

Supplementary Material

Table S1. Corticosteroid use by Treatment Group

	IE	IT	SE	ST	p-value*
N (%) of total in treatment arm	244 (32.3)	132 (17.5)	255 (33.8)	124 (16.4)	
N (%) using oral steroids at baseline	106 (43.4)	61 (46.2)	112 (43.9)	42 (33.9)	0.1788
N (%) using at baseline that discontinued use during trial	42/109 (38.5)	24/61 (39.3)	30/112 (26.8)	15/43 (34.9)	0.2166
N (%) not using at baseline that used during trial	101/138 (73.2)	57/71 (80.3)	104/143 (72.7)	68/82 (82.9)	0.2148
N (%) receiving one or more injections during trial	32 (13.1)	20 (15.2)	33 (12.9)	13 (10.5)	0.7394
Number Injections during trial, Median (range)	0 (0-4)	0 (0-3)	0 (0-3)	0 (0-2)	0.6992

***Unadjusted p-values**

Table S2. P-values for model effect utilizing various missing data approaches

	Completers Cohort²	LOCF³	NRI⁴	Observed⁵
N	365	755	755	See Below
p-values¹				
Treatment	0.9672	0.9170	0.8431	0.4793
Timing	0.0958	0.2144	0.8826	0.5501
Visit Month	0.0002	0.0076	0.1769	0.3600
Baseline DAS	<0.0001	<0.0001	<0.0001	<0.0001
Trt*Time	0.3015	0.7903	0.3679	0.2672
Trt*Visit	0.8036	0.4266	0.7324	0.6136
Trt*BL DAS	0.3869	0.1051	0.9862	0.8570
Time*Visit	0.1721	0.4654	0.1628	0.3618
Time*BL DAS	0.1682	0.5080	0.9612	0.1009
BL DAS*Visit	0.1434	0.0277	<0.0001	0.0583

1-Model selection: Full repeated measures mixed model with all interactions assessed, non-significant interactions removed, and the model fit with main effects and significant interactions. P-values for main effects and significant interactions are shown. P-values shown, effect estimates interpretations given under each specific method.

Treatment (Trt): MTX+ETN or MTX+SSZ+HCQ; Timing (Time): Immediate or Step-up; Visit Month: 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120; Baseline DAS (BL DAS): DAS28-ESR at initial TEAR Visit

2-Completers: 365 participants with all DAS28-ESR scores for all week 48-102; 127 (52%) IE, 59 (16%) ST; p-value on % with complete data weeks 48-102 = 0.29

Week 48 DAS28-ESR higher than weeks 72, 84, 96 and 102 (3.2 vs 3.0, 3.0, 3.0, 2.9, respectively)
Baseline DAS28-ESR: Effect estimate interpretation, every 1.0 higher at Baseline resulted in 0.4 higher DAS28-ESR

3-LOCF (Last Observation Carried Forward): Last observed DAS28-ESR carried forward for early terminations. Mean DAS28-ESR from adjacent visits given mean DAS28-ESR from adjacent visits

Baseline DAS28-ESR*Visit Interaction: Those with higher DAS28-ESR scores showed more improvement over time. Lower baseline DAS28-ESR scores showed less improvement over time

4-NRI (Non Responders Imputation): All early terminations were assigned a DAS28-ESR of 5.1 for all subsequent visits handled under LOCF assumptions

Baseline DAS28-ESR*Visit Interaction: Same interpretation as LOCF

5-Observed: All observed DAS28-ESR scores were used regardless of subsequent termination status. N for each visit: Week 48 (582), Week 60 (522), Week 84 (508), Week 96 (485), Week 102 (476)

Baseline DAS28-ESR*Visit Interaction: Same interpretation as LOCF

Table S3. Mean DAS28-ESR at each visit week utilizing various missing data techniques and at time of early termination

Analysis Set ¹	Mean DAS28-ESR at Visit Week (N if different from Baseline)									
	Baseline	12	24	36	48	60	72	84	96	
Completers Cohort										
IE	5.8	3.6	3.4	3.2	3.2	3.2	3.0	3.1	3.1	
IT	5.8	3.8	3.4	3.3	3.1	3.1	2.9	3.1	3.0	
SE	5.9	4.6	4.3	3.3	3.5	3.1	3.2	3.2	3.1	
ST	5.8	4.3	3.9	3.3	3.0	2.8	2.9	2.8	2.7	
LOCF										
IE	5.8	4.0	3.8	3.6	3.6	3.6	3.5	3.5	3.5	
IT	5.8	4.1	3.8	3.6	3.5	3.6	3.5	3.6	3.4	
SE	5.8	4.7	4.5	3.7	3.7	3.6	3.6	3.6	3.6	
ST	5.8	4.6	4.3	3.9	3.7	3.7	3.7	3.6	3.6	
NRI										
IE	5.8	3.9	3.8	3.6	3.6	3.7	3.6	3.7	3.7	
IT	5.8	4.1	3.8	3.7	3.5	3.7	3.7	3.8	3.7	
SE	5.8	4.7	4.4	3.7	3.7	3.7	3.7	3.7	3.8	
ST	5.8	4.4	4.2	3.8	3.6	3.6	3.7	3.6	3.6	
Observed										
IE	5.8	3.8	3.6	3.3	3.3	3.2	3.1	3.1	3.1	
IT	5.8	4.0	3.6	3.3	3.2	3.3	3.1	3.2	3.0	
SE	5.8	4.6	4.3	3.4	3.4	3.2	3.3	3.2	3.1	
ST	5.8	4.3	4.1	3.4	3.2	3.0	3.0	3.0	2.9	
Early Terminations DAS28-ESR at TEAR Quarterly Visit (N with Visit)										
IE	5.7(76)	4.2(60)	3.9(48)	3.6(43)	3.6(43)	3.4(21)	3.8(14)	3.3(7)	3.4(4)	
IT	5.6(46)	4.1(35)	3.9(28)	3.6(21)	3.5(21)	4.1(11)	3.3(7)	3.6(3)	4.1(2)	
SE	5.8(73)	4.8(56)	4.4(38)	3.8(31)	3.8(30)	3.3(16)	2.9(8)	3.7(6)	3.1(1)	
ST	5.9(43)	4.4(30)	4.5(21)	4.2(17)	4.2(17)	3.6(19)	3.5(5)	4.1(5)	5.3(2)	

1- Completers (N=365): Those with DAS28-ESR at all visits; LOCF (N=755): Last Observation Carried Forward with missing interim visits assigned mean value of adjacent visits; NRI (N=755): Non-Res Imputation with early terminations assigned DAS28-ESR of 5.1, missing interim visits handled under missingness assumptions; Observed (N varies by visit) utilizes all available DAS28-ESR regardless of subsequent termination status; IE, Immediate ETN+MTX; IT, Immediate SSZ+HCQ+MTX; SE, Step-up from MTX to SSZ+MTX+ETN if DAS28-ESR≥3.2 at Week 24; ST, Step-up from MTX to MTX+SSZ+HCQ if DAS28-ESR≥3.2 at Week 24.