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EXTENDED REPORT

Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

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ABSTRACT

Objectives Assess the efficacy and safety of tocilizumab in patients with systemic sclerosis (SSc) in a phase II study.

Methods Patients with SSc were treated for 48 weeks in an open-label extension phase of the faSScinate study with weekly 162 mg subcutaneous tocilizumab. Exploratory end points included modified Rodnan Skin Score (mRSS) and per cent predicted forced vital capacity (%pFVC) through week 96.

Results Overall, 24/44 (55%) placebo-tocilizumab and 27/43 (63%) continuous-tocilizumab patients completed week 96. Observed mean (SD (95% CI)) change from baseline in mRSS was -3.1 (6.3 (-5.4 to -0.9)) for placebo and -5.6 (9.1 (-8.9 to -2.4)) for tocilizumab at week 48 and -9.4 (5.6 (-8.9 to -2.4)) for placebo-tocilizumab and -9.1 (8.7 (-12.5 to -5.6)) for continuous-tocilizumab at week 96. Of patients who completed week 96, any decline in %pFVC was observed for 10/24 (42% (95% CI 22% to 63%)) placebo-tocilizumab and 12/26 (46% (95% CI 27% to 67%)) continuous-tocilizumab patients in the open-label period; no patients had >10% absolute decline in %pFVC. Serious infection rates/100 patient-years (95% CI) were 10.9 (3.0 to 27.9) with placebo and 34.8 (18.0 to 60.8) with tocilizumab during the double-blind period by week 48 and 19.6 (7.2 to 42.7) with placebo-tocilizumab and 0.0 (0.0 to 12.2) with continuous-tocilizumab during the open-label period.

Conclusions Skin score improvement and FVC stabilisation in the double-blind period were observed in placebo-treated patients who transitioned to tocilizumab and were maintained in the open-label period. Safety data indicated increased serious infections in patients with SSc but no new safety signals with tocilizumab.

Trial registration number NCT01532869; Results.

cause of scleroderma-related deaths.^{1 5} Few treatment options are available for patients with SSc, and there is an unmet need for disease-modifying therapy.⁶

Interleukin 6 (IL-6) appears to play a role in SSc pathogenesis.^{7 8} Patients with SSc have increased IL-6 expression in endothelial cells and skin fibroblasts.⁹ Serum IL-6 levels are elevated in patients with SSc,^{10 11} particularly those with early diffuse cutaneous skin involvement.^{12 13} Furthermore, some studies have suggested a role for IL-6 as a marker for disease progression and clinical outcome in patients with SSc.¹¹ C reactive protein (CRP) is correlated with IL-6, and CRP levels are elevated in patients with active SSc, especially those with early diffuse cutaneous SSc.¹⁴

Tocilizumab is a monoclonal anti-IL-6 receptor- α antibody for the treatment of patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and giant cell arteritis.¹⁵ Initial investigations of tocilizumab in patients with SSc demonstrated improvements in skin sclerosis and SSc-associated polyarthritis.^{16 17} The faSScinate clinical trial was the first double-blind, randomised controlled trial investigating the efficacy and safety of subcutaneous tocilizumab in patients with SSc. Results from the 48-week double-blind period of faSScinate, including the primary end point, were published previously and demonstrated that treatment with tocilizumab resulted in a clinically meaningful but not statistically significant decline in modified Rodnan Skin Score (mRSS) compared with placebo through week 48 for patients receiving tocilizumab.¹⁸ Exploratory efficacy results and safety through week 96 of the faSScinate trial, including the 48-week open-label period, are now reported.

INTRODUCTION

Systemic sclerosis (SSc) is a rare, debilitating autoimmune disorder of the connective tissue and vasculature that is characterised by inflammation, fibrosis and microvascular injury of multiple organs.¹⁻³ Patients with SSc experience high morbidity and mortality rates,² particularly those who have pulmonary, cardiac or renal organ involvement.⁴ Indeed, lung disease is the primary

METHODS

Study design

faSScinate was a multicentre, randomised, double-blind, placebo-controlled, two-arm, parallel-group, phase II clinical trial conducted at 35 hospitals across Canada, France, Germany, the UK and USA. The study design and patient enrolment criteria have been published.¹⁸ Briefly, the 96-week trial consisted of a 48-week double-blind period



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followed by a 48-week open-label period. Patients were randomly assigned (1:1) to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo during the 48-week double-blind period (tocilizumab group or placebo group, respectively) with the option for escape therapy with methotrexate, hydroxychloroquine or mycophenolate mofetil (MMF) after 24 weeks if they had worsening SSc. Randomisation was stratified according to joint involvement at baseline (<4 or \geq 4 joints on the 28 tender joint count). At week 48, all 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).

Patients

Eligible patients were 18 years of age or older; received a diagnosis of SSc according to the 1980 American College of Rheumatology Criteria,¹⁹ with less than 5 years since their first non-Raynaud's sign or symptom; had an mRSS score of 15 to 40 with clinical skin involvement proximal to the elbows, knees or both, with or without facial involvement; and had active disease. Active disease was defined as at least one of the following features at screening: increase \geq 3 in mRSS units compared with the last visit within the previous 1 month to 6 months or new-onset SSc within 1 year before screening, involvement of one new body area with \geq 2 mRSS units or two new body areas with \geq 1 mRSS unit, documentation of worsening skin thickening (patients with new-onset SSc only), or \geq 1 tendon friction rub plus CRP level \geq 10 mg/L, erythrocyte sedimentation rate \geq 28 mm/hour

or platelet count \geq 330 \times 10³/ μ L. All patients provided written informed consent.

Assessments

Exploratory efficacy end points included mean change from baseline to week 96 in mRSS; proportions of patients with improvements in mRSS of \geq 20%, \geq 40% and \geq 60%; proportions of patients achieving minimal clinically important difference (MCID) in mRSS (change from baseline of \geq 4.7)²⁰; per cent predicted forced vital capacity (%pFVC); per cent predicted diffusing capacity for carbon monoxide corrected for haemoglobin (%pDLCO (Hb corr)) and Clinician Global Visual Analogue Scale (VAS). Patient-reported outcomes included Health Assessment Questionnaire-Disability Index (HAQ-DI), Patient Global VAS, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score and Pruritus 5-D Itch Scale. Safety was reported as rates of adverse events (AEs) and serious AEs (SAEs) per 100 patient-years (PY) with 95% CIs.

Statistical analysis

Although a mixed-model, repeated-measures analysis was performed on the placebo-controlled period at weeks 24 and 48, observed data were analysed for the week 96 period because all end points during the open-label period were exploratory. Exploratory efficacy end points in the open-label period were assessed in the modified intent-to-treat population (all randomly assigned patients who received any study drug). Safety was

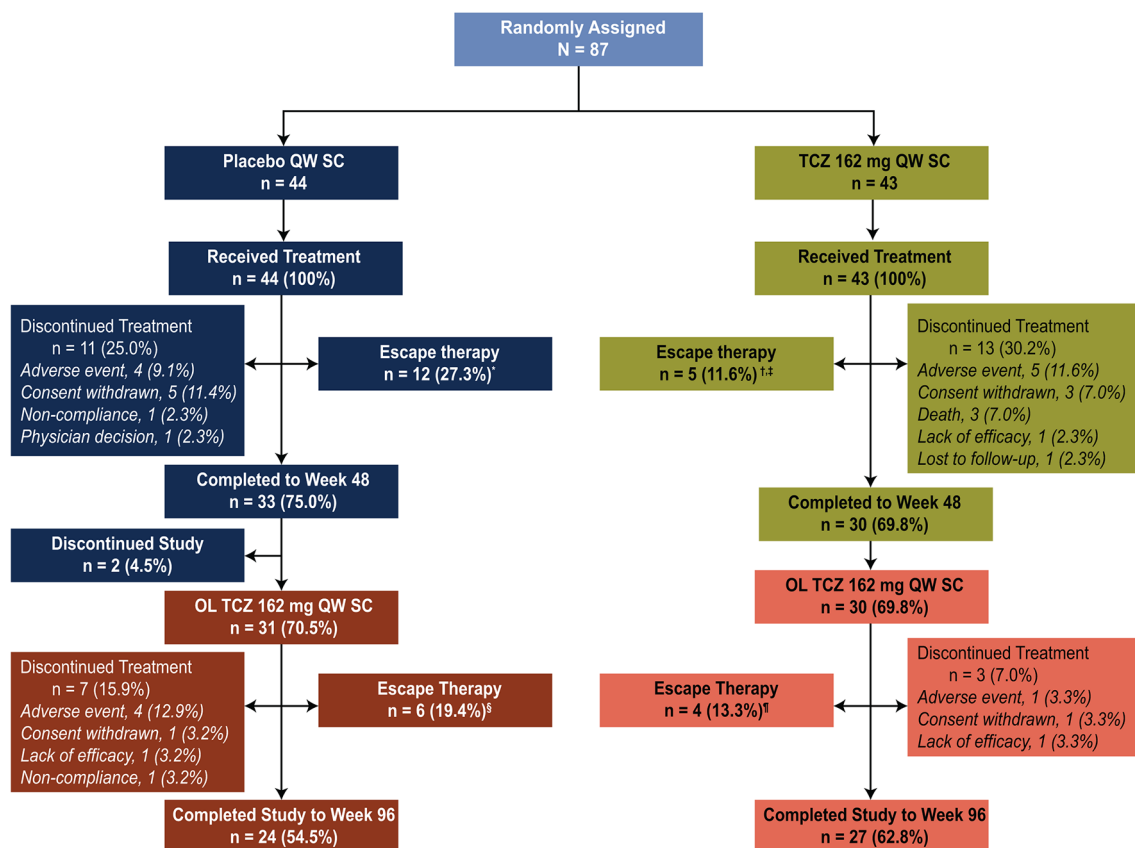


Figure 1 Patient disposition (intent-to-treat population). *Methotrexate, n=5; hydroxychloroquine, n=2; mycophenolate mofetil, n=5. †Methotrexate, n=2; hydroxychloroquine, n=2; mycophenolate mofetil, n=1. ‡One patient who continued as an escape patient at week 48¹⁸ was later removed by the site and was not included at week 96. §Methotrexate, n=1; hydroxychloroquine, n=1; mycophenolate mofetil, n=4 (1 patient who received mycophenolate mofetil in the double-blind period and received it again in the open-label period was not counted in the open-label period). ¶Hydroxychloroquine, n=2; mycophenolate mofetil, n=2. OL, open-label; QW, every week; SC, subcutaneously; TCZ, tocilizumab.

Table 1 Baseline demographics and disease characteristics (safety population)

	Patients randomly assigned in the double-blind period		Patients who transitioned to the open-label period*	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo- tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Age, years	48 (12.9)	51 (11.7)	47 (11.9)	52 (11.8)
Female, n (%)	35 (80)	32 (74)	26 (84)	23 (77)
White, n (%)	40 (91)	38 (88)	28 (90)	26 (87)
Duration of SSc, months	19.5 (17.0)	17.6 (13.9)§	20.0 (18.2)	17.7 (13.5)
Total mRSS†	25.6 (5.9)	26.4 (7.2)	24.6 (5.4)	25.2 (6.9)
TJC28	7.4 (8.5)‡	7.4 (8.9)	8.3 (9.1)	8.1 (10.0)
TJC28 ≥4, n (%)	21 (49)‡	20 (47)	16 (52)	12 (40)
Overall HAQ-DI Score	1.4 (0.7)	1.3 (0.6)§	1.2 (0.7)	1.2 (0.6)¶
Clinician Global VAS, mm	60.9 (15.2)	64.1 (15.1)	57.9 (15.2)	62.5 (15.7)
Patient Global VAS, mm	61.9 (21.0)	59.8 (18.3)	60.2 (22.9)	56.6 (18.3)
FACIT-Fatigue	26.5 (11.6)‡	25.6 (11.4)	27.9 (12.1)**	26.2 (10.5)
Pruritus 5-D Itch	13.5 (5.1)‡	13.1 (4.5)§	13.2 (4.8)**	13.0 (4.2)¶
CRP, mg/L	10.3 (13.5)‡	10.0 (13.5)	7.7 (7.2)	7.4 (12.7)
%pFVC	82 (13)§	80 (14)	83 (14)**	78 (13)
%pDLCO (Hb corr)	74 (21)‡	73 (19)§	75 (23)**	73 (17)

All values are mean (SD) unless stated otherwise.

*Original baseline data for patients who entered the OL period.

†Possible scores: mRSS, 0–51; HAQ-DI, 0–3; Clinician Global VAS, 0–100; ULN for CRP, 3 mg/L.

‡n = 43.

§n = 42.

¶n = 29.

**n = 30.

%pDLCO (Hb corr), per cent predicted diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; %pFVC, per cent predicted forced vital capacity; CRP, C reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; mRSS, modified Rodnan Skin Score; QW, every week; SC, subcutaneously; SSc, systemic sclerosis; TJC28, tender joint count based on 28 joints; ULN, upper limit of normal; VAS, Visual Analogue Scale.

assessed in all patients who received study drug and provided at least one safety assessment after treatment (safety population) and was summarised by treatment received. The study was not designed or powered for formal statistical comparison of the two treatment arms within the open-label period or with the original tocilizumab arm at week 48 because of inherent biases of open-label results. However, 95% CIs were calculated as descriptive statistics using the Pearson Clopper method for exact binomial, and CIs for rates of AEs were based on Poisson distribution.²¹ Data from escape patients were not censored.

RESULTS

Patients

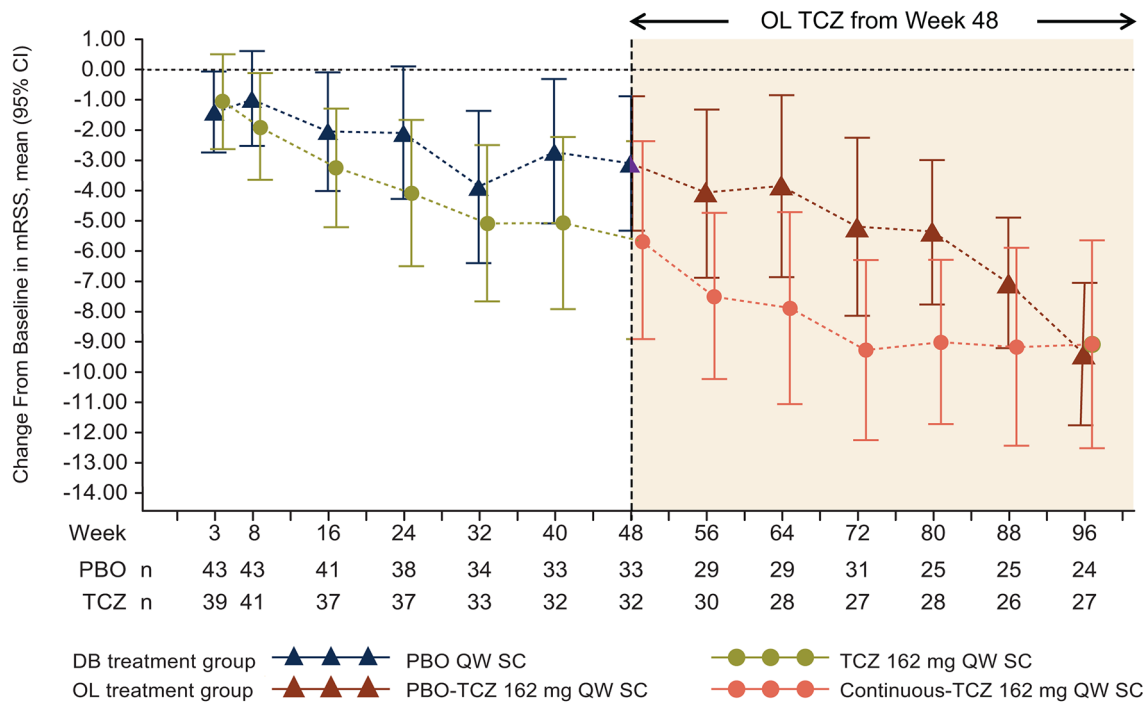
Eighty-seven patients were enrolled in the faSScinate trial (figure 1); in the double-blind period, 44 patients were originally assigned to receive weekly subcutaneous placebo (placebo group) and 43 patients were originally assigned to receive weekly subcutaneous tocilizumab 162 mg (tocilizumab group). At week 48, 31 (70.5%) patients originally assigned to double-blind placebo transitioned to open-label weekly tocilizumab 162 mg (placebo-tocilizumab group) and 30 (69.8%) patients originally assigned to double-blind tocilizumab transitioned to open-label weekly subcutaneous tocilizumab 162 mg (continuous-tocilizumab group) until they completed the study or withdrew from treatment. Twenty-four (54.5%) patients in the placebo-tocilizumab group and 27 (62.8%) patients in the continuous-tocilizumab group completed week 96. During the open-label period, five patients discontinued because of AEs (four patients in the placebo-tocilizumab group and one patient in the continuous-tocilizumab group). Other reasons for study withdrawal were non-compliance (one patient in the placebo-tocilizumab group),

lack of efficacy (one patient in each treatment group) and patient consent withdrawn (one patient in each treatment group). Escape therapy was received by 18 patients originally assigned to receive placebo (12 in the placebo group during the double-blind period and 6 in the placebo-tocilizumab group during the open-label period) and by 9 patients originally assigned to receive tocilizumab (5 in the tocilizumab group during the double-blind period and 4 in the continuous-tocilizumab group during the open-label period) (figure 1).

Baseline characteristics were similar between patients who were randomly assigned in the double-blind period and those who transitioned to open-label treatment, with the exception of HAQ-DI scores and CRP values, which were numerically lower, on average, in patients who transitioned to the open-label period (table 1).

Efficacy

Improvements in mRSS were observed during the double-blind period with tocilizumab treatment (mean (SD; 95% CI) change from baseline to week 48: –5.6 (9.1; –8.9 to –2.4)). In addition to the –5.6 improvement from baseline to week 48 with tocilizumab treatment, further improvement was seen in the open-label period, bringing the total mean improvement to –9.1 (8.7; –12.5 to –5.6) from baseline to week 96 (figure 2). Furthermore, patients in the placebo group experienced similar improvements after receiving open-label tocilizumab from week 48 to week 96 (figure 2) (mean (SD; 95% CI) change from baseline –3.1 (6.3; –5.4 to –0.9) to week 48 during double-blind placebo treatment and –9.4 (5.6; –11.8 to –7.0) to week 96 after 48 weeks of open-label tocilizumab treatment). There were incremental improvements between weeks 48 and 96 in the proportions of patients who experienced improvements in mRSS of ≥20%, ≥40% and



Wk	PBO		TCZ	
	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score
24	-2.1 (6.7) [-4.3, 0.1]	23.2 (9.3) [20.2, 26.3]	-4.1 (7.3) [-6.5, -1.7]	21.8 (9.9) [18.5, 25.1]
48	-3.1 (6.3) [-5.4, -0.9]	22.3 (8.1) [19.4, 25.1]	-5.6 (9.1) [-8.9, -2.4]	19.6 (10.1) [15.9, 23.2]
72	-5.2 (7.9) [-8.1, -2.3]	19.8 (8.0) [16.9, 22.7]	-9.3 (7.5) [-12.2, -6.3]	16.0 (9.1) [12.4, 19.7]
96	-9.4 (5.6) [-11.8, -7.0]	15.3 (7.6) [12.1, 18.6]	-9.1 (8.7) [-12.5, -5.6]	16.2 (9.8) [12.3, 20.1]

Figure 2 Mean change (95% CI) in mRSS from baseline to week 96 (intent-to-treat population; observed data). Negative values denote improvement. Patients randomly assigned to PBO 162 mg QW SC received OL TCZ 162 mg QW SC from week 48. BL, baseline; DB, double-blind; mRSS, modified Rodnan Skin Score; OL, open-label; PBO, placebo; %pFVC, per cent predicted forced vital capacity; QW, every week; SC, subcutaneously; TCZ, tocilizumab.

$\geq 60\%$ and change in mRSS equal to or greater than the MCID of 4.7 units in the continuous-tocilizumab group (table 2).

Improvements in Clinician Global VAS and patient-reported outcomes, as indicated by negative change in HAQ-DI, Clinician Global VAS, and Patient Global VAS and positive change in FACIT-Fatigue Score, observed at week 48 in the tocilizumab group were maintained through the open-label period in the continuous-tocilizumab group (table 2). Furthermore, greater improvements in patient-reported outcomes were observed in placebo-tocilizumab patients after they switched to tocilizumab during the open-label period than during the double-blind placebo period. Patients in the placebo group experienced mean (95% CI) changes from baseline in HAQ-DI of 0.17 (0.05 to 0.30) after 48 weeks of double-blind placebo treatment and -0.29 (-0.46 to -0.13) at week 96 after 48 weeks of open-label tocilizumab treatment (placebo-tocilizumab). Changes from baseline in Clinician Global VAS were -7.69 (-15.06 to -0.32) and -20.61 (-29.52 to -11.7), respectively; changes in Patient Global VAS were -4.03 (-12.42 to 4.36) and -23.75 (-38.95 to -3.46), respectively,

and changes in FACIT-Fatigue Scores were 1.37 (-1.37 to 4.11) and 11.26 (5.72 to 16.81), respectively.

Among patients who completed the study to week 96 (completers analysis), similar proportions in both treatment groups experienced worsening in %pFVC (figure 3); 42% of patients in the placebo-tocilizumab group and 46% of patients in the continuous-tocilizumab group had absolute decreases (>0) in %pFVC during the open-label period from weeks 48 to 96 compared with 83% of patients receiving placebo and 54% of patients receiving tocilizumab during the double-blind period from weeks 0 to 48. During the open-label period, no patients in either treatment group who completed week 96 or withdrew experienced $>10\%$ absolute decline in %pFVC after receiving tocilizumab, in contrast to three in the placebo group and one in the tocilizumab group during the double-blind period.

Safety

SAE rates (95% CIs) were 76.1 (50.6–110.0) in the placebo group and 66.7 (42.3–100.1) in the tocilizumab group by week

Clinical and epidemiological research

Table 2 Change from baseline to week 48 (double-blind period) or week 96 (including open-label period) in exploratory end points (intent-to-treat population; observed data)

	Double-blind period, week 48		Open-label period, week 96	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo- tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Change from baseline in mRSS, n (% (95% CI))*				
≥ 20%	13 (29.5 [16.8 to 45.2])	18 (41.9 [27.0 to 57.9])	18 (40.9 [26.3 to 56.8])	22 (51.2 [35.5 to 66.7])
≥ 40%	3 (6.8 [1.4 to 18.7])	10 (23.3 [11.8 to 38.6])	13 (29.5 [16.8 to 45.2])	15 (34.9 [21.0 to 50.9])
≥ 60%	0 (0.0 [0.0 to 8.0])	5 (11.6 [3.9 to 25.1])	7 (15.9 [6.6 to 30.1])	6 (14.0 [5.3 to 27.9])
≥4.7 units (MCID) ²⁰	12 (27.3 [15.0, 42.8]) n=33	18 (41.9 [27.0, 57.9]) n=32	19 (43.2 [28.3, 59.0]) n=24	22 (51.2 [35.5, 66.7]) n=27
TJC28, mean (95% CI) change from baseline	-0.97 (-2.85 to 0.91)	-2.28 (-4.16 to -0.40)	-4.88 (-7.99 to -1.76)	-3.39 (-6.14 to -0.65)
[min, max]	[-16, 12] n=33	[-14, 9] n=32	[-23, 2] n=24	[-25, 7] n=28
HAQ-DI, mean (95% CI) change from baseline†	0.17 (0.05 to 0.30)	-0.01 (-0.25 to 0.23)	-0.29 (-0.46 to -0.13)	-0.13 (-0.33 to 0.08)
[min, max]	[-0.63, 0.88] n=34	[-1.13, 1.75] n=31	[-1.25, 0.50] n=24	[-1.25, 1.38] n=27
Clinician Global VAS, mean (95% CI) change from baseline†	-7.69 (-15.06 to -0.32)	-18.57 (-26.89 to -10.25)	-20.61 (-29.52 to -11.7)	-21.30 (-31.05 to -11.54)
[min, max]	[-45, 39] n=32	[-60, 14] n=30	[-57, 21] n=23	[-73, 14] n=27
Patient Global VAS, mean (95% CI) change from baseline†	-4.03 (-12.42 to 4.36)	-9.13 (-18.68 to 0.43)	-23.75 (-38.95 to -8.55)	-11.11 (-18.75 to -3.46)
[min, max]	[-64, 57] n=34	[-59, 36] n=32	[-90, 38] n=24	[-44, 33] n=28
FACIT-Fatigue score, mean (95% CI) change from baseline†	1.37 (-1.37 to 4.11)	3.69 (0.34 to 7.04)	11.26 (5.72 to 16.81)	4.15 (1.51 to 6.79)
[min, max]	[-18.0, 15.0] n=32	[-15.0, 22.0] n=32	[-15.0, 29.0] n=23	[-10.0, 19.0] n=27
Pruritus 5-D Itch Score, mean (95% CI) change from baseline†	-1.87 (-3.26 to -0.48)	-2.03 (-3.91 to -0.16)	-4.43 (-6.32 to -2.55)	-3.23 (-5.38 to -1.09)
[min, max]	[-10, 5] n=30	[-15, 7] n=30	[-14, 1] n=23	[-14, 9] n=26
%pFVC, mean (95% CI) change from baseline	-0.06 (-0.10 to -0.03)	-0.02 (-0.04 to 0.00)	-0.03 (-0.07 to 0.01)	-0.01 (-0.03 to 0.02)
[min, max]	[-0.33, 0.13] n=32	[-0.15, 0.04] n=30	[-0.25, 0.20] n=25	[-0.15, 0.15] n=28
% pDLCO (Hb corr), mean (95% CI) change from baseline	-0.03 (-0.07 to 0.01)	-0.03 (-0.06 to 0.00)	-0.03 (-0.10 to 0.05)	-0.03 (-0.08 to 0.01)
[min, max]	[-0.23, 0.28] n=31	[-0.26, 0.12] n=27	[-0.71, 0.25] n=24	[-0.25, 0.21] n=25

n denotes number of patients with valid assessments at the time point. Escape data were not censored.

*Percentages were calculated based on n=43 (tocilizumab) and n=44 (placebo), the intent-to-treat population; thus, patients with missing change in mRSS Scores were considered non-responders.

†Negative change from baseline indicated improvement for all efficacy measures except FACIT-Fatigue, FVC and DLCO, for which positive change from baseline indicated improvement.

%pDLCO (Hb corr), per cent predicted diffusing capacity of lung for carbon monoxide corrected for haemoglobin; %pFVC, per cent predicted forced vital capacity; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; max, maximum; MCID, minimal clinically important difference; min, minimum; mRSS, modified Rodnan Skin Score; QW, every week; SC, subcutaneously; TJC28, tender joint count based on 28 joints; VAS, Visual Analogue Scale.

48 compared with 36.0 (18.0–64.4) in the placebo-tocilizumab group and 16.5 (5.4–38.5) in the continuous-tocilizumab group from week 48 to week 96 (table 3). Infections were the most frequently reported AEs and SAEs during double-blind tocilizumab treatment and in placebo patients who transitioned to open-label tocilizumab. In the placebo-tocilizumab group, rates of serious infection increased after the switch to open-label tocilizumab; the rate (95% CI) of serious infections was 10.9 (3.0–27.9) per 100 PY during the 48 weeks of double-blind placebo treatment compared with 19.6 (7.2–42.7) per 100 PY from week 48 to 96, with four patients (12.9%) in this group reporting at least one serious infection after switching to open-label tocilizumab (see online supplementary appendix table 1

for details of serious infections). Patients in the tocilizumab group had a serious infection rate of 34.8 (95% CI 18.0 to 60.8) per 100 PY by week 48. No serious infections were reported after the switch from double-blind to open-label tocilizumab (continuous-tocilizumab).

No deaths were reported during the open-label period in either treatment group, and no serious hepatic AEs, anaphylactic reactions, gastrointestinal perforations or demyelination SAEs were reported during the 96-week treatment period. Changes in laboratory parameters of interest for tocilizumab, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, neutrophil counts and platelet counts, were usually $\leq 5 \times$ the upper limit of normal (ULN) over the 96-week treatment period.

Table 3 Adverse events (AEs, safety population)

	Double-blind period		Open-label period	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo-tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Exposure, PY	36.8	34.5	30.6	30.3
AEs, n	244	283	126	153
Rate/100 PY (95% CI)	663.5 (582.9 to 752.2)	820.6 (727.8 to 922.0)	412.4 (343.5 to 491.0)	504.4 (427.6 to 590.9)
SAEs, n	28	23	11	5
Rate/100 PY (95% CI)	76.1 (50.6 to 110.0)	66.7 (42.3 to 100.1)	36.0 (18.0 to 64.4)	16.5 (5.4 to 38.5)
Patients with ≥ 1 SAE, n (%)	16 (36.4)	14 (32.6)	7 (22.6)	4 (13.3)
Patients with ≥ 1 serious infection, n (%)*	3 (6.8)	9 (20.9)	4 (12.9)	0
AEs leading to death, n	1	3	0	0
Rate/100 PY	2.72	8.70	0.00	0.00
Patients with AEs leading to withdrawal, n (%)	5 (11.4)	6 (14.0)	4 (12.9) [†]	0
Rate/100 PY	13.60	17.40	13.09	0.00
Patients with injection site reactions, n*	2 (4.5)	3 (7.0)	4 (12.9)	1 (3.3)
SAEs according to system organ class, ‡ number of events (rate/100 PY [95% CI])				
Infections and infestations	4 (10.9 [3.0 to 27.9])	12 (34.8 [18.0 to 60.8])	6 (19.6 [7.2 to 42.7])	0 (0.0 [0.0 to 12.2])
Cardiac disorders	5 (23.6 [4.4 to 31.7])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Gastrointestinal disorders	6 (16.3 [6.0 to 35.5])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Musculoskeletal and connective tissue disorders	2 (5.4 [0.7 to 19.7])	2 (5.8 [0.7 to 21.0])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
Skin and subcutaneous tissue disorders	2 (5.4 [0.7 to 19.7])	2 (5.8 [0.7 to 21.0])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Vascular disorders	4 (10.9 [3.0 to 27.9])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Blood and lymphatic system disorders	1 (2.7 [0.1 to 15.2])	1 (2.9 [0.1 to 16.2])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
Renal and urinary disorders	2 (5.4 [0.7 to 19.7])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
General disorders and administration site conditions	0 (0.0 [0.0 to 10.0])	2 (5.8 [0.7 to 21.0])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Neoplasms, benign, malignant and unspecified	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	1 (3.3 [0.1 to 18.4])
Nervous system disorders	2 (5.4 [0.7 to 19.7])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Endocrine disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Psychiatric disorders	0 (0.0 [0.0 to 10.0])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Reproductive system and breast disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Respiratory, thoracic and mediastinal disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])

*Multiple occurrences in the same patient are counted once.

[†]Osteomyelitis (one case serious, one case not serious), scleroderma renal crisis and breast cancer metastatic.

[‡]According to the Medical Dictionary for Regulatory Activities, version 18.0.

AEs, adverse events; PY, patient-years; QW, every week; SAEs, serious adverse events; SC, subcutaneously.

there were improvements for individual patients between weeks 72 and 96. Of the 27 patients receiving continuous tocilizumab who completed the study through week 96, 14/27 (52%) had further, primarily modest, improvements (range, -1 to -8 change in mRSS). However, there were two outliers who experienced considerable worsening ($+9$ and $+14$ change in mRSS) during this period. Overall, this culminates in a flattened average response. The potential for improvement may be more limited at this time point; 7/27 (26%) patients among the continuous tocilizumab completers had observed mRSS scores ≤ 9 at week 72 compared with 2/24 (8%) among the placebo-tocilizumab group.

Improvements from weeks 48 to 96 in mRSS were supported by improvements in patient-reported outcomes, including HAQ-DI, Patient Global VAS and FACIT-Fatigue Scores, observed in patients initially assigned to placebo who transitioned to open-label tocilizumab and were comparable to those of patients who received tocilizumab continuously, consistent with trends observed with tocilizumab treatment during the double-blind period.¹⁸ Consistent as well with exploratory analyses in the double-blind period showing fewer tocilizumab-treated (10%) than placebo-treated (23%) patients experienced absolute decline ($>10\%$) in %pFVC after 48 weeks,¹⁸ no patients

who completed week 96 of the study experienced $>10\%$ decline in %pFVC during the open-label period while receiving tocilizumab. Of note, the primary end point was change in mRSS, and, at the time the study was designed, the patient populations had not been enriched for patients with SSc-associated interstitial lung disease.

Safety results over the 96-week treatment period were consistent with the known safety profile of tocilizumab; infections were the most frequently reported AEs and SAEs, and an increased rate of serious infections was observed after patients transitioned from placebo to tocilizumab. AEs tended to occur more frequently in the first few months after patients transitioned from placebo to tocilizumab but less frequently in longer-term follow-up. Infections were the most frequently reported SAEs in clinical trials of tocilizumab in patients with rheumatoid arthritis (RA).^{23 24} Rates of SAEs and serious infections in this study in patients with SSc were approximately five times and eight times higher, respectively, than those reported in patients with RA,^{23 24} which is expected given the high morbidity and mortality in patients with SSc.¹ The frequencies of SAEs and serious infections observed in faSScinate are consistent with those in other SSc studies.^{25–27} Patients with SSc may be prone to digital ulcers,¹ and complications of digital ulcers occur in 15%

of patients with SSc.²⁸ The occurrence of two cases of infected digital ulcers and one of osteomyelitis in patients who transitioned from placebo to open-label tocilizumab suggested that tocilizumab may increase infections in patients with SSc-associated digital ulcers, likely over pressure areas such as proximal interphalangeal joints.

The present study had some important limitations. First, all patients received open-label tocilizumab after week 48; therefore, the data collected during the open-label period were uncontrolled. There was a high discontinuation rate. During the open-label period, 7 of the 31 (23%) patients originally assigned to placebo who entered the open-label period and 3 of the 30 (10%) patients originally assigned to tocilizumab who entered the open-label period withdrew from the study. The discontinuation rate from 48 to 96 weeks (16%) was lower than it was in the first 48 weeks of the study (28%). Overall, 63% of patients originally assigned to receive tocilizumab and 55% of patients originally assigned to receive placebo completed the full 96 weeks of treatment. It is likely that patients who completed week 48 and entered the open-label period were less ill or responded better to treatment and perhaps had already experienced more improvement. This selection bias is a common problem associated with open-label, long-term extension studies.²⁹ Withdrawal of patients who experience AEs leads to the selection of healthier patients, which should be considered when interpreting the longer-term rates of AEs and SAEs. Second, patients with elevated acute-phase reactants were enrolled in this study; therefore, further studies may be needed to investigate the efficacy and safety of tocilizumab in other patient subsets. Third, given the limited numbers of patients with serious infections, analysis of the data to identify potential risk factors, in particular for any interaction of risk factors with tocilizumab, would be underpowered and was not performed. A phase III study with a larger sample size is under way. Last, another limitation is that the study was not designed or powered for formal statistical comparison of the two treatment arms during the open-label period, and formal testing of this exploratory data was not prespecified. For the same reason, a comparison of placebo patients who completed the open-label phase with those in the tocilizumab treatment arm at week 48 is not appropriate. Therefore, although trends can be observed, comparative analyses could not be interpreted in a meaningful way, and formal statistical testing was not feasible.

No disease-modifying therapies have been approved for the treatment of patients with SSc, but some may control symptoms. Treatment options for patients with SSc are largely dependent on the organs affected.^{30–31} For example, cyclophosphamide has demonstrated improvement³² or trends for improvement³³ in lung function in patients with SSc and interstitial lung disease, though its use has been associated with significant toxicity.³⁰ Similarly, stem cell transplantation has resulted in improvements in skin fibrosis and prevention of lung decline and mortality but is associated with significant costs and risks.^{34–36} Methotrexate has demonstrated trends for improvement in skin scores in randomised controlled trials in patients with early SSc.^{37–38} Recently, MMF has shown efficacy similar to that of cyclophosphamide for lung and skin fibrosis.^{39–40} Tocilizumab may be the first targeted agent to show benefit in the amelioration of skin sclerosis and the prevention of pulmonary decline in patients with SSc.¹⁸

Overall, the open-label results of the faSScinate study support observations reported from the double-blind period in that the placebo and tocilizumab groups improved similarly when placebo patients were switched to active treatment. Further studies are required to investigate the efficacy and safety of tocilizumab in the treatment of patients with SSc and to determine whether tocilizumab produces significant improvement in skin sclerosis and

stabilisation of lung function. A double-blind, phase III randomised controlled trial (NCT02453256) will investigate the efficacy and safety of tocilizumab compared with placebo in a 48-week double-blind period and a 48-week open-label period to further investigate the findings of the phase II faSScinate trial.

In conclusion, together with the results from the first 48 weeks of double-blind treatment,¹⁸ results from the open-label period of the faSScinate trial suggest that treatment with tocilizumab is associated with benefits for skin fibrosis, lung fibrosis and physical function in patients with SSc but increased risk for serious infections. Tocilizumab may be a promising targeted therapy for patients with progressive SSc who have few treatment options.

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Patient consent Obtained.

Ethics approval Informed consent forms and other recruitment materials were approved by the Institutional Review Board/Ethics Committee before study initiation. The study was conducted in compliance with the International Conference on Harmonisation for Good Clinical Practice Guidelines and the Declaration of Helsinki.

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Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

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