ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis–Interstitial Lung Disease

Open-Label Extension of a Phase 3 Randomized Controlled Trial

Dinesh Khanna[1], Celia J. F. Lin[2*], Daniel E. Furst[3,4], Bridget Wagner[2], Mauro Zucchetto[5], Ganesh Raghu[6], Fernando J. Martinez[7], Jonathan Goldin[8], Jeffrey Siegel[2‡], and Christopher P. Denton[9]; for the focuSSced Investigators

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; [2]Genentech, South San Francisco, California; [3]Department of Medicine, University of California, Los Angeles, Los Angeles, California; [4]Division of Rheumatology, University of Washington, Seattle, Washington; [5]Global Data Operations, Functional Service Provider, Biostatistics, Parexel International, Milan, Italy; [6]Division of Pulmonary and Critical Care Medicine, University of Washington Medical Center, Seattle, Washington; [7]Department of Medicine, Weill Cornell Medicine, New York, New York; [8]Department of Radiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; and [9]Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom

Abstract

Rationale: Tocilizumab, an anti–IL-6 receptor antibody, had no statistically significant effect on skin sclerosis but preserved lung function over 48 weeks in patients with early systemic sclerosis (SSc)-associated interstitial lung disease (ILD) in a phase 3 randomized controlled trial.

Objectives: Assess long-term safety and efficacy of tocilizumab.

Methods: Adults with diffuse cutaneous SSc for ⩽60 months and elevated acute-phase reactants, including those with ILD, received weekly placebo or tocilizumab 162 mg subcutaneously in the 48-week, double-blind period and then open-label tocilizumab from Weeks 48 to 96 (placebo-tocilizumab; continuous-tocilizumab).

Measurements and Main Results: Eighty-two of 107 patients in the placebo-tocilizumab group and 85 of 105 patients in the continuous-tocilizumab group completed 96 weeks. Mean age and disease duration were 48 years and 23 months; high-resolution computed tomography revealed ILD in 61%. Mean (95% confidence interval [CI]) change in modified Rodnan skin score from baseline to week 96 was −8.4 (−10.0 to −6.8) for placebo-tocilizumab and −9.6 (−10.9 to −8.4) for continuous-tocilizumab. Mean (95% CI) change in FVC (percent predicted) from baseline to week 96 was −3.3 (−5.1 to −1.5) for placebo-tocilizumab and −0.5 (−2.4 to 1.3) for continuous-tocilizumab among completers and, in a *post hoc* analysis, −4.1 (−6.7 to −1.6) and −0.6 (−3.1 to 2.0), respectively, among completers with ILD (mean [95% CI] change from Weeks 48 to 96: 0.9 [−0.8 to 2.7] and −0.4 [−2.3 to 1.5], respectively). Rates per 100 patient-years of serious adverse events from Weeks 48 to 96 were 14.8 for placebo-tocilizumab and 15.8 for continuous-tocilizumab.

Conclusions: Tocilizumab preserved lung function, slowing decline in FVC, in patients with SSc, including those with ILD. Long-term safety was consistent with the known safety profile of tocilizumab.

Clinical trial registered with www.clinicaltrials.gov (NCT02453256).

Keywords: biological therapy; lung diseases, interstitial; respiratory function tests; systemic scleroderma

(Received in original form March 19, 2021; accepted in final form November 30, 2021)

*Present address: Vera Therapeutics, South San Francisco, California.

‡Present address: Office of Drug Evaluation Science, U.S. Food and Drug Administration, Silver Spring, Maryland.

Supported by F. Hoffmann-La Roche. Funding for manuscript preparation was provided by F. Hoffmann-La Roche Ltd. The study sponsor was involved in the study design, analysis and interpretation of data, and writing the report.

Author Contributions: All authors attest that they fulfilled the following requirements: substantial contributions to the conception and design or the acquisition, analysis, or interpretation of the data; drafting of the article or critical revision for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 205, Iss 6, pp 674–684, Mar 15, 2022

Originally Published in Press as DOI: 10.1164/rccm.202103-0714OC on December 1, 2021
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: In a randomized, double-blind, placebo-controlled phase 3 trial of tocilizumab, an anti–IL-6 receptor antibody, in patients with early systemic sclerosis, including those with associated interstitial lung disease, preservation of lung function was observed with tocilizumab treatment.

What This Study Adds to the Field: This open-label extension of the trial showed that preservation of FVC observed with tocilizumab in the double-blind period was maintained during the open-label period up to 96 weeks, suggesting continued preservation of lung function with long-term tocilizumab treatment.

Systemic sclerosis (SSc) is a rare autoimmune inflammatory disease characterized by diffuse fibrosis and vascular abnormalities that can affect the skin and can result in pulmonary manifestations such as interstitial lung disease (ILD) and impairment of gastrointestinal, cardiac, and renal function (1–4). With 10-year survival rates approaching 66%, SSc has the highest mortality rate of any rheumatic disease, and lung manifestations are the most frequent cause of SSc-related death (1, 5, 6).

Increased expression of the proinflammatory cytokine IL-6 has been reported in patients with SSc, particularly those with early diffuse cutaneous skin involvement (7, 8), suggesting that IL-6 plays a role in SSc pathogenesis (9, 10). Furthermore, IL-6 is a marker for disease progression and clinical outcome in patients with SSc, indicating that treatment targeted at IL-6 signaling might be beneficial in SSc (11). Serum IL-6 levels are associated with SSc-ILD and predictive of decline in FVC and mortality (11, 12). It is postulated that early ILD is driven by immune-mediated inflammatory pathways and that later disease is driven by fibrotic pathways, with IL-6 a key driver of progression (13, 14).

Tocilizumab is an anti–IL-6 receptor-α antibody indicated for the treatment of patients with rheumatoid arthritis, systemic and polyarticular juvenile idiopathic arthritis, and giant cell arteritis (15). In the phase 2 faSScinate trial, tocilizumab demonstrated clinically relevant, though not statistically significant, improvement in skin thickness and FVC preservation (16, 17). In focuSSced, the subsequent phase 3 randomized controlled trial of tocilizumab in patients with SSc, the primary endpoint of improvement in modified Rodnan skin score (mRSS) at Week 48 was not met, although clinically relevant differences in FVC and improvement in lung fibrosis measured by high-resolution computed tomography (HRCT) were observed, including in the two-thirds of patients who had SSc-ILD at baseline (18). We report the 96-week, long-term safety and efficacy of tocilizumab in the 48-week, double-blind period and in the 48-week, open-label period of focuSSced. Some of the results from this study have been previously reported in the form of congress abstracts (19–21) and a published article (22).

Methods

Study Design

focuSSced was a multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group phase 3 study conducted in Europe, North America, Latin America, and Japan (18). The study consisted of a 48-week, double-blind, placebo-controlled period followed by a 48-week, open-label treatment period (*see* Figure E1 in the online supplement).

Patients were randomly assigned (1:1) to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo during the double-blind period (tocilizumab and placebo groups, respectively). Randomization was centralized and stratified by IL-6 level (<10 or ≥ 10 pg/ml) at screening. At Week 48, patients in the tocilizumab and placebo groups transitioned to open-label weekly injections of tocilizumab 162 mg for another 48 weeks (continuous-tocilizumab and placebo-tocilizumab groups, respectively).

The protocol was approved by the appropriate institutional review boards or ethics committees. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Patients

Patients were eligible if they were 18 years of age or older and were classified as having SSc according to the 2013 American College of Rheumatology/European League Against Rheumatism criteria with the diffuse subset, <60 months had passed since their first non-Raynaud sign or symptom, and their mRSS score was between 10 and 35. Patients had to have active disease, defined as at least one of the following criteria at screening: disease duration ≤ 18 months (defined as time from the first non-Raynaud phenomenon manifestation), increase ≥ 3 in mRSS units compared with the last visit in the previous 6 months, involvement of one new body area and increase in ≥ 2 mRSS units compared with the most recent assessment performed within the previous 6 months, involvement of two new body areas within the previous 6 months, or one or more tendon friction rubs. Evidence of SSc-ILD was not required. Other key inclusion criteria included CRP ≥ 6 mg/L, erythrocyte sedimentation rate ≥ 28 mm/h, or platelet count $\geq 330 \times 10^9/\mu l$; no other rheumatic autoimmune disease; and no other background immunomodulatory therapy.

Outcomes

Efficacy analysis at Week 96 was exploratory and included mRSS, absolute FVC, percent predicted FVC (ppFVC), percent predicted D_{LCO} (ppD_{LCO}) corrected for hemoglobin,

Data sharing statement: Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available from https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, *see* https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Correspondence and requests for reprints should be addressed to Dinesh Khanna, M.D., Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, Suite 7C27 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109. E-mail: khannad@med.umich.edu.

and physician global assessment measured using a 100-mm visual analog scale (VAS) as exploratory outcomes. Patient-reported outcomes included Health Assessment Questionnaire–Disability Index (HAQ-DI), patient global VAS, Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Score, EuroQol Five-Dimension Questionnaire (EQ-5D), St. George's Respiratory Questionnaire (SGRQ), and Work Productivity and Activity Impairment Questionnaire–General Health (WPAI-GH).

Safety was reported as rates of adverse events (AEs) and serious AEs (SAEs) per 100 patient-years (PY) with 95% confidence intervals (CIs). Digital ulcers were defined as an ulcer at or distal to the metacarpophalangeal joint on either the dorsal or volar surface with loss of surface epithelialization, not including fissures, cracks, or calcium extrusions from calcinosis cutis. The change in digital ulcer count from baseline was reported.

Statistical Analysis

Efficacy was assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients who received any study drug by Week 48. Patients were analyzed according to the treatment group to which they were randomly assigned (placebo, tocilizumab) from baseline to Week 48, according to the open-label treatment group (placebo-tocilizumab, continuous-tocilizumab) from Weeks 48 to 96 and according to all-tocilizumab exposure (tocilizumab group from baseline to Week 48 and placebo-tocilizumab and continuous-tocilizumab groups from Weeks 48 to 96). Efficacy endpoints were analyzed at Week 48 (double-blind) and Week 96 (double-blind plus open-label). Analyses were also performed among completers (patients who had measurements at Week 96), which allowed comparison between similar patient cohorts in the double-blind and open-label periods. Descriptive unadjusted estimates were computed on change from baseline values. *Post hoc* analysis was performed in the subgroup of patients who had SSc-ILD at baseline (based on HRCT visualization). All baseline HRCT scans were revised by a thoracic radiologist (J.G.) and assessed for the presence or absence of ILD. Patients who had minimal interstitial changes without defined ILD at baseline were characterized as having no ILD and were screened for other causes of parenchymal abnormalities not related to SSc-ILD, including body habitus, atelectasis, bronchitis, aspiration, infection, congestive heart failure, and bronchiectasis, which may impact the quantitative ILD score; these patients were excluded. Summary descriptive statistics were calculated for quantitative variables, and absolute and relative frequencies were calculated for discrete variables. No imputation algorithm was adopted for missing data.

Safety was assessed in the safety population, which included all patients who received any study medication and provided one or more postdose safety assessments. Patients were included in the group for the treatment they most frequently received during the double-blind period. Safety analyses were performed based on data from baseline to Week 48, baseline to Week 96, and Week 48 to Week 96 and were summarized descriptively. Cumulative incidences (number of patients experiencing the AE/total number of patients) and AE rates per 100 PY [number of events/(exposure in PY/100) with 95% CIs based on Poisson distribution of the event rate] were computed.

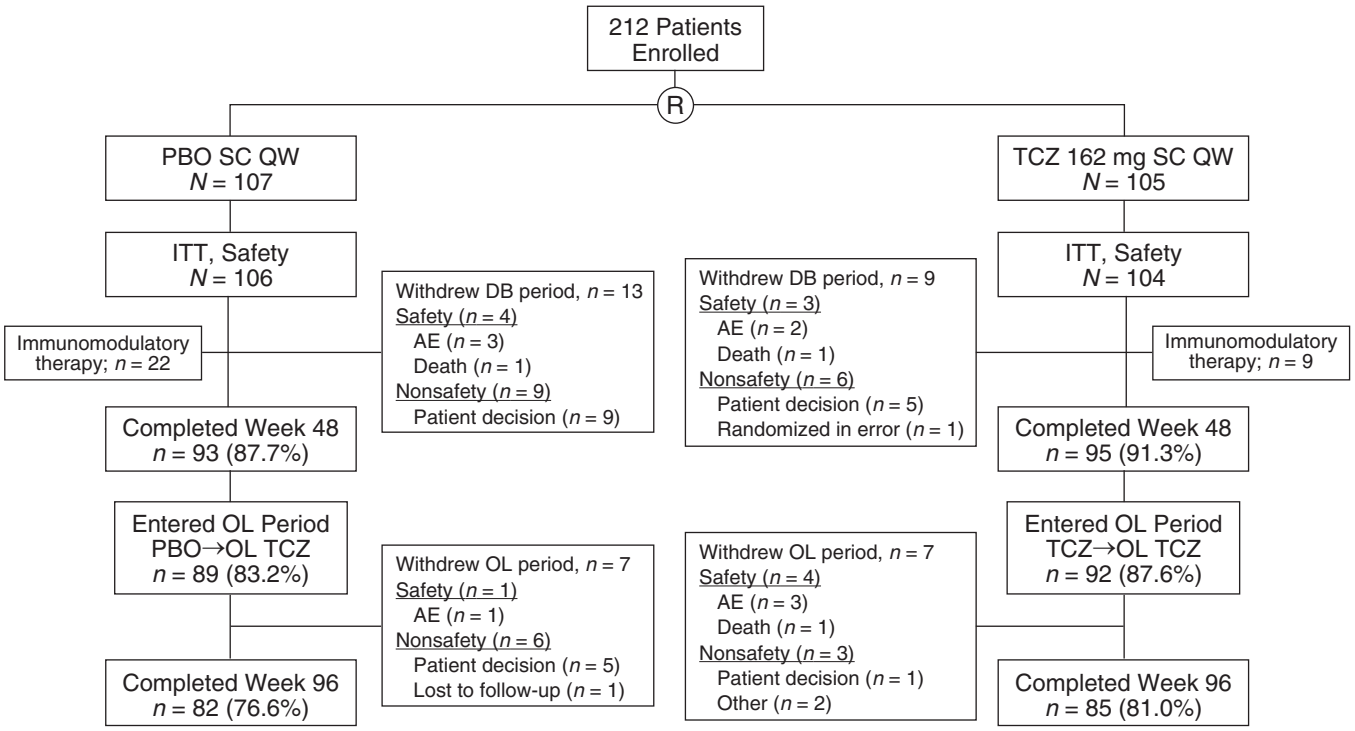

Figure 1. Randomization and follow-up during the 48-week, double-blind study period and the 48-week, long-term extension of the focuSSced trial. AE = adverse events; DB = double-blind; ITT = intention-to-treat; OL = open-label; PBO = placebo; QW = every week; R = randomization; SC = subcutaneous; SSc = systemic sclerosis; TCZ = tocilizumab.

Table 1. Baseline Characteristics of Patients Who Entered the Double-Blind and Open-Label Periods

	Double Blind (Week 0–48)				Open Label* (Week 48–96)			
	All Patients		Patients with SSc-ILD		All Patients		Patients with SSc-ILD	
	PBO (*N* = 106)	TCZ (*N* = 104)	PBO (*N* = 68)	TCZ (*N* = 68)	PBO-TCZ (*N* = 89)	Continuous-TCZ (*N* = 92)	PBO-TCZ (*N* = 54)	Continuous-TCZ (*N* = 60)
Females, *n* (%)	90 (84.9)	81 (77.9)	55 (80.9)	53 (77.9)	78 (87.6)	71 (77.2)	45 (83.3)	47 (78.3)
Age, yr	49.3 (12.6)	47.0 (12.2)	48.7 (13.3)	47.6 (12.5)	48.6 (12.5)	47.2 (12.2)	47.2 (13.2)	47.7 (12.6)
Duration of SSc, mo	23.1 (17.0)	22.2 (16.0)	22.6 (16.6)	23.0 (17.2)	24.2 (17.1)	22.7 (16.0)	23.7 (16.6)	24.3 (17.2)
Total mRSS (range, 0–51)	20.4 (7.0)	20.3 (6.7)	20.9 (7.2)	20.7 (6.8)	20.1 (7.0)	19.7 (6.1)	20.4 (7.2)	19.8 (6.0)
ppFVC	83.9 (15.0)	80.3 (14.4)	81.5 (14.9)	77.7 (13.9)	84.9 (14.5)	80.6 (14.4)	82.6 (14.9)	78.3 (14.1)
ppD_{LCO} (normal, ⩾80%)	76.8 (18.6)	74.4 (19.2)	72.1 (16.9)	68.7 (16.8)	78.0 (17.2) (*n* = 88)	74.5 (19.4) (*n* = 91)	73.9 (17.4)	69.5 (17.4)
HAQ-DI (range, 1–3)	1.3 (0.7) (*n* = 104)	1.1 (0.8)	1.3 (0.7)	1.1 (0.8)	1.2 (0.7) (*n* = 88)	1.1 (0.7) (*n* = 92)	1.2 (0.6)	1.1 (0.7)
Patient VAS, mm (range, 0–100)	59.3 (21.3) (*n* = 104)	54.3 (24.3) (*n* = 103)	58.5 (21.6)	53.5 (23.7)	57.8 (21.6) (*n* = 88)	53.0 (24.4) (*n* = 91)	56.9 (22.6)	50.9 (23.2) (*n* = 59)
CRP, mg/L (normal, ⩽10)	7.0 (11.1)	8.9 (14.8)	8.1 (13.1)	11.2 (17.4)	6.3 (8.3)	7.7 (11.7)	7.4 (10.0)	9.3 (13.6)
CRP > 6 mg/L, *n* (%)	40 (37.7)	39 (37.5)	26 (38.2)	31 (45.6)	33 (37.1)	34 (37.0)	20 (37.0)	26 (43.3)
ESR, mm/h (normal, ⩽20)	34.7 (18.5) (*n* = 103)	34.8 (16.3) (*n* = 100)	36.2 (19.3)	37.2 (17.8)	34.2 (17.8) (*n* = 87)	35.6 (16.7) (*n* = 89)	36.1 (18.2) (*n* = 52)	38.4 (18.1) (*n* = 57)
ESR ⩾ 28 mm/h, *n* (%)	73 (70.9)	72 (72.0)	48 (72.7)	47 (73.4)	61 (70.1)	65 (73.0)	38 (73.1)	43 (75.4)
Platelet count, 10^9/L (normal, 140–400)	298.7 (96.0)	311.1 (88.2)	297.0 (92.2)	323.7 (95.1)	302.0 (95.1)	304.8 (80.7)	303.4 (88.4)	317.9 (85.7)
Platelet count ⩾ 330×10^9/L	34 (32.1)	39 (37.5)	19 (27.9)	29 (42.6)	30 (33.7)	31 (33.7)	17 (31.5)	24 (40.0)
ANA positive, *n*/*N* (%), LLQ < 20 units	90/98 (91.8)	91/98 (92.9)	58/61 (95.1)	64/65 (98.5)	74/82 (90.2)	82/88 (93.2)	46/49 (93.9)	57/58 (98.3)
Antitopoisomerase positive, *n*/*N* (%), LLQ < 20 units	49/100 (49.0)	52/100 (52.0)	43/63 (68.3)	45/66 (68.2)	39/84 (46.4)	49/90 (54.4)	34/51 (66.7)	43/59 (72.9)
Anti-RNA polymerase positive, *n*/*N* (%) LLQ = 1 unit	16/100 (16.0)	19/100 (19.0)	6/63 (9.5)	13/66 (19.7)	13/84 (15.5)	17/90 (18.9)	5/51 (9.8)	10/59 (16.9)
Anticentromere positive, *n*/*N* (%), LLQ titer < 1:40	9/100 (9.0)	8/100 (8.0)	1/63 (1.6)	1/66 (1.5)	9/84 (10.7)	7/90 (7.8)	1/51 (2.0)	1/59 (1.7)
SSc-ILD, *n*/*N* (%), HRCT visual read	68/104 (65.4)	68/102 (66.7)	68/68 (100)	68/68 (100)	54/89 (60.7)	60/92 (65.2)	54/54 (100)	60/60 (100)
QLF-LM, median (IQR)	2.1 (1.0–4.4) (*n* = 84)	1.8 (0.7–4.9) (*n* = 73)	2.9 (1.2–7.2) (*n* = 51)	3.5 (1.5–7.7) (*n* = 45)	2.0 (0.9–4.2) (*n* = 69)	2.2 (0.7–4.9) (*n* = 63)	2.6 (1.1–7.6) (*n* = 39)	4.2 (1.6–13.2) (*n* = 39)
QLF-WL, median (IQR)	1.1 (0.5–2.1) (*n* = 102)	1.2 (0.5–3.0) (*n* = 100)	1.6 (0.7–2.9) (*n* = 66)	1.7 (0.8–4.7) (*n* = 67)	1.0 (0.5–1.8) (*n* = 85)	1.3 (0.5–3.1) (*n* = 88)	1.3 (0.7–2.9) (*n* = 52)	1.9 (1.0–5.2) (*n* = 59)
QILD-WL, median (IQR)	12.3 (7.5–20.2) (*n* = 102)	14.2 (7.0–24.4) (*n* = 100)	14.8 (10.5–21.9) (*n* = 66)	17.0 (9.6–27.3) (*n* = 67)	11.8 (7.2–19.6) (*n* = 85)	14.2 (6.9–24.4) (*n* = 88)	14.5 (10.1–22.0) (*n* = 52)	17.8 (11.2–29.9) (*n* = 59)

Definition of abbreviations: ANA = antinuclear antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IQR = interquartile range; LLQ = lower limit of quantification; mRSS = modified Rodnan skin score; PBO = placebo; ppD_{LCO} = percent predicted D_{LCO}; ppFVC = percent predicted FVC; QILD-WL = quantitative interstitial lung disease–whole lung; QLF-LM = quantitative lung fibrosis–lobe of maximal involvement; QLF-WL = quantitative lung fibrosis–whole lung; SSc = systemic sclerosis; TCZ = tocilizumab; VAS = visual analog scale.
All data are mean (SD) based on the total number of patients in each group (*N*) unless stated otherwise.
*All patients who received one or more doses of open-label treatment were included.

Results

Patients

Overall, 212 patients were enrolled in the focuSSced trial (Figure 1); in the double-blind period, 107 patients were assigned to the placebo group and 105 were assigned to the tocilizumab group. At Week 48, 89 patients (83.2%) originally assigned to double-blind placebo transitioned to open-label tocilizumab (placebo-tocilizumab group), and 92 patients (87.6%) originally assigned to double-blind tocilizumab transitioned to open-label tocilizumab (continuous-tocilizumab group) until they completed the study or withdrew from treatment. Eighty-two patients (76.6%) in the placebo-tocilizumab group and 85 patients (81.0%) in the continuous-tocilizumab group completed Week 96. During the open-label period, four patients discontinued because of AEs (one in the placebo-tocilizumab group and three in the continuous-tocilizumab group). Other reasons for study withdrawal were patient decision (five patients in the placebo-tocilizumab group and one patient in the continuous-tocilizumab group).

Mean (SD) treatment duration during the open-label period of the trial was 319.8 (60.6) days in the placebo-tocilizumab group and 318.8 (65.6) days in the continuous-tocilizumab group. Treatment compliance was high in both open-label treatment groups, with mean (SD) dose compliance of 91.8% (12.9) and 92.9% (16.3), respectively.

Baseline demographic and clinical features of patients overall and those who entered the open-label period were generally balanced in the double-blind and open-label groups (Table 1). Characteristics of patients who entered the open-label period were comparable to those of the overall cohort; most (82.3%) were female, and their mean (SD) age was 47.9 (12.3) years and mean duration of SSc was 23.4 (16.5) months. Baseline ppFVC showed normal to mildly impaired lung function (mean, 84.9% and 80.6% in the placebo-tocilizumab and continuous-tocilizumab groups, respectively), and baseline ppD_{LCO} demonstrated mild impairment (mean, 78.0% and 74.5%, respectively). Among those who entered the open-label period, 54 of 89 patients (60.7%) in the placebo-tocilizumab group and 60 of 92 patients (65.2%) in the continuous-tocilizumab group had SSc-ILD at baseline according to HRCT visual read. Median quantitative lung fibrosis and quantitative ILD scores at baseline were generally higher in patients with SSc-ILD than in all patients.

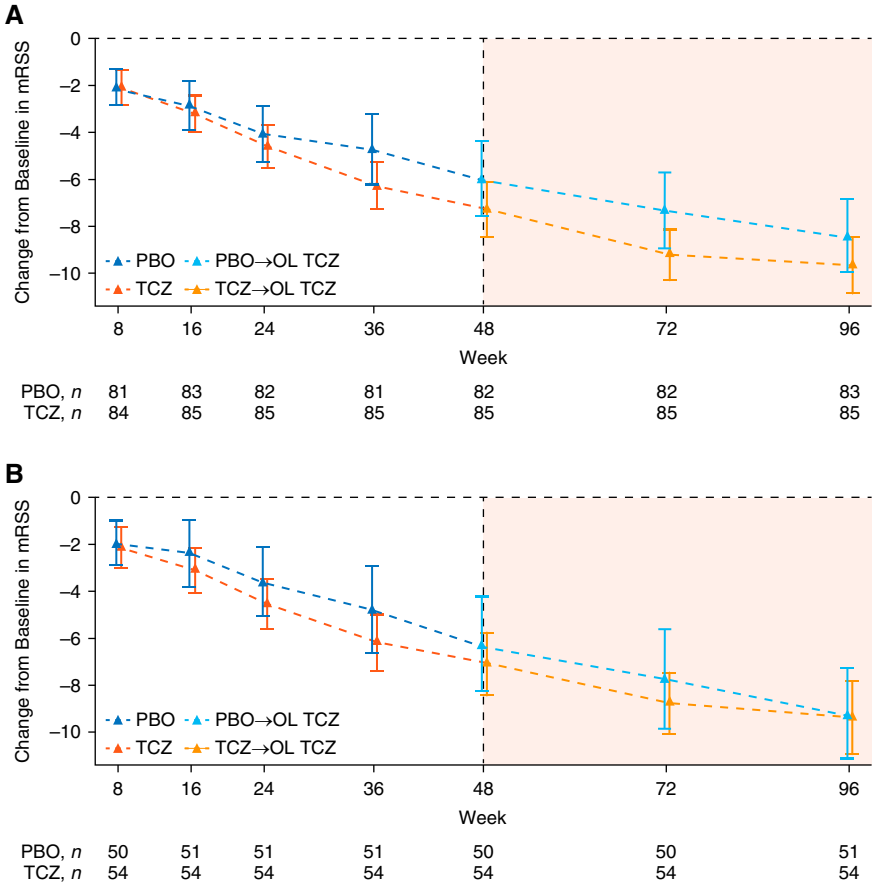

Figure 2. Mean (95% confidence interval) change from baseline in modified Rodnan skin score (*A*) in all patients, and (*B*) in patients with systemic sclerosis–interstitial lung disease at baseline (intention-to-treat population completers). Tocilizumab was administered open-label from Week 48 to Week 96. Completers were patients with change from baseline measurements at Week 96. Analysis in patients with systemic sclerosis–interstitial lung disease at baseline was performed *post hoc*. mRSS = modified Rodnan skin score; OL = open label; PBO = placebo; TCZ = tocilizumab.

Table 2. Change from Baseline to Week 48 or 96 and from Weeks 48 to 96 in Efficacy Endpoints (Intention-to-Treat Population and Intention-to-Treat Population Completers)

	ITT Population				ITT Population Completers			
	Double Blind, Baseline to Week 48		Double-Blind + Open Label, Baseline to Week 96		Double Blind, Baseline to Week 48		Open Label, Week 48 to Week 96	
	PBO	TCZ	PBO-TCZ	Continuous-TCZ	PBO	TCZ	PBO-TCZ	Continuous-TCZ
Absolute FVC, ml								
Mean (95% CI)	−161.0 (−232.4 to −89.6)	−14.6 (−64.7 to 35.6)	−124.6 (−193.0 to −56.1)	−23.3 (−89.7 to 43.0)	−153.3 (−226.3 to −80.4)	−15.0 (−70.7 to 40.7)	25.8 (−22.1 to 73.6)	−8.0 (−57.2 to 41.1)
Median	−120.0	−20.0	−120.0	−55.0	−120.0	−30.0	10.0	0.0
n	92	94	79	84	78	82	78	82
ppFVC								
Mean (95% CI)	−4.1 (−5.8 to −2.4)	−0.2 (−1.6 to 1.2)	−3.3 (−5.1 to −1.5)	−0.5 (−2.4 to 1.3)	−4.0 (−5.8 to −2.2)	−0.2 (−1.8 to 1.3)	0.6 (−0.7 to 1.9)	−0.3 (−1.7 to 1.1)
Median	−3.9	−0.7	−3.1	−1.4	−3.9	−0.9	0.3	0.0
n	92	94	79	84	78	82	78	82
ppD_{LCO}								
Mean (95% CI)	−2.8 (−5.3 to −0.3)	−0.5 (−2.8 to 1.8)	−6.0 (−8.4 to −3.5)	−0.3 (−3.0 to 2.4)	−2.3 (−5.0 to 0.4)	−0.3 (−2.8 to 2.3)	−3.4 (−5.8 to −1.0)	0.7 (−1.5 to 2.8)
Median (95% CI)	−2.3 (−4.6 to −0.6)	−2.0 (−3.8 to 1.3)	−6.2 (−7.9 to −1.7)	0.6 (−3.9 to 2.2)	−2.6 (−4.6 to −0.6))	−1.9 (−2.8 to 1.9)	−2.7 (−7.3 to −0.0)	0.8 (−1.2 to 3.2)
n	87	81	71	78	68	71	68	72
mRSS								
Mean (95% CI)	−5.3 (−6.9 to −3.7)	−6.7 (−8.0 to −5.4)	−8.4 (−10.0 to −6.8)	−9.6 (−10.9 to −8.4)	−6.0 (−7.6 to −4.4)	−7.3 (−8.5 to −6.1)	−2.5 (−3.3 to −1.6)	−2.3 (−3.2 to −1.5)
Median	−5.5	−7.0	−8.0	−9.0	−6.0	−7.0	−2.0	−1.0
n	92	97	83	85	82	85	82	85

Definition of abbreviations: CI = confidence interval; ITT = intention to treat; mRSS = modified Rodnan skin score; PBO = placebo; ppD_{LCO} = percent predicted D_{LCO}; ppFVC = percent predicted FVC; TCZ = tocilizumab.
Negative change indicates improvement in mRSS.

Efficacy

Among Week 96 completers, continued improvement in mRSS from improvement observed in the placebo and tocilizumab groups during the double-blind period from baseline to Week 48 was observed in both groups during the open-label period; mean (95% CI) change in mRSS from Weeks 48 to 96 was −2.5 (−3.3 to 1.6) in the placebo-tocilizumab group and −2.3 (−3.2 to −1.5) in the continuous-tocilizumab group (Figure 2A and Table 2). Continued improvement in mRSS was also observed in both groups in the subset of patients with SSc-ILD at baseline; mean (95% CI) change from Weeks 48 to 96 was −3.1 (−4.1 to −2.0) in the placebo-tocilizumab group and −2.3 (−3.2 to −1.4) in the continuous-tocilizumab group (Figure 2B and Table 3).

Mean (95% CI) change in ppFVC from Week 48 to Week 96 was 0.6 (−0.7 to 1.9) in the placebo-tocilizumab group and −0.3 (−1.7 to 1.1) in the continuous-tocilizumab group in all completers, and it was 0.9 (−0.8 to 2.7) in the placebo-tocilizumab group and −0.4 (−2.3 to 1.5) in the continuous-tocilizumab group in those with SSc-ILD at baseline (Figure 3 and Tables 2 and 3). Similar percentages in each group experienced improvement or worsening of ppFVC in the open-label period in all patients (Table E1 and Figure 4A) and in patients with SSc-ILD (Figure 4B). Median (95% CI) ppD_{LCO} declined from Weeks 48 to 96 in the placebo-tocilizumab group (−2.7 [−7.3 to −0.0]) and was maintained in the continuous-tocilizumab group (0.8 [−1.2 to 3.2]) (Table 2). A similar pattern was observed in patients with SSc-ILD (−2.8 [−8.2 to −1.3] and 1.6 [−2.1 to 4.6]), respectively (Table 3).

Similar improvements from baseline to Week 96 in HAQ-DI scores, patient and physician global assessments on a 100-mm VAS, FACIT-Fatigue scores, Scleroderma Health Assessment Questionnaire overall scores, EQ-5D, and WPAI-GH overall scores were observed between groups (Table E2).

Safety

Rates of AEs and SAEs in the open-label period were similar to or lower than those in the double-blind period and were similar between the placebo-tocilizumab and continuous-tocilizumab groups in all patients and those with SSc-ILD (Table 4). In the open-label period, most patients experienced at least one AE (69 patients [77.5%] in the placebo-tocilizumab group and 66 patients

Table 3. Change from Baseline to Week 48 or 96 and from Weeks 48 to 96 in FVC, Percent Predicted D_{LCO}, and Modified Rodnan Skin Score in Patients with Systemic Sclerosis–Interstitial Lung Disease at Baseline (Intention-to-Treat Population Completers)

	Double-Blind, Baseline to Week 48		Double-Blind + Open-Label, Baseline to Week 96		Open-Label, Week 48 to Week 96	
	PBO	TCZ	PBO-TCZ	Continuous-TCZ	PBO-TCZ	Continuous-TCZ
Absolute FVC, ml						
Mean (95% CI)	−197.2 (−301.6 to −92.8)	−11.1 (−83.8 to 61.6)	−157.6 (−255.9 to −59.3)	−28.9 (−116.9 to 59.1)	39.6 (−28.3 to 107.5)	−15.3 (−80.1 to 49.5)
Median	−105.0	−20.0	−105.0	−40.0	35.0	0.0
n	50	53	50	54	50	53
ppFVC						
Mean (95% CI)	−5.1 (−7.6 to −2.6)	−0.1 (−2.1 to 2.0)	−4.1 (−6.7 to −1.6)	−0.6 (−3.1 to 2.0)	0.9 (−0.8 to 2.7)	−0.4 (−2.3 to 1.5)
Median	−3.1	−0.6	−3.3	−1.0	1.0	0.0
n	50	53	50	54	50	53
ppD_{LCO}						
Mean (95% CI)	−1.4 (−5.2 to 2.3)	0.1 (−3.1 to 3.2)	−5.6 (−8.7 to −2.6)	1.3 (−2.1 to 4.7)	−3.8 (−7.2 to −0.3)	1.6 (−1.0 to 4.2)
Median (95% CI)	−1.6 (−4.6 to 1.0)	−0.6 (−3.1 to 3.9)	−5.6 (−7.5 to −1.0)	1.0 (−4.1 to 4.4)	−2.8 (−8.2 to 1.3)	1.7 (−2.1 to 4.6)
n	43	47	46	51	43	47
mRSS						
Mean (95% CI)	−6.2 (−8.3 to −4.2)	−7.1 (−8.5 to −5.7)	−9.2 (−11.2 to −7.3)	−9.4 (−11.0 to −7.9)	−3.1 (−4.1 to −2.0)	−2.3 (−3.2 to −1.4)
Median	−6.0	−7.0	−9.0	−8.5	−2.0	−2.0
n	50	54	51	54	50	54

Definition of abbreviations: CI = confidence interval; mRSS = modified Rodnan skin score; PBO = placebo; ppD_{LCO} = percent predicted D_{LCO}; ppFVC = percent predicted FVC; TCZ = tocilizumab.
Completers are patients with change from baseline measurements at Week 96. Negative change indicates improvement in mRSS.

[71.7%] in the continuous-tocilizumab group among all patients; 47 patients [87.0%] and 47 patients [78.3%], respectively, in those with SSc-ILD), and most AEs were grade 1 or 2 in severity. Among all patients, rates of SAEs were similar in the placebo-tocilizumab group (14.8 events per 100 PY [95% CI, 7.9–25.3]) and the continuous-tocilizumab group (15.8 events per 100 PY [95% CI, 8.6–26.5]), whereas among patients with SSc-ILD, they were 22.6 (95% CI, 11.7–39.4) and 14.0 (95% CI, 6.0–27.5), respectively. Most SAEs occurred in patients with SSc-ILD; 12 of 13 SAEs (92.3%) reported in the placebo-tocilizumab group and 8 of 14 SAEs (57.1%) reported in the continuous-tocilizumab group were in patients with SSc-ILD (Table 4). Most patients had no digital ulcers at baseline (94 patients [89.5%] in the placebo arm and 94 patients [91.3%] in the tocilizumab arm). From baseline to Week 96, the digital ulcer count did not increase in the placebo-tocilizumab group but did increase in seven patients in the continuous-tocilizumab group. Infected skin ulcers, which could include digital ulcers, were reported in two patients in the placebo group and four patients in the tocilizumab group during the double-blind period and in two patients in the placebo-tocilizumab group and three patients in the continuous-tocilizumab group during the open-label period, resulting in a rate of 4.5 (95% CI, 2.3–7.9) infected skin ulcers overall and 6.5 (95% CI, 3.3–11.7) among patients with SSc-ILD at baseline (Table 4).

Infections were the most frequently reported AEs of special interest for tocilizumab during the open-label period to week 96. Among all patients, 41 (46.1%) in the placebo-tocilizumab group and 36 (39.1%) in the continuous-tocilizumab group had infections; among patients with SSc-ILD, 30 (55.6%) in the placebo-tocilizumab group and 25 (41.7%) in the continuous-tocilizumab group had infections (Table E3). Five serious infections were reported in four patients in the open-label period; three patients in the placebo-tocilizumab group reported one event of grade 3 pneumonia, grade 4 infective tenosynovitis, and grade 4 sepsis, and one patient in the continuous-tocilizumab group reported one event of grade ⩾3 otitis media and one event of grade ⩾3 pneumonia. Only the grade 3 pneumonia and the grade 4 sepsis events in the placebo-tocilizumab group were considered related to study treatment. All serious infections in the placebo-tocilizumab group occurred in

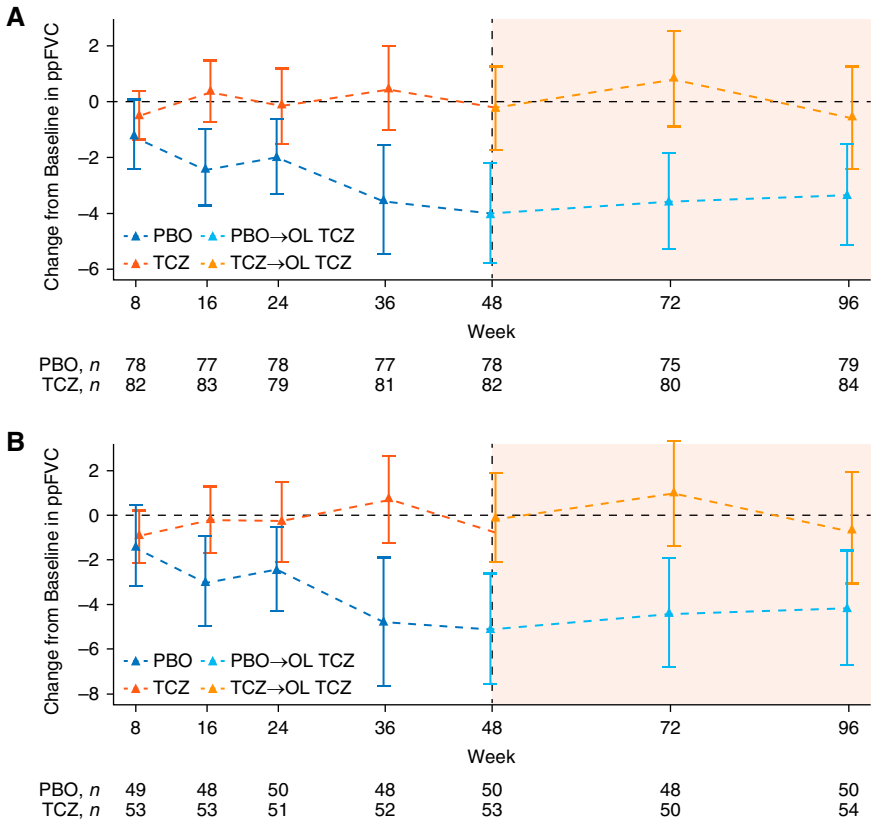

Figure 3. Percent predicted FVC mean (95% confidence interval) change from baseline to Week 96 in (*A*) all patients, and (*B*) patients with systemic sclerosis–interstitial lung disease at baseline (intention-to-treat completers). Completers were patients with change from baseline measurements at Week 96. OL = open label; PBO = placebo; ppFVC = percent predicted FVC; TCZ = tocilizumab.

patients with SSc-ILD, whereas the two serious infections in the continuous-tocilizumab group occurred in a patient without SSc-ILD. Low rates of malignancies, hepatic events, and myocardial infarction were reported during the study (Table E3). No patients experienced serious or medically significant bleeding events during the study. No patients experienced other predefined AEs of special interest: stroke, gastrointestinal perforation, demyelinating disorders, or anaphylactic reactions.

Six deaths occurred during the study, four during the double-blind period and two during the open-label period. Both deaths in the open-label period occurred in patients with SSc-ILD. One death in the open-label period occurred in a patient in the placebo-tocilizumab group who died of brain injury (anoxic brain damage). This patient also had SAEs of arrhythmia, cardiopulmonary arrest, sepsis, and aspiration pneumonia in the week before death (considered by the investigator to be related to study medication and SSc, concurrent illness, or unspecified cause), and the death was deemed related to study treatment and other unspecified cause. The patient had received 45 placebo injections and three tocilizumab injections before the onset of these events. The other death in the open-label period occurred in a patient in the continuous-tocilizumab group who died of progressive pulmonary hypertension diagnosed 3 days earlier. The death was considered by the investigator to be related to study treatment. This patient had a diagnosis of ILD before entering the study and initiated mycophenolate mofetil in the open-label period. The patient also had an SAE of heart failure on day 72 that resolved with sequelae and was considered by the investigator to be unrelated to tocilizumab. The cardiac failure event resulted in discontinuation of tocilizumab during the double-blind period.

Abnormal laboratory parameters of interest for tocilizumab, including alanine aminotransferase and aspartate aminotransferase levels, neutrophil counts, and platelet counts, were reported (Table E4). No clinical manifestations of abnormal laboratory values were observed during the study except one patient in the placebo arm had grade 3 low neutrophil count within 15 days of a serious infection during the double-blind period. No patients tested positive for anti–tocilizumab antibodies during the open-label period.

Discussion

Management of patients with SSc relies on routine screening and follow-up to detect and manage organ-specific involvement (1), and there is only one approved disease-modifying therapy for SSc-ILD (4). Elucidation of the pathogenesis of SSc has revealed specific molecular targets that offer potential for other therapeutic options in the management of this disease (9, 10). The phase 2 faSScinate study indicated that tocilizumab might have a beneficial effect in patients with SSc and provided the impetus for investigation in the phase 3 focuSSced study. Results from the double-blind,

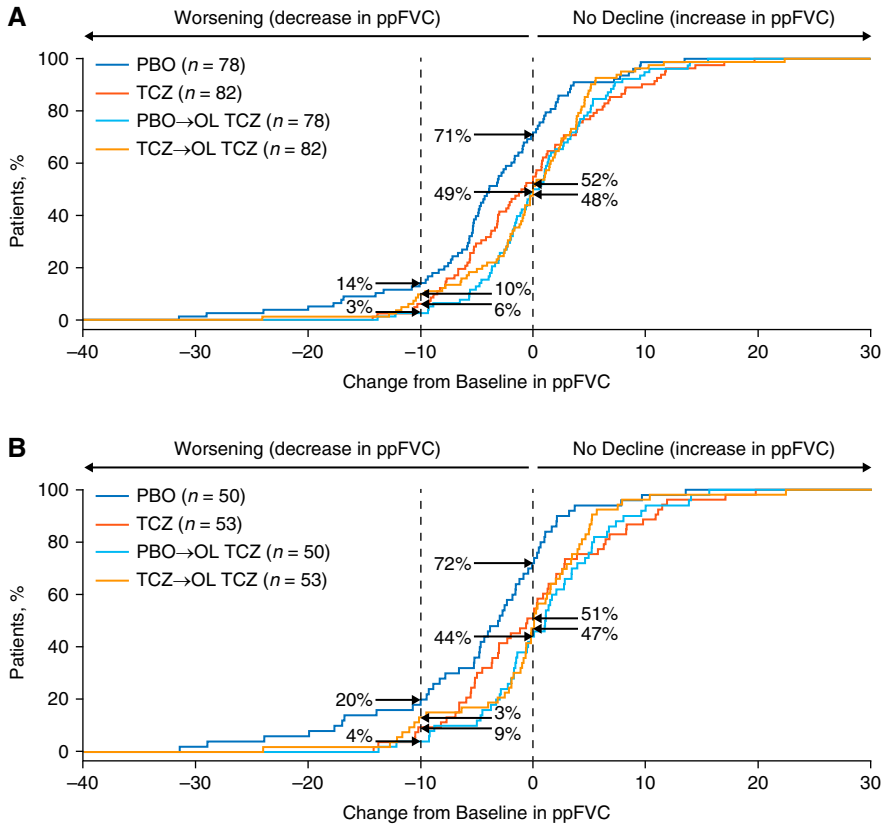

Figure 4. Cumulative distribution of percent predicted FVC change from baseline to Week 48 and from Week 48 to Week 96 in (*A*) all patients, and (*B*) patients with systemic sclerosis–interstitial lung disease at baseline (intention-to-treat completers). Completers were patients with change from baseline measurements at Week 96. Data for tocilizumab (TCZ) and placebo (PBO) show change from baseline to Week 48, and data for PBO→open-label (OL) TCZ and TCZ→OL TCZ show change from Week 48 to Week 96. ppFVC = percent predicted FVC.

placebo-controlled period of focuSSced showed no significant difference between tocilizumab and placebo for the primary endpoint of change in mRSS from baseline to Week 48. However, the key secondary endpoint of shift in distribution of ppFVC favored tocilizumab over placebo, particularly in patients with SSc-ILD (18); these results contributed to the U.S. Food and Drug Administration approval of tocilizumab in March 2021 for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD (15, 23).

Preservation of lung function measured by FVC, which was observed with tocilizumab treatment in the 48-week double-blind period of focuSSced (18), was maintained during the open-label period to Week 96. In a *post hoc* analysis of the focuSSced trial, the efficacy of tocilizumab at Week 48 was observed across the spectrum of mild to severe ILD at baseline (defined as the degree of ILD at baseline on HRCT) (22). Although clinically meaningful decline in FVC occurred in the placebo group from baseline to Week 48 in focuSSced, no further deterioration occurred after transition from placebo to tocilizumab during the open-label period. focuSSced also demonstrated that tocilizumab provided clinical benefit, as evidenced by the clinically meaningful shift in the distribution of change from baseline in ppFVC at Week 48 in favor of tocilizumab. These results support those observed at Week 96 of the phase 2 faSScinate trial, which indicated that ppFVC was stabilized after patients switched from placebo to tocilizumab and was maintained with long-term tocilizumab treatment (17). Additional supportive evidence for tocilizumab is now provided in focuSSced patients who had SSc-ILD at baseline. A lower rate of lung function decline versus placebo has also been reported with nintedanib in SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis), a randomized controlled trial of patients with SSc-ILD (24). In that trial, FVC decline over 1 year was significantly lower in patients who received nintedanib (−52.4 ml) than in those who received placebo (−93.3 ml). It is clear that in the population of patients with ILD, the placebo group experienced a greater decline in FVC over 48 weeks in focuSSced (−197.2 ml) than in SENSCIS, but that could have reflected differences in the study populations. focuSSced participants had a more progressive immunoinflammatory phase of SSc-ILD with lower average extent of lung fibrosis and shorter disease duration than SENSCIS, and the focuSSced population was enriched for participants with elevated acute-phase reactants and progressive skin disease. SENSCIS permitted use of background therapy for at least 6 months with mycophenolate mofetil and methotrexate.

Results from the open-label period of focuSSced show that improvement in skin

Table 4. Adverse Events in the Double-Blind (Baseline to Week 48) and Open-Label (Weeks 48–96) Periods (Safety Population)

	All Patients					Patients with SSc-ILD*				
	Double Blind, Baseline to Week 48		Open Label, Week 48 to Week 96		Baseline to Week 96	Double Blind, Baseline to Week 48		Open Label, Week 48 to Week 96		Baseline to Week 96
	PBO (*N* = 106)	TCZ (*N* = 104)	PBO-TCZ (*N* = 89)	Continuous-TCZ (*N* = 92)	All TCZ (*N* = 193)	PBO (*N* = 68)	TCZ (*N* = 68)	PBO-TCZ (*N* = 54)	Continuous-TCZ (*N* = 60)	All TCZ (*N* = 122)
Exposure, PY	90.5	90.2	87.7	88.8	266.7	56.0	57.9	53.1	57.3	168.4
Patients with ⩾1 AE, *n* (%)	82 (77.4)	89 (85.6)	69 (77.5)	66 (71.7)	161 (83.4)	57 (83.8)	63 (92.6)	47 (87.0)	47 (78.3)	112 (91.8)
AEs, *n*	489	441	293	236	970	328	314	185	144	643
AEs/100 PY (95% CI)	540.2 (493.3–590.2)	488.7 (444.2–536.5)	334.1 (296.9–374.6)	265.8 (233.0–302.0)	363.7 (341.1–387.3)	586.1 (524.4–653.1)	542.0 (483.7–605.4)	348.1 (299.8–402.1)	251.4 (212.1–296.0)	381.9 (353.0–412.6)
AEs leading to withdrawal, *n*	13	7	1	1	9	11	7	1	1	9
AEs leading to withdrawal/100 PY (95% CI)	14.4 (7.6–24.6)	7.8 (3.1–16.0)	1.1 (0.0–6.4)	1.1 (0.0–6.3)	3.4 (1.5–6.4)	19.7 (9.8–35.2)	12.1 (4.9–24.9)	1.9 (0.1–10.5)	1.8 (0.0–9.7)	5.4 (2.4–10.2)
Patients with ⩾1 SAE, *n* (%)	18 (17.0)	13 (12.5)	7 (7.9)	10 (10.9)	28 (14.5)	15 (22.1)	9 (13.2)	6 (11.1)	5 (8.3)	19 (15.6)
SAEs, *n*	30	14	13	14	41	25	10	12	8	30
SAEs/100 PY (95% CI)	33.1 (22.4–47.3)	15.5 (8.5–26.0)	14.8 (7.9–25.3)	15.8 (8.6–26.5)	15.4 (11.0–20.9)	44.7 (28.9–66.0)	17.3 (8.3–31.7)	22.6 (11.7–39.4)	14.0 (6.0–27.5)	17.8 (12.0–25.4)
Serious infections, *n*	8	3	3	2	8	8	3	3	0	6
Serious infections/100 PY (95% CI)	8.8 (3.8–17.4)	3.3 (0.7–9.7)	3.4 (0.7–10.0)	2.3 (0.3–8.1)	3.0 (1.3–5.9)	14.3 (6.2–28.2)	5.2 (1.1–15.1)	5.6 (1.2–16.5)	0.0 (0.0–6.4)	3.6 (1.3–7.8)
Deaths, *n*	3	1	1	1	3	3	1	1	1	3
ISRs/100 PY (95% CI)	3.3 (0.7–9.7)	32.1 (21.5–46.2)	0.0 (0.0–4.2)	0.0 (0.0–4.2)	10.9 (7.3–15.6)	3.6 (0.4–12.9)	13.8 (6.0–27.2)	0.0 (0.0–6.9)	0.0 (0.0–6.4)	4.8 (2.1–9.4)
Hypersensitivity events excluding ISRs/100 PY (95% CI)	8.8 (3.8–17.4)	8.9 (3.8–17.5)	1.1 (0.0–6.4)	7.9 (3.2–16.2)	6.0 (3.4–9.7)	10.7 (3.9–23.3)	6.9 (1.9–17.7)	1.9 (0.1–10.5)	8.7 (2.8–20.4)	5.9 (2.9–10.9)
Infected skin ulcers/100 PY (95% CI)†	3.3 (0.7–9.7)	4.4 (1.2–11.4)	4.6 (1.2–11.7)	4.5 (1.2–11.5)	4.5 (2.3–7.9)	5.4 (1.1–15.7)	5.2 (1.1–15.1)	7.5 (2.1–19.3)	7.0 (1.9–17.9)	6.5 (3.3–11.7)

Definition of abbreviations: AE = adverse event; CI = confidence interval; ISR = injection site reaction; PBO = placebo; PY = patient-years; SAE = serious adverse event; SSc-ILD = systemic sclerosis–interstitial lung disease; TCZ = tocilizumab.

Exposure includes open-label TCZ exposure plus double-blind exposure for patients randomly assigned to the TCZ arm. Event rates were calculated as number of events/exposure in PY. For event rates and number of events, multiple events in a single patient were counted individually. For frequency counts, multiple events in a single patient were counted only once.

**Post hoc* analysis in patients with SSc-ILD at baseline.

†Includes infected digital ulcers.

sclerosis observed in the placebo and tocilizumab treatment arms during the double-blind period, which was not statistically significantly different between the groups (18), continued during the open-label tocilizumab treatment period in both groups. The observed change from baseline to Week 96 in mRSS in the placebo-tocilizumab and continuous-tocilizumab groups was similar in focuSSced (−8.4 and −9.6, respectively) and faSScinate (−9.4 and −9.1, respectively). Changes in mRSS during open-label therapy should be viewed conservatively because of observer bias during open-label treatments.

In the current report on the double-blind and open-label periods of focuSSced, tocilizumab was generally well tolerated over the 96-week study in all patients and in those with SSc-ILD at baseline. There was no clinically meaningful difference in safety between patients who transitioned from double-blind placebo to open-label tocilizumab compared with those who received tocilizumab during the double-blind and open-label periods. Safety was consistent with the known safety profile for tocilizumab, and no new or unexpected AEs were reported with long-term tocilizumab treatment in focuSSced (18). Rates (95% CI) of AEs per 100 PY in the continuous-tocilizumab group were higher in the open-label period of the phase 2 faSScinate study (17) than in the same group in the focuSSced study (faSScinate, 504.4 [427.6–590.9]; focuSSced 265.8 [233.0–302.0]), but rates of SAEs were similar (faSScinate, 16.5 [5.4–38.5]; focuSSced 15.8 [8.6–26.5]). Among patients who switched from double-blind placebo to open-label tocilizumab after 48 weeks, rates of AEs and SAEs in the open-label period were higher in faSScinate (412.4 [343.5–491.0] and 36.0 [18.0–64.4]) than in focuSSced (334.1 [296.9–374.6] and 14.8 [7.9–25.3]). In faSScinate, rates of serious infection increased after transition from double-blind placebo to open-label tocilizumab (10.9 [3.0–27.9] at Week 48; 19.6 [7.2–42.7] at Weeks 48–96), whereas in focuSSced, the rate of serious infections in the placebo group was higher at the end of the 48-week double-blind period (8.8 [3.8–17.4]) than at Week 96 after 48 weeks of open-label tocilizumab (3.4 [0.7–10.0]). Higher rates of AEs in faSScinate than in focuSSced might reflect differences in

inclusion criteria, such as the requirement for mRSS of 15 to 40 units in faSScinate compared with 10 to 35 units in focuSSced, indicating that faSScinate patients had more skin sclerosis. In faSScinate, infected digital ulcers developed in two patients during the open-label period after they transitioned from placebo to tocilizumab, whereas no increase in digital ulcers was observed in the placebo-tocilizumab group in focuSSced.

There are limitations in assessing open-label studies, and results of open-label studies should be interpreted with caution. This study was not designed or powered for formal statistical comparison of treatment arms during the open-label period, and formal testing of these exploratory data was not prespecified. For the same reason, comparison of patients who received placebo and completed the open-label phase with patients in the tocilizumab treatment arm at Week 48 is not appropriate. Therefore, although numerical trends can be observed, comparative analyses could not be interpreted in a meaningful way, and formal statistical testing was not applicable. FVC analysis in the open-label period reports descriptive statistics of the unadjusted change from baseline because no model was prespecified and no hypothesis testing was planned for the long-term extension; this differs from the mixed model repeated measures analysis reported at Week 48 (18). Furthermore, the long-term efficacy and safety of tocilizumab in combination with other treatments for SSc (e.g., mycophenolate mofetil, nintedanib) were not investigated in the current study and requires further assessment.

In conclusion, the preservation of FVC observed in patients with SSc-ILD who were treated with tocilizumab in the double-blind period of focuSSced was maintained during the open-label period. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the teams of study investigators and subinvestigators for contributions to the focuSSced study and the patients who participated in the trial. Writing and editorial assistance was provided by Anna Battershill, M.Sc., and Sara Duggan, Ph.D., of ApotheCom.

References

1. Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–1699.
2. Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. *Clin Exp Rheumatol* 2015; 33:S3–S7.
3. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J Respir Crit Care Med* 2020;201:650–660.
4. Nagaraja V, Matucci-Cerinic M, Furst DE, Kuwana M, Allanore Y, Denton CP, *et al.* Current and future outlook on disease modification and defining low disease activity in systemic sclerosis. *Arthritis Rheumatol* 2020;72:1049–1058.
5. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940–944.
6. Volkmann ER, Fischer A. Update on morbidity and mortality in systemic sclerosis–related interstitial lung disease. *J Scleroderma Relat Disord* 2021;6:11–20.
7. Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. *J Dermatol Sci* 2001;27:140–146.
8. Matsushita T, Hasegawa M, Hamaguchi Y, Takehara K, Sato S. Longitudinal analysis of serum cytokine concentrations in systemic sclerosis: association of interleukin 12 elevation with spontaneous regression of skin sclerosis. *J Rheumatol* 2006;33:275–284.
9. Muangchant C, Pope JE. The significance of interleukin-6 and C-reactive protein in systemic sclerosis: a systematic literature review. *Clin Exp Rheumatol* 2013; 31:122–134.
10. Muangchan C, Pope JE. Interleukin 6 in systemic sclerosis and potential implications for targeted therapy. *J Rheumatol* 2012;39:1120–1124.
11. De Lauretis A, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NS, *et al.* Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J Rheumatol* 2013;40:435–446.
12. Khan K, Xu S, Nihtyanova S, Derrett-Smith E, Abraham D, Denton CP, *et al.* Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. *Ann Rheum Dis* 2012;71: 1235–1242.
13. Nihtyanova SI, Denton CP. Pathogenesis of systemic sclerosis associated interstitial lung disease. *J Scleroderma Relat Disord* 2020; 5:6–16.
14. Gao X, Jia G, Guttman A, DePianto DJ, Morshead KB, Sun K-H, *et al.* Osteopontin links myeloid activation and disease progression in systemic sclerosis. *Cell Rep Med* 2020;1:100140.
15. Actemra (tocilizumab) injection, for intravenous or subcutaneous use [package insert]. South San Francisco, CA: Genenetch Inc.; 2021.
16. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, *et al.* Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387:2630–2640.
17. Khanna D, Denton CP, Lin CJF, van Laar JM, Frech TM, Anderson ME, *et al.* Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Ann Rheum Dis* 2018;77: 212–220.
18. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, *et al.*; focuSSced investigators. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020;8:963–974.
19. Khanna D, Lin CJF, Spotswood H, Siegel J, Furst D, Denton C. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of the phase 3 focuSSced trial [abstract]. *Ann Rheum Dis* 2020;72:396.
20. Khanna D, Lin CJF, Spotswood H, Siegel J, Furst D, Denton C. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase 3 trial [abstract]. Presented at ACR Convergence 2020. Virtual. November 5–9, 2020.
21. Khanna D, Lin CJF, Furst DE, Zucchetto M, Raghu G, Martinez FJ, *et al.* Tocilizumab in systemic sclerosis interstitial lung disease: safety and efficacy in the double-blind and open-label periods of a randomized controlled phase 3 trial [abstract]. *Am J Respir Crit Care Med* 2021; 203:A1025.
22. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, *et al.*; focuSSced Investigators. Tocilizumab prevents progression of early systemic sclerosis associated interstitial lung disease. *Arthritis Rheumatol* 2021;73:1301–1310.
23. Khanna D, Lescoat A, Roofeh D, Bernstein EJ, Kazerooni EA, Roth MD, *et al.* Systemic sclerosis-associated interstitial lung disease: how to incorporate two Food and Drug Administration-approved therapies in clinical practice. *Arthritis Rheumatol* 2022;74:13–27.
24. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, *et al.*; SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019;380: 2518–2528.