

# Long-Term Safety and Efficacy of Subcutaneously Administered Tocilizumab for Adult Rheumatoid Arthritis: A Multicenter Phase 3b Long-term Extension Study

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## ABSTRACT

**Introduction:** To assess the long-term safety and efficacy of subcutaneous tocilizumab (TCZ-SC) in US patients with rheumatoid arthritis (RA) who rolled over from the two global phase 3 studies, SUMMACTA (NCT01194414) and BREVACTA (NCT1232569), into this open-label, single-arm, phase 3b study.

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**Methods:** Patients continued to receive TCZ-SC 162 mg weekly or every other week or switched from intravenous TCZ to TCZ-SC 162 mg qw for up to 84 weeks. The primary endpoint was the proportion of patients with serious adverse events (SAEs). Secondary endpoints included clinical efficacy, laboratory abnormalities, and immunogenicity.

**Results:** Of the 217 patients treated, 76.5% were female, and the mean age was 58.4 years. A total of 23 patients (10.6%) had  $\geq 1$  SAE. The most common SAEs were infections (3.7%). Alanine aminotransferase elevations (38.2%) were not associated with hepatic injury. Grade 3/4 neutropenia (3%) was transient and not associated with serious infections. Immunogenicity was low (<1%) and not associated with SAEs. No anaphylaxis or deaths occurred. Thirteen patients (6.0%) withdrew due to safety reasons. Mean Clinical Disease Activity Index and Disease Activity Score in 28 joints remained stable throughout the trial.

**Conclusions:** The long-term safety of TCZ-SC during the long-term extension period was consistent with the safety profiles from SUMMACTA and BREVACTA, with no new

safety signals. Efficacy improvements observed from baseline remained stable over time. These results demonstrated the durability of the safety and efficacy responses, and low immunogenicity, with long-term exposure to TCZ-SC in patients with RA.

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**Keywords:** Rheumatoid arthritis; Safety; Subcutaneous; Tocilizumab

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by inflammation of the joints that, if left untreated, leads to irreversible joint damage and disability. Biologic disease-modifying antirheumatic drugs (bDMARDs) that block inflammatory cytokines, B cells, or T cells are commonly used for the treatment of RA in combination with conventional synthetic DMARDs (csDMARD) or as monotherapy. Due to the long-term treatment of patients with RA with bDMARDs, it is important to establish that these drugs have lasting efficacy and safety.

Tocilizumab (TCZ) is the first drug approved for the treatment of RA that blocks the biological activity of interleukin 6 (IL-6). TCZ is a humanized monoclonal antibody that competitively interferes with the binding of IL-6 to the IL-6 receptor (IL-6R, also known as IL-6R $\alpha$  or CD126), thereby disrupting receptor association with glycoprotein 130, a co-signal transducer protein (also known as IL-6R $\beta$  or CD130) necessary for initiating intracellular signaling through the JAK-STAT and other pathways [10]. TCZ, in combination with

csDMARDs or as monotherapy, has demonstrated efficacy with a well-established safety profile in patients with RA who had an inadequate response to csDMARDs or anti-tumor necrosis factor agents (aTNFs) [2, 4–6]. Intravenous [IV; 4 and 8 mg/kg every 4 weeks (q4w)] and subcutaneous [SC; 162 mg weekly (qw) or every 2 weeks (q2w)] formulations of TCZ are available for the treatment of patients with RA.

The efficacy and safety of TCZ-SC was demonstrated in two recent global phase 3 clinical trials in patients with RA who had an inadequate response to csDMARDs or aTNFs: BREVACTA (NCT1232569) reported the superiority of TCZ-SC q2w plus csDMARDs to placebo SC plus csDMARDs over 24 weeks [8]. SUMMACTA (NCT01194414) reported the noninferiority of TCZ-SC qw to TCZ-IV 8 mg/kg q4w, in combination with a csDMARDs, over 24 weeks [7]. The extensions of SUMMACTA and BREVACTA with TCZ-SC qw and TCZ-SC q2w, respectively, to 96–97 weeks demonstrated that efficacy and safety remained comparable to the known profile of TCZ-IV [9]. Additionally, the MUSASHI (JapicCTI-101117) trial in Japan reported the noninferiority of TCZ-SC q2w as monotherapy to TCZ-IV 8 mg/kg q4w as monotherapy in patients who had an inadequate response to methotrexate or a bDMARD over a 24-week study period; the continued efficacy and safety of TCZ-SC monotherapy in MUSASHI has been reported out to 2 years [1, 11].

This open-label long-term extension phase 3b study for up to an additional 84 weeks evaluated the long-term safety, immunogenicity, and efficacy of TCZ-SC in patients in the US who completed the SUMMACTA or BREVACTA studies.

## METHODS

### Participants

The study population consisted of adult patients ( $\geq 18$  years of age) with RA ( $\geq 6$  months) in the United States who had moderate-to-high disease activity and completed SUMMACTA [7] or BREVACTA [8] and, on the basis of the investigator's judgment, might have continued to benefit from TCZ-SC treatment.

### Study Design

This was a multicenter phase 3b long-term extension study of SUMMACTA and BREVACTA (Figure S1 in the supplementary material; trial registration number NCT01662063). For enrollment in both SUMMACTA and BREVACTA, patients ( $\geq 18$  years of age) with RA ( $\geq 6$  months, revised 1987 American College of Rheumatology criteria) were included and were required to have had an inadequate response to  $\geq 1$  DMARD (up to 20% of patients may have had inadequate response to  $\geq 1$  aTNF). Patients who completed the 96–97-week BREVACTA and SUMMACTA studies and met the enrollment criteria continued to receive TCZ-SC q2w or TCZ-SC qw, respectively, or switched from TCZ-IV to TCZ-SC 162 mg qw for up to an additional 84 weeks. Thus, all patients in the long-term extension were receiving TCZ-SC. Baseline was defined as the beginning of this long-term extension for all efficacy and safety data. Study treatment at baseline was given at least 6 weeks after the last TCZ-IV dose or at least 4 weeks after the last TCZ-SC dose. The maximum interval allowed between the last dose in the core study and initiation of treatment in the long-term extension study was 3 months.

Concomitant csDMARDs, oral corticosteroids, and non-steroidal anti-inflammatory drugs were permitted up to the maximum dose based on clinical response and the physician's judgment (Figure S2 in the supplementary material).

The end of the study occurred up to 84 weeks of treatment because the SC formulation of TCZ was approved by the US Food and Drug Administration and commercial supplies became available as planned.

### Outcomes and Assessments

The primary study endpoint was the number and percentage of patients with serious adverse events (SAEs) during long-term treatment with TCZ-SC. The secondary safety endpoints were the number and percentage of patients who experienced AEs of special interest, number and percentage of patients with AEs and SAEs causing discontinuation of TCZ, number and percentage of patients who discontinued TCZ for any reason, incidence of clinically significant laboratory abnormalities (hematology, lipid profiles, and liver function), rates of immunogenicity, summary of abnormal vital signs, and patient compliance (drug dispensing logs, patient diary cards, and return records). Clinical efficacy was measured by the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), total tender joint count (TJC), total swollen joint count (SJC), and achievement of Boolean remission (defined as SJC  $\leq 1$ , TJC  $\leq 1$ , patient global assessment visual analog scale score  $\leq 1$  cm, and C-reactive protein level  $\leq 1$  mg/dL).

AEs were monitored throughout the study, and laboratory measurements were assessed every 12 weeks. Efficacy assessments were made every

12 weeks. Blood samples were collected to evaluate TCZ and soluble IL-6R serum levels and development of anti-TCZ antibodies (Figure S3 in the supplementary material).

### Statistical Methods

No formal statistical hypothesis testing was performed. Patients were grouped by their initial dose frequency. Safety analyses included all patients who received  $\geq 1$  dose of study medication and had  $\geq 1$  postdose safety assessment. Efficacy analyses included all patients who received  $\geq 1$  dose of study medication and had  $\geq 1$  efficacy measurement performed. Due to the noncomparative nature of the study, descriptive statistics were produced for all endpoints.

### Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional review boards: Southern Arizona VA Health Care System, St. Vincent Hospital/Reliant Medical Group/Fallon Community Health Plan, Western, Oklahoma Medical Research Foundation, Via Christi Hospitals Wichita, Inc. and Dartmouth Hitchcock Medical Center Quorum) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study.

## RESULTS

### Patient Disposition and Baseline Characteristics

A total of 217 patients who completed BREVACTA or SUMMACTA were enrolled and received treatment, including 44 patients who

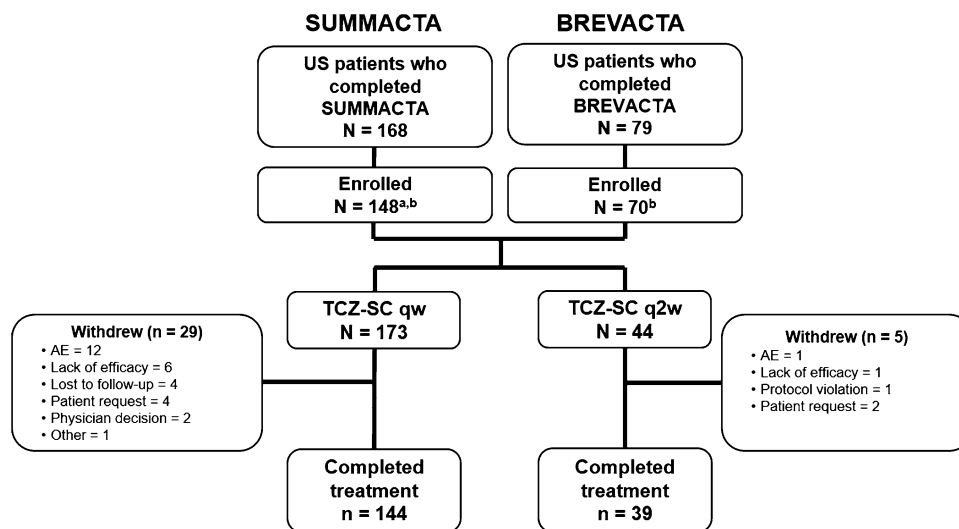
received TCZ-SC q2w and 173 patients who received TCZ-SC qw (Fig. 1). Of the 217 patients, 183 (84.3%) completed the study at the time of TCZ-SC formulation approval. The mean length of TCZ-SC additional exposure was 0.93 years past the original 96-week 2-year studies. The integrated mean duration of TCZ-IV or TCZ-SC exposure (the duration in the core studies combined with the duration in this study) was 2.6 years.

Baseline demographics and clinical characteristics were balanced across the dosing frequency groups (Table 1). The majority of patients (76.5%) were female, and the mean [standard deviation (SD)] age was 58.4 (10.3) years. The mean (SD) duration of RA was 12.8 (9.0) years, the mean (SD) CDAI was 23.1 (16.2), the mean (SD) DAS28 was 4.6 (1.9), and the mean (SD) SDAI was 24.4 (16.8).

### Safety

The rates of AEs and SAEs were stable over time in both TCZ-SC qw and TCZ-SC q2w dosing groups (Table 2). A total of 179 patients (82.5%) experienced 954 AEs (133 AEs in the TCZ-SC q2w group and 821 AEs in the TCZ-SC qw group). The most common AEs for all patients were upper respiratory tract infection (19.8%), sinusitis (11.1%), and nasopharyngitis (10.1%). A total of 23 patients (10.6%) experienced 37 SAEs (7 SAEs in the TCZ-SC q2w group and 30 SAEs in the TCZ-SC qw group). The rate of SAEs was 14.72 events per 100 patient-years (PY), and the most common SAEs for all patients were infections (3.7%), nervous system disorders (2.3%), gastrointestinal (GI) disorders (1.8%), and musculoskeletal and connective tissue disorders (1.8%). There were no deaths.

There were 85 patients (49.1%) in the TCZ-SC qw group and 12 patients (27.3%) in the TCZ-SC q2w group who experienced AEs



**Fig. 1** Overview of patient disposition. <sup>a</sup>One patient was not treated. <sup>b</sup>Fourteen patients did not meet the screening criteria including unable and unwilling to provide written informed consent and to comply with the requirements of the study protocol; any major episode of infection requiring hospitalization or treatment with intravenous antibiotics  $\leq 4$  weeks of screening or oral antibiotics  $\leq 2$  weeks of screening; receiving intraarticular or parenteral corticosteroids  $\leq 4$  weeks prior to baseline;

leading to dose modification or interruption. Seven patients (3.2%) had their dosing frequency reduced from TCZ-SC qw to TCZ-SC q2w due to AEs. Withdrawals occurred in 15.7% of patients, with 6.0% of patients withdrawing due to safety reasons (2.3% in the TCZ-SC q2w group and 6.9% in the TCZ-SC qw group).

There were 11 serious infections in eight patients (4.38 per 100 PY), and there were no opportunistic infections (Table 2). The serious infections reported in the TCZ-SC qw group included cellulitis (3 events), septic arthritis (1 event), endocarditis (1 event), staphylococcal bacteremia (2 events), and bronchopneumonia (1 event). In the TCZ-SC q2w group, endophthalmitis (1 event) and pyelonephritis (2 events) were reported. There were two GI perforation events in the TCZ-SC qw group and no GI perforation events in the TCZ-SC q2w

group. One GI perforation event was a diverticular perforation considered related to study treatment and the other was a gastric ulcer perforation complicated by peritonitis. There were no myocardial infarctions, demyelinating disorders, or serious hepatic events. There were a total of five strokes, all in the TCZ-SC qw group. One patient in the TCZ-SC q2w group experienced a serious bleeding event (hematuria). There were two malignancies, one in the TCZ-SC q2w group (basal cell carcinoma) and one in the TCZ-SC qw group (endometrial stromal sarcoma).

**Hypersensitivity Reactions, Injection Site Reactions and Immunogenicity**

There were six non-serious hypersensitivity reactions defined as all AEs [except for injection site reactions (ISRs)] that occurred

**Table 1** Baseline Patient Demographics and Clinical Characteristics<sup>a</sup>

	TCZ-SC q2w (N = 44)	TCZ-SC qw (N = 173)	All patients (N = 217)
Female, n (%)	33 (75.0)	133 (76.9)	166 (76.5)
Age, mean (SD), years	59.7 (10.2)	58.1 (10.4)	58.4 (10.3)
Duration of RA, mean (SD), years	13.8 (10.1)	12.5 (8.7)	12.8 (9.0)
Weight, mean (SD), kg	77.4 (20.9)	85.2 (22.2)	83.6 (22.1)
BMI, mean (SD), kg/m <sup>2</sup>	29.2 (7.3)	31.3 (7.7)	30.9 (7.6)
DAS28-ESR, mean (SD)	4.6 (1.7)	4.6 (1.9)	4.6 (1.9)
CDAI, mean (SD)	20.1 (15.5)	23.9 (16.4)	23.1 (16.2)
SDAI, mean (SD)	21.5 (15.7)	25.1 (17.0)	24.4 (16.8)
CRP, mean (SD), mg/dL	1.4 (2.3)	1.1 (1.8)	1.2 (1.9)
ESR, mean (SD), mm/h	34.1 (31.0)	29.0 (25.5)	30.0 (26.7)
Tender joints (68-joint count), mean (SD)	13.8 (13.9)	19.1 (18.5)	18.1 (17.7)
Swollen joints (66-joint count), mean (SD)	9.1 (8.9)	10.8 (10.9)	10.5 (10.5)
Physician's global assessment of disease activity, mean (SD)	30.7 (24.2)	38.1 (26.4)	36.6 (26.1)
Patient's global assessment of disease activity, mean (SD)	39.4 (24.5)	47.3 (29.9)	45.7 (29.0)
Patient's global assessment of pain activity, mean (SD)	36.9 (23.0)	45.4 (29.5)	43.7 (28.4)
HAQ-DI, mean (SD)	1.0 (0.7)	1.2 (0.7)	1.2 (0.7)

<sup>a</sup> Data represent the baseline patient characteristics at the start of the 84-week long-term extension. Study treatment at baseline was given at least 6 weeks after the last TCZ-IV dose or at least 4 weeks after the last TCZ-SC dose. Baseline DAS28, CDAI and SDAI are from the last assessment before the first dose of study medication in the long-term extension. BMI body mass index, CDAI clinical disease activity index, CRP C-reactive protein, DAS28-ESR disease activity score in 28 joints based on the erythrocyte sedimentation rate, HAQ-DI Health Assessment Questionnaire—Disability Index, qw every week, q2w every 2 weeks, RA rheumatoid arthritis, SC subcutaneous, SD standard deviation, SDAI simplified disease activity index, TCZ tocilizumab

during or within 24 h of injection and which were not judged 'unrelated' to treatment by the investigator, regardless of whether or not they were consistent with hypersensitivity. There were 29 ISRs in six patients during the study (one patient in the TCZ-SC q2w group and five patients in the TCZ-SC qw group; Table 3). None of the ISRs in any patient was serious, and none of the patients discontinued study treatment due to an ISR. One patient had 24 ISRs. In this patient, ISRs occurred with every TCZ-SC qw injection up to 216 study days, and there were no reports of ISRs  $\approx$ 4 months after

reducing the dose frequency to TCZ-SC q2w; the patient did not discontinue treatment and no clinical sequelae were associated with the ISRs. This patient experienced ISRs with every injection in the core trial as well.

One patient developed antidrug antibodies in the TCZ-SC qw arm (Table 3). No patients experienced anaphylaxis, serious hypersensitivity, or clinically significant hypersensitivity reactions, including the one who developed anti-TCZ antibodies. There was no association between lack of efficacy or loss of therapeutic response and development of

**Table 2** AEs and SAEs During the Long-term Extension

	TCZ-SC q2w 39.7 PY (N = 44)	TCZ-SC qw 211.6 PY (N = 173)	All Patients 251.3 PY (N = 217)
<b>AEs</b>			
Total AEs <sup>a</sup>	133	821	954
AEs per 100 PY (95% CI)	334.9 (280.4–396.9)	388.1 (362.0–415.5)	379.7 (356.0–404.5)
Patients with $\geq 1$ AE, <i>n</i> (%)	33 (75.0)	146 (84.4)	179 (82.5)
Led to dose modification/interruption, <i>n</i> (%) <sup>a</sup>	12 (27.3)	85 (49.1)	97 (44.7)
Led to discontinuation, <i>n</i> (%) <sup>a</sup>	2 (4.5)	14 (8.1)	16 (7.4)
<b>SAEs</b>			
Total SAEs <sup>a</sup>	7	30	37
SAEs per 100 PY (95% CI)	17.6 (7.1–36.3)	14.2 (9.6–20.2)	14.7 (10.4–20.3)
Patients with $\geq 1$ SAE, <i>n</i> (%)	4 (9.1)	19 (11.0)	23 (10.6)
Serious infections per 100 PY (95% CI)	7.6 (1.6–22.1)	3.8 (1.6–7.5)	4.4 (2.2–7.8)
Led to dose modification/interruption, <i>n</i> (%) <sup>a</sup>	1 (2.3)	9 (5.2)	10 (4.6)
Led to discontinuation, <i>n</i> (%) <sup>a</sup>	2 (4.5)	7 (4.0)	9 (4.1)
<b>SAEs by type, no. of events</b>			
Serious infections	3	8	11
Opportunistic infections	0	0	0
Myocardial infarction/acute coronary syndrome	0	0	0
Stroke	0	5	5
Serious bleeding event	1	0	1
<b>Gastrointestinal perforations</b>			
Diverticular perforations	0	1	1
Gastric ulcer perforations <sup>b</sup>	0	1	1
<b>Malignancies</b>			
Basal cell carcinoma <sup>c</sup>	1	0	1
Endometrial stromal sarcoma	0	1	1
Demyelinating disorders	0	0	0
Serious hepatic events	0	0	0
<b>Withdrawals</b>			
Total, <i>n</i> (%)	5 (11.4)	29 (16.8)	34 (15.7)
Due to safety reasons, <i>n</i> (%)	1 (2.3)	12 (6.9)	13 (6.0)
Due to nonsafety reasons, <i>n</i> (%)	4 (9.1)	17 (9.8)	21 (9.7)

AE adverse event, CI confidence interval, PY patient-year, qw every week, q2w every 2 weeks, SAE serious adverse event, SC subcutaneous, TCZ tocilizumab

<sup>a</sup> Multiple occurrences of the same AE in the same individual were counted

<sup>b</sup> This patient had a gastric ulcer perforation complicated by peritonitis

<sup>c</sup> This was a non-serious event

**Table 3** Injection-Related Reactions and Immunogenicity

	TCZ-SC q2w (N = 44)	TCZ-SC qw (N = 173)	All patients (N = 217)
Injection-related reactions			
No. of patients with injection site reaction	1	5	6
Injection site reactions <sup>a</sup>	1	28	29
Hypersensitivity reactions	0	6	6
Anaphylaxis	0	0	0
Immunogenicity			
No. of patients tested by screening at any time point	44	166	210
Positive confirmation assay, <i>n</i> (%)	0	1 (0.6)	1 (0.5)
Positive neutralizing assay, <i>n</i> (%)	0	1 (0.6)	1 (0.5)

<sup>a</sup> Six patients experienced 29 injection site reactions during the study (one patient in the q2w group and five patients in qw group). None of the injection site reactions in any patient were serious, and none of the patients were withdrawn from study treatment due to an injection site reaction. One patient experienced 24 injection site reactions during the study *qw* every week, *q2w* every 2 weeks, *SC* subcutaneous, *TCZ* tocilizumab

anti-TCZ antibodies. None of the patients who withdrew due to insufficient therapeutic response had a positive anti-TCZ antibody screening assay.

### Laboratory Abnormalities

The overall incidence of markedly abnormal laboratory values was  $\leq 5\%$ . Elevations  $>3 \times$  the upper limit of normal (ULN) at any point in alanine aminotransferase (ALT) levels were observed in two patients and in aspartate aminotransferase levels were observed in one patient (Table 4). Two patients in the TCZ-SC qw group had  $\geq 2$  consecutive observations of ALT  $>3 \times$  ULN. No serious hepatic events were observed in any patients. There were six cases of grade 3 neutropenia ( $\geq 500$  to  $<1000$  cells/mm<sup>3</sup>) reported as AEs (one in the TCZ-SC q2w group and five in the TCZ-SC qw group). No patients who experienced neutropenia developed serious or opportunistic infections. One patient in the TCZ-SC qw group experienced grade 3 thrombocytopenia ( $\geq 50,000$  to  $<25,000$

cells/mm<sup>3</sup>) that was reported as an SAE. Among the patients with normal cholesterol levels at baseline, there were nine grade 1 levels ( $>ULN$  to  $\leq 7.75$  mmol/L; 2 in the TCZ-SC q2w group and 7 in the TCZ-SC qw group) and 18 grade 2 levels ( $>7.75$  to  $\leq 10.34$  mmol/L; all in the TCZ-SC qw group). Among patients with normal triglyceride levels as baseline, there were 28 grade 1 ( $>1.71$  to  $\leq 3.42$  mmol/L), 1 grade 2 ( $>3.42$  to  $\leq 5.7$  mmol/L) and 1 grade 3 ( $>5.7$  to  $\leq 11.4$  mmol/L) levels. Seven patients (3%) had markedly high ( $\geq 5.4$  mmol/L) low density lipoprotein cholesterol levels, all of whom were in the TCZ-SC qw group.

### Efficacy

The efficacy of TCZ remained stable over time. Mean DAS28-ESR, CDAI, and SDAI scores decreased from baseline and then remained stable over time (Fig. 2a and Figure S4 in the supplementary material). At the time the study ended due to the SC formulation of TCZ



**Table 4** Laboratory Abnormalities

	TCZ-SC q2w ( <i>N</i> = 44)	TCZ-SC qw ( <i>N</i> = 173)	All patients ( <i>N</i> = 217)
ALT levels, <i>n</i> (%) <sup>a</sup>	<i>n</i> = 38	<i>n</i> = 135	<i>n</i> = 173
>ULN	8 (21.1)	58 (43.0)	66 (38.2)
>1× to 2× ULN	7 (18.4)	48 (35.6)	55 (31.8)
>2× to 3× ULN	0	9 (6.7)	9 (5.2)
>3× ULN	1 (2.6)	1 (0.7)	2 (1.2)
AST levels, <i>n</i> (%) <sup>b</sup>	<i>n</i> = 38	<i>n</i> = 146	<i>n</i> = 184
>ULN	8 (21.1)	42 (28.8)	50 (27.2)
>1× to 2× ULN	8 (21.1)	39 (26.7)	47 (25.5)
>2× to 3× ULN	0	3 (2.1)	3 (1.6)
>3× ULN	0	1 (0.7)	1 (0.5) <sup>c</sup>
Neutropenia, <i>n</i> (%) <sup>d</sup>	<i>n</i> = 41	<i>n</i> = 158	<i>n</i> = 199
Grade 1	8 (19.5)	23 (14.6)	31 (15.6)
Grade 2	3 (7.3)	15 (9.5)	18 (9.0)
Grade 3	1 (2.4)	5 (3.2)	6 (3.0)
Grade 4	0	0	0
Thrombocytopenia, <i>n</i> (%) <sup>e</sup>	<i>n</i> = 43	<i>n</i> = 170	<i>n</i> = 213
Grade 1	4 (9.3)	20 (11.8)	24 (11.3)
Grade 2	0	0	0
Grade 3	0	1 (0.6)	1 (0.5)
Grade 4	0	0	0
Cholesterol, <i>n</i> (%) <sup>f</sup>	<i>n</i> = 41	<i>n</i> = 152	<i>n</i> = 193
Grade 1	2 (4.9)	7 (4.6)	9 (4.7)
Grade 2	0	18 (11.8)	18 (9.3)
Grade 3	0	0	0
Grade 4	0	0	0
Triglycerides, <i>n</i> (%) <sup>g</sup>	<i>n</i> = 39	<i>n</i> = 141	<i>n</i> = 180
Grade 1	5 (12.8)	23 (16.3)	28 (15.6)
Grade 2	0	1 (0.7)	1 (0.6)
Grade 3	0	1 (0.7)	1 (0.6)

**Table 4** continued

	TCZ-SC q2w (N = 44)	TCZ-SC qw (N = 173)	All patients (N = 217)
Grade 4	0	0	0

<sup>a</sup> Denominator is the number of patients who had normal ALT levels at baseline and  $\geq 1$  postbaseline value

<sup>b</sup> Denominator is the number of patients who had normal AST levels at baseline and  $\geq 1$  postbaseline value

<sup>c</sup> This patient had AST levels  $1\times$  to  $2\times$  ULN at baseline

<sup>d</sup> Denominator is the number of patients who had normal neutrophil counts (grade 0) at baseline and  $\geq 1$  postbaseline value. Neutropenia grades were defined as follows: grade 1, <lower limit of normal to  $\geq 1500$  cells/mm<sup>3</sup>; grade 2,  $\geq 1000$  to <1500 cells/mm<sup>3</sup>; grade 3,  $\geq 500$  to <1000 cells/mm<sup>3</sup>; grade 4, <500 cells/mm<sup>3</sup>

<sup>e</sup> Denominator is the number of patients who had normal platelet counts (grade 0) at baseline and  $\geq 1$  postbaseline value. Thrombocytopenia grades were defined as follows: grade 1, <lower limit of normal to  $\geq 75,000$  cells/mm<sup>3</sup>; grade 2,  $\geq 75,000$  to <50,000 cells/mm<sup>3</sup>; grade 3,  $\geq 50,000$  to <25,000 cells/mm<sup>3</sup>; grade 4, <25,000 cells/mm<sup>3</sup>

<sup>f</sup> Denominator is the number of patients who had normal cholesterol levels (grade 0) at baseline. Cholesterol grades were defined as follows: grade 1, >ULN to  $\leq 7.75$  mmol/L; grade 2, >7.75 to  $\leq 10.34$  mmol/L; grade 3, >10.34 to  $\leq 12.92$  mmol/L; >12.92 mmol/L

<sup>g</sup> Denominator is the number of patients who had normal triglyceride levels (grade 0) at baseline. Triglyceride grades were defined as follows: grade 1, >1.71 to  $\leq 3.42$  mmol/L; >3.42 to  $\leq 5.7$  mmol/L; grade 3, >5.7 to  $\leq 11.4$  mmol/L; grade 4, >11.4 mmol/L

ALT alanine aminotransferase, AST aspartate aminotransferase, qw every week, q2w every 2 weeks, SC subcutaneous, TCZ tocilizumab, ULN upper limit of normal

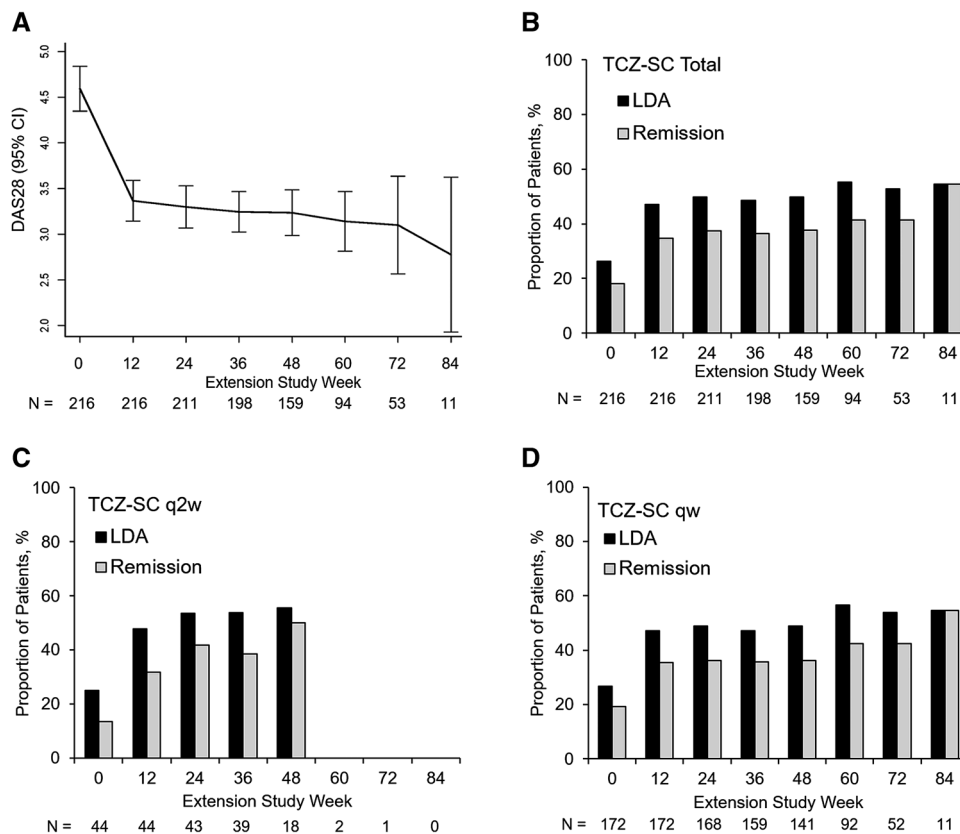
becoming commercially available, only two and one patients from the TCZ-SC q2w group remained up to 60 and 72 weeks, respectively; therefore, the efficacy for this group beyond 60 weeks cannot be accurately evaluated. Overall, the proportion of patients who achieved low disease activity (LDA) and remission based on DAS28-ESR (defined as DAS28-ESR  $\leq 2.6$  and DAS28-ESR  $\leq 3.2$ , respectively) at 36 weeks in the extension period, after which there was not a sufficient number of patients for analysis, was 48.5% and 36.4%, respectively (Fig. 2b; results by group are shown in Fig. 2c, d). A total of 62.0% of patients achieved an ACR20 response at week 36 of the extension period. Based on CDAI, LDA and remission at 36 week of the extension period were achieved in 40.9% and 11.1% of patients, respectively, and based on SDAI, LDA and remission at 36 weeks in the extension period were achieved in 40.9% and 14.1% of patients, respectively. Four patients (1.8%) had their

dosing frequency reduced from TCZ-SC qw to TCZ-SC q2w due to sustained clinical remission.

### Pharmacokinetics and Pharmacodynamics

The mean concentration of serum TCZ in patients in the TCZ-SC qw treatment group increased from baseline (the beginning of the extension period) to week 12, then remained constant until week 72, ranging between 36.6 and 40.4  $\mu\text{g/mL}$ . The mean concentration of serum TCZ in patients in the TCZ-SC q2w treatment group increased from baseline to week 48, ranging between 8.4 and 15.9  $\mu\text{g/mL}$ .

The mean soluble IL-6R concentration in patients receiving TCZ-SC qw increased from baseline to week 12, then stayed constant until week 72, and post baseline, the concentration ranged between 523.2 and 579.4 ng/mL. The mean soluble IL-6R concentration in patients receiving TCZ-SC q2w steadily increased from



**Fig. 2** Efficacy over time. Time is shown in weeks from the beginning of the extension study; total TCZ exposure time is the indicated extension study week plus 96 or 97 weeks from the core trial. Mean (95% CI) DAS28-ESR in patients who received TCZ-SC qw or TCZ-SC q2w (total patients) is shown for each 12 week interval during the study (a). The percentage of patients in DAS28 LDA or remission is shown over the course of the study for the

total population (b) and those who received TCZ-SC q2w (c) or TCZ-SC q2w (d). Remission was defined as DAS28  $\leq 2.6$  and LDA was defined as DAS28  $\leq 3.2$ . CI confidence interval, LDA low disease activity, SC subcutaneous, TCZ tocilizumab, qw weekly, q2w every other week, DAS28-ESR disease activity score in 28 joints using the erythrocyte sedimentation rate

baseline to week 48, and from week 12 to week 48, the concentration ranged between 398.7 and 518.9 ng/mL.

## DISCUSSION

This long-term extension of the SUMMACTA and BREVACTA studies assessed the safety, immunogenicity, and efficacy of the extended use of TCZ-SC qw and TCZ-SC q2w in US patients with RA. The long-term use of TCZ-SC was well tolerated and consistent with the

known safety profile of TCZ. The rate of SAEs (events/100 PY) in this study was 14.7, consistent with the rates observed for TCZ-SC at 96 or 97 weeks in BREVACTA and SUMMACTA [11.2 events/100 PY (TCZ-SC q2w) and 14.6 events/100 PY (TCZ-SC qw), respectively] [9]. Serious infections were the most common SAE, and the overall incidence of serious infections in this study (4.38/100 PY) was similar to that in previous TCZ studies, including the 97-week SUMMACTA trial (3.95/100 PY for TCZ-SC qw and 3.92/100 PY for

TCZ-IV q4w), the long-term cumulative safety analyses of the phase 3 TCZ-IV clinical trials (4.5/100 PY), and the 3-year postmarketing report of TCZ-IV in Japan (3.67/100 PY) [3, 9, 12]. No new safety signals were identified.

Immunogenicity is a concern with biologic therapies. Antidrug antibodies can lead to loss of efficacy, hypersensitivity reactions, and/or allergic responses [13, 14]. In this long-term extension study of TCZ-SC, immunogenicity was very low, which was consistent with previous studies of TCZ-SC and TCZ-IV. [7, 9, 11, 15] Only one patient (0.5%) developed anti-TCZ antibodies, and this patient did not experience anaphylaxis, serious hypersensitivity reactions, or ISRs. Moreover, this patient did not experience a lack of efficacy or loss of therapeutic response associated with the development of anti-TCZ antibodies. Similarly, in the 97-week SUMMACTA study in which patients received TCZ-SC or TCZ-IV, 0.5–1.6% of patients developed anti-TCZ antibodies, with no correlation between anti-TCZ antibody development and clinical response or AEs [9]. This and other studies have shown that TCZ has one of the lowest incidences of antidrug antibody development among bDMARDs [16, 17], even lower than what has recently been reported for a fully human monoclonal antibody against the IL-6R [18].

Overall, the efficacy data in this study showed benefit of the extended use of TCZ-SC, given that patients who remained in the study and continued to receive TCZ-SC remained stable from baseline in mean DAS28-ESR, CDAI, and SDAI. The proportion of patients who achieved LDA increased or remained stable with the continuation of TCZ-SC treatment. Improvements in patient's and physician's global assessment of disease

activity and pain were also maintained over time with the extended use of TCZ-SC.

There were some limitations to this analysis. Whereas SUMMACTA and BREVACTA were global studies, this long-term extension of SUMMACTA and BREVACTA was conducted only in US patients. Despite this difference, the safety and efficacy profiles in this study were comparable with those in the global studies. Overall, the number of patients was low ( $N = 217$ ), with only 44 patients in the TCZ-SC q2w group. In addition, this extension study was limited to patients who completed SUMMACTA and BREVACTA; those who discontinued for any reason, including due to safety or efficacy, were not included. Only 14 patients (6.5%) reduced dosing frequency from TCZ-SC qw to TCZ-SC q2w (7 patients reduced due to AEs and four patients reduced due to sustained remission); therefore, this study provided limited additional information concerning the patients who received less frequent dosing.

## CONCLUSION

In this long-term extension analysis to the SUMMACTA and BREVACTA trials, the long-term use of TCZ-SC showed no increased risk of safety events and efficacy was maintained or improved. Overall, the results of this study supported the long-term safety and efficacy of TCZ-SC qw or TCZ-SC q2w therapy in patients with RA.

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**Compliance with Ethics Guidelines.** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional review boards: Southern Arizona VA Health Care System, St. Vincent Hospital/Reliant Medical Group/Fallon Community Health Plan, Western, Oklahoma Medical Research Foundation via Christi Hospitals Wichita, Inc. and Dartmouth Hitchcock Medical Center Quorum) and with the

Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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