

1 **A randomised placebo-controlled phase 3 trial of tocilizumab in systemic sclerosis**

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9 tocilizumab

1 **Research in Context**

2 *Evidence before this study*

3 We searched PubMed for entries within the last 10 years using the terms (“systemic
4 sclerosis” OR scleroderma) AND “interstitial lung disease” AND treatment) and reviewed
5 the results to identify phase 3 trials for treatment of patients with systemic sclerosis–
6 interstitial lung disease (SSc-ILD). Cyclophosphamide and mycophenolate mofetil
7 demonstrated significant but modest effects on improving lung function in patients with SSc-
8 ILD. A randomised controlled phase 2 trial of the interleukin-6 receptor inhibitor tocilizumab
9 in systemic sclerosis (SSc), which preceded the current trial, showed no statistically
10 significant effect of tocilizumab on skin thickness, but there was evidence of clinically
11 relevant improvement in lung function with tocilizumab treatment. The multi-tyrosine kinase
12 inhibitor nintedanib slowed the decline of lung function in patients with radiographically
13 evident, established SSc-ILD. Nintedanib was recently approved in the United States to slow
14 the rate of decline in pulmonary function in SSc-ILD. There is no approved disease-
15 modifying therapy for the treatment of SSc, and treatment guidelines focus on the
16 management of organ-specific manifestations.

17

18 *Added value of this study*

19 This is the first randomised controlled phase 3 trial of an interleukin-6 receptor antagonist in
20 SSc. Although the primary skin fibrosis endpoint was not met, key secondary analysis of
21 forced vital capacity and exploratory analysis of radiographically determined lung fibrosis
22 suggest that tocilizumab treatment can confer clinically meaningful preservation of lung
23 function and maintenance of pulmonary structure in patients with early diffuse SSc-ILD and
24 elevated acute-phase reactants.

1

2 *Implications of all the available evidence*

3 The potential effect of tocilizumab in preserving lung function in patients with early SSc-ILD
4 in early SSc has important therapeutic implications.

5

1 **ABSTRACT** <<300 of max 250 words>>

2 **Background** We assessed skin fibrosis and systemic sclerosis–interstitial lung disease (SSc-
3 ILD) in a phase 3 trial of tocilizumab, an anti–interleukin-6 receptor antibody, in systemic
4 sclerosis.

5 **Methods** Participants were randomly assigned 1:1 to receive double-blind weekly
6 tocilizumab 162 mg or placebo subcutaneously for 48 weeks (other immunomodulatory
7 therapy was not permitted at baseline). The primary endpoint was the difference in change
8 from baseline to week 48 in modified Rodnan skin score (mRSS). Percent predicted forced
9 vital capacity (ppFVC) at week 48, time-to-treatment-failure, and patient-/physician-reported
10 outcomes were secondary endpoints.

11 **Findings** Among 104 tocilizumab-treated and 106 placebo-treated participants, the least
12 squares mean (LSM) change from baseline to week 48 in mRSS was -6.14 and -4.41 ,
13 respectively (adjusted difference, -1.73 [95% CI -3.78 to 0.32]; $p=0.10$). The shift in
14 distribution of change from baseline in ppFVC at week 48 favoured tocilizumab (van Elteren
15 nominal $p=0.002$ vs placebo) with a difference in LSM change of 4.2 (95% CI 2.0 – 6.4 ;
16 nominal $p=0.0002$). Time-to-treatment-failure favoured tocilizumab (hazard ratio 0.63 [95%
17 CI 0.37 to 1.06]; nominal $p=0.08$). LSM (95% CI) differences between tocilizumab and
18 placebo in change from baseline to week 48 in Health Assessment Questionnaire–Disability
19 Index (-0.05 [-0.19 to 0.09]), patient-global (-2.4 [-8.6 to 3.70]), and physician-global ($-$
20 2.5 [-8.7 to 3.8]) visual analogue scale assessments were not statistically significant.
21 Infections were the most common adverse events (tocilizumab, 54/104 [51.9%]; placebo
22 53/106 [50.0%]). Serious adverse events were reported in 13 tocilizumab-treated participants
23 and 18 placebo-treated participants; primarily infections (tocilizumab, 3 events; placebo, 8
24 events) and cardiac events (tocilizumab, 2 events; placebo, 7 events).

1

2 **Interpretation** The primary skin fibrosis endpoint was not met. Secondary and exploratory
3 results suggest that tocilizumab preserves lung function in patients with early SSc-ILD and
4 elevated acute-phase reactants. Safety was consistent with the tocilizumab safety profile.

5 **Funding** F. Hoffmann-La Roche Ltd.

6 **Trial registration:** ClinicalTrials.gov, NCT02453256

1 **Introduction**

2 Systemic sclerosis (SSc) is a rare, severe disease,¹ and up to 60% of patients diagnosed with
3 SSc die of it.^{2,3} Pulmonary complications, such as interstitial lung disease (ILD), are the
4 primary causes of death,^{1,4,5} and decline in forced vital capacity (FVC) is associated with
5 increased mortality in patients with SSc-ILD.⁵ The multi-tyrosine kinase inhibitor nintedanib
6 slowed the decline of lung function in a study in patients with radiographically evident SSc-
7 ILD.⁶ However, treatment of SSc-ILD is limited to managing organ-specific complications.⁷

8 Circulating levels of interleukin-6 (IL-6) are elevated in patients with SSc⁸ and are associated
9 with the development of skin fibrosis and SSc-ILD.⁹⁻¹¹ Early studies suggested that inhibition
10 of IL-6 signalling via IL-6 receptor blockade with tocilizumab might reduce skin fibrosis in
11 patients with SSc.^{12,13} FaSScinate, a phase 2 randomised controlled trial, investigated the
12 efficacy and safety of tocilizumab in SSc.¹⁴ The primary endpoint was not met in faSScinate;
13 the least squares mean (LSM) change in modified Rodnan skin score (mRSS) from baseline
14 to week 24 was -3.92 with tocilizumab and -1.22 with placebo (difference -2.70; 95%
15 confidence interval [CI] -5.85 to 0.45; p=0.09).¹⁴ Mechanistic support for an antifibrotic
16 effect of tocilizumab in faSScinate came from analysis of explant dermal fibroblasts that
17 highlighted reversal of the activated fibrotic phenotype after 24 weeks of treatment.¹⁵ In a
18 prespecified exploratory analysis in faSScinate, significantly fewer participants treated with
19 tocilizumab than placebo experienced decline in lung function accompanied by reduction in
20 expression of profibrotic M-2 macrophage-associated genes, suggesting that tocilizumab
21 might be able to preserve lung function.¹⁴ These data, together with the high need for
22 effective treatments for SSc patients with severe skin and lung manifestations, supported
23 investigation of tocilizumab in a phase 3 trial. Therefore, the phase 3 randomised controlled
24 trial focuSSced was conducted to assess the effect of tocilizumab and placebo treatment on
25 change in mRSS, with impact on lung function as a key secondary objective.

1

2 **Participants and methods**

3 **Study design**

4 focuSSced was a multicentre, randomised, double-blind, placebo-controlled phase 3 trial
5 (ClinicalTrials.gov, NCT02453256) conducted at 75 sites in 20 countries across Europe,
6 North America, Latin America, and Japan. Eligible participants were randomly assigned 1:1
7 to receive subcutaneous injections of tocilizumab 162 mg or placebo weekly for a 48-week,
8 double-blind period, followed by a 48-week, open-label tocilizumab period. Interim futility
9 analysis conducted at week 24, for which the sponsor remained blinded, was conducted by an
10 independent data coordinating centre. Immunomodulatory therapy could be added to study
11 medication from week 16 for participants who experienced a decline in percent predicted
12 FVC (ppFVC) or from week 24 for those who experienced worsened skin thickening or other
13 significant SSc complications. A dual-assessor approach was used to prevent potential
14 unblinding owing to knowledge of laboratory results. The study was conducted in accordance
15 with the principles of the Declaration of Helsinki and Good Clinical Practice, and approval
16 was obtained from the investigators' independent ethics committees or institutional review
17 boards. All participants provided written informed consent to participate in the study.

18

19 **Randomisation and masking**

20 Participants were randomly assigned using an interactive voice-based or web-based
21 response system. Randomisation was centralised and stratified by serum IL-6 levels at
22 screening (<10 or ≥ 10 pg/mL) because lower IL-6 levels were associated with a more
23 favourable outcome in change from baseline in mRSS in an analysis of data from the phase 2

1 study of tocilizumab in SSc (faSScinate). Participants and study sponsor personnel were
2 blinded to study treatment.

3

4 **Participants**

5 Adults with diffuse cutaneous SSc, classified according to 2013 American College of
6 Rheumatology/European League Against Rheumatism criteria,¹⁶ of ≤ 60 months' duration
7 (from first non-Raynaud phenomenon manifestation) and mRSS 10–35 units at screening
8 were eligible. Participants had to have elevated acute-phase reactant levels (≥ 1 of the
9 following: CRP ≥ 6 mg/L, ESR ≥ 28 mm/h, or platelet count $\geq 330 \times 10^9$ /L) and active disease
10 defined as ≥ 1 of the following at screening: disease duration ≤ 18 months, mRSS increase ≥ 3
11 units, or involvement of one new body area and mRSS increase ≥ 2 units, or involvement of
12 two new body areas (each within the previous 6 months), and ≥ 1 tendon friction rub.
13 Additional eligibility criteria are shown in Supplementary Appendix 2.

14

15 **Outcomes**

16 The primary efficacy endpoint was the difference in change from baseline in mRSS at week
17 48.¹⁷ Key secondary efficacy endpoints were difference in distribution of change from
18 baseline to week 48 in ppFVC (assessed according to standardised methods and reviewed
19 centrally by readers masked to treatment, analysed by van Elteren test as the preplanned
20 FVC outcome), time to treatment failure (defined as time of death, time to decline in ppFVC
21 $> 10\%$, relative increase in mRSS $> 20\%$ and ≥ 5 mRSS points, or occurrence of a predefined
22 and adjudicated SSc-related serious complication [Supplementary Table S1]), and Health
23 Assessment Questionnaire–Disability Index (HAQ-DI). Other secondary endpoints were
24 patient global assessment, and physician global assessment. Exploratory endpoints included

1 proportions of participants with $\geq 10\%$ decline (worsening) in ppFVC and change from
2 baseline in high-resolution computed tomography (HRCT) of quantitative lung fibrosis—most
3 affected lobe (QLF-LM) at week 48 (an HRCT read was planned at baseline and week 48 for
4 all participants), the American College of Rheumatology provisional Composite Response
5 Index in Systemic Sclerosis (ACR-CRISS), and other patient-reported outcomes
6 (Supplementary Appendix 3). HRCT quantitative lung fibrosis—whole lung (QLF-WL) and
7 quantitative interstitial lung disease—whole lung (QILD-WL) were post hoc analyses.
8 Additional exploratory analyses were performed for the subset of participants who had ILD at
9 baseline on visual read of HRCT (hereafter referred to as SSc-ILD). ILD was identified
10 visually post hoc by a thoracic radiologist (J. G.) using a diagnostic algorithm for SSc as the
11 presence of ground-glass opacification and/or fibrosis with a basal predominance. Potential
12 causes other than SSc for the pattern of ground-glass opacification were excluded. Other post
13 hoc analyses are described in Supplementary Appendix 3. Safety was assessed as treatment-
14 emergent adverse events (AEs) according to MedDRA system organ classification and was
15 graded according to the National Cancer Institute Common Toxicity Criteria for Adverse
16 Events, version 4.0.

17

18 **Statistical analysis**

19 One hundred five participants per treatment group provided power in the range of $>75\%$ to
20 80% (depending on an estimated participant dropout rate of 20% to 15%) to detect a
21 between-group difference of 3.55 mRSS units (the treatment effect in the phase 2 faSScinate
22 trial) in change from baseline to week 48 (common standard deviation of 8.43 units using a
23 two-group t test and a 5% two-sided significance level). Efficacy was assessed in the
24 intention-to-treat population, which included all randomly assigned participants who received

1 ≥ 1 dose of study treatment according to their originally assigned treatment group. Safety was
2 assessed in the safety population, which included all participants who received ≥ 1 dose of
3 study treatment and had ≥ 1 postdose safety assessment. A statistical testing hierarchy was
4 conducted based on significance for the primary endpoint at the 5% level (Supplementary
5 Figure S1). Analysis of the primary endpoint was performed using mixed model for repeated
6 measures. An unstructured covariance matrix was used to model within-participant errors,
7 and the Kenward-Roger approximation was used to estimate the denominator degrees of
8 freedom. The model included fixed categorical effects for treatment, visit, IL-6 stratification
9 criteria, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well
10 as the continuous covariates of baseline mRSS and baseline mRSS-by-visit interaction; there
11 was no imputation for missing data. The study was not stratified by site because the large
12 number of sites with small participant numbers predicted at each site made this impractical;
13 site was therefore not included in the primary analysis. The LSM, differences in mean, 95%
14 CI, and p value were reported with the significance test based on a two-sided alpha of 0.05.
15 LSMs and differences in means for other endpoints, including FVC, used similar methods.
16 The Cochran-Mantel-Haenszel test adjusted for IL-6 stratification factors (<10 or ≥ 10 pg/mL)
17 was used for binary mRSS endpoints, and participants with missing mRSS assessments at
18 week 48 were considered nonresponders. Change from baseline in FVC and HRCT variables
19 was assessed primarily with the use of nonparametric analysis (van Elteren test; the 95% CI
20 for the between-arm difference in medians was derived using bootstrapping) assuming a non-
21 normal distribution stratified by screening IL-6 level. Time to treatment failure was
22 summarised descriptively by Kaplan–Meier curves, and treatment groups were compared
23 using a Cox proportional hazards model adjusted for IL-6 stratification. An analysis of log
24 cumulative hazard plotted against log survival time gave approximately parallel curves
25 accounting for treatment group and baseline IL-6 stratification, indicating that a proportional

1 hazards assumption was appropriate. For time to treatment failure, data were censored from
2 the time of discontinuation for participants who discontinued the study before week 48. No
3 analyses included censoring for participants who initiated immunomodulatory therapy or
4 discontinued study drug.

5

6 **Role of the funding source**

7 F. Hoffmann-La Roche Ltd. was involved in the design and conduct of the study; collection,
8 management, analysis, and interpretation of the data; writing and review of the manuscript;
9 and decision to submit the manuscript for publication. DK, CJFL, HS, and BW had access to
10 the raw data. The corresponding author had full access to all of the data and the final
11 responsibility to submit for publication.

12

13 **Results**

14 **Participants**

15 Among 343 participants screened, 212 were randomly assigned to receive weekly
16 subcutaneous placebo (n=107) or tocilizumab 162 mg (n=105). The first participant was
17 randomly assigned on November 20, 2015, and the last participant completed the week 48
18 assessment on January 15, 2018. Ninety-three participants (86.9%) in the placebo group and
19 95 participants (90.5%) in the tocilizumab group completed 48 weeks (Figure 1). The
20 intention-to-treat and safety populations comprised 106 participants in the placebo group and
21 104 participants in the tocilizumab group.

22 Baseline demographics and disease characteristics were similar between treatment groups for
23 the intention-to-treat population and for the subgroup of participants who had SSc-ILD at

1 baseline according to HRCT visual read (Table 1; Supplementary Tables S2 and S3). Most
2 participants were female (n=171/210; 81.4%), and the mean (SD) age was 48.2 (12.4) years.
3 Median disease duration was <2 years, and skin involvement was moderate to severe with a
4 mean (SD) baseline mRSS of 20.4 (7.0) in the placebo group and 20.3 (6.7) in the
5 tocilizumab group. Participants had normal to mild impairment in lung function at baseline
6 (mean [SD] ppFVC was 83.9 [15.0] in the placebo group and 80.3 [14.4] in the tocilizumab
7 group, and percent predicted diffusing capacity for carbon monoxide was 76.8 [18.6] and
8 74.4 [19.2], respectively), and 136/210 (64.8%) had evidence of SSc-ILD on HRCT.

9

10 By week 48, immunomodulating therapy was initiated by 22 participants (20.8%) in the
11 placebo group and nine participants (8.7%) in the tocilizumab group (Figure 1); most
12 participants started immunomodulating therapy after week 36.

13

14 **Efficacy**

15 The primary endpoint of change from baseline in mRSS at week 48 for tocilizumab versus
16 placebo was not met, though participants treated with tocilizumab had a numerically greater
17 reduction in skin sclerosis after 48 weeks; LSM change from baseline to week 48 in mRSS
18 was -4.41 in the placebo group and -6.14 in the tocilizumab group (adjusted difference in
19 LSM, -1.73 [95% CI -3.78 to 0.32]; p=0.10) (Table 2; Figure 2). Because the primary
20 analysis did not meet statistical significance at the 5% level, none of the secondary endpoints
21 were considered to have achieved statistical significance according to the hierarchy
22 (Supplementary Figure S1), and all p values for secondary, exploratory, and post hoc
23 analyses were nominal.

1 At week 48, the LSM change from baseline in ppFVC was -4.6 in the placebo group and $-$
2 0.4 in the tocilizumab group (difference, 4.2 [95% CI 2.0 to 6.4]; nominal $p=0.0002$) (Figure
3 3A; Table 3), and the absolute LSM change was -190 mL and -24 mL, respectively
4 (difference, 167 mL (95% CI 83 to 250); nominal $p=0.0001$). The difference in change from
5 baseline in ppFVC was confirmed in sensitivity analyses (Supplementary Table S4). Based
6 on prespecified exploratory analysis, the proportion of participants who experienced absolute
7 decline in FVC $\geq 10\%$ was 16.5% ($15/91$) in the placebo group and 5.4% ($5/93$) in the
8 tocilizumab group. There was a clinically meaningful¹⁸ shift in the distribution of change
9 from baseline in ppFVC at week 48 (key secondary endpoint) favouring tocilizumab (van
10 Elteren nominal $p=0.002$ vs placebo) (Figure 3B). Preplanned exploratory analysis of QLF-
11 LM and post hoc analysis of QLF-WL and QILD-WL showed numeric improvements in lung
12 fibrosis in participants treated with tocilizumab, supporting FVC results and consistent in
13 participants with SSc-ILD at baseline (Table 3; Supplementary Figure S2). Among
14 participants with SSc-ILD on visual read at baseline, the LSM change from baseline to week
15 48 in ppFVC was -6.40 in the placebo group and 0.07 in the tocilizumab group (difference,
16 6.47 [95% CI 3.43 to 9.50]; nominal $p<0.0001$), and the absolute LSM change was -255 mL
17 and -14 mL, respectively (difference: 241 mL [95% CI 124 to 358]; nominal $p<0.0001$)
18 (Figure 3C; Table 3). Among the participants with SSc-ILD on visual read at baseline and
19 available week 48 FVC data, the proportion who experienced absolute decline in FVC $\geq 10\%$
20 to week 48 was 25.0% ($14/56$) in the placebo group and 8.5% ($5/59$) in the tocilizumab group
21 (Figure 3D).

22 Kaplan–Meier analysis of time to treatment failure (key secondary endpoint) favoured
23 tocilizumab over placebo; hazard ratio adjusted for baseline IL-6 stratification factors was
24 0.63 (95% CI 0.37 to 1.06); nominal $p=0.08$ (Figure 4); unadjusted hazard ratio was 0.58

1 (95% CI 0.34 to 0.98). At week 48, numerically fewer participants in the tocilizumab group
2 than the placebo group experienced treatment failure in any of its components (Table 2).
3 There was no difference between placebo and tocilizumab for patient- or physician-reported
4 outcomes of HAQ-DI, patient global assessment, or physician global assessment (secondary
5 endpoints) or for Functional Assessment of Chronic Illness Therapy–Fatigue, Scleroderma
6 HAQ, or Saint George’s Respiratory Questionnaire (exploratory endpoints) at week 48 (Table
7 2).

8

9 **Safety**

10 Most participants experienced ≥ 1 AE during the study (Table 4; Supplementary Table S5).
11 Infections and infestations were the most frequently reported AEs for both groups (53/106
12 [50.0%] placebo, 54/104 [51.9%] tocilizumab). Thirty serious AEs (SAEs) were reported in
13 18/106 participants (17.0%) in the placebo group compared with 14 SAEs in 13/104
14 participants (12.5%) in the tocilizumab group; this difference was primarily driven by more
15 serious infections (placebo, 8 events in 7 participants; tocilizumab, 3 events in 2 participants)
16 and serious cardiac events (placebo, 7 events in 6 participants; tocilizumab, 2 events in 2
17 participants) in the placebo group. All serious infections were grade 3 in severity except for a
18 soft tissue infection reported in a placebo-treated participant, which was grade 4. Three
19 placebo-treated participants developed pneumonia and one developed a respiratory tract
20 infection; two of these participants had a history of ILD, two were former smokers, and two
21 were receiving prednisone. None of the serious infections reported in the placebo arm started
22 after initiation of escape therapy. Infected skin ulcers were reported in 12/106 participants
23 (11.3%) in the placebo group and 15/104 participants (14.4%) in the tocilizumab group; one
24 event in the placebo group was an SAE. No demyelinating AEs, SAEs or medically

1 significant hepatic AEs or bleeding events, gastrointestinal perforations, stroke, or
2 anaphylactic reactions were reported. Four participants died during the study: three in the
3 placebo group (chronic cardiac failure, myocarditis, myocardial infarction) and one in the
4 tocilizumab group (unknown cause); none of the events were considered related to study
5 treatment. Laboratory abnormalities are shown in Supplementary Table S6.

6

7 **Discussion**

8 The primary mRSS endpoint was not met in this phase 3 trial of tocilizumab in early, active
9 SSc. This suggests that there was no difference in change in skin thickness between
10 participants treated with tocilizumab and those treated with placebo after 48 weeks. However,
11 secondary FVC results suggest stabilization of lung function in participants who received
12 tocilizumab treatment; this replicates the effect observed in the phase 2 faSScinate trial¹⁴ and
13 the exploratory and post hoc HRCT results confirm the antifibrotic effect of tocilizumab¹⁵ in
14 radiologically evident lung fibrosis. In addition to previous studies of explant dermal
15 fibroblasts from the faSScinate clinical trial,¹⁵ a direct effect of IL-6 is supported by recent
16 reports of reduced myofibroblast activity after inhibition of STAT3, a putative link between
17 IL-6 and TGF β intracellular signalling.¹⁹⁻²¹ focuSSced is the first placebo-controlled phase 3
18 clinical trial to assess structural and functional pulmonary changes in early, active SSc. The
19 effect of tocilizumab on disease progression was supported by numerical improvement in
20 time to treatment failure and the fact that 21% of participants in the placebo group received
21 immunomodulating rescue therapy compared with 9% in the tocilizumab group. Safety was
22 consistent with the safety profile of tocilizumab and complications of SSc, and no new safety
23 concerns emerged.

1 ILD is one of the leading causes of death in patients with early, diffuse SSc. Current clinical
2 practice, supported by treatment recommendations,^{7,22} is to treat patients with SSc-ILD after
3 clinically significant disease, defined by symptoms and evidence of restrictive lung disease,
4 has developed. This practice is based on the fact that most patients with early SSc will not
5 develop clinically meaningful progressive disease and on a limited understanding of risk
6 factors for progression of ILD.

7 Putative predictive factors for progression include diffuse cutaneous phenotype, anti-Scl-70
8 (anti-topoisomerase I) positivity, elevated acute-phase reactants, and ethnicity.²³ The
9 focuSSced eligibility criteria enriched the study population for participants with these factors,
10 and indeed 65% had evidence of ILD on baseline HRCT. The clinically meaningful¹⁸ shift in
11 distribution of change from baseline in ppFVC favouring tocilizumab over placebo and the
12 observation that fewer tocilizumab-treated than placebo-treated participants experienced a
13 decline $\geq 10\%$ in ppFVC suggest that tocilizumab can preserve lung function. This trial
14 confirms the data from faSScinate; additionally, in the focuSSced trial, FVC benefit was
15 supported by quantitative HRCT analysis showing stabilisation of ILD; post hoc HRCT
16 results for the subset of participants with SSc-ILD also supported FVC results.

17 In the trials of tocilizumab in early SSc, the difference between tocilizumab and placebo was
18 120 mL in the phase 2 faSScinate trial¹⁴ and 167 mL overall and 238 mL among participants
19 with baseline SSc-ILD in the phase 3 focuSSced trial. focuSSced participants were selected
20 for worsening skin disease and increased acute-phase reactants; therefore, most had early,
21 mild ILD, which might explain the lack of statistical differences we observed in patient-
22 reported outcomes because participants might not have had overt respiratory symptoms. The
23 mean change in QLF-LM was 1.4% with tocilizumab treatment in our study and -2.6% with
24 cyclophosphamide treatment in the scleroderma lung study (SLS-1),²⁴ possibly because
25 focuSSced participants had early, mild lung involvement whereas SLS-1 participants had to

1 have definitive evidence of lung disease based on HRCT or bronchoalveolar lavage and were
2 therefore likely to have had more severe ILD.

3 Our findings relate to recently reported results from the Safety and Efficacy of Nintedanib in
4 Systemic Sclerosis (SENSCIS) trial in which nintedanib slowed the progression of
5 established lung fibrosis in a large cohort of participants with SSc-ILD.⁶ The SENSCIS trial
6 reported a difference of 46.4 mL in absolute FVC decline over 1 year in favour of nintedanib
7 (-54.6 mL) versus placebo (-101.0 mL), with a 1.2% difference in mean change in ppFVC.
8 Results from SENSCIS provide context for our findings but cannot be directly compared
9 because of substantial differences between the study designs and populations of the trials.
10 focuSSced recruited a population with earlier stage SSc, and all participants had diffuse,
11 inflammatory, progressive skin involvement and were therefore at high risk for ILD, whereas
12 SENSCIS recruited a population with established, clinically relevant ILD, including
13 participants in the limited and diffuse SSc subsets. Indeed, the SENSCIS cohort had mean
14 baseline ppFVC of approximately 72% and lung fibrosis on HRCT of 35% to 37%, whereas
15 the focuSSced cohort had mean baseline ppFVC of 82% and lung fibrosis on HRCT of 2% to
16 17%.

17 A higher rate of progression, assessed by absolute decline in FVC, was observed in the
18 focuSSced cohort, who had early, active diffuse SSc enriched for skin activity, which is
19 consistent with an association between progressive skin fibrosis and FVC decline.²⁵ The
20 difference in mean change in ppFVC between tocilizumab and placebo was 4.2% overall and
21 6.4% in the ILD subgroup in focuSSced. In the SLS-1 trial, there was a 2.5% difference in
22 ppFVC between cyclophosphamide and placebo,²⁶ and in SENSCIS, there was a 1.2%
23 difference in ppFVC between nintedanib and placebo. These differences might reflect the
24 earlier disease of focuSSced participants. The absolute FVC decline observed with placebo
25 treatment in focuSSced is comparable to the rate of decline observed in idiopathic pulmonary

1 fibrosis.^{27,28} Our results might indicate that IL-6 is a more important driver of lung fibrosis
2 progression in early SSc, but this requires further investigation.

3 The focuSSced trial did not meet its primary endpoint: change in skin sclerosis measured by
4 mRSS. Skin thickness was chosen as the primary endpoint because it is universally present in
5 SSc and can have a profound impact on function and quality of life²⁹ and because mRSS is a
6 feasible, reliable, and valid outcome measure (including for sensitivity to change).³⁰ The
7 difference in change in mRSS results between the phase 2 faSScinate trial and the phase 3
8 focuSSced trial might reflect differences in inclusion criteria and a possible effect of
9 unknown genetic differences and molecular heterogeneity on mRSS. Several recently
10 completed placebo-controlled trials have highlighted the limitation of mRSS as a primary
11 outcome given the variable natural history of SSc and a tendency for improvement in placebo
12 treatment arms,^{31,32} which was also observed in focuSSced. It is likely that other endpoints,
13 such as the composite ACR-CRISS responder index,³³ will emerge as more robust and
14 reliable for testing disease-modifying therapies in SSc. Our ACR-CRISS data highlight the
15 importance of global assessment in a multisystem heterogeneous disease such as systemic
16 sclerosis. At present, our findings, together with those from the SENSICIS and faSScinate
17 trials, support the use of FVC as a robust endpoint to demonstrate a treatment effect in SSc-
18 ILD and show that this is not associated with a significant difference in mRSS.

19

20 The design of the focuSSced trial offers strengths and limitations. This phase 3 trial was
21 powered to determine the difference in mRSS as the primary endpoint assuming a dropout
22 rate of 15% and a between-group difference of 3.55 mRSS units based on the effect observed
23 in the phase 2 faSScinate study. Clinical significance and statistical significance were
24 considered in powering the focuSSced study to avoid statistical significance associated with a

1 negligible treatment effect. A difference of 1.7 mRSS units between tocilizumab and placebo
2 (primary endpoint) was observed, possibly reflecting the heterogeneity of SSc and a strong
3 placebo effect. This difference was not statistically significant; therefore, any differences in
4 secondary endpoints, including FVC, could not be considered statistically significant despite
5 the strength of the evidence. Missing data from dropouts or missed assessments were
6 accounted for in the analyses according to the methods described for handling of missing
7 data. Sensitivity analyses for FVC showed that the FVC results were robust to different
8 assumptions regarding the missing data. Patients in focuSSced and faSScinate had early
9 disease and mild lung involvement, which limited comparison to other trials, but provided
10 novel results in this patient population that support further investigation. Examining FVC and
11 composite endpoints, such as ACR-CRISS as primary endpoints is an important consideration
12 for future trials. A limitation of the lung findings is that DLCO was measured using the
13 investigators' own equipment, which limits the comparability and reliability of the DLCO
14 data.

15 The results for FVC and other secondary outcome measures should be interpreted with
16 caution because the primary outcome was not statistically significant. However, the effect on
17 FVC supported by two randomised controlled trials shows a clinically meaningful impact on
18 preservation of lung function. In conclusion, the skin primary endpoint was negative in this
19 phase 3 trial, but results suggest that tocilizumab preserves lung function in early diffuse
20 cutaneous SSc.

21

1 **Contributors**

2 Dr Khanna had full access to all data in the study and takes responsibility for the integrity of
3 the data and the accuracy of the data analysis.

4 *Concept and design:* DK, CPD, AJ, CJFL, HS, JS, DEF

5 *Acquisition, analysis, or interpretation of data:* All authors

6 *First draft of manuscript:* DK, CPD, AJ, CJFL, HS

7 *Critical revision of the manuscript for important intellectual content:* All authors

8 *Statistical analysis:* HS

9 *Approval of final version for submission:* All authors

10

11 **Declaration of interests**

12 D. Khanna has ownership interest in Eicos Sciences; has received grants from the National
13 Institutes of Health (NIAID and NIAMS); has received consulting fees from Actelion,
14 AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, ChemomAb, Corbus, CSL
15 Behring, Cytori, GlaxoSmithKline, Horizon, Pfizer, Regeneron, Roche/Genentech, Sanofi
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17 C. J. F. Lin owns stock in and is an employee of Genentech (a member of the Roche group).

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23 H. Spotswood owns stock in and is an employee of Roche Products Limited.

1 B. Wagner is an employee of and owns stock/stock options in Genentech.
2 J. Siegel is a former employee of Roche and a current employee of Gilead Sciences and owns
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4 A. Jahreis is an employee of and owns stock in Roche/Genentech and her institution has a
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21

22 **Data Sharing Statement**

1 Qualified researchers may request access to data through the clinical study data request
2 platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible
3 studies are available here ([https://clinicalstudydatarequest.com/Study-Sponsors/Study-](https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx)
4 [Sponsors-Roche.aspx](https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx)). For further details on Roche's Global Policy on the Sharing of
5 Clinical Information and how to request access to related clinical study documents, see here
6 ([https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_tri](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)
7 [als/our_commitment_to_data_sharing.htm](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)).

8

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1 **FIGURE LEGENDS**

2 ***Figure 1: Screening, randomisation, and follow-up***

3 The most frequent immunomodulating treatment received was mycophenolate mofetil (13
4 participants [12.3%] in the placebo group; five participants [4.4%] in the TCZ group)
5 followed by methotrexate (four participants [3.8%] in the placebo group; three participants
6 [2.9%] in the TCZ group). Only deaths reported as the reason for withdrawal are shown; two
7 additional participants in the placebo arm withdrew for other reasons (one not stated and one
8 because of an adverse event) before they died. QW, weekly; SC, subcutaneous; TCZ,
9 tocilizumab.

10

11 ***Figure 2: Mean change from baseline in mRSS (ITT population)***

12 Mixed-model repeated measures analysis was implemented that included the fixed
13 categorical effects of treatment, visit, IL-6 stratification (<10 or ≥ 10 pg/mL at screening), IL-
14 6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the
15 continuous covariates of baseline score and baseline score-by-visit interaction. BL, baseline;
16 IL-6, interleukin-6; ITT, intention-to-treat; LSM, least squares mean; mRSS, modified
17 Rodnan skin score; PBO, placebo; TCZ, tocilizumab.

18

19 ***Figure 3: Cumulative distribution (A, B) and mean change from baseline (C, D) for***
20 ***ppFVC at week 48***

21 Data are shown (A, C) for all participants and (B, D) for participants with SSc-ILD at
22 baseline (subset of participants who had ILD on visual read of HRCT by a thoracic
23 radiologist). A mixed model repeated measures analysis was implemented that included the
24 fixed categorical effects of treatment, visit, IL-6 stratification (<10 or ≥ 10 pg/mL at
25 screening), IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as

1 well as the continuous covariates of baseline score and baseline score-by-visit interaction.
2 Change from baseline was assessed using nonparametric analysis assuming a normal
3 distribution. HRCT, high-resolution computed tomography; IL, interleukin; ILD, interstitial
4 lung disease; PBO, placebo; ppFVC, percent predicted forced vital capacity; SSc, systemic
5 sclerosis; TCZ, tocilizumab.

6

7 **Figure 4: Kaplan-Meier analysis of time-to-treatment failure (ITT population).**

8 Treatment groups were compared using a Cox proportional hazards model adjusted for
9 baseline IL-6 stratification factors (<10 pg/mL; ≥ 10 pg/mL). Data were censored from the
10 time of discontinuation for participants who discontinued before week 48 but not for
11 participants who initiated immunomodulatory therapy. HR, hazard ratio; IL-6, interleukin-6;
12 ITT, intention-to-treat; PBO, placebo; TCZ, tocilizumab.

13

14

1 **Table 1: Baseline demographics and disease characteristics (intention-to-treat**
 2 **population)**

Characteristic	Placebo SC QW N=106	Tocilizumab 162 mg SC QW N=104
Female, n (%)	90 (84.9)	81 (77.9)
Age, years, mean (SD)	49.3 (12.6)	47.0 (12.2)
Former or current smoker, n (%)	40 (37.7)	32 (30.8)
Race, n (%)		
American Indian or Alaskan native	3 (2.8)	1 (1.0)
Asian	9 (8.5)	16 (15.4)
Black or African American	3 (2.8)	2 (1.9)
White	90 (84.9)	85 (81.7)
Other	1 (0.9)	0
Duration of SSc, months		
Mean (SD)	23.1 (17.0)	22.2 (16.0)
Median (IQR)	17.9 (9.4 to 33.2)	17.2 (9.0 to 34.9)
mRSS		
Mean (SD)	20.4 (7.0)	20.3 (6.7)
Median (IQR)	19.0 (15.0 to 26.0)	19.0 (15.0 to 24.5)
ppFVC ^a		
Mean (SD)	83.9 (15.0)	80.3 (14.4)
Median (IQR)	85.9 (72.4 to 95.9)	80.0 (69.3 to 90.2)
ppDLCO, ^a Hb corrected		

Mean (SD)	76.8 (18.6)	74.4 (19.2)
Median (IQR)	75.6 (65.7 to 85.8)	71.5 (59.1 to 89.3)
	n=105	n=104
Baseline SSc-ILD, n (%) ^b	68 (65)	68 (67)
	n=104	n=102
Baseline QLF-LM		
Mean [95% CI] ^c	4.2 [2.4 to 6.0]	5.4 [3.0 to 7.8]
Median (IQR)	2.1 (1.0 to 4.4)	1.8 (0.7 to 4.9)
	n=84	n=73
Baseline QLF-WL		
Mean [95% CI] ^c	1.8 [1.2 to 2.4]	2.7 [1.8 to 3.5]
Median (IQR)	1.1 (0.5 to 2.1)	1.2 (0.5 to 3.0)
	n=102	n=100
Baseline QILD-WL		
Mean [95% CI] ^c	14.1 [12.0 to 16.1]	16.9 [14.1 to 19.6]
Median (IQR)	12.3 (7.5 to 20.2)	14.2 (7.0 to 24.4)
	n=102	n=100
HAQ-DI		
Mean (SD)	1.3 (0.7)	1.1 (0.8)
Median (IQR)	1.3 (0.9 to 1.8)	1.1 (0.4 to 1.8)
	n=104	n=104
IL-6 at screening, pg/mL		

<10, n (%)	77 (72.6)	77 (74.0)
≥10, n (%)	29 (27.4)	27 (26.0)
CRP, mg/mL		
Mean (SD)	7.0 (11.1)	8.9 (14.8)
Median (IQR)	3.8 (1.1 to 8.7)	4.0 (1.3 to 9.1)
ESR, mm/h		
Mean (SD)	34.7 (18.5)	34.8 (16.3)
Median (IQR)	33.0 (23.0 to 43.0)	33.5 (26.0 to 42.0)
	n=103	n=100
Platelet count, ×10 ⁹ /L		
Mean (SD)	298.7 (96.0)	311.1 (88.2)
Median (IQR)	286.5 (231.0 to 358.0)	306.0 (243.0 to 361.0)
Antinuclear antibody positive, n (%)	90 (91.8)	91 (92.9)
	n=98	n=98
Anti-centromere antibody positive, n (%)	9 (9.0)	8 (8.0)
	n=100	n=100
Anti-RNA polymerase III antibody positive, n (%)	16 (16.0)	19 (19.0)
	n=100	n=100
Anti-topoisomerase I antibody positive, n (%)	49 (49.0)	52 (52.0)
	n=100	n=100

- 1 CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI; Health Assessment
- 2 Questionnaire–Disability Index; HRCT, high-resolution computed tomography; ILD,
- 3 interstitial lung disease; IL-6, interleukin-6; IQR, interquartile range; mRSS, modified

1 Rodnan skin score; ppDLCO, percent predicted diffusing capacity for carbon monoxide;
2 ppFVC, percent predicted forced vital capacity; QILD-WL, quantitative interstitial lung
3 disease–whole lung; QLF-LM, quantitative lung fibrosis–most affected lobe; QLF-WL,
4 quantitative lung fibrosis–whole lung; QW, every week; SC, subcutaneously; VAS, visual
5 analog scale.

6 ^aFVC was measured using a centralized spirometry system provided to all sites and DLCO
7 was measured using each site’s equipment.

8 ^bSubset of participants who had ILD on visual read of HRCT by a thoracic radiologist.

9 ^cParticipants who had available baseline and week 48 data.

10 The number of participants with evaluable data for each characteristic is 106 for placebo and
11 104 for tocilizumab unless shown otherwise.

1 **Table 2: Efficacy endpoints (intention-to-treat population)**

	Placebo SC QW N=106	Tocilizumab 162 mg SC QW N=104	Difference between treatment groups^a
mRSS			
Primary endpoint, LSM change in mRSS from baseline to week 48 [95% CI]	-4.4 [-6.0 to -2.9]	-6.1 [-7.7 to -4.6]	-1.7 [-3.8 to 0.3] p=0.10 ^b
LSM change in mRSS from baseline to week 24, LSM [95% CI]	-3.1 [-4.3 to -1.8]	-3.7 [-5.0 to -2.4]	-0.6 [-2.3 to 1.0] Nominal p=0.455
Improvement in mRSS from baseline \geq 20%, n (%) [95% CI]	53 (50.0) [40.0 to 60.0]	75 (72.1) [63.0 to 81.2]	21.9 [9.2 to 34.6] Nominal p=0.0007 ^c
Improvement in mRSS from baseline \geq 40%, n (%) [95% CI]	40 (37.7) [28.0 to 47.4]	44 (42.3) [32.3 to 52.3]	4.3 [-8.7 to 17.3] Nominal p=0.51 ^c
Improvement in mRSS from baseline \geq 60%, n (%) [95% CI]	24 (22.6) [14.2 to 31.1]	18 (17.3) [9.6 to 25.1]	-5.4 [-16.2 to 5.4] Nominal p=0.33 ^c
Treatment failure			

Treatment failure, n (%)	37 (34.9)	23 (22.1)	HR [95% CI],
Median TTF, weeks [95% CI]	NE [48.7, NE]	NE [NE]	0.6 [0.4 to 1.1] Nominal p=0.08 ^d
Components of treatment failure			
ppFVC >10% decrease, n (%)	25 (23.6)	13 (12.5)	HR, 0.55 [0.3 to 1.1]
Median TTF, weeks [95% CI]	NE [NE]	NE [NE]	Nominal p=0.08 ^d
mRSS increase >20% and ≥5 points, n (%)	16 (15.1)	10 (9.6)	HR, 0.64 [0.3 to 1.4]
Median TTF, weeks [95% CI]	NE [NE]	NE [NE]	Nominal p=0.26 ^d
SSc-related complication, n (%)	7 (6.6)	5 (4.8)	HR, 0.79 [0.3 to 2.5]
Median TTF, weeks [95% CI]	NE [NE]	NE [NE]	Nominal p=0.68 ^d
Death, n (%)	3 (2.8)	1 (1.0)	HR, 0.37 [0.0 to 3.6]
Median TTF, weeks [95% CI]	NE [NE]	NE [NE]	Nominal p=0.39 ^d
Treatment failure excluding decline in ppFVC, n (%)	20 (18.9)	13 (12.5)	HR, 0.67 [0.3 to 1.4]
Median TTF, weeks [95% CI] ^e	NE [NE]	NE [NE]	Nominal p=0.26 ^d

Treatment failure excluding increase in mRSS, n (%)	29 (27.4)	17 (16.3)	HR, 0.62 [0.3 to 1.1] Nominal p=0.12 ^d
Median TTF, weeks [95% CI] ^e	NE [NE]	NE [NE]	
Patient- and physician-reported outcomes, LSM change from baseline to week 48			
HAQ-DI [95% CI]	-0.06 [-0.16 to 0.05] n=102	-0.11 [-0.22 to -0.01] n=103	-0.05 [-0.19 to 0.09] Nominal p=0.45 ^b
Patient global assessment VAS [95% CI]	-7.7 [-12.3 to - 3.0] n=102	-10.1 [-14.8 to -5.4] n=102	-2.4 [-8.6 to 3.70] Nominal p=0.43 ^b
Physician global assessment VAS [95% CI]	-20.0 [-24.8 to - 15.22] n=96	-22.5 [-27.3 to -17.6] n=98	-2.5 [-8.7 to 3.8] Nominal p=0.44 ^b
FACIT-Fatigue [95% CI]	2.6 n=102	5.1 n=103	2.40 [0.08 to 4.73] Nominal p=0.04 ^b
SHAQ VAS [95% CI]	-0.3 [-0.5 to -0.1]	-0.3 [-0.5 to -0.2]	NA
SGRQ [95% CI]	-2.1 [-6.0 to 1.7]	-3.2 [-5.9 to -0.4]	NA

ACR-CRISS			
Median (IQR)	0.3 (0.0 to 1.0) n=82	0.9 (0.1 to 1.0) n=84	Nominal p=0.02 ^f
Predicted probability of improvement from baseline ≥ 0.6 , n (%) [95% CI] ^g	39 (36.8) [27.1 to 46.4]	53 (51.0) [40.9 to 61.1]	13.9% [1.0 to 26.8] Nominal p=0.04 ^h

1 ACR-CRISS, American College of Rheumatology–Combined Response Index in Systemic
2 Sclerosis; HR, hazard ratio; mRSS, modified Rodnan skin score; NA, not assessed; NE, not
3 estimable; QW, every week; SC, subcutaneously; SHAQ, Scleroderma Health Assessment
4 Questionnaire; SRGQ, St George’s Respiratory Questionnaire; TTF, time to treatment failure;
5 VAS, visual analogue scale.

6 ^aAll p values are nominal because the primary endpoint analysis was not significant.

7 ^bBased on difference in means using mixed-model repeated measures analysis including the
8 fixed categorical effects of treatment, visit, IL-6 at screening stratification, IL-6 at screening-
9 by-visit interaction, and treatment-by-visit interaction and the continuous covariates of
10 baseline score and baseline score-by-visit interaction.

11 ^cWald with continuity correction for 95% CI. Weighted difference in proportions with 95%
12 CI using the Cochran-Mantel-Haenszel test adjusted for the stratification factor (IL-6 <10 or
13 ≥ 10 pg/mL at screening). Participants with missing week 48 assessment were considered
14 nonresponders for p value.

15 ^dCox proportional hazards model adjusted for the stratification factor (IL-6 <10 or ≥ 10
16 pg/mL) at screening. Comparison of the two treatment groups with a non-parametric test of
17 survival time gave consistent results (Wilcoxon p=0.045).

- 1 ^ePost hoc analysis.
- 2 ^fVan Elteren test stratified by IL-6 level at screening (<10 or ≥10 pg/mL).
- 3 ^gWald with continuity correction.
- 4 ^hCochran-Mantel-Haenszel test stratified by IL-6 level at screening (<10 or ≥10 pg/mL).
- 5 All endpoints are shown at week 48 unless stated otherwise.

1 **Table 3: Lung function efficacy endpoints**

	Intention-to-treat population			Participants with SSc-ILD^a		
	Placebo SC QW N=106	Tocilizumab 162 mg SC QW N=104	Difference between treatment groups^b	Placebo SC QW N=68	Tocilizumab 162 mg SC QW N=68	Difference between treatment groups^b
ppFVC change from baseline, median [95% CI]	n=91 -3.9 [-4.8 to -1.6]	n=93 -0.6 [-2.4 to 0.9]	3.3 [0.9 to 4.8] Nominal p=0.002	n=56 -4.0 [-5.3 to -1.7]	n=59 -0.6 [-3.2 to 2.0]	3.4 [0.4 to 5.6] Nominal p=0.002
ppFVC change from baseline, LSM [95% CI]	n=104 -4.6	n=104 -0.4	4.2 [2.0 to 6.4] Nominal p=0.0002 ^c	n=66 -6.4	n=68 -0.1	6.5 [3.4 to 9.5] Nominal p<0.0001 ^c

ppFVC \geq 10% decline, n/N (%)	15/91 (16.5)	5/93 (5.4)	NA ^d	14/56 (25.0)	5/59 (8.5)	NA ^d
Improvement in ppFVC (increase \geq 0%), n/N (%)	26/91 (28.6)	43/93 (46.2)	NA ^d	13/56 (23.2)	27/59 (45.8)	NA ^d
Absolute change from baseline in FVC, mL, LSM [95% CI]						
Week 24	n=104 -101	n=104 -13	88 [24 to 152] Nominal p=0.008 ^c	n=66 -133	n=68 -15	118 [31 to 205] Nominal p=0.008 ^c
Week 48	n=104 -190	n=104 -24	167 [83 to 250] Nominal p=0.0001 ^c	n=66 -255	n=68 -14	241 [124 to 358] Nominal p<0.0001 ^c
Observed ppDLCO	-2.1 [-4.4 to -0.4]	-2.4 [-4.1 to 1.0]	NA ^d	NA	NA	NA

Change from baseline, median [95% CI]						
Participants with $\geq 15\%$ decline in ppDLCO, n/N (%)	8/82 (9.8)	7/79 (8.9)		NA	NA	NA
Change from baseline in observed HRCT QLF-LM ^e	n=66	n=60		n=36	n=35	
Median [95% CI]	0.3 [0.0 to 0.8]	0.0 [-0.3 to 0.2]	-0.3 [-0.6 to 0.0] Nominal p=0.02 ^f	1.4 [0.3 to 2.1]	-0.2 [-2.2 to 0.2]	-1.6 [-3.3 to -0.4] Nominal p=0.002 ^f
Mean [95% CI]	0.9 [0.1 to 1.7]	-1.4 [-2.8 to 0.0]		1.9 [0.6 to 3.2]	-2.2 [-4.5 to 0.2]	

Change from baseline in observed HRCT QLF-WL ^{e,g}	n=81	n=84		n=48	n=54	
Median	0.1	0.0	-0.1	0.4	-0.2	-0.6
[95% CI]	[0.0 to 0.3]	[-0.2 to 0.1]	(95% CI: -0.3 to -0.05)	[0.1 to 0.9]	[-0.8 to 0.0]	(-1.2 to -0.3)
Mean [95% CI]	0.4 [0.0 to 0.7]	-0.4 [-0.9 to 0.1]	Nominal p=0.005 ^f	0.7 [0.3 to 1.2]	-0.6 [-1.4 to 0.2]	Nominal p=0.0008 ^f
Change from baseline in observed HRCT QILD-WL ^{e,g}	n=80	n=84		n=47	n=54	
Median [95% CI]	0.4 [-1.0 to 2.0]	-0.9 [-2.0 to -0.2]	-1.3 [-2.8 to -0.3]	1.6 [-1.1 to 2.8]	-1.7 [-2.3 to -0.7]	-3.3 [-4.3 to -0.7]

Mean [95% CI]	0.1 [-1.4 to 1.6]	-1.7 [-3.0 to - 0.4]	Nominal p=0.04 ^f	1.5 [-0.3 to 3.4]	-2.1 [-4.0 to - 0.2]	Nominal p=0.008 ^f
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1 HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NA, not assessed; ppDLCO, percent predicted diffusing capacity
2 for carbon monoxide; ppFVC, percent predicted forced vital capacity; QILD-WL, quantitative interstitial lung disease–whole lung; QLF-LM,
3 quantitative lung fibrosis–most affected lobe; QLF-WL, quantitative lung fibrosis–whole lung; QW, every week; SC, subcutaneously.

4 ^aSubset of participants who had ILD on visual read of HRCT by a thoracic radiologist.

5 ^bAll p values are nominal because the result of the primary endpoint analysis was not significant.

6 ^cBased on difference in means using mixed-model repeated measures analysis including the fixed categorical effects of treatment, visit, IL-6 at
7 screening stratification, IL-6 at screening-by-visit interaction, and treatment-by-visit interaction and the continuous covariates of baseline score
8 and baseline score-by-visit interaction. Exploratory analysis of FVC with a mixed-model repeated measures analysis including a treatment
9 baseline IL-6 interaction gave a similar treatment effect in both IL-6 stratification subgroups: IL-6 <10 pg/mL, treatment difference 160 mL
10 (95% CI 60 to 260); IL-6 ≥10 pg/mL, treatment difference 180 mL (95% CI 10 to 340). Therefore, an interaction term with treatment was not
11 fitted for the mixed-model repeated measures analysis of FVC.

12 ^dExploratory endpoint; no statistical comparison.

13 ^eNegative change indicates improvement.

- 1 ^fBased on van Elteren test of the medians adjusted for the stratification factor (IL-6 <10 or ≥10 pg/mL) at screening.
- 2 ^gPost hoc analysis.
- 3 FVC was measured using a centralised spirometry system provided to all sites, and DLCO was measured using each site's equipment. All
- 4 endpoints are shown at week 48 unless stated otherwise.

1 **Table 4: Safety (safety population)**

	Placebo SC QW N=106	Tocilizumab 162 mg SC QW N=104
Participants with ≥ 1 AE	82 (77.4)	89 (85.6)
Participants with ≥ 1 infectious AE	53 (50.0)	54 (51.9)
Participants with injection site reactions	3 (2.8)	8 (7.7)
Participants with ≥ 1 SAE	18 (17.0)	13 (12.5)
Participants with ≥ 1 infectious SAE	7 (6.6)	2 (1.9)
Participants with ≥ 1 noninfectious SAE	11 (10.4)	11 (10.6)
Withdrawal because of an AE	4 (3.8)	3 (2.9)
Deaths	3 (2.8)	1 (1.0)
Most frequent ($\geq 5\%$ of participants in either treatment arm) SAEs by SOC		
Infections and infestations, no. of events	8	3
Pneumonia	3 (2.8)	0
Infected skin ulcer	1 (0.9)	0
Osteomyelitis	0	1 (1.0)
Pelvic inflammatory disease	0	1 (1.0)
Chronic pyelonephritis	1 (0.9)	0
Respiratory tract infection	1 (0.9)	0
Sepsis	1 (0.9)	0
Soft tissue infection	1 (0.9)	0
Wound infection	0	1 (1.0)
Cardiac disorders, no. of events	7	2

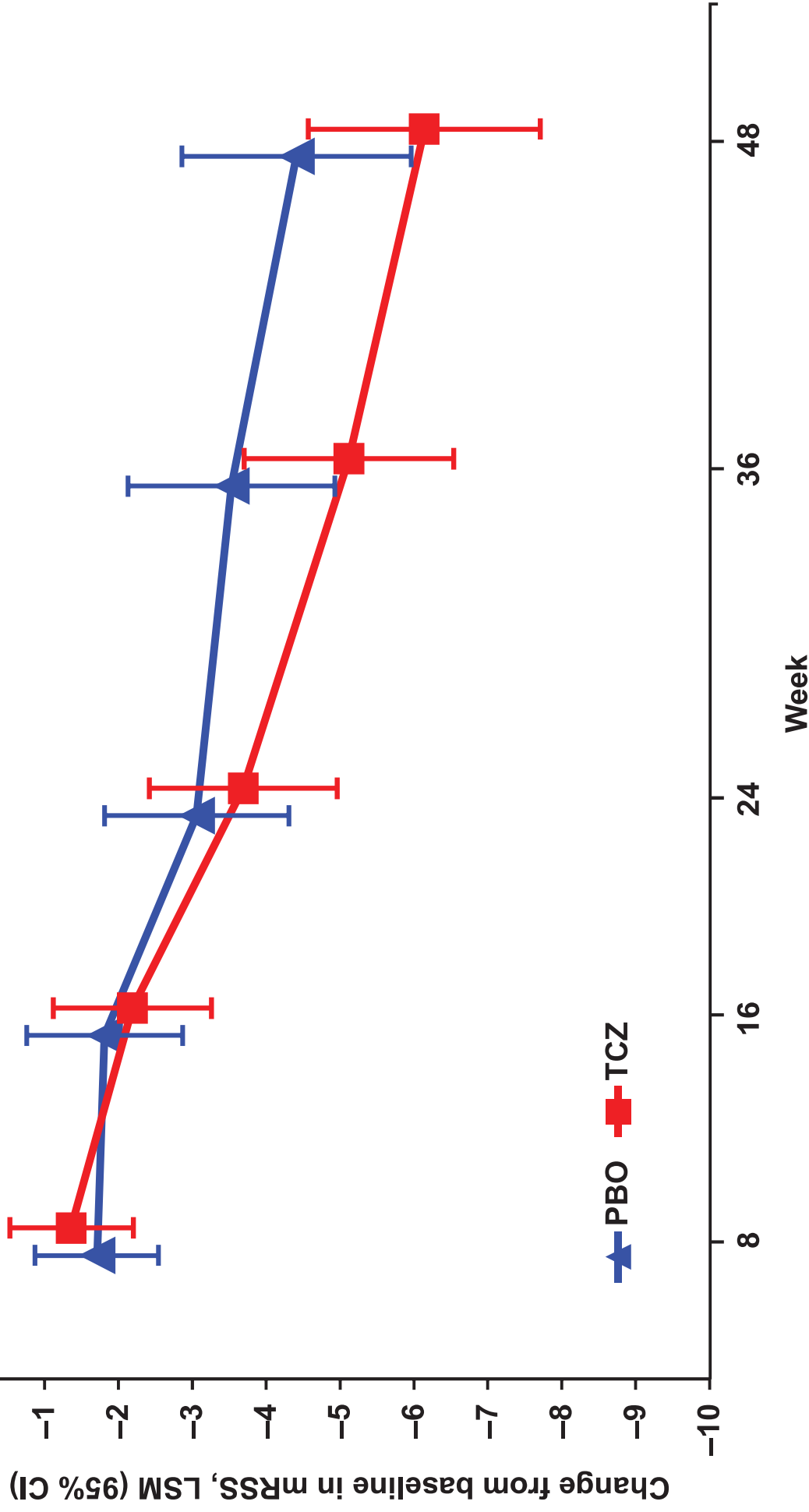
Acute myocardial infarction	1 (0.9)	0
Angina pectoris	0	1 (1.0)
Atrial fibrillation	1 (0.9)	0
Cardiac failure	0	1 (1.0)
Chronic cardiac failure	1 (0.9)	0
Microvascular coronary artery disease	1 (0.9)	0
Myocardial infarction	1 (0.9)	0
Myocarditis	1 (0.9)	0

- 1 AE, adverse event; QW, every week; SAE, serious adverse event; SC, subcutaneously; SOC,
- 2 system organ class.
- 3 Data are number of participants with event (%) unless stated otherwise.

4

5

Figure 2



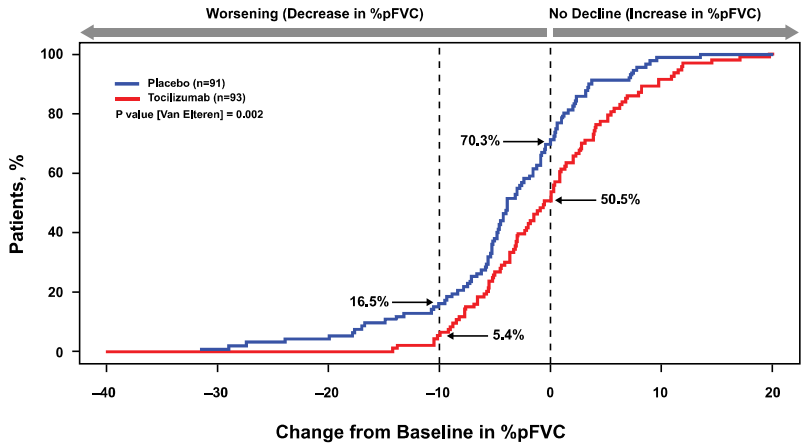
Difference (95% CI); p value

LSM change from BL at week 48 (primary outcome) PBO n=106 TCZ n=104 -1.7 (-3.8 to 0.3); p=0.10

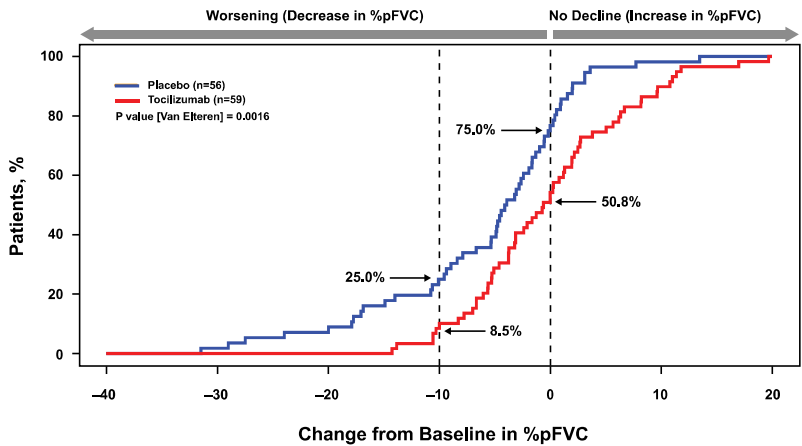
LSM change from BL at week 24 (exploratory outcome) PBO n=106 TCZ n=104 -0.6 (-2.3 to 1.0); nominal p=0.45

Figure 3A-D

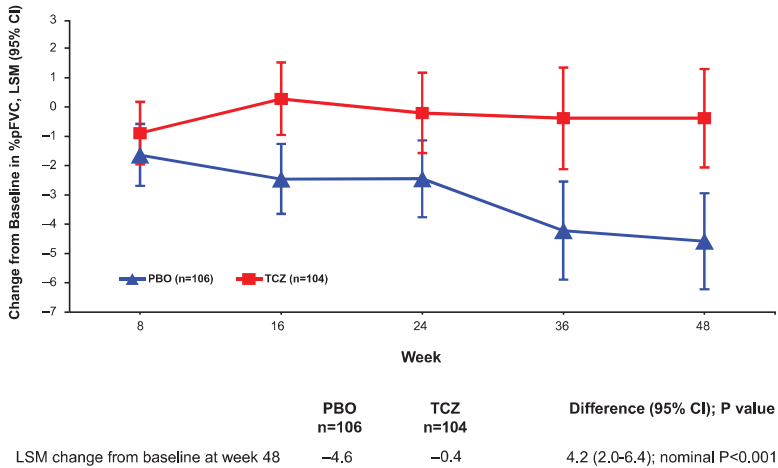
A



B



C



D

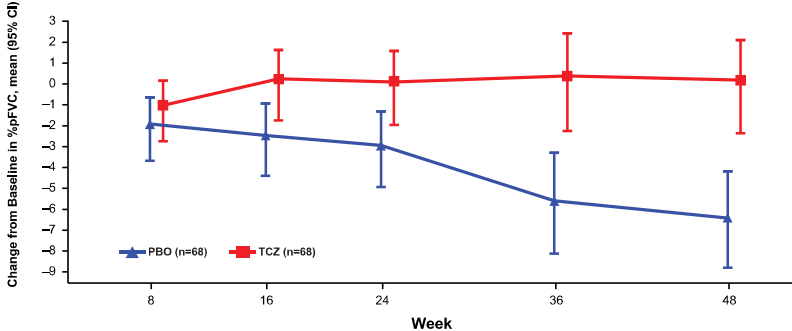


Figure 4

