Online Appendix

Methods: RAPID3 scores during the first week of treatment

The initial printing of the case report form had an error in question 1 of the Patient Take Home Form, where the time frame "Over the past week" was used rather than the correct time frame "Over the past 24 hours." This error was corrected, and updated CRF pages were released to the study sites. Because of the printing error that affected 214 patients, the analyses were also performed for the subset of the intent-to-treat population not affected by the CRF error. In this second analysis, mean improvement in Routine Assessment of Patient Index Data score was still greater in the tocilizumab vs placebo group at day 7, but the difference was not statistically significant (–0.88 vs –0.50 in the tocilizumab and placebo groups, respectively).

FIGURES

Figure S5 Mean CRP levels over time. *$p<0.0001$; adjusted mean change from baseline for TCZ plus DMARDs vs placebo plus DMARDs. CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; TCZ, tocilizumab.

TABLES

Table S4 Summary of serious infections

Treatment Group	Infection (AE preferred term)	Start Day (from first infusion)
Tocilizumab plus DMARDs	Cellulitis	32
	Pneumonia	45
	Cellulitis	66
	Pneumonia	66
	Cellulitis	69
	Urosepsis	76
	Pyelonephritis	94
	Staphylococcal infection	115
	Pneumonia	122
	Anal abscess	138
	Septic shock*	138
	Urinary tract infection*	141
	Enterobacter sepsis*	157
	Gastroenteritis viral	170
Placebo plus DMARDs	Lung infection pseudomonal	22

*Infections occurring in the same patient. AE, adverse event; DMARDs, disease-modifying antirheumatic drugs.

Table S5 Percentages of patients with shifts in liver enzyme levels (ALT and AST) from normal at baseline to above the ULN

From Normal to:	**>ULN – 1.5x ULN**	**>1.5x – 2x ULN**	**>2x – 3x ULN**	**>3x – 5x ULN**	**>5x ULN**
ALT:					
TCZ 8 mg/kg + DMARDs (N=379)	89 (23.5%)	48 (12.7%)	19 (5.0%)	10 (2.6%)	2 (0.5%)
Placebo + DMARDs (N=180)	20 (11.1%)	4 (2.2%)	3 (1.7%)	1 (0.6%)	1 (0.6%)
AST:					
TCZ 8 mg/kg + DMARDs (N=388)	101 (26.0%)	19 (4.9%)	9 (2.3%)	3 (0.8%)	0
Placebo + DMARDs (N=188)	18 (9.6%)	3 (1.6%)	2 (1.1%)	1 (0.5%)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DMARDs, disease-modifying antirheumatic drugs; ULN, upper limit of normal.

Table S6 Changes in lipid parameters in patients treated with TCZ 8 mg/kg plus DMARDs (safety population)

	TC, mmol/L	LDL-C, mmol/L	HDL-C, mmol/L	TG, mmol/L
Mean Values Over Time in Patients Treated with Tocilizumab 8 mg/kg + DMARDs				
Baseline				
n	404	396	404	409
Mean (SD)	4.96 (1.03)	2.86 (0.85)	1.38 (0.44)	1.57 (0.91)
Week 4				
n	401	390	402	401
Mean (SD)	5.51 (1.24)	3.20 (0.98)	1.48 (0.45)	1.83 (1.35)
Week 8				
n	395	381	395	395
Mean (SD)	5.60 (1.32)	3.25 (1.02)	1.48 (0.47)	1.83 (1.25)
Week 12				
n	375	360	374	375
Mean (SD)	5.63 (1.25)	3.28 (1.02)	1.46 (0.46)	1.93 (1.50)
Week 16				
n	357	346	357	357
Mean (SD)	5.62 (1.18)	3.32 (1.01)	1.46 (0.44)	1.84 (1.11)
Week 20				
n	295	281	294	295
Mean (SD)	5.58 (1.22)	3.24 (0.96)	1.48 (0.44)	1.90 (1.47)
Week 24				
n	281	274	281	281
Mean (SD)	5.63 (1.28)	3.32 (1.04)	1.47 (0.44)	1.87 (1.60)
Patient Shifts From Normal at Baseline to Above ATPIII Thresholds at End of Study:				
	≥6.22 mmol/L (≥240 mg/dL)	≥3.37 mmol/L (≥130 mg/dL)	≥1.55 mmol/L (≥60 mg/dl)	≥5.65 mmol/L (≥500 mg/dL)
TCZ 8 mg/kg + DMARDs	78/356 (21.9%)	97/300 (32.3%)	59/292 (20.2%)	5/407 (1.2%)
Placebo + DMARDs	13/168 (7.7%)	12/130 (9.2%)	25/146 (17.1%)	1/198 (0.5%)

ATPIII, Adult Treatment Panel III [22]; DMARDs, disease-modifying antirheumatic drugs; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; TCZ, tocilizumab.