HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Arthritis Rheumatol. 2021 July ; 73(7): 1301–1310. doi:10.1002/art.41668.

Tocilizumab Prevents Progression of Early Systemic Sclerosis Associated Interstitial Lung Disease

David Roofeh, MD[1], **Celia J F Lin, MD**[2], **Jonathan Goldin, MD**[3], **Grace Hyun Kim, PhD**[3], **Daniel E Furst, MD**[3,4,5], **Christopher P Denton, FRCP**[6], **Suiyuan Huang, MPH**[1], **Dinesh Khanna, MD, MS**[1], **on behalf of the focuSSced investigators**

[1]University of Michigan Scleroderma Program, Ann Arbor, MI, USA

[2]Genentech, South San Francisco, CA, USA

[3]University of California, Los Angeles, Los Angeles, CA, USA

[4]University of Washington, Seattle, Washington, USA

[5]University of Florence, Florence, Italy

[6]University College London, London, UK

Abstract

Objective: Tocilizumab has demonstrated lung function preservation in two randomized controlled trials in early systemic sclerosis (SSc). This effect has yet to be characterized in terms of quantitative radiographic lung involvement. In this post-hoc analysis, we assess tocilizumab's impact on lung function preservation, stratifying treatment arms by the degree of radiographic lung involvement.

Methods: The focuSSced trial was a phase 3, randomized placebo-controlled trial of tocilizumab in patients with SSc and progressive skin disease. Participants had baseline and serial spirometry along with high resolution chest CT at baseline and week 48. Quantitative interstitial lung disease and fibrosis were derived using computer software. We divided quantitative interstitial lung disease in mild (5-10%), moderate (>10-20%), or severe (>20%) categories.

Results: Of 210 participants recruited in the trial, 136 [65%] had interstitial lung disease. The majority of these participants had moderate-to-severe involvement defined by >10% lung involvement (77%). The tocilizumab arm demonstrated preservation of forced vital capacity over 48 weeks (least squared mean change in %predicted = −0.1) compared to placebo (−6.3%). For mild, moderate, and severe QILD, the mean decline in the %pFVC in the tocilizumab arm at 48 weeks were −4.1, 0.7, and 2.1, and in the placebo group were −10.0, −5.7, and −6.7, respectively. Similar treatment-related preservation findings were seen independent of fibrosis severity.

Corresponding Author: Dinesh Khanna, Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, 300 North Ingalls Street, Ann Arbor, MI 48109, USA, khannad@med.umich.edu, Phone:734.763.7182, Fax: 734.763.5761.

Author Contributions: All named authors provided substantial contributions to study conception and design, acquisition of data, analysis and interpretation of data; have drafted or revised the article critically and approved the final version to be published.

Conclusion: Tocilizumab in early SSc- associated interstitial lung disease with progressive skin disease stabilized forced vital capacity over 48 weeks, independent of the extent of quantitative radiographic interstitial lung disease or fibrosis.

Keywords

Clinical Trial; Tocilizumab; Systemic Sclerosis; Quantitative Interstitial Lung Disease; Quantitative Lung Fibrosis

Introduction

The majority of systemic sclerosis patients will develop interstitial lung disease (SSc-ILD) (1, 2). The SSc-ILD disease process usually proceeds through different phases—the initial phase is associated with high resolution chest computed tomography (HRCT) findings of predominantly ground glass opacity with minimal fibrotic changes (that has been considered by some to be immuno-inflammatory) followed by more dense fibrotic changes with a non-specific interstitial pneumonia pattern on HRCT, although some patients may present with findings of usual interstitial pneumonitis(3). Those at risk for progressive disease have an archetype: early, diffuse cutaneous systemic sclerosis (dcSSc), with elevated acute phase reactants like C-reactive protein (CRP) and topoisomerase-1 antibody positivity (4–7). Patients with these high-risk features, especially those with disease in the initial phase of development, represent an important target for early intervention as ILD is largely irreversible in SSc (4, 8).

Tocilizumab (TCZ) is an anti-IL 6 agent (IgG1 humanized anti-IL-6 receptor monoclonal antibody), approved for the use of rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, Castleman's disease, and other immune-mediated diseases. Two well-designed randomized controlled trials of TCZ in early dcSSc demonstrated a significant lung preservation effect in the treatment arm compared to placebo (PBO) (9, 10). This effect has yet to be characterized in terms of quantitative radiographic lung involvement.

In this post-hoc analysis, we comprehensively characterized the ILD participants in the focuSSced trial (10), assessed the relationship between degree of total lung involvement and fibrosis (using well-established quantitative HRCT measurements) and lung physiology, and evaluated TCZ's treatment effect compared to PBO on FVC and quantitative HRCT. Investigating the treatment effects in terms of radiographic changes in this cohort at high risk for progression of ILD provides an important insight into disease pathophysiology and potential mechanisms of therapeutic benefit.

Patients and Methods

Study Design

This phase III trial (ClinicalTrials.gov, NCT02453256) was a multicenter, randomized, double-blind placebo-controlled trial with 1:1 randomization to active treatment (TCZ 162 mg subcutaneous injection/week) vs PBO for 48 weeks (10). Background immunosuppressive therapy was not allowed in the trial but escape therapy was allowed for prespecified skin and lung function progression, and SSc-related complications.

Participants

All participants met 2013 American College of Rheumatology/European League Against Rheumatism classification criteria, with disease onset <60 months from the onset of their first non-Raynaud's Phenomenon sign or symptom, and had a modified Rodnan Skin Score (mRSS) between 10-35 units; all had early progressive skin disease with diffuse cutaneous distribution as the main goal of the trial was to see a beneficial impact of TCZ on the mRSS. Participants also had elevated acute-phase reactants (≥1 of the following: CRP >6mg/L, ESR >28mm/h, or platelet count >330 $\times 10^9$/L) and active disease defined as >1 of the following at screening: disease duration ≤18 months, mRSS increase ≥3 units, or involvement of one new body area and mRSS increase ≥2 units, or involvement of two new body areas (each within the previous 6 months), and ≥1 tendon friction rub. The presence of lung disease was not required for enrollment. The study was approved by the institutional review boards of all participating sites, written informed consent was obtained from all participants and the study was conducted in compliance with the Helsinki Declaration.

Outcome Measures

Serial spirometry plus diffusing capacity for carbon monoxide corrected for hemoglobin (DLco) was conducted at weeks 8, 16, 24, 36, and 48, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement recommendations. Participants performed three to eight exhalations into a spirometer with the highest value recorded. Participants received a baseline and week 48 HRCT, completed at maximal inspiration. Images were acquired from 30 different multidetector CT scanner models from four manufacturers using a standardized procedure following strict quality control protocols. HRCT quantification was performed on all scans based on previous publications (11–13).

Quantitative ILD (QILD) refers to the summation of ground glass opacities, honeycombing, and fibrotic reticulation, while quantitative lung fibrosis (QLF) refers to the quantitative fibrosis (fibrotic reticulation) alone. Both scores range from 0-100% of the whole lung(14). All scans had QILD and QLF measurements; ILD was identified visually by a thoracic radiologist (J. G.) as the presence of ground-glass opacification and/or fibrosis with a basal predominance. Participants who had minimal interstitial changes without defined ILD were characterized as no ILD; these cases were screened for factors other than SSc-ILD and excluded (these included body habitus, atelectasis, bronchitis, aspiration, bronchiectasis). QILD cutoff points were set as minimal (≥5%), mild (5-10%), moderate (>10-20%), or severe (>20%) based on 1) a chest radiologist's (J.G.) classification and 2) publication by Goh et al., where total lung involvement of >20% was associated with higher mortality in a longitudinal cohort(15). Cutoff points for QLF were set into tertiles given the range (0.1-18.5%) of involvement.

Statistics

Continuous and categorical variables were summarized using means and standard deviations (SD), and percentages, respectively. T test was used to compare baseline %pFVC by baseline QILD and QLF cutoffs. Spearman correlation coefficients were calculated for scatter plots of baseline %pFVC by numerical baseline QILD and QLF, separately. To assess how the baseline QILD or QLF affects the change of %pFVC over time, we fitted linear

mixed effect models, with change of %pFVC as the outcome. Covariates included: 1) baseline %pFVC, 2) treatment arm, 3) study time points, 4) baseline QILD/QLF group, 5) interaction of baseline %pFVC and study time point, 6) interaction of treatment arm and study time point, 7) interaction of baseline QILD/QLF group and treatment arm, 8) interaction of baseline QILD/QLF group and study time point, 9) three-way interaction of treatment arm, study time point, and baseline QILD/QLF group. We obtained least squares means (LSM) from the models, and plotted the LSM to show the FVC change trend. No data were imputed. All analyses were done via SAS software (Version 9.4).

Results

Baseline characteristics of participants with ILD

Supplemental Figure 1 shows the distribution of patients as it relates to their treatment arm and baseline radiographic assessments. Two hundred and ten participants were randomized and received treatment: 106 to the PBO arm and 104 to the TCZ arm. Of these participants, 136 were confirmed by a thoracic radiologist to have ILD on HRCT done at baseline. Table 1 shows the baseline characteristics of the overall population (n= 210) compared to the subset of participants with ILD (n=136), which is further divided by treatment arm. Three participants had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing. Compared to those without ILD, the remaining 133 participants with ILD had numerically lower %pFVC and %pDLco, higher CRP, and a greater percentage of anti-topoisomerase-1 antibody positivity. ILD participants had a mean (SD) %pFVC of 79.6 (14.5) and 18.7% (11.1) QILD with most of that being ground-glass opacities (14.9% (8.3)); QLF accounted for a mean (SD) of 3.0% (3.6)). There were no significant differences between TCZ and PBO arms in the ILD groups at baseline. (Table 1).

Majority of ILD participants had moderate-to-severe whole lung involvement with limited fibrosis

The baseline QILD of 133 participants were stratified into 4 groups corresponding to minimal (≤5%), mild (>5-10%), moderate (>10-20%), and severe (>20%) lung involvement. The majority of participants (77%, or 102/133) with ILD had moderate or severe lung involvement, as defined by QILD of >10% (range 10.2 −52.6, Table 2). Higher degrees of QILD scores were associated with increasing mRSS, percentages of anti-topoisomerase-1 antibody positivity, lower baseline %pFVC and %pDLco, and higher percentages of QLF. Table 2 also shows ILD participants stratified by QLF into tertiles (0.1-1.0%, 1.1-2.7%, 2.8-18.5%), with approximately 2/3rds of participants having ≤2.8% fibrosis (89/133 or 67%). Similar to QILD, increasing QLF% was associated with higher percentages of anti-topoisomerase-1 antibody positivity and QILD, and lower baseline %pFVC and %pDLco.

QILD and QLF Inversely Correlates with the Forced Vital Capacity

Figure 1 demonstrates an inverse relationship between the baseline %pFVC and degree of QILD (Panel A); baseline %pFVC significantly declined with each escalating QILD cutoff point. The mean baseline %pFVC for those with severe QILD was significantly lower (mean 73.6, SD 12.9) when compared to those with minimal (mean 88.4, SD 18.3, p=0.01), mild

(mean 85.4, SD 13.1, p=0.00), and moderate QILD (mean 81.1, SD 14.4, p=0.01). There is an inverse correlation between the baseline %pFVC and QILD, with a correlation coefficient of −0.36, p=0.00. Figure 1 also demonstrates a similar inverse relationship of the baseline %pFVC with QLF (Panel B), with the mean baseline %pFVC significantly higher in the first tertile compared to the third tertile (p=0.00). The Spearman correlation was also −0.36 (p=0.00).

TCZ Stabilizes FVC Over 48 Weeks for Baseline Mild-to-Severe QILD and All Ranges of Baseline QLF

The TCZ arm demonstrated preserved %pFVC over 48 weeks: the least squared means (LSM) of FVC change was −0.1% for TCZ, and −6.3% for PBO. The difference between treatment group was 6.2% (P<0.0001). Figure 2 shows the mean trend over 48 weeks of the %pFVC change, accounting for covariates listed in methods; the results are separated by treatment arm (TCZ vs PBO) and stratified by the extent of QILD. As there were only 2 and 4 evaluable patients in the PBO and TCZ groups, respectively, with ≤5% QILD over 48 weeks, they were excluded from Figure 2. Specifically, those with >5% QILD in the TCZ group showed %pFVC stabilization over 48 weeks; this preservation was not influenced by the escalating degree of QILD involvement. For mild, moderate, and severe QILD, the mean change in the %pFVC in the TCZ arm at 48 weeks were −4.1 (SD: 2.5), N=11, 0.7 (SD: 1.9), N=19, 2.1 (SD: 1.6), N=26 and in the PBO group was −10.0 (SD: 2.6), N=11, −5.7 (SD: 1.6), N=26, −6.7 (SD: 2.0), N=16, respectively. A pairwise comparison at week 48 in the TCZ arm showed no significant differences between the mild, moderate, or severe QILD strata. Those with >5% QILD in the PBO arm showed worsening %pFVC decline, also with no significant pairwise differences in the trajectory of the decline by QILD severity.

Figure 3 shows a similar preservation effect in the TCZ arm, not present in the PBO arm when stratified by QLF severity. The mean trend over time of the %pFVC change, accounting for covariates listed in methods, separated by treatment arm (TCZ vs PBO) do not differ by the extent of QLF for either the TCZ or the PBO arms.

TCZ Stabilizes QILD and QLF Over 48 Weeks, for All Ranges of Baseline QILD and QLF

Table 3 reports QILD and QLF scores at baseline and 48-week follow-up by treatment arm (TCZ vs. PBO), and is stratified by the baseline QILD and QLF cutoff points. As expected, higher baseline QILD and QLF have higher QILD and QLF values at 48 weeks. At 48 weeks, the overall QILD for the TCZ arm showed a statistically significant improvement (mean change (95% CI) −1.8 (−3.5, −0.2), p=0.02). This benefit appears to be largely driven by those with the highest degrees of QILD at baseline; those with >20% QILD had the largest improvement of any of the subsets (−4.9 (−7.8, −1.9), p=0.01). In terms of fibrosis, there was a statistically significant increase in QLF scores at 48 weeks in the PBO arm (0.7 (0.3, 1.1), p=0.00) that was not seen in the TCZ arm (−0.5 (−1.1, 0.2), p=0.12). This decline in the PBO appears to be driven by worsening of QLF in the 1st and 2nd tertiles.

Discussion

In a Phase 2 trial (9), TCZ showed preservation of FVC compared to the PBO group in a population of early dcSSc; fewer patients in the TCZ arm had a decline in the percent predicted FVC (%pFVC): 10% in the TCZ group compared to 23% in the PBO group had ≥10% absolute decrease in the %pFVC. Based on these preliminary findings, focuSSced (10) trial was designed in early dcSSc, which replicated the effect of lung function preservation over 48 weeks: the mean decline in the TCZ group was −0.6% and −4.0% in PBO, p=0.002. In our current manuscript, we performed a post-hoc analysis using the individual patient data from the focuSSced trial and showed that approximately 65% of patients with early dcSSc have HRCT-defined ILD, with 77% of participants having >10% total lung involvement (as assessed by QILD). The preservation of FVC in the TCZ arm did not vary by the baseline degree of QILD or QLF, emphasizing the importance of early intervention to retard progression for those even with mild lung involvement. In addition, PBO arm showed worsening of lung fibrosis on HRCT at 48 weeks whereas TCZ attenuated the development of progressive fibrosis.

Our population in the focuSSced trial included an at-risk group for progressive ILD – early dcSSc with progressive skin disease and elevated acute phase reactants. This cohort may represent an immuno-inflammatory phase, rather than advanced-stage fibrotic ILD studied in previous SSc-ILD trials. Four large prior studies (e.g., the Scleroderma Lung Study I(16) and II(17), FAST(18), and the SENSCIS(19) trials) included participants with both limited and diffuse cutaneous SSc, with a median disease duration of ≤ 7 years, and enriched for clinical ILD based on respiratory symptoms (at least grade 2 exertional dyspnea according to baseline Mahler Dyspnea Index in the SLS-I and SLS-II studies), and fibrosis (≥10% of the lungs) in the SENSCIS trial(4, 20, 21). Participants in these trials had moderate-to-severe fibrotic disease: SLS-II had an average (SD) QLF of 8.6% (6.9) and SENSCIS reporting a visual fibrosis score of 36.8 (21.8) in the treatment arm and 35.2 (20.7) in the PBO arm(17, 19). With the exception of the FAST trial (%pFVC of 80.1% and 81.0% in the treatment and PBO arms, respectively), the studies' participants had %pFVC impairment: 68.1% in SLS-I, 66.5% in SLS-II, and 72% in SENSCIS(16, 17, 19).

Placebo-controlled trials and observational cohort studies inform our understanding of the natural progression of SSc-ILD; our data have an important role in understanding the pathogenesis of SSc-ILD progression in our enriched group(22–26). The resulting average rate of decline (SD) of FVC in the focuSSced PBO group was 228.2 mL (394.2) over 48 weeks, or a p%FVC of about 6.5% and considerably higher than those previously reported: the FAST trial(18) had an average decline of 3.0%, which was similar to that of the SLS-I trial (2.6%), and the SENSCIS cohort showed a decline of 2.6%, or 93.3 mL (13.5) over 52 weeks(16, 19). As such, our current analysis may influence trial design by providing a template to target early ILD, where the participants may have none-to-minimal respiratory symptoms, and enrich for progressive fibrotic ILD where treatment impact may be easier to detect(27).

Considerable variability in screening for SSc-ILD with HRCT still exists (28). There is increasing consensus that all patients with systemic sclerosis receive screening with

HRCT(29). Our data demonstrate the value of obtaining HRCT at the time of diagnosis: PFTs are not sensitive enough to accurately assess the presence of ILD and delays in treatment initiation may lead to irreversible disease(21, 30). Recently, Fleischner Society Writing Committee for Position Paper on interstitial lung abnormalities published consensus statement on interstitial lung abnormalities (ILAs)(31). They acknowledged that abnormalities identified during screening for ILD in high-risk groups (e.g., those with systemic sclerosis) are not considered as ILAs because they are not incidental(31). Analysis of our data shows that participants with >5% QILD involvement (majority of whom had involvement of their lower zones) was associated with a large decline in FVC% in the PBO group over 48 weeks, that mirrored in those with >10% QILD in the PBO group, highlighting the need for universal screening with HRCT in early dcSSc.

A unified treatment algorithm does not yet exist for SSc-ILD. Recent published work has established evidence-based consensus statements on medical management of SSc-ILD; however these do not address the varying subsets of SSc-ILD severity that impact clinical treatment decisions in practice(4, 20, 21). Our treatment algorithm divides patients into subclinical ILD (those with minimal ILD and preserved lung function) and clinical ILD (those with moderate-to-severe ILD and/or decline in PFTs). Based on current data, we propose to treat those with subclinical ILD but with at-risk features(4, 20, 21). As evidence accumulates for treatment effects in subsets of SSc-ILD, practice guidelines may favor targeted immunomodulatory therapies in early disease vs. anti-fibrotic therapy in later disease.

Strengths of our analysis include well-characterized data from a clinical trial and utilization of a well-established quantitative lung disease program to provide finer granularity for understanding TCZ's lung preservation effect. This study serves as an example of the use of quantitative HRCT measurements in understanding SSc-ILD pathophysiology and its response to treatment(11, 32).

The analysis is not without limitations. First, the analysis is post-hoc and should be considered as hypothesis generating. Second, while the reduction in vital capacity reflects having fewer functional alveolar units(33), it is an indirect measurement of the flow-resistive properties of the lung(34) and other factors in early SSc may confound the results (e.g., hide-bound chest thickness can cause thoracic restriction, poor patient effort, an inability to form a tight seal around the mouthpiece). This was addressed by standardizing spirometry in the clinical trial. Finally, the minimal QILD group (<5%) has too few patients to establish any meaningful assumptions. Nevertheless, as the field of quantitative radiomics advances its ability to reliably identify interstitial disease changes this small, even this low percentage of lung involvement may prove to have clinical implications.

In conclusion, early dcSSc is associated with high prevalence of ILD, with 77% having moderate-to-severe ILD (defined as QILD>10%). TCZ was effective in preserving the lung function, irrespective of the degree of QILD and QLF at baseline. This likely represents targeting of the immuno-inflammatory, early fibrotic phase of the disease(35) and may be a window of therapeutic opportunity to preserve lung function in early dcSSc. We also

highlight the natural history of early ILD that may serve as a template for other fibrotic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the sites and the patients who participated in the trial.

We also thank the focuSSced investigators from around the world:

Argentina: Eleonora Lucero, Bernardo Pons-Estel, Mariano Rivero, Guillermo Tate

Belgium: Vanessa Smith, Ellen De Langhe

Bulgaria: Rasho Rashkov, Anastas Batalov, Ivan Goranov, Rumen Stoilov

Canada: James Dunne, Sindhu R. Johnson, Janet E. Pope

Croatia: Dušanka Martinović Kaliterna

Denmark: Mette Mogensen, Anne Braae Olesen

France: Yannick Allanore

Germany: Joerg Christoph Henes, Ulf Müller-Ladner, Gabriela Riemekasten, Alla Skapenko

Greece: Panayiotis Vlachoyiannopoulos

Hungary: Emese Kiss, Tünde Minier

Italy: Lorenzo Beretta, Elisa Gremese, Marco Matucci-Cerinic, Gabriele Valentini

Japan: Yoshihide Asano, Tatsuya Atsumi, Hironobu Ihn, Tomonori Ishii, Osamu Ishikawa, Masataka Kuwana, Yoshihito Shima, Hiroki Takahashi, Kazuhiko Takehara, Yoshiya Tanaka, Yoshioki Yamasaki

Lithuania: Loreta Bukauskiene, Irena Butrimiene

Mexico: Gabriel Medrano Ramirez, Cesar Ramos-Remus, Tatiana Sofia Rodriguez Reyna

Netherlands: Jeska de Vries-Bouwstra, Jacob M. van Laar

Poland: Bogdan Batko, Slawomir Jeka, Eugeniusz Kucharz, Maria Majdan, Marzena Olesinska, Zaneta Smolenska

Portugal: Jose Alves, Maria Santos

Romania: Carmen Marina Mihai, Simona Rednic

Spain: Ivan Castellvi Barranco, Francisco Javier Lopez Longo, Carmen Simeon Aznar, Patricia Carreira

Switzerland: Oliver Distler, Ulrich A. Walker

United Kingdom: Emma Derrett-Smith, Bridget Griffiths, Neil McKay

United State: Jacob Aelion, Michael Borofsky, Roy Fleischmann, Joseph Z. Forstot, Suzanne Kafaja, M. Faisal Khan, Michael D. Kohen, Richard W. Martin, Fabian Mendoza-Ballesteros, Alireza Nami, Shirley Pang, Grissel Rios, Robert Simms, Keith Michael Sullivan, Virginia D. Steen

Funding: Dr. Roofeh was funded by the NIH/NIAMS T32 grant (AR007080). Dr. Khanna's work was supported by the NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (K24-AR-063129 & 1R01-AR070470-01A1).

Conflict of interest: Dr. Khanna reports grants and personal fees from Bristol Meyer Squib, during the conduct of the study; grants from NIH, grants from Immune Tolerance Network, grants and personal fees from Bayer, grants from Bristol Meyer Squib, grants from Horizon, grants from Pfizer, personal fees from Acceleron, personal fees from Acetlion, personal fees from Amgen, personal fees from Blade Therapeutics, personal fees from Boehringer Ingelheim, personal fees from CSL Behring, personal fees from Corbus, personal fees from Cytori, personal fees from Galapagos, personal fees from Genentech/Roche, personal fees from GSK, personal fees from Horizon, personal fees from Merck, personal fees from Mitsubishi Tanabe Pharma, personal fees from Regeneron, personal fees from Sanofi-Aventis, personal fees from United Therapeutics, other from Impact PH, personal fees from Eicos Sciences, Inc, personal fees and other from CiviBioPharma/Eicos Sciences, Inc., outside the submitted work.

Dr. Goldin reports other from MedQIA LLC, outside the submitted work.

Dr. Kim reports other from MedQIA, LLC. In addition, Dr. Kim has a patent US-2015-0324982-A1(Scores of Quantitative Interstitial Lung Disease) pending.

Dr. Lin reports other from Genentech, during the conduct of the study; other from Genentech, outside the submitted work; and Dr. Lin owns stock in Roche.

Dr. Furst reports grants and personal fees from Corbus, grants and personal fees from CSL Behring, grants and personal fees from Galapagos, grants and personal fees from Gilead, grants from GSK, grants from Kadmon, grants from PICORI, grants and personal fees from Pfizer, grants and personal fees from Talaris, personal fees from Abbvie, personal fees from Amgen, personal fees from Novartis, personal fees from Roche/Genentech, personal fees from Boehringer Ingelheim, personal fees from Speakers Bureau, outside the submitted work.

Dr. Denton reports personal fees from Actelion, grants and personal fees from GlaxoSmithKline, personal fees from Sanofi, grants and personal fees from Inventiva, personal fees from Boehringer Ingelheim, personal fees from Roche, grants and personal fees from CSL Behring, personal fees from Corbus, personal fees from Acceleron, personal fees from Horizon, during the conduct of the study.

Dr. Roofeh and Suiyuan Huang have nothing to disclose.

References

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–1699. [PubMed: 28413064]
2. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, Varga J. Systemic sclerosis. Nat Rev Dis Prim 2015;1:1–21.
3. De Lauretis A, Veeraraghavan S, Renzoni E. Connective tissue disease-associated interstitial lung disease: How does it differ from IPF? How should the clinical approach differ? Chron Respir Dis 2011;8:53–82. [PubMed: 21339375]
4. Roofeh D, Distler O, Allanore Y, Denton CP, Khanna D. Treatment of systemic sclerosis–associated interstitial lung disease: Lessons from clinical trials. *J Scleroderma Relat Disord* 2020;5:61–71.
5. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, Wells AU, Denton CP. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625–1635. [PubMed: 24591477]
6. Liu X, Mayes MD, Pedroza C, Draeger HT, Gonzalez EB, Harper BE, Reveille JD, Assassi S. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res 2013;65:1375–1380.
7. Assassi S, Leyva AL, Mayes MD, Sharif R, Nair DK, Fischbach M, Nguyen N, Reveille JD, Gonzalez EB, McNearney TA. Predictors of interstitial lung disease in early Systemic Sclerosis: A Prospective Longitudinal Study of the GENISOS Cohort. PLoS One 2011;6:e26061. [PubMed: 22022507]
8. Distler O, Volkmann ER, Hoffmann-Vold AM, Maher TM. Current and future perspectives on management of systemic sclerosis-associated interstitial lung disease. Expert Rev Clin Immunol 2019;15:1009–1017. [PubMed: 31566449]
9. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, Baron M, Chung L, Fierlbeck G, Lakshminarayanan S, Allanore Y, Pope JE, Riemekasten G, Steen V, Müller-Ladner U,

Lafyatis R, Stifano G, Spotswood H, Chen-Harris H, Dziadek S, Morimoto A, Sornasse T, Siegel J, Furst DE. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–2640. [PubMed: 27156934]

10. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, Allanore Y, Matucci-Cerinic M, Distler O, Shima Y, van Laar JM, Spotswood H, Wagner B, Siegel J, Jahreis A, Denton CP, Lucero E, Pons-Estel B, Rivero M, Tate G, Smith V, De Langhe E, Rashkov R, Batalov A, Goranov I, Stoilov R, Dunne J, Johnson SR, Pope JE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2020;8:963–974. [PubMed: 32866440]
11. Kim GHJ, Tashkin DP, Lo P, Brown MS, Volkmann ER, Gjertson DW, Khanna D, Elashoff RM, Tseng CH, Roth MD, Goldin JG. Using Transitional Changes on High-Resolution Computed Tomography to Monitor the Impact of Cyclophosphamide or Mycophenolate Mofetil on Systemic Sclerosis–Related Interstitial Lung Disease. Arthritis Rheumatol 2020;72:316–325. [PubMed: 31430058]
12. Goldin JG, Kim GHJ, Tseng CH, Volkmann E, Furst D, Clements P, Brown M, Roth M, Khanna D, Tashkin DP. Longitudinal Changes in Quantitative Interstitial Lung Disease on Computed Tomography after Immunosuppression in the Scleroderma Lung Study II. Ann Am Thorac Soc 2018;15:1286–1295. [PubMed: 30265153]
13. Volkmann ER, Tashkin DP, Sim M, Li N, Khanna D, Roth MD, Clements PJ, Hoffmann-Vold AM, Furst DE, Kim G, Goldin J, Elashoff RM. Cyclophosphamide for systemic sclerosis-related interstitial lung disease: A comparison of scleroderma lung study I and II. J Rheumatol 2019;46:1316–1325. [PubMed: 30770517]
14. Kim HJ, Tashkin DP, Clements P, Li G, Brown MS, Elashoff R, Gjertson DW, Abtin F, Lynch DA, Strollo DC, Goldin JG. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol 2010;28:S-26-S-35. [PubMed: 21050542]
15. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, Du Bois RM, Wells AU. Interstitial lung disease in systemic sclerosis: A simple staging system. Am J Respir Crit Care Med 2008;177:1248–1254. [PubMed: 18369202]
16. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel DE, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–2666. [PubMed: 16790698]
17. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, Goldin J, Arriola E, Volkmann ER, Kafaja S, Silver R, Steen V, Strange C, Wise R, Wigley F, Mayes M, Riley DJ, Hussain S, Assassi S, Hsu VM, Patel B, Phillips K, Martinez F, Golden J, Connolly MK, Varga J, Dematte J, Hinchcliff ME, Fischer A, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–719. [PubMed: 27469583]
18. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NSLL, Roberts C, Desai S, Herrick AL, McHugh NJ, Foley NM, Pearson SB, Emery P, Veale DJ, Denton CP, Wells AU, Black CM, du Bois RM. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962–3970. [PubMed: 17133610]
19. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Raghu G, Sauter W, Girard M, Alves M, Clerisme-Beaty E, Stowasser S, Tetzlaff K, Kuwana M, Maher TM. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518–2528. [PubMed: 31112379]
20. Roofeh D, Khanna D. Management of Systemic Sclerosis: The First Five Years. Curr Opin Rheumatol 2020;32:228–237. [PubMed: 32205570]
21. Roofeh D, Jaafar S, Vummidi D, Khanna D. Management of systemic sclerosis-associated interstitial lung disease. Curr Opin Rheumatol 2019;31:241–249. [PubMed: 30870216]

22. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Aetiology, Risk Factors, and Biomarkers in Systemic Sclerosis with Interstitial Lung Disease. Am J Respir Crit Care Med 2019;Epub ahead:1–57.
23. Khanna D, Nagaraja V, Tseng C hong, Abtin F, Suh R, Kim G, Wells A, Furst DE, Clements PJ, Roth MD, Tashkin DP, Goldin J. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: Implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. Arthritis Res Ther 2015;17:1–10. [PubMed: 25566937]
24. Steen VD, Conte C, Owens GR, Medsger T a. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994;37:1283–1289. [PubMed: 7945490]
25. Steen V Predictors of end stage lung disease in systemic sclerosis. Ann Rheum Dis 2003;62:97–99. [PubMed: 12525376]
26. Winstone TA, Assayag D, Wilcox PG, Dunne J V., Hague CJ, Leipsic J, Collard HR, Ryerson CJ. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: A systematic review. Chest 2014;146:422–436. [PubMed: 24576924]
27. Silver RM. Systemic sclerosis: Choosing patients wisely when treating interstitial lung disease. Nat Rev Rheumatol 2017;13:455–456. [PubMed: 28680133]
28. Bernstein EJ, Khanna D, Lederer DJ. Screening High-Resolution Computed Tomography of the Chest to Detect Interstitial Lung Disease in Systemic Sclerosis: A Global Survey of Rheumatologists. Arthritis Rheumatol 2018;70:971–972. [PubMed: 29426066]
29. Hoffmann-Vold A- M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, Bruni C, Carducci P, Carreira PE, Castellví I, Galdo F Del, Distler JHW, Foeldvari I, Fraticelli P, George PM, Griffiths B, Paul S, Rotondo C, Rubio-rivas M, Seferian A, Tomčík M, Uzunhan Y, Walker UA, Więsik-szewczyk E, Distler O. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020;9913:1–13.
30. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TDLL, Maurer B, Jordan S, Speich R, Frauenfelder T, Distler O Pulmonary function tests: High rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol 2015;67:3256–3261. [PubMed: 26316389]
31. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, Verschakelen J, Nicholson AG, Beasley MB, Christiani DC, San José Estépar R, Seo JB, Johkoh T, Sverzellati N, Ryerson CJ, Graham Barr R, Goo JM, Austin JHM, Powell CA, Lee KS, Inoue Y, Lynch DA. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med* 2020;8:726–737.
32. Montesi SB, Caravan P. Novel Imaging Approaches in Systemic Sclerosis-Associated Interstitial Lung Disease. Curr Rheumatol Rep 2019;21:.
33. O'Donnell D Physiology of interstitial lung disease. In: Schwartz M, King T, editors. Interstitial lung Dis 1998. p. 51–70.
34. Grippi MA, Tino G. Pulmonary Function Testing. In: Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM SM, editor. Fishman's Pulm Dis Disord, 5th ed. New York: 2015.
35. Denton CP, Ong VH, Xu S, Chen-Harris H, Modrusan Z, Lafyatis R, Khanna D, Jahreis A, Siegel J, Sornasse T. Therapeutic interleukin-6 blockade reverses transforming growth factor-beta pathway activation in dermal fibroblasts: Insights from the faSScinate clinical trial in systemic sclerosis. Ann Rheum Dis 2018;77:1362–1371. [PubMed: 29853453]

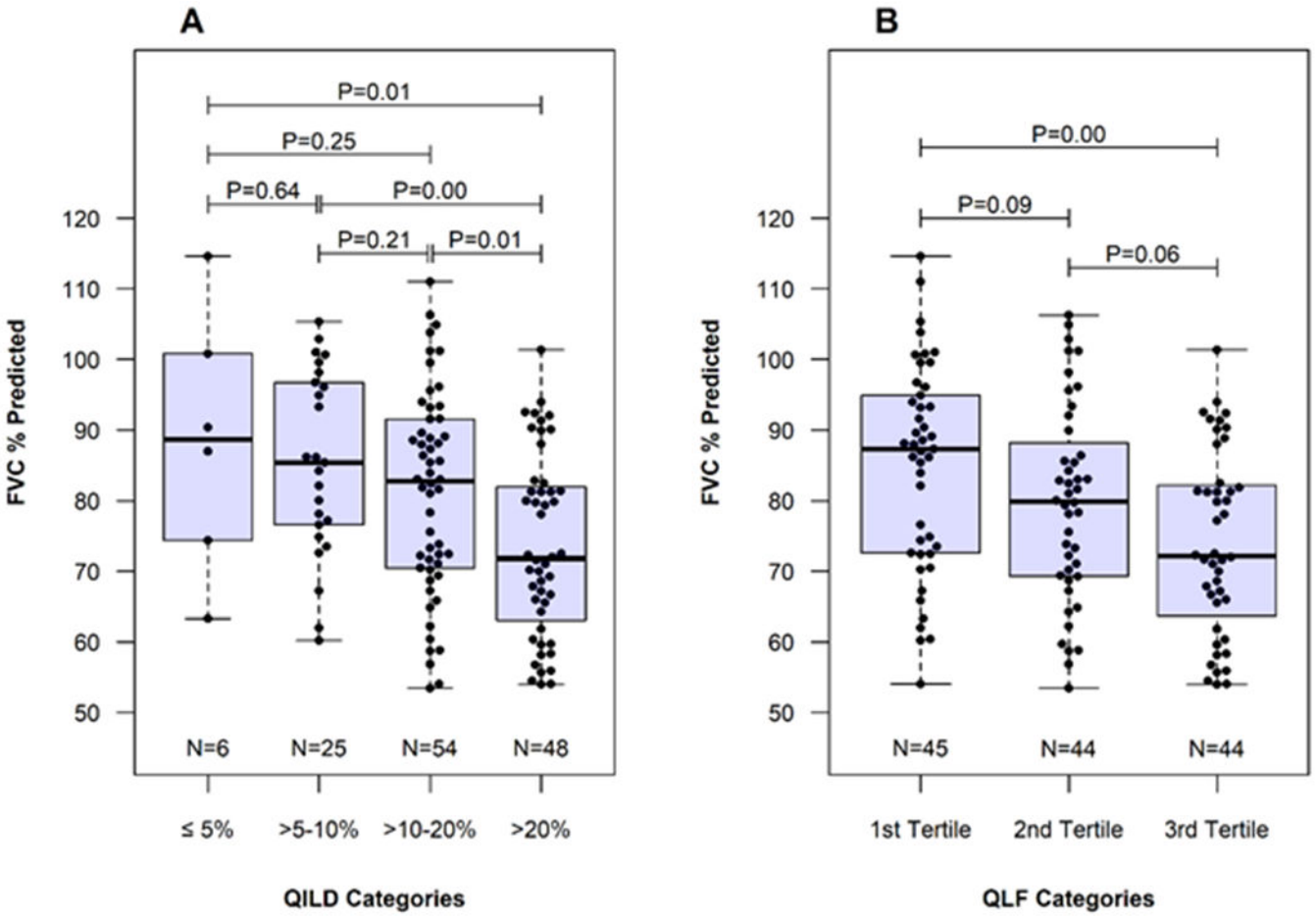
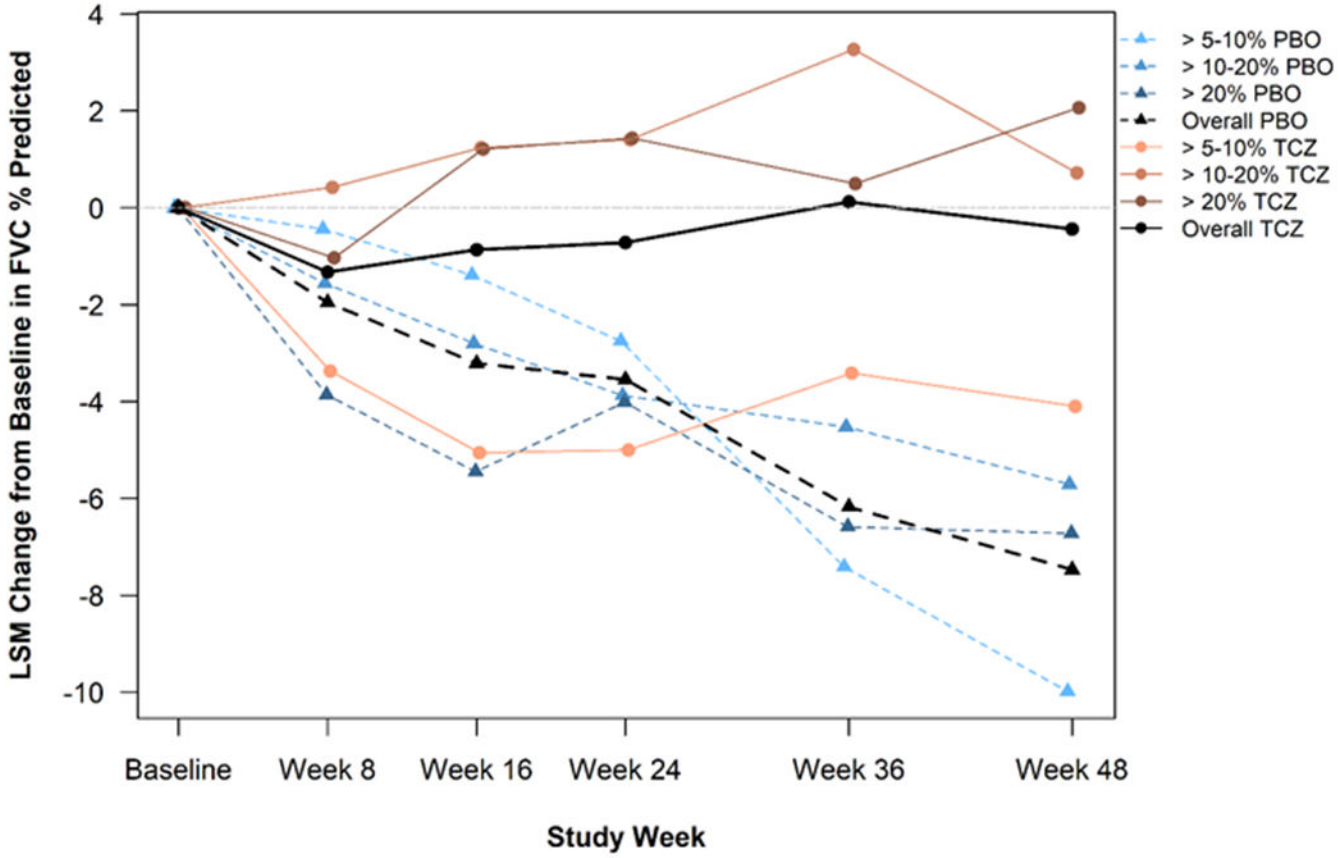


Figure 1:

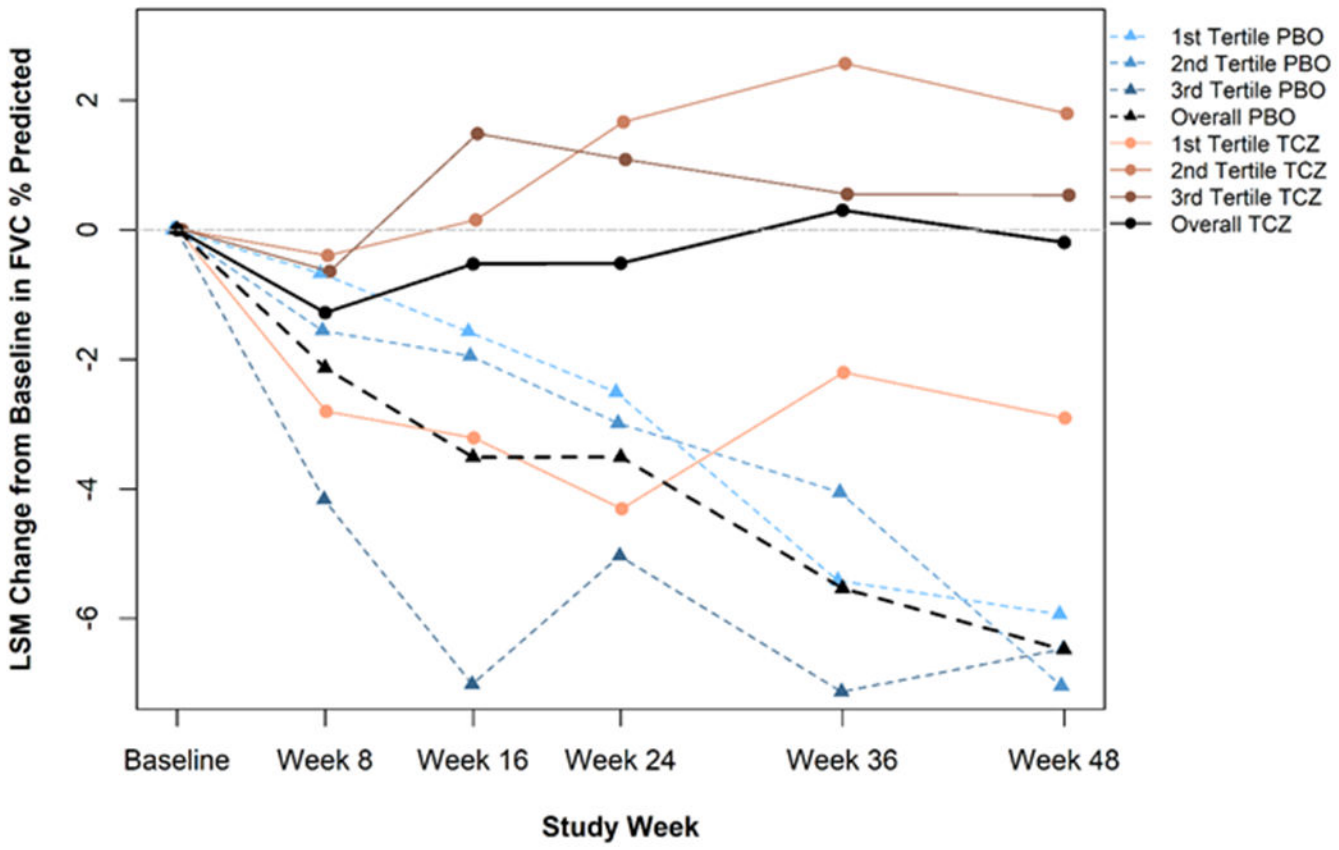
Relationship between forced vital capacity % predicted and increasing severity of baseline QILD (A) and increasing severity of baseline QLF (B). FVC= Forced Vital Capacity, QILD= Quantitative Interstitial Lung Disease, QLF= Quantitative Lung Fibrosis



		BSL	WK8	WK16	WK24	WK36	WK48
<=5%	TCZ, N	4	4	3	2	3	3
	PBO, N	2	2	1	2	1	2
> 5-10%	TCZ, N	13	13	11	11	11	11
	PBO, N	12	10	11	11	11	11
> 10-20%	TCZ, N	22	21	21	19	18	19
	PBO, N	32	30	31	29	27	26
> 20%	TCZ, N	28	27	27	24	25	26
	PBO, N	20	19	17	17	16	16

Figure 2:

ILD participants showing a mean trend over time of forced vital capacity change by treatment and quantitative ILD of the whole lung. Note: <5% is removed from this model as there were only 2 evaluable patients in the placebo group and 4 evaluable patients in the treatment group with <5% QILD over 48 weeks. FVC= Forced Vital Capacity; ILD= Interstitial Lung Disease; QILD= quantitative ILD; PBO= Placebo; TCZ= Tocilizumab



		BSL	WK8	WK16	WK24	WK36	WK48
1st Tertile	TCZ, N	19	19	16	15	15	15
	PBO, N	26	23	23	22	21	22
2nd Tertile	TCZ, N	23	22	21	19	18	21
	PBO, N	21	20	21	21	19	19
3rd Tertile	TCZ, N	25	24	25	22	24	23
	PBO, N	19	18	16	16	15	14

Figure 3:

ILD participants showing a mean trend over time of forced vital capacity change by treatment and quantitative lung fibrosis of the whole lung. FVC= Forced Vital Capacity; ILD= Interstitial Lung Disease; PBO= Placebo; TCZ= Tocilizumab

Table 1:

Baseline characteristics of the overall focuSSced population and those with ILD on HRCT

	All Patients N=210			ILD N=136			Tocilizumab N=68			Placebo N=68		
Demographics												
Females, %	81.4			79.4			77.9			80.9		
Age, mean years (SD)	48.2	(12.4)		48.1	(12.9)		47.6	(12.5)		48.7	(13.3)	
Duration of SSc months, (SD)	22.6	(16.5)		22.8		(16.8)	23.0	(17.2)		22.6	(16.6)	
Disease Features												
Total mRSS, units (SD)	20.3	(6.8)		20.8	(7.0)		20.7	(6.8)		20.9	(7.2)	
CRP, mg/L, (SD)	7.9	(13.1)		9.6	(15.4)		11.2	(17.4)		8.0	(13.1)	
ANA positive, n/N (%)	183/198	(92.4)		124/128	(96.9)		65/66	(98.5)		59/62	(95.2)	
Anti-topoisomerase +, n/N (%)	103/202	(51.0)		90/131	(68.7)		46/67	(68.7)		44/64	(68.8)	
Anti-RNA polymerase +, n/N (%)	35/202	(17.3)		19/131	(14.5)		13/67	(19.4)		6/64	(9.4)	
Anti-centromere +, n/N (%)	17/202	(8.4)		2/131	(1.5)		1/67	(1.5)		1/64	(1.6)	
Baseline Pulmonary Function Assessments												
FVC, in ml, (SD)	2996.7	(836.8)		2885.4	(835.8)		2826.8	(873.7)		2944.1	(798.3)	
%pFVC, % (SD)	82.1	(14.8)		79.6	(14.5)		77.7	(13.9)		81.5	(14.9)	
$\%pDL_{CO}$, % (SD)	75.6	(18.9)	n=208	70.4	(16.9)	n=135	68.7	(16.8)	n=68	72.1	(17.0)	n=67
Baseline Quantitative ILD Measurements, Whole Lung % *												
HRCT QILD, % (SD)	15.9	(11.4)	n=202	18.7	(11.1)	n=133	20.5	(12.8)	n=67	16.8	(8.8)	n=66
GGO, % (SD)	13.0	(8.8)	n=202	14.9	(8.3)	n=133	16.2	(9.5)	n=67	13.6	(6.7)	n=66
QLF, % (SD)	2.3	(3.3)	n=202	3.0	(3.6)	n=133	3.5	(4.2)	n=67	2.5	(3.0)	n=66
HC, % (SD)	0.4	(1.2)	n=202	0.4	(1.3)	n=133	0.5	(1.5)	n=67	0.3	(1.2)	n=66

* Three subjects had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing. None of the differences between tocilizumab and placebo are statistically significant at $p< 0.05$.

SSc= Systemic Sclerosis; mRSS= Modified Rodnan Skin Score; CRP= C-Reactive Protein; ANA= Antinuclear Antibody; FVC- Forced Vital Capacity; pFVC= Predicted Forced Vital Capacity; pDLco= Predicted Diffusing Capacity for carbon monoxide corrected for haemoglobin; HRCT = High resolution CT; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; GGO = Ground glass opacities; QLF= Lung fibrosis (reticulations) on computer quantification; HC = Honeycombing

Table 2:

ILD Participants Stratified by Quantitative Interstitial Lung Disease and Lung Fibrosis involving the Whole Lung

	ILD	Quantitative Interstitial Lung Disease (QILD) by Ascending Severity				Quantitative Lung Fibrosis (QLF) by Ascending Severity		
Severity Cut-Off	**-**	**Minimal <5%**	**Mild >5-10%**	**Moderate >10-20%**	**Severe >20%**	**1st Tertile 0.1-1.0%**	**2nd Tertile 1.1-2.7%**	**3rd Tertile 2.8-18.5%**
N	**N=133***	**N=6**	**N=25**	**N=54**	**N=48**	**N=45**	**N=44**	**N=44**
Demographics								
Females, %	79.0	66.7	76.0	83.3	77.1	77.8	81.8	77.3
Age, mean years (SD)	48.0 (13.0)	45.2 (16.6)	45.5 (11.3)	45.9 (13.3)	52.1 (12.3)	43.2 (12.7)	48.5 (12.4)	52.5 (12.3)
Duration of SSc months, (SD)	22.9 (16.9)	24.4 (13.5)	22.3 (16.6)	27.0 (17.2)	18.5 (16.5)	22.3 (13.5)	26.5 (19.6)	19.9 (16.9)
Disease Features								
Total mRSS, units (SD)	20.8 (7.1)	16.6 (7.3)	18.8 (5.8)	20.9 (7.6)	22.3 (6.7)	19.7 (6.9)	20.9 (7.4)	21.9 (6.8)
CRP, mg/L, (SD)	9.8 (15.5)	31.0 (39.6)	5.4 (8.3)	11.4 (16.8)	7.5 (9.0)	10.9 (18.7)	11.5 (17.0)	6.8 (9.1)
ANA positive, n/N (%)	121/125 (96.8)	6/6 (100)	24/24 (100)	48/50 (96.0)	43/45 (95.6)	42/43 (97.7)	40/41 (97.6)	39/41 (95.1)
Anti-topoisomerase +, n/N (%)	88/128 (68.8)	4/6 (66.7)	15/24 (62.5)	33/50 (66.0)	36/48 (75.0)	28/43 (65.1)	26/41 (63.4)	34/44 (77.3)
Anti-RNA polymerase +, n/N (%)	19/128 (14.8)	1/6 (16.7)	3/24 (12.5)	5/50 (10.0)	10/48 (20.8)	4/43 (9.3)	9/41 (22.0)	6/44 (13.6)
Anti-centromere +, n/N (%)	2/128 (1.6)	0/6 (0.0)	1/24 (4.2)	1/50 (2.0)	0/48 (0.0)	1/43 (2.3)	1/41 (2.4)	0/44 (0.0)
Baseline Pulmonary Function Assessments								
FVC, in ml, (SD)	2881.4 (833.6)	3483.3 (1079.0)	3268.8 (1031.4)	2945.7 (672.4)	2532.1 (720.8)	3216.4 (908.1)	2817.5 (656.4)	2602.7 (810.8)
%pFVC, % (SD)	79.5 (14.5)	88.4 (18.3)	85.4 (13.1)	81.1 (14.4)	73.6 (12.9)	84.8 (14.6)	79.6 (13.9)	74.0 (13.1)
%pDL_{CO}, % (SD)	70.4 (17.1); n=132	88.5 (19.7)	85.3 (17.2)	67.3 (12.9)	63.6 (14.9); n=47	75.9 (17.4)	70.9 (17.0)	64.0 (14.9); n=43
Baseline Quantitative ILD Measurements, Whole Lung %*								
HRCT QILD, % (SD)	18.7 (11.1)	4.0 (0.9)	7.8 (1.4)	14.5 (2.8)	30.8 (8.6)	9.8 (4.2)	16.4 (5.6)	30.1 (10.3)
GGO, % (SD)	14.9 (8.3)	3.7 (0.8)	6.9 (1.2)	12.3 (2.7)	23.5 (7.2)	8.9 (3.9)	14.0 (5.4)	22.0 (8.8)
QLF, % (SD)	3.0 (3.6)	0.3 (0.1)	0.8 (0.6)	1.5 (1.0)	6.1 (4.5)	0.6 (0.3)	1.7 (0.4)	6.8 (4.3)
HC, % (SD)	0.43 (1.3)	0 (0)	0 (0)	0.3 (0.9)	0.8 (2.0)	0.1 (0.5)	0.3 (0.9)	0.9 (2.0)

*Three subjects had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing.

SSc=Systemic Sclerosis; mRSS= Modified Rodnan Skin Score; CRP= C-Reactive Protein; ANA= Antinuclear Antibody; FVC- Forced Vital Capacity; pFVC= Predicted Forced Vital Capacity; pDLco= Predicted Diffusing Capacity for carbon monoxide corrected for haemoglobin; HRCT = High resolution CT; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; GGO = Ground glass opacities; QLF= Lung fibrosis (reticulations) on computer quantification; HC = Honeycombing

Table 3:

Quantitative ILD and Fibrosis Scores Comparing Baseline to 48 weeks

	Baseline Mean (95% CI)		48 week Mean (95% CI)		Change from Baseline Mean (95% CI)*	
	Tocilizumab	**Placebo**	**Tocilizumab**	**Placebo**	**Tocilizumab**	**Placebo**
Whole Lung QILD (TCZ n=55; PBO n=48)						
Overall n=103	21.1 (18.2, 23.9) n=55	16.0 (14.2, 17.8) n=48	19.2 (16.7, 21.8) n=55	17.4 (15.4, 19.5) n=48	−1.8 (−3.5, −0.2) n=55, p=0.02	1.5 (−0.03, 3.0) n=48, p=0.13
≤5% n=4	3.9 (2.2, 5.5) n=3	4.3 (-) n=1	3.6 (0.3, 6.8) n=3	5.9 (-) n=1	−0.3 (−2.7, 2.1) n=3	1.6 (-) n=1
>5-10% n=19	7.2 (6.3, 8.1) n=9	8.0 (7.2, 8.8) n=10	7.8 (5.5, 10.0) n=9	11.6 (7.5, 15.7) n=10	0.6 (−1.1, 2.3) n=9, p=0.82	3.6 (−0.07, 7.3) n=10, p=0.11
>10-20% n=43	15.1 (14.0, 16.2) n=19	14.4 (13.4, 15.4) n=24	15.7 (13.2, 18.2) n=19	16.8 (14.6, 19.0) n=24	0.6 (−1.8, 2.9) n=19, p=0.57	2.4 (0.5, 4.3) n=24, p=0.08
>20% n=37	33.2 (30.1, 36.2) n=24	25.8 (23.2, 28.4) n=13	28.3 (25.1, 31.5) n=24	24.0 (19.3, 28.7) n=13	−4.9 (−7.8, −1.9) n=24, p=0.01	−1.9 (−5.2, 1.5) n=13, p=0.39
Whole Lung QLF (TCZ n=55; PBO n=49)						
Overall n=104	3.7 (2.7, 4.7) n=55	3.0 (1.5, 3.0) n=49	3.3 (2.5, 4.1) n=55	3.0 (2.1, 3.9) n=49	−0.5 (−1.1, 0.2) n=55, p=0.12	0.7 (0.3, 1.1) n=49, p=0.00
1st Tertile n = 35	0.6 (0.4, 0.7) n=15	0.0.6 (0.5, 0.7) n=20	0.7 (0.4, 0.9) n=15	1.1 (0.8, 1.4) n=20	0.09 (−0.1, 0.3) n=15, p=1.00	0.5 (0.1, 0.8) n=20, p=0.00
2nd Tertile n = 36	1.7 (1.5, 1.9) n=18	1.7 (1.5, 1.9) n=18	1.7 (1.2, 2.2) n=18	3.1 (2.2, 3.9) n=18	0.01 (−0.6, 0.6) n=18, p=0.42	1.4 (0.7, 2.1) n=18, p=0.00
3rd Tertile n = 33	7.6 (5.8, 9.3) n=22	6.3 (3.7, 8.8) n=11	6.3 (4.9, 7.7) n=22	6.4 (3.1, 9.7) n=11	−1.3 (−2.9, 0.4) n=22, p=0.21	0.1 (−1.0, 1.3) n=11, p=1.00

*Negative score denotes improvement; (-) indicates 95% CI cannot be calculated as n=1. All P values were obtained from Wilcoxon signed rank test.

CI=Confidence Interval; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; QLF= Lung fibrosis (reticulations) on computer quantification

QILD is missing n=33: 19 dropped out between week 0 and 48 (7 in TCZ arm, 12 in PBO arm) and 14 were active through week 48, but had missing data at week 48 (6 in TCZ arm, 8 in PBO arm).

QLF is missing n=32: 19 dropped out between week 0 and 48 (7 in TCZ arm, 12 in PBO arm) and 13 were active through week 48, but had missing data at week 48 (6 in TCZ arm, 7 in PBO arm).