

## **Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis: week 48 results from the randomised controlled faSScinate trial**

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**Summary** (309 words; maximum, 250)

**Background** Systemic sclerosis (SSc) is a rare disabling autoimmune disease with few treatment options. The efficacy and safety of the interleukin-6 receptor- $\alpha$  inhibitor tocilizumab were assessed in the faSScinate phase 2 trial in patients with SSc.

**Methods** This global, double-blind, placebo-controlled study enrolled adult patients with progressive SSc of  $\leq 5$  years' duration from first non-Raynaud sign or symptom. Patients were randomly assigned (1:1) to weekly subcutaneous tocilizumab 162 mg or placebo for 48 weeks. The primary efficacy endpoint was the difference in mean change from baseline in modified Rodnan skin score (mRSS) at week 24. Gene expression analysis was performed on skin biopsy specimens collected at baseline and week 24. Cartilage oligomeric matrix protein, periostin, autotaxin, and CCL18 serum levels were determined using immunoassays.

**Findings** Eighty-seven patients received tocilizumab (n=43) or placebo (n=44). The primary endpoint showed a treatment difference of  $-2.70$  mRSS units (95% CI:  $-5.85, 0.45$ ) in favour of tocilizumab at week 24 but did not meet statistical significance ( $p=0.0915$ ). At week 48, the treatment difference was  $-3.55$  mRSS units (95% CI:  $-7.23, 0.12$ ), favouring tocilizumab over placebo ( $p=0.0579$ ). Exploratory analysis of lung function showed that fewer patients in the tocilizumab arm had a decline in percent predicted forced vital capacity than in the placebo arm by comparison of the cumulative distribution (week 48,  $p=0.0373$ ). Tocilizumab downregulated the expression of myeloid-associated genes in the skin and decreased circulating levels of CCL18, a chemokine associated with fibrosis and progression of SSc-associated lung disease. Proportion of patients with adverse events/serious adverse events were not different between tocilizumab (42/43 [97.7%]/14/43 [32.6%]) and placebo (40/44 [90.9%]/15/44 [34.1%]), but those with serious infections were higher in the tocilizumab group (7 patients) vs. in the placebo group (2 patients).

**Interpretation** Tocilizumab was associated with a numerical reduction in skin thickening and less decline in forced vital capacity. These efficacy outcomes along with safety data and insights into the potential mechanism of action of tocilizumab support pursuing a phase 3 study.

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## Introduction

Systemic sclerosis (SSc) is a rare connective tissue disorder characterised by fibrosis, inflammation, and microvascular injury with heterogeneous clinical presentations. Pulmonary, cardiac, gastrointestinal (GI), and renal complications contribute to patient morbidity and decreased survival.<sup>1</sup>

Increasing evidence supports important roles for interleukin-6 (IL-6) in the pathogenesis of SSc,<sup>2</sup> including B-cell differentiation towards immunoglobulin-secreting plasma cells, T-cell differentiation towards Th17 and Th2 cell types, and transformation of fibroblasts to myofibroblasts leading to extracellular matrix synthesis.<sup>2</sup> In patients with SSc<sup>3</sup> or SSc-interstitial lung disease (ILD), increased IL-6 levels have been associated with higher mortality, more severe skin involvement, and increased incidence of progressive pulmonary decline.<sup>4</sup> Although the exact cellular mechanisms of the effects of IL-6 on fibrosis are unknown, myeloid cells are implicated in SSc skin pathogenesis.<sup>5</sup> mRNA expression of a cluster of macrophage genes, including CD14 in the skin, correlates strongly with modified Rodnan skin score (mRSS), and CD14 expression is prognostic for progressive skin disease.<sup>6</sup> M2 macrophages appear to play an important role in mediating inflammation and promoting fibrosis through the release of profibrotic factors.<sup>7,8</sup>

Blockade of the IL-6 pathway reduced skin fibrosis,  $\alpha$ -smooth-muscle actin protein expression,<sup>9</sup> hydroxyproline content, and myofibroblast counts in the bleomycin mouse model.<sup>10</sup> Initial data in SSc patients indicated that treatment with tocilizumab improved skin sclerosis and SSc-associated polyarthritis.<sup>11,12</sup> Certain circulating biomarkers are associated with the cardinal features of SSc, namely fibrosis, vasculopathy, and inflammation. Autotaxin (ENPP2) is an IL-6-induced biomarker associated with the development of fibrosis that is elevated in the circulation of SSc patients<sup>13</sup>. ENPP2 catalyzes production of lysophosphatidic

acid (LPA)<sup>14</sup> and elevated levels of circulating LPA have been associated with the pathobiology of SSc.<sup>15,16</sup> Serum levels of cartilage oligomeric matrix protein (COMP) correlate with skin fibrosis and predict mortality in SSc patients.<sup>17</sup> Elevated serum levels of chemokine (C-C motif) ligand 18 (CCL18) are associated with scleroderma-associated pulmonary fibrosis and ILD progression,<sup>18,19</sup> and elevated serum levels of periostin (POSTN) are associated with the degree of skin fibrosis in patients with SSc.<sup>20</sup>

The faSScinate phase 2 trial was conducted to investigate the efficacy and safety of IL-6 blockade with tocilizumab in SSc and to perform exploratory analysis of biomarkers.

## **Methods**

### **Study design and participants**

This randomised, double-blind, placebo-controlled study was conducted in 35 centres across Canada, France, Germany, the United Kingdom, and the United States. Investigators from each centre enrolled eligible patients 18 years of age or older who met the 1980 American College of Rheumatology criteria for SSc<sup>21</sup> with  $\leq 5$  years' disease duration since their first non-Raynaud sign or symptom and mRSS from 15 to 40 units. At screening, active progressive disease of  $< 1$  year's duration was required—increase of  $\geq 3$  mRSS units, involvement of one new body area with increase in mRSS  $\geq 2$  units or two new body areas with increase in mRSS  $\geq 1$  unit, other documentation of worsening skin thickening in the previous 6 months, or  $\geq 1$  tendon friction rub plus  $\geq 1$  laboratory criterion (C-reactive protein [CRP]  $\geq 10.0$  mg/L, erythrocyte sedimentation rate  $\geq 28$  mm/h, or platelets  $\geq 330 \times 1000/\mu\text{L}$ ). All patients provided written informed consent. Patients or their caregivers could provide subcutaneous (SC) investigational product injections. Eligible patients had clinically uninvolved skin at, at least one body areas for study drug injections.

Each site's institutional review board/ethics committee approved the protocol before the study commenced. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice.

### **Randomisation and masking**

Patients were randomly assigned (1:1) using an interactive voice/web response system to receive weekly subcutaneous treatment with tocilizumab 162 mg or placebo for 48 weeks followed by open-label weekly tocilizumab for 48 weeks. Randomisation numbers were generated by the sponsor, and randomisation was stratified by joint involvement at baseline (<4 or  $\geq$ 4 joints on the 28 tender joint count). Investigators, patients, and sponsor personnel were blinded to treatment assignment. To prevent potential unblinding due to observed efficacy or laboratory changes, separate assessors evaluated efficacy and safety. Both assessors were blinded to treatment assignment. The efficacy assessor did not have access to any patient safety or laboratory data during the double blind phase of the trial. However, the safety assessor had access to efficacy, as well as safety data. Although some sponsor personnel were unblinded after the primary analysis at week 24, the treatment blind was maintained for personnel interacting with sites and site staff until the week 48 database lock.

### **Procedures**

Escape therapy with methotrexate, hydroxychloroquine, or mycophenolate mofetil was permitted after week 24 for patients with  $\geq$ 20% worsening mRSS from baseline, worsening SSc-associated complications such as arthritis and ILD, or both, as determined by the treating investigator. The primary endpoint was the difference in mean change from baseline in mRSS to week 24. Secondary endpoints included patient-/physician-reported outcomes to weeks 24 and 48 (Health Assessment Questionnaire–Disability Index [HAQ-DI] score, patient global visual analogue scale [VAS, 0-100], physician global VAS, Functional Assessment of

Chronic Illness Therapy [FACIT]-Fatigue score, and pruritus 5-D Itch), change from baseline in mRSS to week 48, proportion of patients with change from baseline in the mRSS at Week 48 greater than or equal to the change from baseline in the mRSS at Week 24, change in VAS scores from baseline (intestinal, breathing, Raynaud's, finger ulcers, overall disease VAS scores from SHAQ-DI). Exploratory endpoints included proportion of patients achieving minimum clinically important difference (change  $\geq 0.22$ ) in the HAQ-DI at week 48, proportion of patients with 20%/40%/60% improvement in mRSS at weeks 24 and 48, change from baseline at weeks 24 and 48 in pulmonary function measured by forced vital capacity (FVC; mL), percent predicted FVC (%pFVC), and percent predicted diffusing capacity for carbon monoxide (%pDLCO) and change from baseline at week 24 and 48 in 28 TJC in patients with joint involvement at baseline (defined as  $\geq 4$  tender joints). Safety monitoring for adverse events (AEs) and serious AEs (SAEs) and laboratory monitoring were performed at least every 8 weeks. Exploratory biomarker analyses included gene expression analysis of skin biopsy specimens collected at baseline and at week 24 and COMP, POSTN, and CCL18 serum levels determined using immunoassays (see appendix).

### **Statistical analyses**

A sample size of 36 patients per group (86 patients total, allowing for 15% dropout) was determined to provide 80% power to detect a difference in means for the change in mRSS from baseline to week 24 of 4.7 units, based on an estimated common standard deviation of 6.99<sup>22</sup> using a two-group t-test with a 5% two-sided significance level.

The primary endpoint was analysed using a mixed-model repeated-measures (MMRM) approach. There was no imputation of missing data before the MMRM analyses, and all were stratified by joint involvement at baseline. Patients discontinuing their treatment before week 24 had their last evaluation at the time of discontinuation. Except for exploratory



analysis of pulmonary function, which included all available data, all week 48 MMRM analyses of secondary endpoints used data that were censored after initiation of escape therapy. The MMRM approach assumes that data are missing at random; therefore, sensitivity analyses were performed on the primary endpoint to account for data that might not have been missing due to random chance (appendix table 1).

Patients with a missing mRSS assessment at week 24 or week 48 were considered non-responders for analysis of 20/40/60% improvement in mRSS from baseline. Similarly a non-responder approach was used for the MCID of the HAQ-DI and the maintenance of mRSS response at week 48. The van Elteren test (stratified by joint involvement) was used to compare the treatment effect on the cumulative distribution of change from baseline in %pFVC and %pDLCO. There was no adjustment for multiplicity in statistical testing for any of the analyses. For SAE rates per 100 patient-years, multiple occurrences of events in a patient were counted, and the confidence intervals were based on the Poisson distribution. The analysis population for efficacy was the modified intent-to-treat (mITT) population, which included all randomly assigned patients that received any study drug. No randomized patients were excluded from the mITT. The safety population included all patients that received study drug and provided at least one post-dose safety assessment. Again this included all randomized patients.

### **Role of the funding source**

The sponsor designed the study in collaboration with the authors. The sponsor collected, analysed, and interpreted the data and drafted the report. All authors contributed to data interpretation, revised the manuscript, and attest to the accuracy and completeness of the reported data. The corresponding author had full access to all data congregates in the study and made the final decision to submit the manuscript for publication.

## Results

Patients were randomly assigned from March 13, 2012, to June 18, 2013; the last patient completed the week 48 visit on May 19, 2014. Eighty-seven patients were randomly assigned to treatment and were included in the intent-to-treat and safety populations (figure 1). At week 48, 12 of 44 placebo-treated patients and 6 of 43 tocilizumab-treated patients had received escape therapy. The numbers of patients who withdrew were similar between treatment arms: tocilizumab—safety (n=8 [five AEs, three deaths]), non-safety (n=5 [three patient decision, one lack of efficacy, one lost to follow-up]); placebo—safety (n=4 [AEs]), non-safety (n=7 [five patient decision, one clinician decision, one non-compliance]). Baseline demographics and disease characteristics as well as dose intensity of the investigational treatment were well balanced between treatment arms (table 1).

The primary endpoint was not met at week 24. A numerically larger, but not statistically significant, improvement in mRSS was seen with tocilizumab compared with placebo (table 2, figure 2). Least-squares mean (LSM) change in mRSS from baseline to week 24 was  $-3.92$  in tocilizumab patients and  $-1.22$  in placebo patients (treatment difference,  $-2.70$  [95% confidence interval (CI):  $-5.85, 0.45$ ];  $p=0.0915$ ). The observed mean (SD) mRSS at week 24 was  $21.84$  ( $9.89$ ) for tocilizumab ( $n = 37$ ) and  $23.21$  ( $9.26$ ) for placebo ( $n = 38$ ). Results through week 48 showed a continued numerically larger treatment benefit beyond 24 weeks, with LSM change from baseline was  $-6.33$  with tocilizumab and  $-2.77$  with placebo (treatment difference,  $-3.55$  [95% CI:  $-7.23, 0.12$ ];  $p=0.0579$ ) (table 2, figure 2). The observed mean (SD) mRSS at week 48 was  $19.56$  ( $10.08$ ) for tocilizumab ( $n = 32$ ) and  $22.27$  ( $8.05$ ) for placebo ( $n = 33$ ). Among improvers in mRSS at Week 24, more tocilizumab patients maintained or had further improvement in their mRSS at week 48 compared to placebo (placebo: 8 of 18 patients [44.4%] and tocilizumab: 15 of 22 patients [68.2%]). At

week 48, a numerically higher proportion of patients receiving tocilizumab had mRSS improvement of at least 20%, 40%, or 60% compared with placebo (figure 2).

For patient- and physician-reported outcomes at weeks 24 and 48, the treatment difference between tocilizumab and placebo patients in LSM change from baseline was not statistically significant. For clinician and patient global VAS and FACIT-fatigue scores, favourable responses for tocilizumab compared to placebo were observed at week 48 (table 2). For the HAQ-DI result at week 48—though not statistically significant—the treatment difference of  $-0.207$  (95% CI:  $-0.471, 0.056$ ;  $p=0.1212$ ) favoured tocilizumab versus placebo. In addition, at week 48, a numerically higher proportion of patients receiving tocilizumab than placebo achieved an improvement of  $\geq 0.22$  in HAQ-DI (28% vs 7%, respectively;  $p=0.0111$ ), with identical results for improvement defined as  $\geq 0.14$ . Overall, with the exception of the breathing VAS score, all other SHAQ VAS scores (intestinal disease, Raynaud syndrome, digital ulcers, and overall disease) at week 48 showed a numerical, however not statistically significant, difference between treatment groups favoring tocilizumab; (See appendix and Table S3).

Twenty-one patients in the tocilizumab and 20 patients in the placebo arm had joint involvement defined as  $\geq 4$  tender joints at baseline. Over the 48-week treatment-blinded period, mean (median) tender joint counts declined from baseline by 4.3(2.5), ( $n=16$ ) and 5.10 (4.5) ( $n=10$ ) in the TCZ arm and 2.1 (2.0), ( $n=17$ ) and 2.9 (2.5) ( $n=12$ ) in the PBO arm amongst patients with joint involvement at weeks 24 and 48 respectively.

Patients with SSc are at risk to develop ILD and progressive decline in FVC.<sup>23</sup> Pulmonary function testing showed, on average, a smaller decrease in FVC from baseline for tocilizumab than for placebo at weeks 24 (LSM difference, 136 mL [95% CI: 9, 264];  $p=0.0368$ ) and 48 (LSM difference, 120 mL [95% CI:  $-23, 262$ ];  $p=0.0990$ ) (figure 3A). Cumulative

distribution plots of change from baseline in %pFVC at weeks 24 (figure 3B) and 48 (figure 3C) indicated that fewer tocilizumab than placebo patients experienced worsening of %pFVC ( $p=0.009$ , week 24;  $p=0.0373$ , week 48). At weeks 24 and 48, respectively, 3% and 10% of tocilizumab-treated patients compared with 19% and 23% of placebo-treated patients experienced >10% (absolute) decreases in %pFVC from baseline. LSM changes from baseline in %pFVC for tocilizumab versus placebo at weeks 24 and 48, respectively, were  $-0.7$  (95% CI:  $-3.2, 1.8$ ) versus  $-4.5$  (95% CI:  $-7.0, -1.9$ ) and  $-2.6$  (95% CI:  $-5.2, -0.1$ ) versus  $-6.3$  (95% CI:  $-8.9, -3.8$ ). At week 48, change from baseline in %pDLCO did not reveal differences between placebo and tocilizumab (appendix figure 1). Correlations between improvements in mRSS and change in %pFVC from baseline to week 48 were similar for both treatment arms (tocilizumab,  $r=-0.311$ ,  $p=0.121$ ; placebo,  $r=-0.278$ ,  $p=0.223$ ; appendix figure 2). Correlations between baseline CRP and change in mRSS over week 48 were xxxx for both treatment arms (tocilizumab,  $r=-0.xx$ ,  $p=xx$ ; placebo,  $r=yy$ ,  $p=yy$ ). Among patients with available week 48 mRSS data, 4 of 32 (13%) tocilizumab-treated patients and 9 of 33 (27.3%) placebo-treated patients received escape therapy.

Exploratory analysis of the circulating biomarkers COMP, POSTN, ENPP2, and CCL18 was conducted on serum samples from all available patients and time points using specific immunoassays (figure 4). The serum levels of COMP, POSTN, ENPP2, and CCL18 at Baseline were all significantly elevated compared to age and gender matched Healthy Volunteers (COMP  $p < 0.0001$ , POSTN  $p < 0.0001$ , ENPP2  $p < 0.0001$ , CCL18  $p < 0.0001$ ; two-tail t-test assuming unequal variance). Treatment with tocilizumab resulted in a significant decrease in serum levels of CCL18 (figure 4A) whereas tocilizumab had no apparent effect on COMP (figure 4B), POSTN (figure 4C), or ENPP2 (figure 4D).

Exploratory gene expression analysis was conducted on skin biopsies collected at baseline and week 24 from the forearm region of a subset of patients (placebo baseline = 39, placebo

week 24 = 30, tocilizumab baseline = 34, and tocilizumab week 24 = 28) and of 20 age- and gender-matched healthy volunteers. First, Gene Set Enrichment Analysis (GSEA) for Fibrosis-, IFN-, IL-6-, TGF $\beta$ -, M1 Macrophage-, and M2-Macrophage-gene sets (Supplementary tables S4, S5, S6, S7, S8, and S9, respectively) was conducted on the microarray data obtained from all available samples. While the expression levels of the Fibrosis-, IFN-, IL-6-, TGF $\beta$ -, M1 Macrophage-, and M2 Macrophage-gene sets were significantly higher in the SSc samples compared to the HV samples ( $p(\text{seeing } t \leq \text{observed}) = 1.000$ ,  $p(\text{seeing } t \geq \text{observed}) = 0.005$  for all), no significant difference in expression levels was detected in the TCZ Week 24 samples compared to tocilizumab Baseline samples. However, we observed non-significant trends in reduction of expression levels between tocilizumab Week 24 and tocilizumab Baseline in the IFN- ( $p(\text{seeing } t \leq \text{observed}) = 0.070$ ,  $p(\text{seeing } t \geq \text{observed}) = 0.935$ ), IL-6- ( $p(\text{seeing } t \leq \text{observed}) = 0.095$ ,  $p(\text{seeing } t \geq \text{observed}) = 0.910$ ), and M2 Macrophage-gene sets ( $p(\text{seeing } t \leq \text{observed}) = 0.105$ ,  $p(\text{seeing } t \geq \text{observed}) = 0.900$ ), motivating us to investigate further these pathways.

Next, based on a genome-wide analysis of gene expression in these biopsies, a set of 83 genes was selected (see supplementary material) for confirmatory analysis using nCounter technology (Nanostring Technologies; figure 5) Out of these 83 genes representing the Fibrosis/TGF- $\beta$ , IL-6, IFN, and Myeloid pathways, 62 transcripts were significantly over expressed and 2 were significantly under expressed in SSc patients vs. HV (t-test, Bonferroni correction for multiple comparisons). Clustering analysis of the average gene expression (Log<sub>10</sub> transformed and Normalized) for the placebo Baseline, placebo Week 24, tocilizumab Baseline, and tocilizumab Week 24 groups yielded 9 clusters representing the TGF- $\beta$ , IL-6/STAT3, M1-Macrophage, M2-Macrophage, and IFN pathways based on the classification provided by Ingenuity Pathway Analysis (Qiagen, USA; figure 5). Analysis of the effect of treatment on the change in gene expression levels at week 24 identified 16 genes specifically

down regulated by tocilizumab vs. placebo (Uncorrected  $p < 0.05$  ANCOVA on change in gene expression levels at week 24 with Baseline Expression Level as linear covariate and Treatment as categorical classifier). While the majority of these genes (12/16) belonged to the “M2 Mac” cluster, two genes belonged to the “M1 Mac” cluster, suggesting an inhibitory activity of tocilizumab on macrophage in general and M2 macrophage in particular.

Although gene expression in the “IL-6/STAT3” cluster tended to be reduced by tocilizumab at week 24 compared to placebo, only two genes (CCL2 and SOCS3) were significantly down regulated by tocilizumab vs. placebo, possibly reflecting the substantial heterogeneity in gene expression across patients.

Finally, using the same data set, we tested the differential effect of treatment with tocilizumab on a recently developed multi-analyte, longitudinal pharmacodynamic biomarker (2GSSc skin biomarker<sup>24</sup>). This biomarker, which yields predicted mRSS values based on the weighted values for THBS1 and MS4A4A mRNA expression values, was validated and has been applied to two clinical trials, indicating that it is a robust surrogate outcome measure for the extent of SSc skin disease.<sup>25</sup> At Baseline, the predicted mRSS values were similar between the placebo and tocilizumab groups (placebo Mean [95% CI]: 16.4 [15.1 – 17.8]; tocilizumab Mean [95% CI]: 15.5 [14.1 – 17.0]; figure 6). Comparison of the change in predicted mRSS at Week 24 between placebo and tocilizumab indicated that treatment with tocilizumab resulted in a significant decrease in predicted mRSS as compared to treatment with placebo ( $\Delta$  placebo Mean [95% CI]: -0.98 [- 2.99 – 1.03];  $\Delta$  tocilizumab Mean [95% CI]: -4.03 [-7.58 – - 0.49];  $p = 0.0488$ ; figure 6).

## **Safety**

At weeks 24 and 48, the proportion of patients with AEs in the tocilizumab (38/43 [88.4%]; 42/43 [97.7%]) and placebo (40/44 [90.9%]; 40/44 [90.9%]) arms were comparable, as were withdrawal rates due to AEs (table 3). The most frequently reported AEs included infections, GI disorders, skin/subcutaneous disorders, and musculoskeletal/connective tissue disorders (appendix table 10). Serious infections were more frequent with tocilizumab (seven patients) than placebo (two patients), whereas non-infectious SAEs, including cardiac disorders, GI disorders, and renal and urinary disorders, were more frequent with placebo. Osteomyelitis involving proximal interphalangeal joints occurred in two tocilizumab patients and one placebo patient. No anaphylaxis, GI perforations, or malignancies were observed and SC injections were well tolerated. Total exposure to study drug before open-label treatment in patient-years (PY) was 34.49 for tocilizumab and 36.77 for placebo. The overall SAE rate was 66.7% (95% CI: 42.3, 100.1)/100 PY with tocilizumab and 76.1 (95% CI: 50.6, 110.0)/100 PY with placebo, the serious infection rate was 34.8 (95% CI: 18.0, 60.8)/100 PY and 10.9 (95% CI: 3.0, 27.9)/100 PY, and the rate of noninfectious SAEs was 31.9 (95% CI: 15.9, 57.1)/100 PY and 65.3 (95% CI: 41.8, 97.1), respectively.

Four deaths were reported by week 48. One placebo patient died of cardiac failure, and three tocilizumab patients died of one event each of arrhythmia, multiorgan failure, and lung infection. Only one event, lung infection, was considered related to study drug. (For details see appendix)

Laboratory parameters of interest for tocilizumab (elevated alanine/aspartate aminotransferase, decreased neutrophils, and decreased platelets) were mostly grade 1/2 in intensity and were not temporally associated with clinically relevant sequelae such as hepatic events, serious infections, or serious bleeding events.

## Discussion

In this first phase 2 randomised controlled trial of tocilizumab for the treatment of SSc, the primary (mRSS) and secondary efficacy endpoints were not met at week 24 or 48. However, consistent improvements in skin thickness through week 48 in the tocilizumab arm were evident, with mRSS improvement at weeks 24 and 48 within published minimal clinically important differences for early, diffuse SSc.<sup>26</sup> HAQ-DI, clinician global VAS, and other patient-reported outcomes favored tocilizumab over placebo, though they did not reach statistical significance. Significantly fewer patients receiving tocilizumab had absolute FVC declines of >10% compared with patients receiving placebo.

The current study shows a clinically meaningful decline in mRSS<sup>26</sup> over 1 year in the tocilizumab group compared with the placebo group. Careful selection of patients with early progressive disease might have been important to observe this effect. Skin thickness is a surrogate marker for internal organ involvement and mortality in SSc, and patients with attenuated skin thickness have improved survival and physical function.<sup>27,28</sup> Conversely, patients with high mRSS have greater internal organ involvement<sup>29</sup> and are at greater risk for death.<sup>27</sup>

SSc has the highest case fatality among rheumatic diseases, with a cumulative survival from diagnosis of 74.9% at 5 years.<sup>30</sup> Cardiopulmonary involvement is the leading cause of death,<sup>1</sup> and FVC is the primary outcome measure in most SSc-ILD and idiopathic pulmonary fibrosis trials.<sup>31</sup> Elevated CRP levels have been associated with progressive ILD, and observational cohorts suggest that baseline elevated CRP predicts long-term FVC decline.<sup>3,32</sup> Although our study was not specifically designed to enroll patients with progressive SSc-ILD, enrolling patients with early progressive skin disease and elevated acute-phase reactants



likely enriched for SSc patients at high risk for ILD. Our data suggest that tocilizumab may have a disease-modifying effect by slowing the decline in lung function of patients with SSc.

Treatment with tocilizumab resulted in the specific downregulation of skin myeloid-associated genes, including M2-macrophage-associated genes. Perivascular macrophages (resident and/or recruited) contribute to vascular inflammation,<sup>33</sup> and M2-macrophages may play an important role in SSc skin pathology through the release of inflammatory and profibrotic factors.<sup>8</sup> It is therefore tempting to speculate that the improvement in skin disease in patients treated with tocilizumab may be due to the inactivation and/or depletion of skin macrophages in general and M2-macrophages in particular. Furthermore, treatment with tocilizumab resulted in rapid, sustained reductions in serum levels of the M2-macrophage-associated chemokine CCL18, strengthening the hypothesis that tocilizumab may act, at least in part, by modulating the activity of M2-macrophages. Given that serum CCL18 is a prognostic biomarker that identifies patients at higher risk for the progression of scleroderma lung disease,<sup>18</sup> it is possible that the effect of tocilizumab on circulating CCL18 may be related to the positive clinical effect of tocilizumab on lung function deterioration. These hypotheses will be further explored in the ongoing phase 3 study of tocilizumab in SSc patients.

Tocilizumab did not affect the serum levels of ENPP2, COMP and POSTN, three biomarkers related to fibrosis, suggesting that the effect of tocilizumab on mRSS is not directly due to change in the expression of these fibrotic markers. It is also possible that these fibrosis-related biomarkers are not sensitive measures of clinical improvement in skin fibrosis or may require additional time to show significant improvements. Finally, in keeping with the clinical effect of tocilizumab on skin fibrosis as measured by mRSS, treatment with

tocilizumab resulted in a significant decrease in the 2-Gene SSc Skin Biopsy predicted mRSS. Of note, the magnitude of change in predicted mRSS was similar to that observed clinically.

Overall, after 48 weeks of treatment, safety in faSScinate was consistent with the natural history of SSc and the known safety profile for tocilizumab (table 3, appendix table 10). Reflecting the high morbidity and mortality rates seen in SSc,<sup>1</sup> greater incidences of SAEs, serious infections, and deaths were seen in faSScinate than in clinical trials of tocilizumab in RA.

There were 3 deaths in the tocilizumab group vs. 1 in the placebo group, with only one death judged as related to tocilizumab by the study investigator. Based on the higher number of deaths in faSScinate on tocilizumab compared to placebo, it will be important to carefully assess the mortality rates as well as cause of death during the phase 3 tocilizumab study in SSc that has just been initiated.

Furthermore a higher rate of serious infections was observed in the tocilizumab arm. The serious infections observed include bronchitis, lung infection, pneumonia and sepsis, which are similar to the types of events observed during treatment with tocilizumab in RA. However, small bone osteomyelitis and infected digital ulcers are infections not commonly observed during therapy with tocilizumab in patients with RA and thus may require particular vigilance in patients with SSc.

Although the GI tract is the most frequently affected internal organ in patients with SSc,<sup>1</sup> no patients in faSScinate had GI perforations. Injection site reactions, elevations in alanine/aspartate aminotransferase levels, and decreases in neutrophil and platelet counts were mostly grade 1/2 and involved no clinically relevant sequelae.

No disease-modifying therapy is yet approved for SSc, and its management is based on organ involvement.<sup>34,35</sup> Methotrexate affected skin thickening without establishing positive effects in patients with other organ manifestations,<sup>34,36</sup> whereas oral cyclophosphamide modestly improved lung function and skin thickness in studies of patients with SSc-ILD.<sup>37</sup> Recent data from a clinical trial<sup>38</sup> in haematopoietic stem cell transplantation suggested a disease-modifying effect in patients with SSc; thus, haematopoietic stem cell transplantation may be considered an option for selected patients with rapidly progressing and severe SSc. Data from this trial suggest that tocilizumab may have a broader effect on SSc skin and lung disease than methotrexate and a more favourable risk/benefit profile than cyclophosphamide.

Limitations of this study include selection of week 24 for the primary endpoint based on the assumption that the rapid response of tocilizumab seen in clinical trials of RA would translate to a rapid response in patients with SSc. The relatively high discontinuation rate should be taken into account when interpreting data from this study. FVC was an exploratory endpoint, and high-resolution chest tomography, which was not performed to substantiate the pulmonary function data, is planned for a phase 3 study. Cohort enrichment of patients with a probability of skin progression and elevated acute phase reactants may have contributed to the treatment responses observed. Whether the results are generalizable to other patients with SSc will require further study

## **Conclusion**

faSScinate is the first placebo-controlled study in SSc demonstrating improvement of skin sclerosis, albeit not statistically significant, and a clinically relevant improvement in lung function, with an acceptable safety profile. The safety profile was consistent with known SSc complications and the safety profile of tocilizumab. The propensity of SSc patients to develop

digital ulcers could increase susceptibility to develop small bone osteomyelitis and infections of digital ulcers during TCZ therapy. Overall, the data suggest a positive risk/benefit profile for tocilizumab in SSc, warranting further investigation.

## **Research in Context**

### **Evidence before this study**

In vivo data demonstrating elevated IL-6 levels in serum and skin biopsy samples of patients with SSc, associated with greater disease activity and higher mortality rates, provided evidence that IL-6 may play an important role in the pathogenesis of SSc. In addition, serum IL-6 levels in patients with early SSc have been shown to predict the extent of future progression of skin disease. Supportive evidence for a role of IL-6 in skin fibrosis was provided by the bleomycin-induced mouse model of scleroderma in which an IL-6 blocking antibody reduced dermal sclerosis in both a prevention model and a therapeutic model. Furthermore, the extent of fibrosis was attenuated in IL-6 knockout mice. Additional preliminary evidence of efficacy came from two therapy-refractory patients with SSc, who experienced improvement in skin thickening after treatment with tocilizumab for 6 months. Myeloid cells have been increasingly implicated in SSc skin pathogenesis. In particular, alternatively activated macrophages appear to play an important role in the pathobiology of SSc by mediating fibrosis through the release of profibrotic mediators such as CCL18.

Several literature searches through the US National Library of Medicine, National Institutes of Health were conducted prior to protocol finalization 23 August 2011. These included the search terms “systemic sclerosis”, or “scleroderma” as well as a combination of systemic sclerosis with any of the following search terms: IL-6, biomarkers, CCL-18, review, modified Rodnan skin score, clinical trials and interstitial lung disease. In addition, standard English

language rheumatology text books were reviewed and an advisory board with experts in the field of systemic sclerosis was convened.

### **Added value of this study**

This is the first placebo-controlled study in patients with early SSc to show efficacy, as evidenced by a clinical, however not a statistically significant amelioration of skin sclerosis, better patient-reported outcomes, and clinically relevant improvement in lung function in patients treated with the anti-IL-6 receptor-alpha inhibitor tocilizumab. Tocilizumab had an acceptable safety profile in these patients. The biomarker findings suggest that tocilizumab may ameliorate SSc skin disease by inhibiting skin myeloid cells in general and alternatively activated macrophages in particular.

### **Implications of all the available evidence**

Given the lack of disease-modifying treatment options for patients with SSc, combined with the morbidity and mortality associated with this disease, data from the faSScinate trial provide hope regarding a potential future treatment for patients with SSc. faSScinate was a phase 2 study; therefore, the efficacy and safety of tocilizumab must be further investigated in an adequate, randomised, well-controlled phase 3 trial before definitive conclusions can be drawn about its risk/benefit profile.

## **Contributors**

All authors revised the draft for important intellectual content and approved the final draft for publication. In addition, each made the following contributions:

DK conceived of the study design, participated in patient recruitment, gave advice on data analysis, interpreted the data, drafted the manuscript, reviewed the comments of all coauthors, and made the decision to submit the manuscript for publication.

CPD conceived of and designed the study; acquired, analysed, and interpreted the data; and drafted the manuscript.

AJ designed the study, provided study oversight, interpreted the data, and drafted the manuscript.

JMvL conceived of and designed the study and acquired data.

TMF acquired data.

MEA designed the study.

MB acquired and interpreted data.

LC acquired and interpreted data and drafted the manuscript.

GF acquired, analysed, and interpreted data and recruited patients.

SL acquired data.

YA acquired, analysed, and interpreted data.

JEP conducted a literature search; developed the protocol; acquired, analysed and interpreted data; and drafted the manuscript.

GR designed the study (endpoints and inclusion/exclusion criteria), acquired and interpreted data, and performed basic research supporting the rationale.

VS designed the study and acquired data.

UM-L analysed and interpreted data.

RL acquired, analysed, and interpreted data.

GS designed the study and acquired, analysed, and interpreted data.

HS conceived of and designed the study and analysed and interpreted data.

HC-H acquired and analysed data and wrote the manuscript.

SD conceived of and designed the study and acquired data.

AM acquired, analysed and interpreted data and wrote the manuscript.

TS acquired, analysed and interpreted data and wrote the manuscript.

JS conceived of and designed the study and acquired data.

DEF designed the study, acquired and analysed data, and wrote the manuscript.

## **Declaration of interests**

DK has received grants from Bristol-Myers Squibb, Genentech/Roche, NIH/NIAID, NIH/NIAMS, PCORI, and the Scleroderma Foundation; and consultancy fees from Bayer, Cytori, EMD Serono (Merck), GSK, Sanofi Aventis, Genentech/Roche, and Seattle Genetics.

CPD has received grants from CSL Behring and GlaxoSmithKline (paid to his institution); consultancy fees from GlaxoSmithKline and Roche (paid to his institution); consultancy fees from Merck-Serono; and speaker fees from Actelion and Bayer.

AJ is an employee of and owns stock options in Genentech, a member of the Roche group, and has been issued a patent (US 8580264 B2).

JMvL has received honoraria from Merck Sharp & Dohme, Pfizer, Roche, and Eli Lilly.

TMF has nothing to disclose.

MEA has received ad board and related fees from Actelion and honoraria from Actelion and Bristol-Myers Squibb and has served as principal investigator of clinical trials for Actelion and Roche.

MB has nothing to disclose.

LC has served on an advisory board for Gilead and a data monitoring committee for Cytori.

GF has nothing to disclose.

SL has nothing to disclose.

YA has received grants from Bristol-Myers Squibb, Roche/Genentech, Inventiva, Pfizer, Sanofi, and Servier; and personal fees from Actelion, Bayer, Roche/Genentech, Inventiva, Medac, Pfizer, Sanofi, Servier, and UCB.



JEP has received research and consulting fees from Roche and consulting fees from Actelion, Bayer, Biogen, Celgene, and Genentech.

GR has received honoraria for lectures and advisory boards outside the submitted work.

VS has received a grant and advisory board fees from Roche.

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GS has nothing to disclose.

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DEF has received grants from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, National Institutes of Health, Novartis, Pfizer, Roche/Genentech, UCB;

consultancy fees from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Cytori, Janssen, Gilead, GlaxoSmith Kline, National Institutes of Health, Novartis, Pfizer, Roche/Genentech, UCB; and speaker fees from AbbVie, Actelion, and UCB.

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## TABLES AND FIGURES

|  | Placebo 162 mg qw<br>SC<br>n=44 | Tocilizumab 162 mg qw<br>SC<br>n=43 |
|--|---------------------------------|-------------------------------------|
| Age, years   | 48 (12.9)                       | 51 (11.7)                           |
| Female, n (%)  | 35 (80)                         | 32 (74)                             |
| White, n (%)   | 40 (91)                         | 38 (88)                             |
| Mean duration of SSc, <sup>a</sup> months                              | 19.5 (17.0)                     | 17.6 (13.9)                         |
| Anti-RNA polymerase antibody positive, n (%)                           | 17 (38.6)                       | 13 (30.2)                           |
| Previous biologic agents, n (%)  | 2 ( 4.5)                        | 0                                   |
| Previous immunosuppressive agents, n (%)                               | 5 ( 11.4)                       | 1 ( 2.3)                            |
| Previous/concomitant prednisone/corticosteroid use, n (%) <sup>b</sup> | 18 (40.9)                       | 25 (58.1)                           |
| Anti-topoisomerase antibody positive, n (%)                            | 20 (45.5)                       | 18 (41.9)                           |
| Patients with $\geq 1$ tendon friction rub, n (%)                      | 22 (50.0)                       | 20 (46.5)                           |
| TJC28 $\geq 4$ , n (%)   | 21 (49) <sup>c</sup>            | 20 (47)                             |
| TJC28, n (%)   | 7 (8.5) <sup>c</sup>            | 7 (8.9)                             |
| Total mRSS   | 26 (5.9)                        | 26 (7.2)                            |
| Overall HAQ-DI score   | 1 (0.7)                         | 1 (0.6) <sup>e</sup>                |
| Clinician global VAS   | 61 (15.2)                       | 64 (15.1)                           |
| CRP, mg/L  | 10 (13.5) <sup>d</sup>          | 10 (13.5)                           |
| Platelet count, 10 <sup>9</sup> /L                                     | 308 (88.9)                      | 306 (82.4)                          |
| % Predicted FVC  | 82% (13) <sup>e</sup>           | 80% (14)                            |
| % Predicted DLCO (Hb corr)   | 74% (21) <sup>c</sup>           | 73% (19) <sup>e</sup>               |
| Patients with $\geq 1$ digital ulcer, <sup>c</sup> n (%)               | 10 (23)                         | 11 (26)                             |

<sup>a</sup>Disease duration calculated from time of first non-Raynaud sign or symptom.

<sup>b</sup>See Appendix, Table S2 for additional information on previous and concomitant corticosteroid use

<sup>c</sup>Ulcer at or distal to the proximal interphalangeal joint, with loss of surface epithelialisation.

<sup>d</sup>n=43.

<sup>e</sup>n=42.

Data are mean (SD) unless stated otherwise. CRP=C-reactive protein; DLCO (Hb corr)=diffusing capacity for carbon monoxide corrected for haemoglobin; FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire–Disability Index; mRSS=modified Rodnan skin score; qw=every week; TJC28=tender joint count using 28 joints; VAS=visual analogue scale.

**Table 1: Baseline demographics and disease characteristics (safety population)**

|                             | <b>PBO 162 mg qw<br/>SC<br/>n=44</b> | <b>TCZ 162 mg qw<br/>SC<br/>n=43</b> | <b>Difference in means<br/>TCZ-PBO<br/>(95% CI)</b> | <b>p</b> |
|-----------------------------|--------------------------------------|--------------------------------------|---|----------|
| <b>mRSS</b>                 |                                      |                                      |   |          |
| Week 24                     | -1.22<br>n=43                        | -3.92<br>n=41                        | -2.70<br>(-5.85, 0.45)                              | 0.0915   |
| Week 48                     | -2.77<br>n=43                        | -6.33<br>n=41                        | -3.55<br>(-7.23, 0.12)                              | 0.0579   |
| <b>HAQ-DI</b>               |                                      |                                      |   |          |
| Week 24                     | 0.118<br>n=42                        | 0.137<br>n=41                        | 0.020<br>(-0.186, 0.225)                            | 0.8503   |
| Week 48                     | 0.205<br>n=41                        | -0.002<br>n=41                       | -0.207<br>(-0.471, 0.056)                           | 0.1212   |
| <b>Clinician Global VAS</b> |                                      |                                      |   |          |
| Week 24                     | -7.25<br>n=41                        | -8.24<br>n=39                        | -0.99<br>(-9.20, 7.23)                              | 0.8118   |
| Week 48                     | -9.39<br>n=41                        | -18.41<br>n=40                       | -9.02<br>(-19.04, 1.00)                             | 0.0768   |
| <b>Patient Global VAS</b>   |                                      |                                      |   |          |
| Week 24                     | 1.53<br>n=42                         | -2.33<br>n=42                        | -3.85<br>(-13.04, 5.34)                             | 0.4063   |



|                              |               |                |                         |        |
|------------------------------|---------------|----------------|-------------------------|--------|
| Week 48                      | -2.70<br>n=41 | -11.00<br>n=42 | -8.30<br>(-19.31, 2.71) | 0.1371 |
| <b>FACIT (Fatigue) Score</b> |               |                |                         |        |
| Week 24                      | 1.26<br>n=41  | 2.68<br>n=42   | 1.43<br>(-2.97, 5.82)   | 0.5197 |
| Week 48                      | 0.36<br>n=40  | 3.11<br>n=42   | 2.75<br>(-1.38, 6.88)   | 0.1886 |
| <b>5-D Itch Scale</b>        |               |                |                         |        |
| Week 24                      | -1.73<br>n=41 | -0.94<br>n=41  | 0.79<br>(-0.94, 2.51)   | 0.3651 |
| Week 48                      | -1.08<br>n=40 | -2.19<br>n=41  | -1.11<br>(-3.16, 0.94)  | 0.2841 |

<sup>a</sup>Negative change from baseline shows improvement for all efficacy measures, except for the FACIT-Fatigue Scale, where positive change from baseline indicates improvement. A mixed-model repeated-measures analysis was conducted that included the fixed categorical effects of treatment, visit, stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction and the continuous covariates of baseline score and baseline score-by-visit interaction. FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire– Disability Index; ITT=intent to treat; PBO=placebo; qw=every week; TCZ=tocilizumab; VAS=visual analogue scale.

**Table 2: Least square mean change from baseline<sup>a</sup> to weeks 24 and 48 in mRSS (primary endpoint) and in patient- and physician-reported outcomes (ITT population)**

| AEs/SAEs, n (%) <sup>a</sup>                      | Baseline to week 24                      |  | Baseline to week 48                      |  |
|---|--|--|--|--|
|   | <b>PBO<br/>162 mg qw<br/>SC<br/>n=44</b> | <b>TCZ<br/>162 mg qw<br/>SC<br/>n=43</b> | <b>PBO<br/>162 mg qw<br/>SC<br/>n=44</b> | <b>TCZ<br/>162 mg qw<br/>SC<br/>n=43</b> |
| Total patients with ≥1 AE                         | 40 (90.9)                                | 38 (88.4)                                | 40 (90.9)                                | 42 (97.7)                                |
| Total patients with ≥1 infectious AE              | 18 (40.9)                                | 17 (39.5)                                | 22 (50.0)                                | 24 (55.8)                                |
| Total patients with injection site reactions      | 1 (2.3) <sup>b</sup>                     | 2 (4.7) <sup>c</sup>                     | 2 (4.5) <sup>b</sup>                     | 3 (7.0) <sup>c</sup>                     |
| Total patients with ≥1 SAE                        | 11 (25.0)                                | 9 (20.9)                                 | 15 (34.1)                                | 14 (32.6)                                |
| Total patients with ≥1 infectious SAE             | 1 (2.3)                                  | 6 (14.0)                                 | 2 (4.5)                                  | 7 (16.3)                                 |
| Total patients with ≥1 non-infectious SAE         | 10 (23.0)                                | 5 (11.6)                                 | 14 (31.8)                                | 10 (23.3)                                |
| Total patients who withdrew due to an AE          | 5 (11.4)                                 | 4 (9.3)                                  | 5 (11.4)                                 | 6 (14.0)                                 |
| Deaths  | 1 (2.3)                                  | 1 (2.3)                                  | 1 (2.3)                                  | 3 (7.0)                                  |
| <b>SAEs by SOC and preferred term<sup>a</sup></b> |  |  |  |  |
| Infections and infestations                       | 1 (2.3)                                  | 6 (14.0)                                 | 2 (4.5)                                  | 7 (16.3)                                 |
| Osteomyelitis                                     | 0  | 2 (4.7)                                  | 1 (2.3)                                  | 2 (4.7) <sup>d</sup>                     |
| Bronchitis  | 0  | 1 (2.3)                                  | 0  | 1 (2.3)                                  |
| Cellulitis  | 1 (2.3) <sup>e</sup>                     | 0  | 1 (2.3) <sup>e</sup>                     | 0  |
| Infected skin ulcer                               | 0  | 1 (2.3)                                  | 0  | 1 (2.3)                                  |

|                                   |                      |                      |                      |                      |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Lower respiratory tract infection | 1 (2·3) <sup>e</sup> | 0                    | 1 (2·3) <sup>e</sup> | 0                    |
| Lung infection                    | 0                    | 1 (2·3) <sup>f</sup> | 0                    | 1 (2·3) <sup>f</sup> |
| Oesophageal candidiasis           | 0                    | 1 (2·3)              | 0                    | 1 (2·3)              |
| Pneumonia                         | 0                    | 0                    | 0                    | 1 (2·3) <sup>d</sup> |
| Postprocedural cellulitis         | 0                    | 0                    | 0                    | 1 (2·3)              |
| Sepsis                            | 0                    | 0                    | 0                    | 1 (2·3) <sup>d</sup> |
| Cardiac disorders                 | 3 (6·8)              | 0                    | 4 (9·1)              | 1 (2·3)              |
| Acute myocardial infarction       | 1 (2·3)              | 0                    | 1 (2·3)              | 0                    |
| Cardiac failure                   | 1 (2·3)              | 0                    | 1 (2·3)              | 0                    |
| Cyanosis                          | 1 (2·3)              | 0                    | 1 (2·3)              | 0                    |
| Arrhythmia                        | 0                    | 0                    | 0                    | 1 (2·3)              |
| Atrioventricular block            | 0                    | 0                    | 1 (2·3)              | 0                    |
| Gastrointestinal disorders        | 2 (4·5)              | 0                    | 4 (9·1)              | 1 (2·3)              |
| Colonic pseudo-obstruction        | 1 (2·3)              | 0                    | 1 (2·3)              | 0                    |
| Gastric antral vascular ectasia   | 1 (2·3)              | 0                    | 1 (2·3)              | 0                    |
| Abdominal distension              | 0                    | 0                    | 1 (2·3)              | 0                    |
| Abdominal pain                    | 0                    | 0                    | 1 (2·3)              | 0                    |
| Gastritis                         | 0                    | 0                    | 0                    | 1 (2·3)              |

|  |         |         |         |         |
|--|---------|---------|---------|---------|
| Retroperitoneal fibrosis                             | 0       | 0       | 1 (2·3) | 1 (2·3) |
| Musculoskeletal and connective tissue disorders      | 2 (4·5) | 0       | 2 (4·5) | 2 (4·7) |
| Scleroderma/systemic sclerosis (worsening)           | 2 (4·5) | 0       | 2 (4·5) | 0       |
| Osteoarthritis                                       | 0       | 0       | 0       | 1 (2·3) |
| Skin and subcutaneous tissue disorders               | 0       | 1 (2·3) | 1 (2·3) | 2 (4·7) |
| Skin ulcer   | 0       | 1 (2·3) | 1 (2·3) | 2 (4·7) |
| Vascular disorders                                   | 2 (4·5) | 1 (2·3) | 2 (4·5) | 1 (2·3) |
| Hypertension   | 0       | 1 (2·3) | 0       | 1 (2·3) |
| Hypertensive emergency                               | 1 (2·3) | 0       | 1 (2·3) | 0       |
| Raynaud's phenomenon                                 | 1 (2·3) | 0       | 1 (2·3) | 0       |
| Blood and lymphatic system disorders                 | 1 (2·3) | 1 (2·3) | 1 (2·3) | 1 (2·3) |
| Haemolytic uraemic syndrome                          | 0       | 1 (2·3) | 0       | 1 (2·3) |
| Iron deficiency anaemia                              | 1 (2·3) | 0       | 1 (2·3) | 0       |
| General disorders and administration site conditions | 0       | 1 (2·3) | 0       | 2 (4·7) |
| Impaired healing                                     | 0       | 1 (2·3) | 0       | 1 (2·3) |
| Multiorgan failure                                   | 0       | 0       | 0       | 1 (2·3) |
| Nervous system disorders                             | 0       | 0       | 2 (4·5) | 0       |
| Headache   | 0       | 0       | 1 (2·3) | 0       |

|                             |         |         |         |         |
|-----------------------------|---------|---------|---------|---------|
| Subarachnoid haemorrhage    | 0       | 0       | 1 (2·3) | 0       |
| Renal and urinary disorders | 2 (4·5) | 0       | 2 (4·5) | 0       |
| Renal failure acute         | 1 (2·3) | 0       | 1 (2·3) | 0       |
| Scleroderma renal crisis    | 1 (2·3) | 0       | 1 (2·3) | 0       |
| Psychiatric disorders       | 0       | 1 (2·3) | 0       | 1 (2·3) |
| Psychotic disorder          | 0       | 1 (2·3) | 0       | 1 (2·3) |

<sup>a</sup>Total number of patients with  $\geq 1$  event; multiple occurrences of the same event in a patient were counted once.

<sup>b</sup>Grade 1 haematoma (baseline to week 24) and grade 1 injection site bruising (baseline to week 48).

<sup>c</sup>Two patients had grade 1 injection site erythema, and one patient had grade 2 injection site rash (baseline to week 24) and grade 1 contusion (baseline to week 24).

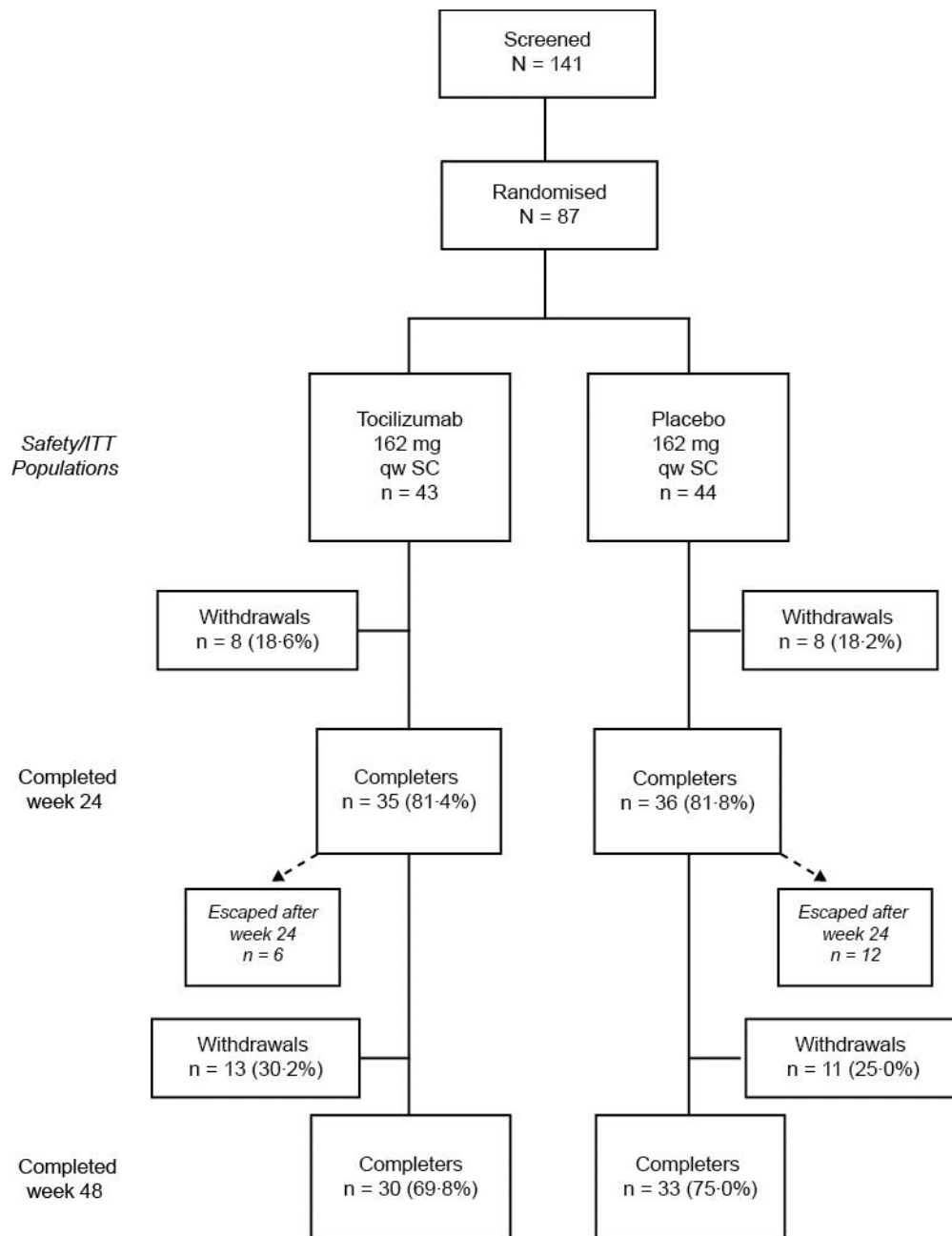
<sup>d</sup>One TCZ patient who had osteomyelitis by week 24 subsequently had pneumonia and sepsis by week 48.

<sup>e</sup>Both events occurred in the same patient.

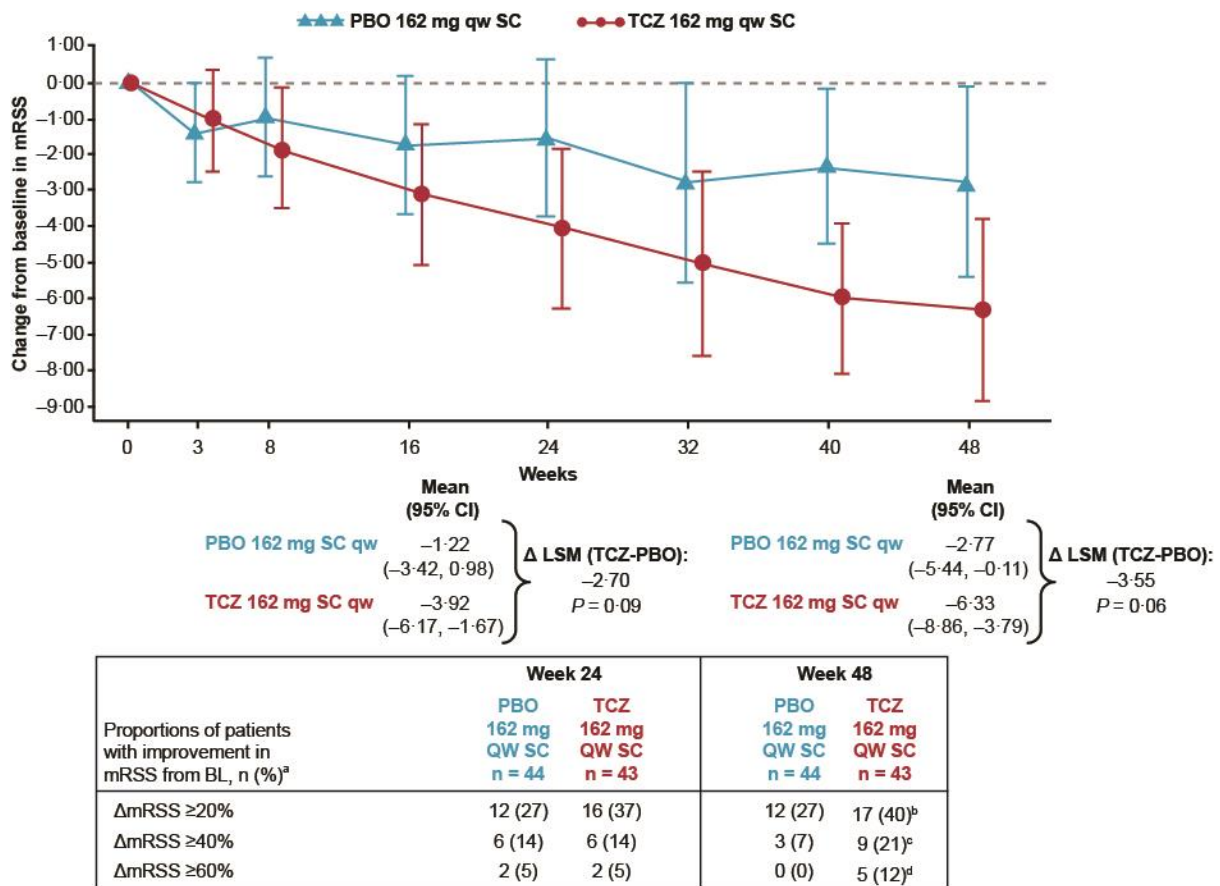
<sup>f</sup>Event was fatal.

AE=adverse event; qw = every week; SAE=serious adverse event; SOC=system organ class; TCZ=tocilizumab.

**Table 3. Safety**



**Figure 1: Patient disposition**



**Figure 2: Change from baseline in mRSS**

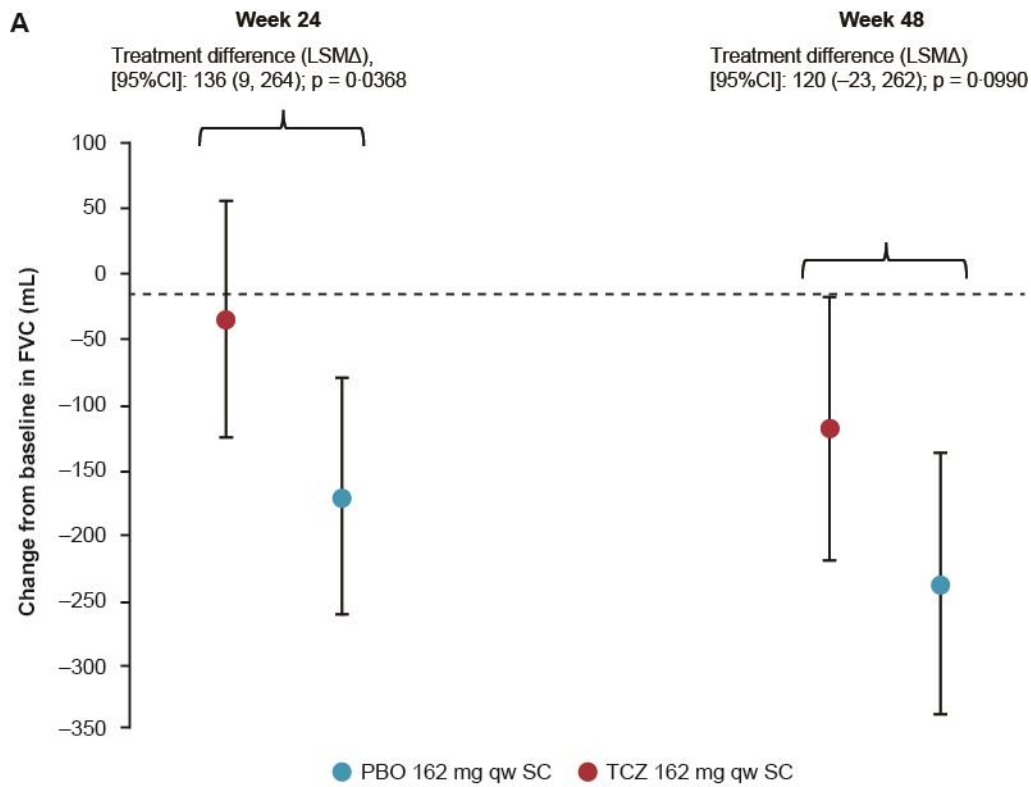
$\Delta$  LSM (TCZ-PBO): Difference in least-square means between treatment arms.

Negative change represents an improvement. Means and 95% CI are from the repeated-measures model.

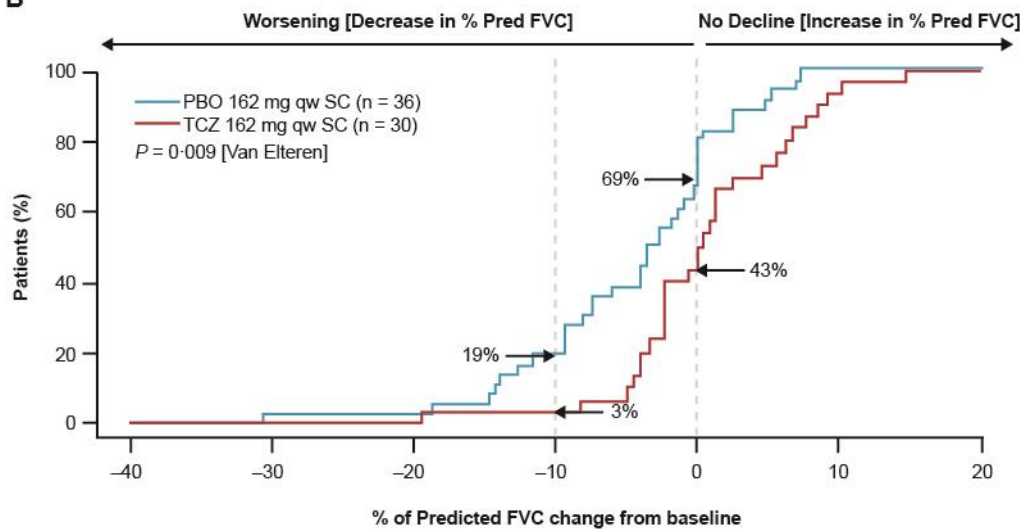
<sup>a</sup>Non-responder assumption for missing data. Patients can be counted more than once. For example, a patient with a 40% improvement would be counted as a 20% responder and a 40% responder.

<sup>b</sup>p=0.2607. <sup>c</sup>p=0.0685. <sup>d</sup>p=0.0261.

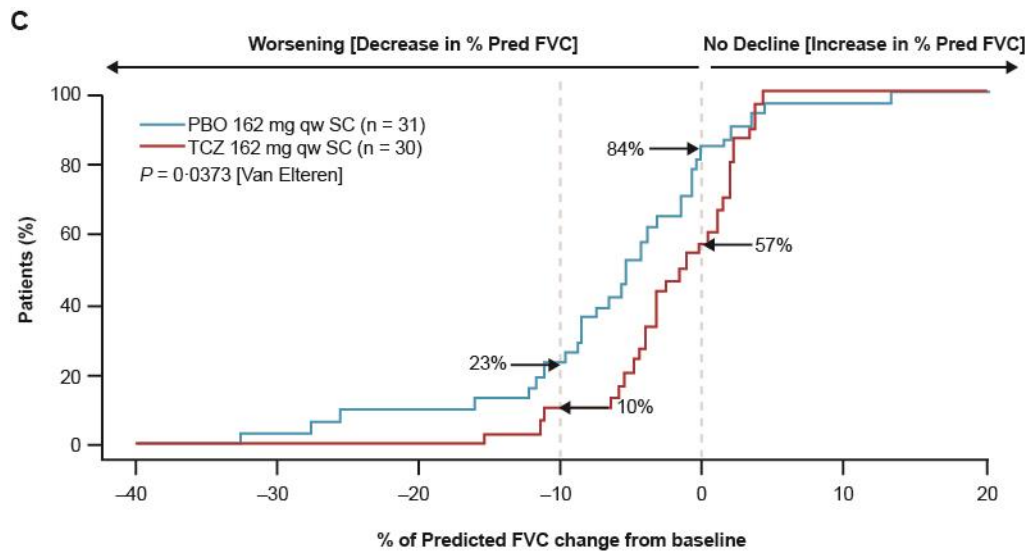
**A**



**B**



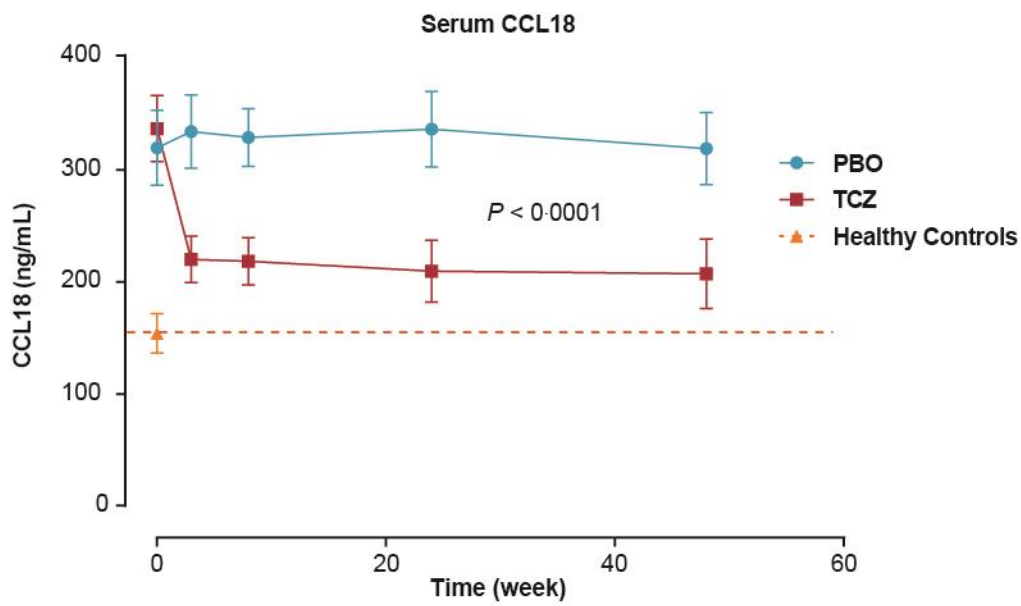




**Figure 3: Mean change from baseline**

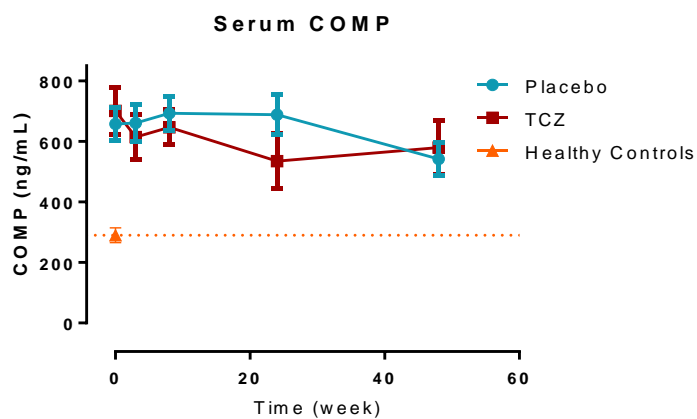
Mean change from baseline in FVC (mL) at weeks 24 and 48 (A). Error bars show 95% confidence intervals for the means for each treatment arm. p value refers to treatment difference. Cumulative distribution of patients by change in percent predicted FVC from baseline to week 24 (B) and week 48 (C) (exploratory analysis).

A



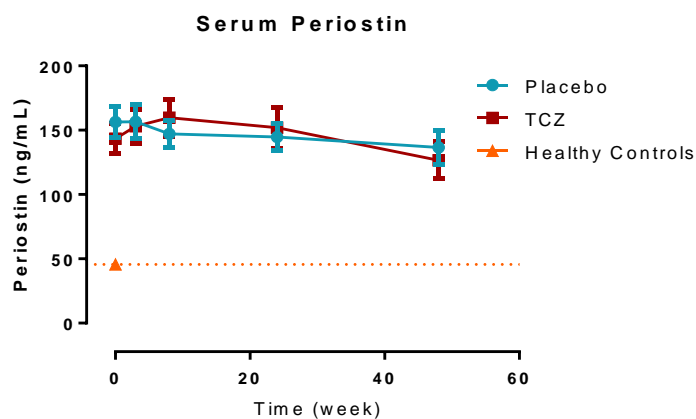
|                  | Patient Numbers |        |        |         |         |
|------------------|-----------------|--------|--------|---------|---------|
|                  | Baseline        | Week 3 | Week 8 | Week 24 | Week 48 |
| Healthy controls | 24              | —      | —      | —       | —       |
| Tocilizumab      | 41              | 41     | 38     | 34      | 26      |
| Placebo          | 43              | 42     | 42     | 36      | 28      |

B



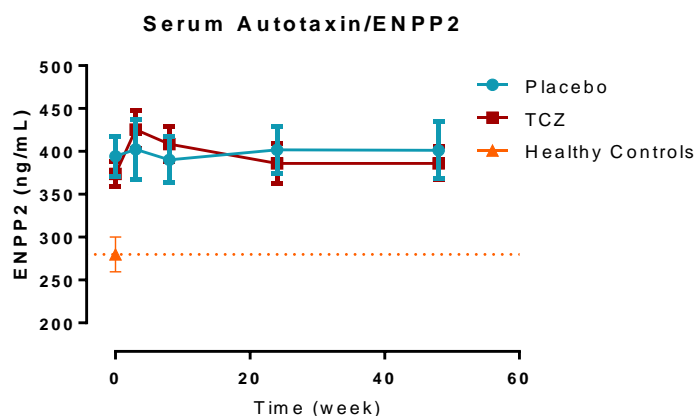
|                  | Patient Numbers |        |        |         |         |
|------------------|-----------------|--------|--------|---------|---------|
|                  | Baseline        | Week 3 | Week 8 | Week 24 | Week 48 |
| Healthy controls | 25              | -      | -      | -       | -       |
| Tocilizumab      | 41              | 40     | 36     | 32      | 26      |
| Placebo          | 43              | 43     | 41     | 25      | 26      |

C



|                  | Patient Numbers |        |        |         |         |
|------------------|-----------------|--------|--------|---------|---------|
|                  | Baseline        | Week 3 | Week 8 | Week 24 | Week 48 |
| Healthy controls | 24              | -      | -      | -       | -       |
| Tocilizumab      | 36              | 38     | 37     | 32      | 25      |
| Placebo          | 41              | 41     | 40     | 32      | 25      |

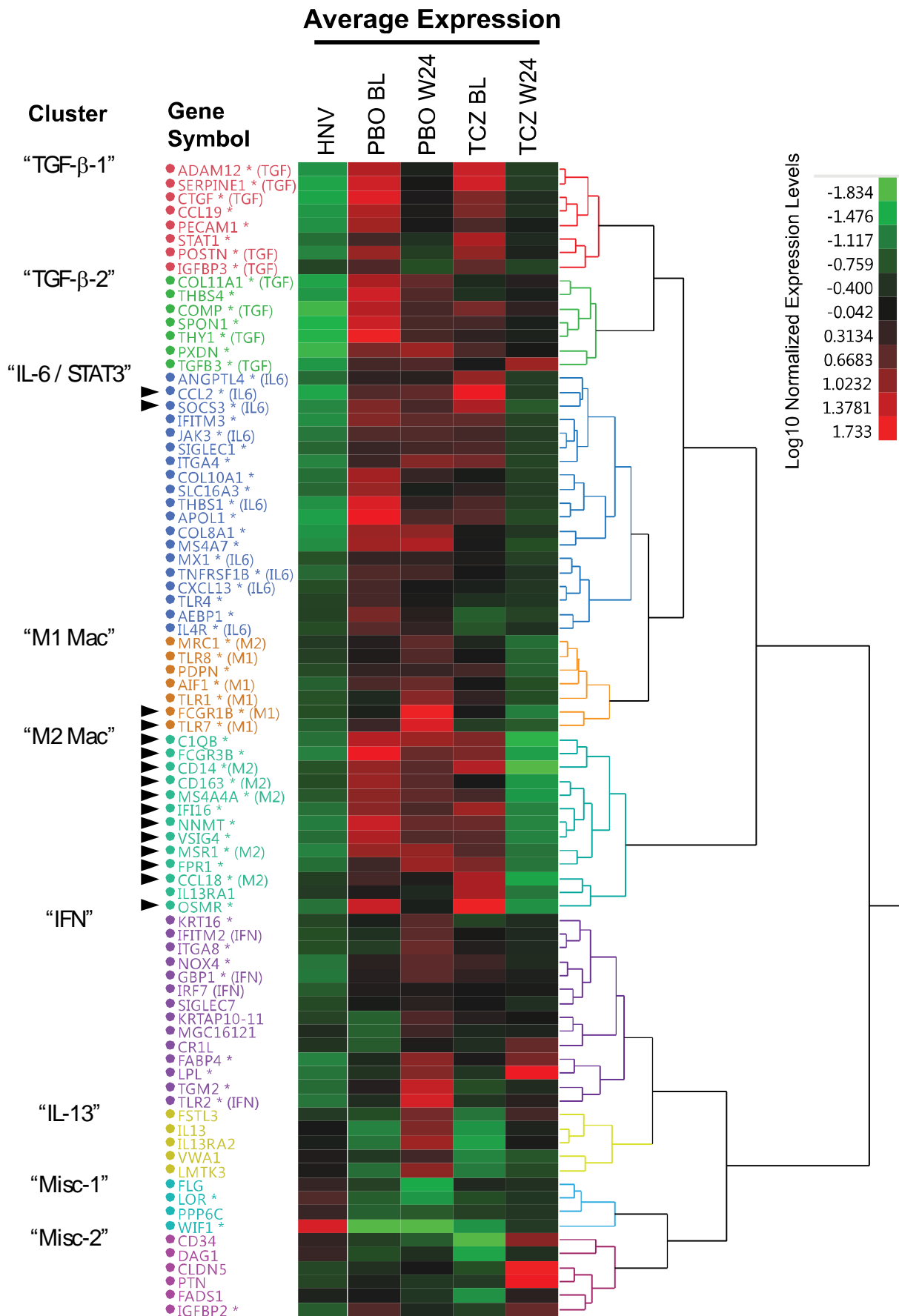
D



|                  | Patient Numbers |        |        |         |         |
|------------------|-----------------|--------|--------|---------|---------|
|                  | Baseline        | Week 3 | Week 8 | Week 24 | Week 48 |
| Healthy controls | 25              | N/A    | N/A    | N/A     | N/A     |
| Tocilizumab      | 42              | 43     | 40     | 35      | 26      |
| Placebo          | 41              | 38     | 38     | 34      | 25      |

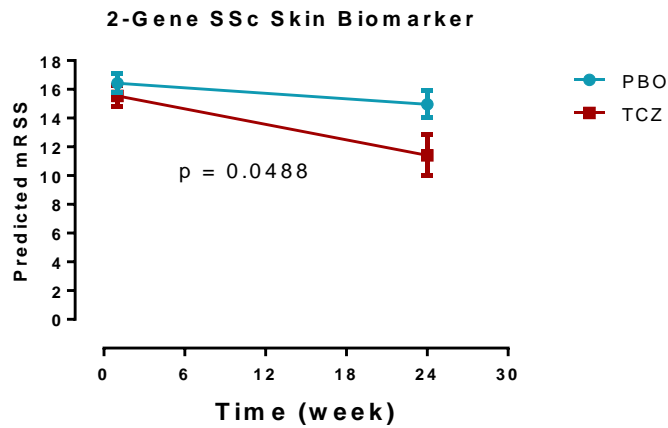
**Figure 4: Observed mean  $\pm$  standard error serum levels of CCL18 (A), COMP (B), POSTN (C), and ENPP2 (D) (ng/mL) at baseline and at weeks 3, 8, 24, and 48 in patients treated with tocilizumab or placebo (exploratory analysis) plus age- and gender-matched healthy controls (baseline only)**

P value is for the overall treatment effect of tocilizumab versus placebo based on two-way analysis of variance with treatment, time, and treatment\*time as factors. Serum CCL18, COMP, POSTN, and ENPP2 levels in healthy volunteers (triangles), tocilizumab-treated patients (squares), and placebo-treated patients (circles).



**Figure 5: Unsupervised one-way clustering of the mean log<sub>10</sub> normalized expression of 83 genes measured using nCounter technology (Nanostring Technologies) in the skin**

**biopsies of 20 healthy controls and of 42 placebo baseline, 34 placebo week 24, 36 tocilizumab baseline, and 29 tocilizumab week 24 patients. Shades of green denote low expression levels while shades of red denote high expression levels. Genes significantly over or under expressed in SSc patients vs. healthy controls are marked by an asterisk. The 14 genes highlighted with arrows represent the genes specifically down regulated by TCZ at week 24 as compared to placebo ( $p < 0.05$ , analysis of covariance on difference in gene expression levels between week 24 and baseline with baseline expression levels as linear covariate and treatment as categorical predictor).**



**Figure 6.** Mean  $\pm$  Standard Error of the 2-Gene SSc Skin Biomarker predicted mRSS derived from the skin biopsy RNA samples from 42 placebo baseline, 33 placebo week 24, 36 tocilizumab baseline and 29 tocilizumab week 24 patients; tocilizumab-treated patients (squares), and placebo-treated patients (circles). P value is for the treatment effect of tocilizumab versus placebo based on an analysis of covariance on change in predicted mRSS with baseline predicted mRSS as linear covariate and treatment as categorical predictor.