N = 204

6.R Outline of the review conducted by PMDA

The applicant compared the pharmacokinetics in patients with RA with those in patients with osteoporosis, for which denosumab has already been approved, and discussed as follows:

When the pharmacokinetics of denosumab in patients with postmenopausal osteoporosis (Study 20050172) were compared with those in patients with RA (Study AMG162-D-J201), the exposure in patients with RA was no greater than that in patients with osteoporosis and the exposure levels were within almost the same range (Table 4). Table 5 shows the change in the serum CTX-I concentration, a bone resorption marker. There was a trend towards decreased percent inhibition in CTX-I in patients with RA compared with that in patients with osteoporosis; however, this is probably attributable to the difference in baseline values.

Table 4. Pharmacokinetic parameters in both patients with RA and patients with osteoporosis following multiple subcutaneous administration of denosumab

Disease to be treated	Dosage regimen	Time point	AUC_{183day} (ng·day/mL)	C_{max} (ng/mL)	t_{max} (day)
Patients with RA (Study AMG162-D-J201)	60 mg Q6M (N = 84-85)	After the first dose	230,000 ± 110,000 [60,300, 724,000]	4350 ± 1500 [1440, 8780]	28 [19, 41]
	60 mg Q6M (N = 78-81)	After the second dose	251,000 ± 123,000 [34,000, 746,000]	4660 ± 1550 [1010, 9470]	28 [16, 56]
Patients with osteoporosis (Study 20050172)	60 mg Q6M (N = 54)	After the first dose	317,000 ± 120,000 [52,900, 635,000]	5720 ± 1530 [1870, 10,300]	30 [24, 41]
	60 mg Q6M (N = 49-51)	After the second dose	310,000 ± 125,000 [83,400, 581,000]	5780 ± 1770 [1500, 10,400]	34 [16, 44]

Mean ± standard deviation [range]; median [range] for t_{max}

Table 5. Change in serum CTX-I concentrations in both patients with RA and patients with osteoporosis following multiple subcutaneous administration of denosumab

Disease to be treated	Dosage regimen	Index	Baseline	Month 1	Month 3	Month 6 (trough)	Month 12 (trough)
Patients with RA (Study AMG162-D-J201)	60 mg Q6M (N = 72-85)	Serum concentration (ng/mL)	0.41 ± 0.25	0.14 ± 0.02	0.14 ± 0.06	0.21 ± 0.13	0.24 ± 0.18
		Change from baseline (%)	–	−52.77 ± 27.05	−51.29 ± 27.05	−36.30 ± 32.44	−46.30 ± 32.44
Patients with osteoporosis (Study 20050172)	60 mg Q6M (N = 49-54)	Serum concentration (ng/mL)	0.52 ± 0.20	0.05 ± 0.00	0.05 ± 0.00	0.11 ± 0.08	0.16 ± 0.13
		Change from baseline (%)	–	−88.43 ± 8.76	−87.90 ± 9.34	−83.29 ± 33.84	−57.00 ± 66.55

Mean ± standard deviation

PMDA's view:

As in the applicant's explanation, there were no clear differences between the pharmacokinetics in patients with RA and those in patients with osteoporosis.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Evaluation data submitted by the applicant included data from Japanese clinical studies conducted in patients with RA (CTD 5.3.5.1-1 and 5.3.5.1-2).

7.1 Phase II study (CTD 5.3.5.1-2, Study AMG162-D-J201 [[redacted] to [redacted]])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted in patients with RA to assess the efficacy and safety of denosumab (target sample size, 320 subjects [80 per group]). Eligible patients had to meet all the following criteria in (a), (b), and (c):

(a) having at least 6 swollen joints;

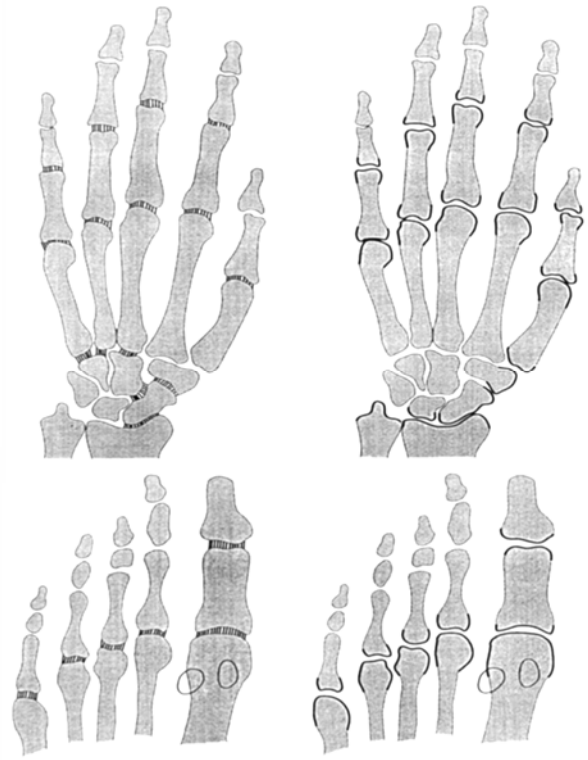
(b) showing bone erosions on radiographs, or meeting the following conditions:
C-reactive protein (CRP) ≥1.0 mg/dL, or erythrocyte sedimentation rate (ESR) ≥28 mm/h, and also positive for anti-citrullinated peptide antibodies, or rheumatoid factor ≥20 IU/mL; and

(c) Undergoing methotrexate (MTX) treatment for ≥8 weeks, and receiving a stable dose of MTX for 4 weeks prior to administration of the study drug.

Subjects were to receive denosumab 60 mg or placebo Q6M, Q3M, or Q2M as a subcutaneous injection for 12 months in combination with MTX. Further, native vitamin D ≥400 IU/day and calcium ≥600 mg/day were administered to all the subjects receiving the study drug to reduce hypocalcaemia induced by denosumab.

Randomization was stratified by adrenocortical hormone agent (used vs. not used) and rheumatoid factor (positive vs. negative). Of 350 randomized subjects, 346 subjects who received the study drug (86 subjects in the Q6M group, 85 subjects in the Q3M group, 85 subjects in the Q2M group, and 88 subjects in the placebo group) were included in the safety analysis set. Of the 346 subjects, 6 subjects with no baseline or post-baseline radiographic data were excluded from analysis, and the remaining 340 subjects (85 subjects in the Q6M group, 82 subjects in the Q3M group, 88 subjects in the Q2M group, and 88 subjects in the placebo group) were included in the full analysis set (FAS), which was used as the efficacy analysis set. Treatment discontinuation occurred in 8 of 87subjects (9.2%) in the Q6M group, 13 of 87 subjects (14.9%) in the Q3M group, 8 of 88 subjects (9.1%) in the Q2M group, and 6 of 88 subjects (6.8%) in the placebo group. The main reasons for treatment discontinuation included disease progression (3 subjects in the Q6M group, 4 subjects in the Q3M group, 3 subjects in the Q2M group, and 1 subject in the placebo group).

The primary efficacy endpoint for the study was the change in the total score for radiographic bone erosions in the joints of the hands and feet. Radiographic bone erosions were scored in 32 joints of the hands and 12 joints of the feet, and the bone erosion score was obtained by summing the score of each joint (Figure 1). Table 6 shows the change from baseline in bone erosion score at Month 12, which served as the primary analysis. The pairwise comparisons of each denosumab dose versus placebo showed a statistically significant difference. Table 6 also shows the change from baseline in the joint space narrowing (JSN) score (Figure 1). The JSN score was obtained by scoring radiographic joint space narrowing, ankylosis, and dislocation in 30 joints of the hands and 12 joints of the feet, and summing the score of each joint. Figure 2 shows the cumulative distribution of changes from baseline in the bone erosion score and JSN score at Month 12.



Joints assessed for JSN (shown in vertical lines); joints assessed for erosion (shown in bold lines)

■ Bone erosion score
0 = No erosion
1 = Small erosion
2 = Less than half the joint space
3 to 4 = Half the joint space or more
5 = Complete collapse
* Hands: 5 points per joint at maximum, 160 points in total
* Feet: 10 points per joint at maximum, 120 points in total

■ Joint space narrowing (JSN) score
0 = Normal
1 = Focal or slight
2 = ≥50% of the original joint space is remaining
3 = <50% of the joint space is remaining, subluxation
4 = Disappearance of joint space, complete luxation
* Hands: 4 points per joint at maximum, 120 points in total
* Feet: 4 points per joint at maximum; 48 points in total

■ Modified total Sharp score
Bone erosion score + JSN score

Based on the radiographic findings, bone erosion (32 joints of the hands and 12 joints of the feet) and joint space narrowing (30 joints of the hands and 12 joints of the feet) were scored, and points for each score are summed (adapted from Baillieres, *Clin Rheumatol*. 1996;10:435-53).

Figure 1. Calculation of bone erosion score, JSN score, and modified total Sharp score

Table 6. Changes from baseline in bone erosion score and JSN score at Month 12 (FAS, linear interpolation[a])

	Q6M (N = 85)	Q3M (N = 82)	Q2M (N = 85)	Placebo (N = 88)
Bone erosion score				
Baseline	6.39 ± 7.77	5.95 ± 6.75	7.41 ± 8.68	6.61 ± 10.35
Month 12	6.66 ± 7.97	6.09 ± 6.78	7.50 ± 9.00	7.60 ±10.60
Change from baseline *p*-value[b]	0.27 ± 0.98 p = 0.0082	0.14 ± 0.53 p = 0.0036	0.09 ± 1.52 p<0.0001	0.99 ± 2.69
JSN score				
Baseline	5.04 ± 8.31	4.07 ± 8.06	5.33 ± 8.70	6.94 ± 14.29
Month 12	5.36 ± 8.51	4.42 ± 8.54	5.86 ± 9.49	7.48 ± 14.67
Change from baseline	0.32 ± 0.83	0.35 ± 1.40	0.53 ± 2.10	0.53 ± 1.70

Mean ± standard deviation

a) Missing values were interpolated by linear extrapolation using baseline and measurement values closest to Month 12.

b) Based on the Shirley-Williams's multiple comparison method (2.5% one-sided significance level), tests for null hypotheses were performed in the following order: (1) the change from baseline is the same in the placebo, Q6M, Q3M, and Q2M groups; (2) the change from baseline is the same in the placebo, Q6M, and Q3M groups; and (3) the change from baseline is the same in the placebo and Q6M groups.

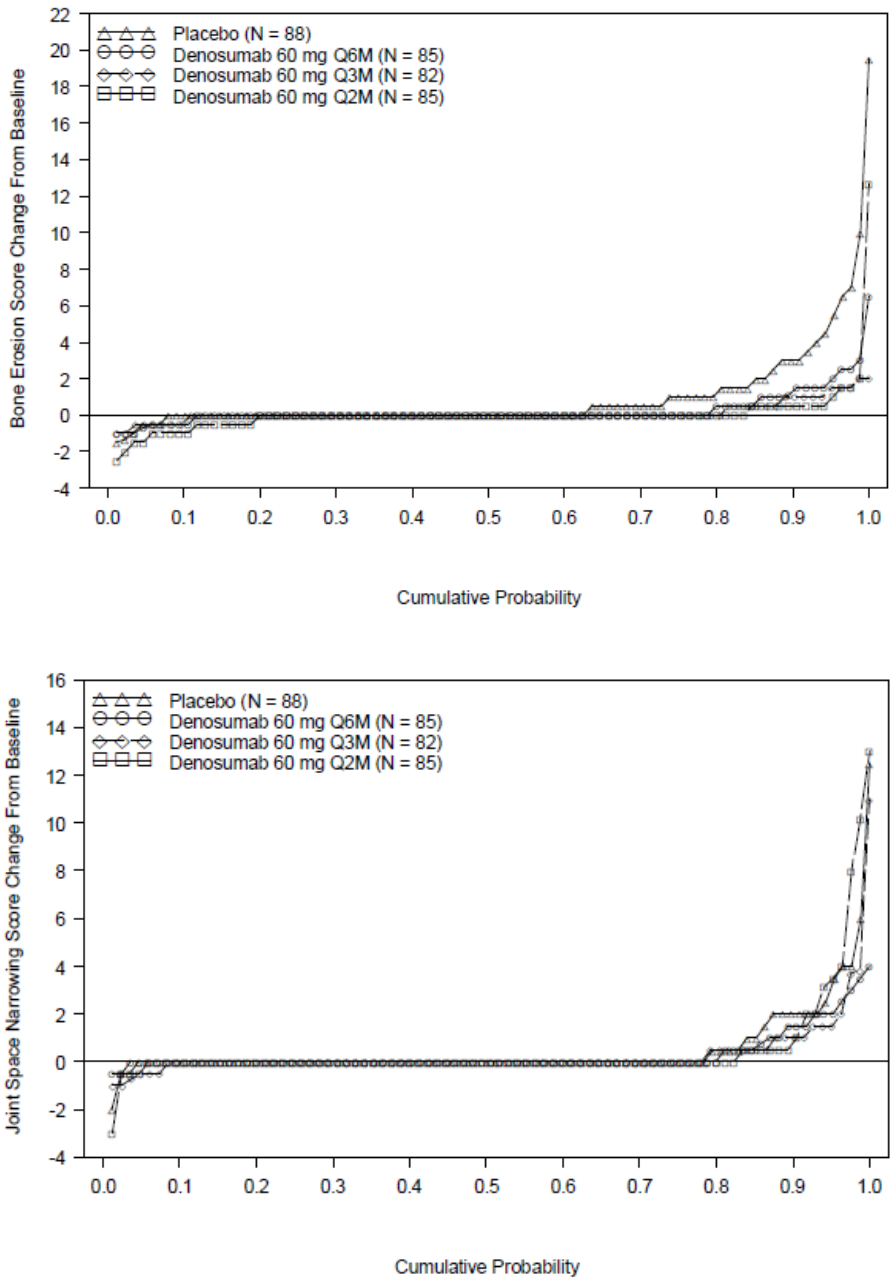


Figure 2. Cumulative distribution of the changes from baseline at Month 12 in bone erosion score (top) and JSN score (bottom) (FAS, linear interpolation)

Adverse events occurred in 69 of 86 subjects (80.2%) in the Q6M group, 65 of 85 subjects (76.5%) in the Q3M group, 82 of 87 subjects (94.3%) in the Q2M group, and 73 of 88 subjects (83.0%) in the placebo group. Table 7 shows major adverse events. No deaths occurred.

Serious adverse events occurred in 4 of 86 subjects (4.7%) in the Q6M group (intervertebral disc protrusion [1 subject], pneumonia bacterial [1], subcutaneous abscess [1], and tonsillitis [1]), 6 of 85 subjects (7.1%) in the Q3M group (bartholinitis [1], herpes zoster [1], cervical dysplasia [1], cerebral haemorrhage [1], gallbladder cancer [1], and colitis ischaemic/lymphoma [1]), 8 of 87 subjects (9.2%) in the Q2M group (prostate cancer [1], cellulitis [1], enteritis infectious [1], pyelonephritis/ureteral calculus [1], bronchopneumonia [1], mucosal ulceration/Douglas' abscess [1], blood pressure

increased/renal cell carcinoma [1], and oesophageal carcinoma/gastric cancer [1]), and 9 of 88 subjects (10.2%) in the placebo group (intervertebral disc protrusion [1], intervertebral disc protrusion/asthma [1], spinal compression fracture/cervical myelopathy [1], oesophageal carcinoma [1], pneumonia bacterial [1], angina pectoris [1], colonic polyp [1], gastroenteritis bacterial [1], and thrombotic cerebral infarction [1]). A causal relationship to the study drug could not be ruled out for intervertebral disc protrusion in the Q6M group, herpes zoster and cerebral haemorrhage in the Q3M group, and oesophageal carcinoma and colonic polyp in the placebo group, but the outcomes of these events were reported as either “resolved” or “resolving.”

Adverse events leading to treatment discontinuation occurred in 3 of 86 subjects (3.5%) in the Q6M group (dental caries [1], idiopathic thrombocytopenic purpura [1], and pneumonia bacterial [1]), and 5 of 85 subjects (5.9%) in the Q3M group (cerebral haemorrhage [1], gallbladder cancer [1], interstitial lung disease [1], loose tooth [1], and lymphoma [1]), 3 of 87 subjects (3.4%) in the Q2M group (oesophageal carcinoma [1], prostate cancer [1], and toothache [1]), and 3 of 88 subjects (3.4%) in the placebo group (dental caries/periodontitis/periodontal disease [1], periodontitis [1], and asthma [1]).

Adverse drug reactions occurred in 16 of 86 subjects (18.6%) in the Q6M group, 12 of 85 subjects (14.1%) in the Q3M group, 18 of 87 subjects (20.7%) in the Q2M group, and 16 of 88 subjects (18.2%) in the placebo group. The most common adverse drug reaction was hepatic function abnormal (1 subject in the Q3M group, 6 subjects in the Q2M group, and 3 subjects in the placebo group).

Table 7. Adverse events occurring in ≥3% of subjects in any of the denosumab groups (Safety analysis set)

Adverse event	Q6M (N = 86)	Q3M (N = 85)	Q2M (N = 87)	Placebo (N = 88)
Nasopharyngitis	21 (24.4)	20 (23.5)	28 (32.2)	23 (26.1)
Hepatic function abnormal	7 (8.1)	9 (10.6)	17 (19.5)	14 (15.9)
Pharyngitis	7 (8.1)	4 (4.7)	5 (5.7)	7 (8.0)
Stomatitis	6 (7.0)	5 (5.9)	9 (10.3)	5 (5.7)
Back pain	5 (5.8)	3 (3.5)	6 (6.9)	2 (2.3)
Constipation	5 (5.8)	1 (1.2)	3 (3.4)	3 (3.4)
Upper respiratory tract inflammation	4 (4.7)	10 (11.8)	6 (6.9)	5 (5.7)
Nausea	4 (4.7)	2 (2.4)	2 (2.3)	3 (3.4)
Dental caries	3 (3.5)	5 (5.9)	4 (4.6)	3 (3.4)
Insomnia	3 (3.5)	2 (2.4)	1 (1.1)	3 (3.4)
Contusion	3 (3.5)	0	2 (2.3)	1 (1.1)
Bronchitis	2 (2.3)	5 (5.9)	5 (5.7)	3 (3.4)
Eczema	2 (2.3)	3 (3.5)	6 (6.9)	2 (2.3)
White blood cell count decreased	2 (2.3)	3 (3.5)	3 (3.4)	2 (2.3)
Device breakage	2 (2.3)	1 (1.2)	3 (3.4)	0
Conjunctivitis allergic	2 (2.3)	0	4 (4.6)	2 (2.3)
Dizziness	2 (2.3)	0	3 (3.4)	0
Periodontitis	1 (1.2)	5 (5.9)	2 (2.3)	5 (5.7)
Herpes zoster	1 (1.2)	4 (4.7)	1 (1.1)	0
Gastrooesophageal reflux disease	1 (1.2)	4 (4.7)	0	2 (2.3)
Ligament sprain	1 (1.2)	3 (3.5)	0	3 (3.4)
Gastroenteritis	1 (1.2)	1 (1.2)	3 (3.4)	2 (2.3)
Gastritis	0	5 (5.9)	2 (2.3)	2 (2.3)
Eczema asteatotic	0	3 (3.5)	0	0
Alanine aminotransferase increased	0	2 (2.4)	3 (3.4)	2 (2.3)
Aspartate aminotransferase increased	0	2 (2.4)	3 (3.4)	2 (2.3)
Seasonal allergy	0	0	3 (3.4)	1 (1.1)

n (%)

7.2 Phase III study (CTD 5.3.5.1-1, Study AMG162-D-J301 [from October 2013 until the data cut-off of [redacted]])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted in patients with RA to assess the efficacy and safety of denosumab (target sample size, 642 subjects [214 per group]). Eligible patients had to meet all the following criteria in (a), (b), and (c):

(a) having at least 6 swollen joints;

(b) showing radiographic bone erosions, or meeting the following conditions:
CRP ≥1.0 mg/dL or ESR ≥28 mm/h, and also positive for anti-citrullinated peptide antibodies or positive for rheumatoid factor; and

(c) undergoing treatment with at least 1 disease-modifying anti-rheumatic drug (DMARD)[1)] for ≥8 weeks, and receiving a stable dose of DMARDs for 4 weeks prior to administration of the study drug.

1) The DMARDs include MTX, iguratimod, leflunomide, bucillamine, and salazosulfapyridine (biopharmaceuticals and tofacitinib are excluded).

Subjects were to receive denosumab 60 mg or placebo Q6M or Q3M as a subcutaneous injection for 12 months (double-blind period) to patients on DMARDs treatment, and thereafter, subjects were to continue to receive denosumab 60 mg Q6M or Q3M (extension treatment period).[2)] Further, native vitamin D ≥400 IU/day and calcium ≥600 mg/day were administered to all the subjects receiving the study drug to reduce hypocalcaemia induced by denosumab.

Randomization was stratified by adrenocorticosteroid (used vs. not used). Of 679 randomized subjects, 667 subjects who received the study drug (222 subjects in the Q6M group, 222 subjects in the Q3M group, and 223 subjects in the placebo group) were included in the safety analysis set. Of the 667 subjects, 13 subjects with no baseline or post-baseline radiographic data were excluded from analysis, and the remaining 654 subjects were included in the FAS, which was used as the efficacy analysis set. Treatment discontinuation occurred in 23 of 228 subjects (10.1%) in the Q6M group, 22 of 225 subjects (9.8%) in the Q3M group, and 15 of 226 subjects (6.6%) in the placebo group. The main reasons for treatment discontinuation included adverse events (9 subjects in the Q6M group, 2 subjects in the Q3M group, and 4 subjects in the placebo group). Among the subjects included in the safety analysis set of the double-blind period, 562 subjects who continued to receive denosumab in the extension treatment period (182 subjects in the Q6M/Q6M group, 187 subjects in the Q3M/Q3M group, 97 subjects in the placebo/Q6M group, and 96 subjects in the placebo/Q3M group) were included in the long-term safety analysis set.

The primary efficacy endpoint for the study was the modified total Sharp score (mTSS), which was the sum of the JSN and bone erosion scores. Change from baseline in mTSS at Month 12, the primary endpoint, is shown in Table 8. Pairwise comparisons between placebo and denosumab 60 mg Q6M or denosumab 60 mg Q3M showed a statistically significant difference, demonstrating the superiority of denosumab 60 mg Q6M and Q3M over placebo. Figure 3 shows the cumulative distribution of changes from baseline in TSS at Month 12. Table 9 shows the proportion of patients who had a change of ≤0 from baseline in the mTSS, bone erosion score, or JSN score at Month 12.

2) In the double-blind period, subjects were randomized to the following groups at a ratio of 1:1:2:2: the placebo/Q6M group (denosumab 60 mg Q6M, switched from placebo), the placebo/Q3M group (denosumab 60 mg Q3M, switched from placebo), the Q6M/Q6M group (continued treatment with denosumab 60 mg Q6M), and the Q3M/Q3M group (continued treatment with denosumab 60 mg Q3M).

Table 8. The mTSS, bone erosion score, and JSN score, and their changes from baseline (FAS; linear interpolation[a])

	Q6M (N = 217)		Q3M (N = 219)		Placebo (N = 218)	
	Score	Change	Score	Change	Score	Change
mTSS						
Baseline	15.92 ± 22.21	–	15.17 ± 18.97	–	13.14 ± 21.44	–
Month 6	16.54 ± 23.06	0.62 ± 2.66	15.65 ± 19.39	0.48 ± 1.79	14.06 ± 22.06	0.92 ± 2.33
Month 12	16.91 ± 23.47	0.99 ± 3.77 $P = 0.0235$[b), c)]	15.89 ± 19.65	0.72 ± 2.32 $P = 0.0055$[b), c)]	14.63 ± 22.49	1.49 ± 3.76
Bone erosion score						
Baseline	7.53 ± 10.11	–	7.16 ± 9.41	–	6.55 ± 10.58	–
Month 6	7.87 ± 10.37	0.34 ± 1.38	7.30 ± 9.53	0.13 ± 0.78	7.14 ± 11.06	0.58 ± 1.45
Month 12	8.04 ± 10.58	0.51 ± 2.15	7.38 ± 9.59	0.22 ± 0.95	7.53 ± 11.47	0.98 ± 2.48
JSN score						
Baseline	8.39 ± 13.82	–	8.01 ± 10.86	–	6.59 ± 11.94	–
Month 6	8.67 ± 14.36	0.28 ± 1.61	8.36 ± 11.16	0.35 ± 1.36	6.92 ± 12.15	0.33 ± 1.13
Month 12	8.87 ± 14.60	0.48 ± 2.08	8.51 ± 11.35	0.50 ± 1.76	7.10 ± 12.25	0.51 ± 1.72

Mean ± standard deviation

a) Missing values were interpolated by linear extrapolation using baseline and measurement values closest to Month 6 or 12.

b) The van Elteren stratified test was performed with the stratification factor, baseline status of adrenocorticosteroid use (used vs. not used).

c) Multiplicity adjustment was performed by a hierarchical procedure in the specified hierarchical order: comparison of placebo with Q3M and with Q6M.

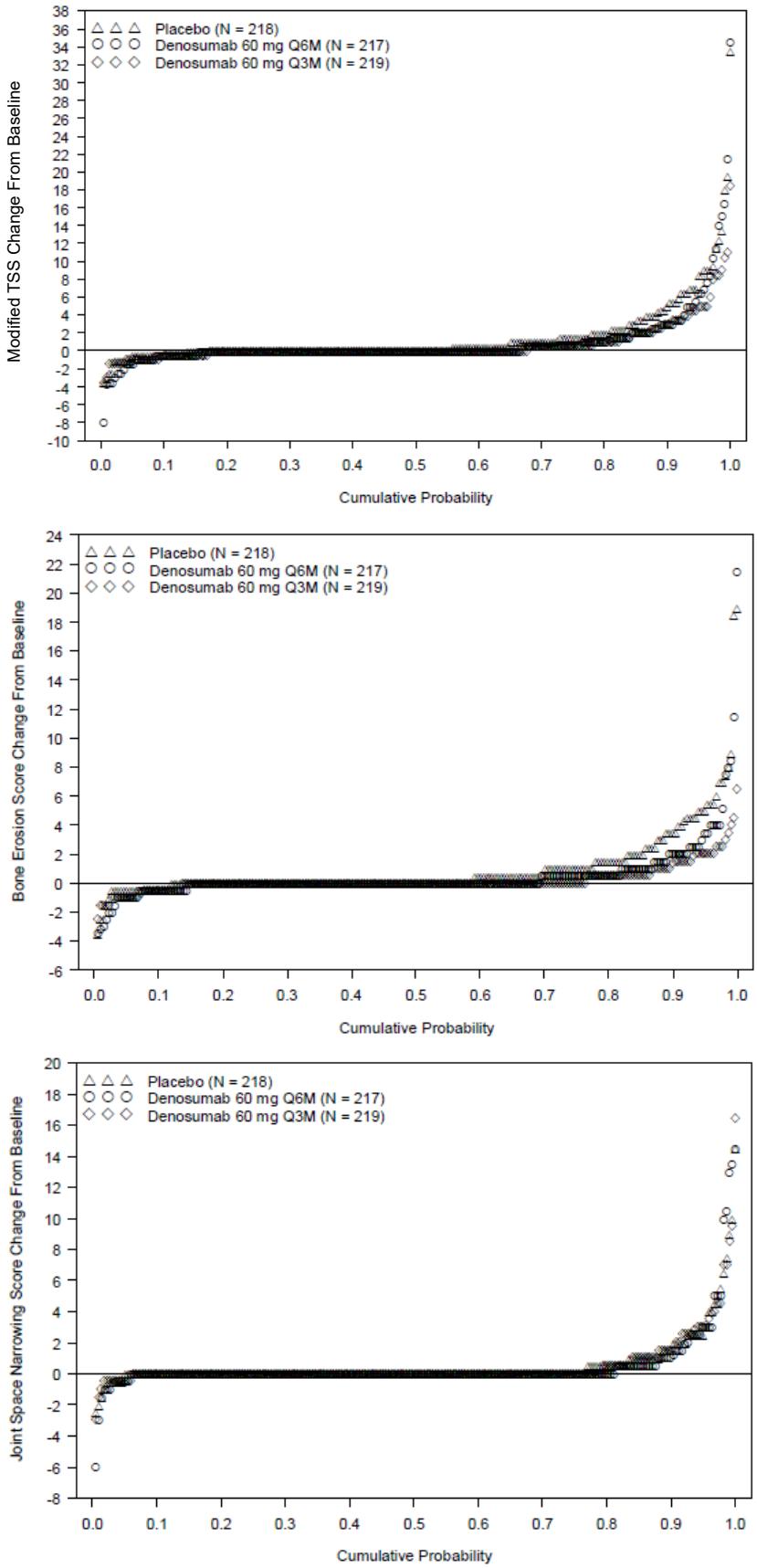


Figure 3. Cumulative distribution of the changes from baseline in the mTSS, bone erosion score, and JSN score at Month 12 (top, mTSS; middle, bone erosion score; and bottom, JSN score; FAS, linear interpolation)

Table 9. The proportion of patients who had a change of ≤0 from baseline in the mTSS, bone erosion score, or JSN score at Month 12 (FAS)

	Q6M	Q3M	Placebo
mTSS	66.4 (144/217)	67.6 (148/219)	55.5 (121/218)
Bone erosion score	69.1 (150/217)	76.3 (167/219)	58.7 (128/218)
JSN score	81.1 (176/216)	79.0 (173/219)	76.6 (167/218)

% (n/N)

During the double-blind period, adverse events occurred in 188 of 221 subjects (85.1%) in the Q6M group, 185 of 222 subjects (83.3%) in the Q3M group, 186 of 224 subjects (83.0%) in the placebo group. The major adverse events are shown in Table 10. A death occurred in the Q3M group (interstitial pneumonia), for which a causal relationship to the study drug could not be ruled out.

Non-fatal serious adverse events occurred in 19 of 221 subjects (8.6%) in the Q6M group (benign prostatic hyperplasia [1], abscess jaw [1], pyelonephritis acute/sepsis/acute kidney injury [1], tuberculosis [1], colon cancer/tumour invasion [1], gastric cancer/synovitis [1], renal cell carcinoma [1], breast cancer [1], diffuse large B-cell lymphoma/immune thrombocytopenic purpura [1], squamous cell carcinoma of lung [1], cerebral infarction [1], brain stem infarction [1], dizziness [1], intervertebral disc protrusion [1], spondylolisthesis [1], prostatitis [1], enterocolitis [1], calculus bladder/prerenal failure/benign prostatic hyperplasia [1], and interstitial lung disease [1]), 19 of 222 subjects (8.6%) in the Q3M group (arthritis bacterial [1], atypical mycobacterial infection [1], colon cancer [1], lymphoproliferative disorder/ventricular tachycardia [1], rectal cancer [1], cerebral infarction [1], transient ischaemic attack [1], lumbar spinal stenosis [1], osteoarthritis [1], inguinal hernia [1], spinal compression fracture [1], foot fracture [1], arrhythmia [1], cholecystitis acute [1], cholelithiasis [1], platelet count decreased [1], spinal muscular atrophy [1], device dislocation [1], and hypotension [1]), and 13 of 224 subjects (5.8%) in the placebo group (cellulitis [1], diverticulitis [1], colon cancer [1], intraductal proliferative breast lesion [1], lung neoplasm malignant [1], laceration/subarachnoid haemorrhage/subdural haematoma [1], large intestine polyp [1], ankle fracture [1], femoral neck fracture [1], muscle rupture [1], mass [1], sudden hearing loss [1], and dizziness [1]). A causal relationship to the study drug could not be ruled out for the following cases: brain stem infarction, abscess jaw, and squamous cell carcinoma of lung in the Q6M group; and lymphoproliferative disorder/ventricular tachycardia, platelet count decreased, and rectal cancer in the Q3M group, lung neoplasm malignant, diverticulitis, and sudden hearing loss in the placebo group. While the outcomes for the cases of squamous cell carcinoma of lung and rectal cancer were reported as “not resolved,” all of the remaining cases were reported as either “resolved” or “resolving.”

Adverse events leading to treatment discontinuation occurred in 10 of 221 subjects (4.5%) in the Q6M group, 9 of 222 subjects (4.1%) in the Q3M group, and 8 of 224 subjects (3.6%) in the placebo group. Adverse events occurring in ≥2 subjects in any of the denosumab groups were dental caries (1 subject each in the Q6M, Q3M, and placebo groups), interstitial pneumonia (1 subject each in the Q6M and Q3M groups), and rheumatoid arthritis (2 subjects in the Q3M group).

Adverse drug reactions occurred in 39 of 221 subjects (17.6%) in the Q6M group, 37 of 222 subjects (16.7%) in the Q3M group, and 38 of 224 subjects (17.0%) in the placebo group, and the most frequently occurring adverse drug reaction was chronic gastritis (6 subjects in the Q6M group and 1 subject in the Q3M group).

Table 10. Adverse events occurring in ≥3% of subjects in any of the denosumab groups (safety analysis set; double-blind period)

Adverse event	Q6M (N = 221)	Q3M (N = 222)	Placebo (N = 224)
Nasopharyngitis	81 (36.7)	69 (31.1)	73 (32.6)
Stomatitis	22 (10.0)	27 (12.2)	13 (5.8)
Upper respiratory tract inflammation	17 (7.7)	8 (3.6)	9 (4.0)
Hepatic function abnormal	14 (6.3)	13 (5.9)	20 (8.9)
Pharyngitis	13 (5.9)	16 (7.2)	16 (7.1)
Dental caries	12 (5.4)	7 (3.2)	9 (4.0)
Gastroenteritis	10 (4.5)	4 (1.8)	8 (3.6)
Eczema	9 (4.1)	5 (2.3)	4 (1.8)
Influenza	8 (3.6)	10 (4.5)	12 (5.4)
Bronchitis	8 (3.6)	7 (3.2)	10 (4.5)
Cystitis	8 (3.6)	7 (3.2)	5 (2.2)
Diarrhoea	8 (3.6)	4 (1.8)	8 (3.6)
Chronic gastritis	8 (3.6)	3 (1.4)	1 (0.4)
Constipation	8 (3.6)	2 (0.9)	3 (1.3)
Rash	7 (3.2)	5 (2.3)	8 (3.6)
Dizziness	7 (3.2)	4 (1.8)	3 (1.3)
Abdominal pain upper	7 (3.2)	1 (0.5)	0
Oral herpes	6 (2.7)	8 (3.6)	4 (1.8)
Back pain	5 (2.3)	12 (5.4)	7 (3.1)
Contusion	4 (1.8)	8 (3.6)	7 (3.1)
Gastrooesophageal reflux disease	3 (1.4)	8 (3.6)	2 (0.9)
White blood cell count decreased	3 (1.4)	7 (3.2)	7 (3.1)

n (%)

Hypocalcaemia-related events occurred in 2 of 221 subjects (0.9%) in the Q6M group (hypocalcaemia [1] and blood calcium decreased [1]), 3 of 222 subjects (1.4%) in the Q3M group (blood calcium decreased [3]), and 3 of 224 subjects (1.3%) in the placebo group (blood calcium decreased [3]). While a causal relationship to the study drug could not be ruled out for these cases excluding 2 subjects in the placebo group, these events were mild in severity.

The incidence of adverse events in the overall period including the extension treatment period was 92.8% (205 of 221 subjects) in the Q6M/Q6M group, 89.6% (199 of 222 subjects) in the Q3M/Q3M group. The major adverse events are shown in Table 11. During the extension treatment period, another death occurred in the Q3M/Q3M group (pneumocystis jirovecii pneumonia); however, a causal relationship to the study drug was ruled out for this case.

During the extension treatment period, serious adverse events occurred in 5 of 105 subjects (4.8%) in the placebo/Q6M group (pneumonia [1], back pain [1], fracture nonunion [1], acute myocardial infarction [1], tendon rupture/postoperative wound infection [1]), 8 of 103 subjects (7.8%) in the

placebo/Q3M group (bile duct stone [2], pneumonia [1], pneumocystis jirovecii pneumonia [1], lumbar spinal stenosis [1], histiocytosis haematophagic [1], large intestine polyp [1], and dizziness postural [1]), 13 of 199 subjects (6.5%) in the Q6M/Q6M group (laceration [1], large intestine polyp [1], anal prolapse [1], Guillain-Barre syndrome [1], loss of consciousness [1], herpes zoster [1], cataract [1], asthma [1], cardiac arrest [1], prostate cancer [1], iron deficiency anaemia [1], Meniere's disease [1], and musculoskeletal stiffness [1]), 19 of 200 subjects (9.5%) in the Q3M/Q3M group (pneumonia [2], enterocolitis [2], interstitial lung disease [2], osteomyelitis [1], acute myocardial infarction/diverticulitis/large intestine polyp/angina pectoris [1], cataract [1], bronchitis [1], postrenal failure [1], Parkinsonism/cholecystitis [1], intestinal obstruction [1], humerus fracture [1], large intestine polyp [1], tendon rupture [1], clavicle fracture [1], ureterolithiasis [1], and gastric cancer [1]). A causal relationship to the study drug could not be ruled out for the following cases: Guillain-Barre syndrome and loss of consciousness in the Q6M/Q6M group; osteomyelitis, acute myocardial infarction/diverticulitis/large intestine polyp/angina pectoris, pneumonia, large intestine polyp, ureterolithiasis, and gastric cancer in the Q3M/Q3M group; acute myocardial infarction, pneumonia, and fracture nonunion in the placebo/Q6M group; and pneumonia in the placebo/Q3M group. However, the outcomes of these events were reported as either "resolved" or "resolving."

The incidence of adverse drug reactions in the overall period including the extension treatment period was 25.8% (57 of 221 subjects) in the Q6M/Q6M group, and 25.2% (56 of 222 subjects) in the Q3M/Q3M group, and commonly reported events included chronic gastritis (8 subjects in the Q6M/Q6M group and 3 subjects in the Q3M/Q3M group), nasopharyngitis (4 subjects in the Q6M/Q6M group and 3 subjects in the Q3M/Q3M group), and blood calcium decreased (3 subjects in the Q6M/Q6M group and 3 subjects in the Q3M/Q3M group).

Table 11. Adverse events occurring in ≥5% of subjects in either of the denosumab groups (safety analysis set, overall period including the extension treatment period)

Adverse event	Q6M/Q6M (N = 221)	Q3M/Q3M (N = 222)
Nasopharyngitis	107 (48.4)	95 (42.8)
Stomatitis	31 (14.0)	35 (15.8)
Upper respiratory tract inflammation	31 (14.0)	14 (6.3)
Hepatic function abnormal	19 (8.6)	18 (8.1)
Pharyngitis	20 (9.0)	23 (10.4)
Dental caries	17 (7.7)	17 (7.7)
Gastroenteritis	19 (8.6)	8 (3.6)
Eczema	16 (7.2)	12 (5.4)
Constipation	16 (7.2)	6 (2.7)
Back pain	12 (5.4)	17 (7.7)
Bronchitis	14 (6.3)	14 (6.3)
Influenza	15 (6.8)	15 (6.8)
Cystitis	11 (5.0)	7 (3.2)
Chronic gastritis	12 (5.4)	6 (2.7)
Dizziness	11 (5.0)	6 (2.7)
Contusion	13 (5.9)	15 (6.8)
White blood cell count decreased	11 (5.0)	9 (4.1)
Oral herpes	6 (2.7)	13 (5.9)
Gastrooesophageal reflux disease	6 (2.7)	12 (5.4)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the efficacy of denosumab:

The primary endpoint for the phase III study (Study J301) was the change from baseline in mTSS (the sum of the bone erosion and JSN scores) which was selected based on the "Guidelines for Clinical Evaluation of Antirheumatic Drugs" (Notification No. 0217001 dated on February 17, 2006, issued from the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau, MHLW) and taking the pharmacological action of denosumab into account. This primary endpoint was expected to demonstrate the preventive effect of denosumab on structural joint damage. In Study J301, treatment response was evaluated according to the American College of Rheumatology (ACR) response criteria, an outcome measure for RA joint symptoms. As assumed from the pharmacological action of denosumab, no difference was observed between denosumab and placebo.

In Study J301, the results of pairwise comparisons of the changes from baseline in mTSS at Month 12, the primary endpoint, between denosumab 60 mg Q6M and placebo and between denosumab 60 mg Q3Mand placebo (Table 8) showed a statistically significant difference, demonstrating the superiority of denosumab over placebo. The changes from baseline in bone erosion score (the secondary endpoint) in both denosumab groups tended to differ from that of the placebo group, but the changes from baseline in JSN score did not tend to differ between the denosumab groups and the placebo group (Table 8). The phase II study (Study J201) showed a similar trend (Table 6), suggesting that denosumab would not inhibit the worsening in JSN score. Based on the above, the applicant concluded that the observed effect

of denosumab on the change from baseline in mTSS was primarily attributable to denosumab-related reduction in bone erosion score.

Published literature has reported the relationship between the bone erosion score and the Health Assessment Questionnaire (HAQ) score,[3)] a measure for physical function (*Ann Rheum Dis.* 2013;72:870-4, *Rheumatology.* 2015;54:83-90). This suggests that inhibition of the worsening in bone erosion score contributes to maintaining the physical function of patients with RA; therefore, inhibition of worsening in the bone erosion score is clinically meaningful to a certain extent.

Further, RA patients with advanced bone destruction in the joints may need arthroplasty or other forms of surgical treatment; therefore, inhibition of bone destruction may contribute to reducing the need for surgical treatment.

PMDA's view:
The applicant's explanation (the change from baseline in mTSS, which demonstrated the superiority of denosumab over placebo in Study J301, was attributable to denosumab-related reduction in bone erosion score) is reasonable. The results from the clinical studies in patients with RA on DMARDs including MTX has demonstrated that denosumab inhibits progression of bone destruction in the joints when used in combination with existing RA therapy. Therefore, denosumab can be expected to be effective in the treatment of patients with RA when used in combination with existing RA therapy. Furthermore, denosumab can inhibit the progression of bone destruction in the joints of the patients with RA, thereby contributing to maintaining the physical function of patients with RA; therefore, the applicant's explanation (inhibition of worsening in the bone erosion score is clinically meaningful) is understandable.

In the clinical studies of denosumab, there was no evidence showing improvement in RA joint symptoms, as measured by the ACR20 criteria etc. or inhibition of worsening in JSN score which represents the degree of RA-related destruction of cartilages, tendons, and other soft tissues; therefore, this should be kept in mind when studying the indication of denosumab [see Section 7.R.4].

The PMDA's conclusion above will be discussed in the Expert Discussion.

7.R.2 Safety

7.R.2.1 Safety in patients with RA

The applicant's explanation about the safety of denosumab:
Table 12 shows the incidence of adverse events in the Japanese clinical studies in patients with RA. No clear difference was observed between the placebo and denosumab groups.

3) An indicator which was obtained by summing scored daily activity questions.

Table 12. Summary of adverse events in Studies J201 and J301

	Study J301 (double-blind period)			Study J201			
	Q6M (N = 221)	Q3M (N = 222)	Placebo (N = 224)	Q6M (N = 86)	Q3M (N = 85)	Q2M (N = 87)	Placebo (N = 88)
Adverse events	188 (85.1)	185 (83.3)	186 (83.0)	69 (80.2)	65 (76.5)	82 (94.3)	73 (83.0)
Adverse drug reactions	39 (17.6)	37 (16.7)	38 (17.0)	16 (18.6)	12 (14.1)	18 (20.7)	16 (18.2)
Deaths	0	1 (0.5)	0	0	0	0	0
Serious adverse events	19 (8.6)	19 (8.6)	13 (5.8)	4 (4.7)	6 (7.1)	8 (9.2)	9 (10.2)
Adverse events leading to study discontinuation	9 (4.1)	2 (0.9)	4 (1.8)	2 (2.3)	4 (4.7)	2 (2.3)	2 (2.3)
Adverse events leading to treatment discontinuation	10 (4.5)	9 (4.1)	8 (3.6)	3 (3.5)	5 (5.9)	3 (3.4)	3 (3.4)

n (%)

Three subjects died during Study J301, and the cause of death was interstitial pneumonia in 2 subjects (1 subject in the Q3M group [double-blind period], and 1 subject in the Q6M/Q6M group [after the study discontinuation]), and pneumocystis jirovecii pneumonia in 1 subject (Q3M/Q3M group [extension treatment period]). A causal relationship to denosumab could not be ruled out for the case of interstitial pneumonia reported in the Q3M group during the double-blind period.

Table 13 shows the incidence of adverse events in the Japanese clinical studies in patients with RA or osteoporosis. While hepatic function abnormal and stomatitis occurred more frequently in patients with RA than in patients with osteoporosis, there was no clear difference in the incidence of hepatic function abnormal between the placebo and denosumab groups [see Section 7.2]; therefore, the higher incidence of hepatic function abnormal was attributed to the effect of concomitant drugs etc. Stomatitis occurred more frequently in the denosumab group than in the placebo group [see Section 7.2], but there were only 4 cases for which a causal relationship to the study drug could not be ruled out. All the cases were mild in severity. Furthermore, other events that tended to occur at a higher incidence in patients with RA are all known to occur in patients with osteoporosis; therefore, no additional measures will be necessary.

Table 13. Incidence of adverse events in patients with RA or osteoporosis

	RA[a)]		Osteoporosis[b)]
	60 mg Q6M (N = 221)	60 mg Q3M (N = 222)	Denosumab pooled analysis group (N = 633)
All adverse events (n [%])	213 (96.4)	210 (94.6)	593 (93.7)
Serious adverse events (n [%])	31 (14.0)	33 (14.9)	78 (12.3)
Exposure person-year	399.3	404.5	1035.9
Major adverse events (n [incidence per 100 person-year])			
Nasopharyngitis	248 (62.1)	217 (53.6)	515 (49.7)
Stomatitis	66 (16.5)	64 (15.8)	46 (4.4)
Upper respiratory tract inflammation	43 (10.8)	18 (4.4)	60 (5.8)
Bronchitis	26 (6.5)	15 (3.7)	19 (1.8)
Hepatic function abnormal	25 (6.3)	23 (5.7)	10 (1.0)
Dental caries	24 (6.0)	17 (4.2)	88 (8.5)
Pharyngitis	22 (5.5)	34 (8.4)	36 (3.5)
Gastroenteritis	20 (5.0)	8 (2.0)	30 (2.9)

a) Results of Study AMG162-D-J301 in patients with RA including the results of the extension treatment period.
b) A pooled analysis of denosumab 14 mg Q6M, 60 mg Q6M, and 100 mg Q6M in Study AMG162-A-J301 conducted in patients with osteoporosis.

On the basis of the results of Studies J201 and J301 etc., PMDA concluded that the safety of denosumab in patients with RA is manageable, provided precautionary statements similar to those for patients with osteoporosis are included in the package insert.

Adverse events of interest associated with denosumab are discussed in the following sections.

7.R.2.2 Hypocalcaemia

The applicant's explanation about the risk of hypocalcaemia associated with the use of denosumab:
The pooled analysis of data from the 2 Japanese studies in patients with RA showed that the incidence of hypocalcaemia-related adverse events[4)] was 0.7% (2 of 307 subjects) in the Q6M group, 1.3% (4 of 307 subjects) in the Q3M group, and 1.0% (3 of 312 subjects) in the placebo group. There was no trend towards increased incidence in the denosumab groups compared with the placebo group. All the events were mild in severity. The incidence was not greatly different from the incidence (0.5% [3 of 633 subjects]) in the clinical studies in patients with osteoporosis (Studies AMG162-A-J301 and 20050172).

As shown in Figure 4, there were denosumab-related decreases in albumin-corrected serum calcium levels in the denosumab groups. Subsequently, the values tended to return to the baseline levels. While the serum calcium levels in the Q6M group returned to the baseline level at Month 6, the serum calcium levels in the Q3M group remained below the baseline level throughout the treatment period.

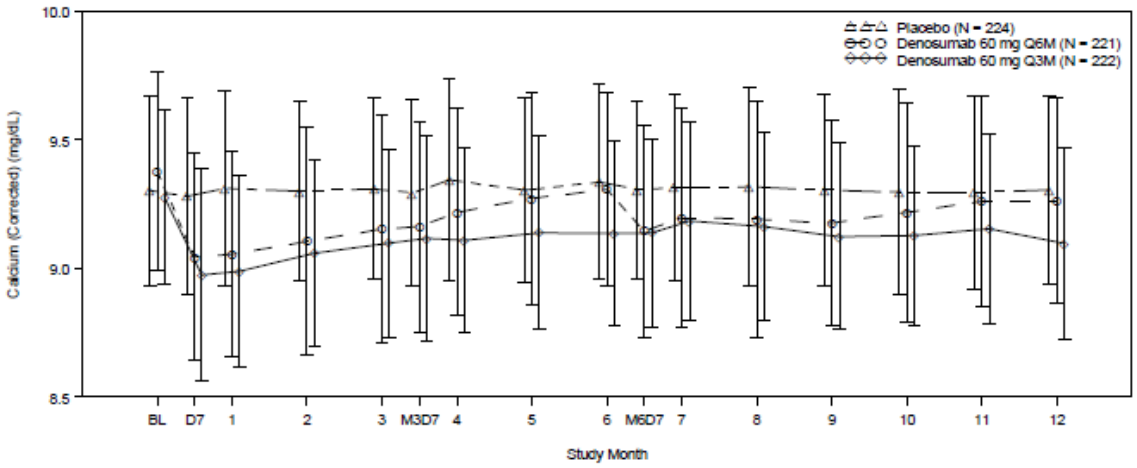


Figure 4. The time-course of albumin-corrected serum calcium levels in Study J301 (Mean ± standard deviation)

An analysis of post-marketing safety data from patients with osteoporosis in Japan revealed 65 cases of serious hypocalcaemia. It has been confirmed that 39 patients reporting serious hypocalcaemia had severe renal impairment (CLcr <30 mL/min or serum creatinine ≥3 mg/mL). The interim analysis of a specified use-results survey in patients with osteoporosis showed that the incidence of hypocalcaemia was 1.6% (3 of 194 subjects) in the group of patients with normal renal function and 7.6% (19 of 249

4) Defined as adjusted calcium decreased, blood calcium decreased, calcium deficiency, calcium ionised decreased, Chvostek's sign, hypocalcaemia, hypocalcaemic seizure, and Trousseau's sign.

subjects) in the group of patients with severe renal impairment, indicating a trend toward an increase in incidence with increasing severity of renal impairment.

The results of the clinical studies showed no trend towards increased risk of hypocalcaemia in patients with RA compared with patients with osteoporosis. However, given that post-marketing safety data from patients with osteoporosis have indicated that serious hypocalcaemia was reported in patients with severe renal impairment, vigilance is required due to the risk of developing hypocalcaemia when denosumab is administered in RA patients with severe renal impairment. In addition, based on the time-course of albumin-corrected serum calcium levels, the risk of hypocalcaemia is potentially higher for the regimen of denosumab 60 mg every 3 months than the regimen of denosumab 60 mg every 6 months.

Further, fatal cases due to serious hypocalcaemia were reported in the post-marketing period for Ranmark Subcutaneous Injection 120 mg. As a consequence, a "Dear Healthcare Professional Letter of Rapid Safety Communication" was issued in September 2012, and the package insert was revised to add a warning regarding the risk of serious hypocalcaemia. Accordingly, the package insert of Pralia Subcutaneous Injection 60 mg Syringe was revised to add "patients with hypocalcaemia" to the Contraindication section and "patients with severe renal impairment" to the Careful Administration section. In addition, the following precautionary statements were added: (1) serum calcium concentrations should be determined on a regular basis; (2) calcium and vitamin D should be supplemented unless albumin-corrected serum calcium levels are high; (3) medical care should be given to a patient who is experiencing hypocalcaemia-related symptoms (e.g., seizure, numbness, and tetany). The package insert will advise that patients with RA on denosumab be monitored for the risk of hypocalcaemia in a similar manner to the approved indication.

PMDA's view:
The clinical data submitted do not suggest a trend towards increased risk of hypocalcaemia in patients with RA compared with patients with osteoporosis. However, given that post-marketing safety data in patients with osteoporosis have indicated that serious hypocalcaemia was reported in patients with severe renal impairment, and that the proportion of RA patients with renal impairment is higher than that of osteoporosis patients with renal impairment (*Rheumatology.* 2008;47:350-4), the incidence of hypocalcaemia in patients with RA may increase after marketing approval. Therefore, the applicant should gather information regarding the risk of hypocalcaemia associated with the use of denosumab (including data on relationship with supplementation of calcium and vitamin D). The appropriateness of the measures including advice on the risk of hypocalcaemia associated with the use of denosumab will be determined based on the discussions in the Expert Discussion.

7.R.2.3 Osteonecrosis of the jaw

The applicant's explanation about the incidence of osteonecrosis of the jaw associated with the use of denosumab:
In Study J301, a non-serious case of osteonecrosis of the jaw occurred in 1 patient in the denosumab

Q3M/Q3M group who had undergone tooth extraction after study discontinuation. According to analysis of the post-marketing safety data collected in Japan, serious osteonecrosis of the jaw was reported in 15 patients with osteoporosis. Of the 15 patients, 9 were confirmed to have risk factors including invasive dental treatment and poor oral hygiene. Currently, osteonecrosis of the jaw is listed in the "Clinically Significant Adverse Reaction" section of the package insert, and methods to prevent osteonecrosis of the jaw are included in the "Important Precautions" section. The package insert will advise that patients with RA on denosumab be monitored for the risk of osteonecrosis of the jaw in a similar manner to the approved indication, so as to prevent osteonecrosis of the jaw from occurring or progressing to a more severe state.

PMDA's view:
The clinical data submitted do not suggest a trend towards increased risk of osteonecrosis of the jaw in patients with RA compared with patients with osteoporosis. However, due to the limited number of patients examined in clinical studies, the risk of osteonecrosis of the jaw is difficult to evaluate based on the submitted data. Given that RA has been reported to be a risk factor for osteonecrosis of the jaw (*Oral Dis*. 2016;22:543-8), the applicant should gather post-market information regarding the occurrence of osteonecrosis of the jaw.

7.R.2.4 Interstitial pneumonia

The applicant's explanation:
Two deaths[5)] were reported in Study J301. Both subjects had developed interstitial pneumonia before starting the denosumab treatment. RA-associated interstitial pneumonia worsened in one of the 2 subjects on Day 228, and re-exacerbation of interstitial pneumonia occurred in the other subject on Day 424. A causal relationship between the event and denosumab was ruled out for one of these subjects. Although a causal relationship between the event and denosumab could not be ruled out for the other subject, interstitial pneumonia may be attributable to exacerbation of the underlying condition. Denosumab treatment is unlikely to have led to the development of interstitial pneumonia.

Analysis of post-marketing safety data from patients with osteoporosis in Japan showed that serious interstitial pneumonia-related events were reported in 4 patients (interstitial lung disease, pneumonitis, or lung disorder). These patients included RA patients who had concurrent idiopathic pulmonary fibrosis etc., and patients who developed RA as a complication of another primary disease and used anti-rheumatic drugs. There was no evidence suggesting any relationship between denosumab and interstitial pneumonia. Also, the data from non-clinical studies of denosumab have not indicated toxicity to lung tissue or any effect on the immune system, and therefore, denosumab is unlikely to cause or exacerbate interstitial pneumonia. Based on the above, no data so far have suggested the existence of a clear relationship between denosumab and interstitial pneumonia.

5) One subject in the Q3M group died during the double-blind period, and another subject in the Q6M/Q6M group died after treatment discontinuation.

PMDA's view:

Patients with RA often develop interstitial pneumonia. No data so far have suggested a clear relationship between denosumab and interstitial pneumonia. However, given that fatal cases were reported in the clinical study and that reports of interstitial pneumonia have been accumulated after marketing approval of denosumab for the treatment of osteoporosis, investigation of the risk of interstitial pneumonia associated with the use of denosumab should be continued in the post-marketing setting.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of denosumab:

The Japanese guidelines for the management of RA recommend that treatment with DMARDs including MTX should be started from the early stage of RA; and that if the patient fails to achieve clinical remission, an increased dose of DMARDs or the use of biological products such as tumor necrosis factor (TNF) inhibitors or Janus kinase (JAK) family inhibitors should be considered. However, an increased dose of DMARDs and use of TNF inhibitors and JAK inhibitors may cause serious infections or other adverse drug reactions, which may potentially result in fatal outcomes. Because of these safety concerns, the increased dose of DMARDs and the use of TNF inhibitors etc. are not allowed in some patients who failed to achieve clinical remission after treatment with DMARDs. Currently, no effective therapy to achieve clinical remission is available for such patients, and as a result, remaining disease activity would contribute to progression of bone destruction in the joints (*Ann Rheum Dis*. 2009;68:823-7, *Ann Rheum Dis.* 2010;69:631-7). Denosumab can be used as an additional therapy in patients experiencing progression of bone destruction in the joints during treatment with DMARDs.

In Studies J201 and J301 conducted in patients with RA who had been on MTX or other DMARDs for ≥8 weeks, denosumab appeared to inhibit the progression of bone destruction when it was used in combination with an existing RA therapy [see Sections 7.1, 7.2, and 7.R.1]. Therefore, denosumab can be offered as an additional therapy for patients with RA experiencing progression of bone destruction in the joints during treatment with DMARDs, which is of clinical significance.

Patients who have progression of bone destruction in the joints while being treated with TNF inhibitors and DMARD-naïve patients who are newly diagnosed as having RA and who are suspected to be at a higher risk of progression of bone destruction were not eligible for enrollment in the clinical studies. However, such patients can be treated with denosumab, given the pharmacological action of denosumab, which is direct inhibition of bone resorption, and other aspects.

PMDA's view:

Based on the bone destruction inhibition demonstrated in the clinical studies [see Section 7.R.1], denosumab is positioned as a supportive therapy which can be used in patients who experience bone destruction despite adequate anti-inflammatory treatment with DMARDs.

On the other hand, the Japanese guidelines for the management of RA recommend that the use of biological products such as TNF inhibitors or JAK family inhibitors should be considered in patients who have inadequate response to DMARDs. Because denosumab has not been used in patients with progressive bone destruction after treatment with these drugs, the efficacy and safety of denosumab have not been established when used in combination with these drugs. Therefore, the necessity of treatment with denosumab should be determined with care only after thoroughly examining the benefits and risks in each patient.

DMARDs or other therapy may be effective for the inhibition of progression of bone destruction in patients who are newly diagnosed as having RA. For this reason, denosumab can be used in DMARD-naïve patients with newly diagnosed RA only when they are at a very high risk for progression of bone destruction and under special conditions such as limited treatment options due to comorbid diseases. In this case, the necessity of treatment with denosumab should be particularly carefully determined only after thoroughly examining the benefits and risks in each patient.

The PMDA's conclusion above will be discussed in the Expert Discussion.

7.R.4 Indication

PMDA asked the applicant to reconsider the indication for the following reasons: (i) the inhibition of joint space narrowing by denosumab was not demonstrated in the clinical studies supporting the present application and (ii) the effect that can be expected from denosumab is inhibition of progression of bone destruction in the joints [see Section 7.R.1].

The applicant's response:
The proposed indication for the present application is changed to "Inhibition of bone destruction in the joints associated with rheumatoid arthritis" from "Prevention of structural joint damage associated with rheumatoid arthritis."

PMDA's view:
The proposed indication should be modified as follows, taking into account that progression of bone destruction occurs in the joints of patients with RA. The following precautions for indication should be added based on the discussion of Sections 7.R.1 and 7.R.3.

Indication
Inhibition of progression of bone destruction associated with rheumatoid arthritis

Precautions for indication

- In principle, denosumab should be used in patients who have progression of bone destruction after appropriate treatment with anti-rheumatic drugs such as methotrexate.

- Improvement of joint symptoms has not been demonstrated in the clinical studies of denosumab. While the inhibitory effect of denosumab on the progression of bone destruction has been demonstrated, no inhibition of joint space narrowing has been demonstrated. Before determining the eligibility of patients, physicians should be fully aware of the pharmacological action of denosumab and the results of the clinical studies.

The PMDA's conclusion above will be discussed in the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation about the rationale for the proposed dosage and administration of denosumab (Administer 60 mg of denosumab as a subcutaneous injection once every 6 months. Depending on the patient's condition, denosumab may be administered as a subcutaneous injection once every 3 months):

Study J301 demonstrated the superiority of denosumab 60 mg Q6M and Q3M over placebo, and there was no significant difference in the incidence of adverse events between the denosumab 60 mg Q6M group and the Q3M group [see Section 7.2]. However, albumin-corrected serum calcium levels in the Q3M group remained below the baseline level (Figure 4). Taking the risk for developing hypocalcaemia into consideration, denosumab 60 mg every 6 months should be appropriate as the usual dosage.

Subgroup analysis of data from Study J301 was performed by patient characteristics. According to the subgroup analysis, patients with high disease activity failed to achieve adequate response to denosumab 60 mg Q6M. The results suggest that Q3M is more appropriate for this patient population (Table 14). Therefore, the proposed dosage and administration was specified so that denosumab 60 mg Q3M can be selected from the start of treatment for patients with high disease activity who are considered to have rapid progression of bone destruction in the joints, based on the symptoms, radiographic findings for the joints, laboratory test values, etc.

Based on the results of clinical studies, denosumab must be used in combination with DMARDs, and healthcare professionals should be fully advised of this information.

Table 14. Subgroup analysis of change from baseline in the bone erosion score at Month 12
(pooled analysis of Studies J201 and J301, linear interpolation[a])

	Baseline CRP < 1 mg/dL			Baseline CRP ≥ 1 mg/dL		
	Denosumab Q6M (N = 246)	Denosumab Q3M (N = 263)	Placebo (N = 262)	Denosumab Q6M (N = 56)	Denosumab Q3M (N = 38)	Placebo (N = 44)
Baseline	6.67 ± 7.59	6.30 ± 8.53	6.11 ± 10.01	9.57 ± 15.19	10.51 ± 9.60	9.30 ± 12.84
Month 12	6.93 ± 7.81	6.42 ± 8.58	6.92 ± 10.57	10.83 ± 5.94	11.24 ± 10.12	11.30 ± 14.00
Change from baseline	0.26 ± 1.23	0.12 ± 0.76	0.81 ± 2.07	1.26 ± 3.47	0.73 ± 1.22	2.00 ± 4.30
	Baseline swollen joint count < 10			Baseline swollen joint count ≥ 10		
	Denosumab Q6M (N = 187)	Denosumab Q3M (N = 179)	Placebo (N = 179)	Denosumab Q6M (N = 115)	Denosumab Q3M (N = 122)	Placebo (N = 127)
Baseline	7.27 ± 10.56	6.88 ± 9.39	6.78 ± 9.13	7.11 ± 7.52	6.76 ± 7.82	6.28 ± 12.20
Month 12 months	7.58 ± 10.88	7.01 ± 9.54	7.74 ± 9.99	7.77 ± 8.17	7.05 ± 7.96	7.30 ± 12.77
Change from baseline	0.31 ± 1.99	0.13 ± 0.76	0.96 ± 2.58	0.66 ± 1.71	0.29 ± 0.97	1.02 ± 2.47

Mean ± standard deviation
a) Missing values were interpolated by linear extrapolation using baseline and measurement values closest to Month 12.

PMDA's view:

The efficacy of denosumab 60 mg administered every 6 months was demonstrated in Study J301 [see Section 7.R.1], and the safety is acceptable [see Section 7.R.2]; therefore, it is concluded that the usual dosage can be specified as denosumab 60 mg administered every 6 months.

On the other hand, although there was a trend towards increasing efficacy for the regimen of denosumab 60 mg Q3M compared with that of denosumab 60 mg Q6M (Table 8), patients who need to be treated with the former regimen cannot be identified based on the results of the subgroup analysis (Table 14 etc.), which was conducted with a small sample of patients. Furthermore, the risk of developing hypocalcaemia was considered to be potentially higher in patients receiving denosumab 60 mg Q3M [see Section 7.R.2.1]. Given the reasons above, the starting dosage should be denosumab 60 mg Q6M, and if progression of bone destruction is confirmed, the use of denosumab 60 mg Q3M may be considered only after examining dose increase or a change in concomitant anti-rheumatic drugs.

Based on the above, it is reasonable to specify the dosage and administration, and precautions for dosage and administration as follows; however, this should be finalized after discussion in the Expert Discussion.

Dosage and administration

The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months. If progression of bone destruction is still observed when denosumab is administered once every 6 months, denosumab may be administered as a subcutaneous injection once every 3 months.

Precautions for dosage and administration

When denosumab is used for inhibition of progression of bone destruction associated with rheumatoid arthritis, the following cautions should be exercised.

- Denosumab should be used in combination with anti-rheumatic drugs with anti-inflammatory effects, such as methotrexate.
- If radiographic progression of bone destruction is confirmed in patients receiving denosumab once every 6 months, denosumab once every 3 months may be considered taking the risks and benefits of denosumab treatment into consideration.

7.R.6 Post-marketing investigations

PMDA's view:

It is necessary to advise caution regarding the risk of hypocalcaemia and osteonecrosis of the jaw, as well as measures to prevent those events when using denosumab in patients with RA, in a similar manner to the caution provided for the treatment of patients with osteoporosis. Furthermore, given that the disease activity of RA will not be inhibited by denosumab, and that the clinical effects that can be expected from denosumab differ from those of conventional anti-rheumatic drugs, it is important to ensure that information on the characteristics of denosumab, its methods of use, and eligible patients should be provided sufficiently to healthcare professionals in clinical practice, and that denosumab is used by physicians familiar with RA therapy.

The PMDA's conclusion above will be discussed in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1 and CTD5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that overall, the clinical trial were conducted in accordance with GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the inspection revealed the following issues at a study site used by the applicant, albeit with no major impact on the overall study evaluation. These issues were notified to the head of the study site as findings requiring corrective action.

Findings requiring corrective action:

Study site

- Insufficient description in the written contract concerning the subcontract on the conduct of the clinical trial
- Insufficiency relating to the re-consent procedure in some subjects using revised consent documents

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that denosumab has efficacy in the inhibition of progression of bone destruction in the joints associated with RA, and that has acceptable safety in view of its benefits. Denosumab represents a new option for the treatment of RA, and it is considered clinically meaningful. No particular safety concerns have been identified based on the clinical study results and other data, compared with that of the approved indication, but the safety and efficacy of denosumab in clinical use should be further evaluated in post-marketing surveillance.

PMDA has concluded that denosumab may be approved if denosumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 12, 2017

Product Submitted for Approval

Brand Name	Pralia Subcutaneous Injection 60 mg Syringe
Non-proprietary Name	Denosumab (Genetical Recombination)
Applicant	Daiichi Sankyo Co., Ltd.
Date of Application	September 23, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Safety

The conclusion of PMDA regarding the safety of Pralia Subcutaneous Injection 60 mg Syringe (Pralia or denosumab) described in Review Report (1) was supported by the expert advisors at the Expert Discussion.

1.2 Efficacy, clinical positioning, indication, and dosage and administration

The conclusion of PMDA regarding the efficacy, clinical positioning, indication, and dosage and administration of Pralia (denosmab) as described in Review Report (1) was supported by the expert advisors at the Expert Discussion. Furthermore, the following comments were raised by the expert advisors.

- The clinical studies demonstrated only the inhibitory effect of denosumab on the progression of bone erosion. This fact should be more clearly stated in the “Indication” section.
- The state of progression of bone erosion should be assessed before selecting patients eligible for treatment with denosumab or changing the treatment interval from every 6 months to every 3 months. At present, the assessment should be based on radiographic findings.
- Denosumab plays a supportive role in the treatment of rheumatoid arthritis (RA). A physician with adequate knowledge about treatment with denosumab and sufficient experience in RA pharmacotherapy should initiate appropriate therapy with basic anti-rheumatic drugs before determining the use of denosumab based on its risks and benefits.

- It is desirable that the applicant gather as much information as possible on how denosumab can contribute to the maintenance of patients' physical function, and reduction in need for surgical treatment such as arthroplasty through inhibition of progression of bone erosion during long-term treatment with Pralia, and provide the gathered information to healthcare professionals as needed.

PMDA requested that the applicant specify the indication, dosage and administration, and precautions in the package insert as follows, based on the discussions at the Expert Discussion, and the applicant implemented such action accordingly. The applicant also explained their post-marketing plans. The applicant is planning to evaluate the effects of long-term treatment with denosumab on the physical functions of the patients through investigation and observational research led by the company, in addition to specified use-results surveys, and the results will be provided to healthcare professionals as needed. PMDA accepted the applicant's explanation.

Indication

Inhibition of progression of bone erosion associated with rheumatoid arthritis

Precautions for indication

(1) The product should be used in patients who have radiographic progression of bone destruction after appropriate treatment with anti-rheumatic drugs with an anti-inflammatory action, such as methotrexate.

(2) Clinical studies (treatment duration of 1 year) demonstrated the inhibitory effect of the product on the progression of bone erosion. However, improvement of joint symptoms or physical function, or inhibition of joint space narrowing has not been demonstrated. Before determining the eligibility of patients, physicians should be fully aware of the information in the "Clinical Studies" section and of the fact that the product play a supportive role for treatment with anti-rheumatic drugs.

Dosage and administration

The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months. If progression of bone erosion is still observed when denosumab is injected once every 6 months, denosumab may be administered as a subcutaneous injection once every 3 months.

Precautions for dosage and administration

(1) The product should be used in combination with anti-rheumatic drugs with anti-inflammatory effects, such as methotrexate.

(2) If radiographic progression of bone erosion is confirmed in patient receiving the product once every 6 months, the product once every 3 months may be considered taking the risks and benefits of denosumab treatment into consideration, only after examining dose increase or a change in concomitant anti-rheumatic drugs.

1.3 Risk management plan (draft)

The following comments regarding the post-marketing surveillance were given by the expert advisors at the Expert Discussion.

- The survey should be planned so that the safety profile in patients who have changed their regimen from denosumab 60 mg every 6 months to every 3 months can also be evaluated.
- Based on the pharmacological action of denosumab, the risk of atypical fracture in patients with rheumatoid arthritis who have normal bone metabolism should be evaluated in the survey.

In view of the discussions presented in Section 7.R.6. of Review Report (1) and discussions at the Expert Discussion, PMDA concluded that the safety and efficacy specifications presented in Table 15 for the current risk management plan (draft) of the product are appropriate, and the applicant should conduct additional pharmacovigilance and risk minimization actions presented in Table 16.

Table 15. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypocalcaemia • Osteonecrosis of the jaw/osteomyelitis of the jaw • Anaphylaxis • Atypical fracture of the femur • Serious skin infections • Multiple vertebral fracture after administration discontinuation (osteoporosis)	• Cardiovascular events • Interstitial pneumonia (associated with rheumatoid arthritis)	• Safety of the product when administered to men (osteoporosis)
Efficacy specification		
• Efficacy of denosumab in patients with osteoporosis in clinical settings • Efficacy of denosumab in patients with rheumatoid arthritis in clinical sttings		

Table 16. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified use-results surveys on long-term use in patients with osteoporosis • Specified use-results surveys on long-term use in patients with rheumatoid arthritis • Pharmacovigilance activities using medical information databases (hypocalcaemia) • Early post-marketing phase vigilance (rheumatoid arthritis)	• Providing information materials to healthcare professionals (proper use guide) • Providing information materials to patients • Disseminate data gathered during early post-marketing phase vigilance (rheumatoid arthritis)

PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above issues.

The applicant's explanation about the main investigations:

As shown in Table 17, the applicant has planned to conduct a specified use-results survey regarding long-term use of the product in patients with rheumatoid arthritis with a target sample size of 1000 as the safety analysis set, with an observation period of 2 years to gather clinical data on the safety and efficacy specifications for the risk management plan (draft) as summarized in Table 15. The applicant has also planned to conduct pharmacovigilance activities utilizing medical information databases to investigate the trend in blood calcium concentrations and status of proper use of the product.

Table 17. Outline of specified use-results survey (draft)

Objective	To identify problems related to the long-term safety and efficacy of denosumab in clinical settings.
Survey method	Central registry system
Population	Patients with rheumatoid arthritis
Observation period	2 years
Planned sample size	1000 patients (as safety analysis set)
Main survey items	• Patient characteristics (disease duration, severity, complications, medical history, prior treatment, and laboratory test results) • Use conditions of the product • Use and implementation status of concomitant medications/therapy • Efficacy evaluation • Adverse events

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration shown below, with the condition shown below. As the product is a drug with a new indication and a new dosage, the re-examination period for the indication and dosage and administration for the present application is 4 years.

Indication

1. Osteoporosis
2. Inhibition of progression of bone erosion ~~Prevention of structural joint damage~~ associated with rheumatoid arthritis

(Underline denotes addition to and strike-through portion denotes deletion from the proposed indication)

Dosage and Administration

1. Osteoporosis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months.
2. Inhibition of progression of bone erosion ~~Prevention of structural joint damage~~ associated with rheumatoid arthritis

   The usual adult dosage is 60 mg of denosumab (genetical recombination) administered as a subcutaneous injection once every 6 months. If progression of bone erosion is still observed when denosumab is injected once every 6 months, ~~Depending on the patient's condition,~~ denosumab may be administered as a subcutaneous injection once every 3 months.

(Underline denotes addition to and strike-through portion denotes deletion from the proposed dosage and administration)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.