SUPPLEMENTAL

SUPPLEMENTAL TABLES

Supplemental Table 1. Baseline patient demographics and clinical characteristics (ITT population)

	TCZ-SC 162 mg qw (n=521)	TCZ-IV 8 mg/kg q4w (n=372)	TCZ-IV–SC (n=186)	TCZ-SC–IV (n=48)
Female, n (%)	437 (83.9)	311 (83.6)	150 (80.6)	36 (75.0)
Age, mean (SD), years	52.6 (12.16)	52.1 (12.44)	53.3 (12.51)	54.7 (12.41)
Weight group, n (%)				
<60 kg	119 (22.8)	84 (22.6)	46 (24.7)	12 (25.0)
60-100 kg	353 (67.8)	249 (66.9)	125 (67.2)	33 (68.8)
≥100 kg	49 (9.4)	39 (10.5)	15 (8.1)	3 (6.3)
Duration of RA, mean (SD), years	8.9 (8.46)	8.7 (8.12)	8.7 (8.46)	9.4 (8.09)
Tender joints (68-joint count), mean (SD)	27.3 (15.64)	29.1 (16.29)	27.0 (16.21)	29.2 (16.80)
Swollen joints (66-joint count), mean (SD)	15.2 (9.43)	16.9 (10.70)	15.7 (10.25)	15.3 (8.59)
HAQ-DI, mean (SD)	1.6 (0.6)	1.6 (0.7)	1.7 (0.6)	1.6 (0.6)
Patient assessment of pain, mean (SD)	60.4 (22.86)	61.9 (21.46)	59.6 (22.04)	56.1 (21.60)
Patient Global Assessment of disease, mean (SD)	67.5 (21.92)	67.6 (21.78)	65.5 (21.45)	65.0 (19.58)
Physician Global Assessment of disease, mean (SD)	61.4 (17.91)	63.0 (18.36)	61.0 (18.89)	61.3 (15.69)
RF positive, n (%)	388 (75.9)	273 (74.0)	145 (78.4)	33 (68.8)
ACPA positive, n (%)	374 (74.5)	276 (75.0)	153 (83.2)	29 (67.4)
DAS28, mean (SD)	6.6 (1.01)	6.7 (1.03)	6.6 (1.04)	6.6 (1.09)
CRP level, mean (SD), mg/dL	2.2 (2.29)	2.3 (2.53)	2.2 (2.03)	2.1 (1.82)
Patients receiving glucocorticoids at baseline, n (%)	296 (56.8)	197 (53.0)	105 (56.5)	21 (43.8)
Patients who were aTNF inadequate responders at baseline, n (%)	110 (21.1)	87 (23.4)	31 (16.7)	13 (27.1)

ACPA, anti–citrullinated protein antibodies; aTNF, anti-tumor necrosis factor agent; CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joints; HAQ-DI, Health Assessment Questionnaire Disability Index; ITT, intent-to-treat; IV, intravenous; qw, weekly; q4w, every 4 weeks; RA, rheumatoid arthritis; RF, rheumatoid factor; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab.

Supplemental Table 2. Overview of cumulative AEs and SAEs at week 97 (safety population[a])

Rate/100 PY (95% CI) [No. of events]	TCZ-SC 162 mg qw (n=631)		TCZ-IV 8 mg/kg q4w (n=631)		TCZ-IV–SC (n=186)	TCZ-SC–IV (n=48)
	24 Weeks	97 Weeks	24 Weeks	97 Weeks	97 Weeks	97 Weeks
No. of PYs of exposure	289.82	1013.26	288.39	816.53	255.75	66.19
AEs	602.79 (574.85-631.73) [1747]	415.89 (403.42-428.64) [4214]	588.44 (560.77-617.12) [1697]	408.56 (394.81-422.66) [3336]	394.92 (370.94-420.05) [1010]	271.93 (233.66-314.69) [180]
AEs leading to withdrawal	14.15 (10.15-19.19) [41]	8.98 (7.23-11.03) [91]	18.72 (14.07-24.43) [54]	9.80 (7.77-12.19) [80]	6.26 (3.58-10.16) [16]	3.02 (0.37-10.91) [2]
Infections	120.07 (107.79-133.38) [348]	108.66 (102.34-115.27) [1101]	124.83 (112.27-138.42) [360]	105.57 (98.64-112.86) [862]	96.97 (85.28-109.82) [248]	84.60 (63.91-109.86) [56]
Injection site reactions[b]	57.97 (49.53-67.43) [168]	26.05 (23.01-29.39) [264]	32.59 (26.34-39.89) [94]	33.63 (27.08-41.29) [91]	93.45 (81.98-106.08) [239]	0 (0-5.57) [0]
Anaphylaxis	0 (0-1.27) [0]	0 (0-0.36) [0]	0 (0-1.28) [0]	0 (0-0.45) [0]	0 (0-1.44) [0]	0 (0-5.57) [0]
Serious demyelinating disorders	0 (0-1.27) [0]	0 (0-0.36) [0]	0 (0-1.28) [0]	0 (0-0.45) [0]	0 (0-1.44) [0]	0 (0-5.57) [0]
Serious hepatic events	0 (0-1.27) [0]	0 (0-0.36) [0]	0.35 (0.01-1.93) [1]	0.37 (0.08-1.07) [3]	0 (0-5.57) [0]	0 (0-5.57) [0]
Serious stroke	0 (0-1.27) [0]	0.39 (0.11-1.01) [4]	1.39 (0.38-3.55) [4]	1.22 (0.59-2.25) [10]	0 (0.00-1.44) [0]	0 (0-5.57) [0]
Serious myocardial infarction	0.35 (0.01-1.92) [1]	0.20 (0.02-0.71) [2]	0 (0-1.28) [0]	0 (0-0.45) [0]	0.39 (0.01-2.18) [1]	0 (0-5.57) [0]

[a] Data are included from the DB and OL periods for all treatment arms; therefore, safety analyses for the TCZ-IV and TCZ-SC arms include all data from patients who received TCZ-IV and TCZ-SC, respectively, up to week 24 (n=631 for each arm) as well as those who remained on TCZ-IV and TCZ-SC during the OL period.

[b] Data on injection-site reactions were not collected in the TCZ-IV group after week 24 as no SC injections were given.

AE, adverse event; DB; double-blind; IV, intravenous; OL, open-label; PY, patient-year; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab.

Supplemental Table 3. Laboratory abnormalities: newly occurring decreased neutrophils and platelets by worst NCI CTCAE grade, shifts in ALT and AST from normal at baseline to worst post-baseline value above the ULN, and shifts in lipid profile (ITT population)

	TCZ-SC 162 mg qw	TCZ-IV 8 mg/kg q4w	TCZ-IV–SC	TCZ-SC–IV
	Week 97	Week 97	Week 97	Week 97
Neutrophils (/µL), n	521	372	186	48
Grade 1 (1500 to <LLN), n (%)	112 (21.5)	74 (19.9)	27 (14.5)	7 (14.6)
Grade 2 (1000 to <1500), n (%)	89 (17.1)	44 (11.8)	17 (9.1)	2 (4.2)
Grade 3 (500 to <1000), n (%)	28 (5.4)	25 (6.7)	3 (1.6)	0
Grade 4 (<500), n (%)	3 (0.6)	0	0	0
Grade 3 or 4 neutropenia on ≥2 consecutive visits, n (%)	10 (1.9)	10 (2.7)	2 (1.1)	0
Platelets (/µL), n	521	372	186	48
Grade 1 (75,000 to <LLN), n (%)	66 (12.7)	61 (16.4)	12 (6.5)	4 (8.3)
Grade 2 (50,000 to <75,000), n (%)	2 (0.4)	2 (0.5)	0	0
Grade 3 (25,000 to <50,000), n (%)	0	1 (0.3)	0	0
Grade 4 (<25,000), n (%)	0	0	0	0
ALT[a], n	521	372	186	48
Normal (≤ULN), n (%)	139 (26.7)	123 (33.1)	60 (32.3)	15 (31.3)
Grade 1 (ULN to 3 × ULN), n (%)	306 (58.7)	195 (52.4)	92 (49.5)	23 (47.9)
Grade 2 (>3 to 5 × ULN), n (%)	30 (5.8)	20 (5.4)	11 (5.9)	4 (8.3)
Grade 3 (>5 to 10 × ULN), n (%)	8 (1.5)	2 (0.5)	6 (3.2)	1 (2.1)
Consecutive elevations of ALT ≥3 × ULN, n (%)[b]	8 (1.5)	6 (1.6)	3 (1.6)	1 (2.1)
AST[a], n	521	372	186	48
Normal (≤ULN), n (%)	209 (40.1)	167 (44.9)	87 (46.8)	22 (45.8)
Grade 1 (ULN to 3 × ULN), n (%)	278 (53.4)	178 (47.8)	84 (45.2)	23 (47.9)
Grade 2 (>3 to 5 × ULN), n (%)	4 (0.8)	5 (1.3)	3 (1.6)	0
Grade 3 (>5 to 10 × ULN), n (%)	5 (1.0)	0	1 (0.5)	0
Consecutive elevations of AST ≥3 × ULN, n (%)[b]	1 (0.2)	0	0	0

Shift in total cholesterol from baseline <200 mg/dL to last value, n	471	333	168	43
<200 mg/dL, n (%)	121 (23.1)	112 (30.1)	49 (26.3)	13 (27.1)
200 to <240 mg/dL, n (%)	76 (14.6)	47 12.6)	36 (19.4)	9 (18.8)
≥240 mg/dL, n (%)	47 (9.0)	23 (6.2)	10 (5.4)	6 (12.5)
Shift in HDL cholesterol from baseline <40 mg/dL to last value, n	471	333	168	43
<40 mg/dL, n (%)	13 (2.5)	12 (3.2)	2 (1.1)	0
40-60 to mg/dL, n (%)	23 (4.4)	18 (4.8)	4 (2.2)	0
≥60 mg/dL, n (%)	1 (0.2)	4 (1.1)	0	0
Shift in LDL cholesterol from baseline <100 mg/dL to last value, n	470	327	167	43
<100 mg/dL, n (%)	77 (14.8)	73 (19.6)	32 (17.2)	11 (22.9)
100 to <130 mg/dL, n (%)	60 (11.5)	36 (9.7)	27 (14.5)	5 (10.4)
130 to <160 mg/dL, n(%)	28 (5.4)	15 (4.0)	7 (3.8)	5 (10.4)
≥160 mg/dL, n (%)	8 (1.5)	6 (1.6)	2 (1.1)	1 (2.1)
Shift in triglycerides from baseline <150 mg/dL to last value, n	471	332	168	43
<150 mg/dL, n (%)	252 (48.4)	196 (52.7)	78 (41.9)	19 (39.6)
150-500 mg/dL, n (%)	112 (21.5)	58 (15.6)	46 (24.7)	7 (14.6)
≥500 mg/dL, n (%)	0	0	0	0

[a] No patients met Hy's law criteria (defined by the US Food and Drug Administration as elevated ALT or AST >3 ULN, elevated total bilirubin >2 ULN, the absence of initial findings of cholestasis (ie, absence of elevation of alkaline phosphatase to >2 ULN), and no other reason to explain the combination of increased ALT and total bilirubin.

[b] Consecutive elevations are elevations at 2 or more consecutive study visits.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; HDL, high-density lipoprotein; ITT, intent-to-treat; IV, intravenous; LDL, low-density lipoprotein; LLN, lower limit of normal; NCI, National Cancer Institute; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab; ULN, upper limit of normal.

Supplemental Table 4. AEs at week 97 stratified by body weight (safety population)

A. AEs at week 97 for patients weighing <60 kg

	<60 kg			
Rate/100 PY (95% CI) [No. of events]	**TCZ-SC qw (n=144)**	**TCZ-IV q4w (n=146)**	**TCZ-IV–SC (n=46)**	**TCZ-SC–IV (n=12)**
PYs exposure	234.37	188.70	64.13	17.58
AEs	398.52 (373.37-424.92) [934]	407.00 (378.72-436.83) [768]	572.29 (515.23-633.94) [367]	221.85 (157.75-303.27) [39]
SAEs	14.08 (9.69-19.77) [33]	10.6 (6.47-16.37) [20]	12.47 (5.39-24.58) [8]	5.69 (0.14-31.69) [1]

B. AEs at week 97 for patients weighing 60 to 100 kg

	60 to 100 kg			
Rate/100 PY (95% CI) [No. of events]	**TCZ-SC qw (n=425)**	**TCZ-IV q4w (n=422)**	**TCZ-IV–SC (n=125)**	**TCZ-SC–IV (n=33)**
PYs exposure	684.83	544.19	172.13	44.16
AEs	404.19 (389.27-419.53) [2768]	392.88 (376.40-409.89) [2138]	309.66 (283.92-337.10) [533]	305.73 (256.34-361.87) [135]
SAEs	12.41 (9.91-15.35) [85]	18.01 (14.62-21.95) [98]	23.24 (16.60-31.64) [40]	11.32 (3.68-26.43) [5]

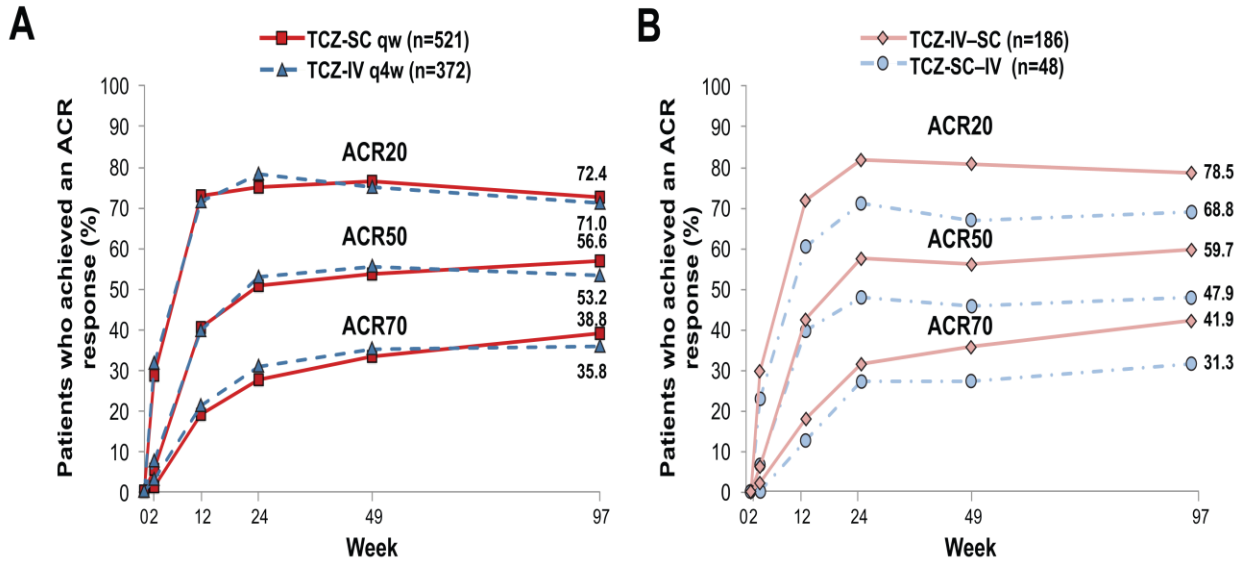
C. AEs at week 97 for patients weighing ≥100 kg

	≥100 kg			
Rate/100 PY (95% CI) [No. of events]	**TCZ-SC qw (n=62)**	**TCZ-IV q4w (n=63)**	**TCZ-IV–SC (n=15)**	**TCZ-SC–IV (n=3)**
PYs exposure	94.06	83.64	19.49	4.46
AEs	544.36 (498.22-593.62) [512]	514.12 (466.67-565.08) [430]	564.37 (463.84-680.22) [110]	134.61 (49.40-293.00) [6]
SAEs	31.9 (21.52-45.53) [30]	9.56 (4.13-18.85) [8]	10.26 (1.24-37.07) [2]	0 - [0]

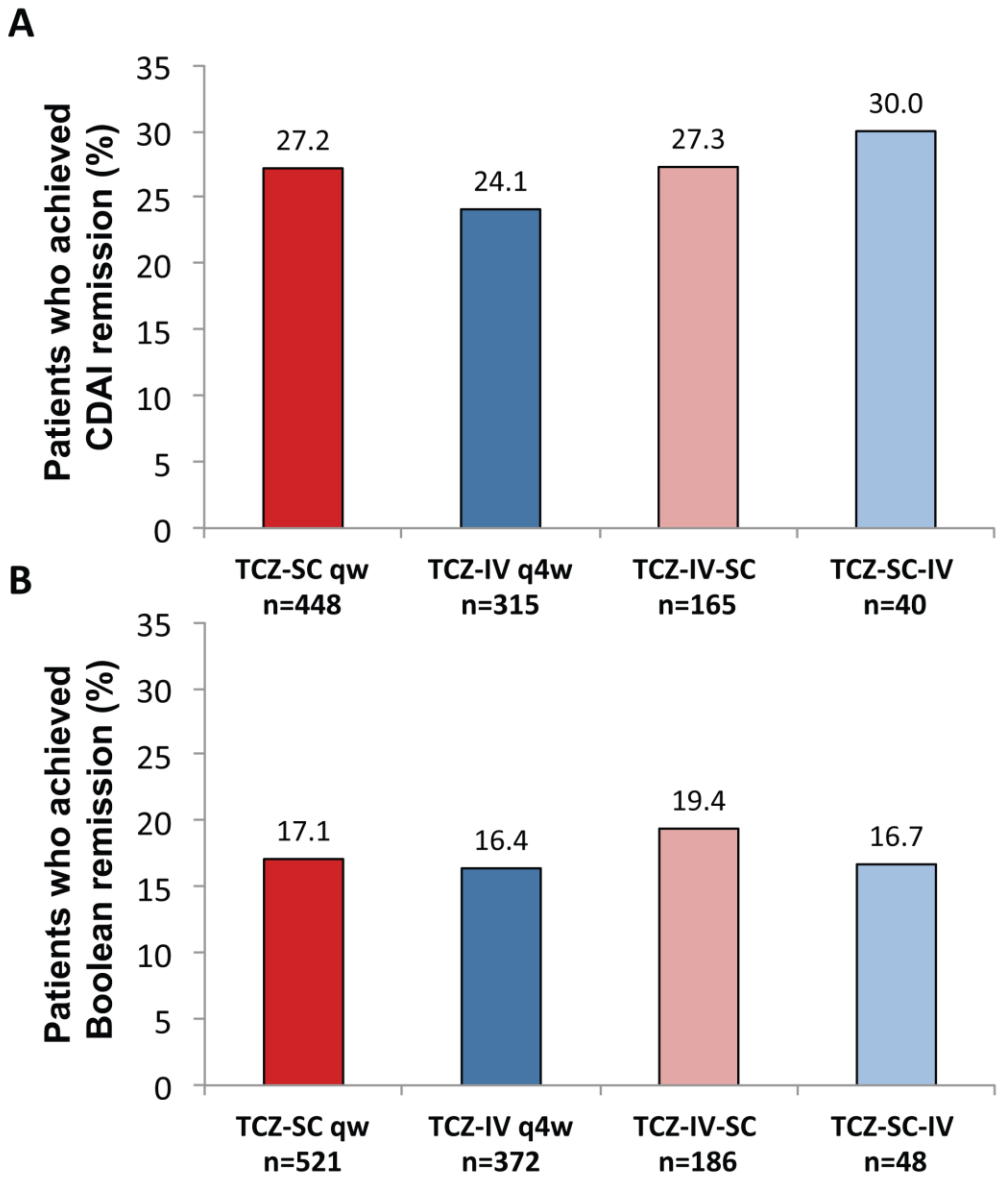
AE, adverse event; IV, intravenous; PY, patient-year; qw, weekly; q4w, every 4 weeks; SAE, serious adverse event; SC, subcutaneous; TCZ, tocilizumab.

SUPPLEMENTAL FIGURE LEGENDS

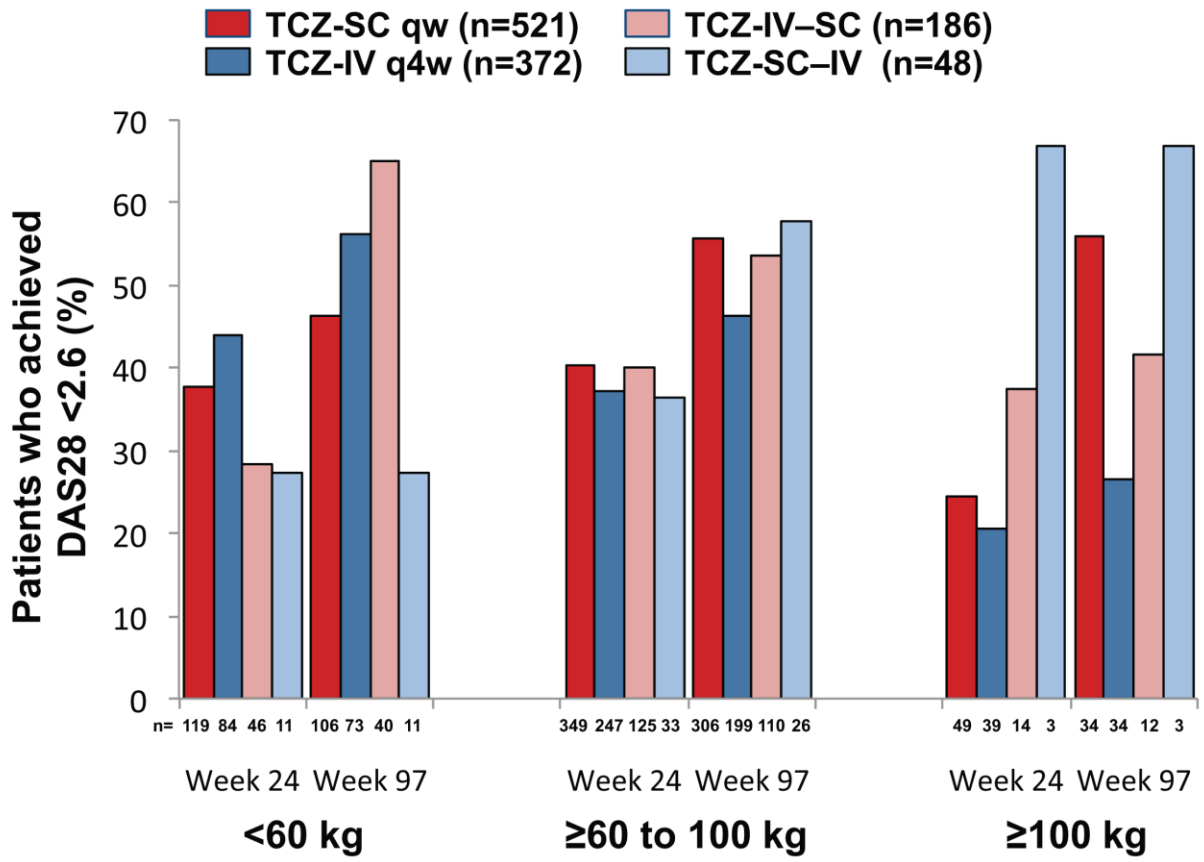
Supplemental Figure 1. Proportion of patients treated with A) either subcutaneous tocilizumab (TCZ-SC; n=521) or intravenous tocilizumab (TCZ-IV; n=372) as well as patients who switched from TCZ-SC to TCZ-IV (TCZ-SC–IV; n=48) and vice versa (TCZ-IV–SC; n=186) achieving 20%, 50%, and 70% improvements per American College of Rheumatology criteria (ACR20, ACR50, and ACR70). The n's refer to the intent-to treat population with non−responder imputation done for missing data points. qw, weekly; q4w, every 4 weeks.



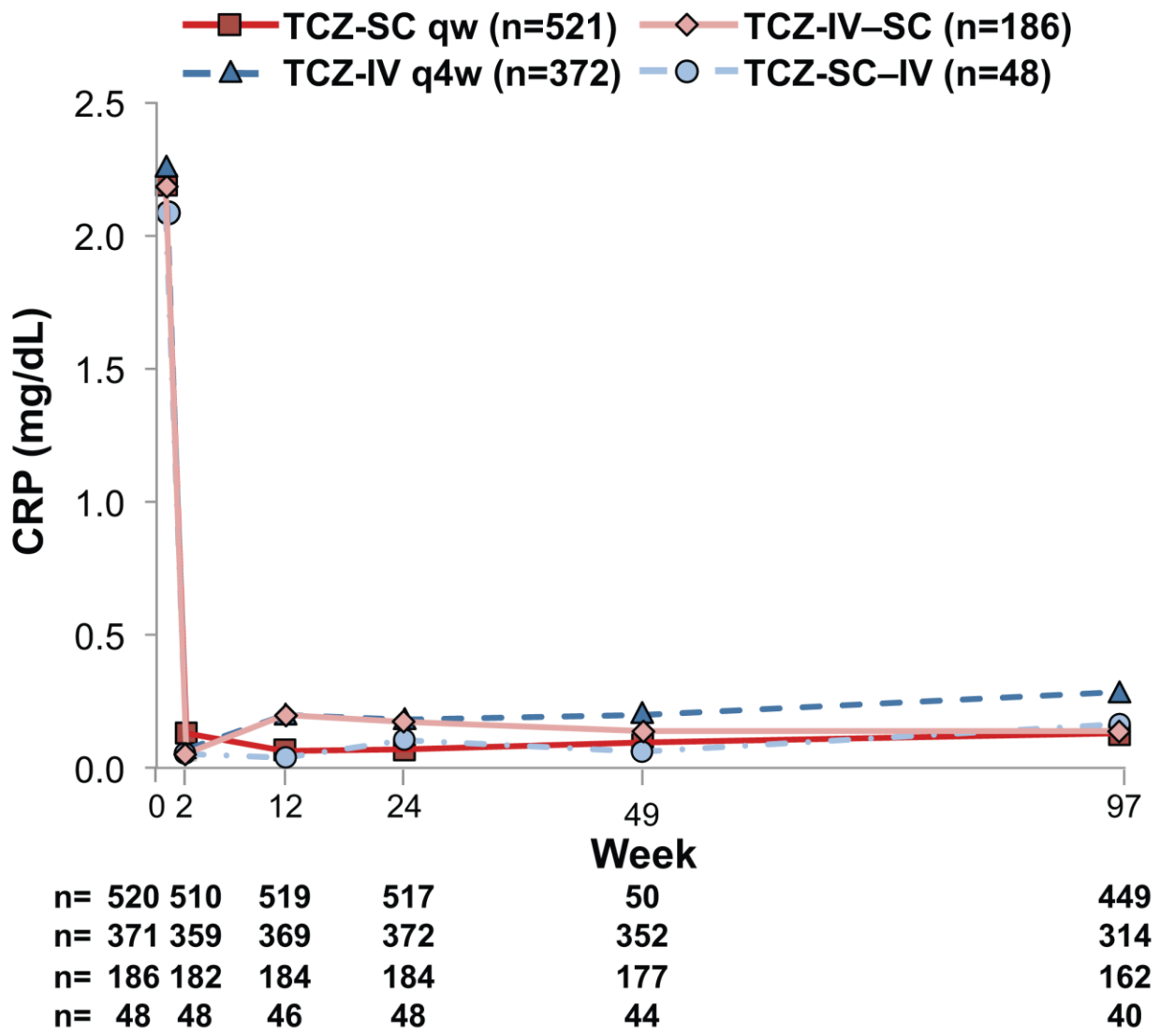
Supplemental Figure 2. Proportion of patients in the ITT population treated with either TCZ-SC (n=521) or TCZ-IV (n=372) as well as patients who switched from TCZ-SC to TCZ-IV (TCZ-SC–IV; n=48) and vice versa (TCZ-IV–SC; n=186) achieving (A) CDAI remission (≤2.8) and (B) Boolean remission at week 97. Boolean remission criteria: both tender and swollen joint counts (28 joints) ≤1, CRP ≤1 mg/dL, and Patient Global Assessment ≤10 (using scale 0-100). CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; IV, intravenous; ITT, intent-to-treat; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab.



Supplemental Figure 3. Proportion of patients stratified by weight treated with either TCZ-SC (n=521) or TCZ-IV (n=372) as well as patients who switched from TCZ-SC to TCZ-IV (TCZ-SC–IV; n=48) and vice versa (TCZ-IV–SC; n=186) achieving remission based on DAS28 at 24 and 97 weeks. DAS28, Disease Activity Score using 28 joints; IV, intravenous; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab.



Supplemental Figure 4. Mean CRP levels over time in patients treated with either TCZ-SC (n=521) or TCZ-IV (n=372) as well as patients who switched from TCZ-SC to TCZ-IV (TCZ-SC–IV; n=48) and vice versa (TCZ-IV–SC; n=186). The predefined CRP upper limit of normal (ULN) for this study was 0.99 mg/dL. CRP, C-reactive protein; IV, intravenous; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab.



Supplemental Figure 5. Mean ESRs over time in patients treated with either TCZ-SC (n=521) or TCZ-IV (n=372) as well as patients who switched from TCZ-SC to TCZ-IV (TCZ-SC–IV; n=48) and vice versa (TCZ-IV–SC; n=186). ESR, erythrocyte sedimentation rate; IV, intravenous; qw, weekly; q4w, every 4 weeks; SC, subcutaneous; TCZ, tocilizumab.