Supplementary material

Supplementary Text S1. Prohibited and restricted concomitant medications

Prohibited concomitant medications were other biological disease-modifying anti-rheumatic drugs (DMARDs) (including rituximab), conventional DMARDs (except methotrexate), corticosteroids (by intravenous, intramuscular, intra-articular, or epidural administration), plasmapheresis therapy, surgical procedure for rheumatoid arthritis, hyaluronan (by intra-articular administration), live viral or bacterial vaccine, and other investigational products.

Restricted concomitant medications were non-steroidal anti-inflammatory drugs (NSAIDs), analgesic drugs, and corticosteroids (oral, suppository, or topical, at a dose ≤10 mg/day prednisone equivalent). Patients who regularly used NSAIDs, analgesic drugs, or corticosteroids were not allowed to change the dose 4 weeks before the study drug administration as well as during the study period, unless there were safety concerns. Necessary temporary treatment with NSAIDs, analgesic drugs, and corticosteroids was permitted in this study, except within 24 hours prior to the visit for joint assessment.

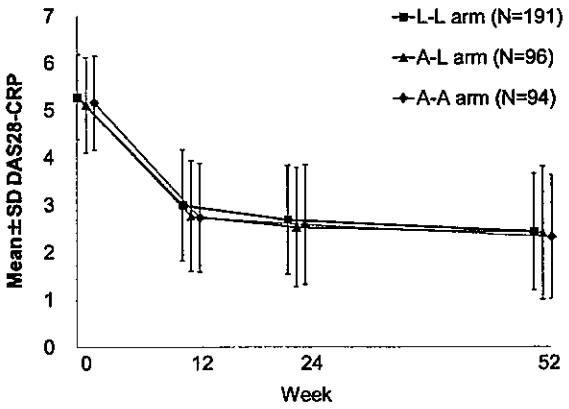
Supplementary Text S2. Analysis set definitions

The full analysis set (FAS) consisted of patients randomised to a study drug and meeting the following criteria: patients who administered at least one injection of study drug, completed all assessments relevant to the Disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR) score at baseline and had at least one post-baseline assessment time.

The per-protocol set (PPS) consisted of patients meeting the FAS criteria as above, and meeting the following additional PPS criteria: patients who met all eligibility criteria, had a DAS28-ESR assessment score at baseline and Week 24 (per analysis visit window), had at least 80% compliance to the study drug during the first 24 weeks of treatment, had not discontinued the study drug for two or more than two consecutive times out of four times prior to the DAS28-ESR assessment at Week 24 (per analysis visit window), had a week-long temporary hold of methotrexate administration for no more than five times in total during the first 24 weeks of treatment period, and had no major protocol violations that could affect DAS28-ESR assessment during the first 24 weeks of treatment period.

The safety set consisted of patients randomised to a study drug and meeting the following criteria: patients who administered at least one injection of the study drug and had at least one post-baseline safety assessment.

The pharmacokinetic analysis set consisted of patients randomised to a study drug and meeting the following criteria: patients who administered at least one injection of the study drug and had at least one serum concentration data after injection of the study drug.



Supplementary Fig. S1. Mean DAS28-CRP at baseline, Week 12, Week 24, and Week 52 (full analysis set).
Error bars show ± SD.
DAS: Disease Activity Score; CRP: C-reactive protein; SD: standard deviation.

Supplementary Table S1. Demographics and clinical characteristics by treatment arm (full analysis set).

Variable	L-L arm n=191	A-L arm n=96	A-A arm n=94
Age, years	55.2 ± 12.1	53.6 ± 10.7	54.5 ± 11.3
Sex, female	161 (84.3)	78 (81.3)	84 (89.4)
Ethnicity, Asian	191 (100.0)	96 (100.0)	94 (100.0)
Weight, kg	57.5 ± 11.0	57.8 ± 11.8	57.1 ± 10.9
Functional status in RA			
I	32 (16.8)	14 (14.6)	15 (16.0)
II	130 (68.1)	74 (77.1)	66 (70.2)
III	29 (15.2)	8 (8.3)	13 (13.8)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Duration since RA diagnosis, years	7.2 ± 8.2	8.2 ± 7.5	6.8 ± 6.9
Rheumatoid factor test result positivity	152 (79.6)	73 (76.0)	80 (85.1)
Tender joint count from 68 joints	14.8 ± 7.9	16.6 ± 10.5	15.9 ± 10.2
Tender joint count from 28 joints	10.4 ± 5.3	10.5 ± 6.3	10.4 ± 5.4
Swollen joint count from 66 joints	11.8 ± 6.0	12.8 ± 8.1	11.2 ± 5.1
Swollen joint count from 28 joints	8.8 ± 4.2	9.0 ± 5.3	8.2 ± 3.7
DAS28-ESR	6.2 ± 0.8	6.1 ± 0.9	6.1 ± 0.9
ESR, mm/hour	55.8 ± 25.3	51.9 ± 22.2	53.2 ± 23.2
CRP, mg/dL	2.2 ± 3.0	1.4 ± 1.7	1.6 ± 1.8
MTX dose, mg/week	11.4 ± 3.0	11.3 ± 2.8	11.5 ± 3.1
HAQ-DI	1.3 ± 0.7	1.1 ± 0.7	1.3 ± 0.8
PtAP, mm	61.9 ± 22.6	61.6 ± 21.4	61.2 ± 26.0
PtGADA, mm	61.8 ± 21.1	60.1 ± 21.5	59.2 ± 25.2
PhGADA, mm	61.9 ± 18.0	59.6 ± 18.2	61.4 ± 18.9
Patients who used bDMARDs previously	34 (17.8)	22 (22.9)	20 (21.3)
Patients who used corticosteroids at baseline	121 (63.4)	66 (68.8)	61 (64.9)

Data are presented as mean ± SD or n (%)
A: adalimumab reference product; bDMARD: biological disease-modifying anti-rheumatic drug; DAS: disease activity score; ESR: erythrocyte sedimentation rate; L: LBAL; MTX: methotrexate; PhGADA: physician's global assessment of disease activity; PtAP: patient's assessment of pain; PtGADA: patient's global assessment of disease activity; RA: rheumatoid arthritis; SD: standard deviation.

Supplementary Table S2. Subgroup analysis for the change from baseline in DAS28-ESR at Week 24 (full analysis set).

		LBAL group		ADL group	
		n	Mean±SD	n	Mean±SD
Overall		191	-2.52 ± 1.12	190	-2.57 ± 1.25
Age	<65 years	143	-2.51 ± 1.14	149	-2.55 ± 1.33
	≥65 years	48	-2.53 ± 1.05	41	-2.63 ± 0.92
Sex	Male	30	-2.86 ± 1.15	28	-2.92 ± 1.31
	Female	161	-2.45 ± 1.10	162	-2.51 ± 1.23
Previous use of a biological DMARD	Yes	34	-2.54 ± 1.09	42	-2.79 ± 1.43
	No	157	-2.51 ± 1.13	148	-2.50 ± 1.19
Country	Japan	113	-2.70 ± 1.11	113	-2.81 ± 1.17
	Korea	78	-2.26 ± 1.09	77	-2.21 ± 1.29
Baseline DAS28-ESR	<5.1	93	-2.24 ± 1.04	97	-2.15 ± 1.07
	≥5.1	98	-2.78 ± 1.14	93	-3.00 ± 1.28
Baseline MTX dose	≤10 mg/week	97	-2.47 ± 1.08	97	-2.55 ± 1.35
	>10 mg/week	94	-2.57 ± 1.16	93	-2.58 ± 1.14

ADL: adalimumab; DAS: disease activity score; DMARD: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; MTX: methotrexate; SD: standard deviation.

Supplementary Table S3. Low disease activity rates and remission rates in DAS28-ESR (full analysis set).

	L-L arm (n=191)	A-L arm (n=96)	A-A arm (n=94)
Low disease activity rates, n (%)			
Week 12	52 (27.2)	38 (39.6)	39 (41.5)
Week 24	66 (34.6)	45 (46.9)	41 (43.6)
Week 52	91 (47.6)	47 (49.0)	48 (51.1)
Remission rates, n (%)			
Week 12	25 (13.1)	14 (14.6)	14 (14.9)
Week 24	36 (18.8)	24 (25.0)	22 (23.4)
Week 52	47 (24.6)	33 (34.4)	29 (30.9)

A: adalimumab reference product; DAS: disease activity score; ESR: erythrocyte sedimentation rate; L: LBAL.

Supplementary Table S4. EULAR response.

A: Full analysis set

	L-L arm (n=191)	A-L arm (n=96)	A-A arm (n=94)
Week 12, n (%)			
Good response	52 (27.2)	37 (38.5)	39 (41.5%
Moderate response	115 (60.2)	47 (49.0)	46 (48.9)
No response	24 (12.6)	12 (12.5)	9 (9.6)
Week 24, n (%)			
Good response	65 (34.0)	45 (46.9)	40 (42.6)
Moderate response	102 (53.4)	40 (41.7)	44 (46.8)
No response	24 (12.6)	11 (11.5)	10 (10.6)
Week 52, n (%)			
Good response	91 (47.6)	46 (47.9)	48 (51.1)
Moderate response	69 (36.1)	36 (37.5)	37 (39.4)
No response	31 (16.2)	14 (14.6)	9 (9.6)

Missing data were imputed as "no response".

B: Per protocol set

	L-L arm (n=153)	A-L arm (n=78)	A-A arm (n=82)
Week 12, n (%)			
Good response	45 (29.4)	33 (42.3)	37 (45.1)
Moderate response	96 (62.7)	37 (47.4)	38 (46.3)
No response	12 (7.8)	8 (10.3)	7 (8.5)
Week 24, n (%)			
Good response	60 (39.2)	38 (48.7)	38 (46.3)
Moderate response	87 (56.9)	36 (46.2)	41 (50.0)
No response	6 (3.9)	4 (5.1)	3 (3.7)
Week 52, n (%)			
Good response	87 (56.9)	41 (52.6)	47 (57.3)
Moderate response	65 (42.5)	35 (44.9)	35 (42.7)
No response	1 (0.7)	2 (2.6)	0

A: adalimumab reference product; EULAR: European League Against Rheumatism; L: LBAL.

Supplementary Table S5. Serious infections (safety set).

	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)
Overall (Baseline to Week 56)			
Peritoneal tuberculosis	1.0 (2)	0	0
Pneumonia	1.0 (2)	0	0
Urinary tract infection	1.0 (2)	1.0 (1)	0
Atypical mycobacterial infection	0.5 (1)	0	0
Cellulitis	0.5 (1)	1.0 (1)	0
Cytomegalovirus enterocolitis	0.5 (1)	0	0
Herpes zoster	0.5 (1)	0	0
Meningitis	0.5 (1)	0	0
Osteomyelitis	0.5 (1)	0	0
Pneumocystis jirovecii pneumonia	0.5 (1)	0	0
Post-procedural infection	0.5 (1)	0	0
Pulmonary tuberculosis	0.5 (1)	0	0
Sepsis	0.5 (1)	0	0
Staphylococcal infection	0.5 (1)	0	0
Upper respiratory tract infection	0.5 (1)	0	0
Appendicitis	0	1.0 (1)	0
Influenza	0	1.0 (1)	0

A: adalimumab reference product; L: LBAL.

Supplementary Table S6. Adverse events of special interest according to treatment period (safety set).

	Period I (Baseline to Week 24)		Period II (Week 24 to Week 52)		
	LBAL group (n=192) % (n)	ADL group (n=191) % (n)	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)
Any AESIs	42.2 (81)	40.8 (78)	29.7 (57)	29.2 (28)	32.6 (31)
Infections (serious, non-serious, overall)	32.8 (63)	32.5 (62)	24.5 (47)	25.0 (24)	27.4 (26)
Allergic reaction	6.8 (13)	2.6 (5)	4.2 (8)	2.1 (2)	5.3 (5)
Hepatic function disorder	5.2 (10)	2.1 (4)	1.0 (2)	0 1.1 (1)	
Injection site reactions	3.6 (7)	7.3 (14)	1.0 (2)	4.2 (4)	3.2 (3)
Tuberculosis	2.1 (4)	0	1.6 (3)	1.0 (1)	0
Interstitial lung disease	2.1 (4)	1.0 (2)	0.5 (1)	0	0
Heart failure	0.5 (1)	1.0 (2)	0.5 (1)	0	2.1 (2)
Psoriasis	0.5 (1)	0	0.5 (1)	0	0
Blood disorder	0.5 (1)	0.5 (1)	0	0	0
Malignancies	0	0	0.5 (1)	1.0 (1)	0
Lupus erythematosus	0	0.5 (1)	0	0	0
Demyelinating disorders:	0	0	0	0	0
Hepatitis B reactivation	0	0	0	0	0
Sarcoidosis	0	0	0	0	0

A: adalimumab reference product; ADL: adalimumab; AESI: adverse events of special interest; L: LBAL.

Supplementary Table S7. Incidence rates of anti-drug antibody and neutralising antibody (safety set).

Treatment arm	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)
ADA			
Baseline	0	0	1.1 (1)
Week 12	3.1 (6)	4.2 (4)	5.3 (5)
Week 24	4.7 (9)	7.3 (7)	4.2 (4)
Week 52	2.6 (5)	5.2 (5)	3.2 (3)
Anytime during the study period	8.3 (16)	11.5 (11)	8.4 (8)
New positive during period II	0.5 (1)	2.1 (2)	1.1 (1)
nAb			
Baseline	0	0	0
Week 12	3.1 (6)	4.2 (4)	5.3 (5)
Week 24	4.2 (8)	7.3 (7)	4.2 (4)
Week 52	2.6 (5)	4.2 (4)	3.2 (3)
Anytime during the study period	7.8 (15)	10.4 (10)	8.4 (8)
New positive during period II	0.5 (1)	1.0 (1)	1.1 (1)

ADA: anti-drug antibody; A: adalimumab reference product; L: LBAL; nAb: neutralising antibodies.

Supplementary Table S8. EULAR response and ACR response rates by presence of ADA.

		L-L arm	A-A arm
Rate of patients having change from baseline in DAS28-ESR ≤0.6			
ADA Positive [a]	Week 12	13.3% (2/15)	0% (0/8)
	Week 24	6.3% (1/16)	25.0% (2/8)
	Week 52	12.5% (2/16)	25.0% (2/8)
ADA Negative	Week 12	5.1% (9/175)	5.8% (5/86)
	Week 24	4.0% (7/175)	1.2% (1/86)
	Week 52	3.4% (6/175)	1.2% (1/86)
ACR20 response rate			
ADA Positive [a]	Week 12	56.3% (9/16)	100% (8/8)
	Week 24	62.5% (10/16)	62.5% (5/8)
	Week 52	56.3% (9/16)	50.0% (4/8)
ADA Negative	Week 12	80.6% (141/175)	83.7% (72/86)
	Week 24	85.7% (150/175)	89.5% (77/86)
	Week 52	81.7% (143/175)	84.9% (73/86)

[a]All patients who had a positive test at any time during the study period are included.
A: adalimumab reference product; ACR: American College of Rheumatology; ADA: anti-ADL antibodies; ADL: DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; L: LBAL

Supplementary Table S9. Incidence rates of adverse events and adverse drug reactions by presence of ADA (safety set).

		L-L arm	A-A arm
AE	Total	81.3% (156/192)	85.3% (81/95)
	ADA positive [a]	87.5% (14/16)	75.0% (6/8)
	ADA negative	80.7% (142/176)	86.2% (75/87)
ADR	Total	49.0% (94/192)	46.3% (44/95)
	ADA positive [a]	50.0% (8/16)	50.0% (4/8)
	ADA negative	48.9% (86/176)	46.0% (40/87)

[a]All patients who had a positive test at any time during the study period were included.
A: adalimumab reference product; ADA: anti-drug antibody; ADR: adverse drug reaction; AE: adverse event; L: LBAL.

Supplementary Table S10. Prevalence rates of risk factors for infection occurrence at baseline (safety set).

Risk factors	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)	Difference [L-L] – [A-A] %	Difference [A-L] – [A-A] %
1. Concomitant pulmonary disease [a]	22.4 (43)	20.8 (20)	14.7 (14)	7.7	6.1
2. Concomitant diabetes [b]	13.0 (25)	8.3 (8)	10.5 (10)	2.5	-2.2
3. MTX >8 mg/week	73.4 (141)	79.2 (76)	77.9 (74)	–4.5	1.3
4. Corticosteroids >5 mg/day	14.6 (28)	10.4 (10)	10.5 (10)	4.1	-0.1
5. Age ≥65 years	25.0 (48)	20.8 (20)	22.1 (21)	2.9	-1.3

[a] Pulmonary disease: disease including "lung", "pulmonary", "tuberculous" and "emphysema" as a preferred term "in Concomitant Disease or Previous Condition" coded using MedDRA.
[b] Diabetes: disease including "diabetes" as a preferred term "in Concomitant Disease or Previous Condition" coded using MedDRA.
A: adalimumab reference product; L: LBAL; MedDRA: medical dictionary for regulatory activities; MTX: methotrexate.