SUPPLEMENTAL

Supplemental methods

Sample size. The primary analysis was based on the per protocol (PP) population. Data from the initial three pivotal Phase III intravenous tocilizumab (TCZ-IV) studies (WA17823, WA17822, and WA18063), evaluating 8 mg/kg of tocilizumab (TCZ) in combination with methotrexate (MTX) versus placebo in combination with MTX in DMARD−inadequate responders, showed ACR20 response rates for the PP population at Week 24 of 58.5% (WA17823), 63.3% (WA17822), and 64.3% (WA18063). The pooled ACR20 response rate for these three studies was 62.5%.

Assuming that TCZ-SC had an ACR20 response rate of 62.5%, 450 patients per treatment arm would be required to provide 90% power to demonstrate that TCZ-IV was non-inferior to subcutaneous TCZ (TCZ-SC) using a 12-percentage point non-inferiority margin and assuming that TCZ-IV was 1% worse than TCZ-SC. From the Phase III TCZ-IV studies described above, it was estimated that approximately 25% of patients would not be eligible for the PP population. Therefore, a total sample size of 600 patients per arm was planned to be randomized into the study to ensure adequate patient numbers for the primary analysis.

Randomization. Eligible patients who fulfilled the inclusion and exclusion criteria were randomly assigned to two treatment groups at baseline for the 24 week double-blind period utilizing an interactive voice response system (IVRS). Randomization numbers were generated by Perceptive Informatics, Inc. and were linked to a unique patient identification number through the IVRS. Randomization was by minimization and stratified by geographic region (Europe, North America, South America, rest of world) and body weight category (< 60 kg, 60 to 100 kg, ≥ 100 kg). The minimization procedure was implemented by Perceptive. This involved maintaining an updated record of treatment assignments by stratification factors and was used to determine the treatment of choice for a newly recruited patient. The minimization procedure

was based on an 80:20 random element, i.e., a patient was assigned to the treatment of choice with a probability of 0.8.

Blinding. This study was blinded during the first 24 weeks, and a "dual assessor" approach was used to evaluate first efficacy and then safety data to prevent potential unblinding because of observed efficacy or laboratory changes. The efficacy assessor was a rheumatologist or other skilled arthritis assessor but could not be the principal investigator. The efficacy assessor was responsible for assessing the joint counts and the Physician's Global Assessment of Disease VAS components but was not allowed access to other patient data. The safety assessor was a rheumatologist or medically qualified physician with access to both the safety and efficacy data and was permitted to be the principal investigator. The study centers, Roche monitors, and study team members were blinded to some laboratory data (i.e., TCZ, CRP, IL-6, and sIL-6R) before the primary analysis.

Blinding of the treatment received was maintained for patients, investigators, and Roche personnel until after completion of the last patient visit at Week 24 and subsequent database lock.

Recruitment. Participants were recruited from August 2010 to August 2011. Participants attended clinic visits at the time of randomization (baseline) and at weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24.

Supplemental Data

Supplemental Table 1 Adverse events of patients who required dose modification or interruption

	TCZ-SC qw (N=631) 289.82 PY	**TCZ-IV q4w (N=631) 288.39 PY**
Adverse events, n (%)		
Discontinuation due to AE	30 (4.8)	42 (6.7)
Infections and infestations	91 (14.4)	30 (4.8)
Investigation	56 (8.9)	38 (6.0)
Blood and lymphatic systems disorders	19 (3.0)	18 (2.9)
Gastrointestinal disorders	11 (1.7)	9 (1.4)
Respiratory, thoracic and mediastina disorders	4 (0.6)	7 (1.1)
Musculoskeletal and connective tissue disorders	5 (0.8)	5 (0.8)
Skin and subcutaneous tissue disorders	4 (0.6)	4 (0.6)
Vascular disorders	2 (0.3)	5 (0.8)
Injury, poisoning and procedural complications	4 (0.6)	2 (0.3)
General disorders and administration site conditions	4 (0.6)	1 (0.2)
Hepatobiliary disorders	4 (0.6)	1 (0.2)
Eye disorders	3 (0.5)	
Nervous system disorders	2 (0.3)	2 (0.3)
Reproductive system and breast disorders	2 (0.3)	2 (0.3)
Cardiac disorders	3 (0.5)	-
Renal and urinary disorders	2 (0.3)	1 (0.2)
Ear and labyrinth disorders	1 (0.2)	1 (0.2)
Immune system disorders	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	2 (0.3)	-
No coding (infusion rate decreased)	1 (0.2)	-

Supplemental Table 2 Adverse events as stratified by body weight

	< 60 kg		60 – 100 kg		≥ 100 kg	
	TCZ-SC qw N = 144	**TCZ-IV q4w N = 146**	**TCZ-SC qw N = 425**	**TCZ-IV q4w N = 422**	**TCZ-SC qw N = 62**	**TCZ-IV q4w N = 63**
Adverse events						
Total AEs	331	105	998	964	186	183
Patients with ≥ 1 AE, n (%)	105 (72.9)	105 (71.9)	322 (75.8)	328 (77.7)	54 (87.1)	53 (84.1)
Serious adverse events						
Total SAEs	11	9	20	28	2	4
Patients with ≥ 1 SAE, n (%)	11 (7.6)	6 (4.1)	17 (4.0)	22 (5.2)	2 (3.2)	4 (6.3)

Supplemental Table 3 Laboratory variables (safety population)

Variable	TCZ-SC 162 mg qw (n=631)	TCZ-IV 8 mg/kg q4w (n=631)
Change in ALT from normal at baseline to worst value		
n	582	571
≤ULN, n (%)	263 (41.7)	293 (46.4)
>ULN to 3 × ULN, n (%)	289 (45.8)	246 (39.0)
>3 × to 5 × ULN, n (%)	24 (3.8)	26 (4.1)
>5 × ULN, n (%)	6 (1.0)	6 (1.0)
Change in AST from normal at baseline to worst value		
n	599	590
≤ULN, n (%)	360 (57.1)	367 (58.2)
>ULN to 3 × ULN, n (%)	233 (36.9)	215 (34.1)
>3 × to 5 × ULN, n (%)	5 (0.8)	6 (1.0)
>5 × ULN, n (%)	1 (0.2)	2 (0.3)
CTCAE grade for neutrophil levels, ANC/mm^3		
n	631	631
Normal (≥LLN), n (%)	406 (64.3)	464 (73.5)
Grade 1 (1500 to <LLN), n (%)	126 (20.0)	86 (13.6)
Grade 2 (1000 to <1500), n (%)	81 (12.8)	61 (9.7)
Grade 3 (500 to <1000), n (%)	17 (2.7)	20 (3.2)
Grade 4 (<500), n (%)	1 (0.2)	0 (0)
CTCAE grade for platelet levels, platelets/mm^3		
n	630	630
Normal (≥LLN), n (%)	575 (91.3)	568 (90.2)
Grade 1 (75,000 to <LLN), n (%)	54 (8.6)	59 (9.4)
Grade 2 (50,000 to <75,000), n (%)	1 (0.2)	2 (0.3)
Grade 3 (25,000 to <50,000), n (%)	0 (0)	1 (0.2)
Grade 4 (<25,000), n (%)	0 (0)	0 (0)
Shift in cholesterol from baseline <200 mg/dL to last value		
n	299	313
<200 mg/dL (ie, no change), n (%)	149 (23.6)	183 (29.0)
200 to <240 mg/dL, n (%)	106 (16.8)	104 (16.5)
≥240 mg/dL, n (%)	44 (7.0)	26 (4.1)
Shift in HDL cholesterol from baseline <40 mg/dL to last value		
n	42	46
<40 mg/dL (ie, no change), n (%)	21 (3.3)	18 (2.9)
40–60 mg/dL, n (%)	20 (3.2)	24 (3.8)
≥60 mg/dL, n (%)	1 (0.2)	4 (0.6)
Shift in LDL cholesterol from baseline <100 mg/dL to last value		

n	214	221
<100 mg/dL (ie, no change), n (%)	113 (17.9)	127 (20.1)
100 to <130 mg/dL, n (%)	71 (11.3)	76 (12.0)
130 to <160 mg/dL, n (%)	25 (4.0)	13 (2.1)
≥160 mg/dL, n (%)	5 (0.8)	5 (0.8)
Shift in triglycerides from baseline <150 mg/dL to last value		
n	422	419
<150 mg/dL (ie, no change), n (%)	304 (48.2)	322 (51.0)
150–500 mg/dL, n (%)	117 (18.5)	97 (15.4)
≥500 mg/dL, n (%)	1 (0.2)	0 (0)

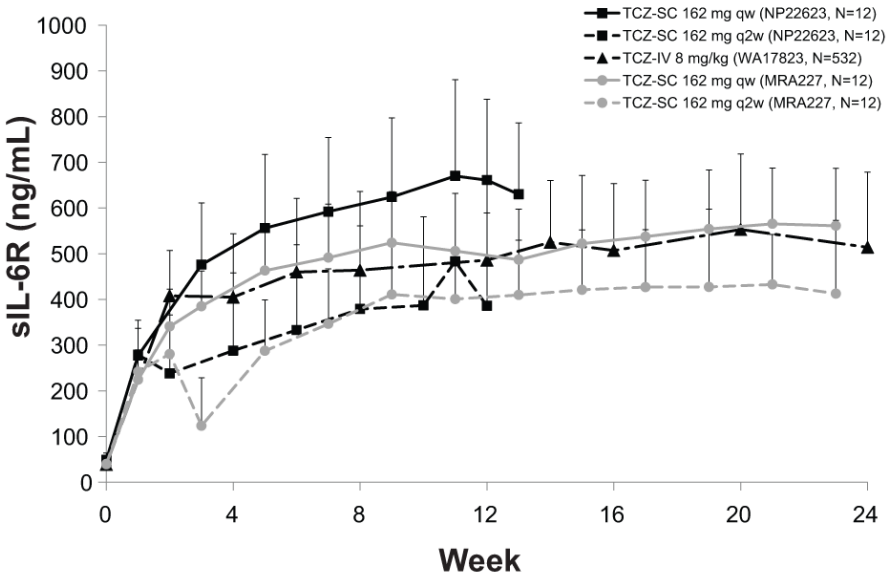
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; HDL, high-density lipoprotein; IV, intravenous; LDL, low-density lipoprotein; LLN, lower limit of normal; qw, every week; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab; ULN, upper limit of normal.

Supplemental Figure Legend

Supplemental Figure 1 The selection of the subcutaneous tocilizumab (TCZ-SC) 162 mg weekly (qw) dose regimen was based on results from previous phase 1/2 TCZ-SC and phase 3 intravenous tocilizumab (TCZ-IV) studies. TCZ-SC has been investigated in phase 1/2 studies in healthy subjects and Japanese and Caucasian patients with rheumatoid arthritis (RA). In one of the studies, Japanese patients with RA received TCZ-SC at a dosage of 81 or 162 mg every 2 weeks (q2w) or 162 mg qw (MRA227).[3] In another study, Caucasian patients with RA received TCZ-SC 162 mg q2w or 162 mg qw (NP22623). For both TCZ-SC patient studies, the pharmacodynamic (PD) profiles of TCZ-SC 162 mg qw were the most consistent with those in previous TCZ-IV 8 mg/kg studies. Profiles of both soluble interleukin-6 receptor (sIL-6R), a PD marker of TCZ mechanism, and C-reactive protein (CRP), a PD marker of inflammation, for the TCZ-SC 162 mg qw regimen were mostly close to those observed for TCZ-IV 8 mg/kg every 4 weeks (q4w)[6] with respect to the rapidity and magnitude of rise or reduction (supplemental figure 1A and 1B). The TCZ-SC 162 mg q2w dose regimen did not yield sIL-6R or CRP levels comparable to those for TCZ-IV 8 mg/kg q4w. Furthermore, the limited observed efficacy profile of TCZ-SC was similar to that of TCZ-IV 8 mg/kg IV. Given that the mean exposure (area under the curve) is generally higher for TCZ-IV 8 mg/kg than for any of the tested TCZ-SC dose regimens, the safety profile of TCZ-SC 162 mg qw was expected to be similar to that of TCZ-IV 8 mg/kg IV q4w. **Supplemental Figure 1A** Time course of soluble interleukin-6 receptor (sIL-6R; mean±standard deviation) for subcutaneous tocilizumab (TCZ-SC) 162 mg weekly (qw) and TCZ-SC 162 mg every 2 weeks (q2w) from the NP22623 and MRA227 studies and for intravenous tocilizumab (TCZ-IV) 8 mg/kg from the LITHE (WA17823) study.[7] **Supplemental Figure 1B** Time course of mean (±standard deviation) C-reactive protein (CRP) levels for subcutaneous tocilizumab (TCZ-SC) 162 mg weekly (qw) and TCZ-SC 162 mg every 2 weeks (q2w) from the NP22623 and MRA227 studies and for intravenous tocilizumab (TCZ-IV) 8

mg/kg from the OPTION (WA17822) study.[5] The predefined CRP upper limit of normal for this study was 0.33 mg/dL.

A



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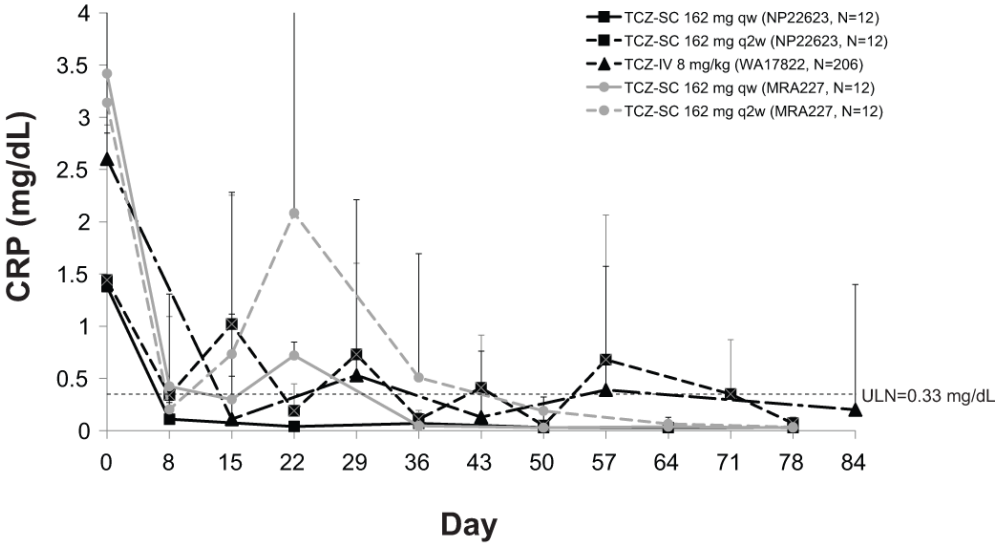
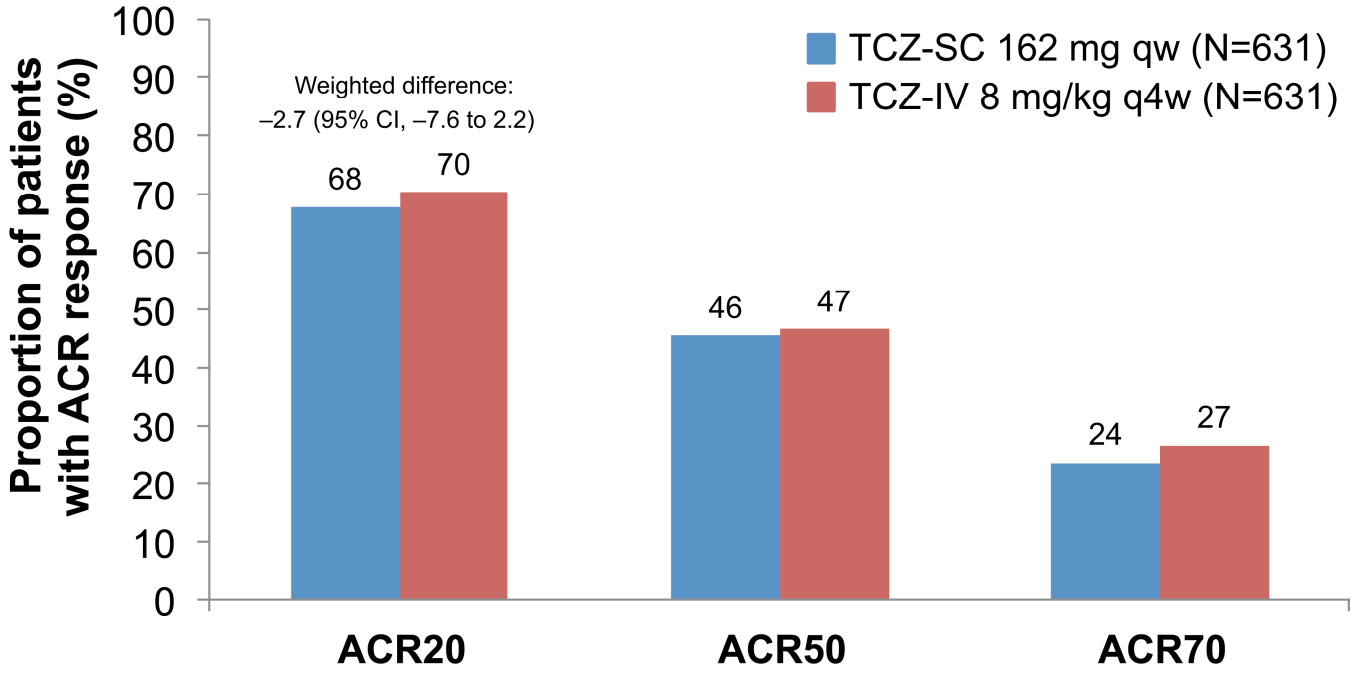
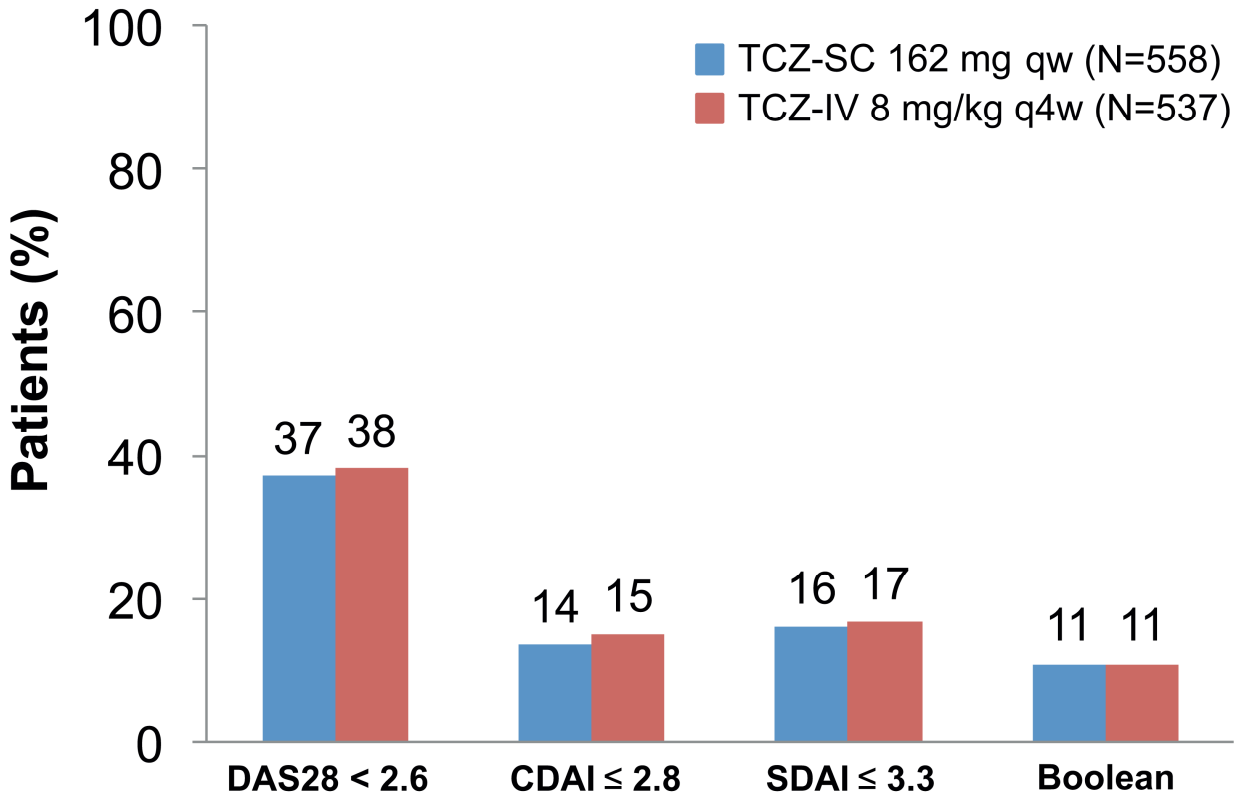


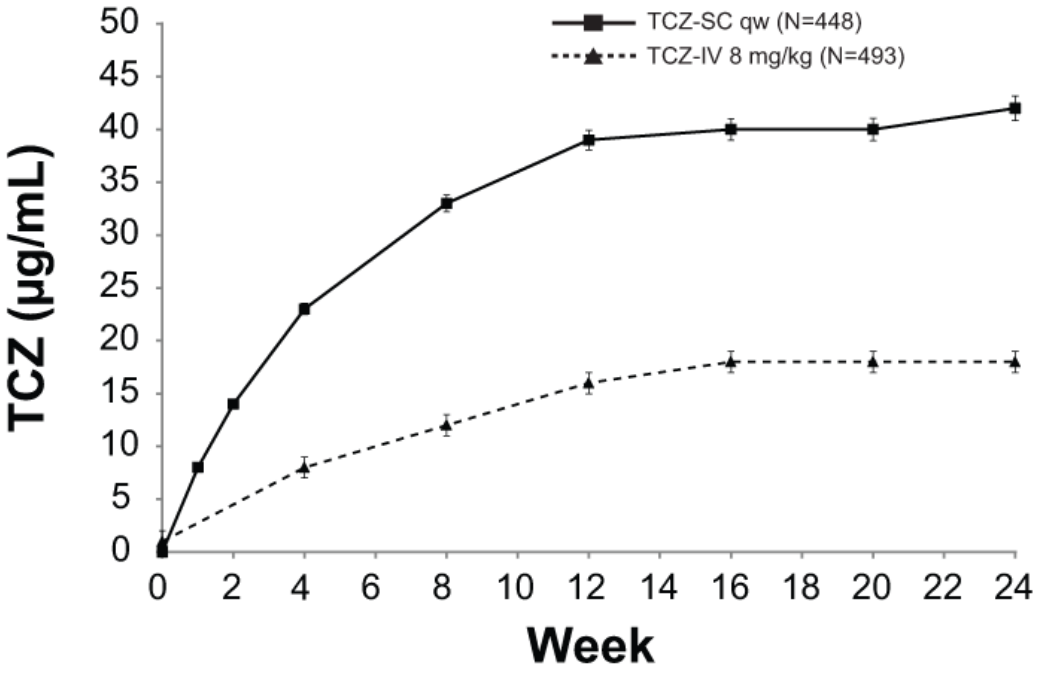
Supplemental Figure 2 Proportion of patients in the ITT population treated with either subcutaneous tocilizumab (TCZ-SC; n=631) or intravenous tocilizumab (TCZ-IV; n=631) achieving 20%, 50% and 70% improvements per American College of Rheumatology criteria (ACR20, ACR50 and ACR70) over 24 weeks.



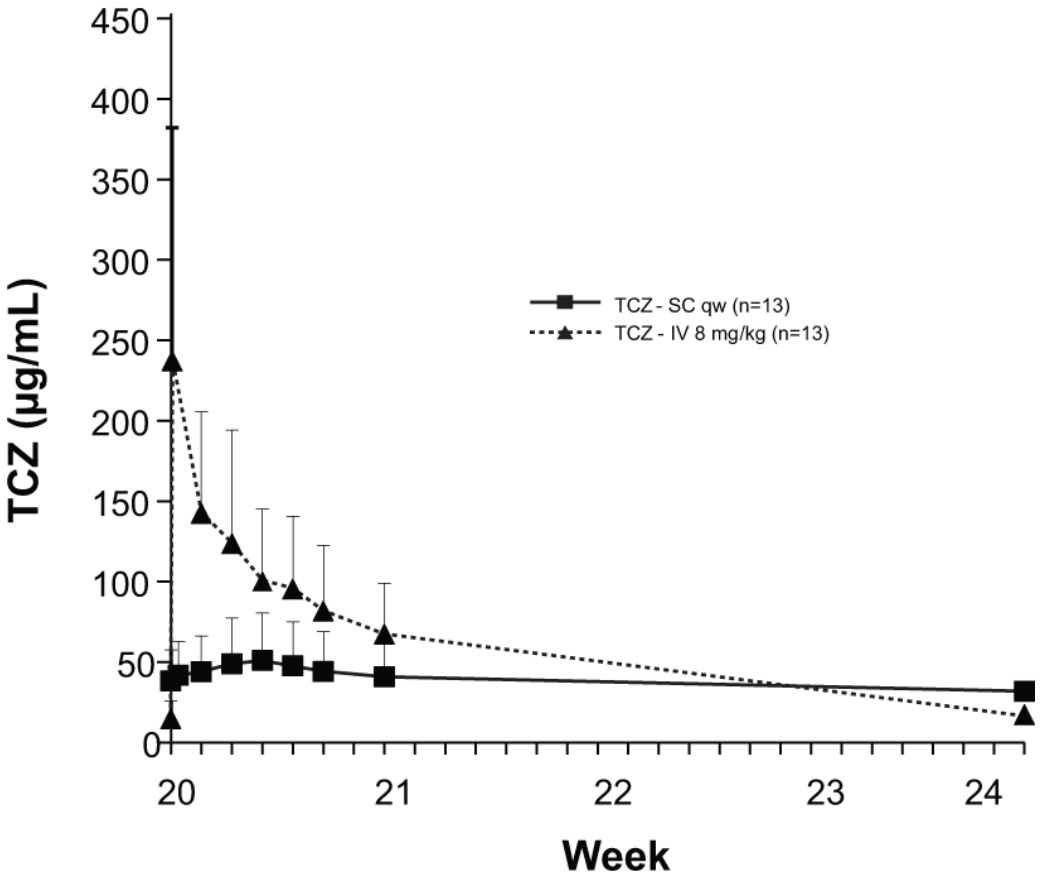
Supplemental Figure 3 Proportion of patients in the PP population treated with either subcutaneous tocilizumab (TCZ-SC; n=558) or intravenous tocilizumab (TCZ-IV; n=537) achieving DAS28 (<2.6), CDAI (≤2.8), SDAI (≤3.3) and Boolean (TJC/SJC ≤1 [28 joints] and CRP ≤1mg/dl and patients global Assessment ≤10 [using scale 0–100]) remission at week 24.



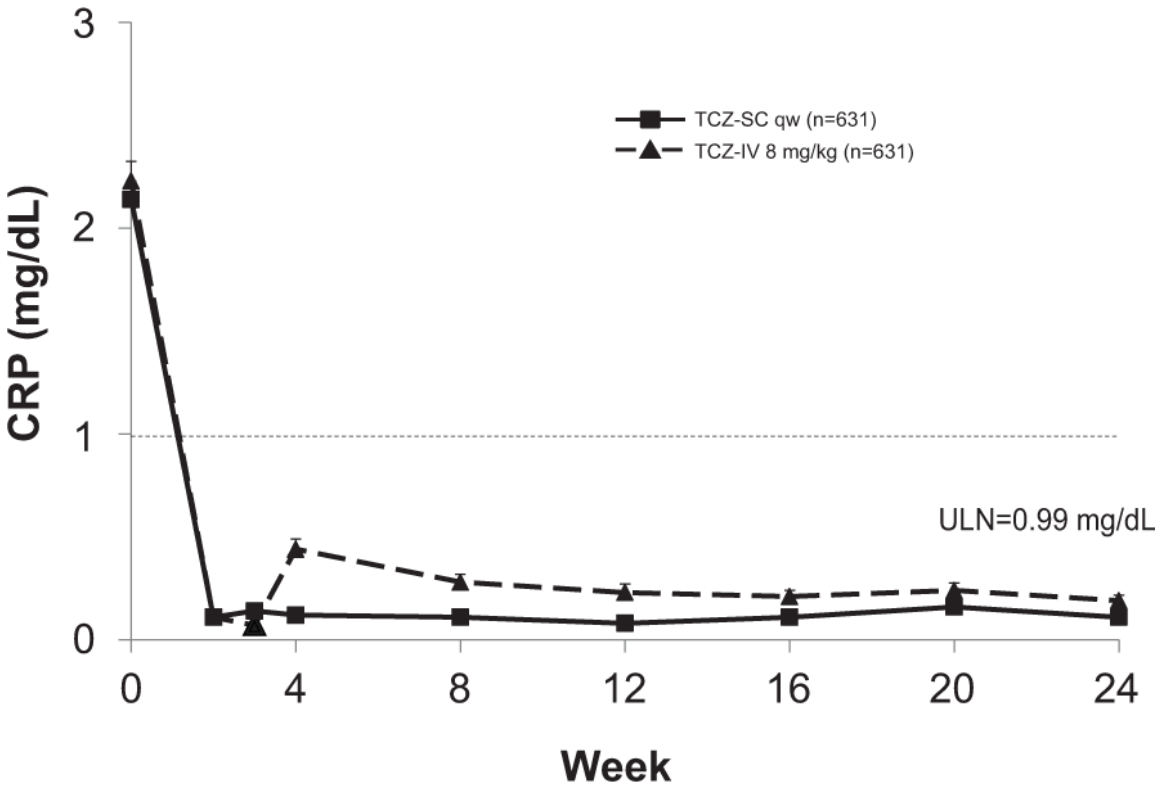
Supplemental Figure 4 Mean (±standard error of the mean) observed pre-dose tocilizumab (TCZ) concentrations (C_{trough}) over time in patients treated with either TCZ-SC or TCZ-IV in the SUMMACTA main study.



Supplemental Figure 5 Mean (±standard deviation) tocilizumab (TCZ) concentrations from weeks 20 to 24 in patients treated with either subcutaneous TCZ (TCZ-SC) or intravenous TCZ (TCZ-IV) in the SUMMACTA pharmacokinetic substudy.



Supplemental Figure 6 Mean (±standard error of the mean) C-reactive protein (CRP) levels over time in patients treated with either subcutaneous tocilizumab (TCZ-SC) or intravenous tocilizumab (TCZ-IV) in the SUMMACTA study. The predefined CRP upper limit of normal (ULN) for this study was 0.99 mg/dL.



Supplemental Figure 7 Mean (±standard error of the mean) erythrocyte sedimentation rates (ESRs) over time in patients treated with either subcutaneous tocilizumab (TCZ-SC) or intravenous tocilizumab (TCZ-IV) in the SUMMACTA study.