**Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase 2 randomised controlled trial (faSScinate)**

Dinesh Khanna, MD,1 Christopher P. Denton, FRCP,2 Celia J. F. Lin, MD,3 Jacob M. van Laar, MD,4 Tracy M. Frech, MD,5 Marina E. Anderson, FRCP,6 Murray Baron, MD,7 Lorinda Chung, MD,8 Gerhard Fierlbeck, MD,9 Santhanam Lakshminarayanan, MD,10 Yannick Allanore, PhD,11 Janet E. Pope, MD,12 Gabriela Riemekasten, PhD,13 Virginia Steen, MD,14 Ulf Müller-Ladner, MD,15 Helen Spotswood, PhD,16 Laura Burke, BSc (Hons),16 Jeffrey Siegel, MD,3 Angelika Jahreis, MD,3 Daniel E. Furst, MD17

1University of Michigan Scleroderma Program, Ann Arbor, Michigan, USA; 2University College London Medical School, London, UK; 3Genentech, South San Francisco, California, USA; 4University Medical Center Utrecht, Utrecht, Netherlands; 5University of Utah, Veterans Affairs Medical Center, Salt Lake City, Utah, USA; 6University of Liverpool and Aintree University Hospital, Liverpool, UK; 7Jewish General Hospital, Montreal, Quebec, Canada; 8Stanford University School of Medicine and Palo Alto VA Health Care System, Palo Alto, California, USA; 9University of Tübingen, Tübingen, Germany; 10University of Connecticut Health Center, Farmington, Connecticut, USA; 11Paris Descartes University, Paris, France; 12Schulich School of Medicine and Dentistry, University of Western Ontario, St Joseph’s Health Care, London, Ontario, Canada; 13University of Lübek and Charité University Hospital, Berlin, Germany; 14Georgetown University, Washington, DC, USA; 15Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany; 16Roche Products Ltd., Welwyn Garden City, UK; 17University of California, Los Angeles, California, USA

**Corresponding Author**

Dinesh Khanna**,** MD

Division of Rheumatology

Department of Internal Medicine

University of Michigan Scleroderma Program

300 North Ingalls Street

Ann Arbor, MI 48109, USA

Phone: 734.232.2014

Fax: 734.763.5761

Email: khannad@med.umich.edu

**Word Count:** 3257(3000 limit)

**Tables/Figures:** 3/3(6 max), + 2 supplementary tables

**References:** 40(50 max)

**Section head**: Clinical and epidemiological research

**ABSTRACT** (290 words; maximum 250)

**Objectives** Assess the efficacy and safety of tocilizumab in systemic sclerosis (SSc) patients.

**Methods** SSc patients were randomly assigned (1:1) to weekly double-blind tocilizumab 162 mg or placebo subcutaneously for 48 weeks followed by open-label tocilizumab for 48 weeks. Exploratory endpoints included modified Rodnan skin score (mRSS) and percent predicted forced vital capacity (%pFVC) through week 96.

**Results** Overall, 31/44 (70%) placebo and 30/43 (70%) tocilizumab patients transitioned to open-label tocilizumab, and 24/44 (55%) placebo-tocilizumab and 27/43 (63%) continuous-tocilizumab patients completed week 96. Observed mean (SD [95% CI]) change from baseline in mRSS was –3.1 (6.3 [–5.4, –0.9]) for placebo and –5.6 (9.1 [–8.9, –2.4]) for tocilizumab at week 48 and –9.4 (5.6 [–8.9, –2.4]) for placebo-tocilizumab and –9.1 (8.7 [–12.5, –5.6]) for continuous-tocilizumab at week 96. Of patients who completed week 96, any decline in %pFVC was observed for 20/24 (83% [95% CI: 63%, 95%]) placebo and 14/26 (54% [95% CI: 33%, 73%]) tocilizumab patients by week 48 and 10/24 (42% [95% CI: 22%, 63%]) placebo-tocilizumab and 12/26 (46% [95% CI: 27%, 67%]) continuous-tocilizumab patients between weeks 48 and 96 in the open-label period; no patients had >10% decline in %pFVC between weeks 48 and 96. Serious infection rates/100 patient-years [95% CI] were 10.9 [3.0, 27.9] with placebo and 34.8 [18.0, 60.8] with tocilizumab during the double-blind period by week 48 and 19.6 [7.2, 42.7] with placebo-tocilizumab and 0.0 [0.0, 12.2] with continuous-tocilizumab during the open-label period between weeks 48 and 96.

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

**Trial registration number** ClinicalTrials.gov, number NCT01532869.

**Keywords:** systemic sclerosis (SSc), treatment, DMARDs (biologic), scleroderma, tocilizumab, interleukin-6

**INTRODUCTION**

Systemic sclerosis (SSc) is a rare, debilitating autoimmune disorder of the connective tissue and vasculature that is characterised by inflammation, fibrosis and microvascular injury of multiple organs.1,2 Patients with SSc experience high morbidity and mortality rates,2 particularly those who have pulmonary, cardiac or renal organ involvement.3 Indeed, lung disease is the primary cause of scleroderma-related deaths.1,4 Few treatment options are available for patients with SSc, and there is an unmet need for disease-modifying therapy.5

Interleukin-6 (IL-6) appears to play a role in SSc pathogenesis.6,7 Patients with SSc have increased IL-6 expression in endothelial cells and skin fibroblasts8. Serum IL-6 levels are elevated in patients with SSc,9,10 particularly those with early diffuse cutaneous skin involvement.11,12 8Furthermore, some studies have suggested a role for IL-6 as a marker for disease progression and clinical outcome in patients with SSc.10 C-reactive protein (CRP) is correlated with IL-6, and CRP levels are elevated in patients with active SSc, especially those with early diffuse cutaneous SSc.13

Tocilizumab is a monoclonal anti–IL-6 receptor-alpha antibody for the treatment of patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular-course juvenile idiopathic arthritis14,15 and giant cell arteritis.14,15 Initial investigations of tocilizumab in patients with SSc demonstrated improvements in skin sclerosis and SSc-associated polyarthritis.16,17 The faSScinate clinical trial was the first double-blind, randomised controlled trial investigating the efficacy and safety of subcutaneous tocilizumab in patients with SSc. Results from the 48-week double-blind period of faSScinate were published previously and demonstrated that treatment with tocilizumab resulted in a clinically meaningful but not statistically significant decline in modified Rodnan skin score (mRSS) compared with placebo through week 48 for patients receiving tocilizumab.18 Exploratory efficacy results and safety through week 96 of the faSScinate trial, including the 48-week open-label period, are now reported.

**METHODS**

**Study design**

faSScinate was a multicentre, randomised, double-blind, placebo-controlled, two-arm, parallel-group, phase 2 clinical trial conducted at 35 hospitals across Canada, France, Germany, United Kingdom and United States. The study design and patient enrolment criteria have been published.18 Briefly, the 96-week trial consisted of a 48-week double-blind period followed by a 48-week open-label period. Patients were randomly assigned (1:1) to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo during the 48-week double blind period (tocilizumab group and placebo group, respectively) with the option for escape therapy with methotrexate, hydroxychloroquine or mycophenolate mofetil (MMF) after 24 weeks if they had worsening SSc. Randomisation was stratified according to joint involvement at baseline (<4 or ≥4 joints on the 28 tender joint count). At week 48, all patients in the tocilizumab and placebo groups transitioned to open-label weekly injections of tocilizumab 162 mg for another 48 weeks (continuous-tocilizumab and placebo-tocilizumab groups, respectively).

**Patients**

Eligible patients were 18 years of age or older; received a diagnosis of SSc according to the 1980 American College of Rheumatology Criteria,19 with less than 5 years since their first non-Raynaud’s sign or symptom; had an mRSS score of 15 to 40 with clinical skin involvement proximal to the elbows, knees or both, with or without facial involvement; and had active disease. Active disease was defined as at least one of the following features at screening: increase ≥3 in mRSS units compared with the last visit within the previous 1 to 6 months or new-onset SSc within 1 year before screening, involvement of one new body area with ≥2 mRSS units or two new body areas with ≥1 mRSS, documentation of worsening skin thickening (patients with new-onset SSc only), or ≥1 tendon friction rub plus CRP level ≥10 mg/L, erythrocyte sedimentation rate (ESR) ≥28 mm/hour or platelet count ≥330 × 103/µL. All patients provided written informed consent.

**Assessments**

Exploratory efficacy endpoints included mean change from baseline to week 96 in mRSS; proportions of patients with improvements in mRSS of ≥20%, ≥40% and ≥60%; proportions of patients achieving minimal clinically important difference (MCID) in mRSS (change from baseline of ≥4.7)20; percent predicted forced vital capacity (%pFVC); and percent predicted diffusing capacity for carbon monoxide corrected for haemoglobin (%pDLCO [Hb corr]). Patient-reported outcomes included Health Assessment Questionnaire–Disability Index (HAQ-DI), Clinician Global visual analogue scale (VAS), Patient Global VAS, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score and pruritus 5-D itch scale. Safety was reported as rates of adverse events (AEs) and serious AEs (SAEs) per 100 patient-years (PY) with 95% confidence intervals (CIs).

**Statistical analysis**

Although a mixed-model, repeated-measures analysis was performed on the placebo-controlled period at weeks 24 and 48,18 observed data were analysed for the week 96 period because all endpoints during the open-label period were exploratory. Exploratory efficacy endpoints in the open-label period were assessed in the modified intent-to-treat population (all randomly assigned patients who received any study drug). Safety was assessed in all patients who received study drug and provided at least one safety assessment after treatment (safety population) and was summarised by treatment received. . The study was not designed or powered for formal statistical comparison of the two treatment arms within the open-label period or with the original tocilizumab arm at week 48 because of inherent biases of open label results. However, 95% confidence intervals (CIs) were calculated as descriptive statistics using the Pearson Clopper method for exact binomial, and CIs for rates of AEs were based on the Poisson distribution.21 Data from escape patients were not censored.

**RESULTS**

**Patients**

Eighty-seven patients were enrolled in the faSScinate trial (Figure 1); in the double-blind period, 44 patients were originally assigned to receive weekly subcutaneous placebo (placebo group), and 43 patients were originally assigned to receive weekly subcutaneous tocilizumab 162 mg (tocilizumab group). At week 48, 31 (70.5%) patients originally assigned to double-blind placebo transitioned to open-label weekly tocilizumab 162 mg (placebo-tocilizumab group), and 30 (69.8%) patients originally assigned to double-blind tocilizumab transitioned to open-label weekly subcutaneous tocilizumab 162 mg (continuous-tocilizumab group) until they completed the study or withdrew from treatment. Twenty-four (54.5%) patients in the placebo-tocilizumab group and 27 (62.8%) patients in the continuous-tocilizumab group completed week 96. During the open-label period, five patients discontinued because of AEs (four patients in the placebo-tocilizumab group and one patient in the continuous-tocilizumab group). Other reasons for study withdrawal were non-compliance (one patient in the placebo-tocilizumab group), lack of efficacy (one patient in each treatment group) and patient consent withdrawn (one patient in each treatment group). Escape therapy was received by 18 patients originally assigned to receive placebo (12 in the placebo group during the double-blind period and six in the placebo-tocilizumab group during the open-label period) and by nine patients originally assigned to receive tocilizumab (five in the tocilizumab group during the double-blind period and four in the continuous-tocilizumab group during the open-label period) (Figure 1).

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

**Efficacy**

Improvements in mRSS were observed during the double-blind period with tocilizumab treatment (mean [SD; 95% CI] change from baseline to week 48: –5.6 [9.1; –8.9, –2.4]). In addition to the –5.6 improvement from baseline to week 48 with tocilizumab treatment, further improvement was seen in the open-label period, bringing the total mean improvement to –9.1 [8.7; –12.5, –5.6] from baseline to week 96 (Figure 2). Furthermore, patients in the placebo group experienced similar improvements after receiving open-label tocilizumab from week 48 to week 96 (Figure 2) (mean [SD; 95% CI] change from baseline –3.1 [6.3; –5.4, –0.9] to week 48 and –9.4 [5.6; –11.8, –7.0] to week 96). There were incremental improvements between weeks 48 and 96 in the proportions of patients who experienced improvements in mRSS of ≥20%, ≥40% and ≥60% and change in mRSS equal to or greater than the MCID of 4.7 units in the continuous-tocilizumab group (Table 2). The proportions of patients in the placebo-tocilizumab group who achieved these endpoints at week 96 after 48 weeks of open-label tocilizumab were comparable to the proportions of patients in the tocilizumab group at week 48. For example, the proportions of patients with change in mRSS ≥20%/40%/60% were 41.9%/23.3%/11.6% at week 48 in the tocilizumab group and 40.9%/29.5%/15.9% at week 96 in the placebo-tocilizumab group; 41.9% of patients in the tocilizumab group at week 48 and 43.2% of placebo-tocilizumab patients at week 96 experienced improvements in mRSS ≥4.7 units.

Improvements in patient-reported outcomes, as indicated by negative change in HAQ-DI, Clinician Global VAS, and Patient Global VAS and positive change in FACIT-Fatigue score, observed at week 48 in the tocilizumab group were maintained through the open-label period in the continuous-tocilizumab group (Table 2). Furthermore, greater improvements in patient-reported outcomes were observed in placebo-tocilizumab patients after they switched to tocilizumab during the open-label period than during the double-blind placebo period. Patients in the placebo group experienced mean (95% CI) changes from baseline in HAQ-DI of 0.17 (0.05, 0.30) after 48 weeks of double-blind placebo treatment and –0.29 (-0.46, –0.13) at week 96 after 48 weeks of open-label tocilizumab treatment (placebo-tocilizumab). Changes from baseline in Clinician Global VAS were –7.69 (-15.06, –0.32) and –20.61 (-29.52, –11.7), respectively, changes in Patient Global VAS were –4.03 (–12.42, 4.36) and –23.75 (–38.95, –3.46), respectively, and changes in FACIT-Fatigue scores were 1.37 (–1.37, 4.11) and 11.26 (5.72, 16.81), respectively.

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

**Safety**

SAE rates (95% CIs) were 76.1 (50.6-110.0) in the placebo group and 66.7 (42.3-100.1) in the tocilizumab group by week 48 compared with 36.0 (18.0-64.4) in the placebo-tocilizumab group and 16.5 (5.4-38.5) in the continuous-tocilizumab group from week 48 to week 96 (Table 3). Infections were the most frequently reported AEs and SAEs during double-blind tocilizumab treatment and in placebo patients who transitioned to open-label tocilizumab. In the placebo-tocilizumab group, rates of serious infection increased after the switch to open-label tocilizumab; the rate (95% CI) of serious infections was 10.9 (3.0-27.9) per 100 PY during the 48 weeks of double-blind placebo treatment compared with 19.6 (7.2-42.7) per 100 PY from week 48 to 96, with four patients (12.9%) in this group reporting at least one serious infection after switching to open-label tocilizumab (see online supplementary appendix table S1 for details of serious infections). Patients in the tocilizumab group had a serious infection rate of 34.8 (95% CI, 18.0-60.8) per 100 PY by week 48. No serious infections were reported after the switch from double-blind to open-label tocilizumab (continuous-tocilizumab).

No deaths were reported during the open-label period in either treatment group, and no serious hepatic AEs, anaphylactic reactions, gastrointestinal perforations or demyelination SAEs were reported during the 96-week treatment period. Changes in laboratory parameters of interest for tocilizumab, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, neutrophil counts and platelet counts, were usually ≤5× the upper limit of normal (ULN) over the 96-week treatment period. ALT elevation >5× ULN was reported in one patient receiving placebo and one patient receiving tocilizumab during the double-blind period and one placebo-tocilizumab patient after switching to open-label tocilizumab. AST elevation >5× ULN was reported in one patient receiving placebo during the double-blind period. Two patients experienced neutrophil count decreases to <0.5 × 109/L while they received double-blind tocilizumab (see online supplementary appendix table S2).

**DISCUSSION**

The phase 2 faSScinate study was the first double-blind, randomised controlled trial to show evidence of a potential disease-modifying effect in patients with SSc. By week 48, at the end of the double-blind period of the study, treatment with tocilizumab was associated with clinically relevant, though not statistically significant, improvements in skin thickness measured by mRSS and lung function measured by %pFVC.18 It has been suggested that tocilizumab may be the first efficient, molecularly targeted treatment for patients with SSc.22

Results from the open-label period of the faSScinate trial show that patients originally assigned to receive placebo in the double-blind period who transitioned to open-label tocilizumab at week 48 experienced improvements in mRSS by week 96 that were similar to those of patients who received tocilizumab throughout the study. tocilizumab during the double-blind period maintained and continued the improvements in mRSS observed during the first 48 weeks of treatment on receiving another 48 weeks of open-label tocilizumab. Although the mean change in mRSS appeared to flatten from week 72 in the continuous-tocilizumab group, there were improvements for individual patients between weeks 72 and 96. Of the 27 patients receiving continuous-tocilizumab who completed the study through week 96, 14/27 (52%) had further, primarily modest, improvements (range; –1 to –8 change in mRSS). However, there were 2 outliers who experienced considerable worsening (+9 and +14 change in mRSS) during this period. Overall, this culminates in a flattened average response. The potential for improvement may be more limited at this time point; 7/27 (26%) patients among the continuous-tocilizumab completers had observed mRSS scores ≤9 at week 72 compared with 2/24 (8%) among the placebo-tocilizumab group.

Improvements from weeks 48 to 96 in mRSS were supported by improvements in patient-reported outcomes, including HAQ-DI, Clinician and Patient Global VAS and FACIT-Fatigue scores, observed in patients initially assigned to placebo who transitioned to open-label tocilizumab and were comparable to those of patients who received tocilizumab continuously, consistent with trends observed with tocilizumab treatment during the double-blind period.18 Consistent as well with exploratory analyses in the double-blind period showing fewer tocilizumab-treated (10%) than placebo-treated (23%) patients experienced absolute decline (>10%) in %pFVC after 48 weeks,18 no patients who completed week 96 of the study experienced >10% decline in %pFVC during the open-label period while receiving tocilizumab. Of note, the primary endpoint was change in mRSS, and, at the time the study was designed, the patient populations had not been enriched for patients with SSc-associated interstitial lung disease.

Safety results over the 96-week treatment period were consistent with the known safety profile of tocilizumab; infections were the most frequently reported AEs and SAEs, and an increased rate of serious infections was observed after patients transitioned from placebo to tocilizumab. AEs tended to occur more frequently in the first few months after patients transitioned from placebo to tocilizumab but less frequently in longer term follow-up. Infections were the most frequently reported SAEs in clinical trials of tocilizumab in patients with RA.23,24 Rates of SAEs and serious infections in this study in patients with SSc were approximately five times and eight times higher, respectively, than those reported in patients with RA,23,24 which is expected given the high morbidity and mortality in patients with SSc.1 The frequencies of SAEs and serious infections observed in faSScinate are consistent with those in other SSc studies.25-27 Patients with SSc may be prone to digital ulcers,1 and complications of digital ulcers occur in 15% of patients with SSc.28 The occurrence of two cases of infected digital ulcers and one of osteomyelitis in patients who transitioned from placebo to open-label tocilizumab suggested that tocilizumab may increase infections in patients with SSc-associated digital ulcers, likely over pressure areas such as proximal interphalangeal joints.

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

No disease-modifying therapies have been approved for the treatment of patients with SSc, but some may control symptoms. Treatment options for patients with SSc are largely dependent on the organs affected.30,31 For example, cyclophosphamide has demonstrated improvement32 or trends for improvement33 in lung function in patients with SSc and interstitial lung disease, though its use has been associated with significant toxicity.30 Similarly, stem cell transplantation has resulted in improvements in skin fibrosis and prevention of lung decline and mortality but is associated with significant costs and risks.34-36 Methotrexate has demonstrated trends for improvement in skin scores in randomised controlled trials in patients with early SSc.37,38 Recently, MMF has shown efficacy similar to that of cyclophosphamide for lung and skin fibrosis.3940 Tocilizumab may be the first targeted agent to show benefit in the amelioration of skin sclerosis and the prevention of pulmonary decline in patients with SSc.18

Overall, the open-label results of the faSScinate study support observations reported from the double-blind period in that the placebo and tocilizumab groups improved similarly when placebo patients were switched to active treatment. Further studies are required to investigate the efficacy and safety of tocilizumab in the treatment of patients with SSc and to determine whether tocilizumab produces significant improvement in skin sclerosis and stabilization of lung function. A double-blind, phase 3 randomised controlled trial (NCT02453256) will investigate the efficacy and safety of tocilizumab compared with placebo in a 48-week double-blind period and a 48-week open-label period to further investigate the findings of the phase 2 faSScinate trial.

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

The Corresponding Author has the right to grant on behalf of all authors, and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in ARD and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

**Acknowledgements**

The first draft of the manuscript was prepared by the authors with professional writing and editorial assistance provided by Jennifer Adlington, PhD, and Sara Duggan, PhD, on behalf of F. Hoffmann-La Roche Ltd.

**Contributors**

All authors were involved in drafting the article or revising it critically for important intellectual content, approved the final draft to be published, and agree be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DK contributed to the conception and design of the study and the acquisition, analysis and interpretation of data.

CPD contributed to the conception and design of the study and the acquisition, analysis and interpretation of data.

CJFL contributed to the analysis and interpretation of data.

JMvL contributed to the acquisition of data.

TMF contributed to the acquisition of data.

MEA contributed to conception and design of the study and acquisition of data.

MB contributed to acquisition of data.

LC contributed to acquisition of data.

GF contributed to acquisition of data.

SL contributed to acquisition of data.

YA contributed to analysis and interpretation of data.

JEP contributed to acquisition, analysis and interpretation of data.

GR contributed to conception and design of the study and acquisition of data.

VS contributed to acquisition of data.

UM-L contributed to conception and design of the study and analysis and interpretation of data.

HS contributed to conception and design of the study and analysis and interpretation of data.

LB contributed to acquisition, analysis, and interpretation of data.

JS contributed to conception and design of the study and analysis and interpretation of data.

AJ contributed to the conception and design of the study and the acquisition, analysis and interpretation of data.

DEF contributed to conception and design of the study and analysis and interpretation of data.

**Funding**

This study was funded by Roche. Funding for manuscript preparation was provided by F. Hoffman-La Roche Ltd.

**Competing interests**

DK reports personal fees from Actelion, Boehringer-Ingelheim, Covis, Corbus, Cytori, EMD Serono, Genentech/Roche, GSK, Sanofi-Aventis and UCB,; grants from BMS, Bayer and Pfizer; stocks in Eicos Sciences, Inc, during the conduct of the study; and personal fees from Astra Zeneca outside the submitted work.

CPD reports personal fees from Roche, Actelion, EMD Serono, Sanofi and Boehringer Ingelheim; grants and personal fees from GSK and Inventiva; and grants from CSL Behring during the conduct of the study.

CJFL is an employee of Genentech.

JMvL reports grants and personal fees from MSD and Genentech and personal fees from BMS, Eli Lilly and Pfizer outside the submitted work.

TMF has nothing to disclose.

MEA reports funding to Hospital Trust from Roche during the conduct of the study and personal fees from Actelion Pharmaceuticals outside the submitted work.

MB has nothing to disclose.

LC has nothing to disclose.

GF has nothing to disclose.

SL has nothing to disclose.

YA has received research support and grants related to the submitted work from BMS, Roche/Genentech, Inventiva, Pfizer and Sanofi; consulting honoraria and personal fees related to the current work from Actelion, Bayer, Boehringer, Roche/Genentech, Galapagos, Inventiva, Medac, Pfizer, Sanofi, Servier and UCB; and personal fees outside the submitted work from Sandoz.

JEP reports funding for the current trial by Roche.

GR has received lecturer’s fees from Roche and Chugai outside the submitted work.

VS has no conflicts of interest to disclose.

UM-L is a speaker and advisor to Roche and Chugai related to the submitted work.

HS is an employee of and has nonvoting shares in Roche Products Limited.

LB is an employee of Roche.

JS is an employee of Genentech.

AJ is an employee of Genentech, owns stock and options in Roche and owns a patent for subcutaneous tocilizumab.

DEF has nothing to disclose.

**Ethics approval**

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

**REFERENCES**

1 Nikpour M, Stevens WM, Herrick AL, Proudman SM. Epidemiology of systemic sclerosis. *Best Practice Res Clin Rheumatol* 2010;24(6):857-69.

2 Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. *Clin Exp Rheumatol.* 2015;33(suppl 92):S3-7.

3 Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, *et al*. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005;118(1):2-10.

4 Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66(7):940-4.

5 Khanna D, Distler JHW, Sandner P, Distler O. Emerging strategies for treatment of systemic sclerosis. *J Scleroderma Relat Disord.* 2016;1(2):186-93.

6 Muangchant C, Pope JE. The significance of interleukin-6 and C-reactive protein in ystemic sclerosis: a systematic literature review. *Clin Exp Rheumatol.* 2013;31(suppl 76):122-34.

7 Muangchan C, Pope JE. Interleukin 6 in systemic sclerosis and potential implications for targeted therapy. *J Rheumatol.* 2012;39(6):1120-4.

8 Koch AE, Kronfeld-Harrington LB, Szekanecz Z, *et al*. In situ expression of cytokines and cellular adhesion molecules in the skin of patients with systemic sclerosis: their role in early and late disease. *Pathobiology* 1993;61(5-6):239-46.

9 Khan K, Xu S, Nihtyanova S, *et al*. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. *Ann Rheum Dis* 2012;71(7):1235-42.

10 De Lauretis A, Sestini P, Pantelidis P, *et al*. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J Rheumatol* 2013;40(4):435-46.

11 Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. *J Dermatol Sci* 2001;27(2):140-146.

12 Matsushita T, Hasegawa M, Hamaguchi Y, Takehara K, Sato S. Longitudinal analysis of serum cytokine concentrations in systemic sclerosis: association of interleukin 12 elevation with spontaneous regression of skin sclerosis. *J Rheumatol.* 2006;33(2):275-84.

13 Muangchan C, Harding S, Khimdas S, Bonner A, Baron M, Pope J. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research Group. *Arthritis Care Res* 2012;64(9):1405-14.

14 ACTEMRA® (tocilizumab) injection, for intravenous use injection, for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2014.

15 Stone JH, Tuckwell K, Dimonako S, *et al*. Efficacy and safety of tocilizumab in patients with giant cell arteritis: primary and secondary outcomes from a phase 3, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2017;68(suppl 10).

16 Shima Y, Kuwahara Y, Murota H, *et al*. The skin of patients with systemic sclerosis softened during the treatment with anti-IL-6 receptor antibody tocilizumab. *Rheumatology* 2010;49(12):2408-12.

17 Elhai M, Meunier M, Matucci-Cerinic M, *et al*. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. *Ann Rheum Dis* 2013;72(7):1217-20.

18 Khanna D, Denton CP, Jahreis A, *et al*. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387(10038):2630-40.

19 van den Hoogen F, Khanna D, Fransen J, *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72(11):1747-55.

20 Khanna D, Furst DE, Hays RD, *et al*. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. *Ann Rheum Dis* 2006;65(10):1325-9.

21 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika* 1934;26:404-13.

22 Distler O, Distler JH. Tocilizumab for systemic sclerosis: implications for future trials. *Lancet* 2016;387:2580-1.

23 Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13(5):R141.

24 Genovese MC, Rubbert-Roth A, Smolen JS, *et al*. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol* 2013;40(6):768-80.

25 Denton CP, Merkel PA, Furst DE, *et al*. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. *Arthritis Rheum* 2007;56(1):323-33.

26 Spiera RF, Gordon JK, Mersten JN, *et al*. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. *Ann Rheum Dis* 2011;70(6):1003-9.

27 Foocharoen C, Siriphannon Y, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Incidence rate and causes of infection in Thai systemic sclerosis patients. *Int J Rheum Dis* 2012;15(3):277-83.

28 Muangchan C, Baron M, Pope J. The 15% rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. A systematic review. *J Respir Dis* 2013;40(9):1545-56.

29 Buch MH, Aletaha D, Emery P, Smolen JS. Reporting of long-term extension studies: lack of consistency calls for consensus. *Ann Rheum Dis* 2011;70(6):886-90.

30 Kowal-Bielecka O, Landewe R, Avouac J, *et al*. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68(5):620-8.

31 Nagaraja V, Denton CP, Khanna D. Old medications and new targeted therapies in systemic sclerosis. *Rheumatology* 2015;54:1944-53.

32 Tashkin DP, Elashoff R, Clements PJ, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354(25):2655-66.

33 Hoyles RK, Ellis RW, Wellsbury J, *et al*. 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 Rheumatol* 2006;54(12):3962-70.

34 Burt RK, Shah SJ, Dill K, *et al*. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011;378(9790):498-506.

35 van Laar JM, Farge D, Sont JK, *et al*. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014;311(24):2490-8.

36 McSweeney PA, Nash RA, Sullivan KM, *et al*. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. *Blood* 2002;100(5):1602-10.

37 Pope JE, Bellamy N, Seibold JR, *et al*. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001;44(6):1351-8.

38 van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, Van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996;35(4):364-72.

39 Tashkin DP, Roth MD, Clements PJ, *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(9):708-19.

40 Namas R, Tashkin DP, Furst DE, *et al*. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the Scleroderma Lung Study I and II. *Arthritis Care Res* 2017 May 23. Epub ahead of print.

**FIGURE LEGENDS**

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

**Figure 2** Mean change (95% CI) in mRSS from baseline to week 96 (intent-to-treat population; observed data). Negative values denote improvement. Patients randomly assigned to PBO 162 mg QW SC received OL TCZ 162 mg QW SC from week 48.BL, baseline; CI, confidence interval; DB, double-blind; mRSS, modified Rodnan skin score; NA, not applicable, OL, open-label; PBO, placebo; %pFVC, percent predicted forced vital capacity; QW, every week; SC, subcutaneously; TCZ, tocilizumab.

**Figure 3** Cumulative distribution plot of change from baseline in %pFVC (completers analysis).

Data for TCZ 162 mg QW SC and PBO 162 mg QW SC treatment groups show change from baseline to week 48. Patients receiving PBO-TCZ 162 mg QW SC and continuous-TCZ 162 mg QW SC started OL TCZ from week 48, and change from week 48 to week 96 is shown. Only patients with data at week 96 are included in any arm (completers); one completer had a missing FVC assessment at week 96 and was excluded from the completers analysis. DB, double-blind; CI, confidence interval; OL, open-label; PBO, placebo; %pFVC, percent predicted forced vital capacity; QW, every week; SC subcutaneously; TCZ, tocilizumab.

**TABLES**

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

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

All values are mean (SD) unless stated otherwise.

aOriginal baseline data for patients who entered the OL period. bPossible scores: mRSS, 0-51; HAQ-DI, 0-3; Clinician Global VAS, 0-100; ULN for CRP, 3 mg/L. cn = 43. dn = 42. en = 29. fn = 30.

%pDLCO (Hb corr), percent predicted diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; %pFVC, percent predicted forced vital capacity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; mRSS, modified Rodnan skin score; OL, open-label; QW, every week; SC, subcutaneously; SD, standard deviation; SSc, systemic sclerosis; TJC28, tender joint count based on 28 joints; ULN, upper limit of normal; VAS, visual analogue scale.

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

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

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

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

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

%pDLCO (Hb corr), percent predicted diffusing capacity of lung for carbon monoxide corrected for haemoglobin; %pFVC, percent predicted forced vital capacity; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; max, maximum; MCID, minimal clinically important difference; min, minimum; mRSS, modified Rodnan skin score; OL, open-label; QW, every week; SC, subcutaneously; TJC28, tender joint count based on 28 joints; VAS, visual analogue scale.

**Table 3** Adverse events (safety population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Double-blind period** | | **Open-label period** | |
| **Placebo**  **QW SC**  **n = 44** | **Tocilizumab**  **162 mg QW SC**  **n = 43** | **Placebo- tocilizumab**  **162 mg QW SC**  **n = 31** | **Continuous-tocilizumab**  **162 mg QW SC**  **n = 30** |
| Exposure, PY | 36.8 | 34.5 | 30.6 | 30.3 |
| AEs, n | 244 | 283 | 126 | 153 |
| Rate/100 PY (95% CI) | 663.5 (582.9, 752.2) | 820.6 (727.8, 922.0) | 412.4 (343.5, 491.0) | 504.4 (427.6, 590.9) |
| SAEs, n | 28 | 23 | 11 | 5 |
| Rate/100 PY (95% CI) | 76.1 (50.6, 110.0) | 66.7  (42.3, 100.1) | 36.0 (18.0, 64.4) | 16.5 (5.4, 38.5) |
| Patients with ≥1 SAE, n (%) | 16 (36.4) | 14 (32.6) | 7 (22.6) | 4 (13.3) |
| Patients with ≥1 serious infection, n (%)a | 3 (6.8) | 9 (20.9) | 4 (12.9) | 0 |
| Rate of serious infection AE/100 PY (95% CI) | 10.9 (3.0, 27.9) | 34.8 (18.0, 60.8) | 19.6 (7.2, 42.7) | 0.0 (0.0, 12.2) |
| AEs leading to death, n | 1 | 3 | 0 | 0 |
| Rate/100 PY | 2.72 | 8.70 | 0.00 | 0.00 |
| Patients with AEs leading to withdrawal, n (%) | 5 (11.4) | 6 (14.0) | 4 (12.9)b | 0 |
| Rate/100 PY | 13.60 | 17.40 | 13.09 | 0.00 |
| Patients with injection site reactions, na | 2 (4.5) | 3 (7.0) | 4 (12.9) | 1 (3.3) |

aMultiple occurrences in the same patient are counted once.

bOsteomyelitis (one case serious, one case not serious), scleroderma renal crisis and breast cancer metastatic.

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