

APPENDIX (SUPPLEMENTARY MATERIAL)

METHODS

Safety

For patients who discontinued prematurely, safety was assessed at 7, 28, 56 and 85 days after the last dose of study medication. Events in the DB period are reported up to and including 56 days after last dose of study medication for patients who discontinued, and up to first dose in the OLE for patients who continued; for the OLE, events up to and including 56 days after last study dose are reported.

MRI data

The subject's hand/wrist with the most synovitis based on a clinical assessment at baseline was selected for imaging. MRI data collected for the trial were sent to a central reading facility for interpretation according to the OMERACT 2002 RAMRIS (OMERACT 6)^{18, 35} method in the manner described below. The central reader was blinded to the identity of the study drug assignment and order of the time points.

Scoring was standardised and performed in the following manner according to the OMERACT 2002 RAMRIS grading scheme:

Synovitis: Synovitis was assessed as above-normal post-gadolinium enhancement in three wrist regions (the distal radioulnar joint; the radiocarpal joint; the intercarpal and carpometacarpal [CMC] joints) using a 0–3 scale, representing the presumed maximum volume of enhancing tissue in the synovial compartment. A score of 0 represents no synovitis, while a score of 3 indicates that the volume of gadolinium enhancing tissue comprised more than two-thirds of the assessed synovial compartment. A total synovitis score was calculated as the sum of the individual scores at each location (maximum achievable score for each hand/wrist was 9). Minimum score per wrist ranges from 0, indicating no damage, to 9 (score of 3x3 wrist regions), indicating most severe damage. Change in synovitis = Follow-up synovitis score – baseline score.

Erosion: The degree of erosion at 15 anatomical locations in each wrist (distal radius and ulna, eight carpal bones [trapezium, trapezoid, capitate, hamate, scaphoid, lunate, triquetrum, pisiform] and all five proximal metacarpals) and eight locations in each hand (four proximal interphalangeal and four distal MCP joints [joints 2–5]) was scored separately using a 0–10 scale, with each unit increment representing a 10% loss of articular bone compared

with the assessed bone volume (the peripheral 1 cm of articular bone for long bones, such as the radius, ulna, metacarpals and proximal phalanges, but the entire bone for carpals). A score of 10 represents > 90% compromise of the assessed bone by erosions. A total erosion score was calculated as the sum of the individual scores at each location (maximum achievable score for each hand/wrist was 230).

Osteitis: The degree of oedema at each of the same 23 anatomical locations as for the erosion assessments was scored separately using a 0–3 scale (mildest to strongest involvement), with each unit increment representing 33% of the volume of the peripheral 1 cm original (eroded + residual) articular bone. Thus, as articular bone erodes, the maximum potential score for oedema decreases. A total oedema score was calculated as the sum of the individual scores at each location (maximum achievable score for each hand/wrist was 69 [23x3]).

RESULTS

Safety

The SAEs reported were atrial fibrillation (resolved ≤ 3 days) and study drug overdose (due to planned weight loss; resolved ≤ 1 day) in the DB period. In the OLE, 10 events were reported in six patients; pneumonia, hyperthyroidism and post-operative wound infection (in the same patient), study drug overdose and coronary artery disease (in the same patient), angina pectoris and study drug overdose (in the same patient) and chronic anaemia, worsening of RA, depression (all in one patient each). No SAEs resulted in discontinuation. The events of depression, hyperthyroidism, and coronary artery disease were considered severe; all other events were mild or moderate in intensity.

None of the infections reported in the DB period were serious. Twelve events were observed in 10 abatacept-treated patients; sinusitis (two patients [7.4%]), bronchitis, folliculitis, gastroenteritis, *Helicobacter* gastritis, mild herpes simplex, nasopharyngitis, rhinitis, upper respiratory tract infection, urinary tract infection and vaginal infection (one event each [3.7%]). The most common infection in the OLE were nasopharyngitis (11 patients [22.4%]) and oral herpes (three patients [6.1%]); all other infections occurred in two patients or fewer ($\leq 5\%$). One patient, originally randomised to placebo, experienced two serious infections in the OLE; post-operative wound infection and pneumonia. The latter was considered mild and unlikely related to study drug, and did not result in discontinuation.

No malignancy was reported during the trial. The one autoimmune event reported was hyperthyroidism (patient originally treated with placebo plus MTX), considered severe but not resulting in discontinuation.

(A)

	Abatacept + MTX (n=25)	Placebo + MTX (n=23)
Baseline mean scores (SD)		
Synovitis (wrists)	4.48 (2.10)	3.52 (2.43)
Erosion (wrist and hand)	12.60 (9.41)	9.65 (10.11)
Osteitis (wrist and hand)	7.72 (7.04)	8.00 (9.72)
Month 4 mean scores (SD)		
Synovitis (wrists)	4.04 (1.57)	4.04 (2.48)
Erosion (wrist and hand)	13.00 (9.39)	10.65 (9.97)
Osteitis (wrist and hand)	5.80 (5.31)	9.52 (10.88)
Adjusted mean change from baseline to Month 4 (SE)		
Synovitis (wrists; sensitivity analysis)	-0.31 (0.26)	0.38 (0.27)
Erosion (wrist and hand)	0.45 (0.43)	0.95 (0.45)
Osteitis (wrist and hand)	-1.94 (0.86)	1.54 (0.90)
Data are for the initial reading of the Month 4 MRIs, for patients with MRIs available.		

FIGURES



