SUPPLEMENTARY MATERIAL

A randomised phase IIb study of mavrilimumab, a novel GM−CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis

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Study-stopping criteria

Study-stopping criteria included, death related to the investigational product, any life-threatening event considered related to mavrilimumab, any unforeseen events or clinically significant pulmonary abnormalities that might contraindicate further dosing, hepatic function abnormality, and anaphylaxis and severe hypersensitivity reaction.

Randomisation and masking

A patient was considered randomised into the study when the investigator's designee notified the interactive web response system (IWRS) that the patient met eligibility criteria and the IWRS provided the assignment of blinded investigational product kit numbers for the patient. The IWRS was managed at the site by an unblinded team who acted as the unblinded investigational product manager (site investigational product manager).

The procedure for using IWRS was as follows:

- The site investigational product manager contacted the IWRS and provided the patient identification (SID) number and patient's baseline characteristic(s) used to verify that it was the same patient
- The IWRS assigned a treatment arm and investigational product kit number(s) to the patient from the appropriate stratum
- Confirmation of this information was sent to the site investigational product manager who dispensed the investigational product to the patient per the response system and recorded the appropriate information in the patient's medical records and investigational product accountability log

The investigational product (mavrilimumab or placebo) had to be administered on the same day the investigational product was assigned. If there was a delay in the administration of the investigational product such that it would not be administered within the specified timeframe, the study monitor had to be notified immediately.

Blinding

This was a double-blind study in which mavrilimumab and placebo were distinguishable in appearance/viscosity. However, neither the patients nor any of the investigators or sponsor staff who were involved in the treatment or clinical evaluation of the patients, were aware of the treatment received (International Conference on Harmonisation [ICH] E9). Since mavrilimumab and placebo were distinguishable, the investigational product was handled by an unblinded investigational product manager at the site and was administered by an unblinded study team member who was not involved in the management of study patients. An independent investigational product monitor was also unblinded to perform investigational product accountability. In the event that the treatment allocation for a patient became known to the investigator or other study staff involved in the management of study patients, or needed to be known to treat an individual patient for an adverse event, the sponsor had to be notified immediately by the investigator.

Assessments for primary outcomes

DAS28−CRP assessments consisted of 28 of the 68 tender joint counts (TJC) and 28 of the 66 swollen joint counts (SJC), and patient's global health using patient global assessment (PGA) of disease activity and visual analogue scale of 0 (=no pain), and 100 (=severe pain), plus CRP concentration. The core components of the ACR response criteria were TJC, SJC, CRP/ESR, patient assessment of pain, physician's global assessment of disease activity, PGA of disease activity, and health assessment questionnaire disability index. The derivation of ACR20 and DAS28 was done by the sponsor using the above components.

Sensitivity analyses

Two sensitivity analyses were performed for the change from baseline DAS28−CRP analysis to allow for patients withdrawing from treatment. Firstly, a Last Observation Carried Forward (LOCF) approach was used where the DAS28−CRP change from baseline at the time of withdrawal was carried forward to all subsequent visits. Secondly, a Baseline Observation Carried Forward (BOCF) approach was used where a change from baseline of zero was used for all visits after withdrawal.

Anti-drug antibodies (ADA) summary

Methods

Mavrilimumab concentrations were measured as previously described.[1] In brief, ADA responses to mavrilimumab were determined by a validated homogeneous double antigen bridging assay that was conducted with biotin and digoxigenin conjugated mavrilimumab and ADA/drug complexes were captured onto streptavidin plates with horse radish peroxidase-labelled anti-digoxigenin used for detection. Screening and confirmatory cut points were statistically determined. A cell-based proliferation assay was applied to detect neutralising antibodies to mavrilimumab using TF-1 cells, a GM–CSF-dependent cell line. Briefly, GM–CSF, which stimulates cell proliferation by binding to its receptor, and mavrilimumab, a competitive inhibitor of GM–CSF, were added to cells to maintain a basal level of growth. In the presence of neutralising antibody, mavrilimumab is blocked and GM–CSF binds to its receptor resulting in cell proliferation.

Results

Thirteen patients tested ADA positive in the mavrilimumab 30 mg eow group, three patients in the mavrilimumab 100 mg eow group, and two patients in the placebo group (table). Among ADA-positive patients receiving mavrilimumab 30 mg eow, only one tested neutralising antibody positive. Thus, 1/81 patients or 1·2% of the patients developed a persistent neutralising ADA response in the 30 mg group**.**

Table

	Mavrilimumab			
	150 mg eow	**100 mg eow**	**30 mg eow**	**Placebo**
ADA positive	0	3	13	2
Pre-dose ADA positive	–	0	1	NA
Post-dose ADA positive	–	3	12	NA
Persistent ADA*	–	0	2	NA
Neutralising antibody positive	–	0	1†	NA
Transient ADA	–	3	10	NA

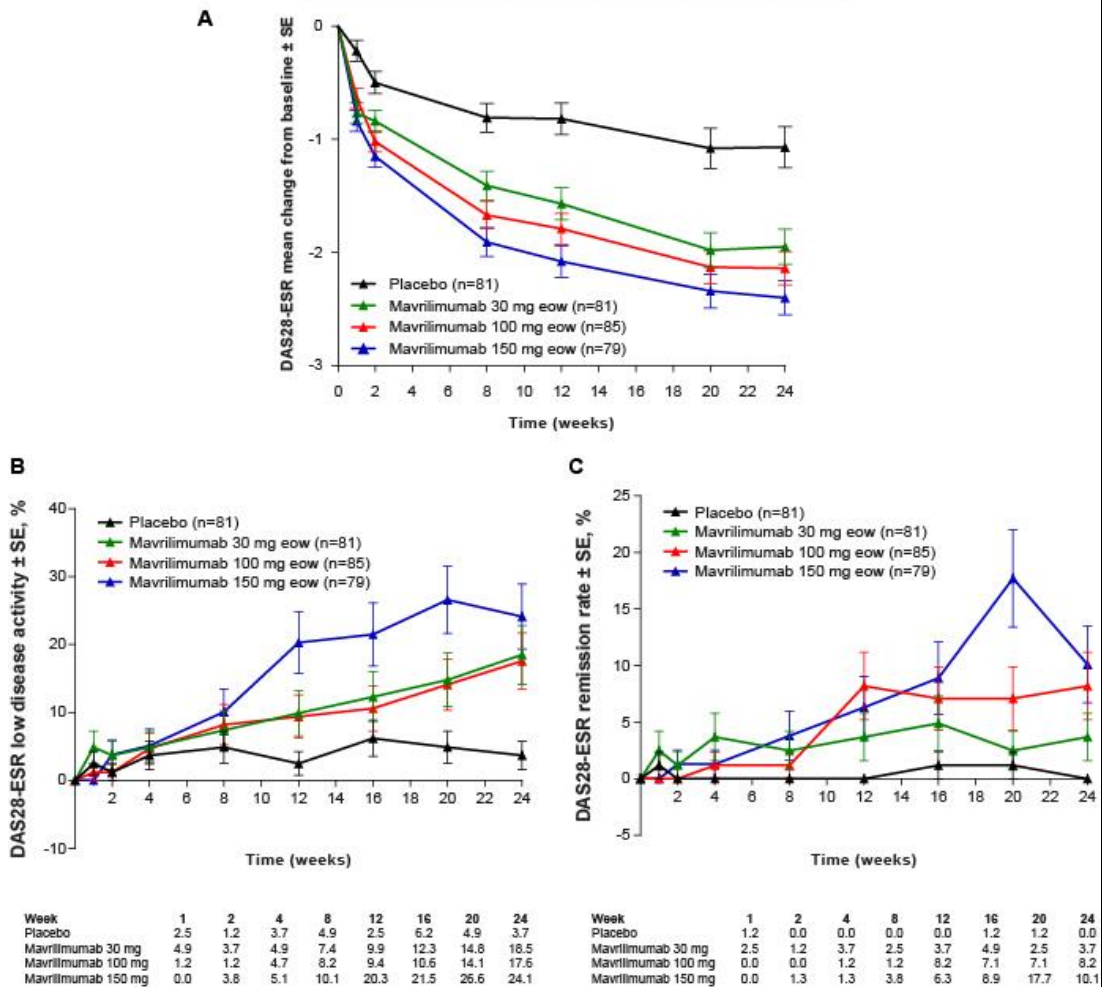
*Two or more positive ADA time points ≥16 weeks apart. †One of the two patients with persistent ADA tested positive for neutralising antibody and consistently displayed low drug concentrations from day 85 through the rest of the study. ADA=anti-drug antibodies. Eow= every other week. NA=not available.

Reference

1. Burmester GR, Feist E, Sleeman MA, Wang B, White B, Magrini F. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-α, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study. *Ann Rheum Dis* 2011; **70**(9): 1542-9.

Figure S1: **Changes from baseline in DAS28−ESR score (A), DAS28−ESR low disease activity responders (B) DAS28−ESR remission rate (C)**

	Mavrilimumab			
	150 mg eow (n=79)	100 mg eow (n=85)	30 mg eow (n=81)	Placebo (n=81)
Baseline mean	6.52	6.68	6.67	6.58
Adjusted mean change from baseline at Week 1	-0.84	-0.64	-0.77	-0.22
Adjusted mean change from baseline at Week 12	-2.08	-1.79	-1.57	-0.82
Adjusted mean change from baseline at Week 24	-2.40	-2.14	-1.95	-1.07

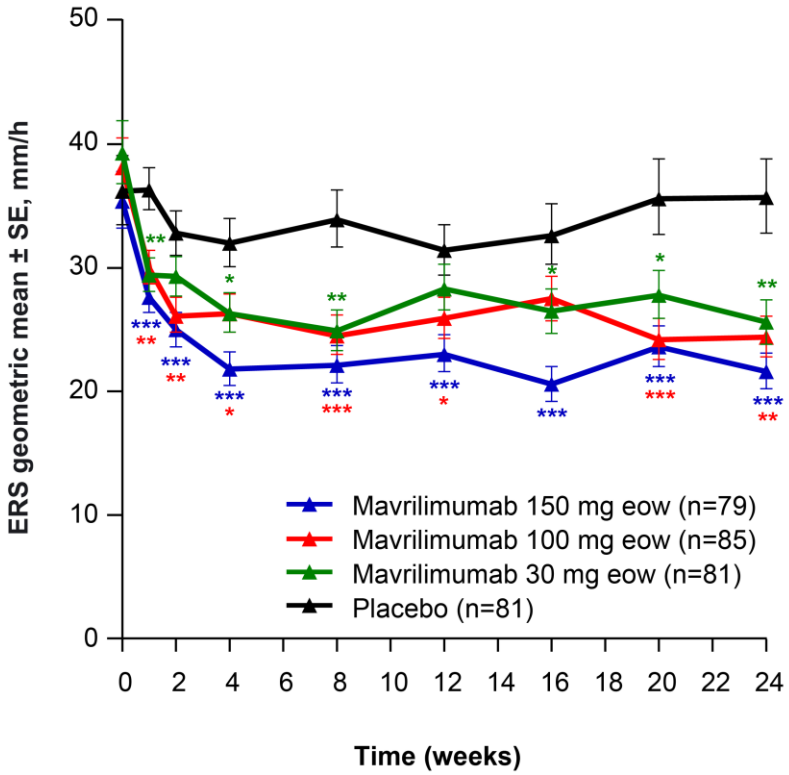


Week	1	2	4	8	12	16	20	24
Placebo	2.5	1.2	3.7	4.9	2.5	6.2	4.9	3.7
Mavrilimumab 30 mg	4.9	3.7	4.9	7.4	9.9	12.3	14.8	16.5
Mavrilimumab 100 mg	1.2	1.2	4.7	8.2	9.4	10.6	14.1	17.6
Mavrilimumab 150 mg	0.0	3.8	5.1	10.1	20.3	21.5	26.6	24.1

Week	1	2	4	8	12	16	20	24
Placebo	1.2	0.0	0.0	0.0	0.0	1.2	1.2	0.0
Mavrilimumab 30 mg	2.5	1.2	3.7	2.5	3.7	4.9	2.5	3.7
Mavrilimumab 100 mg	0.0	0.0	1.2	1.2	8.2	7.1	7.1	8.2
Mavrilimumab 150 mg	0.0	1.3	1.3	3.8	6.3	8.9	17.7	10.1

DAS28=disease activity score 28. ESR=erythrocyte sedimentation rate.

Figure S2: **Adjusted geometric mean ESR (mm/hr)**



Week	1	2	4	8	12	16	20	24
Placebo	36.3	32.8	32.0	33.9	31.4	32.6	35.6	35.7
Mavrilimumab 30 mg	29.4	29.3	26.3	24.9	28.3	26.5	27.8	25.6
Mavrilimumab 100 mg	30.0	26.1	26.3	24.5	25.9	27.5	24.2	24.4
Mavrilimumab 150 mg	27.6	25.0	21.8	22.1	23.0	20.6	23.6	21.6

*p<0·05; **p<0·01; ***p<0·001 mavrilimumab versus placebo. eow=every other week. ESR=erythrocyte sedimentation rate. SE=standard error.

Table S1: **Number of patients randomised by country.**

	Mavrilimumab			
Country	**150 mg eow (n=79)**	**100 mg eow (n=85)**	**30 mg eow (n=81)**	**Placebo (n=81)**
Number of patients randomised, n (%)				
Argentina	8 (10·1)	8 (9·4)	8 (9·9)	7 (8·6)
Bulgaria	2 (2·5)	2 (2·4)	2 (2·5)	3 (3·7)
Chile	8 (10·1)	9 (10·6)	10 (12·3)	10 (12·3)
Colombia	4 (5·1)	4 (4·7)	4 (4·9)	5 (6·2)
Czech Republic	13 (16·5)	14 (16·5)	13 (16·0)	13 (16·0)
Estonia	5 (6·3)	6 (7·1)	6 (7·4)	6 (7·4)
Germany	2 (2·5)	3 (3·5)	2 (2·5)	2 (2·5)
Hungary	2 (2·5)	2 (2·4)	1 (1·2)	2 (2·5)
Poland	10 (12·7)	10 (11·8)	8 (9·9)	9 (11·1)
Russian Federation	8 (10·1)	8 (9·4)	9 (11·1)	8 (9·9)
Serbia	6 (7·6)	6 (7·1)	6 (7·4)	6 (7·4)
South Africa	1 (1·3)	0 (0·0)	1 (1·2)	0 (0·0)
Spain	0 (0·0)	1 (1·2)	0 (0·0)	0 (0·0)
Ukraine	10 (12·7)	12 (14·1)	11 (13·6)	10 (12·3)

eow=every other week.

Table S2: **Prior traditional and biologic DMARDs**

	Mavrilimumab			
	150 mg eow (n=79)	**100 mg eow (n=85)**	**30 mg eow (n=81)**	**Placebo (n=81)**
Traditional DMARD, n (%)				
Aurotioprol	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Azathioprine	1 (1.3)	1 (1.2)	3 (3.7)	0 (0.0)
Chloroquine	4 (5.1)	1 (1.2)	0 (0.0)	2 (2.5)
Chloroquine phosphate	1 (1.3)	3 (3.5)	6 (7.4)	6 (7.4)
Ciclosporin	1 (1.3)	0 (0.0)	4 (4.9)	1 (1.2)
Cyclophosphamide	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fostamatinib	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)
Fostamatinib disodium	1 (1.3)	2 (2.4)	0 (0.0)	0 (0.0)
Gold	1 (1.3)	2 (2.4)	1 (1.2)	0 (0.0)
Hydroxychloroquine	1 (1.3)	1 (1.2)	1 (1.2)	1 (1.2)
Hydroxychloroquine sulphate	4 (5.1)	4 (4.7)	5 (6.2)	3 (3.7)
Investigational drug	1 (1.3)	1 (1.2)	2 (2.5)	1 (1.2)
Leflunomide	9 (11.4)	11 (12.9)	10 (12.3)	9 (11.1)
Methotrexate	23 (29.1)	29 (34.1)	30 (37.0)	29 (35.8)
Methotrexate sodium	2 (2.5)	1 (1.2)	2 (2.5)	2 (2.5)
Other antineoplastic agents	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Penicillamine	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Sodium aurothiomalate	2 (2.5)	1 (1.2)	5 (6.2)	3 (3.7)
Sulfasalazine	17 (21.5)	14 (16.5)	20 (24.7)	10 (12.3)
Tofacitinib	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Biologic DMARD				
Abatacept	0 (0.0)	1 (1.2)	1 (1.2)	1 (1.2)
Adalimumab	2 (2.5)	2 (2.4)	0 (0.0)	0 (0.0)
Brodalumab	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Certolizumab pegol	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Entanercept	1 (1.3)	2 (2.4)	1 (1.2)	4 (4.9)
Golimumab	0 (0.0)	2 (2.4)	4 (4.9)	0 (0.0)
Immunoglobulin G human	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Immunosuppressants	0 (0.0)	1 (1.2)	0 (0.0)	2 (2.5)
Infliximab	0 (0.0)	1 (1.2)	2 (2.5)	0 (0.0)

Investigational drug	1 (1.3)	1 (1.2)	3 (3.7)	1 (1.2)
Ofatumumab	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Rituximab	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.7)
Tocilizumab	4 (5.1)	3 (3.5)	0 (0.0)	0 (0.0)

DMARD=disease-modifying antirheumatic drug.

Table S3: **ACR20 subgroup analysis at week 24**

	Mavrilimumab			
	150 mg eow	**100 mg eow**	**30 mg eow**	**PBO**
ACR20 responders: subgroup analysis				
Baseline CRP concentration				
Normal, n	27	22	32	24
Number (%) of responders	21 (77.8)	14 (63.6)	21 (65.6)	6 (25.0)
Greater than ULN, n*	52	63	49	57
Number (%) of responders	37 (71.2)	38 (60.3)	20 (40.8)	14 (24.6)
Rheumatoid factor- and ACPA-negative				
at baseline, n	16	16	11	16
Number (%) of responders	12 (75.0)	11 (68.8)	5 (45.5)	4 (25.0)
Prior use of biologics, n	10	13	12	12
Number (%) of responders	8 (80.0)	3 (23.1)	3 (25.0)	3 (25.0)
Smoking status				
Smoker, n	12	14	16	15
Number (%) of responders	10 (83.3)	10 (71.4)	7 (43.8)	3 (20.0)
Non-smoker, n	67	71	65	66
Number (%) of responders	48 (71.6)	42 (59.2)	34 (52.3)	17 (25.8)

*The upper limit of normal for CRP (high sensitivity) was 3 mg/L. ACPA=anti-citrullinated protein antibody. ACR=American College of Rheumatology. CRP=C–reactive protein. Eow=every other week. ULN=Upper limit of normal.

Table S4: **ACR and DAS28 components (top) and SF-36 MCS and PCS (bottom) at weeks 12 and 24**

	Week 12				Week 24			
	Mavrilimumab				Mavrilimumab			
	150 mg eow (n=79)	100 mg eow (n=85)	30 mg eow (n=81)	PBO (n=81)	150 mg eow (n=79)	100 mg eow (n=85)	30 mg eow (n=81)	PBO (n=81)
ACR and DAS28 components*								
SJC†								
Adjusted mean change from BL (SE)	–10.6 (0.770)	–9.69 (0.748)	–9.34 (0.768)	–3.34 (0.772)	–11.96 (0.787)	–11.18 (0.771)	–10.65 (0.809)	–4.97 (0.932)
Adjusted mean difference from PBO (SE)	–7.26 (1.089)	–6.35 (1.076)	–6.00 (1.091)		–7.00 (1.219)	–6.21 (1.211)	–5.68 (1.237)	
(95% CI)‡	(–9.40, –5.12)	(–8.47, –4.24)	(–8.14, –3.85)		(–9.40, –4.59)	(–8.60, –3.82)	(–8.12, –3.24)	
p-value‡	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
TJC†								
Adjusted mean change from BL (SE)	–15.97 (1.233)	–14.72 (1.196)	–13.13 (1.227)	–5.62 (1.231)	–18.32 (1.234)	–16.35 (1.207)	–15.14 (1.265)	–7.90 (1.447)
Adjusted mean difference from PBO (SE)	–10.34 (1.742)	–9.10 (1.716)	–7.51 (1.738)		–10.42 (1.901)	–8.45 (1.884)	–7.24 (1.922)	
(95% CI)‡	(–13.77, –6.91)	(–12.47, –5.72)	(–10.93, –4.09)		(–14.17, –6.67)	(–12.16, –4.74)	(–11.02, –3.45)	
p-value‡	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Physician global assessment of disease activity§								
Adjusted mean change from BL (SE)	–3.52 (0.239)	–3.42 (0.232)	–3.24 (0.237)	–1.68 (0.239)	–3.95 (0.243)	–3.85 (0.241)	–3.81 (0.254)	–2.39 (0.305)
Adjusted mean difference from PBO (SE)	–1.84 (0.338)	–1.73 (0.333)	–1.56 (0.337)		–1.56 (0.391)	–1.46 (0.389)	–1.41 (0.397)	
(95% CI)‡	(–2.51, –1.18)	(–2.39, –1.08)	(–2.22, –0.89)		(–2.33, –0.79)	(–2.23, –0.69)	(–2.20, –0.63)	
p-value‡	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	

Patient global assessment of disease activity†§								
Adjusted mean change	–21.95	–17.89	–16.75	–9.94	–25.69	–22.40	–21.06	–20.21
from BL (SE)	(2.441)	(2.370)	(2.432)	(2.446)	(2.600)	(2.560)	(2.685)	(3.148)
Adjusted mean difference	–12.01	–7.95	–6.80		–5.48	–2.19	–0.85	
from PBO (SE)	(3.457)	(3.405)	(3.449)		(4.083)	(4.058)	(4.137)	
(95% CI)‡	(–18.81, –5.21)	(–14.65, –1.25)	(–13.59, –0.02)		(–13.52, 2.55)	(–10.18, 5.79)	(–8.99, 7.29)	
p-value‡	<0.001	0.020	0.049		0.180	0.589	0.837	
Patient assessment of pain§								
Adjusted mean change	–23.35	–19.15	–16.30	–8.11	–26.53	–23.31	– 23.14	–15.20
from BL (SE)	(2.392)	(2.321)	(2.383)	(2.394)	(2.483)	(2.446)	(2.563)	(3.006)
Adjusted mean difference	–15.24	–11.05	–8.19		–11.32	–8.11	–7.94	
from PBO (SE)	(3.384)	(3.335)	(3.378)		(3.899)	(3.876)	(3.950)	
(95% CI)‡	(–21.90, –8.58)	(–17.61, –4.48)	(–14.84, –1.55)		(–19.00, –3.65)	(–15.73, –0.48)	(–15.72, –0.17)	
p-value‡	<0.001	0.001	0.016		0.004	0.037	0.045	
HAQ DI§								
Adjusted mean change	–0.47	–0.39	–0.27	–0.26	–0.55	–0.46	–0.37	–0.29
from BL (SE)	(0.058)	(0.056)	(0.058)	(0.058)	(0.069)	(0.068)	(0.072)	(0.081)
Adjusted mean difference	–0.21	–0.13	–0.01		–0.26	–0.16	–0.08	
from PBO (SE)	(0.082)	(0.080)	(0.082)		(0.107)	(0.106)	(0.108)	
(95% CI)‡	(–0.37, –0.05)	(–0.29, 0.03)	(–0.17, 0.15)		(–0.47, –0.05)	(–0.37, 0.04)	(–0.29, 0.14)	
p-value‡	0.010	0.099	0.871		0.017	0.124	0.479	
SF-36								
MCS								
Adjusted mean change	5.63	5.06	3.07	1.64	5.38	4.17	3.94	3.11
from BL (SE)	(1.025)	(1.002)	(1.025)	(1.046)	(1.069)	(1.058)	(1.117)	(1.345)
Adjusted mean difference	3.99	3.42	1.43		2.27	1.07	0.84	
from PBO (SE)	(1.464)	(1.449)	(1.464)		(1.718)	(1.712)	(1.749)	
(95% CI)‡	(1.11, 6.87)	(0.57, 6.27)	(-1.45, 4.31)		(-1.11, 5.65)	(-2.30, 4.43)	(-2.61, 4.28)	
p-value‡	0.007	0.019	0.331		0.187	0.534	0.633	

PCS								
Adjusted mean change	6.24	5.13	4.29	2.84	7.58	6.55	5.44	3.21
from BL (SE)	(0.753)	(0.736)	(0.757)	(0.767)	(0.883)	(0.875)	(0.924)	(1.097)
Adjusted mean difference	3.40	2.29	1.45		4.38	3.34	2.23	
from PBO (SE)	(1.075)	(1.064)	(1.077)		(1.408)	(1.403)	(1.434)	
(95% CI)‡	(1.29, 5.52)	(0.20, 4.38)	(-0.67, 3.57)		(1.60, 7.15)	(0.58, 6.10)	(-0.59, 5.06)	
p-value‡	0.002	0.032	0.178		0.002	0.018	0.120	

*Adjusted geometric mean ratio to baseline in CRP and ESR concentrations are reported in figures 4A and S3 respectively. †DAS28 component. ‡Adjusted mean difference for mavrilimumab–placebo. §ACR component. BL=baseline. eow=every other week. HAQ DI=Health assessment questionnaire disability index. MCS=Mental Component Summary. PBO=placebo. PCS=Physical Component Summary. SE=standard error. SF-36= Short-Form 36 Health Survey. SJC=swollen joint count. TJC=tender joint count.

Table S5: **Mean change from baseline in pulmonary function tests, dyspnoea score, and oxygen saturation at weeks 12 and 24.**

	Week 12				Week 24			
	Mavrilimumab				Mavrilimumab			
	150 mg eow (n=79)	100 mg eow (n=85)	30 mg eow (n=81)	PBO (n=81)	150 mg eow (n=79)	100 mg eow (n=85)	30 mg eow (n=81)	PBO (n=81)
Pulmonary function tests								
FEV_1, L (SD)	−0·028 (0·339)	−0·003 (0·340)	−0·027 (0·203)	−0·005 (0·284)	−0·088 (0·299)	−0·001 (0·311)	−0·034 (0·226)	−0·053 (0·240)
Percentage predicted FEV_1, % (SD)	−0·7 (10·6)	−0·1 (11·7)	−0·3 (6·6)	0·1 (10·0)	−3·3 (10·3)	0·1 (10·9)	0·0 (6·8)	−1·1 (10·3)
FEV_6, L (SD)	−0·069 (0·339)	−0·085 (0·393)	−0·063 (0·342)	0·019 (0·297)	−0·136 (0·424)	−0·060 (0·330)	−0·064 (0·348)	0·004 (0·324)
Percentage predicted FEV_6, % (SD)	−1·6 (10·7)	−0·6 (11·3)	−3·1 (9·7)	0·6 (9·2)	−3·2 (14·1)	0·1 (11·8)	−1·2 (7·4)	1·5 (11·6)
FVC, L (SD)	−0·057 (0·374)	−0·034 (0·452)	−0·022 (0·216)	0·072 (0·500)	−0·103 (0·395)	0·008 (0·378)	−0·032 (0·233)	−0·038 (0·319)
Percentage predicted FVC, % (SD)	−1·7 (11·0)	−0·4 (13·5)	−0·4 (6·8)	2·1 (13·8)	−3·2 (10·5)	0·5 (11·5)	−0·3 (6·9)	−0·3 (11·1)
Dyspnoea score								
Dyspnoea score (SD)	−0·10 (1·27)	0·02 (0·62)	−0·04 (0·68)	−0·07 (0·71)	−0·16 (0·84)	−0·02 (0·66)	−0·08 (0·42)	0·01 (0·73)
Oxygen saturation								
Oxygen saturation level (SD)	0·2 (1·6)	0·2 (1·3)	0·1 (1·4)	0·0 (1·4)	0·1 (1·4)	−0·1 (1·4)	−0·1 (1·3)	−0·2 (1·3)

BL=baseline. eow=every other week. FEV_1=forced expiratory volume in 1 second. FEV_6=forced expiratory volume in 6 seconds. FVC=forced vital capacity. PBO=placebo. SD=standard deviation.

Table S6: **ACR/EULAR response criteria**

DAS28 improvement	**>1·2**	**>0·6 and ≤1·2**	**≤0·6**
Present DAS28			
≤3·2	Good response	Moderate response	No response
>3·2 and ≤5·1	Moderate response	Moderate response	No response
>5·1	Moderate response	No response	No response

ACR=American College of Rheumatology. DAS28=disease activity score 28. EULAR= European League Against Rheumatism.