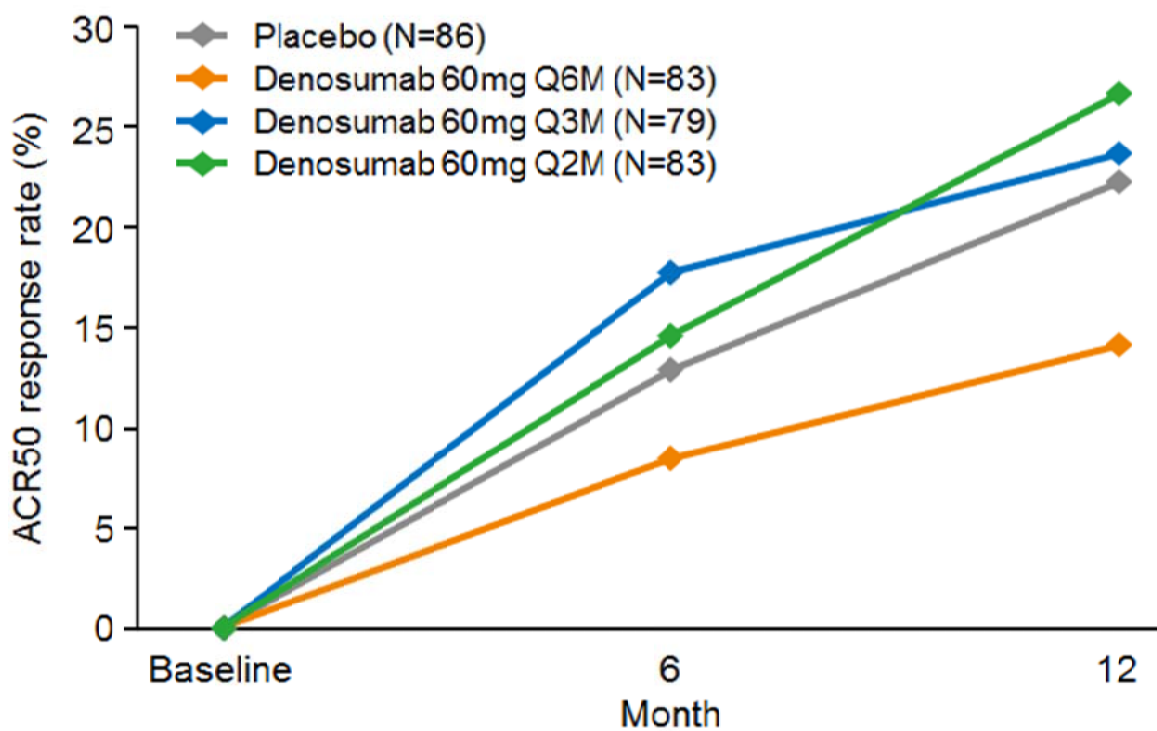**Figure S1. ACR20/50/70 response rate**
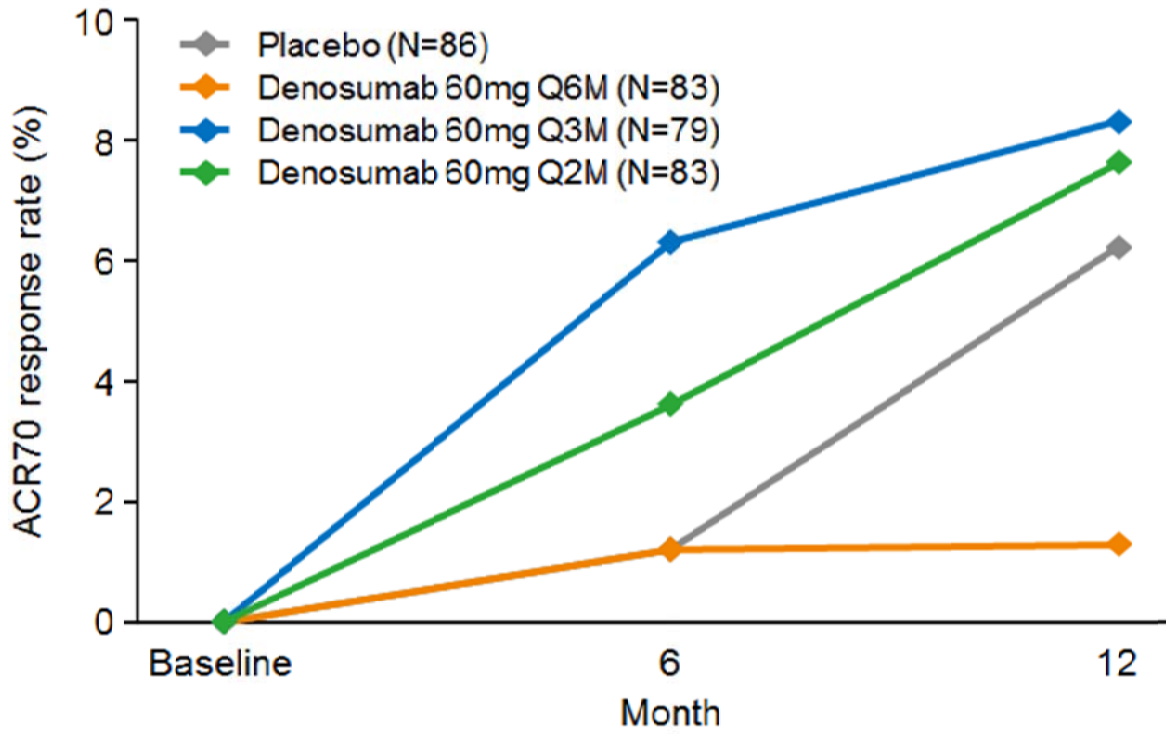
A
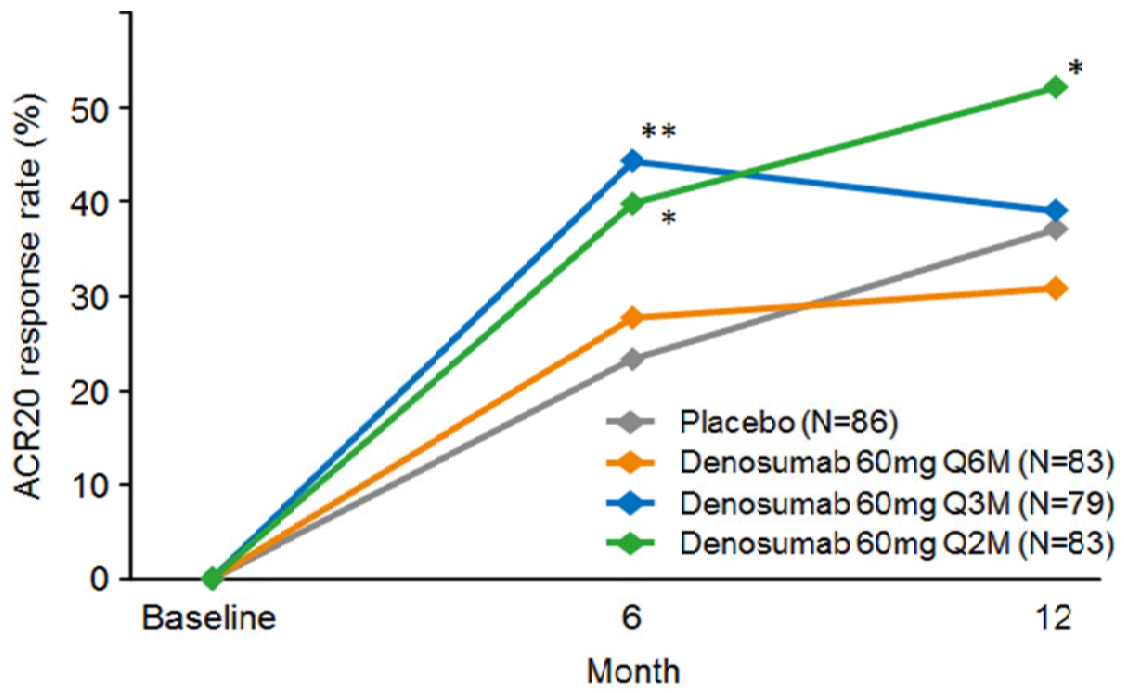
B

C

(A) ACR20 response rate, (B) ACR50 response rate, and (C) ACR70 response rate.

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.

ACR = American College of Rheumatology

*p<0.05, **p<0.01, vs. placebo, based on the Cochran-Mantel-Haenszel test adjusted for randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor)

Figure S2 Change from the baseline in DAS28-CRP
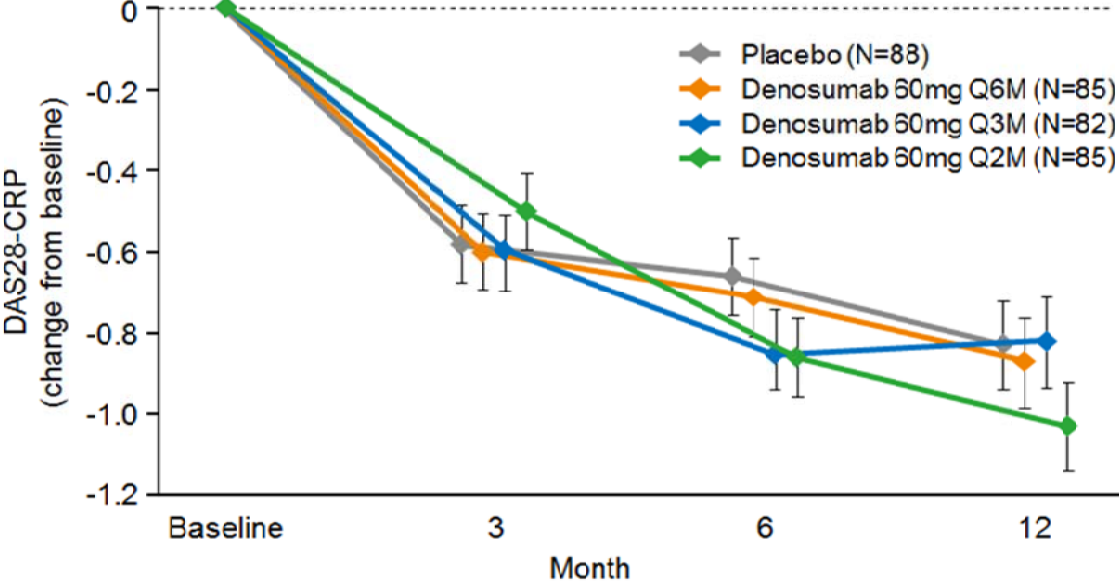
N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Least square mean (Standard error)
Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

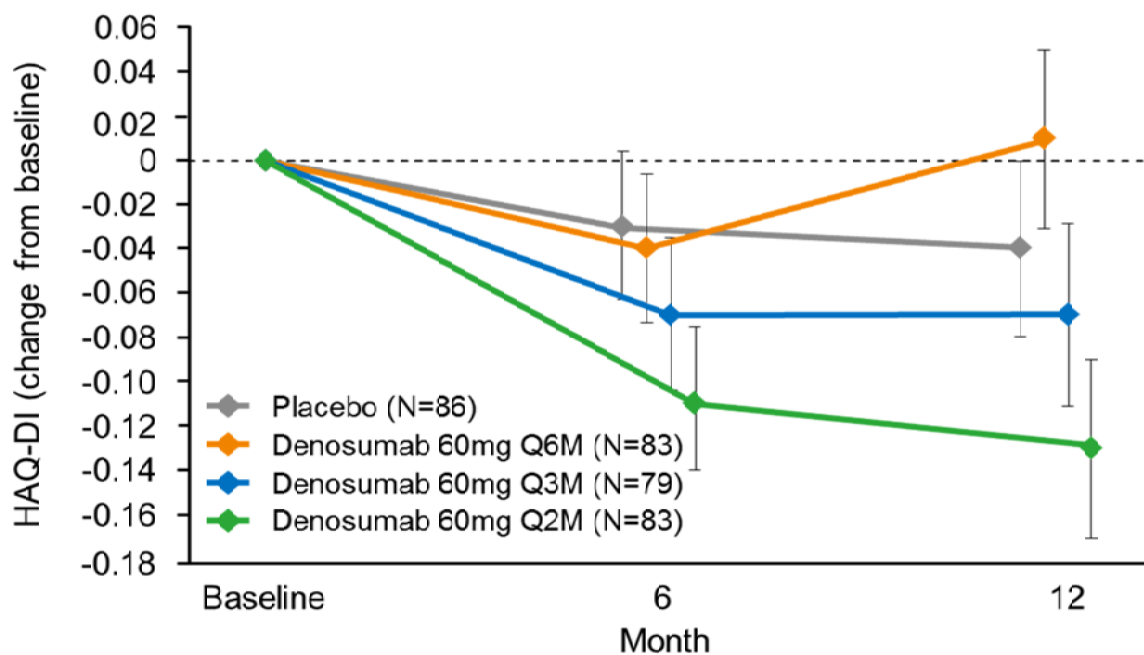**Figure S3 Change from the baseline in HAQ-DI**

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Least square mean (Standard error)
Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

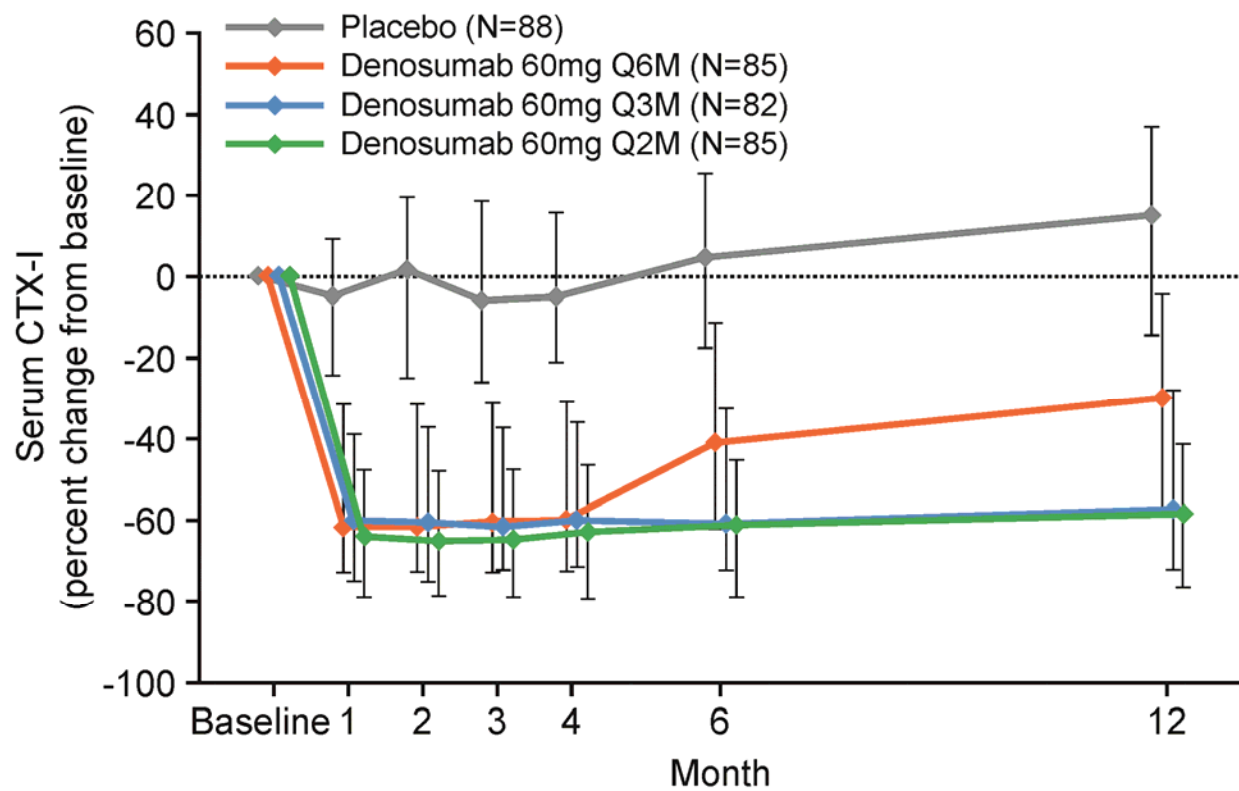**Figure S4 Change from the baseline in CTX-I**

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Median (Interquartile range)
CTX-I: C-telopeptide of type I collagen

Figure S5 Change from the baseline in PINP

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Median (Interquartile range)
PINP: N-propeptide of type I collagen

Figure S6 Change from the baseline in COMP
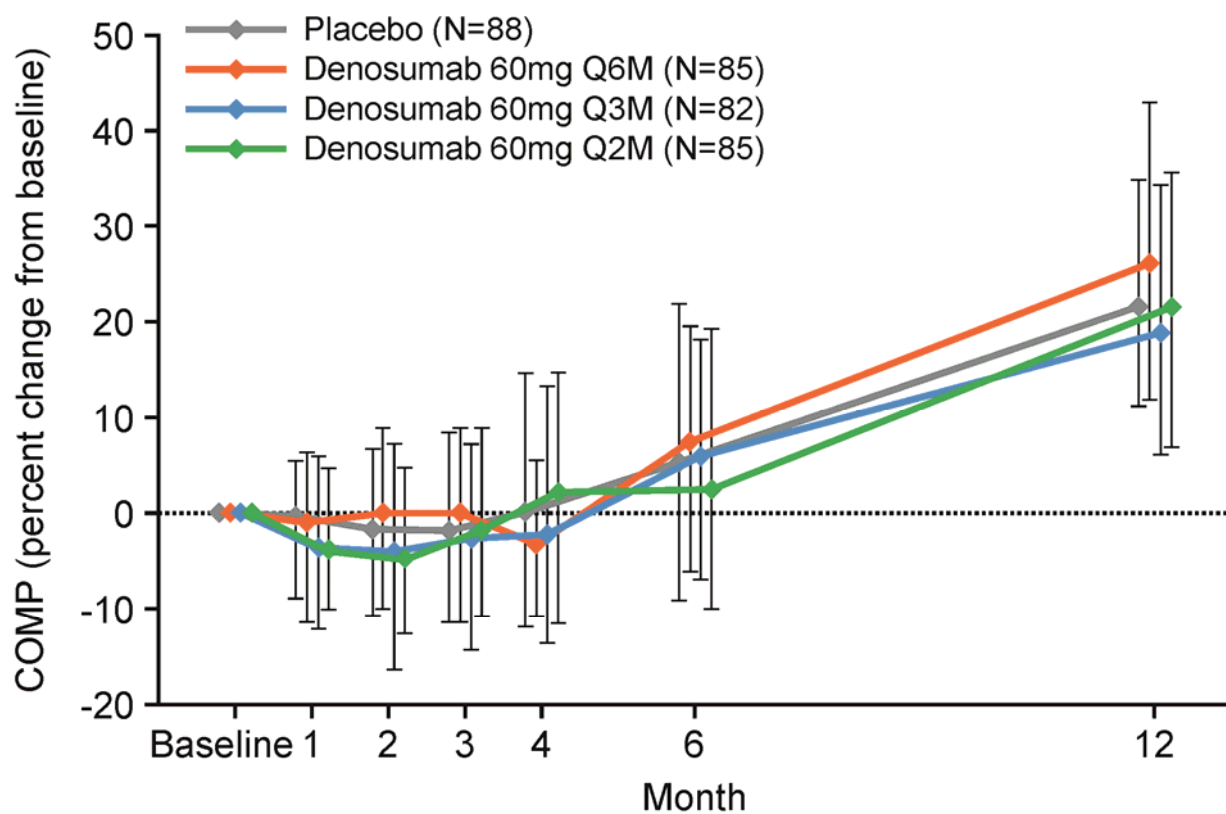
N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Median (Interquartile range)
COMP: cartilage oligomeric matrix protein

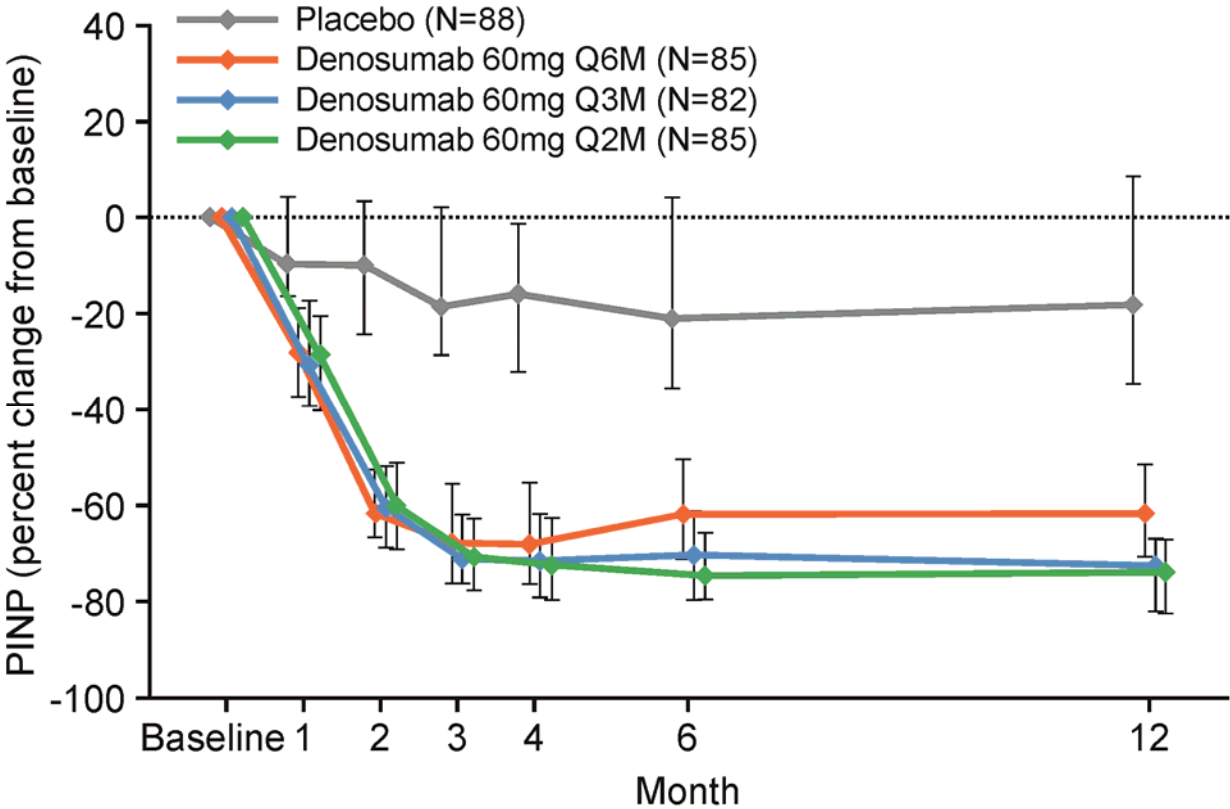**Figure S7 Change from the baseline in CTX-II/Creatinine**
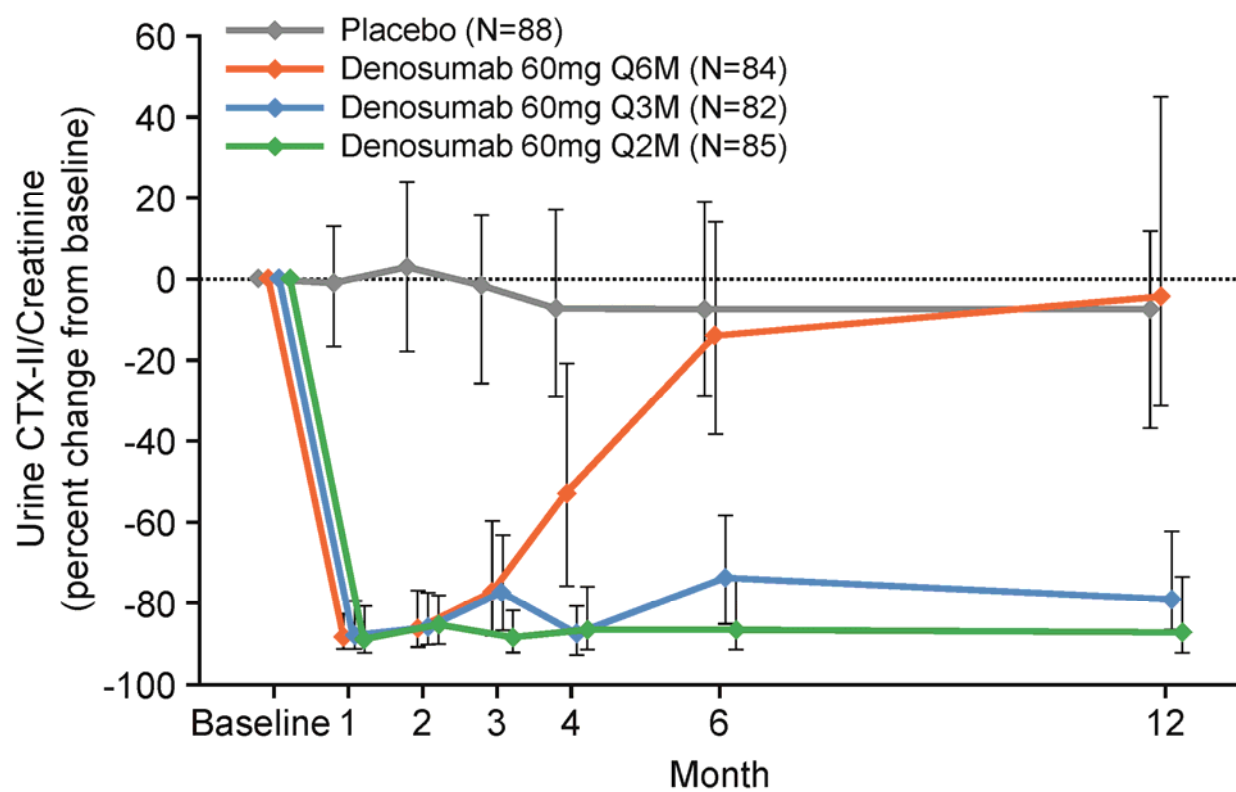
N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement.
Median (Interquartile range)
CTX-II: C-telopeptide of type II collagen

Figure S8. Serum denosumab concentration-time profiles

A
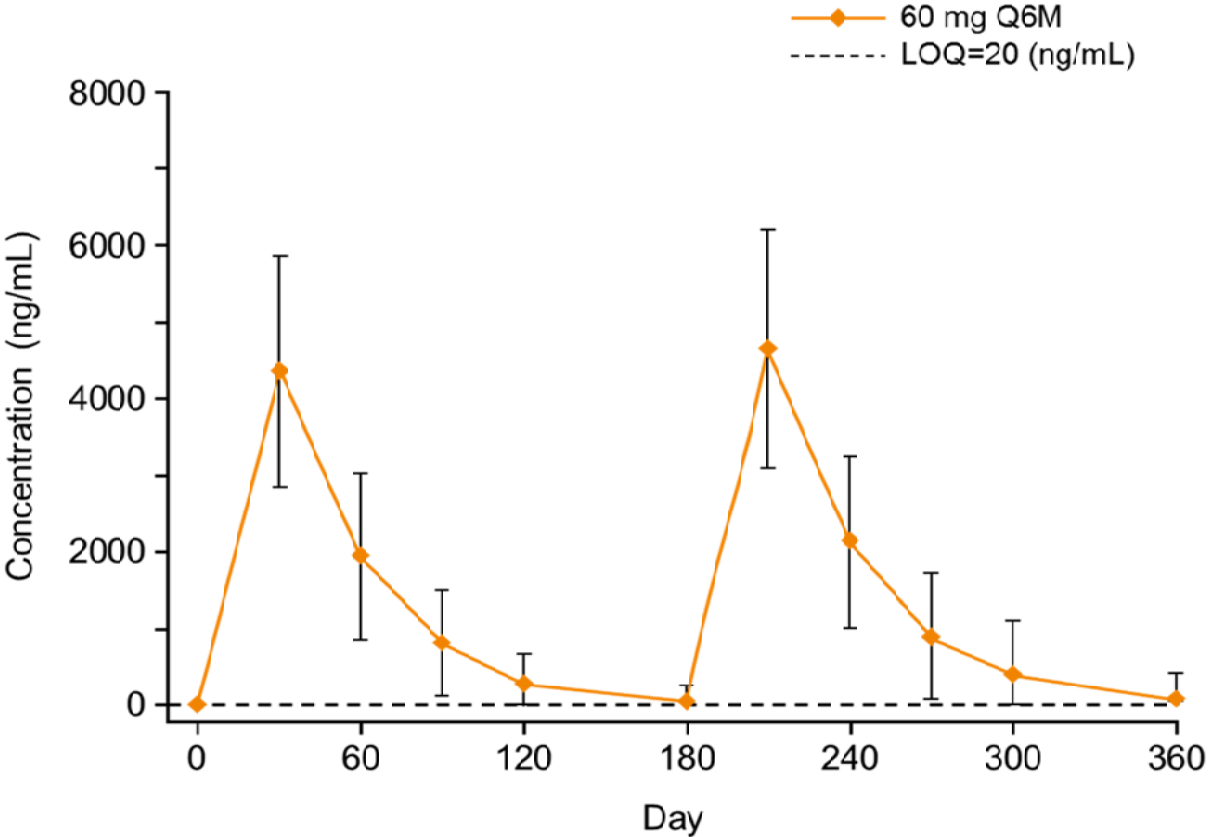
B
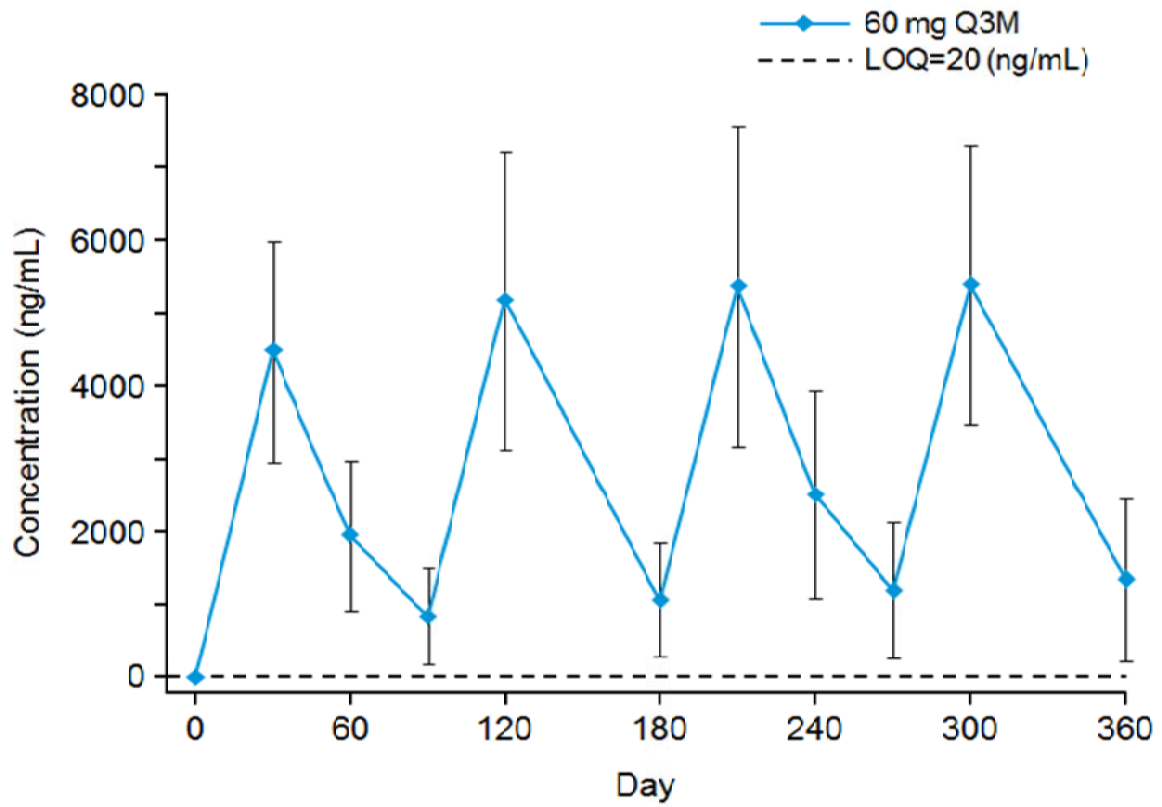
C
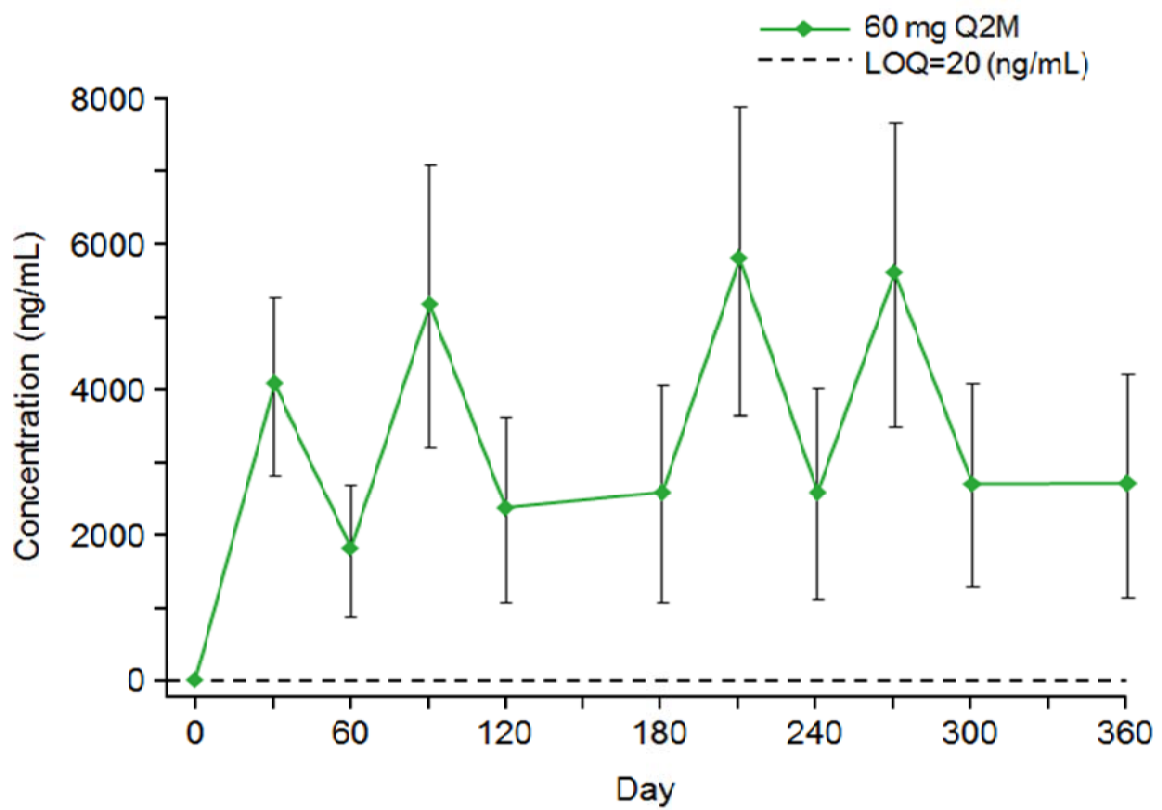
(A) Denosumab 60 mg Q6M, (B) Denosumab 60 mg Q3M, and (C) Denosumab 60mg Q2M
Blood samples for pharmacokinetics were obtained at baseline, 1, 2, 3, 4, 6, 7, 8, 9, 10, and 12 months.
Mean(SD)
LOQ: limit of quantification

Table S1. Percent change of BMD from the baseline at the lumbar spine by baseline use of glucocorticoid (present or absent)

	Placebo (N = 88)	Denosumab		
		60 mg Q6M (N = 85)	60 mg Q3M (N = 82)	60 mg Q2M (N = 85)
Present				
6 months				
n	36	35	35	36
LS Mean (SE)[*]	-0.32 (0.468)	3.04 (0.479)	3.24 (0.473)	4.53 (0.467)
P-value[*]	-	<0.0001	<0.0001	<0.0001
12 months				
n	34	33	33	34
LS Mean (SE)[*]	-1.35 (0.512)	3.99 (0.522)	4.26 (0.516)	6.26 (0.510)
P-value[*]	-	<0.0001	<0.0001	<0.0001
Absent				
6 months				
n	51	49	44	47
LS Mean (SE)[*]	0.87 (0.419)	3.32 (0.424)	3.55 (0.447)	4.31 (0.431)
P-value[*]	-	<0.0001	<0.0001	<0.0001
12 months				
n	48	45	39	45
LS Mean (SE)[*]	0.58 (0.433)	4.69 (0.441)	5.83 (0.469)	5.93 (0.444)
P-value[*]	-	<0.0001	<0.0001	<0.0001

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of radiograph score.

n = Number of patients with observed data at the baseline and at the time point of interest.

LS = Least square, SE = Standard Error

[*] Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S2. Percent change of BMD from the baseline at the total hip by baseline use of glucocorticoid (present or absent)

		Denosumab		
	Placebo (N = 88)	60 mg Q6M (N = 85)	60 mg Q3M (N = 82)	60 mg Q2M (N = 85)
Present				
6 months				
n	36	35	35	36
LS Mean (SE)[*]	-0.28 (0.318)	1.64 (0.326)	1.95 (0.321)	1.91 (0.318)
P-value[*]	-	<0.0001	<0.0001	<0.0001
12 months				
n	34	33	33	34
LS Mean (SE)[*]	-0.64 (0.394)	2.36 (0.401)	2.33 (0.398)	2.69 (0.393)
P-value[*]	-	<0.0001	<0.0001	<0.0001
Absent				
6 months				
n	51	49	44	47
LS Mean (SE)[*]	-0.10 (0.318)	1.78 (0.321)	1.85 (0.337)	2.44 (0.330)
P-value[*]	-	<0.0001	<0.0001	<0.0001
12 months				
n	48	45	39	45
LS Mean (SE)[*]	-0.92 (0.364)	2.64 (0.371)	2.58 (0.396)	2.66 (0.377)
P-value[*]	-	<0.0001	<0.0001	<0.0001

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of radiograph score.

n = Number of patients with observed data at the baseline and at the time point of interest.

LS = Least square, SE = Standard Error

[*] Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S3. Pharmacokinetic parameter of denosumab

Parameter	Unit	N	Denosumab 60 mg Q6M	N	Denosumab 60 mg Q3M	N	Denosumab 60 mg Q2M
0 month (First administration)							
AUC_{last}	ng·day/mL	84	224000 (110000)	80	210000 (84700)	84	147000 (46500)
C_{max}	ng/mL	85	4350 (1500)	81	4480 (1510)	84	4060 (1240)
$t_{max}{}^a$	day	85	28.0 (19.0, 41.0)	81	28.0 (16.9, 38.0)	84	28.0 (16.0, 35.8)
6 months (The second, third or fourth doses for Q6M, Q3M or Q2M, respectively)							
AUC_{last}	ng·day/mL	78	245000 (121000)	72	274000 (127000)	78	255000 (109000)
C_{max}	ng/mL	81	4660 (1550)	74	5390 (2220)	78	5780 (2130)
$t_{max}{}^a$	day	81	28.1 (16.0, 56.0)	74	28.0 (19.0, 63.0)	78	28.0 (6.0, 48.9)
R_{obs}		78	1.17 (0.477)	71	1.32 (0.381)	78	1.74 (0.635)

N = Analyzed number
Mean (SD)
a: Median (minimum, maximum)
R_{obs}: Observed cumulative coefficient

Table S4. Change from the baseline in tender joint count

	Placebo (N = 88)	Denosumab 60 mg Q6M (N = 85)	Denosumab 60 mg Q3M (N = 82)	Denosumab 60 mg Q2M (N = 85)
Tender joint count				
3 months				
n	88	85	82	85
LS Mean (SE)[a]	-2.26 (0.600)	-2.89 (0.610)	-2.65 (0.618)	-2.15 (0.607)
P-value[a]	-	0.4543	0.6461	0.8942
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-2.12 (0.545)	-3.18 (0.554)	-3.61 (0.563)	-3.40 (0.551)
P-value[a]	-	0.1660	0.0547	0.0953
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-3.75 (0.567)	-4.61 (0.576)	-3.38 (0.592)	-4.34 (0.571)
P-value[a]	-	0.2818	0.6421	0.4592

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.

n = Number of patients with observed data at baseline and at the time point of interest.

LS = Least square, SE = Standard error

a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S5. Change from the baseline in swollen joint count

| | Placebo (N = 88) | Denosumab | | |
		60 mg Q6M (N = 85)	60 mg Q3M (N = 82)	60 mg Q2M (N = 85)
Swollen joint count				
3 months				
n	88	85	82	85
LS Mean (SE)[a]	-3.73 (0.437)	-3.35 (0.446)	-4.26 (0.451)	-3.81 (0.443)
P-value[a]	-	0.5356	0.3928	0.8952
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-4.70 (0.426)	-4.80 (0.435)	-5.60 (0.442)	-5.12 (0.432)
P-value[a]	-	0.8710	0.1373	0.4860
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-5.75 (0.466)	-5.13 (0.475)	-5.48 (0.488)	-6.19 (0.471)
P-value[a]	-	0.3434	0.6857	0.5010

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.

n = Number of patients with observed data at baseline and at the time point of interest.

LS = Least square, SE = Standard error

a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S6. Change from the baseline in the physician's global assessment of disease activity

	Placebo (N = 88)	Denosumab 60 mg Q6M (N = 85)	Denosumab 60 mg Q3M (N = 82)	Denosumab 60 mg Q2M (N = 85)
Physician's global assessment of disease activity				
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-10.52 (1.438)	-12.31 (1.468)	-14.21 (1.490)	-12.04 (1.455)
P-value[a]	-	0.3734	0.0706	0.4491
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-12.43 (1.708)	-10.93 (1.740)	-12.49 (1.790)	-16.40 (1.722)
P-value[a]	-	0.5340	0.9782	0.0968

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.
n = Number of patients with observed data at baseline and at the time point of interest.
LS = Least square, SE = Standard error
a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S7. Change from the baseline in the subject's global assessment of disease activity

	Placebo (N = 88)	Denosumab		
		60 mg Q6M (N = 85)	60 mg Q3M (N = 82)	60 mg Q2M (N = 85)
Subject's global assessment of disease activity				
3 months				
n	88	85	82	85
LS Mean (SE)[a]	-2.80 (1.879)	-3.59 (1.912)	-2.77 (1.940)	-4.19 (1.907)
P-value[a]	-	0.7634	0.9899	0.5983
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-4.87 (1.860)	-4.48 (1.895)	-5.48 (1.930)	-8.71 (1.887)
P-value[a]	-	0.8799	0.8197	0.1434
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-5.33 (2.057)	-5.48 (2.093)	-3.50 (2.161)	-10.29 (2.077)
P-value[a]	-	0.9572	0.5354	0.0868

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.

n = Number of patients with observed data at baseline and at the time point of interest.

LS = Least square, SE = Standard error

a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S8. Change from the baseline in the subject's assessment of pain

	Placebo (N = 88)	Denosumab 60 mg Q6M (N = 85)	60 mg Q3M (N = 82)	60 mg Q2M (N = 85)
Subject's assessment of pain				
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-4.54 (1.977)	-4.36 (2.012)	-4.91 (2.046)	-7.10 (2.001)
P-value[a]	-	0.9462	0.8961	0.3574
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-7.14 (2.076)	-3.57 (2.108)	-5.22 (2.174)	-10.58 (2.090)
P-value[a]	-	0.2211	0.5167	0.2377

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.

n = Number of patients with observed data at baseline and at the time point of interest.

LS = Least square, SE = Standard error

a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction

Table S9. Change from the baseline in CRP

	Placebo (N = 88)	Denosumab 60 mg Q6M (N = 85)	Denosumab 60 mg Q3M (N = 82)	Denosumab 60 mg Q2M (N = 85)
CRP				
3 months				
n	88	85	82	85
LS Mean (SE)[a]	0.07 (0.102)	-0.20 (0.104)	-0.10 (0.105)	0.11 (0.103)
P-value[a]	-	0.0636	0.2539	0.7458
6 months				
n	86	83	79	83
LS Mean (SE)[a]	-0.18 (0.102)	-0.23 (0.104)	-0.07 (0.106)	0.04 (0.104)
P-value[a]	-	0.7490	0.4502	0.1256
12 months				
n	81	78	72	79
LS Mean (SE)[a]	-0.11 (0.075)	-0.15 (0.076)	-0.23 (0.079)	-0.12 (0.076)
P-value[a]	-	0.6749	0.2323	0.9207

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.

n = Number of patients with observed data at baseline and at the time point of interest.

LS = Least square, SE = Standard error

a: Based on a repeated measures model adjusted for treatment, visit, baseline value, randomized strata (4 strata from the combination of the baseline use of glucocorticoid and the baseline rheumatoid factor) and treatment-by-visit interaction