SUPPLEMENTAL DATA

Supplemental Table 1. Study designs

Study	Description	Arms	Patient population	Time	Primary end point
SUMMACTA (ClinicalTrials.gov identifier NCT01194414)	Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter trial	TCZ-SC 162 mg qw + csDMARDs (N = 631) TCZ-IV 8 mg/kg q4w + csDMARDs (N = 631)	Patients with moderate-to-severe active RA with an inadequate response to ≥ 1 DMARD(s) that may have included aTNFs	24 weeks, double blind 72-week OLE: patients were subsequently re-randomized to be treated with a different formulation	ACR20 response at week 24
BREVACTA (NCT01232569)	Phase 3, 2-arm, randomized, double-blind, parallel-arm, multicenter trial	PBO + csDMARDs (N = 219) TCZ-SC 162 mg q2w + csDMARDs (N = 437)	Patients with moderate-to-severe active RA with an inadequate response to ≥ 1 DMARD(s) that may have included aTNFs	24 weeks, double blind 72-week OLE: at week 24, the PBO arm received TCZ-SC q2w and the TCZ-SC arm continued receiving TCZ-SC q2w. Patients could receive open-label TCZ-SC qw as escape therapy at 12 weeks	ACR20 response at week 24
MUSASHI (JAPICCTI-101117)	Phase 3, randomized, double-dummy, double-blind, parallel-arm, multicenter trial	TCZ-SC monotherapy 162 mg q2w (N = 173) TCZ-IV monotherapy 8 mg/kg q4w (N = 173)	Japanese patients with RA with an inadequate response to synthetic and/or biologic DMARDs	24 weeks, double blind 84-week OLE: after 24 weeks, patients received open-label TCZ-SC monotherapy 162 mg q2w	ACR20 response at week 24
LTE rollover (NCT01662063)	Phase 3b, open-label, single-arm, US-based study	Continued receiving TCZ-SC 162 mg q2w (N = 44) Continued receiving TCZ-SC 162 mg qw or switched from TCZ-IV to TCZ-SC qw (N = 173)	Patients who completed SUMMACTA and BREVACTA	84 weeks	Serious adverse events
TOZURA (interim analysis)*	Phase 4, open-label, single-arm, multicenter umbrella study comprising 7 single-country and 4 regional multicountry	TCZ-SC 162 mg qw monotherapy (N = 283) TCZ-SC 162 mg qw + csDMARDs (N = 963)	Patients with moderate to severe RA and an inadequate response to synthetic and/or biologic DMARDs	24 weeks	Efficacy and safety at week 24

	protocols				
AMBITION (NCT00109408)	Phase 3, randomized, double-dummy, double-blind, parallel-arm, multicenter trial	TCZ-IV monotherapy 8 mg/kg q4w (N = 288) MTX monotherapy 7.5-20 mg/week (N = 284) PBO for 8 weeks then TCZ-IV monotherapy 8 mg/kg q4w for 16 weeks (N = 101)	Patients with moderate-to-severe active RA for whom previous treatment with MTX or biologics had not failed; 6 months MTX free	24 weeks, double blind 5-year OLE: after 24 weeks, patients received open-label TCZ-IV ± MTX	ACR20 response at week 24
TOWARD (NCT00106574)	Phase 3, randomized double-blind, placebo-controlled, multicenter trial	PBO + csDMARDs (N = 415) TCZ-IV 8 mg/kg q4w + csDMARDs (N = 805)	Patients with moderate-to-severe active RA with an inadequate response to csDMARDs	24 weeks, double blind 5-year OLE: after 24 weeks, patients received open-label TCZ-IV ± csDMARDs	ACR20 response at week 24
RADIATE (NCT00106522)	Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter study	TCZ-IV 8 mg/kg q4w + MTX (N = 170) TCZ-IV 4 mg/kg q4w + MTX (N = 161) PBO + MTX (N = 158)	Patients with moderate-to-severe active RA with an inadequate response to ≥ 1 aTNF	24-weeks, double blind 5-year OLE: after 24 weeks, patients received open-label TCZ-IV ± MTX	ACR20 response at week 24
LITHE (NCT00106535)	Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter trial	TCZ-IV 8 mg/kg q4w + MTX (N = 398) TCZ-IV 4 mg/kg q4w + MTX (N = 399) PBO + MTX (N = 393)	Patients with moderate-to-severe active RA with an inadequate response to MTX	1 year, double blind 3- to 5-year OLE: after 24 weeks, patients received TCZ-IV + MTX	Change from baseline in mTSS at week 52 Change from baseline in HAQ-DI at week 52
OPTION (NCT00106548)	Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter trial	TCZ-IV 8 mg/kg q4w + MTX (N = 205) TCZ-IV 4 mg/kg q4w + MTX (N = 214) PBO + MTX (N = 204)	Patients with moderate-to-severe active RA with an inadequate response to MTX	24 weeks, double blind 5-year OLE: after 24 weeks, patients received TCZ-IV + MTX	ACR20 response at week 24
FUNCTION (NCT01007435)	Phase 3, randomized, double-blind, double-dummy, parallel-arm,	TCZ-IV 8 mg/kg q4w + MTX (N = 291) TCZ-IV 8 mg/kg	Patients with moderate-to-severe active RA of ≤ 2 years' duration who were	52 weeks, double blind	DAS28-ESR < 2.6 at week 24

	multicenter trial	q4w + PBO (N = 292) TCZ-IV 4 mg/kg q4w + MTX (N = 290) PBO + MTX (N = 289)	MTX and biologic naive	
Clinical pharmacology study	Open-label, randomized safety study	MTX qw + TCZ-IV 10 mg/kg single dose (N = 23)	Patients with RA	8 weeks 5-year OLE: patients received TCZ-IV 8 mg/kg q4w ± MTX

* TOZURA aimed to enroll ≈ 1850 patients, and the interim analysis used here evaluated 1246 patients who were included by the end of 2014 and had completed 24 weeks in the program.

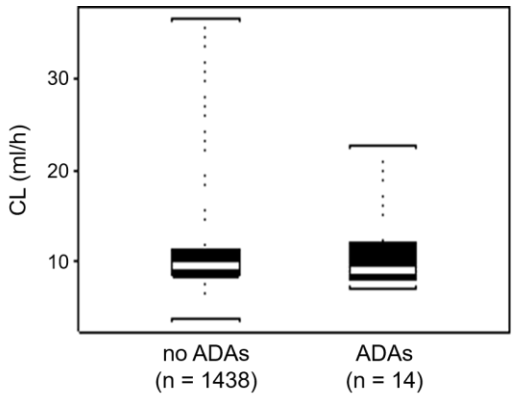
TCZ = tocilizumab; SC = subcutaneous; qw = once weekly; csDMARD = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; q4w = every 4 weeks; RA = rheumatoid arthritis; aTNF = anti–tumor necrosis factor-α agent; OLE = open-label extension; ACR20 = American College of Rheumatology criteria for 20% improvement; PBO = placebo; q2w = every 2 weeks; MTX = methotrexate; mTSS = Genant-modified total Sharp score; HAQ-DI = Health Assessment Questionnaire Disability Index; DAS28 = disease activity score based on 28 joints; ESR = erythrocyte sedimentation rate.

Supplemental Table 2. Transient ADA development in ADA-positive patients (excluding the Japanese study)

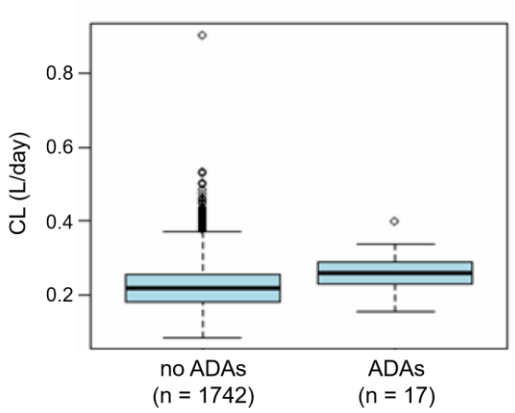
	ADA-Positive Patients (N = 109)
Patients who developed ADAs, n	109
Patients who were ADA positive at a single time point only, n (%)	79 (72.5)
≤ 16 weeks from 1st positive sample to 2nd positive sample, n (%)	22 (20.2)
> 16 weeks from 1st positive sample to 2nd positive sample, n (%)	8 (7.3)
Sustained from 1st positive sample to last sampling, n (%)	11 (10.1)

ADA = anti-drug antibody; TCZ = tocilizumab

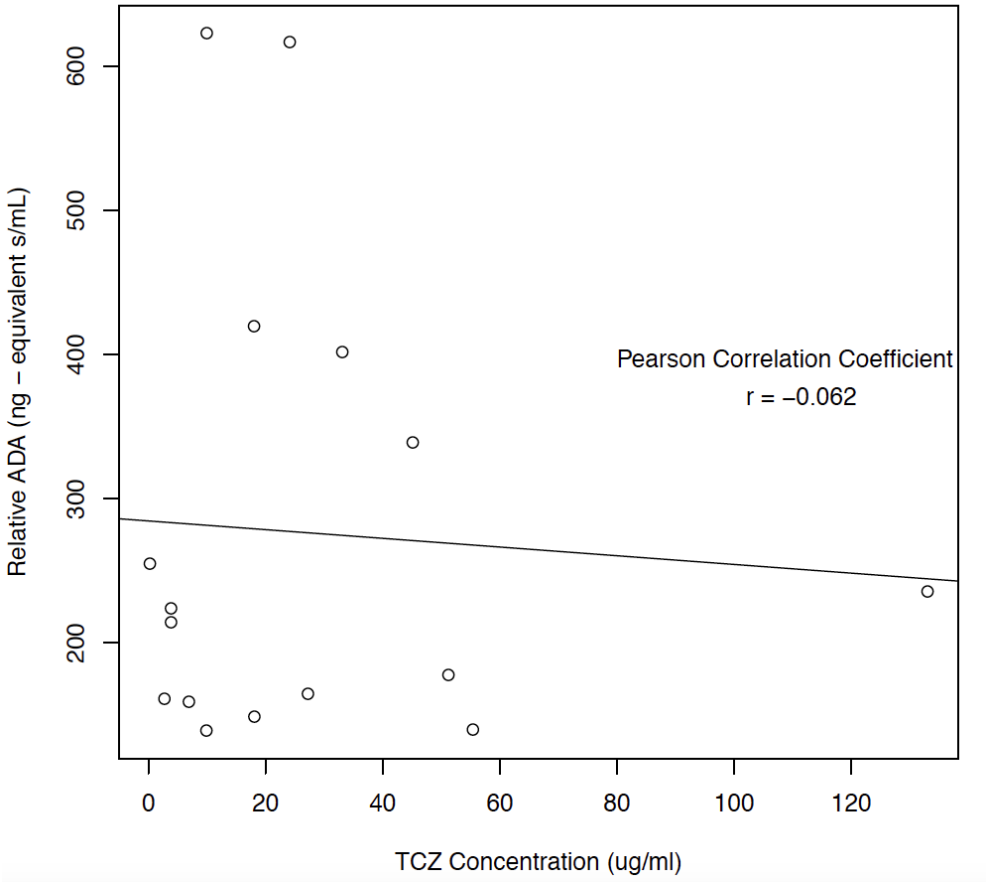
Supplemental Figure 1. Comparison of linear clearance of serum TCZ for patients who developed ADA and those who did not during treatment with TCZ-IV. A total of 1452 patients from 3 Phase III TCZ-IV studies [13, 16, 17] for whom PK parameters could be estimated and who had at least 1 neutrophil count value were included in the population PK analysis. Among these patients, 14 were positive for neutralizing anti-TCZ antibodies. ADA = antidrug antibody; CL = clearance; IV = intravenous; PK = pharmacokinetic; TCZ = tocilizumab.



Supplemental Figure 2. Comparison of linear clearance of serum TCZ for patients who developed ADA and those who did not during treatment with TCZ-SC. A total of 1759 patients from 2 Phase III TCZ-SC studies [20, 22] were included in the population PK analysis. Among these patients, 17 were positive for confirmatory anti-TCZ antibodies. ADA = antidrug antibody; CL = clearance; PK = pharmacokinetic; SC, subcutaneous; TCZ = tocilizumab.



Supplemental Figure 3. Correlation of relative ADA concentration vs. PK in ADA-positive patients (SUMMACTA).



ADA = anti-drug antibody; PK = pharmacodynamics; TCZ = tocilizumab.