7 September 2023
EMA/CHMP/PRAC/422809/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0114

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	17 Sep 2022	17 Sep 2022	☐
☐	CHMP Rapporteur Assessment Report	11 Nov 2022	11 Nov 2022	☐
☐	PRAC Rapporteur Assessment Report	18 Nov 2022	18 Nov 2022	☐
☐	PRAC members comments	23 Nov 2022	23 Nov 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	24 Nov 2022	24 Nov 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	01 Dec 2022	01 Dec 2022	☐
☐	CHMP members comments	05 Dec 2022	05 Dec 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 Dec 2022	08 Dec 2022	☐
☐	Re-Start of procedure	26 Feb 2023	26 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	28 Mar 2023	28 Mar 2023	☐
☐	PRAC Rapporteur Assessment Report	31 Mar 2023	31 Mar 2023	☐
☐	PRAC members comments	4 Apr 2023	N/a	☐
☐	Updated PRAC Rapporteur Assessment Report	5 Apr 2023	N/a	☐
☐	PRAC Outcome	14 Apr 2023	14 Apr 2023	☐
☐	Comments from CHMP	17 Apr 2023	17 Apr 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Apr 2023	20 Apr 2023	☐
☐	2nd Request for supplementary information	26 Apr 2023	26 Apr 2023	☐
☐	Submission	14 July 2023	14 July 2023	☐
☐	Re-Start of procedure	17 July 2023	17 July 2023	☐
☐	CHMP Rapporteur Assessment Report	21 Aug 2023	21 Aug 2023	☐
☐	CHMP members comments	04 Sep 2023	05 Sep2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 Sep 2023	07 Sep 2023	☐
☐	Withdrawal letter	n/a	13 Sep 2023	☐
☐	Opinion/RSI	14 Sep 2023	n/a	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to

imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
CHMP Rapporteur:	Jan Mueller-Berghaus (DE)

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List of abbreviations

ACA	anti-centromere antibody
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector
ATA	anti-topoisomerase autoantibody
AUCT	area under the concentration-time curve over dosing interval
CI	confidence interval
Cmean	mean drug concentration over dosing interval
Ctrough	trough drug concentration
CRISS	Combined Response Index for Systemic Sclerosis
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	Clinical Study Report
CYC	cyclophosphamide
dcSSc	diffuse cutaneous systemic sclerosis
DLCO	diffusion capacity of the lung for carbon monoxide
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EUSTAR	European Scleroderma Trials and Research
FDA	Food and Drug Administration
FVC	forced vital capacity
GCA	giant cell arteritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HF	Human Factors
HRCT	high-resolution computed tomography
HSCT	hematopoietic stem-cell transplantation
IFU	Instructions For Use
IgG1	immunoglobulin G1
IL-6	interleukin 6
IL-6R	interleukin 6 receptor
ILD	interstitial lung disease
ISR	Injection site reaction
ITT	intent-to-treat
IV	intravenous

lcSSc	limited cutaneous systemic sclerosis
LSM	least squares mean
mIL-6R	membrane-bound interleukin 6 receptor
MMF	mycophenolate mofetil
mRSS	modified Rodnan skin score
MTX	methotrexate
PBRER	Periodic Benefit Risk Evaluation Report
PD	pharmacodynamic
PFS	pre-filled syringe
PFT	pulmonary function test
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
ppDLCO	percent predicted diffusion capacity of the lung for carbon monoxide
ppFVC	percent predicted forced vital capacity
PT	preferred term
PY	patient years
QILD-WL	quantitative interstitial lung disease-whole lung
QLF-LM	quantitative lung fibrosis-lobe of most involvement
QLF-WL	quantitative lung fibrosis-whole lung
QW	weekly
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SBP	Summary of Biopharmaceutics and Analytical Methods
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
sIL-6R	soluble interleukin 6 receptor
sJIA	systemic juvenile idiopathic arthritis
SLS	Scleroderma Lung Study
SSc	systemic sclerosis
SSc-ILD	systemic sclerosis with interstitial lung disease
TAK	Takayasu’s arteritis
TCZ	tocilizumab
TTF	time to treatment failure
US	United States

1. Bakground information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 29 August 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of new indication for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for RoActemra, based on final results from the pivotal Phase III Study WA29767 (focuSSced) entitled, "A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis" and the supportive Phase II/III Study WA27788 (faSScinate) entitled, "A Phase II/III, Multicenter, Randomized, Double-blind, Placebo-controlled Study To Assess The Efficacy And Safety Of Tocilizumab Versus Placebo In Patients With Systemic Sclerosis".
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 28 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0181/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0181/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Scientific discussion

2.1 Introduction

2.1.1 Problem statement

Disease or condition

Systemic sclerosis (SSc, also known as a form of scleroderma) is a rare, multisystem, connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs. It is characterized by microvascular damage and fibrosis of the skin and of various internal organs. Although the pathogenesis of SSc is not yet fully understood, it is believed to result from increased systemic fibrosis, vasculopathy, and immune dysfunction.

The clinical manifestations of SSc can range from limited skin involvement to severe internal organ dysfunction. Internal visceral organ pathology is a major factor contributing to the morbidity of this disease, with the kidneys, oesophagus, heart, and lungs being the most frequently involved.

State the claimed the therapeutic indication

Tocilizumab is indicated for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Epidemiology and risk factors, screening tools/prevention

SSc affects primarily women and has an incidence and prevalence that varies by geographic region and ethnicity. In the United States, the incidence is estimated to be 14-21 cases per 1,000,000 in 1 year (Steen et al. 1997; Mayes et al. 2003; Barnes and Mayes 2012). Multiple population-based studies estimate the prevalence of SSc in the United States as 105-300 cases per 1,000,000 (Ranque and Mouthon 2010; Furst et al. 2012). In a systematic literature review, Chifflot et al. (2008) identified 32 articles published from 1969 to 2006 and determined that SSc prevalence was higher in the United States (276 cases per 1,000,000 in 1990) and Australia (233 cases per 1,000,000 in 1999) than in Japan and Europe, where a north-south gradient was observed (England: 88 cases per 1,000,000 in 2000 and France: 158 cases per 1,000,000 in 2001), with fewer number of cases in England and Iceland compared to France and Greece. SSc is most prevalent in adults aged 30 - 50 years (Chifflot et al. 2008; National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS] 2012).

SSc has the highest mortality of any rheumatic disease. SSc overall has a 10-year survival rate of approximately 70% (Steen 2001). Of the SSc-related deaths, 35% are attributed to pulmonary fibrosis, 26% to PAH, and 26% to cardiac causes (mainly, heart failure and arrhythmias). Among the non–SSc-related causes, infections (33%) and malignancies (31%) are followed by cardiovascular causes (29%) (Tyndall et al. 2010).

CHMP comment

Systemic sclerosis (SSc) is a rare disease.

The prevalence is estimated at about 1/6,500 adults. Women are predominantly affected (F/M sex ratio around 4:1) (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=90291)

Biologic features

One of the most important mediators in the pathogenesis of SSc-ILD is thought to be IL-6. IL-6 levels are elevated in the skin and serum of patients with SSc (Koch et al. 1993; Hasegawa et al. 2011; Desallais et al. 2014; Khan et al. 2012), and particularly in patients with SSc-ILD (Sakkas 2016). Further, increased serum IL-6 level predicts higher mortality risk, worse skin involvement and increased pulmonary decline (De Lauretis et al. 2013; Khan et al. 2012). IL-6 is produced by fibroblasts (Feghali et al. 1994) and stimulated B cells (Sakkas 2016) especially after exposure to B-cell activating factor. It promotes collagen synthesis in fibroblasts and switches macrophage polarisation towards a profibrotic M2-like phenotype (Sakkas 2016). In SSc-ILD, IL-6 production is believed to occur locally, through the interaction between pulmonary B cells and resident fibroblasts (Kondo et al. 2001). There is therefore a strong scientific rationale for investigating therapies which block the action of IL-6 as a treatment option for SSc.

CHMP comment

The MAH provide a rational for treatment of SSc-ILD with an anti-IL-6 MAB. One of the most important mediators in the pathogenesis of SSc-ILD is thought to be elevated IL-6 in the skin and serum of patients with SSc. It is suggested that increased serum IL-6 level predicts higher mortality risk, worse skin involvement and increased pulmonary decline (De Lauretis et al. 2013; Khan et al. 2012). The published evidence is accepted.

It is well documented that IL-6 levels are elevated in SSc serum and also localised in skin biopsies, it is especially prominent in early stages of disease. Moreover, IL-6 levels correlate tightly with skin thickness scores indicating a causal relationship (van Laar et all 2013). Thus, it is striking that no benefit of TCZ on the mRSS PBO could be demonstrated.

The MAH brings forward the argumentation that in SSc-ILD, IL-6 production is believed to occur locally, through the interaction between pulmonary B cells and resident fibroblasts (Kondo et al. 2001). This statement can be accepted, and might be the scientific rational for an investigation TCZ in well-designed trials in SSc-ILD.

Clinical presentation, diagnosis and stage/prognosis

SSc is also called scleroderma, as skin fibrosis is a prominent feature of SSc. Initially there is an inflammatory oedematous disease stage, followed by fibrosis, and finally atrophy of the skin. The initial inflammatory oedematous stage is characterized by a puffy appearance of the skin, mostly at the fingers, with loss of skin creases. Thereafter, the affected skin becomes tight, indurated, and firmly bound to the subcutaneous (SC) tissue, often most prominently seen as acrosclerosis. This is combined with atrophy of the hair follicles and sweat and sebaceous glands. In dcSSc, fibrosis can progressively spread from the distal regions (fingers, toes, face) of the body to the more proximal regions, including the chest and abdomen. In lcSSc, skin fibrosis is usually limited to areas distal to the elbows.

Raynaud's phenomenon is one of the earliest clinical symptoms of SSc. Clinical symptoms include initial skin blanching, skin cyanosis, and reactive erythema of the distal extremities. Of patients with dcSSc, 94% report episodes of secondary Raynaud phenomenon (Distler and Distler 2010). Vascular endothelial damage can lead to digital pits, very painful fingertip ulcerations, acral ischemic tissue necrosis (dry gangrene), and amputations.

Pulmonary involvement has the worst prognosis of any organ manifestation for patients with SSc and leads to the highest mortality. The two most common pulmonary disease manifestations are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). ILD usually occurs within the first 4 years of diagnosis in patients who develop ILD. It is characterized by basilar pulmonary fibrosis. Subclinical ILD

can be detected in approximately 80% of patients, and 40% of patients develop clinical symptoms, which include tachypnoea, exertional dyspnoea, and dry cough. PAH is the second most frequent lung disease in patients with SSc. Clinical symptoms include dyspnoea, fatigue, atypical chest pain, lower extremity swelling, or syncope.

Musculoskeletal disease occurs in 57% of patients (Steen 2008). Symptoms include myalgia, muscle weakness, arthralgia, and generalized fatigue.

The gastrointestinal (GI) tract is a commonly involved internal organ. Reduced pressure of the lower oesophageal sphincter and dysmotility lead to reflux disease, heartburn, dysphagia, GI strictures, and odynophagia. Poor gastric emptying and dysmotility of the small intestine may result in abdominal distention, malabsorption, diarrhoea, bacterial overgrowth, and weight loss.

Cardiac involvement has been reported in approximately 23% of patients with dcSSc. Myocardial fibrosis can cause arrhythmias or heart block. Cor pulmonale may develop in patients with PAH. Asymptomatic pericardial effusions occur in approximately half of patients.

SSc-associated renal crisis is the most severe renal disease manifestation. Approximately 10% of patients with SSc develop renal crisis, which typically occurs within the first 3 years after diagnosis. It is characterized by sudden onset of arterial hypertension and rapidly progressive renal insufficiency. If treated with angiotensin-converting enzyme (ACE) inhibitors, it is usually reversible.

The modified Rodnan skin score (mRSS) is a validated outcome measure to assess skin involvement. It is an accurate reflection of skin biopsy thickness in SSc (Furst et al. 1998). Higher scores correlate with more severe overall disease and reduced survival (Steen 2001). Peak skin scores occur at 24 to 40 months of disease duration. Later in the course of the disease, skin atrophy may occur (Merkel et al. 2005). Other skin and glandular manifestations include telangiectasias, calcinosis cutis, keratoconjunctivitis sicca, and xerostomia.

Management

Existing therapies for SSc-ILD are limited. As the benefits of existing therapies are modest and the toxicities significant, patients with SSc-ILD are treated on an individualised basis when their disease is extensive and/or progressive. The goal of treatment is stabilisation or prevention of progressive disease as SSc-ILD is largely irreversible.

Traditional management focuses on treating those with significant baseline impairment in FVC, extensive involvement on HRCT, or evidence of progressive disease. Proposed definitions identifying those with clinically significant disease include FVC less than 70%, and extensive ILD on baseline HRCT of greater than 20%, and a decline of FVC by at least 5%–10% and/or DLCO of more than 10%–15% within a 12-month period (Roofeh and Khanna 2020).

Nintedanib is the only approved therapy in SSc-ILD. The multi-tyrosine kinase inhibitor slowed the decline of lung function in patients with radiographically evident, established SSc-ILD (Distler et al. 2019). In the primary endpoint analysis, the adjusted annual rate of change in FVC was −52.4 mL per year in the nintedanib group and −93.3 mL per year in the placebo group (difference, 41.0 mL per year; 95% CI: 2.9, 79.0; P =0.04). Nintedanib is indicated in patients with SSc-ILD who demonstrate disease progression despite MMF or CYC, or as alternative treatment for SSc-ILD in patients who are unable to take MMF or CYC. Nintedanib is an oral medication and is associated with gastrointestinal side effects such as diarrhoea and vomiting which may preclude use in certain SSc patients with gastric involvement.

CYC is widely used in the treatment of SSc-ILD, especially in induction therapy as reflected by the EULAR recommendations for SSc-ILD treatment (Kowal-Bielecka et al. 2017). Evidence from the SLS I suggests that CYC imparts modest benefit in SSc patients with early, symptomatic lung disease (Tashkin et al. 2006). Unfortunately, the toxicity of CYC makes it unsuitable for long-term use with significant adverse effects such as myeloproliferative or lymphoproliferative malignancies, haemorrhagic cystitis, sterility, and teratogenicity

MMF has been suggested as an alternative for induction and maintenance based on the results from SLS II which showed a comparable efficacy to CYC and a better adverse effect profile for MMF (Tashkin et al. 2016). The optimal duration of MMF therapy is unknown. In SLS II, treatment with MMF was continued for 24 months, but most experts continue MMF for several years as maintenance therapy in patients who show stabilization of lung function.

Lung transplantation may be an option for carefully selected SSc patients with severe ILD and no extrapulmonary complications that is not responsive to pharmacologic interventions (Crespo et al. 2016).

Autologous hematopoietic stem-cell transplantation (HSCT) has been evaluated in three randomized controlled trials which report stabilization of lung function and improvement in event-free survival in patients with SSc as compared with CYC. However, it has been associated with significant treatment related toxicity and fatality.

CHMP comment

The therapy options for treatment of SSc including SSc-ILD are limited. However immunosuppressive therapy is an important and established aspect of the treatment for SSC including SSc-ILD.

Effective treatment differs by each organ involvement, which requires clinicians to combine multiple therapeutic modalities to treat SSc patients. Some medications have pivotal effect on each organ involvement, making the treatment further difficult. For instance, systemic corticosteroids are used in treating skin fibrosis and SSc-ILD (Matsuda et al. Arthritis Research & Therapy: https://doi.org/10.1186/s13075-019-1919-6).

2.1.2 About the product

TCZ is a recombinant humanized anti-human monoclonal antibody of IgG1 subclass directed against the soluble (sIL-6R) and membrane-bound interleukin 6 receptor (mIL-6R). TCZ binds specifically to both receptor types and thereby inhibits IL-6 mediated signalling.

The potential for TCZ in the treatment of SSc stems from the putative role of IL-6 as a key link between inflammation and fibrosis.

TCZ has been approved in various countries, including the United States, Japan, and the European Union, for the treatment of RA. In several countries, including the United States, TCZ has been approved in combination with disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy at a recommended starting dose of 4 mg/kg followed by an increase to 8 mg/kg based on clinical response (Actemra [tocilizumab] Package Insert). In other countries, TCZ has been approved at a dose of 8 mg/kg. The dose can be reduced to 4 mg/kg if necessary. TCZ has also been approved for the treatment of sJIA in the United States and Europe, as well as for sJIA, pcJIA, and Castleman’s disease in India and Japan.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical data in this submission includes pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety results from two clinical studies investigating TCZ, one pivotal Phase III Study WA29767 and one supportive Phase II/III Study WA27788; approximately 300 patients with SSc were treated with TCZ.

A summary of key Health Authority correspondence and interactions is provided below

CHMP comment

In the absence of CHMP guidelines for the clinical development in the claimed indication, requesting Scientific Advice could have been beneficial.

2.1.4. General comments on compliance with GCP

The Market Authorization Holder (MAH), Roche Registration GmbH, herewith confirms that all clinical trials carried out by the MAH outside the European Union meet the ethical requirements of the EU Clinical Trial Directive [2001/20/EC].

The pivotal Study WA29767 and supportive Study WA27788 included in this application were conducted in accordance with the principles of the "Declaration of Helsinki", the US FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and applicable local, state, and country laws. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all studies.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Tocilizumab, the pharmaceutical active ingredient in RoActemra, is a recombinant humanised immunoglobulin IgG1 monoclonal antibody produced by recombinant DNA technology. Tocilizumab is a protein with a molecular mass of approximately 145 kDa and the Chemical Abstracts Services (CAS) number 375823-41-9. As an unaltered protein, being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, Tocilizumab is unlikely to result in a significant environmental exposure.

The EMA 2006 Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products (EMEA/CHMP/SWP/4447/00 corr. 2) requires an ERA for the Marketing Authorisation Application or Extension Applications of all new medicinal products in the European Union. For proteins and peptides, however, the 'ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment'.

CHMP comment

It is considered justified that the MAH is not providing a full environmental risk assessment for the extension Application for RoActemra (Tocilizumab) (for details on the justification please refer to Module 1.6.1 Non-GMO).

2.3. Quality aspects

Module 3.2.R

DELIVERY DEVICE-ADDENDUM SSC-ILD [TOCILIZUMAB, PRE-FILLED SYRINGES IN NEEDLE SAFETY DEVICE, 162 MG/0.9 ML]

The Actemra SC pre-filled syringe with needle safety device (PFS+NSD) has been approved for the treatment of Rheumatoid Arthritis (RA), for the treatment of Giant Cell Arteritis (GCA) in patients ≥ 18 years old, systemic juvenile idiopathic arthritis (sJIA) in patients ≥ 1 years and polyarticular juvenile idiopathic arthritis (pJIA) in patients ≥ 2 years. In addition, MAH is extending the use of Actemra SC PFS+NSD to Systemic Sclerosis-Interstitial Lung Disease (SSc-ILD) patients ≥ 18 years.

Details about the Human Factors activities have been provided in the Human Factors Engineering Summary Report (VAL-0152458). The document is an addendum to the existing 3.2.R Delivery Device-Addendum pJIA.

Caregivers, healthcare professionals and adult patients diagnosed with SSc-ILD are intended users for self-injection in a home environment, when considered as suitable by their healthcare professional (HCP).

It has been shown with a supplemental Human Factors Validation study that the Actemra PFS+NSD can be also used safely and effectively by SSc patients. As the SSc- ILD is a sub-patient population that does not reveal any differences in their physical, cognitive or perception characteristics from a broader SSc patient population. They are deemed equivalent from a usability perspective. Therefore, the data collected are also applicable for SSc-ILD patients.

Actemra SC PFS+NSD has already been validated in respective Human Factors Validation studies with HCPs, Caregivers and RA patients (refer to Module 3.2, Subsection 4 Design Validation in Section 3.2.R Delivery Device Actemra SC, Needle Safety Device).

The training and suitability assessment of self-injecting patients and by the HCPs is described in the labeling (refer to Module 1.14.1, Draft Labeling).

Risk management is performed in accordance with the Sponsor's procedures, which are in compliance with EN ISO 14971. The process is applied throughout the lifecycle of the product (refer also to refer to Module 3.2, Subsection 5 Risk Management in Section 3.2.R Delivery Device Actemra SC, Needle Safety Device).

Conclusion (MAH)

The Actemra PFS-NSD is safe, effective and meets SSc-ILD patients' needs when used as intended according to the Intended Use Statement. The design is considered as safe and effective as all use related residual risks have been mitigated as far as possible, that the clinical benefits of use outweigh the use related risks, and that further changes are not required.

The outcome of the user-related risk assessment informed by all the Human Factors activities outcome demonstrates that SSc patients can safely and effectively perform all essential and critical tasks without serious use errors or problems, for the intended uses and under the expected use conditions when following the IFU. Therefore, this product is considered by the sponsor as validated for safe use in SSc-ILD patients.

CHMP comment

According to Guideline on quality documentation for medicinal products when used with a medical device the MAH has submitted usability studies in Module 3.2.R as the pre-filled syringe has not been used in the

intended user population before. Based on the data provided the conclusion of the MAH is endorsed and the Actemra PFS-NSD is considered validated for safe use in SSc-ILD patients.

2.4. Clinical aspects

2.4.1. Introduction

The clinical data in this submission includes pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety results from two clinical studies investigating TCZ, one pivotal Phase III Study WA29767 and one supportive Phase II/III Study WA27788; approximately 300 patients with SSc were treated with TCZ

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Number	EU Countries	Non-EU Countries
WA29767 (FocuSSced)	Belgium, Bulgaria, Denmark, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Spain	Argentina, Canada, Japan, Mexico, Switzerland, United Kingdom, United States
WA27788 (FaSScinate)	France, Germany.	Canada, United Kingdom, United States.

2.4.2. Pharmacokinetics

TCZ is directed against the soluble (sIL-6R) and membrane-bound interleukin 6 receptor (mIL-6R). TCZ binds specifically to both receptor types and thereby inhibits IL-6 mediated signalling.

The potential for TCZ in the treatment of SSc stems from the putative role of IL-6 as a key link between inflammation and fibrosis.

One of the mediators in the pathogenesis of SSc-ILD is thought to be IL-6. IL-6 levels are elevated in the skin and serum of patients with SSc (Koch et al. 1993; Hasegawa et al. 2011; Desallais et al. 2014; Khan et al. 2012), and particularly in patients with SSc-ILD (Sakkas 2016). Further, increased serum IL-6 level predicts higher mortality risk, worse skin involvement and increased pulmonary decline (De Lauretis et al. 2013; Khan et al. 2012). IL-6 is produced by fibroblasts (Feghali et al. 1994) and stimulated B cells (Sakkas 2016) especially after exposure to B-cell activating factor. It promotes collagen synthesis in fibroblasts and switches macrophage polarisation towards a profibrotic M2-like phenotype (Sakkas 2016). In SSc-ILD, IL-6 production is believed to occur locally, through the interaction between pulmonary B

cells and resident fibroblasts (Kondo et al. 2001). There is therefore a strong scientific rationale for investigating therapies which block the action of IL-6 as a treatment option for SSc.

The clinical data in this submission includes pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety results from two clinical studies investigating TCZ, one pivotal Phase III Study WA29767 and one supportive Phase II/III Study WA27788; approximately 300 patients with SSc were treated with TCZ.

Both studies included a 48-week blinded period to evaluate TCZ SC compared against PBO SC followed by a 48-week open label period, for a total study duration of 96 weeks.

Table 1 Overview of Clinical Studies Included in Submission

Study No. (Phase)	Study Design, Control Type	Population	Dose, Route, and Regimen	Primary and Secondary Endpoints	No. of Patients	Status
Pivotal Study						
WA29767 (FocuSSced) (Phase III)	Multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study (TCZ vs. PBO)	Adult patients with SSc	Double-blind period: TCZ 162 mg SC QW or PBO SC QW Open-label period: TCZ 162 mg SC QW	Primary efficacy: mRSS at Week 48 Secondary efficacy: ppFVC, HAQ-DI, patient's global assessment, and physician's global assessment at Week 48, time to treatment failure up to Week 48 Safety, PK, PD, immunogenicity	212 [a] Double-blind period: PBO: 106 TCZ: 104 Open-label period: PBO→TCZ: 89 TCZ→TCZ: 92	Completed
Supportive Study						
WA27788 (FaSScinate) (Phase II/III)	Multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study (TCZ vs. PBO)	Adult patients with SSc	Double-blind period: TCZ 162 mg SC QW or PBO SC QW Open-label period: TCZ 162 mg SC QW	Primary efficacy: mRSS at Week 24 Secondary efficacy: HAQ-DI, SHAQ-VAS, patient's global assessment, physician's global assessment, FACIT-Fatigue score, 5-D Itch Scale, mRSS improvement from Week 24 to 48, mRSS at Week 48 Safety, PK, PD, immunogenicity	87 Double-blind period: PBO: 44 TCZ: 43 Open-label period: PBO→TCZ: 31 TCZ→TCZ: 30	Completed

ADA = anti-drug antibodies; FACIT = Functional Assessment of Chronic Illness Therapy; FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire-Disability Index; ITT = intent-to-treat; mRSS = modified Rodnan skin score; PBO = placebo; PD = pharmacodynamics; PK = pharmacokinetics; ppFVC = percent predicted forced vital capacity; QW = weekly; SC = subcutaneous; SHAQ-VAS = Scleroderma Health Assessment Questionnaire visual analogue scale; SSc = systemic sclerosis; TCZ = tocilizumab.

[a] Two patients (1 in each treatment arm) withdrew from the study prior to receiving the first dose of study treatment and were excluded from the ITT and Safety populations.

The development program for use of TCZ in patients with SSc/SSc-ILD a priori knowledge on the mechanism of action of TCZ in other diseases such as RA was used for dose selection in patients with SSc/SSc-ILD. The dosing regimen tested in both Studies WA29767 and WA27788 was 162 mg TCZ SC QW.

The choice to investigate this dosing regimen in patients with SSc in the Phase II/III Study WA27788 was based on:

- Baseline range of IL-6 concentrations in patients with SSc reported in the literature (Khan et al. 2012) was similar to baseline values in RA patients.
- Assumption that IL-6R−mediated TCZ clearance in SSc patients was comparable to the clearance in RA patients.
- Assumption that TCZ PK was comparable in SSc and RA.

CHMP comment

Priori knowledge on the mechanism of action of TCZ in other diseases such as RA was used for dose selection in patients with SSc/SSc-ILD. Public informations suggests that baseline range of IL-6 concentrations in patients with SSc are similar to baseline values in RA patients. The same TCZ dosing regimen as in RA was proposed to provide a positive clinical benefit/risk in patients with SSc. The SC route of administration was chosen over IV administration for convenience of use and to address

difficulties with IV infusions in patients with SSc with vasculopathies and therefore the dosing regimen tested in both Studies WA29767 and WA27788 was 162 mg TCZ SC QW.

2.4.2.1. Analytical Methods

The bioanalytical methods that measure TCZ, IL-6 and soluble IL-6 receptor (sIL-6R) levels in human serum.

Furthermore, the methods were used to screen for anti-TCZ antibodies (immunogenicity), to determine their potential neutralizing activity and to determine antibodies of the Immunoglobulin E (IgE) type in confirmed positive anti-drug antibody (ADA) samples or in samples of patients showing hypersensitivity reactions.

Table 2 Summary of Assays Used in the Clinical Studies to Measure Serum Concentrations of Tocilizumab, Anti Tocilizumab Antibodies, Interleukin-6 and Soluble Interleukin-6 Receptor

Clinical Studies	Tocilizumab Assay	Anti-Tocilizumab Antibody Assays			IL-6 Assay	sIL-6R Assay
	Tocilizumab PK Assay	Screening/ Confirmation Assay	Inhibition/nAb Assay	IgE Assay (UniCAP)		
Roche Studies						
WA27788	X	X	X	X	X	X
WA29767	X	X	X	X	X	X

IL-6 = interleukin-6 (low and high sensitive assay); PK = pharmacokinetic; sIL-6R = soluble IL-6 receptor.

Assay for the Determination of Tocilizumab Concentrations

A validated sandwich enzyme-linked immunoassay (ELISA) was used to determine the concentration of TCZ in human serum samples. The assay has a lower limit of quantification (LLOQ) of 100 ng/mL for TCZ in human serum.

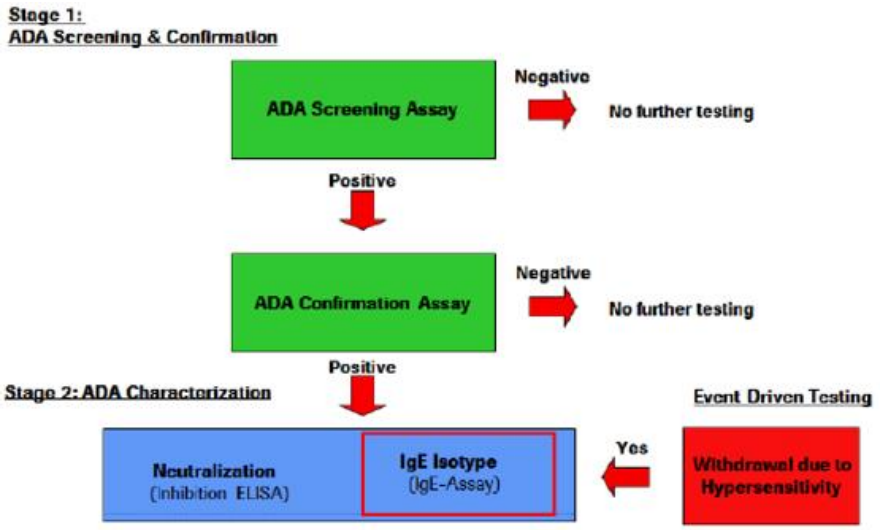
Table 3 Performance Summary of the Tocilizumab Pharmacokinetic Assay in Human Serum from Healthy Volunteers

Assay Range, ng/mL	Accuracy, %		Precision, %	
	Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
100 to 3200	105.0 to 116.0	101.4 to 118.2	2.9 to 9.0	5.8 to 21.6

Assays to Detect Anti-Drug Antibodies to Tocilizumab

The immunogenicity testing strategy for TCZ followed a two-stage analytical approach plus clinical event-triggered exploratory IgE testing

Figure 1 Overview of the Immunogenicity Testing Strategy for Tocilizumab



ADA = anti-drug antibody; ELISA = enzyme-linked immunosorbent assay; IgE = immunoglobulin E.

Anti-Tocilizumab Antibody Assay

A bridging ELISA was applied for the detection (screening) and confirmation of anti-TCZ antibodies in human serum.

Table 4 Performance Summary of the Anti-Tocilizumab Antibody Screening and Confirmation Assay

Assay Range, ng-equiv./mL	Screening Cut-point Sensitivity, ng-equiv./mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
7.81 – 1,000 (HV)	50.8	102.8 to 111.6	86.6 to 113.7	2.2 to 4.1	5.5 to 8.9
7.81 – 1,000 (RA)	123	n.d.	n.d.	n.d.	n.d.

HV = healthy volunteers; n.d. = not done; RA = rheumatoid arthritis.

Neutralizing Antibody Assay, Inhibition Enzyme-Linked Immunosorbent Assay

The relative concentration of neutralizing antibodies to TCZ in human serum was determined by an "inhibition ELISA"

Table 5 Performance Summary of the Inhibition Enzyme-Linked Immunosorbent Assay

LLOQ, ng-equiv./mL	Assay Range, ng-equiv./mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
211	211 to 3,600 [a]	83.4 to 114.3	92.9 to 101.4	6.1 to 38.9	4.3 to 35.9

Anti-Tocilizumab Antibody Assay, IgE Assay (UniCAP)

The method determines serum anti-TCZ antibody (IgE type) titers using an absorption test assay.

Interleukin-6 Assay

A commercial assay (Quantikine Human IL-6 Immunoassay, R&D Systems Inc., Catalog Number D6050) was used to measure serum concentrations of endogenous IL-6. For samples with determined IL-6 concentrations < LLOQ, a commercially available modified version of the assay which uses an amplification enhancer, thereby achieving a higher sensitivity was used (Quantikine HS Human IL-6 Immunoassay, R&D Systems Inc., Catalog Number HS600B)

Table 6 Performance Summary of the Interleukin-6 Assays

LLOQ, pg/mL	Assay Range, pg/mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
3.12[a]	3.12 – 300[a]	94.3 to 105.8[a]	93.0 to 108.2[a]	3.0 to 6.7[a]	5.8 to 7.4[a]
0.156[b]	0.156 – 10.0[b]	82.1 to 94.2[b]	91.5 to 99.6[b]	4.0 to 17.7[b]	8.8 to 20.3[b]

Soluble Interleukin-6 Receptor Assay

A commercial assay (Quantikine Human sIL-6R Immunoassay, R&D Systems Inc., Catalog Number DR600) was used to measure serum concentrations of endogenous sIL-6R.

Table 7 Performance Summary of the Soluble Interleukin-6 Receptor

LLOQ, pg/mL	Assay Range, pg/mL	Accuracy, %		Precision, %	
		Intra- Assay	Inter- Assay	Intra- Assay	Inter- Assay
31.3	31.3 – 2000	91.6 to 112.5	97.1 to 107.4	3.7 to 18.6	4.8 to 13.5

Assessor´s comment

Bioanalytical methods used for determination of tocilizumab and sIL-6R concentrations in human serum are those already established and validated. Thus, no new or updated method validation reports were submitted but the summaries demonstrate that the assays perform accurate and precise and are suitable for their intended use.

2.4.2.2. Observed PK and PD data over 96 weeks of dosing in patients with systemic sclerosis (SSc)

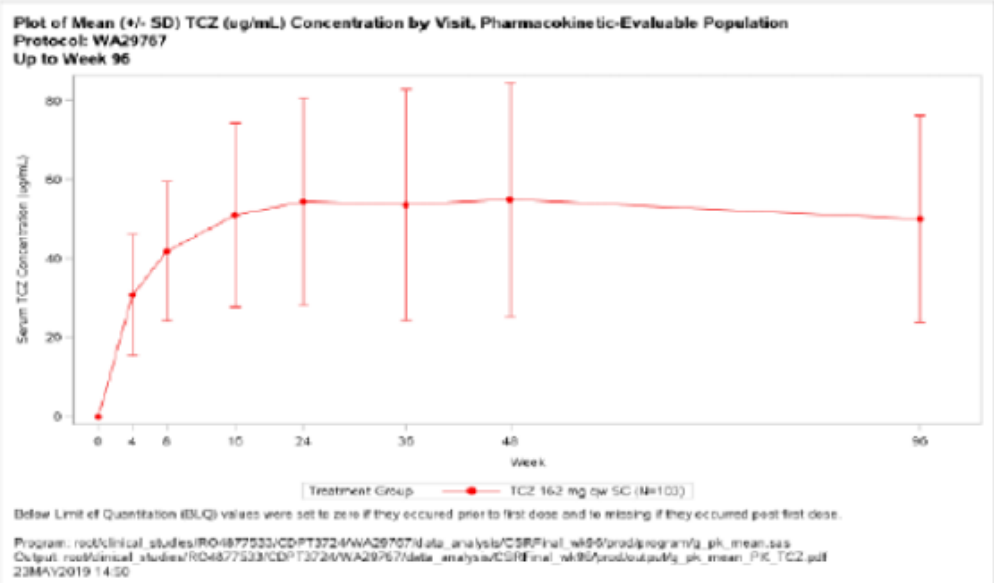
PK data

Patients were randomized in a 1:1 ratio to receive TCZ 162 mg SC once weekly (QW) or PBO QW for 48 weeks during the double-blind treatment period. During the open-label treatment period, all patients were treated with TCZ 162 mg SC QW for up to 48 weeks.

After repeated dosing, the mean pre-dose TCZ concentrations in patients with SSc increased with time and appeared to reach steady state by Week 16 (Figure 2). After administration of 48 doses of TCZ, the observed mean (standard deviation [SD]) Ctrough was 54.7 (29.8) µg/mL at Week 48, with coefficient of variation (CV%) at 54.5%. Exposure was also examined by region; no effect beyond the known effect of body weight on exposure was obvious.

In the OL period of the study pre-dose TCZ concentrations at Week 96 in patients with SSc treated with active drug from study start were comparable to those observed at Week 48, indicating that exposure was maintained with continued TCZ treatment until the end of study

Figure 2 Mean (±SD) TCZ (µg/mL) concentration by Visit, Pharmacokinetic-Evaluable Population



TCZ = Tolicizumab

Table 8 sIL-6R Concentrations (ng/mL) in Studies WA29767 and WA27788

			WA29767	WA27788
TCZ arm	Baseline	Mean (SD)	42.22 (14.56)	39.39 (10.16)
		Median	39.00	37.9
	Week 16	Mean (SD)	583.87 (164.36)	525.48 (164.90)
		Median	589.50	544.0
	Week 48	Mean (SD)	571.48 (167.85)	498.76 (157.91)
		Median	576.50	535.0
PBO arm	Baseline	Mean (SD)	42.16 (32.41)	37.61 (11.12)
		Median	37.10	33.6
	Week 16	Mean (SD)	47.81 (68.22)	37.71 (10.30)
		Median	38.95	36.4
	Week 48	Mean (SD)	49.27 (76.97)	36.52 (9.93)
		Median	36.00	34.2

CHMP comment

After repeated dosing, the mean pre-dose TCZ concentrations in patients with SSc increased with time and appeared to reach steady state by Week 16 and the exposure was maintained with continued TCZ treatment until the end of study at week 96.

Immunogenicity

As in the SSc-ILD subpopulation from Study WA29767 no treatment-induced ADAs were reported, immunogenicity is described for SSc patients only.

Six patients in the placebo arm and 3 patients in the TCZ arm had a positive anti-TCZ antibody as measured by the screening and/or confirmation assay at baseline. Up to Week 48, only one of these patients in the TCZ arm tested positive for post baseline anti-TCZ antibodies at Week 8 (confirmation assay was negative).

Three other patients in the TCZ arm were negative at baseline and tested positive for postbaseline anti-TCZ antibodies, of which 1 patient (1 of 104 patients [1.0%]) had a confirmed positive result at Weeks 8, 16 and 24 by the screening, confirmatory, and neutralizing assays, and was considered to have a treatment-induced ADA response with neutralizing potential. This patient did not have a positive IgE assay result (levels of ADA were below the limit of quantification).

During the OL period of the study, none of the patients tested positive for ADA post baseline.

Pre-specified analysis of the relationship between ADA status and safety, efficacy, and PK endpoints were not analysed via subgroup analyses as there was only one patient with ADA-positive status.

CHMP comment

The incidence of anti-TCZ antibodies in SSc patients was low and there was no clinical significance associated. Overall, treatment-induced ADAs (all neutralizing) were detected and confirmed in only three patients across both studies (1.8% of the pooled safety population of the two studies). No treatment-induced ADAs were reported in the SSc-ILD subpopulation. Therefore, the immunogenicity potential of TCZ appears to be low.

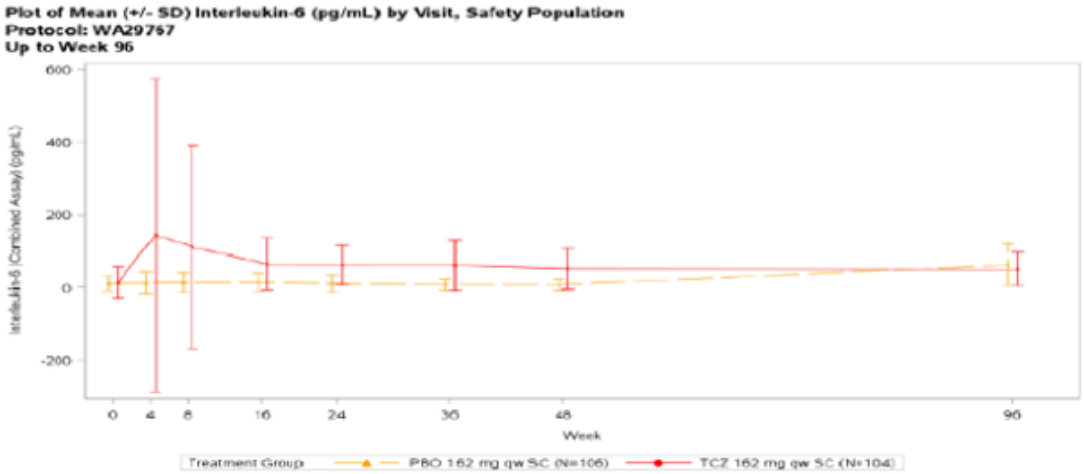
PK/PD relationship

The PD of TCZ was characterized by assessing two mechanistic markers, IL-6 and sIL-6R, both directly linked to the mechanism of action of TCZ and two downstream inflammatory markers, CRP and ESR. In the TCZ group, consistent with the mechanism of action of TCZ, sIL-6R levels increased with time and with increasing exposure reflecting slower clearance of the TCZ-receptor complex relative to the native substrate-receptor complex. A greater increase in sIL-6R levels suggests more binding of TCZ to sIL-6R.

The IL-6 levels increased initially, reflecting displacement of bound IL-6 from its receptor by TCZ, and then decreased with time, reflecting an equilibrium of IL-6 formation and clearance. CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ indicating that the TCZ concentrations are high enough to inhibit the effects of IL-6 and for saturation of the target (IL-6R).

Figure 3 Plot Mean (±SD) Soluble Interleukin-6 Receptor (ng/mL) by Visit, Safety Population

Figure 4 Plot of Mean (±SD) Interleukin-6 (pg/mL) by Visit, Safety Population



Inflammatory biomarkers CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ indicating that the TCZ concentrations are high enough to inhibit the effects of IL-6 and for saturation of the target (IL-6R). Notably, the effects can also be seen in the Placebp group, in which patients received treatment with TZC after 48 weeks supporting the pharmacodynamics response. PD responses observed at Weeks 72 and 96 for CRP, ESR, IL-6 and sIL-6R for patients who initially received PBO and switched to active treatment at Week 48 were comparable with the original TCZ group during the DB period”

Figure 5 Plot of Median and Interquartile Range for C-reactive protein (mg/L) Values by Visit, Safety Population

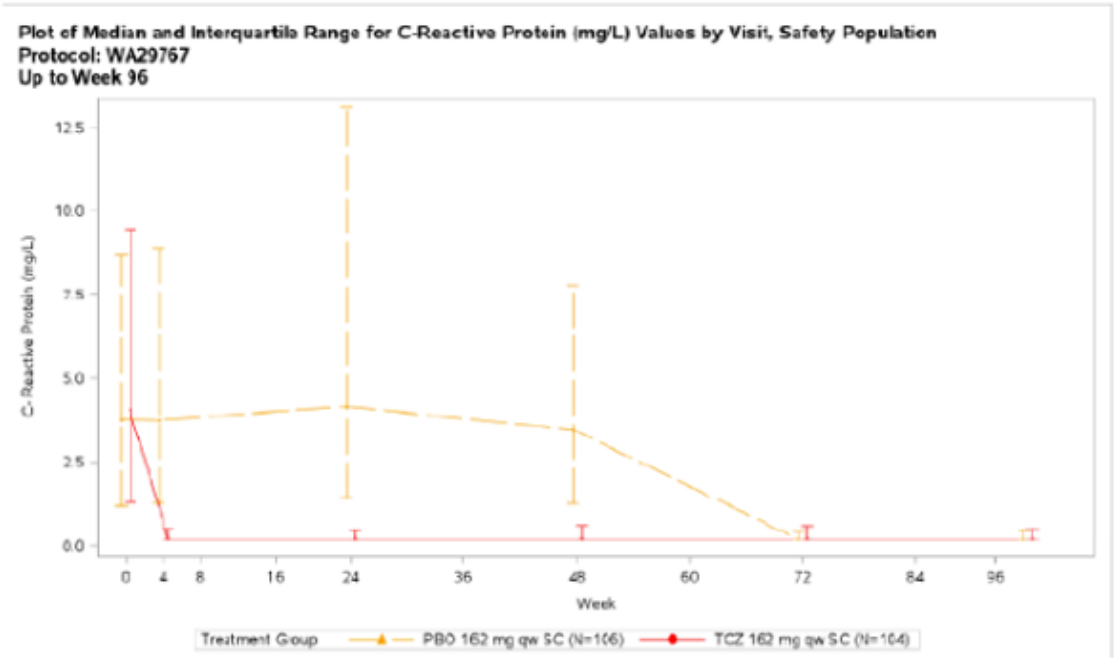


Figure 6 Plot of Median and Interquartile Range for C-reactive Protein (mg/L) Values by Visit, Safety Population

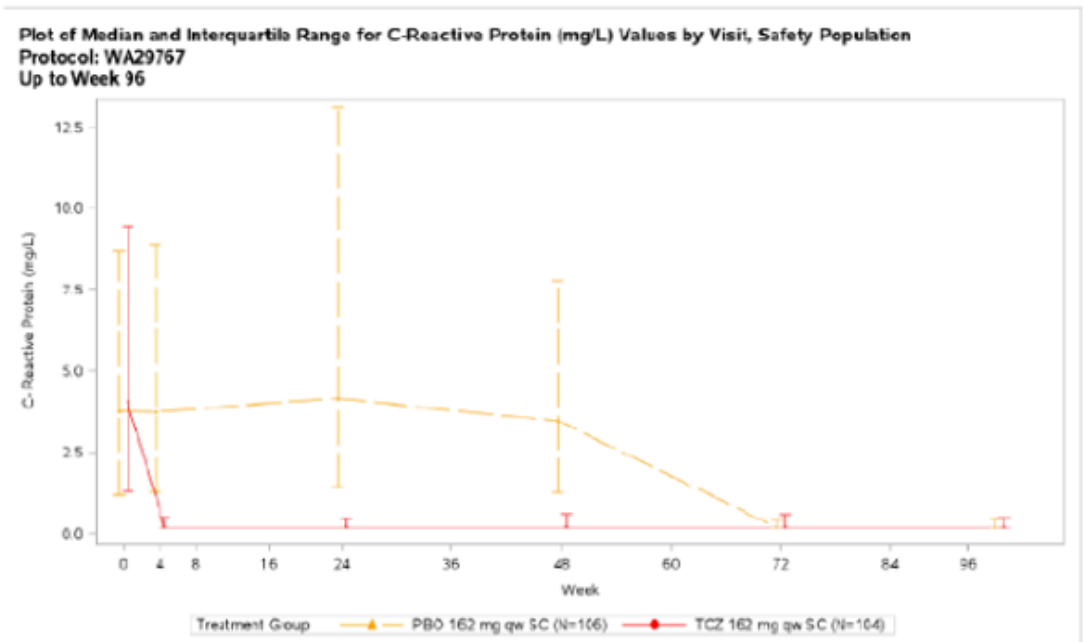


Figure 7 Plot of Median and Interquartile Range for ESR (mm/hr) values by Visit, Safety Population

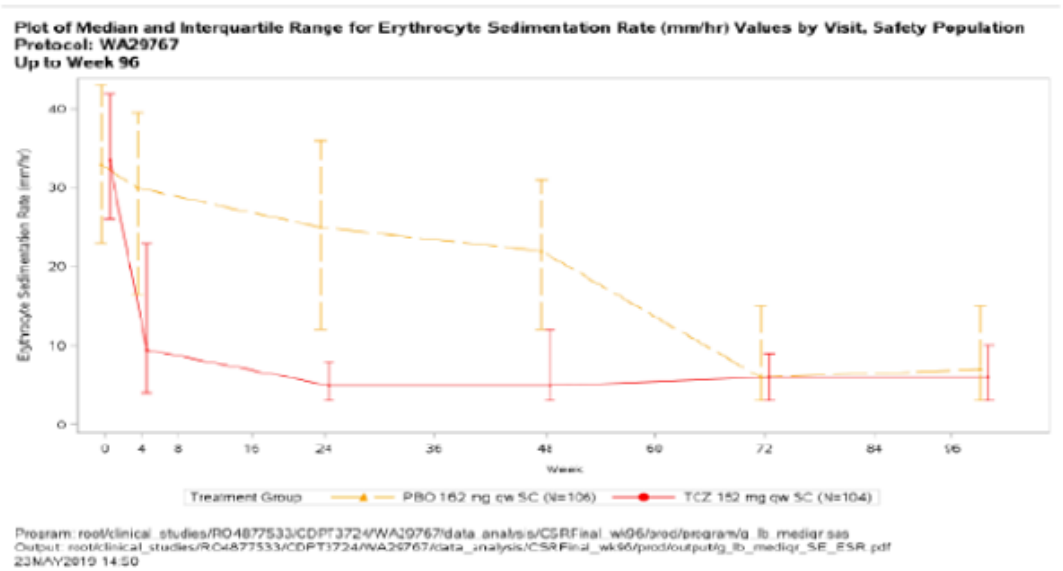


Table 9 CRP Concentrations (mg/L) in Studies WA29767 and WA 27788

			WA29767	WA27788
TCZ arm	Baseline	Mean (SD)	9.00 (14.76)	10.04 (13.54)
		Median	4.05	4.97
	Week 4	Mean (SD)	0.85 (2.52)	NA
		Median	0.20	NA
	Week 8	Mean (SD)	NA	1.00 (3.00)
		Median	NA	0.24
	Week 48	Mean (SD)	1.58 (6.22)	2.66 (10.50)
		Median	0.20	0.31
PBO arm	Baseline	Mean (SD)	7.43 (12.61)	10.63 (13.58)
		Median	3.82	6.72
	Week 4	Mean (SD)	9.81 (20.79)	NA
		Median	3.71	NA
	Week 8	Mean (SD)	NA	19.50 (53.06)
		Median	NA	7.50
	Week 48	Mean (SD)	7.52 (12.80)	8.18 (8.26)
		Median	3.67	5.59

Table 10 ESR (mm/h) in Studies WA29767 and WA27788

			WA29767	WA27788
TCZ arm	Baseline	Mean (SD)	34.83 (16.29)	30.47 (18.75)
		Median	33.50	28.00
	Week 4	Mean (SD)	14.29 (12.98)	NA
		Median	9.50	NA
	Week 8	Mean (SD)	NA	7.89 (9.65)
		Median	NA	5.00
	Week 48	Mean (SD)	10.82 (15.53)	12.11 (16.24)
		Median	5.50	8.00
PBO arm	Baseline	Mean (SD)	34.72 (18.49)	27.17 (21.06)
		Median	33.00	27.00
	Week 4	Mean (SD)	31.38 (19.00)	NA
		Median	30.00	NA
	Week 8	Mean (SD)	NA	24.47 (16.66)
		Median	NA	24.00
	Week 48	Mean (SD)	26.59 (18.62)	27.97 (21.78)
		Median	22.50	23.50

CHMP comment

The PD of TCZ was characterized by assessing IL-6 and sIL-6R, both directly linked to the mechanism of action of TCZ and two downstream inflammatory markers, CRP and ESR. As expected data confirm that sIL-6R levels increased with time as expected and after initially increased IL-6 levels, reflecting displacement of bound IL-6 from its receptor, levels decreased with time, reflecting an equilibrium of IL-6 formation and clearance. Inflammatory biomarkers CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ.

Exposure-Response Relationship

A pre-specified exposure-response analysis including key efficacy and safety endpoints was conducted. All graphical analysis was conducted in the following similar manner. Observed Week 48 Ctrough was grouped into tertiles of high, medium and low exposure (Table 11).

Table 11 Study WA29767: Summary of TCZ Trough Concentrations (µg/mL) at Week 48 by Tertiles (PK Population)

Protocol: WA29767
Up to Week 48

	Ctrough Low (N=30)	Ctrough Medium (N=29)	Ctrough High (N=29)
Ctrough at Week 48			
n	30	29	29
Mean (SD)	25.41 (11.72)	51.66 (5.58)	87.94 (22.61)
Median	25.70	52.10	81.10
Interquartile Range	16.40 - 37.00	47.20 - 56.50	72.20 - 94.70
Min - Max	0.4 - 41.0	42.0 - 61.1	61.2 - 145.0

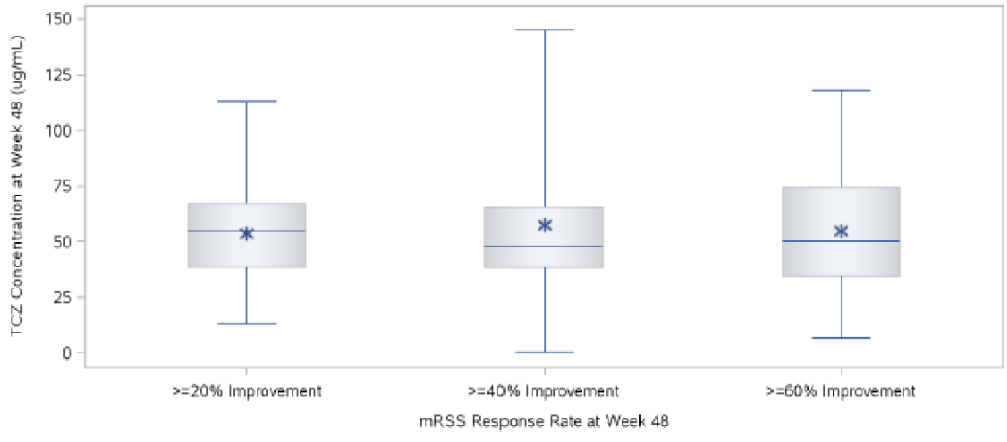
Ctrough Low, 0%-<=33%; Ctrough Medium, 33%-<=67%; Ctrough High, 67%-<=100%.
TCZ patients with no concentration at week 48 are excluded.

Program: /opt/BIOSTAT/prod/cn11935i/i29767a/t_pk_tcz_tert.sas
Output: /opt/BIOSTAT/prod/cn11935i/i29767a/reports/t_pk_tcz_tert_PK_WK48.out
16MAR2018 11:40
Page 1 of 1

Boxplots on response endpoints were generated to evaluate if any trends were visible. Grouping of the patients based on Ctrough exposure resulted in 29 to 30 patients per category with median exposures of 25.7, 52.1 and 81.1 µg/mL reflecting a 3-fold range.

Efficacy endpoints included the following: mRSS, improvement in mRSS by ≥ 20, ≥ 40 and ≥ 60%, pFVC, HAQ-DI, Patients Global Assessment and Physicians Global Assessment; all at Week 48. Analysis of observed TCZ Ctrough concentrations in mRSS responders with an improvement at ≥ 20, ≥ 40 and ≥ 60%, Week 48 indicated no trends related to TCZ exposure.

Box plot of TCZ concentration at Week 48 by >= 20%, >= 40%, and >= 60% improvement in mRSS at Week 48, Pharmacokinetic-Evaluable Population
Protocol: WA29767
Up to Week 48



n	29	24	18
Mean	53.521	57.400	54.711
SD	25.826	38.026	29.277
Median	54.800	47.800	50.100
Interquartile Range	(38.200 - 67.200)	(38.050 - 65.650)	(34.200 - 74.700)
Min - Max	13.100 - 113.000	0.401 - 145.000	6.800 - 118.000

Only patients who have a TCZ reading at Week 48 are included.
Patients are only counted once, and are displayed in their highest response category.

Safety endpoints included the following: SAEs and AEs by SOC, all grades of high ALT and AST, neutrophils and platelets. There were no clear trends observed in the overall incidence of AEs or SAEs at Week 48 by TCZ Ctrough tertiles, indicating there are no safety signals related to increasing TCZ exposure.

Table 12 Study WA29767: Incidence of Adverse Events, Serious Adverse Events, and Selected Laboratory Abnormalities by TCZ C_{trough} tertiles at Week 48 (Safety Population)

Safety Variable	C_{trough} Low (n=30)	C_{trough} Medium (n=29)	C_{trough} High (n=29)
AEs, n (%)	27 (90.0%)	23 (79.3%)	25 (86.2%)
SAEs, n (%)	4 (13.3%)	0	2 (6.9%)
Laboratory parameters, any grade:			
High ALT, n (%)	11 (36.7%)	9 (31.0%)	7 (24.1%)
High AST, n (%)	9 (30.0%)	7 (24.1%)	5 (17.2%)
Low neutrophils, n (%)	6 (20.0%)	9 (31.0%)	9 (31.0%)
Low platelet count, n (%)	2 (6.7%)	3 (10.3%)	3 (10.3%)

CHMP comment

Grouping the patients of Study WA29767 based on Ctrough exposure at week 48 resulted in 29 to 30 patients per category (low, medium, high) with median exposures of 25.7, 52.1 and 81.1 µg/mL reflecting a 3-fold range. However, the number of patients per tertile is low.

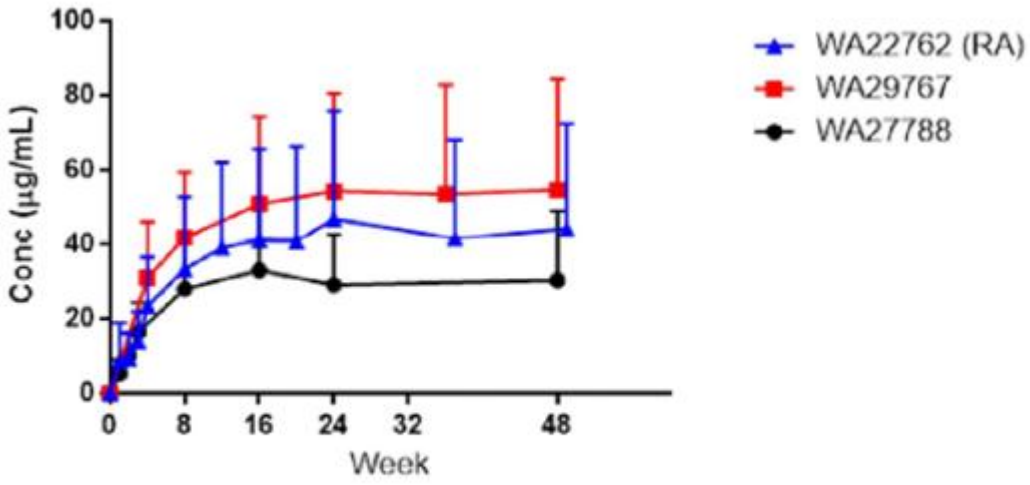
Analysis of observed TCZ Ctrough concentrations in mRSS responders with a ≥20%, ≥40%, and ≥60% improvement at Week 48 as well as changes from baseline in percent predicted forced vital capacity (ppFVC) by TCZ Ctrough tertiles at week 48 indicated no trends related to TCZ exposure.

Based on the provided data, less incidence of AEs and SAEs have been observed in the Ctrough Medium tertile (79.3%; 0%) compared to the Ctrough low (90%; 13.3%) and Ctrough high (86.2%; 6.9%) at 48 Weeks. No exposure response relationship for AEs or SAEs by increasing TCZ exposure were identified. However, a trend that the laboratory parameters high ALT and high AST decreasing by increasing TCZ exposure was observed. In addition, a potential relationship between the TCZ exposure and post-baseline low neutrophil and platelet counts might be present. The applicant is requested to discuss this potential trend **(OC).**

Comparison across studies

Accounting for variability, observed TCZ Ctrough levels were comparable in the two studies WA29767 and WA27788 and similar to levels observed in patients with RA treated with 162 mg TCZ QW SC (Figure 8). Mean (SD) TCZ trough levels at Week 48 were 54.7 (29.8) and 30.3 (18.9) µg/mL, in the studies WA29767 and WA27788, respectively, while in patients with RA it was 44.2 (28.3) µg/mL (Study WA22762). Mean (SD) body weights in studies WA29767 and WA27788 were 68.0 (15.5) kg (n=104), and 71.8 (16.8) kg (n=43), respectively, while in patients with RA it was 74.1 (18.5) kg (n=521).

Figure 8 Mean (±SD) TCZ Concentration by Visit up to Week 48 in Patients with SSc (WA29767 and WA27788) and in Patients with RA (WA22762)



RA = rheumatoid arthritis; SD = standard deviation; SSc = systemic sclerosis; TCZ = tocilizumab
Note: Exposure measured at Week 37 and 49 in patients with RA.

CHMP comment

The TCZ serum concentration in Study WA27788 seems to be lower and the TCZ serum concentration in Study WA29767 appears to be higher in the steady state phase compared to Study WA22762. The mean (SD) TCZ trough levels at Week 48 were 54.7 (29.8) µg/mL in the studies WA29767 and 30.3 (18.9) µg/mL in study WA27788, while in patients with RA it was 44.2 (28.3) µg/mL (Study WA22762).

However, it should be considered that the number of patients included in the studies/data analysis are quite different between studies (WA29767: n=104, WA27788: n=43, WA22762: n=521). The exposure measurement time points varied slightly between the different studies. Differences in baseline characteristics (e.g. body weight) might also affect the comparability between the studies. Therefore, direct comparisons between studies should made with caution. However, the standard deviation at the different exposure measurement time points is high and overlapping so that no clear difference between the TCZ concentrations across the studies could be identified.

Therefore, pre-dose TCZ concentrations in SSc/SSc-ILD patients were more or less comparable with those observed in adult RA patients.

Population PK model

A popPK analysis was performed to describe the PK characteristics of TCZ in patients with SSc/SSc-ILD following multiple SC administrations of TCZ and to investigate the potential effect of selected covariates on the PK parameters. The data set for the popPK analysis comprised a total of 170 patients with SSc treated with TCZ from the DB period of Study WA29767 and from the DB and OL period of Study WA27788. The SSc-ILD dataset for the sub-analysis consisted of 66 patients from the DB period of Study WA29767.

The popPK model that describes SC TCZ concentrations in patients with SSc and SSc-ILD from studies WA29767 and WA27788 has been previously described for the RA population (popPK Report 1053094). Its structural model is a two-compartment PK model with parallel linear and Michaelis-Menten elimination with first-order absorption for SC administration. All the PK properties previously described for TCZ in the RA population remain valid. These include concentration-dependent clearance (CL) leading to dependence of total, linear and nonlinear CL on TCZ serum concentrations, accumulation rates and a half-life which is concentration-dependent.

The PK parameters are similar in patients with RA, in patients with SSc, and in patients with SSc-ILD.

Table 13 Primary and Secondary PK Parameters in RA, SS_c and SS_c-ILD following 162 mg TCZ SC QW

Parameter	RA	SSc	SSc-ILD
V_c (L)	4.51[a]	4.51[a]	4.16[b]
V_p (L)	2.77[a]	2.77[a]	2.58
V_{ss} (L)	7.28[a]	7.28[a]	6.74[b]
CL (L/day)	0.216[a]	0.216[a]	0.211[b]
Ka (1/day)	0.233[a]	0.233[a]	0.233[a]
Fsc	0.795[a]	0.795[a]	0.795[a]
effective $T_{1/2}$ at SS (day)	12.1-13.0[a]	12.1-13.0[a]	12.1-13.0[a]
absorption $T_{1/2}$ (day)	3[a]	3[a]	3[a]
T_{max} (days)	2.8 (1.9-3.6)[c]	2.8 (2.2-3.1)[d]	2.8 (2.3-3.1)[e]
$C_{max,ss}$ (µg/mL)	49.6 (3-150)[c]	53.2 (14.8-134.3)[d]	52.5 (14.8-121)[e]
$C_{trough,ss}$ (µg/mL)	43.1 (1.3-145)[c]	47.2 (10.8-124.7)[d]	47.2 (10.8-114)[e]
$C_{mean,ss}$ (µg/mL)	47.5 (2.3-148)[c]	50.8 (13.4-131)[d]	50.4 (13.4-119)[e]
$AUC_{\tau,ss}$ (µg/mL*day)	333 (16.3-1038)[c]	356 (94-917)[d]	352 (94-830)[e]

$AUC_{\tau,ss}$ = area under the concentration-time curve over dosing interval at steady state; CL = non-specific clearance (linear clearance); $C_{max,ss}$ = maximum drug concentration at steady state; $C_{mean,ss}$ = mean drug concentration over dosing interval at steady state; $C_{trough,ss}$ = trough drug concentration at steady state; F_{sc} = subcutaneous bioavailability; K_a = absorption rate constant; QW = weekly; SSc = systemic sclerosis; SSc-ILD = SSc with interstitial lung disease; $T_{1/2}$ = half-life; T_{max} = time to reach maximum drug concentration; Vc = central volume of distribution; Vp = peripheral volume of distribution; Vss = volume of distribution at steady state.

Sources: Table 4, Table 5, Table 6, Appendix 2 (Table A1-04), popPK Report 1089532 and popPK Report 1053094.

[a] Population estimate

[b] geometric mean of individual predictions of SSc-ILD population

[c] median (range) of individual predictions of RA population

[d] median (range) of individual predictions of SSc population

[e] median (range) of individual predictions of SSc-ILD population

Only body weight had an appreciable impact on clearance and volume terms of TCZ. TCZ clearance and volumes increased with increasing body weight.

Table 14, Table 15 and Table 16 illustrate the dependence of exposure on body weight for 162 mg TCZ SC QW in patients with SSc, SSc-ILD and RA, respectively. Steady-state AUC_{τ} (and Cmean) in the lowest weight category (< 60 kg) were 47%, 31%, and 45% higher in patients with SSc, SSc-ILD, and RA, respectively, than for patients in the middle weight category (60-100 kg). In the highest weight category (> 100 kg) patients with SSc and RA had 43% and 45% lower AUC_{τ} (and Cmean), respectively, compared to patients in the middle weight category. Although the number of patients with SSc above 100 kg was small (N = 6). As there are limited data for patients with SSc-ILD above 100 kg (n =1), no percent change was calculated for SSc-ILD patients with a body weight > 100 kg.

Table 14 Summary of Predicted Individual Steady-State Exposure Parameters in SSc Patients by Weight Category

Mean (SD)						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	51	511 (188)	73 (26.9)	75.7 (27.2)	2.8 (0.2)	67.9 (26.3)
60 ≤ WT ≤ 100 kg	113	347 (127)	49.6 (18.1)	51.6 (18.4)	2.8 (0.1)	45.7 (17.7)
WT > 100 kg	6	197 (90)	28.1 (12.9)	30.1 (13.6)	2.7 (0.1)	24.3 (11.6)
Median [Range]						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	51	511 [147-917]	73 [21-131]	76.1 [22.5-134.3]	2.8 [2.2-3.1]	68.1 [18.1-124.7]
60 ≤ WT ≤ 100 kg	113	338 [114-812]	48.3 [16.2-116]	49.7 [17.5-118.5]	2.8 [2.3-3.1]	43.8 [13.8-111.5]
WT > 100 kg	6	197 [94-345]	28.2 [13.4-49.3]	30.0 [14.8-53.0]	2.7 [2.5-2.8]	24.8 [10.8-42.4]

AUCτ = area under the concentration-time curve over dosing interval; C_{max} = maximum drug concentration; C_{mean} = mean drug concentration over dosing interval; C_{trough} = trough drug concentration; SD = standard deviation; SSc = systemic sclerosis; T_{max} = time to reach maximum drug concentration; WT = weight.

Table 15 Summary of Predicted Individual Steady-State Exposure Parameters in SSc-ILD Patients by Weight Category

Mean (SD)						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	23	453 (192)	64.7 (27.4)	67 (27.6)	2.8 (0.1)	60.1 (27.1)
60 ≤ WT ≤ 100 kg	42	346 (117)	49.4 (16.7)	51.5 (16.8)	2.8 (0.2)	45.5 (16.6)
WT > 100 kg	1	94 (NA)	13.4 (NA)	14.8 (NA)	2.8 (NA)	10.8 (NA)
Median [Range]						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	23	469 [147-830]	67 [21-119]	69.1 [22.5-121]	2.8 [2.6-3]	62.8 [18.1-114]
60 ≤ WT ≤ 100 kg	42	340 [114-643]	48.5 [16.2-91.9]	49.8 [17.5-94]	2.8 [2.3-3.1]	45.1 [13.8-87.6]
WT > 100 kg	1	94 [94- 94]	13.4 [13.4-13.4]	14.8 [14.8-14.8]	2.8 [2.8-2.8]	10.8 [10.8-10.8]

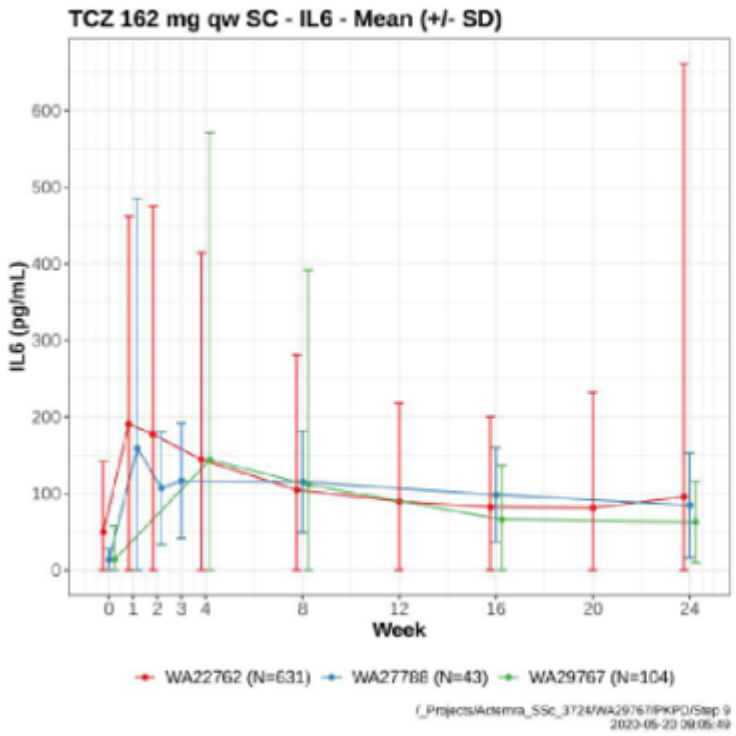
Table 16 Summary of Predicted Individual Steady-State Exposure Parameters in RA Patients by Weight Category

Mean (SD)						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	143	470.5 (157.2)	67.2 (22.5)	69.7 (22.7)	2.8 (0.3)	62.6 (22.1)
60 ≤ WT ≤ 100 kg	420	323.7 (135.7)	46.2 (19.4)	48.3 (19.7)	2.8 (0.3)	42.4 (19.0)
WT > 100 kg	58	178.8 (97.3)	25.5 (13.9)	26.9 (14.2)	2.9 (0.3)	23.0 (13.5)
Median [Range]						
Weight group	**N**	**AUCτ (µg/mL*day)**	**C_{mean} (µg/mL)**	**C_{max} (µg/mL)**	**T_{max} (day)**	**C_{trough} (µg/mL)**
WT < 60 kg	143	452.6 [129-1038]	64.7 [18.4-148.3]	68.0 [19.1-150.1]	3 [2-3.5]	59.8 [17.3-145.2]
60 ≤ WT ≤ 100 kg	420	311.5 [16.3-905.4]	44.5 [2.3-129.3]	46.4 [2.9-132.6]	3 [2-3.5]	40.5 [1.3-123.4]
WT > 100 kg	58	154 [25.4-447.8]	22.0 [3.6-64]	23.2 [4.4-65.6]	3 [2.5-3.5]	19.7 [2.2-61.2]

Pharmacodynamic responses

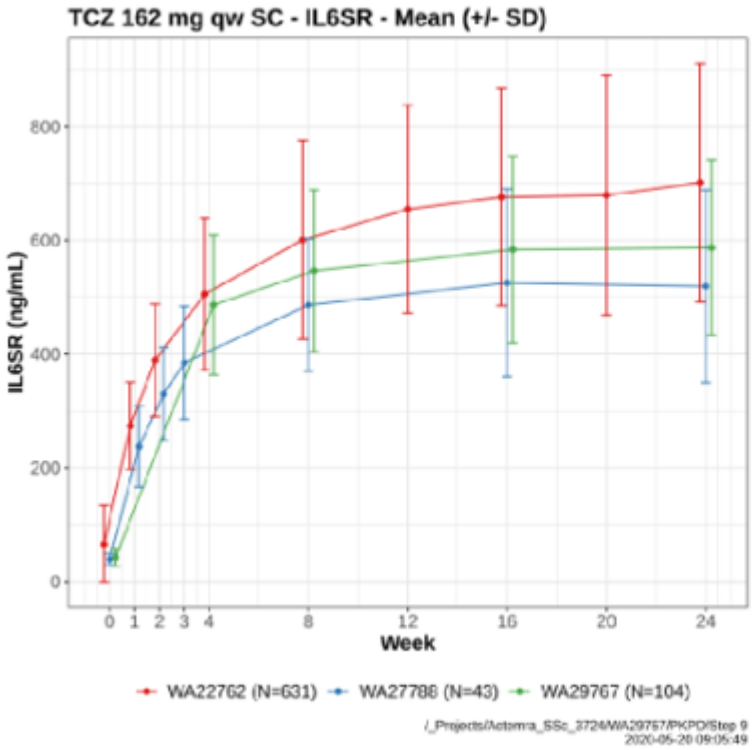
IL-6 concentrations following 162 mg TCZ QW in patients with SSc were overall comparable between Study WA29767 and Study WA27788 (Figure 9). They were consistent with the known TCZ PD profile based on the mechanism of action of TCZ and comparable to the IL-6 levels observed in RA patients following the same dosing regimen i.e. 162 mg TCZ QW

Figure 9 Mean (±SD) IL-6 Concentrations in Patients with SSc WA29767, WA27788) and in Patients with RA (WA22762)



sIL-6R concentrations following 162 mg TCZ QW in patients with SSc were overall comparable between Study WA29767 and Study WA27788. They were consistent with the known TCZ PD profile based on the mechanism of action of TCZ and comparable to the sIL-6R levels observed in RA patients following the same dosing regimen i.e. 162 mg TCZ QW.

Figure 10 Mean (±SD) sIL-6R Concentrations in Patients with SSc WA29767, WA27788) and in Patients with RA (WA22762)



In studies WA29767 and WA27788, both CRP and ESR levels decreased rapidly after the first dose of TCZ. The median CRP levels in the TCZ arm normalized rapidly by Week 4 and remained below 1 mg/L until the end of the study, while median ESR values had stabilized by approximately 8 to 24 weeks after start of TCZ treatment.

Levels of both of these biomarkers were higher in the PBO arm than the TCZ arm and median CRP and ESR levels in PBO-treated patients were relatively unchanged over the study.

Variability in these biomarkers is typically high as seen in the baseline values of both studies. Due to the profound effect of TCZ on the biomarkers CRP and ESR, variability notably reduces in the post-treatment period in the TCZ arm (more pronounced for CRP), indicating a robust PD response in all patients treated with TCZ. CRP and ESR levels following 162 mg TCZ QW in patients with SSc were overall comparable between Study WA29767 and Study WA27788.

Figure 11 Mean (±SD) CRP Concentrations in Patients with SSc WA29767, WA27788) and in Patients with RA (WA22762)

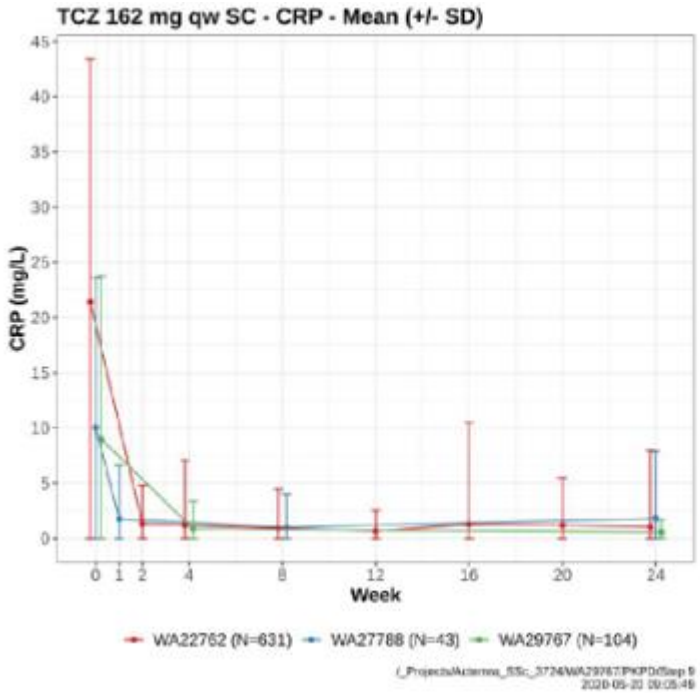
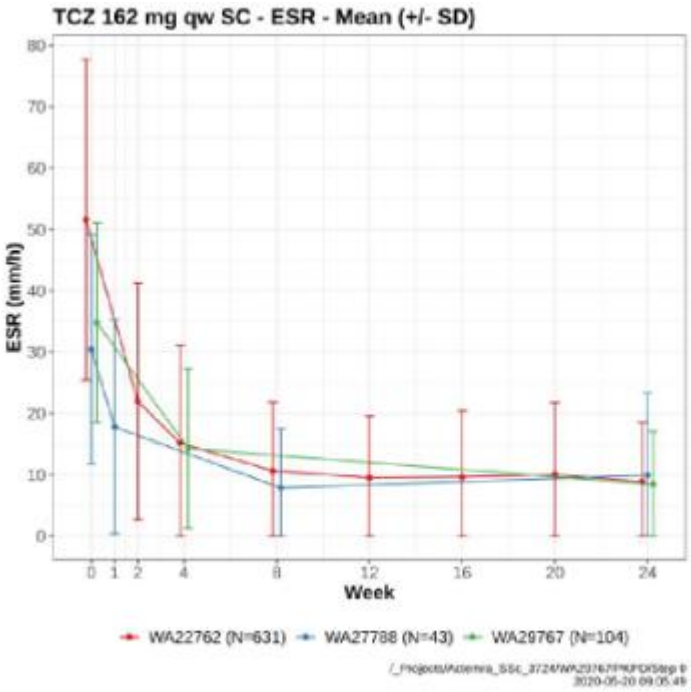


Figure 12 Mean (±SD) ESR in Patients with SSc (WA29767, WA27788) and in Patients with RA (WA22762)



CHMP comment

In general, high variability in these assessed biomarkers (IL-6, sIL-6R, CRP and ESR) was observed (high standard deviation). Based on the data submitted, IL-6 concentrations following 162 mg TCZ QW in patients

with SSc were comparable between Study WA29767 and Study WA27788 as well as comparable with RA patients in Study WA22762.

For sIL-6R, a potential trend was observed that sIL-6R concentrations might be broadly lower in SSc patients than in RA patients. However, it should be noted that the RA study included significantly more patients than the SSc studies and that the variability is also very high. The standard deviation bars overlap and thus no clear conclusion can be drawn.

In addition, both CRP and ESR levels decreased after the first dose of TCZ and remained low until the end of the study. The mean CRP and ESR concentration in patients with SSc and RA appear to be comparable.

Nevertheless, measurement times are not entirely consistent across the studies and thus slightly reduce direct comparability. However, as the standard deviation bars are overlapping and the curve progression of all studies is very similar, also considering the smaller number of patients in the SSc studies (WA27788, n=43; WA29767, n=104) compared to the RA study (n=631), no meaningful differences could be observed for the assessed biomarkers (IL-6, sIL-6R, CRP and ESR).

2.4.3. Pharmacodynamics

Mechanism of action

TCZ is a recombinant humanized anti-human monoclonal antibody of IgG1 subclass directed against the soluble (sIL-6R) and membrane-bound interleukin 6 receptor (mIL-6R). TCZ binds specifically to both receptor types and thereby inhibits IL-6 mediated signalling.

One of the most important mediators in the pathogenesis of SSc-ILD is thought to be IL-6. IL-6 levels are elevated in the skin and serum of patients with SSc and particularly in patients with SSc-ILD (Sakkas 2016). Further, increased serum IL-6 level predicts higher mortality risk, worse skin involvement and increased pulmonary decline. IL-6 is produced by fibroblasts and stimulated B cells especially after exposure to B-cell activating factor. It promotes collagen synthesis in fibroblasts and switches macrophage polarisation towards a profibrotic M2-like phenotype. In SSc-ILD, IL-6 production is believed to occur locally, through the interaction between pulmonary B cells and resident fibroblasts. There is therefore a strong scientific rationale for investigating therapies which block the action of IL-6 as a treatment option for SSc.

The PD of TCZ was characterized by assessing two mechanistic markers, IL-6 and sIL-6R, both directly linked to the mechanism of action of TCZ and two downstream inflammatory markers, CRP and ESR. In the TCZ group, consistent with the mechanism of action of TCZ, sIL-6R levels increased with time and with increasing exposure reflecting slower clearance of the TCZ-receptor complex relative to the native substrate-receptor complex. A greater increase in sIL-6R levels suggests more binding of TCZ to sIL-6R.

The IL-6 levels increased initially, reflecting displacement of bound IL-6 from its receptor by TCZ, and then decreased with time, reflecting an equilibrium of IL-6 formation and clearance. CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ indicating that the TCZ concentrations are high enough to inhibit the effects of IL-6 and for saturation of the target (IL-6R).

Figure 13 Study WA29767: Mean (±SD) TCZ Concentrations by Visit up to Week 48 (PK Population)

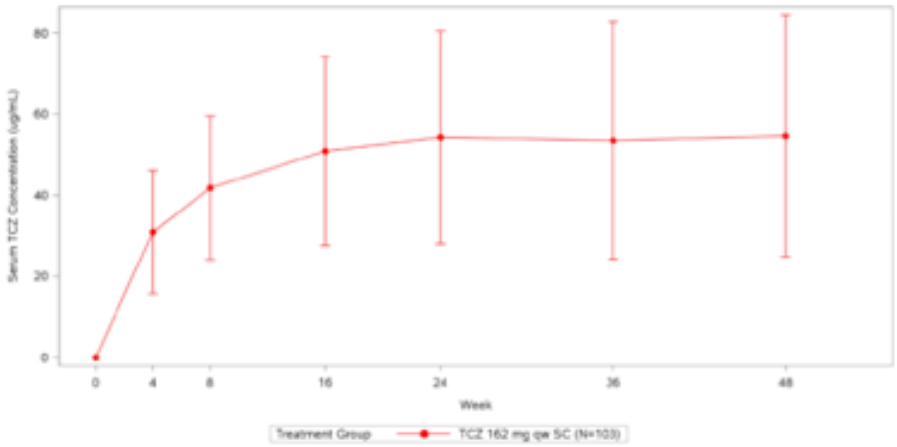


Figure 14 Study WA29767: Mean (±SD) IL-6 Concentrations by Visit up to Week 48 (Safety Population)

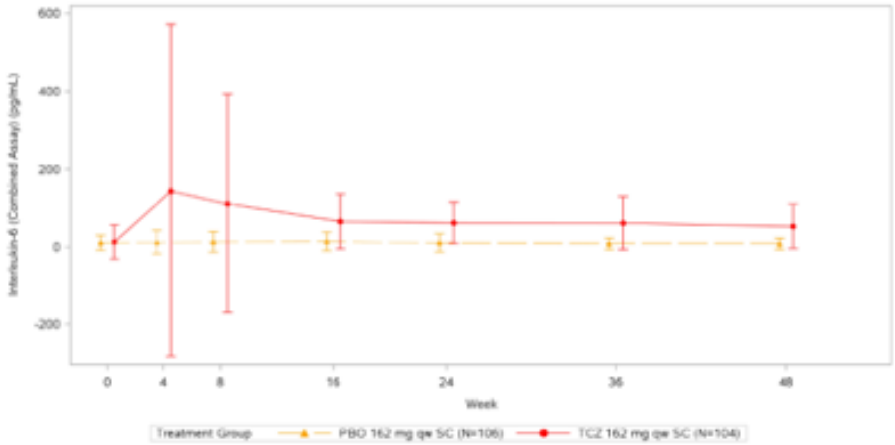
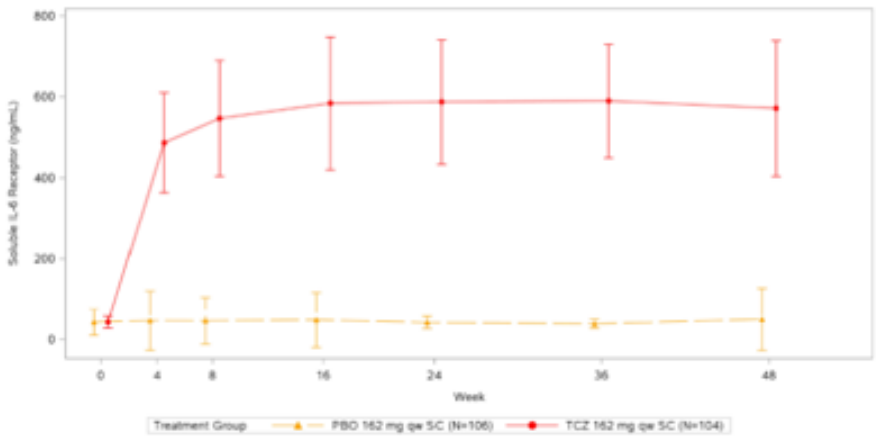


Figure 15 Study WA29767: Mean (±SD) sIL-6R Concentrations by Visit up to Week 48 (Safety Population)



Inflammatory biomarkers CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ indicating that the TCZ concentrations are high enough to inhibit the effects of IL-6 and for saturation of the target (IL-6R).

Figure 16 Study WA29767: Median and IQR for CRP Levels by Visit up to Week 48 (Safety Population)

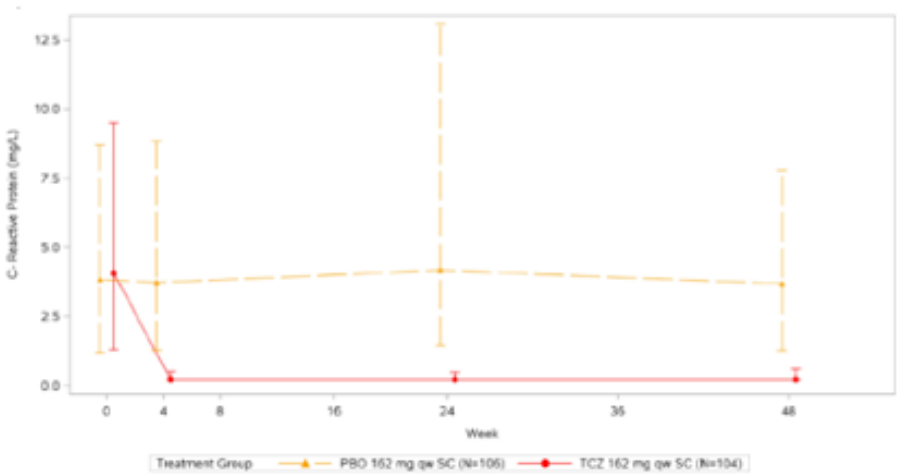
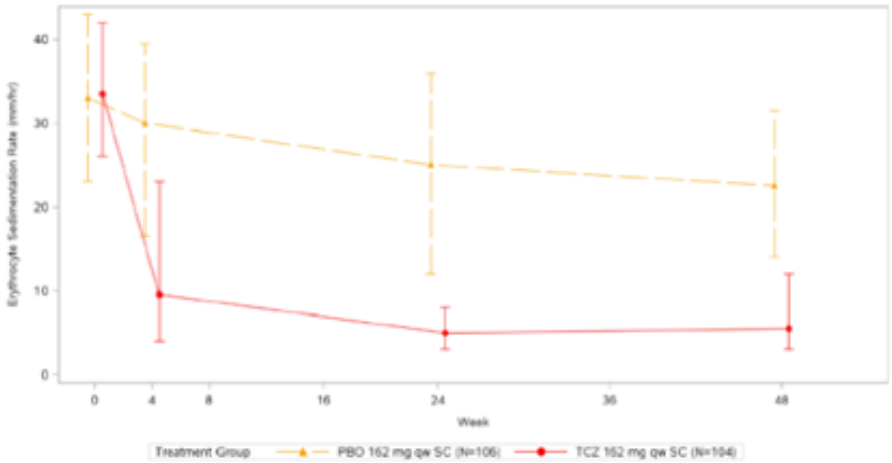


Figure 17 Study WA29767: Median and IQR for ESR Values by Visit up to Week 48 (Safety Population)



2.4.4. PK/PD modelling

TCZ popPK modeling

The used TCZ popPK modelling in SSc was developed previously (popPK Report 1053094) using 13642 quantifiable serum samples from 1759 patients with RA from studies WA22762 and NA25220 following TCZ IV and SC administration. This model was a two-compartment model with first-order absorption and with parallel linear and Michaelis-Menten elimination. The parameter estimates of this model are presented in Table 17. The covariates identified by the model were: body weight on clearance (CL) and inter-compartment clearance (Q), and on central and peripheral volumes (Vc and Vp); HDL-cholesterol on CL; serum albumin and total protein on Vc and Vp; creatinine clearance on Michaelis-Menten parameter Vmax; age on absorption rate constant (ka); and injection site on absolute bioavailability (Fsc). The estimates of ka and of the residual variability were different for the two SC studies used in this model, possibly due to differences between the studies in dosing frequency and sampling schedules.

Data indicate that TCZ serum concentration-time course following SC administration in patients with SSc from studies WA27788 and WA29767 was accurately described by the model developed for RA. The population PK parameter estimates for patients with SSc/SSc-ILD are therefore the same as those for RA.

Table 17 Population Pharmacokinetic Parameter Estimates from the Final Population Pharmacokinetic Model in RA Patients; fixed for SSc Patients and SSc-ILD Patients

Parameter		Estimate	%RSE	95%CI	Variability
CL (L/day)	θ_1	0.216	1.18	0.211 - 0.221	
V_c (L)	θ_2	4.51	1.61	4.37 - 4.65	
Q (L/day)	θ_3	0.274	2.2	0.262 - 0.285	
V_p (L)	θ_4	2.77	1.7	2.68 - 2.87	
V_{max} (µg/mL/day)	θ_5	1.85	1.04	1.82 - 1.89	
K_M (µg/mL)	θ_6	0.343	2.49	0.327 - 0.36	
k_a (1/day)	θ_7	0.233	2.68	0.221 - 0.246	
F_{SC}	θ_8	0.795	1.05	0.779 - 0.811	
$CL_{WT} = Q_{WT}$	θ_9	0.512	4.36	0.468 - 0.555	
$V_{c\,WT} = V_{pWT}$	θ_{10}	0.683	3.86	0.631 - 0.735	
CL_{HDL}	θ_{11}	-0.256	10.9	-0.311 - -0.201	
V_{ALB}	θ_{12}	-0.672	9.38	-0.796 - -0.548	
V_{PROT}	θ_{13}	0.728	12.2	0.554 - 0.901	
$V_{max\,CRCLN}$	θ_{14}	0.229	7.43	0.196 - 0.263	
$k_{a\,AGE}$	θ_{15}	-0.442	17.2	-0.592 - -0.293	
$F_{SC.SJIT3}$	θ_{17}	1.11	0.712	1.09 - 1.12	
ω^2_{CL}	$\Omega(1,1)$	0.076	4.49	0.0693 - 0.0827	CV=27.6
ω^2_{Vc}	$\Omega(2,2)$	0.0507	5.04	0.0457 - 0.0557	CV=22.5
$R\omega_{Vc}\,\omega_{Vp}$	$\Omega(2,3)$	0.045	8.26	0.0377 - 0.0523	R=0.661
ω^2_{Vp}	$\Omega(3,3)$	0.0915	7.22	0.0786 - 0.104	CV=30.3
ω^2_{ka}	$\Omega(4,4)$	0.216	6.3	0.19 - 0.243	CV=46.5
ω^2_{EPS}	$\Omega(5,5)$	0.289	3.72	0.268 - 0.31	CV=53.8
σ^2	$\Sigma(1,1)$	0.0431	3.99	0.0397 - 0.0464	CV=20.7

CI=confidence interval; CV=coefficient of variation; PE=parameter estimate; RSE=relative standard error; SD=standard deviation; SE=standard error.

Note:

Two study effects (on k_a and σ) included in the prior model were removed from the table.

CV=100*SD %

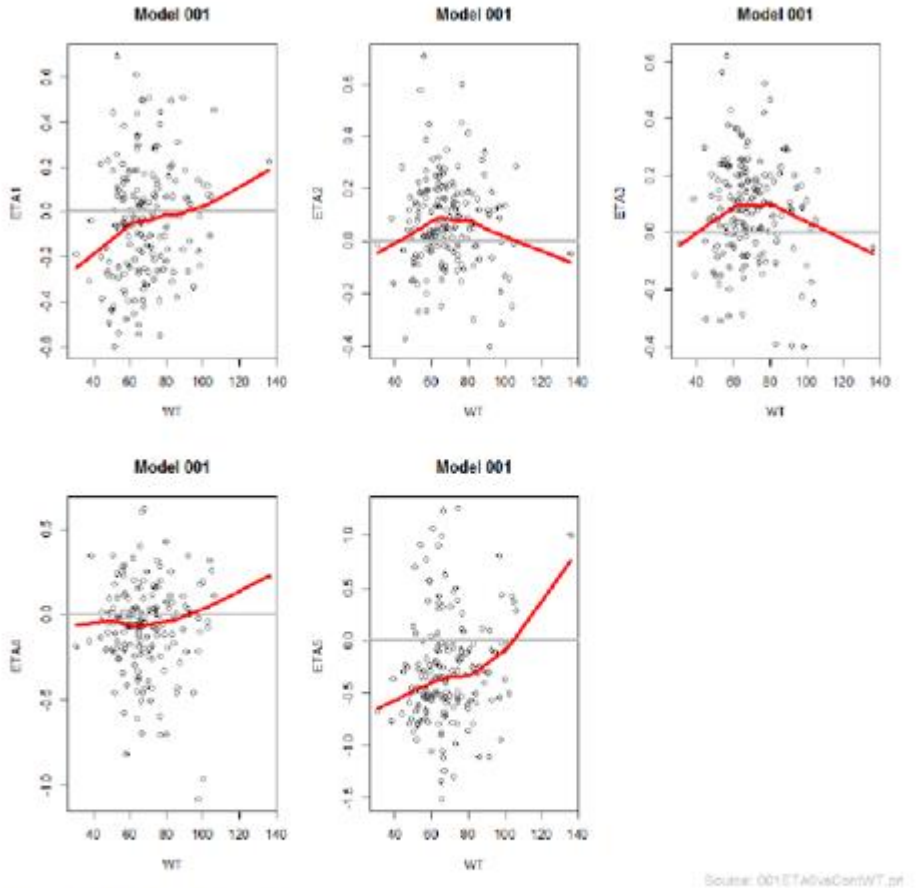
RSE=100 SE/PE

Source: Table 2 from popPK Report (Report 1089532)

The dependencies of the random effects on covariates did not show any trends unaccounted for by the model, except, possibly, stronger than predicted increase of clearance with weight (

Figure 18).

Figure 18 Relationships of Inter-Individual Random Effects with Body Weight. Model 001, SSc Patients



SSc = systemic sclerosis; WT = weight.

The individual random effects are plotted versus weight (WT; kg). **Solid lines** at y = 0 are included for reference. **Red lines** show the lowess trend lines.

ETA1: the random effect on clearance (CL); ETA2: the random effect on central volume of distribution (V_c); ETA3: the random effect on peripheral volume of distribution (V_p); ETA4: the random effect on absorption rate constant (k_a); ETA5: the random effect on residual error.

CHMP comment

PK, PD data and PK/PD modelling indicate a high degree of variability in the data (Ω values). The coefficient of variation ranged from 20.7% up to 53.8%.

With regard to intrinsic and extrinsic factors impacting the PK of TCZ, the only covariate impacting the primary PK parameters for SSc/SSc-ILD was body weight as already described for the RA population following SC administration. TCZ clearance and volumes increased with increasing body weight. Considering that there were no significant differences in exposure-safety and exposure-efficacy relationships across different bodyweights the use of a fixed dose of TCZ instead of a dose adjusted by body weight is justified.

Individual Predictions of Steady-State Exposure

The summary of predicted individual steady-state exposure parameters is presented for patients with SSc in Table 18. The median predicted steady-state values of Cmean, Cmax, and Ctrough were 50.8, 53.2, and 47.2 µg/mL respectively.

The summary of predicted individual steady-state exposure parameters is presented for patients with SSc-ILD, a subpopulation of the SSc patient population, in Table 19. The median predicted steady-state values of Cmean, Cmax, and Ctrough were 50.4, 52.5, and 47.2 µg/mL respectively.

Table 18 Summary of Predicted Individual Steady-State Exposure Parameters in Patients with SSc

	N	AUC_T (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
Mean (SD)	170	391 (168)	55.8 (24.1)	58.1 (24.4)	2.8 (0.1)	51.6 (23.4)
Median [Range]	170	356 [94-917]	50.8 [13.4-131]	53.2 [14.8-134.3]	2.8 [2.2-3.1]	47.2 [10.8-124.7]

AUC_T = area under the concentration-time curve over dosing interval; C_{max} = maximum drug concentration; C_{mean} = mean drug concentration over dosing interval; C_{trough} = trough drug concentration; SD = standard deviation; T_{max} = time to reach maximum drug concentration; WT = weight.

Source: Table 8 in popPK Report (Report 1089532).

Table 19 Summary of Predicted Individual Steady-State Exposure Parameters in Patients with SSc-ILD

	N	AUC_T (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
Mean (SD)	66	379 (158)	54.2 (22.6)	56.4 (22.8)	2.8 (0.1)	50.1 (22.2)
Median [Range]	66	352 [94-830]	50.4 [13.4-119]	52.5 [14.8-121]	2.8 [2.3-3.1]	47.2 [10.8-114]

AUC_T = area under the concentration-time curve over dosing interval; C_{max} = maximum drug concentration; C_{mean} = mean drug concentration over dosing interval; C_{trough} = trough drug concentration; SD = standard deviation; T_{max} = time to reach maximum drug concentration; WT = weight.

Time to Steady-State and Accumulation Ratio

Nonlinear elimination (expressed as a combination of linear clearance and Michaelis-Menten elimination) precludes deriving time to steady-state and the accumulation ratio directly from the primary PK parameters. Therefore, these parameters were determined by conditional simulation.

In patients with SSc, 90% of the steady state for all exposure parameters was reached by Week 13. The AUC_T (and Cmean), Cmax, and Ctrough accumulation ratios were 7.00, 5.82, and 6.37 respectively.

In patients with SSc-ILD, a subpopulation of the SSc patient population, 90% of the steady state for all exposure parameters was reached by Week 13. The AUC_T (and Cmean), Cmax, and Ctrough accumulation ratios were 7.11, 5.89, and 6.56 respectively

CHMP comment

According to the model no differences in Steady-State Exposure Parameters or Time to Steady-State and Accumulation Ratio in Patients with SSc and Patients with SSc-ILD are expected. The effective half-life of TCZ in SSc and SSc-ILD patients was found to vary at the population level between 12.1 and 13.0 days for the 162 mg SC QW dosing regimen. In patients with SSc-ILD the geometric mean linear clearance was 0.21 L/day (8.8 mL/h), the central volume of distribution was 4.16 L, the peripheral volume of distribution was 2.58 L resulting in a volume of distribution at steady state of 6.74 L.

2.4.5. Discussion on clinical pharmacology

TCZ is directed against the soluble (sIL-6R) and membrane-bound interleukin 6 receptor (mIL-6R). TCZ binds specifically to both receptor types and thereby inhibits IL-6 mediated signalling. The potential for TCZ in the treatment of SSc stems from the putative role of IL-6 as a key link between inflammation and fibrosis. One of the most important mediators in the pathogenesis of SSc-ILD is thought to be IL-6. IL-6 levels are elevated in the skin and serum of patients with. There is a scientific rationale for investigating therapies which block the action of IL-6 as a treatment option for SSc.

The provided clinical data submitted with regard to PK/PD, efficacy and safety results from two clinical studies investigating TCZ include one pivotal Phase III Study WA29767 and one supportive Phase II/III Study WA27788.

Priori knowledge on the mechanism of action of TCZ in other diseases such as RA was used for dose selection in patients with SSc/SSc-ILD. The same TCZ dosing regimen as in RA was proposed to provide a positive clinical benefit/risk in patients with SSc. The SC route of administration was chosen over IV administration for convenience of use and to address difficulties with IV infusions in patients with SSc with vasculopathies and therefore the dosing regimen tested in both Studies WA29767 and WA27788 was 162 mg TCZ SC QW. This is acknowledged and one of the important aspects with this regard is the comparable PD/PK behaviour of TZC in SSc/SSc-ILD patients vs. RA patients.

Bioanalytical methods used for determination of tocilizumab and sIL-6R concentrations in human serum are those already established and validated. Thus, no new or updated method validation reports were submitted but the summaries demonstrate that the assays perform accurate and precise and are suitable for their intended use.

After repeated dosing, the mean pre-dose TCZ concentrations in patients with SSc increased with time and appeared to reach steady state by Week 16 and the exposure was maintained with continued TCZ treatment until the end of study at week 96. The incidence of anti-TCZ antibodies was low and there was no clinical significance associated.

The PD of TCZ was characterized by assessing IL-6 and sIL-6R, both directly linked to the mechanism of action of TCZ and two downstream inflammatory markers, CRP and ESR. As expected data confirm that sIL-6R levels increased with time as expected and after initially increased IL-6 levels, reflecting displacement of bound IL-6 from its receptor, levels decreased with time, reflecting an equilibrium of IL-6 formation and clearance. Inflammatory biomarkers CRP and ESR decreased with time and remained low over the treatment period due to inhibition of IL-6 signaling by TCZ.

A pre-specified exposure-response analysis including key efficacy and safety endpoints was conducted. All graphical analysis was conducted by observed Week 48 Ctrough grouped into tertiles of high, medium and low exposure. Efficacy endpoints included the following: mRSS, improvement in mRSS by ≥ 20, ≥ 40 and ≥ 60%, pFVC, HAQ-DI, Patients Global Assessment and Physicians Global Assessment; all at Week 48. Analysis of observed TCZ Ctrough concentrations in mRSS responders with a improvement at ≥ 20, ≥ 40 and ≥ 60%, Week 48 indicated no trends related to TCZ exposure. Safety endpoints included the following: SAEs and AEs by SOC, all grades of high ALT and AST, neutrophils and platelets. There were no clear trends observed in the overall incidence of AEs or SAEs at Week 48 by TCZ Ctrough tertiles, indicating there are no safety signals related to increasing TCZ exposure.

The TCZ serum concentration-time course following 162 mg TCZ SC QW administration in patients with SSc and SSc-ILD was accurately described by the two-compartment PK model with first-order absorption and parallel linear and Michaelis-Menten elimination developed for patients with RA. The used TCZ popPK modelling in SSc was developed previously (popPK Report 1053094) using 13642 quantifiable serum

samples from 1759 patients with RA from studies WA22762 and NA25220 following TCZ IV and SC administration. With regard to intrinsic and extrinsic factors impacting the PK of TCZ, the only covariate impacting the primary PK parameters for SSc/SSc-ILD was body weight as described for the RA population following SC administration. TCZ clearance and volumes increased with increasing body weight. Considering that there were no significant differences in exposure-safety and exposure-efficacy relationships across different bodyweights the use of a fixed dose of TCZ instead of a dose adjusted by body weight is justified.

Steady-state TCZ trough drug concentration (Ctrough) levels in patients with SSc/SSc-ILD were comparable to those in patients with RA and were associated with sustained normalisation of CRP throughout treatment duration. The IL-6Rs are blocked over the dosing interval, resulting in a maximal PD response, i.e., maximal effect in reduction of IL-6 signaling. Saturation of the target (IL-6R) and the absence of a significant exposure-efficacy relationship suggest that maximum efficacy is reached with the dosing regimen of 162 mg TCZ SC QW in patients with SSc/SSc-ILD. Higher TCZ doses leading to higher TCZ concentrations would not be expected to lead to a further improvement in PD response and consequently efficacy, as the IL-6Rs appear to be fully blocked.

2.4.6. Conclusions on clinical pharmacology

Prior knowledge on the mechanism of action of TCZ in other diseases such as RA was used for dose selection in patients with SSc/SSc-ILD. The same TCZ dosing regimen as in RA was proposed to provide a positive clinical benefit/risk in patients with SSc. The SC route of administration was chosen over IV administration for convenience of use and to address difficulties with IV infusions in patients with SSc with vasculopathies and therefore the dosing regimen tested in both Studies WA29767 and WA27788 was 162 mg TCZ SC QW. This is acknowledged and one of the important aspects with this regard is the comparable PD/PK behaviour of TZC in SSc/SSc-ILD patients vs. RA patients. Steady-state TCZ trough drug concentration (Ctrough) levels in patients with SSc/SSc-ILD were comparable to those in patients with RA and were associated with sustained normalisation of CRP throughout treatment duration. The IL-6Rs are blocked over the dosing interval, resulting in a maximal PD response, i.e., maximal effect in reduction of IL-6 signaling. Saturation of the target (IL-6R) and the absence of a significant exposure-efficacy relationship suggest that maximum efficacy is reached with the dosing regimen of 162 mg TCZ SC QW in patients with SSc/SSc-ILD.

Overall the proposed route of administration and dose of 162 mg TCZ SC is considered justified.

2.5. Clinical efficacy

The clinical efficacy is supported by one pivotal Phase III Study WA29767 and one supportive Phase II/III Study WA27788; approximately 300 patients with SSc were treated with TCZ.

Table 20 Overview of Clinical Studies Included in Submission

Study No. (Phase)	Study Design, Control Type	Population	Dose, Route, and Regimen	Primary and Secondary Endpoints	No. of Patients	Status
Pivotal Study						
WA29767 (FocuSSced) (Phase III)	Multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study (TCZ vs. PBO)	Adult patients with SSc	Double-blind period: TCZ 162 mg SC QW or PBO SC QW Open-label period: TCZ 162 mg SC QW	Primary efficacy: mRSS at Week 48 Secondary efficacy: ppFVC, HAQ-DI, patient's global assessment, and physician's global assessment at Week 48, time to treatment failure up to Week 48 Safety, PK, PD, immunogenicity	212 [a] Double-blind period: PBO: 106 TCZ: 104 Open-label period: PBO→TCZ: 89 TCZ→TCZ: 92	Completed
Supportive Study						
WA27788 (FaSScinate) (Phase II/III)	Multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study (TCZ vs. PBO)	Adult patients with SSc	Double-blind period: TCZ 162 mg SC QW or PBO SC QW Open-label period: TCZ 162 mg SC QW	Primary efficacy: mRSS at Week 24 Secondary efficacy: HAQ-DI, SHAQ-VAS, patient's global assessment, physician's global assessment, FACIT-Fatigue score, 5-D Itch Scale, mRSS improvement from Week 24 to 48, mRSS at Week 48 Safety, PK, PD, immunogenicity	87 Double-blind period: PBO: 44 TCZ: 43 Open-label period: PBO→TCZ: 31 TCZ→TCZ: 30	Completed

ADA = anti-drug antibodies; FACIT = Functional Assessment of Chronic Illness Therapy; FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire-Disability Index; ITT = intent-to-treat; mRSS = modified Rodnan skin score; PBO = placebo; PD = pharmacodynamics; PK = pharmacokinetics; ppFVC = percent predicted forced vital capacity; QW = weekly; SC = subcutaneous; SHAQ-VAS = Scleroderma Health Assessment Questionnaire visual analogue scale; SSc = systemic sclerosis; TCZ = tocilizumab.

[a] Two patients (1 in each treatment arm) withdrew from the study prior to receiving the first dose of study treatment and were excluded from the ITT and Safety populations.

In addition to the clinical studies data, a Human Factors Validation study has been performed to demonstrate that the PFS can be used safely and effectively by patients with SSc.

CHMP comment

For Study WA29767 there are two CSR provided, namely a Week 48 and a Week 96 (open label study) report provided. For Study WA27788 there are 3 CSRs, Week 24, Week 48 and Week 96. An integrated final study report for both studies would have been beneficial for the clarity of the submission.

The indication claim is based on Week 48 efficacy data and safety is supported by Week 48 and Week 96 safety data.

The majority of the tables provided are of poor technical quality, which precludes the inclusion of the table in this report.

2.5.1. Dose response study(ies)

No dose response studies were provided.

The potential for TCZ in the treatment of SSc/SSc-ILD stems from the putative role of IL-6 as a key link between inflammation and fibrosis. IL-6 levels are elevated in the skin and serum of adult patients with SSc (Koch et al. 1993; Hasegawa et al. 2011; Desallais et al. 2014; Khan et al. 2012); and particularly in patients with SSc- ILD (Sakkas 2016). It was suggested that inhibition of IL-6mediated signalling by TCZ could lead to improvement of disease state.

Both SSc and RA are associated with elevated IL-6 levels in similar ranges (Table 21), indicating that mechanistically the two diseases may require the same levels of TCZ (i.e., achieve same steady-state trough drug concentration [Ctrough]) for treatment benefit. Thus, the approved dosing regimens for RA may also be applicable to SSc.

Table 21 Baseline Interleukin 6 Concentrations (pg/mL) in Systemic Sclerosis and Rheumatoid Arthritis

	WA29767 SSc [a]	WA27788 SSc [a]	WA22762 RA
N	104	42	481
Mean (SD)	14 (43.8)	14 (14.7)	43 (56.6)
Median	4.65	7.3	22
Min-Max	0–419	NR	3–413

Max = maximum; Min = minimum; NR = not reported; RA = rheumatoid arthritis; SSc = systemic sclerosis; TCZ = tocilizumab.

[a] Only baseline values from the TCZ group are presented; values in the placebo group were comparable.

Sources: WA29767 Primary CSR 1081912, t_pk_mean_SE_IL6; WA27788 Final CSR 1066830, t_pk_cb_SE_IL6IL6R; WA22762 CSR 1048411, stlb10_pk_il6b.

With similar baseline ranges of IL-6, and assuming that TCZ pharmacokinetics, baseline sIL-6R levels, and IL-6R-mediated TCZ clearance are similar between patients with RA and SSc/SSc-ILD, and that the relationship between PK and PD biomarkers in RA holds true for SSc/SSc-ILD, the dosing regimen of 162 mg TCZ SC QW was chosen to be tested in the two clinical studies, WA27788 and WA29767.

For patients with SSc/SSc-ILD the SC route of administration was preferred over the IV route for convenience of use and to address difficulties with IV infusions in SSc/ SSc-ILD patients with vasculopathies.

Steady-state TCZ Ctrough levels in patients with SSc/SSc-ILD were comparable to those in patients with RA and were associated with sustained normalisation of CRP throughout treatment duration (assessment of clinical pharmacology). This suggests that the IL-6Rs are blocked over the dosing interval, resulting in a maximal PD response, i.e., maximal effect in reduction of IL-6 signalling. Saturation of the target (IL-6R) and the absence of a significant exposure-efficacy relationship suggest that maximum efficacy is reached with the dosing regimen of 162 mg TCZ SC QW in patients with SSc/SSc-ILD. Higher TCZ doses leading to higher TCZ concentrations would not be expected to lead to a further improvement in PD response and consequently efficacy, as the IL-6Rsappear to be fully blocked.

Following administration of 162 mg TCZ SC QW in patients with SSc/SSc-ILD the safety was consistent with the known safety profile of TCZ in approved indications and a clinically meaningful effect on preservation of lung function was demonstrated. The benefit-risk profile for TCZ 162 mg SC QW in the SSc-ILD population was shown to be favourable. Thus, the recommended dose of TCZ for adult patients with SSc-ILD is 162 mg SC QW.

CHMP comment

No dose finding studies in SSc/SSc-ILD were provided. The MAH provided a rational for the selected dose based on the similarity of the PD in RA and the pharmacological, safety, and efficacy data of the two studies supporting this submission. The argumentation is acceptable.

2.5.2. Main study

- A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients with Systemic Sclerosis (Study WA29767).

The pivotal study consisted of two periods: a 48-week, double-blind (DB), placebo-controlled period, followed by a 48-week open-label (OL) treatment period (from Week 48 to 96).

The majority of the study objectives, including the primary and secondary efficacy objectives, were related to the first 24 or 48 weeks of the study.

The purpose of the OL treatment period was to assess the long-term safety and efficacy of TCZ in the treatment of SSc, and to evaluate maintenance of efficacy as measured by modified Rodnan Skin Score (mRSS) and forced vital capacity (FVC) at Week 96.

- A Phase II/III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients with Systemic Sclerosis (Study WA27788)

The supportive study consists of two periods. A a 48-week blinded period is followed by a 48-week open-label period. The primary endpoint, the change in mRSS from baseline at Week 24, will be evaluated at Week 24.

Since the study design was comparable overall between Studies WA29767and WA27788 the methods are summarised for both studies below in a comparative manner.

Methods

Study participants

Table 22 Comparison of Key Entry Criteria in Studies WA29767 and WA27788

Study WA29767	Study WA27788
Inclusion criteria	
Diagnosis of SSc, defined using the 2013 ACR/EULAR criteria	Diagnosis of SSc, defined using the 1980 ACR/EULAR criteria
SSc disease duration of ≤60 months (from the first non-Raynaud phenomenon manifestation)	
mRSS of ≥ 10 and ≤ 35 units	mRSS of ≥15 and ≤40 mRSS units
Active disease defined as meeting at least one of the following criteria at screening:	
Disease duration of ≤18 months defined as time from the first non–Raynaud phenomenon manifestation	Patients with new-onset SSc, diagnosed within 1 year prior to screening
Increase in mRSS of ≥ 3 units compared with the most recent assessment performed within the previous 6 months	
Involvement of one new body area and an increase in mRSS of ≥2 units compared with the most recent assessment performed within the previous 6 months	
Involvement of two new body areas with ≥1 mRSS units at screening compared with the last visit within the previous 6 months	
Presence of at least one tendon friction rub	
--	Other documentation of worsening skin thickening at screening compared with the last visit within the previous 1–6 months with source documentation from that time period
At least one of the following criteria at screening:	
High-sensitivity CRP ≥ 6 mg/L (≥ 0.6 mg/dL)	High-sensitivity CRP ≥10 mg/L (≥ 1 mg/dL)
ESR ≥28 mm/h	
Platelet count ≥330×10^3/L (330,000/μL)	
Exclusion criteria	
Rheumatic autoimmune disease other than SSc	
Skin thickening (scleroderma) limited to the face or areas distal to the elbows or knees at screening	Skin thickening (scleroderma) limited to areas distal to the elbows or knees at screening
History of previous/concomitant pulmonary disease:	
• Pulmonary disease with ppFVC ≤55% (best of three acceptable and repeatable measurements), OR • $ppDL_{CO}$ ≤45% (haemoglobin corrected, and the average of the two highest acceptable and repeatable measurements)	• Pulmonary disease with ppFVC ≤50%, OR • $ppDL_{CO}$ ≤40% (haemoglobin corrected)
Class II or higher PAH, as defined by the World Health Organisation	
Other moderately severe pulmonary disease (e.g., asthma, emphysema)	

ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; mRSS = modified Rodnan skin score; PAH = pulmonary arterial hypertension; $ppDL_{CO}$ = percent predicted diffusion capacity of the lung for carbon monoxide; ppFVC = percent predicted forced vital capacity; SSc = systemic sclerosis.

CHMP comment

The patient's population included in Study WA27788 and WA29767 is largely similar. Patients with the diagnosis of SSc were enrolled, organ involvement e.g. cardiac, renal or lung involvement was not an inclusion criterion. Moreover, patient with history of previous/concomitant pulmonary disease defined by certain ppFVC and ppDLCO level were excluded from the study. Please comment these inclusion / exclusion criteria under the light of the indication claim based on a post-hoc subgroup analysis in patients with SSc-ILD at a certain degree as relevant population. (OC)

Table 22 provides an overview of the inclusion exlusion criteria. According the table, patients with SSc disease duration of $\leq$60 months (from the first non-Raynaud phenomenon manifestation) are included in either study. . Two lines further down in the table a different disease duration is specified:

"Study WA29767: Disease duration of $\leq$18 months defined as time from the first non-Raynaud phenomenon manifestation"

and

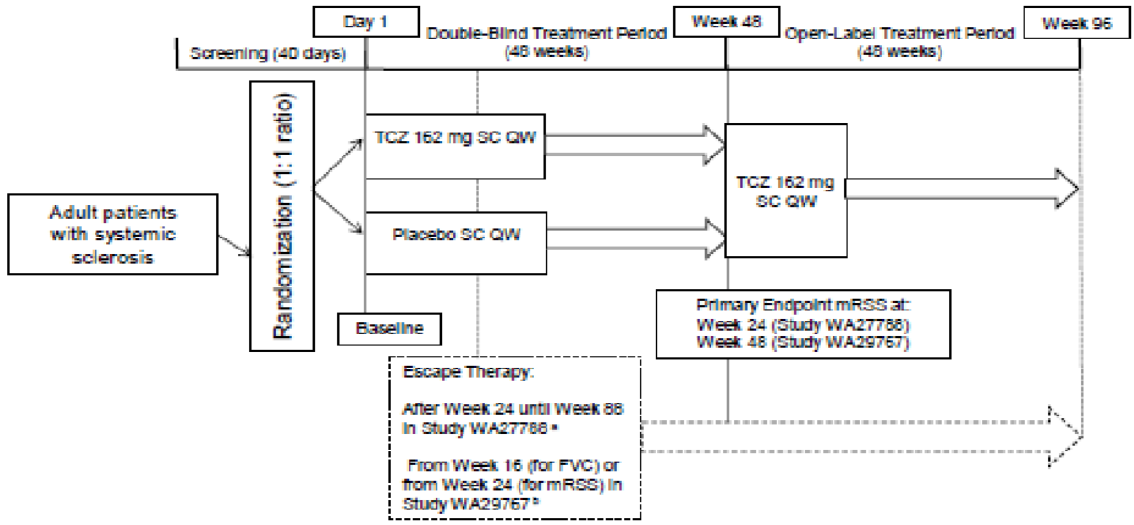
"Study WA27788: Patients with new-onset SSc, diagnosed within 1 year prior to screening."

Please clarify this contradiction (OC)

Treatments

Figure 19 Schema of Studies WA29767 and WA27788

Figure 1 Schema of Studies WA29767 and WA27788



FVC = forced vital capacity; mRSS = modified Rodnan skin score; QW = weekly; SC = subcutaneous; SSc = systemic sclerosis; TCZ = tocilizumab.

Note: Other concomitant treatments for SSc complications and disease manifestations (e.g., IV prostacyclin at study entry for treatment of Raynaud phenomenon or digital ulcers, oral corticosteroids, or nonsteroidal anti-inflammatory drugs and analgesics), including treatments for new and existing organ complications were allowed during the double-blind treatment period.

[a] Escape therapy, consisting of methotrexate, hydroxychloroquine, or mycophenolate mofetil, was permitted after Week 24 for patients with ≥ 20% worsening in mRSS from baseline. Initiation of escape therapy for eligible patients was based on investigator assessment. Mycophenolate mofetil as escape therapy was permitted only after review and approval by the Sponsor.

[b] From Week 24, escape therapy was permitted for patients with worsening of skin thickening or worsening SSc complications, and from Week 16, escape therapy was permitted for patients with decline in FVC compared with baseline.

In both studies patients received TCZ 162 mg SC QW versus placebo for 48 weeks during the double-blind treatment period, followed by the same dose in the open label treatment period.

A difference between studies was the timing of escape therapy. In Study WA29767, escape therapy (i.e., any immuno-modulatory agent discussed with the medical monitor) could be initiated as early as Week 16 in patients with a > 10% reduction in percent predicted forced vital capacity (ppFVC) relative to baseline, and with a decline from baseline confirmed on two separate occasions within a 4-week period, or at Week 24 in patients with worsening SSc complications and/or mRSS of a minimum of 5 points and at least 20% increase, relative to baseline.

In Study WA27788, escape therapy options were limited to methotrexate, hydroxychloroquine, or mycophenolate mofetil (MMF), and could be initiated after Week 24 for worsening skin symptoms (defined as ≥20% worsening in mRSS from baseline) and/or worsening SSc-associated complications. Data were censored following escape therapy for the analysis of Study WA27788 Week 48 data, in contrast to Study WA29767.

Objectives

Table 23 Comparison of Key Efficacy Objectives in Studies WA29767 and WA27788

Study WA29767	Study WA27788 [a]
Primary Efficacy Endpoint in WA29767	
mRSS at Week 48	mRSS at Week 48 (secondary)
Secondary Efficacy Endpoints in WA29767	
ppFVC at Week 48 [b]	ppFVC at Week 48 (exploratory)
Time to treatment failure up to Week 48 [c]	--
HAQ-DI at Week 48	HAQ-DI at Weeks 24 and 48 (secondary)
Proportion of patients with ≥ 20%, ≥ 40%, and ≥ 60% improvement in mRSS at Week 48 [d]	Proportion of patients with ≥ 20%, ≥ 40%, and ≥ 60% improvement in mRSS at Week 48 (post hoc)
--	Proportion of patients with change in mRSS at Week 48 greater than or equal to the change in mRSS at Week 24 (secondary)
Patient's Global Assessment at Week 48	Patient's Global Assessment at Weeks 24 and 48 (secondary)
Physician's Global Assessment at Week 48	Physician's Global Assessment at Weeks 24 and 48 (secondary)
--	Pruritus 5-D Itch Scale at Weeks 24 and 48 (secondary)
Exploratory, Prespecified Efficacy Endpoints in WA29767	
ppFVC at Week 24 [e]	ppFVC at Week 24 (exploratory)
mRSS at Week 24 [c]	mRSS at Week 24 (primary)
FACIT-Fatigue score at Week 48	FACIT-Fatigue score at Weeks 24 and 48 (secondary)
Proportion of patients with ≥ 10% decline in FVC at Week 48	Proportion of patients with ≥ 10% decline in FVC at Week 48 (post hoc) [f]
SHAQ-VAS scores at Week 48	SHAQ-VAS scores at Week 48 (secondary)
DL_{CO} at Week 48 [g]	DL_{CO} at Week 48 (exploratory)
CRISS response at Week 48	CRISS response at Week 48 (post hoc)
HRCT scan results at Week 48	--
SGRQ at Week 48	--

Study WA29767	Study WA27788 [a]
Exploratory, Post Hoc Efficacy Endpoints	
Proportion of patients with improvement/worsening/no change in ppFVC at Week 48	Proportion of patients with improvement/worsening/no change in ppFVC at Week 48 (post hoc)
Subgroup analyses of mRSS and FVC (observed and percent predicted) for patients with SSc-ILD at baseline	--
Analysis of HRCT scan results for patients with SSc-ILD at baseline	--

CRISS=Combined Response Index for Systemic Sclerosis; DLco=diffusion capacity of the lung for carbon monoxide; FACIT=Functional Assessment of Chronic Illness Therapy; FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire-Disability Index; HRCT=high-resolution computed tomography; IL-6=interleukin 6; mRSS=modified Rodnan skin score; ppFVC=percent predicted forced vital capacity; SGRQ=Saint George's Respiratory Questionnaire; SHAQ-VAS=Scleroderma Health Assessment Questionnaire visual analogue scale; SSc-ILD=systemic sclerosis with interstitial lung disease.

Note: Study WA29767 was stratified by screening IL-6 level (<10; ≥10 pg/mL) while Study WA27788 was stratified by joint involvement at baseline (≥4 or <4 tender joints of 28 tender joint count.

[a] Although endpoints other than the primary analysis were classed as secondary and exploratory for Study WA27788 in the Protocol, there was no control of Type 1 error for this study.

[b] Observed and ppFVC.

[c] Time to treatment failure is defined as the time of first death, decline in ppFVC > 10% relative to baseline, increase in mRSS > 20% and an increase in mRSS of ≥ 5 points relative to baseline, occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee, whichever occurs first during the 48-week double-blind treatment period.

[d] Proportion of patients with ≥ 20%, ≥ 40%, and ≥ 60% improvement in mRSS at Week 48 were three separate analyses in WA29767, each with its own position in the hierarchy. See Section 1.2.5.1 for further details.

[e] Change from baseline in mRSS and FVC at Week 24 were listed as exploratory endpoints in the Protocol. However, the analysis of these endpoints was part of the multiplicity testing procedure.

[f] In Study WA27788, the proportion of patients with ≥ 10% decline in FVC (observed) was a prespecified analysis in the Statistical Analysis Plan.

[g] Exploratory endpoints also for the proportion of patients with ≥ 15% decline in observed and percent predicted DL_{CO} at Week 48 relative to baseline.

There was a notable difference in the primary assessment timepoint. The primary efficacy objective was the change from baseline in mRSS in both studies, assessed at Week 48 for Study WA29767 and at Week 24 for Study WA27788.

CHMP comment

In Study WA29767 the primary efficacy objective was assessed at Week 48, while originally in Study WA27788 the assessment of the primary efficacy objective was planned for week 24. In order to provide comparative results, the secondary efficacy objective, change from baseline in mRSS at Week 48, is used for comparison of the outcome of the two studies. For the purpose of the comparison this approach can be accepted.

Of note, in Study WA29767 measurement of ppFVC at Week 48 was a secondary objective, while in Study WA27788 it was an exploratory objective. However, outcome of this measurement is used as main evidence in supporting the claimed indication.

Outcomes/endpoints

Study WA29767

Primary endpoint:

- Change in mRSS from baseline at Week 48

Secondary endpoints:

- Proportions of patients with ≥ 20%, ≥ 40%, and ≥ 60% improvement in mRSS at Week 48 compared with baseline
- Change from baseline to Week 48 in the following: FVC, HAQ-DI, Patient's Global Assessment, and Physician's Global Assessment
- TTF at Week 48

Exploratory endpoints

- Change from baseline at Week 24 in mRSS and ppFVC
- Change from baseline at Week 48 in: percent predicted diffusion capacity of the lung for carbon monoxide (ppDLCO), Saint George's Respiratory Questionnaire, high-resolution computed tomography (HRCT) fibrosis score, Combined Response Index for Systemic Sclerosis (CRISS) score, and Functional Assessment of Chronic Illness Therapy-Fatigue score
- Change from baseline at Week 24 and Week 48 in the following: Scleroderma Health Assessment Questionnaire-Visual Analogue Scale (SHAQ-VAS) score, EuroQoL Five-Dimension Three-Level Questionnaire score, Work Productivity and Activity Impairment Questionnaire: General Health, and Scleroderma Skin Patient-Reported Outcome score (North America only)
- Proportion of patients with a ≥10% decline in observed FVC (L) and the proportion of patients with a ≥10% decline in ppFVC (L) at Week 24 and Week 48 from baseline
- Proportion of patients with a ≥ 15% decline in observed DLCO and the proportion of patients with a ≥15% decline in ppDLCO at Week 48 relative to baseline
- Proportion of patients who achieved a minimal clinically important difference (MCID, change from baseline ≥0.22) in the HAQ-DI at Week 48
- Proportion of patients who achieved a response (predicted probability ≥0.60) using CRISS and the proportion of patients who were non-responders (predicted probability <0.60) at Week 48 Analyses of change from baseline in mRSS and ppFVC at Week 48.

Analyses of change from baseline in mRSS and ppFVC at Week 24, which were listed as exploratory endpoints in the protocol, were added to the multiplicity testing at the time of the final statistical analysis plan and the resulting p-values were not considered exploratory.

Change in the following efficacy parameters from baseline up to week 96 are presented.

- mRSS,
- Pulmonary Function (Absolute FVC in mL),
- Percentage of predicted forced vital capacity (ppFVC),
- Proportion of Patients Improving, Worsening or with No Change in Percent Predicted FVC,
- Proportion of Patients with $\geq$ 15% Decline in Percent Predicted DLCO,
- Health Assessment Questionnaire-Disability Index (HAQ DI)
- ≥20% Improvement in mRSS
- ≥40% Improvement in mRSS,
- ≥60% Improvement in mRSS

- Patient's and Physician's Global Assessment,
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scores,
- Scleroderma Health Assessment Questionnaire (SHAQ) Overall Scores,

Study WA27788

Primary endpoint:

- Change in mRSS from baseline a Week 24

Secondary endpoints:

- Change from baseline at Week 24 and Week 48 in the following: HAQ-DI score, the 5 scleroderma-specific VAS items, clinician's global assessment, patient's global assessment, FACIT-Fatigue score, and 5-D Itch Scale
- Change in mRSS from baseline at Week 48
- Proportion of patients with change from baseline in the mRSS at Week 48 greater than or equal to the change from baseline in the mRSS at Week 24

Exploratory endpoints:

- Change from baseline at Week 24 and Week 48 in the following: 28 TJC, digital ulcer count, TFR count, and pulmonary function (percent predicted FVC; FVC [L])
- Proportion of patients achieving an MCID (change from baseline ≥ 4.7) in the mRSS at Week 24 and Week 48
- Proportion of patients achieving an MCID (change from baseline ≥ 0.22 or change from baseline ≥ 0.14) in the HAQ-DI at Week 24 and Week 48
- Change from baseline in the percent diffusing capacity of the lung for carbon monoxide (DLCO) at Week 48
- Change from baseline at Week 96 in the following:
    - mRSS, HAQ-DI score, the 5 scleroderma-specific VAS items, Patient's Global Assessment, Clinician's Global Assessment, FACIT-Fatigue score, 5-D Itch Scale, TJC, digital ulcer count, TFR, pulmonary function (FVC; DLCO), and EQ-5D-3L™
- Correlation between the change from baseline in the mRSS at Week 96 versus the change from baseline in the HAQ-DI among TCZ-treated patients.

Sample size

Study WA29767

A sample size of approximately 105 patients in the TCZ group and 105 patients in the placebo group (a total of 210 patients) was expected to give power in the range of > 75% to 80%, (allowing for an estimated patient dropout rate of approximately 15% to 20%) to detect a between-group difference of 3.55 units (common standard deviation of 8.43) in mean change in mRSS from baseline to Week 48 using a two-group t-test, with a 5% two-sided significance level.

Study WA27788

A sample size of 36 patients per group was planned to be required to provide 80% power to detect a difference in means in the change in mRSS from baseline to Week 24 of 4.7 (common standard deviation of 6.99) using a two-group t-test with a 5% two-sided significance level. To allow for dropouts (estimated at 15%), 43 patients were planned to be randomized to each group.

CHMP comment

Sample size considerations are acceptable. For both studies, it is noted that a relevant drop-out was expected (15-20%).

In both studies there is no clear justification for the assumptions in the sample size considerations in the study protocol. It is assumed that the assumptions for study WA29767 were based on results from study WA27788, and this would be reasonable.

Randomisation

Study WA29767

Patients were planned to be randomized in a 1:1 ratio to receive SC injections of TCZ 162 mg QW or placebo QW for 48 weeks during the double-blind treatment period. Patients were planned to receive their first dose of open-label TCZ at Week 48. During the open-label treatment period, all patients were planned to receive SC injections of TCZ 162 mg QW for up to 48 weeks.

Randomization was centralized and stratified by IL-6 level (< 10; ≥ 10 pg/mL) at screening.

Study WA27788

Patients were planned to be randomly assigned in a 1:1 ratio to either 162 mg SC qw or placebo SC qw at baseline for the double-blind period utilizing an IVRS. Randomization was planned to be centralized and stratified by joint involvement at baseline (≥ 4 tender joints of 28 TJC).

CHMP comment

A 1:1 randomization is endorsed.

Of note, the stratification variables differ, and this may reflect that study Study WA29767 was designed to confirm findings from study Study WA27788. Stratification in both studies seems feasible and reasonable. However, it is not clear why randomization was not stratified by study site or geographic region. The applicant is asked to clarify and to discuss whether lack of such stratification might have had any impact on study results, in particular in the subgroup of patients with SSc-ILD (OC).

Importantly, randomization was not stratified for SSc-ILD, suggesting that there was no prospective hypothesis for this subgroup.

There are some inconsistencies in the way stratification is described in the study protocol for study WA29767 (i.e. stratification is not mentioned in the section "method of treatment assignment" and the stratum is not included in the listings of treatment allocation). The applicant is asked to please confirm that IL-6 level (< 10; ≥ 10 pg/mL) at screening was used as a stratification factor for randomization and describe the method of randomized allocation (e.g. permuted block randomization with block length x) (OC).

Blinding (masking)

Study WA29767

Prior to the Week 48 database lock, patients, investigators, other study site personnel, and Sponsor personnel (including monitors, project statisticians, and project team members) were planned to remain blinded to treatment assignment. To prevent potential unblinding because of observed efficacy and laboratory changes, a dual-assessor approach will be used to evaluate these data. Details regarding the dual-assessor approach are provided in a separate manual.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator was planned to be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wished to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor planned to break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients were considered generally not needed for the safe conduct or proper interpretation of this trial. Sponsor personnel responsible for performing PK assays was planned to be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm were not planned to be analyzed except by request (i.e., to evaluate a possible error in dosing).

Study WA27788

This is a double-blinded study.

The randomization list was planned not to be made available to the study center, Roche monitors, project statisticians, or the project team at Roche. Unblinding should not occur except in the case of emergency situations. Any request from the investigator for information about the treatment administered to study patients for another purpose was planned to be discussed with Roche. Unblinding was planned to be performed through the IVRS.

CHMP comment

Double blinding is endorsed, and the methods to ensure blinding are in principle appropriate.

It is noted that the applicant has defined a set of variables (laboratory) for which access of personnel was planned to be restricted. This is endorsed.

Statistical methods

Study WA29767

Population

The primary analysis population for efficacy was planned to be the ITT population, which includes all patients who are randomized and who receive any study drug. Patients in the ITT population were planned to be grouped according to the treatment assigned at randomization.

Significance level

Statistical hypotheses were planned to be tested at a nominal 5% significance level (allowing for adjustments for multiplicity as detailed in the SAP) against two-sided alternatives, and 95% CIs were planned to be reported as appropriate. Full details of adjustments for multiplicity and/or sequential order of analyses were planned to be predefined in the SAP prior to unblinding of the treatment groups.

Primary Efficacy Endpoint

The primary efficacy endpoint was planned to be the mean change in mRSS from baseline to Week 48.

The primary hypotheses to be tested are the following:

- H0 (null hypothesis): There is no difference between the TCZ group and the placebo group in mean change in mRSS from baseline to Week 48.
- H1 (alternative hypothesis): There is a difference between the TCZ group and the placebo group in mean change in mRSS from baseline to Week 48.

Similar hypotheses were planned to be tested for the secondary efficacy parameters.

The mean change from baseline was planned to be analyzed using a restricted maximum likelihood−based repeated-measures approach. The analysis was planned to include fixed, categorical effects for treatment, IL-6 stratification level (< 10; ≥ 10 pg/mL) at screening, visit, IL-6 level at screening−by-visit interaction, and treatment-by-visit interaction, as well as continuous covariates of baseline mRSS and baseline mRSS−by-visit interaction. An unstructured covariance structure was planned to be used to model within-patient errors.

The primary treatment comparison was planned to be the contrast between treatment arms at Week 48. Analyses were planned to be implemented in SAS® using PROC MIXED and the Kenward-Roger approximation (Kenward and Roger 1997).

The estimand of interest for the primary analysis was planned to be the difference between treatment arms in the mean change in the mRSS at Week 48 for the ITT population. The study has been designed to continue to capture efficacy data on patients who discontinue study drug prematurely or receive escape therapies during the double-blind treatment period. These data were planned to be included in the primary analysis. However, the applicant considered unrealistic to assume that complete data would be obtained from patients who discontinue study drug prematurely, and the primary analysis specified above assumes a missing-at-random missing-data mechanism whereby patients who are lost to follow-up from the TCZ arm were assumed to have similar efficacy to that of patients on TCZ who remained in the study.

Sensitivity analyses using missing-not-at-random models were planned to be implemented.

Specifically, a pattern-mixture model was planned to be implemented, using multiple imputations, whereby missing data in the placebo arm was planned to be imputed using a missing-at-random assumption and missing data in the TCZ arm was planned to be imputed in a stepwise fashion using multiple calls to PROC MI with a monotone regression statement using data from placebo-treated patients as the basis for the imputation (Ratitch and O'Kelly 2011). This imputation method assumes that patients who are lost to follow-up in the TCZ arm will have a trajectory similar to that of patients in the placebo arm.

Secondary efficacy endpoints

The secondary efficacy endpoints for this study were planned as follows:

- Difference in proportions of patients with ≥ 20%, ≥ 40%, and ≥ 60% improvement in mRSS at Week 48 compared with baseline

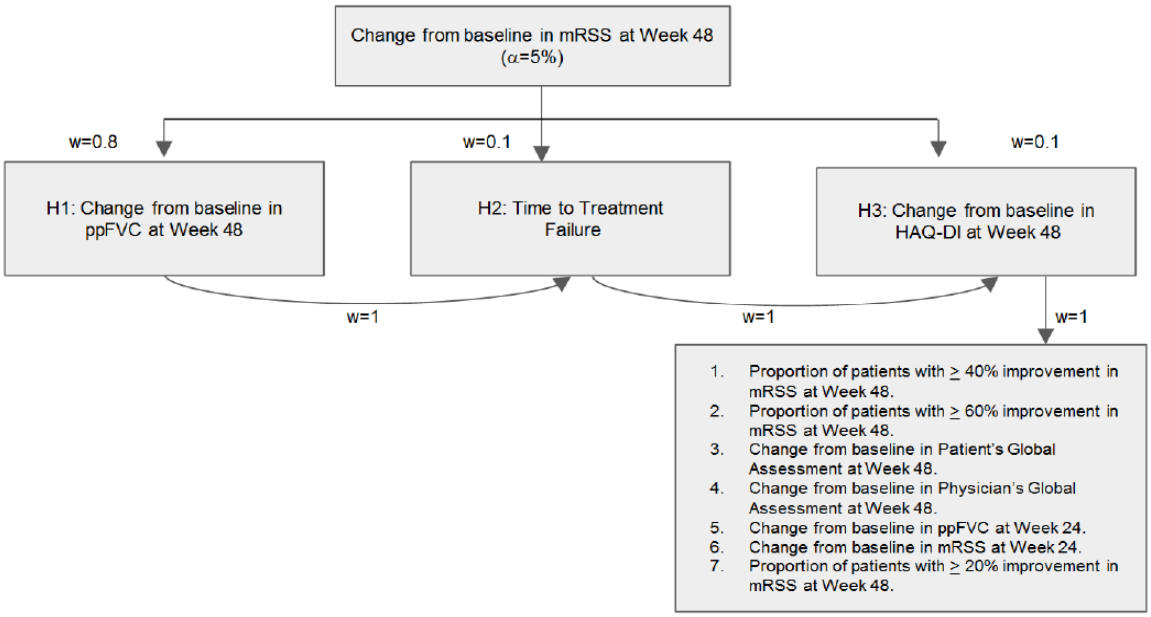
- Difference in mean change in FVC from baseline to Week 48
- Difference in mean change in HAQ-DI from baseline to Week 48
- Difference in mean change in Patient's Global Assessment from baseline to Week 48
- Difference in mean change in Physician's Global Assessment from baseline to Week 48
- Time to treatment failure, defined as the time from randomization to the time of one of the following events (whichever occurs first) during the 48-week double-blind treatment period:
    - death,
    - decline in percent-predicted FVC > 10% relative to baseline > 20% increase in mRSS and an increase in mRSS of ≥ 5 points occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee

For the secondary efficacy endpoints, the TCZ treatment group were planned to be compared with the placebo group using the following methods, which were planned to be specified further in the SAP:

- Continuous variables, such as difference in mean change in observed FVC from baseline to Week 48, was planned to be analyzed using the same methodology as specified for the primary analysis. For the FVC, additional analyses using non-parametric methods were planned to be used alongside cumulative density plots.

For binary response variables, such as the proportion of patients with ≥ 20% improvement in mRSS at Week 48 compared with baseline, the weighted difference in proportion for the specified treatment group comparison were planned to be presented, together with a 95% CI using the extended Mantel-Haenszel method and the p-value calculated using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor, IL-6 level (< 10; ≥ 10 pg/mL) at screening. Patients who receive escape therapy between baseline and Week 48 or have a missing Week 48 assessment were planned to be considered non-responders in the analysis.

In the SAP (Version 2), the following graphical approach was presented for multiplicity control across secondary endpoints:



Interim analyses

A futility analysis was planned to which the Sponsor remained blinded. The analysis was conducted after the first 76 patients reached the Week 24 visit or withdrew and was based on the change from baseline in mRSS at Week 24; the stopping boundary was determined by a β-spending function. No adjustment to the α-level for mRSS at Week 24 (Figure 2) was made to account for the futility analysis. The futility analysis was conducted by an external statistical group, iDCC, and was reviewed by the iDMC. Full details of the futility analysis, along with the rationale and timing are documented in the study iDMC charter and summarized in Section 4.13 of the SAP.

The interim analysis was conducted in December 2016, with a "continue" decision made by the iDMC on 16 December 2016. All documentation, including the closed meeting minutes and recommendations from the iDMC, were made available after study unblinding at Week 48.

CHMP comment

Overall comment

The current application has a focus on the potential effect of tocilizumab on secondary endpoints (change in ppFVC and observed FVC from baseline to week 48) in a subgroup of patients (SSc-ILD). The planned statistical methodology had a different focus, namely to show that tocilizumab is efficacious in reducing mRSS in patients with SSc. Although the methods are in principle acceptable for the originally planned objective, the results supporting the application are not generated with the same scientific/statistical rigor, and are considered exploratory. An ad-hoc interpretation may be possible, but has substantial uncertainties.

Estimand

Estimands for FVC or for SSc-ILD are not discussed.

Given that the analysis of FVC was planned to use the same methodology as the primary analysis, it may be assumed that the estimand for FVC is similar to the primary estimand defined for mRSS, and this could be acceptable.

Only the intercurrent event of premature discontinuation of study drug is discussed, whereby it was defined that data would be used irrespective of this intercurrent event. This approach is endorsed. Further intercurrent event are not discussed and are therefore assumed to be ignored as well.

An additional analysis with censoring following initiation of immuno-modulating therapy, and/or data collected after stopping study drug was provided, and this is acknowledged to address a different estimand (of less interest for the regulatory decision).

Significance level

A two-sided significance level of 5% was defined and is acceptable. Given that the primary endpoint was not met, results on secondary endpoints, in particular FVC, are descriptive only.

Multiplicity control for the secondary endpoint of FVC might provide some reassurance, however the support through prespecification of hypotheses for change in ppFVC and observed FVC to Week 48 is rather weak.

Procedures to account for multiplicity were not specified in the protocol, but only in the SAP. Of note, the first finalized version of the SAP (Version 1), in which the multiplicity approach for secondary endpoints was defined, is dated 08 Aug 2017. This is approximately 6 months after the last patient was randomized (14 Feb 2017) and is considered rather late. Although it is acknowledged that mean change of FVC from

baseline to week 48 was mentioned in early versions of the study protocol as one of several secondary endpoints, the importance of FVC hypotheses for statistical testing is not well supported by early, prospective documentation.

Replication of results

The applicant claims that "the chance that the observed [ppFVC] result represents a spurious finding due to multiplicity is reduced by repeating the positive ppFVC results in both trials. For example, if 21 endpoints are evaluated in two studies and the drug truly has no effect on any of them, an approximate upper bound for the probability of observing statistically significant results in both studies on at least one of the endpoints in both studies is 0.0130". Though numerically correct, assuming a one-sided significance level of 2.5%, this calculation ignores that the study had a primary endpoint. This post-hoc argument does not provide reassurance:

First, the primary endpoint failed and the probabilities of a one-sided false positive would therefore cumulate on top of the already spent α (i.e. cannot be smaller than 2.5%).

Second, due to the multiplicity of several endpoints being analysed there may be upward bias: Conditional on post-hoc selection of an outcome with promising results, the estimates are likely biased (i.e. ppFVC effect is likely overestimated).

Third, there is only very little support from other endpoints, and this seems more plausible under the null than under the alternative.

In summary, replication is acknowledged in principle, but the argumentation with numerical probabilities is not entirely correct and is considered somewhat misleading.

The arguments around the possibility of spurious findings are not agreed. Considering only the pivotal study, it seems that the applicant would have considered a benefit shown at least under the following outcomes: primary endpoint met or any secondary or exploratory finding from study WA27788 replicated with nominal statistical significance at the one-sided level of 0.025. This would result in a much higher probability than claimed by the applicant. Please rediscuss (OC).

There is concern about upward-bias in ppFVC estimates due to the multiplicity of analysing several secondary/exploratory endpoints: Conditional on selecting the outcome with the smallest p-value, even under the null hypothesis of no effect the distribution of the estimator may no longer be centered around zero, but may be biased depending on the number of endpoints analysed. The applicant is asked to discuss and provide bias-adjusted estimates for ppFVC (OC).

Population

The primary analysis was planned to be conducted in all randomized patients who received study treatment. Of note, the current application focusses on SSc-ILD. SSc-ILD is a subgroup and was not prospectively specified as such. Prospective documentation of the subgroup expectation (e.g. through stratification of randomization) might have provided reassurance, but SSc-ILD discussions appear to be entirely post-hoc.

Analysis model

The primary analysis model is a longitudinal mixed model with several covariates and interaction terms. The covariates (treatment, visit, stratification factor IL-6 at baseline and baseline value of mRSS) and respective covariate*visit interaction terms appear reasonable. Nonetheless, there may be a risk of overfitting, given the planned sample size of n=210, and no imputation of missing values.

It was planned that the analysis of FVC endpoints would use the same methodology as specified for the primary analysis. Eventually, the assumption of normally distributed FVC was not considered plausible and a non-parametric model was applied (Van Elteren test stratified by screening IL-6 level (<10; ≥10 pg/mL)). It is acknowledged that results from a MMRM (as planned) are provided as well.

It is assumed that the MMRM for ppFVC is adjusted for baseline ppFVC (instead of mRSS). Please confirm or provide results from a respective model adjusted for baseline ppFVC. Please provide further information on the model, including point estimates, confidence intervals and p-values for the coefficients of all fixed effects included in the model (OC).

Missing data

Missing data in continuous variables were not imputed. Instead the longitudinal model assumes MAR. This assumption may be challenged, as it can be assumed that data would be missing for a reason. The expected 15-20% drop-out is considered relevant. It is acknowledged that sensitivity analyses were provided (tipping point analyses).

The applicant is asked to provide individual longitudinal FVC data for those patients who had missing data in the FVC change from baseline to week 48 analysis (e.g. in a spaghetti plot) and reasons for missingness. Please discuss the plausibility of (i) the MAR assumption (ii) the tipping point for nominal significance derived from the tipping point analyses for these patients (ppFVC difference of 16 points between placebo and tcz patients, according to figure 7 of the CSR) (OC).

Futility analysis

A futility analysis was conducted after the first 76 patients reached the Week 24 visit or withdrew. According to the applicant, this futility analysis was prespecified, but apart from the intention to do a futility analysis, there are no details on the timing or methodology in the study protocol. A blinded futility analysis does not raise any concerns in principle, but the lack of prospective documentation in the study protocol is not optimal.

Study WA27788

The primary efficacy endpoint was planned to be the change in mRSS from baseline at Week 24. Mean changes from baseline were planned to be analysed using a restricted maximum likelihood–based repeated measures approach. The analysis was planned to include the fixed, categorical effects for treatment, joint involvement at baseline, visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score–by–visit interaction.

Joint involvement at baseline was not expected to affect the mRSS response, so no joint involvement-by-visit interaction has been included.

An unstructured covariance structure was planned to be used to model the within-patient errors. In the

event that the analysis fails to converge (after methodology has been applied to assist in the convergence if problems are encountered, details of which will be provided in the DAP), the following covariance structures were planned to be tested: compound symmetry, first-order autoregressive AR(1), Toeplitz, heterogeneous AR(1), and first-order ante-dependence. The covariance structure converging to the best fit was planned to be used as the primary analysis. The Akaike's information criterion was planned to be used to determine the best fit.

The Kenward–Roger approximation (Kenward and Roger 1997) was planned to be used to estimate the denominator degrees of freedom. Significance tests were planned to be based on least-squares means

using a two-sided α=0.05 (two-sided 95% CIs). The primary treatment comparison was planned to be the contrast between treatments at the Week 24 timepoint.

The primary analysis specified above assumes a missing at random missing-data mechanism. As the missing-data mechanism of missing not at random (MNAR) is difficult to rule out, sensitivity analyses using MNAR models were planned to be implemented. In addition, sensitivity analyses using 1) the last mRSS observation available for each patient up to and including Week 24, and 2) only mRSS observations at Week 24 for patients who complete up to that timepoint will be performed. All details about the sensitivity analyses were planned to be specified in the DAP.

CHMP comment

Overall comment

The current application has a focus on the potential effect of tocilizumab on FVC (change in ppFVC and observed FVC from baseline to week 48) in a subgroup of patients (SSc-ILD). FVC endpoints were exploratory and patients with SSc-ILD were not considered as a subgroup in the study protocol.

Methods

The methods are overall agreeable for an exploratory study. Some details were left open in the protocol, such as the covariance structure matrix for the mixed model in case of convergence issues, and that is acceptable for an exploratory study.

Results

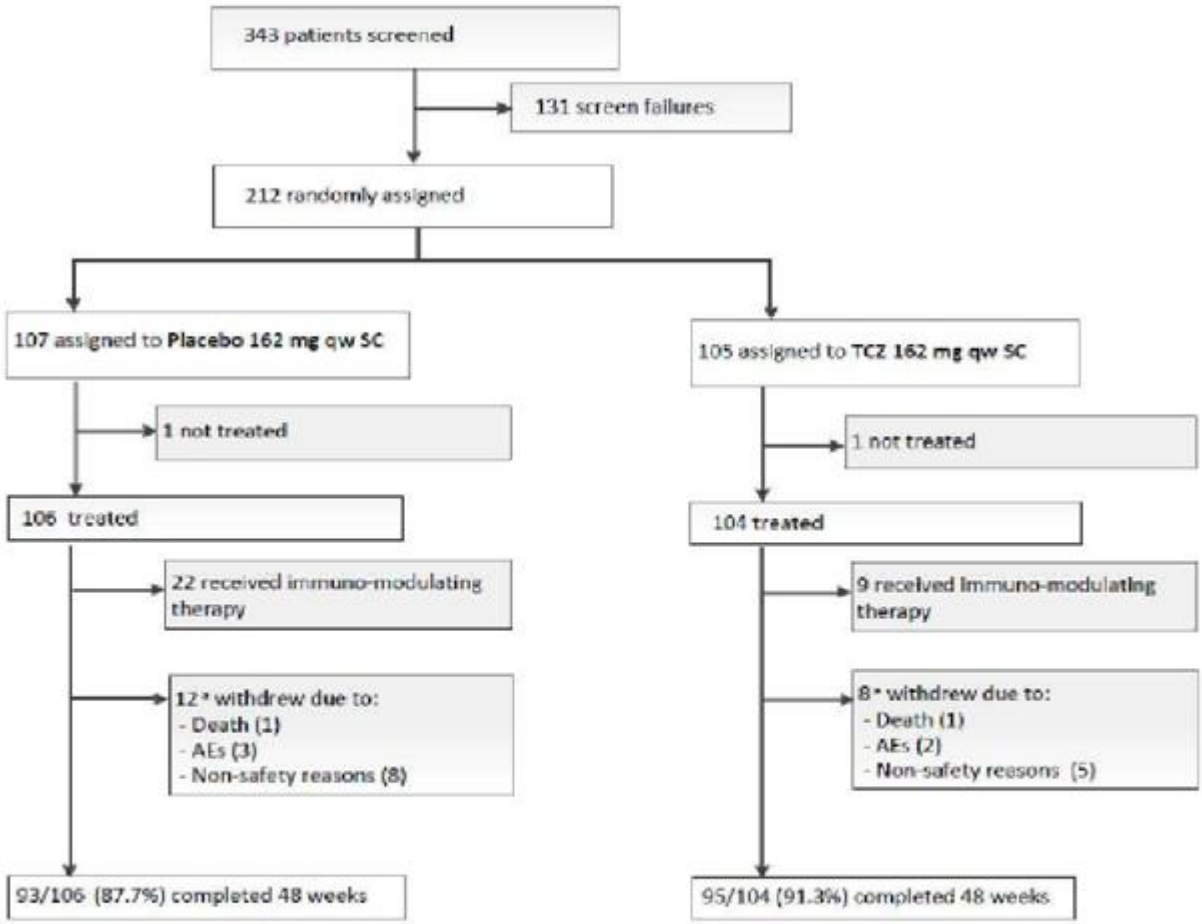
Participant flow

Study WA29767

Of the 343 patients screened, 212 patients were randomized into the study. The main reasons for screen failure (obtained from the IxRS) were: failure to meet exclusion criteria (67 patients), failure to meet inclusion criteria (33 patients), and patient refusal to participate in the study (16 patients).

Of the 212 patients randomized into the study, 107 patients were randomized to the placebo arm and 105 patients were randomized to the TCZ arm (Figure 20). All but two randomized patients received at least one dose of study drug.

Figure 20 Patient Disposition up to Week 48 (All Patients Population)



AE = adverse event; SC = subcutaneous; TCZ = tocilizumab; qw = once weekly.
[a] The number of discontinued patients excludes 2 treated patients (1 in each arm) who did not have a completed disposition record at the CCOD.
Source: Table 7, WA29767-Patient Screen Failure 21NOV2017, l_pop_trtp_AP, t_cm_IT_CONIMM.

In the OL period of the study 89 patients [83.2%] entered from the PBO arm and 92 patients [87.6%] from the TCZ arm. The majority of patients completed the study up to Week 96: 82 patients (76.6%) from the PBO arm and 85 patients (81.0%) from the TCZ arm.

CHMP comment

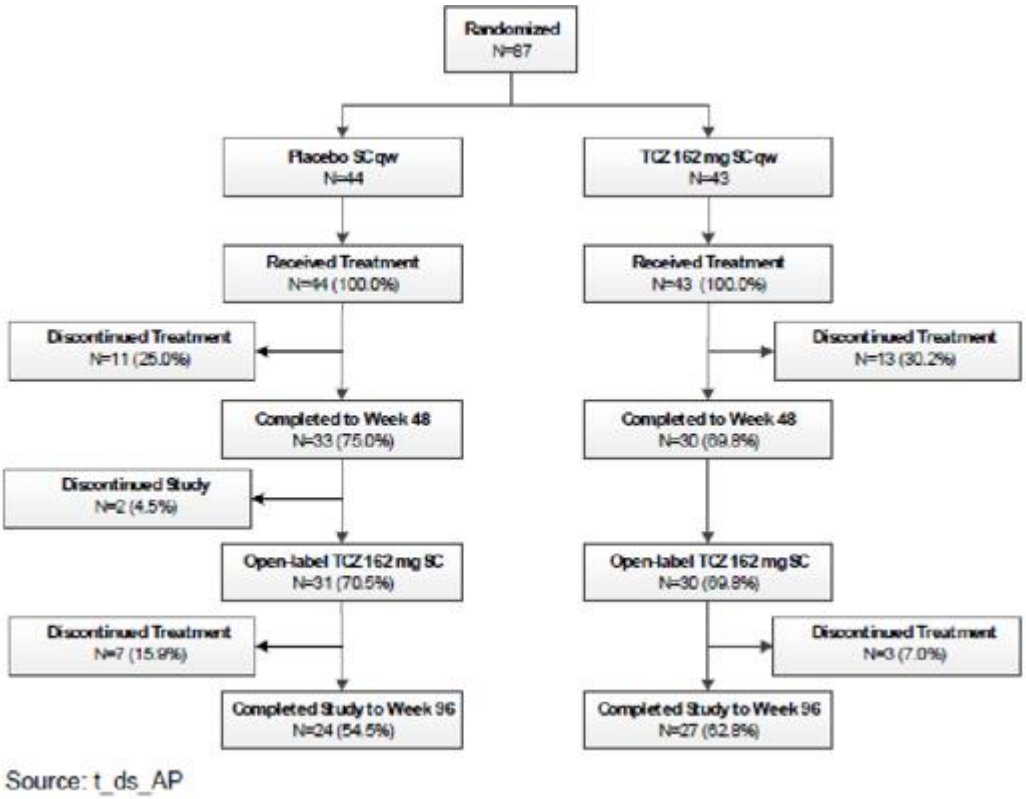
The majority of patients randomised completed Week 48 of the study, namely 87, 7 % in the placebo group and 91,3 % in the TCZ group. In the OL period of the study 89 patients [83.2%] entered from the PBO arm and 92 patients [87.6%] from the TCZ arm. The majority of patients completed the study up to Week 96: 82 patients (76.6%) from the PBO arm and 85 patients (81.0%) from the TCZ arm. The safety data of the OL contributes to this submission, while the efficacy data are not.

Study WA27788

Of the 141 patients screened, 87 patients were randomized into the study. The main reasons for screen failure (obtained from the IVRS) were: active disease not meeting at least one A criterion and one B criterion each (25 patients), mRSS outside the range of 15 – 40 units inclusive at the screening visit (7

patients), and inability or unwillingness to provide written informed consent (5 patients). All randomized patients received at least one dose of study drug. Overall, 24 (54.5%) PBO→TCZ patients and 27 (62.8%) TCZ→TCZ-treated patients completed Week 96 of the study.

Figure 21 Patient Disposition at Week 96 (All Patients Population)



The number and proportion of patients who withdrew prematurely from treatment by Week 48 were similar between treatment arms (Table 26). As reported in the primary CSR (Research Report 1060804), 3 patients withdrew before Day 50. Over the 48-week treatment-blinded period, 7 (15.9%) patients in the placebo group and 5 (11.6%) patients in the TCZ group discontinued for non-safety-related reasons; of these, 3 placebo patients and 4 TCZ-treated patients discontinued in the period up to Week 24. In addition, 4 (9.1%) patients in the placebo arm and 5 (11.6%) patients in the TCZ arm discontinued because of AEs; of these, 2 placebo patients and 2 TCZ-treated patients discontinued in the period up to Week 24.

Three patient deaths (attributed to arrhythmia, lung infection, and multi-organ failure) in the TCZ arm were recorded as the reason for treatment withdrawal. A fourth patient death (cardiac failure) in the placebo arm occurred 133 days after the patient had withdrawn from the study due to an AE of cardiac failure and therefore, the death is not shown as a reason for treatment withdrawal in Table 24.

Table 24 Analysis Population (All Patients Population)

Analysis Population by Actually Received Trial Treatment (All Patients Population)
Protocol: WA27788 (i27788a)

	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=43)
Safety Evaluable Population	44	42
Total Exclusions	0	0
Patient did not receive any study drug	0	0
Patient does not have a post-dose safety assessment	0	0
Pharmacokinetic Evaluable Population	1	43
Total Exclusions	43	0
Patient has not received a dose of TCZ	42	0
Patient does not have a valid PK observation	33	0

The safety population includes all patients who received any study drug and provided at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, vital sign). Patients are included in the treatment arm for the treatment most frequently received at the time of analysis.

Program: /opt/BIOSTAT/prod/cn11935a/i27788a/t_dm_pop_act.sas
Output: /opt/BIOSTAT/prod/cn11935a/i27788a/reports/t_dm_pop_act_AP.out
07FEB2014 15:41 Page 1 of 1

An overview of premature withdrawal during the entire 96-week study is presented in Table 25.

Table 25 Reasons for Premature Withdrawal from Treatment (up to Week 96) (All Patients Population)

Status	Placebo n (%) (N=44)	TCZ 162 mg qw SC n (%) (N=43)
Completed to Week 96	24 (54.5%)	27 (62.8%)
Discontinued by Week 96	20 (45.5%)	16 (37.2%)
Safety	9 (20.5%)	9 (20.9%)
Adverse Event	9 (20.5%)	6 (14.0%)[b]
Pregnancy	0	0
Death	0[a]	3 (7.0%)
Non-Safety	11 (25.0%)	7 (16.3%)
Lost to follow-up	0	1 (2.3%)
Non-compliance	2 (4.5%)	0
Lack of efficacy	1 (2.3%)	2 (4.7%)
Withdrawal by subject	7 (15.9%)	4 (9.3%)
Physician decision	1 (2.3%)	0
Other	0	0
Reason not collected	0	0

Note: Discontinuation and Completion with their reasons is taken from the 'Study Completion/Early Discontinuation' CRF page.

[a] One patient death (2201, cardiac failure) in the placebo arm occurred 133 days after the patient had withdrawn from the study due to an AE of cardiac failure and therefore, the death is not shown as a reason for treatment withdrawal.

[b] Patient 4601 was recorded on the eCRF as having withdrawn from the study due to an AE but no specific event was identified by the investigator.

Source: t_ds_AP.

Table 26 provides the reason for premature withdrawal from treatment in the open-lable period

Table 26 Reasons for Premature Withdrawal from Treatment (Open-Label Period) (All Patients Population)

Status	Placebo n (%) (N=44)	TCZ 162 mg qw SC n (%) (N=43)
Entered Open-Label Treatment	31 (70.5%)	30 (69.8%)
Discontinued Open-Label Treatment	7 (15.9%)	3 (7.0%)
Safety	4 (9.1%)	1 (2.3%)
Adverse Event	4 (9.1%)	1 (2.3%)[b]
Pregnancy	0	0
Death	0[a]	0
Non-Safety	3 (6.8%)	2 (4.7%)
Lost to follow-up	0	0
Non-compliance	1 (2.3%)	0
Lack of efficacy	1 (2.3%)	1 (2.3%)
Withdrawal by subject	1 (2.3%)	1 (2.3%)
Physician decision	0	0
Other	0	0
Reason not collected	0	0

Note: Discontinuation and Completion with their reasons is taken from the 'Study Completion/Early Discontinuation' CRF page.

[a] One patient death (2201, cardiac failure) in the placebo arm occurred 133 days after the patient had withdrawn from the study due to an AE of cardiac failure and therefore, the death is not shown as a reason for treatment withdrawal.

[b] Patient 4601 was recorded on the eCRF as having withdrawn from the study due to an AE but no specific event was identified by the investigator.

Source: t_ds_AP.

CHMP comment

The majority of patients complete Week 48, while the numbers of patients who discontinued was slightly higher during the OL period with a higher number in the patients previously treated with placebo.

Recruitment

Study WA29767

The study was performed at 75 sites in 20 countries. The top recruiting geographical region was Central Europe (63 patients [Bulgaria, Hungary, Poland, Romania, and Lithuania]), followed by Western Europe (57 patients [Belgium, Denmark, Germany, Greece, Italy, Netherlands, Portugal, Spain, United Kingdom, and Switzerland]), North America (43 patients [USA and Canada]), Latin America (29 patients [Argentina and Mexico]), and Japan (20 patients). Allocation between treatment arms was generally well-balanced across regions, except for North America, where a higher proportion of patients were allocated to the placebo arm compared with TCZ (27 patients and 15 patients, respectively

Study WA27788

A total of 87 patients were enrolled at 35 centres in the following 5 countries: United States (36 patients at 14 sites), Germany (19 patients at 9 sites), United Kingdom (19 patients at 6 sites), France (8 patients at 4 sites), and Canada (5 patients at 2 sites).

Conduct of the study

Study WA29767

The original study protocol (Version 1) was finalized on 28 February 2015 and was amended five times. The first and second protocol amendments (Version 2 and Version 3) were implemented before the first patient was randomized on 20 November 2015.

Protocol deviation

No per-protocol analysis was pre-planned and consequently, patients were not excluded from any data analyses due to protocol violations.

Overall, as of the Week 48 database lock, a total of 77 major protocol violations were recorded in the double-blind period: 39 major protocol violations were recorded for 32 patients in the PBO arm and 38 violations for 28 patients in the TCZ arm. The most common protocol deviations were baseline high-resolution computed tomography (HRCT) scans performed prior to randomization or other informed consent deviations, with slight imbalances noted between treatment arms.

During the OL period, a total of 10 major protocol deviations were reported and were classified under three categories; Inclusion criteria (one deviation [informed consent form not signed]), Medication (5 deviations), and Procedural (4 deviations).

Study WA27788

The study protocol was finalized on 23 August 2011 and amended three times. The first amendment was implemented before the first patient was randomized on 13 March 2012.

In addition to the protocol amendments, a change in study conduct was the unblinding of some of the Sponsor's team to individual patient data after the Week 24 data analysis. As per the pre-planned data analysis plan, the study team was to have access only to summary data from the Week 24 data analysis, and not to individual treatment assignments. Following the analysis and initial review of the data from Week 24, the Sponsor agreed that further in-house review and analysis of the data was required. Consequently, some members of the Sponsor's team were completely unblinded and granted access to the data

Protocol deviations

As of the data cut-off date of 11 July 2014, 52 major protocol deviations were recorded in 16 placebo patients and 17 TCZ-treated patients. More patients in the placebo arm had multiple deviations. Only 1 patient (2400 in the placebo arm) was withdrawn from the study by the Sponsor due to lack of compliance with protocol-specified risk mitigation steps for elevated liver enzymes.

CHMP comment

There were 6 protocol amendments for each study.

The protocol for the pivotal study WA29767 was amended five times. The first and second protocol amendments (Version 2 and Version 3) were implemented before the first patient was randomized. None of the changes in the protocol are considered to have an impact on the data supporting the claimed indication.

For Study WA29767 it is reported that the most common protocol deviations were baseline high-resolution computed tomography (HRCT) scans performed prior to randomization or other informed

consent deviations, with slight imbalances noted between treatment arms. This does not impact the integrity of the study.

Baseline data

Study WA29767

Patient Demographics

The study enrolled patients that were predominantly women (84.9% in the placebo arm and 77.9% in the TCZ arm) and White (84.9% and 81.7%, respectively), with a mean age of 48.2 years (range, 18-73 years).

Both treatment arms had similar mean weight and height and had comparable reproductive status. A higher proportion of patients in the placebo arm (37.7%) were previous or current smokers compared with the TCZ arm (30.8%); the median duration of smoking history was also higher in the placebo arm (20.0 years [range, 1.0-44.0 years] in the placebo arm and 15.0 years [range, 2.0-55.0 years] in the TCZ arm).

The number of patients recruited by country were generally well-balanced between the treatment arms, except for those recruited in United States (25 patients [23.6%] in the placebo arm vs. 14 patients [13.5%] in the TCZ arm) and Poland (6 patients [5.7%] in the placebo arm vs. 13 patients [12.5%] in the TCZ arm).

Baseline disease characteristics

In both treatment arms had a median disease duration less than 2 years: 17.9 months in the placebo arm and 17.2 months in the TCZ arm. On average, both treatment arms had moderate skin involvement (Medsger et al. 2003), with a mean (SD) mRSS of 20.4 (6.95) in the placebo arm and 20.3 (6.74) in the TCZarm. Both placebo and TCZ arms had a baseline ppFVC indicative of normal lung function to mild impairment (means: 83.9% and 80.3%, respectively; medians: 85.9% and 80.0%, respectively), and baseline ppDLCO indicative of mild impairment (means: 76.8% and 74.4%, respectively; medians: 75.6% and 71.5%, respectively) (Medsger et al. 2003).

The placebo and TCZ arms had similar mean HAQ-DI scores ≥1.0 indicative of moderate to severe functional impairment (Clements et al. 1999). Mean baseline scores were comparable between placebo and TCZ arms on the Patient's Global Assessment and the Physician's Global Assessment of disease activity.

At screening, the majority of patients tested positive for anti-nuclear antibodies at baseline in both treatment arms (91.8% in the placebo arm and 92.9% in the TCZ arm).

Approximately half the patient population was positive for anti-topoisomerase antibodies in both arms (49.0% in the placebo arm and 52.0% in the TCZ arm) at baseline, with less patients being positive for anti-RNA polymerase antibodies (16.0% in the placebo arm and 19.0% in the TCZ arm). A smaller proportion of patients in both treatment arms tested positive for anti-centromere antibodies (9.0% in the placebo arm and 8.0% in the TCZ arm) (Table 27).

Table 27 Baseline Disease Characteristics (ITT/Safety Population)

Baseline Disease Characteristics, ITT Population
Protocol: WA29767
Up to Week 48

	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)	All Patients (N=210)
Duration of SSc (Days)			
n	106	104	210
Mean (SD)	703.80 (517.11)	674.42 (485.99)	689.25 (500.96)
Median	545.50	523.50	524.50
Min - Max	44.0 - 1822.0	28.0 - 1802.0	28.0 - 1822.0
Duration of SSc (Months)			
n	106	104	210
Mean (SD)	23.12 (16.99)	22.16 (15.97)	22.64 (16.46)
Median	17.92	17.20	17.23
Min - Max	1.4 - 59.9	0.8 - 59.2	0.8 - 59.9
Total Modified Rodnan Skin Score			
n	106	104	210
Mean (SD)	20.44 (6.95)	20.25 (6.74)	20.35 (6.83)
Median	19.00	19.00	19.00
Min - Max	10.0 - 40.0	10.0 - 36.0	10.0 - 40.0
Overall Health Assessment Questionnaire Score			
n	104	104	208
Mean (SD)	1.29 (0.70)	1.08 (0.77)	1.19 (0.74)
Median	1.25	1.13	1.19
Min - Max	0.0 - 2.8	0.0 - 2.8	0.0 - 2.8
Patients Global Visual Analogue Scale			
n	104	103	207
Mean (SD)	59.29 (21.26)	54.31 (24.31)	56.81 (22.91)
Median	58.00	52.00	56.00
Min - Max	8.0 - 100.0	0.0 - 100.0	0.0 - 100.0
Physicians Global Visual Analogue Scale			
n	99	98	197
Mean (SD)	59.91 (16.16)	59.40 (19.75)	59.65 (17.99)
Median	61.00	61.50	61.00
Min - Max	20.0 - 96.0	3.0 - 95.0	3.0 - 96.0
Interleukin-6 level at Screening (pg/mL)			
n	106	104	210
< 10	77 (72.6%)	77 (74.0%)	154 (73.3%)
>= 10	29 (27.4%)	27 (26.0%)	56 (26.7%)
C-reactive protein (mg/L)			
n	106	104	210
Mean (SD)	7.00 (11.12)	8.86 (14.76)	7.92 (13.05)
Median	3.82	4.04	3.86
Min - Max	0.2 - 89.8	0.2 - 85.5	0.2 - 85.5
Erythrocyte Sedimentation Rate (mm/hr)			
n	103	100	203
Mean (SD)	34.72 (18.49)	34.83 (16.29)	34.77 (17.40)
Median	33.00	33.50	33.00
Min - Max	0.0 - 98.0	2.0 - 86.0	0.0 - 98.0
Platelet Count (10^9/L)			
n	106	104	210
Mean (SD)	298.74 (95.95)	311.09 (88.23)	304.85 (92.20)
Median	286.50	306.00	293.00
Min - Max	98.0 - 655.0	165.0 - 647.0	98.0 - 655.0

The IL-6 categories are the stratification from the IxRS.
A patient is considered Anti-topoisomerase positive if they have U/mL >= 20.
A patient is considered Anti-RNA polymerase positive if they have U/mL >= 20.
A patient is considered Anti-centromere positive if they have a dilution >= 1:40.
A patient is considered Anti-nuclear antibodies positive if they have a dilution >= 1:40.

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Previous and concurrent disease and treatments

Previous and concurrent history of tuberculosis and interstitial Lung Disease

A total of 18 patients (12 patients in the placebo arm, and 6 patients in the TCZ arm) were recorded to have previous or concurrent TB at screening.

A total of 66 patients (28 in the placebo arm and 38 in the TCZ arm) were recorded as having previous or concurrent ILD at screening. At study start, ILD was ongoing with treatment in 8 patients in the placebo arm and 10 patients in the TCZ arm (based on manual review of data).

Previous and concurrent diseases other than systemic sclerosis

Fourteen patients in the placebo arm (13.2%) reported General Disorders and Administration Site Conditions compared with 3 patients in the TCZ arm (2.9%), with the greatest difference observed for fatigue (11 patients [10.4%] in the placebo arm and no patients in the TCZ arm). Nervous System Disorders were reported in 24 patients (22.6%) in the placebo arm compared with 6 patients (5.8%) in TCZ arm, with the greatest difference between arms observed for headache (9 patients [8.5%] in the placebo arm and 1 patient [1.0%] in the TCZ arm).

Prior and concurrent use of concomitant medications

The majority of patients in both treatment arms had received previous medications that were stopped prior to the first dose of study drug. Patients most frequently ($\geq$15% of patients in either arm) received antimetabolites (25 patients [23.6%] in the placebo arm and 27 patients [26.0%] in the TCZ; mainly, MTX) and steroids (18 patients [17.0%] in the placebo arm and 15 patients [14.4%] in the TCZ arm; mainly, prednisone).

The majority of patients in both treatment arms were receiving proton-pump inhibitors (62 patients [58.5%] in the placebo arm and 63 patients [60.6%] in the TCZ arm) as prior ongoing medication at baseline or medication initiated on or after the first dose of study drug. Other commonly reported classes of medications were steroids (55 patients [51.9%] in the placebo arm and 55 patients [52.9%] in the TCZ arm) and vitamins and minerals (48 patients [45.3%] in the placebo arm and 51 patients [49.0%] in the TCZ arm). Oral corticosteroids were permitted at a stable dose of $\leq$10 mg/day of prednisone or equivalent; IV or IM corticosteroids were not permitted. Of note, more patients in the placebo arm received NSAIDs (mainly ibuprofen), anti-convulsants (mainly, gabapentin), anti-infectives (anti-fungals [mainly, fluconazole and nystatin] and miscellaneous antimicrobials), and immunosuppressants (mainly, MMF) compared with the TCZ arm. The majority of anticonvulsants and antifungals were commenced after initiation of study drug for the treatment of AEs.

The most frequently used concomitant medication for AEs were analgesics (21 patients [19.8%] in the placebo arm and 21 patients [20.2%] in the TCZ arm). More patients ($\geq$5% difference) in the placebo arm were treated for AEs with supplements (12 patients [11.3%] vs. 5 patients [4.8%], antifungal agents (11 patients [10.4%] vs. 4 patients [3.8%]), muscle relaxants (6 patients [5.7%] vs. no patients), and cephalosporin antibiotics (12 patients [11.3%] vs. 6 patients [5.8%]).

Immuno-modulating treatments

By Week 48, twice as many placebo-treated patients (22 patients [20.8%]) were receiving at least one immuno-modulating treatment compared with TCZ-treated patients (9 patients [8.7%]). The majority of patients who received immuno-modulating therapy in both arms initiated treatment from Week 36 onwards. Mycophenolate mofetil was the most frequent immuno-modulating treatment received in both treatment arms (13 patients [12.3%] in the placebo arm and 5 patients [4.8%] in the TCZ arm), followed by MTX (4 patients [3.8%] in the placebo arm and 3 patients [2.9%] in the TCZ arm). Other immuno-modulating treatments were received by $\leq$2 patients in either treatment arm.

CHMP comment

Patients demographics as well as baseline disease characteristics are well balanced between the groups. Some imbalance was seen in the number of patients recruited by country.

Regarding lung involvement, both placebo and TCZ arms had a baseline ppFVC indicative of normal lung function to mild impairment (means: 83.9% and 80.3%, respectively; medians: 85.9% and 80.0%, respectively), and baseline ppDLCO indicative of mild impairment (means: 76.8% and 74.4%, respectively; medians: 75.6% and 71.5%, respectively). However, a total of 66 patients (28 in the placebo arm and 38 in the TCZ arm) were reported as having previous or concurrent ILD at screening. At study start, ILD was ongoing with treatment in 8 patients in the placebo arm and 10 patients in the TCZ arm (based on manual review of data). A post-hoc subgroup analysis in patients with SSc-ILD was performed to support the indication claim. A total of 136 patients (68 in the placebo group and 68 in the TCZ group) had SSc-ILD at baseline. Thus, the numbers reported in the different sections are contradictory, please clarify. (OC)

Study WA27788

Patient Demographics

The majority of patients were female (TCZ 74.4% or PBO 79.5% in either treatment arm) and Caucasian (88.4% or 90.9%), with a mean age of 49.6 years (range, 19−70 years). Both treatment groups had similar weight and height and were of similar reproductive status. A higher percentage of patients in the TCZ group compared with the placebo group were previous or current smokers (51.2% vs. 38.6%), and the median duration of smoking history was 20.0 years (range, 1.0−50.0 years) and 24.0 years (range, 1.0−40.0 years), respectively.

Baseline disease characteristics

Patients in the placebo arm and TCZ arm had early onset of disease (median disease duration of 335.5 and 357.0 days, respectively) and moderate to severe skin involvement (Medsger et al. 2003) (median mRSS of 25.0 [range, 15.0 − 40.0] and 28.0[range, 15.0 − 42.0], respectively).

The placebo arm and TCZ arm had similar mean HAQ scores ≥ 1.0 indicative of moderate to severe functional impairment (Clements et al. 1999), similar mean FACITFatigue scores (26.5 and 25.6, respectively) indicative of a strong level of fatigue, similar mean scores on the 5-D Itch Scale (13.5 and 13.1, respectively) indicative of a moderate level of pruritus/itching, and comparable mean scores on the Patient's Global Assessment (61.9 and 59.8, respectively) and the Clinician's Global Assessment (60.9 and 64.1, respectively).

At baseline, the placebo arm and TCZ arm had comparable and mildly increased levels of CRP (mean, 1.026 and 1.004 mg/dL, respectively), percent predicted FVC indicative of normal function to mild impairment (Medsger et al. 2003) (0.82% and 0.80%, respectively), and percent predicted DLCO indicative of mild impairment (Medsger et al. 2003) (0.74% and 0.73%, respectively).

Previous and concurrent disease and treatments

Previous and concurrent diseases

The two treatment arms were generally well balanced with respect to previous and concurrent diseases recorded at baseline, with the exception of respiratory, thoracic, and mediastinal disorders. These conditions were observed in 21 (47.7%) placebo patients and 11 (25.6%) TCZ-treated patients, with the greatest difference between arms observed for asthma and pulmonary fibrosis. Asthma was reported in 6 (13.6%) placebo patients and 2 (4.7%) TCZ-treated patients. Only 1 patient with asthma, randomized to the placebo arm, had a concurrent history of pulmonary fibrosis. However, a history of interstitial lung

disease (ILD), pulmonary fibrosis, or SSc lung involvement was reported in similar numbers of patients in each arm (8 [18.2%] placebo patients and 5 [11.6%] TCZ-treated patients).

Prior and concomitant medications

All patients in both treatment arms had been treated or were being treated with at least one previous or concomitant medication. The majority of patients in each treatment arm (placebo: 90.9% and TCZ: 86.0%) had been treated or were receiving proton-pump inhibitors. Other commonly reported classes of medications were calcium channel blocking agents (placebo: 47.7% and TCZ: 46.5%) and analgesics (placebo: 45.5% and TCZ: 53.5%).

More patients in the TCZ arm compared with the placebo arm had been treated or were taking steroids (placebo: 18 [40.9%] patients and TCZ: 25 [58.1%] patients) and ACE inhibitors (placebo: 7 [15.9%] patients and TCZ: 13 [30.2%] patients). Conversely, fewer patients in the TCZ arm (18 [41.9%] patients) compared with the placebo arm (27 [61.4%] patients) had received or were being treated with non-steroidal anti-inflammatory drugs (NSAIDs). Oral corticosteroids were permitted at a stable dose of ≤ 10 mg/day of prednisone or equivalent; intravenous (IV) or intramuscular (IM) corticosteroids were not permitted. No other notable differences with respect to the frequency and types of medications were observed between the two treatment groups.

Escape therapy

Escape therapy with single-agent MTX, hydroxycholoroquine, or MMF was allowed after Week 24 for worsening SSc complications, including skin and arthritis symptoms. At Week 48, 12 of 44 placebo patients and 6 of 43 TCZ-treated patients had received escape medication. Data only up to the first receipt of escape medication were included in the Week 48 analyses of efficacy, with the exception of the analysis of pulmonary function, which was based on all data regardless of the receipt of escape medication.

Numbers analysed

Study WA29767

Four analysis populations were defined for this study: The All patients population, the ITT population, the Safety population, and the PK population

Table 28 Analysis Populations (All Patients Population)

Analysis Populations
Protocol: WA29767
Up to Week 48

	PBO 162 mg qw SC	TCZ 162 mg qw SC
All Patients Population	107	105
Randomized Population	107	105
Intent-to-Treat Population	106	104
Total Exclusions	1	1
Patient was not randomized	0	0
Patient did not receive any study drug	1	1
Safety Evaluable Population	106	104
Total Exclusions	1	1
Patient did not receive any study drug	1	1
Patient does not have a post-dose safety assessment	1	1
Pharmacokinetic-Evaluable Population	0	103
Total Exclusions	107	2
Patient does not have a valid PK observation	107	2
Patient has not received a dose of TCZ	104 *	1

Number of patients for each population is based on the corresponding Planned or Actual treatment group.
The ITT population will include all subjects randomised in the study who received any study drug. The treatment group for this population will be defined according to the treatment assigned at randomisation.
The safety population includes all patients who received any study drug and provided at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, vital sign). Patients will be grouped according to the treatment actually received.
The counts for patients who did not receive any study drug are based on the planned treatment group.
The Pharmacokinetic-Evaluable population includes all patients who received at least one Tocilizumab Injection and had at least one PK sample with detectable results.
* Three placebo patients were incorrectly documented as having received a dose of TCZ; however on bioanalysis of PK samples, they were verified to have received placebo.
Program: /opt/BIOSTAT/prod/cn11935i/i29767a/t_pop.sas
Output: /opt/BIOSTAT/prod/cn11935i/i29767a/reports/t_pop_AP.out
15MAR2018 15:05
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The primary analysis population for efficacy was the ITT population, which included all patients who were randomized and who received at least one dose of study drug, with patients grouped according to the treatment assigned at randomization. Of the 212 randomized patients, 210 patients (106 patients in the placebo arm, and 104 patients in the TCZ arm) were included in the ITT population. Note that for the ITT population, the randomized treatment group was the same as treatment actually received for all patients. Two randomized patients who did not receive a dose of study drug (see Section 4.1) were excluded.

In addition, post-hoc analyses for selected efficacy endpoints were performed for the subset of patients who had ILD at baseline on visual read of HRCT in. A total of 136 patients had SSc-ILD in Study WA29767, including 68 in the TCZ arm and 68 in the placebo arm.

Study WA27788

The intent-to-treat (ITT) and safety populations were identical. All 87 randomized patients received at least one dose of study drug (TCZ or placebo) and were included in the ITT population.

Table 29 Analysis Populations (All Patients Population)

Analysis Population by Actually Received Trial Treatment (All Patients Population)
Protocol: WA27768 (i27768a)

	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=42)
Safety Evaluable Population	44	42
Total Exclusions	0	0
Patient did not receive any study drug	0	0
Patient does not have a post-dose safety assessment	0	0
Pharmacokinetic Evaluable Population	1	42
Total Exclusions	43	0
Patient has not received a dose of TCZ	42	0
Patient does not have a valid PK observation	33	0

The safety population includes all patients who received any study drug and provided at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, vital sign). Patients are included in the treatment arm for the treatment most frequently received at the time of analysis.

Program: /opt/BIOSTAT/prod/cn11935a/i27768a/t_dm_pop_act.sas
Output: /opt/BIOSTAT/prod/cn11935a/i27768a/reports/t_dm_pop_act_AP.out
07FEB2014 15:41 Page 1 of 1

Treatment assignment was unblinded for 3 patients who were randomized to the TCZ Arm. Those patients were not excluded from data analyses

CHMP comment

For both studies no per protocol population was defined, thus the efficacy analysis is based on the ITT population. That is acceptable in this context.

Outcomes and estimation

Study WA29767

Table 30 includes an overview of the results of the efficacy endpoints by statistical testing order.

Table 30 Overview of Key Efficacy Endpoints at Week 24 and Week 48 (ITT Population)

Testing Order	Efficacy Variable [a]	Placebo (N=106)	TCZ (N=104)	Nominal p-value
1	**mRSS at Week 48**			
	Change from BL to Week 48	-4.41	-6.14	
	ΔLSM (95% CI)	-1.73 (-3.78, 0.32)		p=0.0983 [b]
2	**ppFVC at Week 48** [c]			
	Median change from BL to Week 48 (95% CI)	-3.91 (-4.82, -1.62)	-0.60 (-2.38, 0.88)	
	Q1–Q3	-7.16–0.57	-5.25–3.93	p=0.0015
3	**TTF at Week 48** [d]			
	Patients with event	37 (34.9%)	23 (22.1%)	
	Median TTF (days)	NE		
	HR (95% CI)	0.63 (0.37, 1.06)		p=0.0821

Table 30 Overview of Key Efficacy Endpoints at Week 24 and Week 48 (ITT Population)

Testing Order	Efficacy Variable [a]	Placebo (N=106)	TCZ (N=104)	Nominal p-value
4	**HAQ-DI at Week 48**			
	Change from BL to Week 48	-0.06	-0.11	
	ΔLSM (95% CI)	-0.05 (-0.19, 0.09)		p=0.4489
5	**≥40% Improvement in mRSS at Week 48**			
	Responders, n (%)	40 (37.7%)	44 (42.3%)	
	Difference in response (95% CI) [e]	4.32 (-8.7, 17.3)		p=0.5139
6	**≥60% Improvement in mRSS at Week 48**			
	Responders, n (%)	24 (22.6%)	18 (17.3%)	
	Difference in response (95% CI) [e]	-5.41 (-16.2, 5.4)		p=0.3276
7	**Patient's Global Assessment at Week 48**			
	Change from BL to Week 48	-7.66	-10.10	
	ΔLSM (95% CI)	-2.44 (-8.57, 3.70)		p=0.4339
8	**Physician's Global Assessment at Week 48**			
	Change from BL to Week 48	-19.99	-22.45	
	ΔLSM (95% CI)	-2.46 (-8.72, 3.79)		p=0.4378
9	**ppFVC at Week 24** [c]			
	Median change from BL to Week 24 (95% CI)	-2.57 (-3.18, -0.79)	-0.31 (-1.23, 0.76)	p=0.0366
	Q1–Q3	-5.03–1.97	-3.31–3.21	
10	**mRSS at Week 24**			
	Change from BL to Week 24	-3.06	-3.69	
	ΔLSM (95% CI)	-0.63 (-2.29, 1.03)		p=0.4549
11	**≥20% Improvement in mRSS at Week 48**			
	Responders, n (%)	53 (50.0%)	75 (72.1%)	
	Difference in response (95% CI) [e]	21.91 (9.2, 34.6)		p=0.0007

BL=baseline; HAQ-DI=Health Assessment Questionnaire-Disability Index; HR=hazard ratio; LSM=least squares mean; mRSS=modified Rodnan skin score; NE=not estimable; ppFVC=percent predicted forced vital capacity; TCZ=tocilizumab; TTF=time to treatment failure.

[a] negative change from BL indicates improvement for all endpoints, except FVC, time to treatment failure, and binary endpoints.

[b] Statistical significance (p<0.05) of the primary endpoint (mRSS) was not met therefore subsequent secondary endpoints were not formally tested for statistical significance. All observed p-values other than the primary endpoint are considered nominal.

[c] Median change from BL in ppFVC is presented using the Van Elteren test (primary analysis method).

[d] Defined as the time from first dose of study drug to the time of first: death, decline in ppFVC >10% relative to BL, relative increase in mRSS >20% and an increase in mRSS of ≥5 points, or occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee (whichever occurred first, during the Week 48 double-blind treatment period).

[e] The weighted difference in proportion is presented, together with the 95% CI using the extended Mantel-Haenszel method and the p-value calculated using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor, IL-6 level (<10; ≥10 pg/mL) at screening. Patients who had a missing Week 48 assessment were considered non-responders in the analysis.

Source: Table 13, t_ef_cb_van_elteren_IT_PFVC_WK48_RAW, t_ef_cb_median_IT_PFVC_RAW, t_ef_cb_repm_IT_PFVC_WK48_RAW, t_trtfail_IT_TETRFAIL_RAW, t_ef_cb_repm_IT_HAQ_WK48_RAW, t_ef_mcid_IT_MRS40W48_RAW, t_ef_mcid_IT_MRS60W48_RAW, t_ef_cb_repm_IT_PVAS_WK48_RAW, t_ef_cb_repm_IT_CVAS_WK48_RAW, Table 25, t_ef_cb_repm_IT_MRSS_WK24_RAW, t_ef_mcid_IT_MRS20W48_RAW.

Primary efficacy endpoints

Mean change in mRSS at Week 48

The primary endpoint of the difference between treatment arms in the change in mRSS from baseline at Week 48 was not statistically significant or clinically meaningful (placebo: -4.41, TCZ: -6.14, adjusted difference in LSM = -1.73 [95% CI: -3.78, 0.32], p = 0.0983).

Secondary endpoints

mRSS: Patients with ≥20%, ≥40%, and ≥60% Improvement at Week 48

A difference in the proportion of patients with an mRSS improvement of >20% was seen in favour of TCZ over placebo (difference in responses: 21.9% [95% CI: 9.2, 34.6], nominal p-value=0.0007). This difference between treatment arms was not seen at the higher thresholds of >40% and >60% improvement.

CHMP comment

Measurement of skin thickness is used as a surrogate for disease activity, severity and mortality. An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Thus, the endpoint is considered clinically meaningful.

In both treatment groups patients had moderate skin involvement that was comparable at baseline. The Week 48 results showed a numerical improvement in the TCZ arm, but the results were not statistically significant or considered clinically meaningful. The primary endpoint was not met.

A difference in the proportion of patients with an mRSS improvement of >40% and >60% in favour of TCZ over placebo was not observed, a difference in the proportion of patients with an mRSS improvement of >20% in favour of TCZ over placebo was seen.

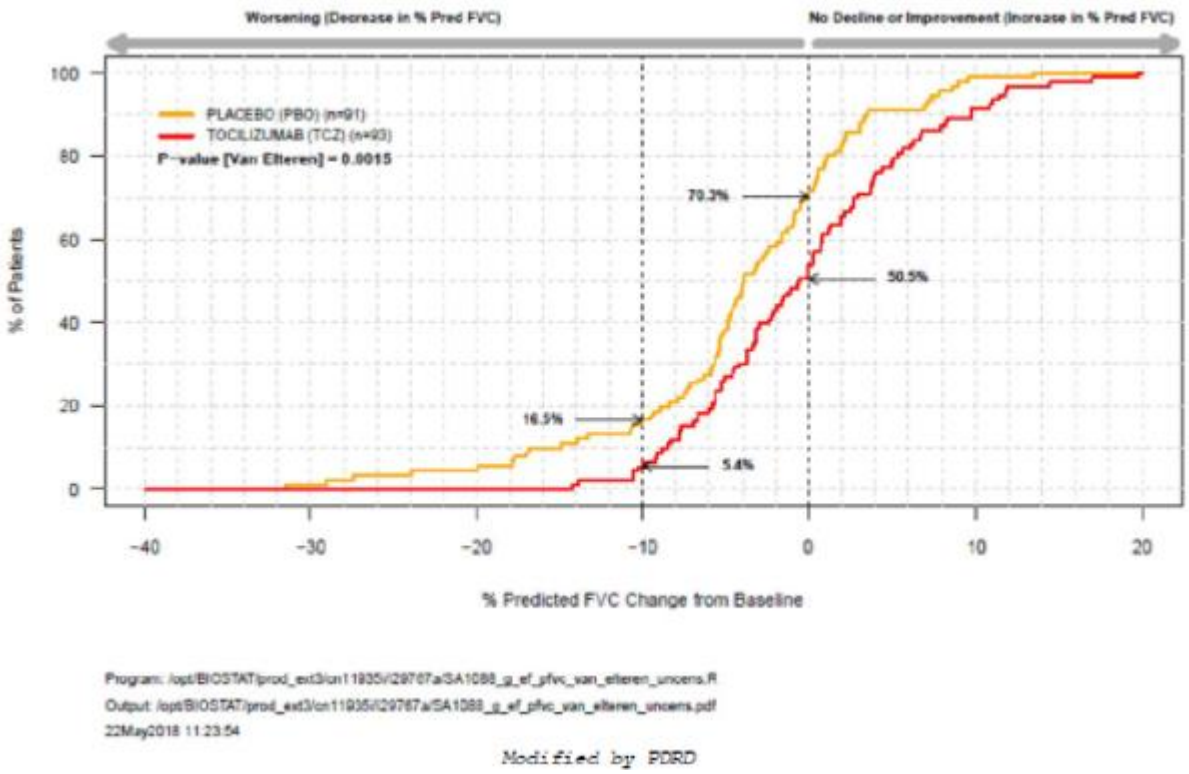
A favourable effect on the overall disease activity could not be demonstrated.

Forced vital capacity at week 48

This was a key secondary endpoint for the study. At baseline, the median ppFVC was 85.9% in the placebo arm and 80.0% in the TCZ arm, indicative of normal to mildly impaired lung function.

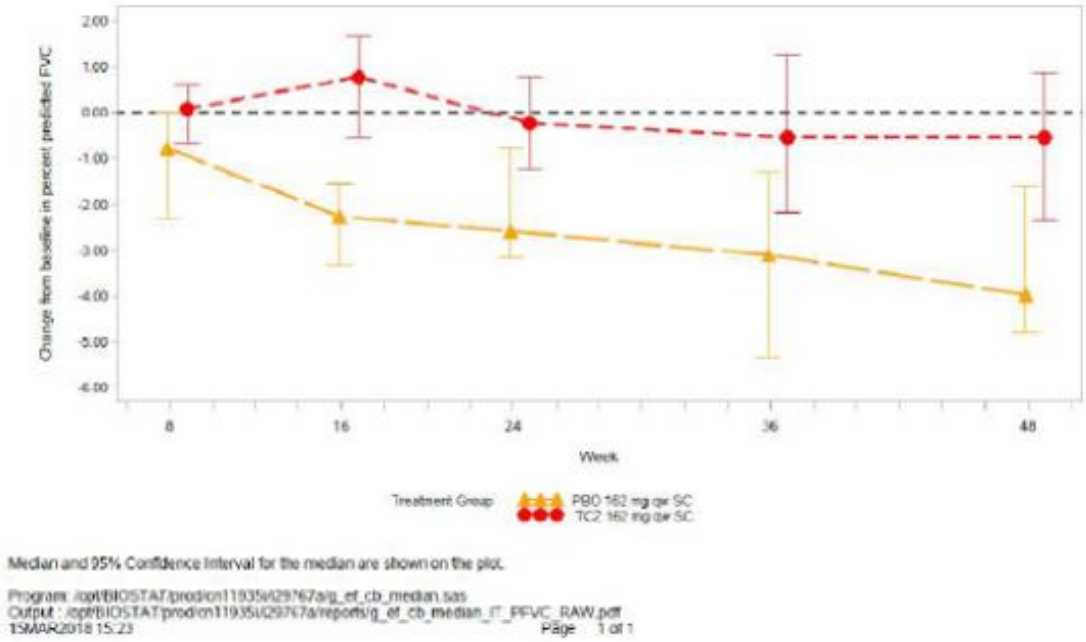
Using a non-parametric Van Elteren test stratified by screening IL-6 level (<10; ≥10 pg/mL), the cumulative distribution plot at Week 48 shows a clinically meaningful shift in the distribution of change from baseline in ppFVC at Week 48 in favour of TCZ over placebo (nominal p = 0.0015, Figure 22).

Figure 22 Cumulative Distribution Plot of Change from Baseline for Percent predicted FVC at Week 48 Using Van Elteren Analysis (ITT Population)



At Week 48, the median change from baseline in ppFVC was -3.91 [95% CI: -4.82, -1.62] in the placebo arm and -0.60 [95% CI: -2.38, 0.88] in the TCZ arm (Figure 23).

Figure 23 Plot of Median Change from Baseline in Percent Predicted FVC by Visit and Treatment up to Week 48 (ITT Population)



The Van Elteren analysis (table and cumulative distribution plot) of the median change from baseline in observed FVC (absolute FVC in mL) at Week 48 also showed clinically meaningful results (-130 mL in the placebo arm and -20 mL in the TCZ arm; nominal p = 0.0031).

CHMP comment

Forced vital capacity at week 48 was a key secondary endpoint for the study. At baseline, the ppFVC values in both arms were indicative of normal to mildly impaired lung function. At Week 48 a median change from baseline in favour of TCT was observed suggesting that TCZ has an impact in conservation of the lung function.

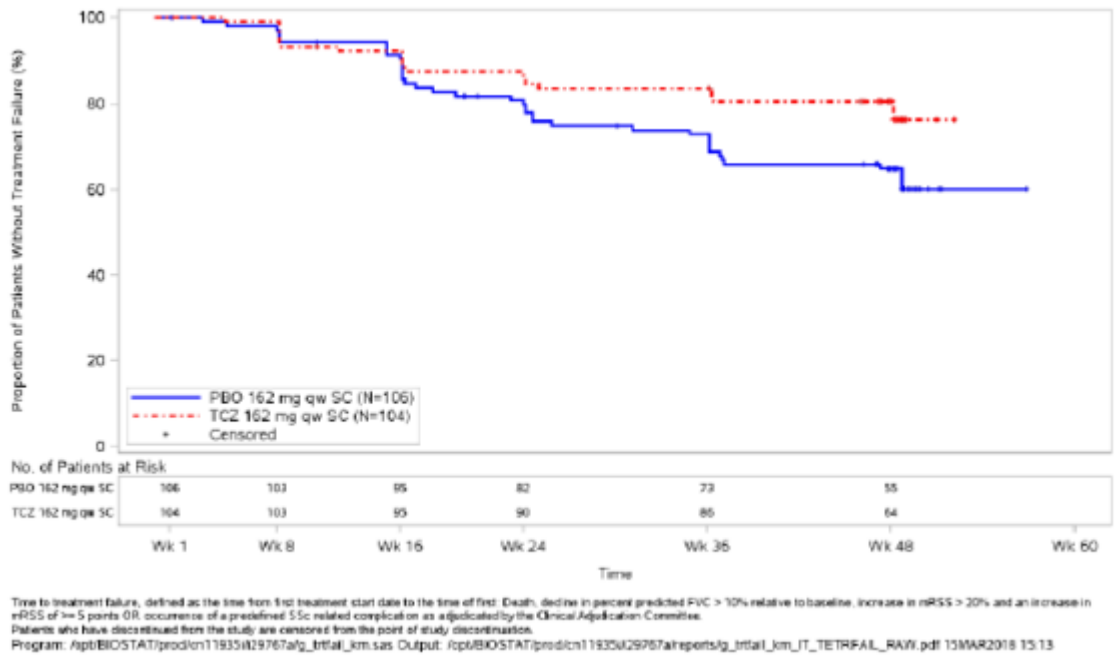
Time to treatment failure at Week 48

This was a key secondary endpoint for the study. TTF was defined as the time from randomization to the time of one of the following events (whichever occurs first) during the 48-week double-blind treatment period:

- death,
- decline in percent-predicted FVC > 10% relative to baseline,
- 20% increase in mRSS and an increase in mRSS of ≥ 5 points occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee

A difference between treatment groups in favour of TCZ can be seen in the TFF Kaplan-Meier curves after Week 16 and the benefit is maintained through Week 48 (Figure 24).

Figure 24 Kaplan–Meier Plot of Time to Treatment Failure in Weeks up to Week 48 (ITT Population)



Time to treatment failure, defined as the time from first treatment start date to the time of first: Death, decline in percent predicted FVC > 10% relative to baseline, increase in mRSS > 20% and an increase in mRSS of >= 5 points OR occurrence of a predefined SSc related complication as adjudicated by the Clinical Adjudication Committee.
Patients who have discontinued from the study are censored from the point of study discontinuation.
Program: /opt/BIOSTAT/prod/cn119335i829767a/g_ttftail_km.sas Output: /opt/BIOSTAT/prod/cn119335i829767a/reports/g_ttftail_km_IT_TETRFAIL_RAW.pdf 15MAR2018 15:13

Overall at Week 48, fewer patients in the TCZ arm experienced treatment failure compared with the placebo arm (37 patients [34.9%] in the placebo arm and 23 patients [22.1%] in the TCZ arm) (stratified HR 0.63 [95% CI: 0.37, 1.06]; nominal p = 0.0821, Cox proportional test) (Table 31). The median TTF was not estimable and is not presented for either treatment arm because of the low number of patients with events at Week 48.

Table 31 Proportion of Patients with Components of Time to Treatment Failure at Week 48 (ITT Population)

	Number of Patients with Event, n (%)				
	Placebo (N=106)	TCZ (N=104)	HR	95% CI	p-value [a]
Treatment Failure	37 (34.9%)	23 (22.1%)	0.63	0.4, 1.1	0.0821
ppFVC >10% decline	25 (23.6%)	13 (12.5%)	0.55	0.3, 1.1	0.0802
mRSS increase >20% and ≥5%	16 (15.1%)	10 (9.6%)	0.64	0.3, 1.4	0.2609
SSc-related complication	7 (6.6%)	5 (4.8%)	0.79	0.3, 2.5	0.6826
Death	3 (2.8%)	1 (1.0%)	0.37	0.0, 3.6	0.3922
Sensitivity Analyses:					
TF excluding Serious Infections	37 (34.9%)	22 (21.2%)	0.59	0.4, 1.0	0.0521
TF, including study discontinuation [b]	41 (38.7%)	25 (24.0%)	0.61	0.4, 1.0	0.0516
Post-Hoc Analyses:					
TF, excluding decline in ppFVC	20 (18.9%)	13 (12.5%)	0.67	0.3, 1.4	0.2608
TF, excluding increase in mRSS	29 (27.4%)	17 (16.3%)	0.62	0.3, 1.1	0.1220

HR=hazard ratio; mRSS=modified Rodnan skin score; ppFVC=percent predicted forced vital capacity; SSc=systemic sclerosis; TCZ=tocilizumab; TF=treatment failure.

Notes: Percentages are based on N. Patients can be counted only once within each category but can be counted in multiple categories.

[a] Nominal p-values from secondary analysis presented for information only.

[b] Includes discontinuation for following reasons as treatment failure: death, lack of efficacy, lost to follow-up, withdrawal by patient, and physician decision.

Source: t_trtfail_IT_TETRFAIL_RAW, t_trtfail_IT_TEFVC_RAW, t_trtfail_IT_TEMRSS_RAW, t_trtfail_IT_TEADJAE_RAW, t_trtfail_IT_TEDEATH_RAW, t_trtfail_IT_TETRFAILX_RAW, t_trtfail_IT_TETRFAILDS_RAW, SA1088_t_trtfail_IT_TETRFAIL_RAW, SA1243_t_trtfail_IT_TETRFAIL_RAW.

Health assessment questionnaire-disability index

At Week 48, a numerical improvement (decline) was seen in the mean change in HAQ-DI from baseline; however, there was no notable difference between treatment arms (Table 30)

Patient's and physician's global assessments

At Week 48, numerical improvements (decline) were seen in the mean change in Patient's and Physician's Global Assessments from baseline; however, there was no notable treatment difference between arms (Table 30).

CHMP comment

Regarding further secondary endpoints, a numerical difference in TTF was seen in favour for TCZ compared to placebo. This numerical difference was seen for all TTF defining event i.e. death, decline in percent-predicted FVC > 10% relative to baseline or 20% increase in mRSS and an increase in mRSS of ≥ 5 points occurrence of a predefined SSc-related complication. The results are not statistically significant and not considered clinical meaningful.

Health assessment questionnaire-disability index and patient's and physician's global assessments did not show a notable difference between treatment arms.

Exploratory efficacy endpoints

A summary of results of key exploratory efficacy analyses at Week 48 is provided in Table 32.

Table 32 Overview of Exploration Efficacy Endpoints at Week 48 in Study WA29767, ITT Population

Efficacy Variable [a,b]	Placebo (N = 106)	TCZ (N = 104)
ppDLco		
Median change from BL (95% CI)	-2.1 (-4.4, -0.4)	-2.4 (-4.1, 1.0)
Mean change from BL	-2.6	-1.3
Proportion of patients with ≥15% decline in observed DL_{CO}, n/N (%)	12/87 (13.8%)	8/84 (9.5%)
SHAQ-VAS Scores		
Overall disease — Mean change from BL (95% CI)	-0.30 (-0.48, -0.12)	-0.30 (-0.45, -0.15)
Breathing — Mean change from BL (95% CI)	0.11 (-0.06, 0.27)	0.05 (-0.07, 0.16)
FACIT-Fatigue Scale Score		
Mean change from BL	2.64	5.05
ΔLSM (95% CI), nominal p-value	2.40 (0.08, 4.73), p = 0.0430	
CRISS Score		
Median change from BL (95% CI)	0.25	0.89
Nominal p-value	p = 0.0230	
Patients with predicted probability of improvement ≥0.60 (CMH) from BL, n/N (%)	39/106 (36.8%)	53/104 (51.0%)
Difference in responses (95% CI), p-value	13.9 (1.0, 26.8), p = 0.0350	
SGRQ Scores		
Overall — Mean change from BL (95% CI)	-2.15 (-6.01, 1.72)	-3.18 (-5.93, -0.44)
Symptoms — Mean change from BL (95% CI)	-1.85 (-5.52, 1.82)	-1.95 (-5.54, 1.65)
Activity — Mean change from BL (95% CI)	-0.62 (-6.44, 5.19)	-4.39 (-8.66, -0.11)
Impact — Mean change from BL (95% CI)	-3.22 (-6.90, 0.45)	-2.65 (-5.65, 0.34)

ΔLSM = difference in least squares mean; BL = baseline; CRISS = Combined Response Index for Systemic Sclerosis; DL_{CO} = diffusion capacity of the lung for carbon monoxide; FACIT = Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; $ppDL_{CO}$ = percent predicted DL_{CO}; SGRQ = Saint George's Respiratory Questionnaire; SHAQ-VAS = Scleroderma Health Assessment Questionnaire visual analogue scale; TCZ = tocilizumab.

[a] Negative change from BL indicates improvement for SHAQ-VAS and SGRQ scores; positive change from BL indicates improvement for FACIT-Fatigue.

[b] All p-values are nominal because the result of the primary endpoint analysis was not significant.

FACIT-fatigue

At Week 48, both treatment arms showed an improvement in FACIT-Fatigue scores, with a numerically greater improvement in the TCZ arm compared with placebo (Table 32).

Combined response index for systemic sclerosis

The results of the composite CRISS index at Week 48 showed a shift toward higher CRISS scores in favour of TCZ over placebo. More patients in the TCZ arm achieved an improvement in CRISS scores of $\geq$0.6 (the minimally clinically important difference [MCID]) compared with the placebo arm (Table 32).

For all other endpoints there was improvement or no worsening in patients' symptoms or disease status in both treatment arms.

HRCT scan results at Week 48

The following HRCT lung scan results were analysed at Week 48: quantitative lung fibrosis-lobe of most involvement (QLF-LM) was a pre-planned exploratory analysis and quantitative lung fibrosis-whole lung (QLF-WL) and quantitative interstitial lung disease-whole lung (QILD-WL) were post hoc analyses.

When fibrosis was visually assessed qualitatively by blinded thoracic radiologists, a greater proportion of patients in the placebo arm had worsening of fibrosis, and a greater proportion of patients in the TCZ arm had an improvement in fibrosis (Table 33).

Table 33 Visual Assessment of Fibrosis per Lobe (Categorical: Worse, Same, Better) at Week 48, Study WA29767, ITT Population

Summary of Categorical Assessment of Change in HRCT by Parameter and Treatment, ITT Population
Protocol: WA29767
Up to Week 48

Parameter: Visual Change Assessment Fibrosis

Location Used for Measurement	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)
LUNG, LEFT LOWER LOBE		
n	89	91
Worse	10 (11.2%)	4 (4.4%)
Same	77 (86.5%)	77 (84.6%)
Better	2 (2.2%)	10 (11.0%)
LUNG, LEFT UPPER LOBE		
n	89	91
Worse	10 (11.2%)	3 (3.3%)
Same	77 (86.5%)	79 (86.8%)
Better	2 (2.2%)	9 (9.9%)
LUNG, RIGHT LOWER LOBE		
n	89	91
Worse	11 (12.4%)	4 (4.4%)
Same	76 (85.4%)	77 (84.6%)
Better	2 (2.2%)	10 (11.0%)
LUNG, RIGHT MIDDLE LOBE		
n	89	91
Worse	11 (12.4%)	3 (3.3%)
Same	76 (85.4%)	80 (87.9%)
Better	2 (2.2%)	8 (8.8%)
LUNG, RIGHT UPPER LOBE		
n	89	91
Worse	11 (12.4%)	3 (3.3%)
Same	76 (85.4%)	80 (87.9%)
Better	2 (2.2%)	8 (8.8%)

Program: /opt/BIOSTAT/prod/cn119351/129767a/SA1106_t_ef_cb_hrct.sas
Output: /opt/BIOSTAT/prod/cn119351/129767a/reports/SA1106_t_ef_cb_hrct_IT.out
20APR2018 16:45 *Modified by FORD* Page 1 of 1

HRCT = high-resolution computed tomography; ITT = intent-to-treat; PBO = placebo; QW = weekly; SC = subcutaneous; TCZ = tocilizumab.

Source: WA29767 Primary CSR 1081912, Table 30.

Subgroup analysis

Change in mRSS at Week 48 by demographic and baseline characteristics

The change from baseline in the mRSS was conducted using a MMRM model with the addition of a treatment-by-IL-6 at screening interaction to compare the treatment effect at Week 48 for the subgroups based on IL-6 levels at screening (<10 pg/mL and ≥10 pg/mL).

Similarly, separate analyses of the change from baseline in mRSS were conducted using MMRM models to compare the treatment effect at Week 48 for the subgroups of baseline CRP, ESR, platelet count, baseline disease duration, baseline mRSS score, sex, and age.

Certain subgroups of patients experienced a greater mean improvement in mRSS on TCZ compared with placebo (e.g., IL-6 <10 pg/mL, CRP >6.0 mg/L, ESR <28 mm/h, platelet count <330 x 10^9/L, disease duration ≥2 years, and age ≥65 years).

However, because the 95% CIs were wide and generally overlapping with the mean treatment difference in the overall population, no firm conclusions on these subgroups.

CHMP comment

Comparing the treatment effect defined as change from baseline in the mRSS at Week 48 for the subgroups based on IL-6 levels at screening and for subgroups of baseline CRP, ESR, platelet count, baseline disease duration, baseline mRSS score, sex, and age suggest that certain subgroups of patients experienced a greater mean improvement in mRSS on TCZ compared with placebo. However, because a treatment effect was not shown in the overall population (primary endpoint not met), an interpretation of subgroup findings is difficult. 95% CIs were wide and generally overlapping with the mean treatment difference in the overall population, no firm conclusions on these subgroups.

Post-hoc analysis SSc-ILD

Change in FVC at Week 48 (Post-hoc analyses)

Post-hoc subgroup analyses on FVC by demographic and baseline characteristics were conducted to identify clinical or laboratory markers predictive of progression of SSc-ILD.

Although some subgroups of patients on placebo experienced a greater decline in FVC (e.g., disease duration <2 years, anti-topoisomerase Ab positive, platelet count ≥330 x 10^9/L, and CRP >6.0 mg/L), all subgroups showed a numeric benefit from TCZ treatment.

Post hoc efficacy analyses

Post hoc subgroup analyses for patients with SSc-ILD at baseline were performed for ppFVC, observed FVC, and mRSS. A total of 136 patients (68 in the placebo group and 68 in the TCZ group) had SSc-ILD at baseline. The post-hoc analysis was conducted to identify if certain subgroups of patients experienced a greater benefit from TCZ.

While some subgroups of patients on placebo experienced a greater decline in FVC, all subgroups showed a numeric benefit from TCZ treatment

Baseline disease characteristics in patients with SSc-ILD

Overall, baseline disease characteristics were similar in SSc-ILD patients compared with the overall ITT population (SSc patients) (Table 34). SSc-ILD patients had baseline scores indicative of poorer lung function compared with SSc patients (i.e., lower median ppFVC and ppDLCO values and higher median QLF-WL, QLF-LM, and QILD-WL scores). Furthermore, a higher proportion of patients with SSc-ILD were anti-topoisomerase antibody-positive, and a lower proportion of patients with SSc-ILD were anti-centromere antibody-positive compared with patients with SSc.

Percent Predicted Forced Vital Capacity in Patients with SSc-ILD

Table 34 Median Change from Baseline in ppFVC at Week 48, Study WA29767, Patients with SSc-ILD

Analysis of the Change from Baseline in Percent Predicted FVC at Week 48 (includes only Patients with ILD positive at baseline based on HRCT), ITT Population
Protocol: WA29767
Up to Week 48

	PBO 162 mg qw SC (N=60)	TCZ 162 mg qw SC (N=65)
n	56	59
Q1	-9.80	-5.27
Median	-4.01	-0.60
Median CI	(-5.84, -1.65)	(-2.20, 1.95)
Q3	-0.09	5.05
P-value		0.0016
Difference in medians		3.40
CI for difference in medians		(0.40, 5.97)

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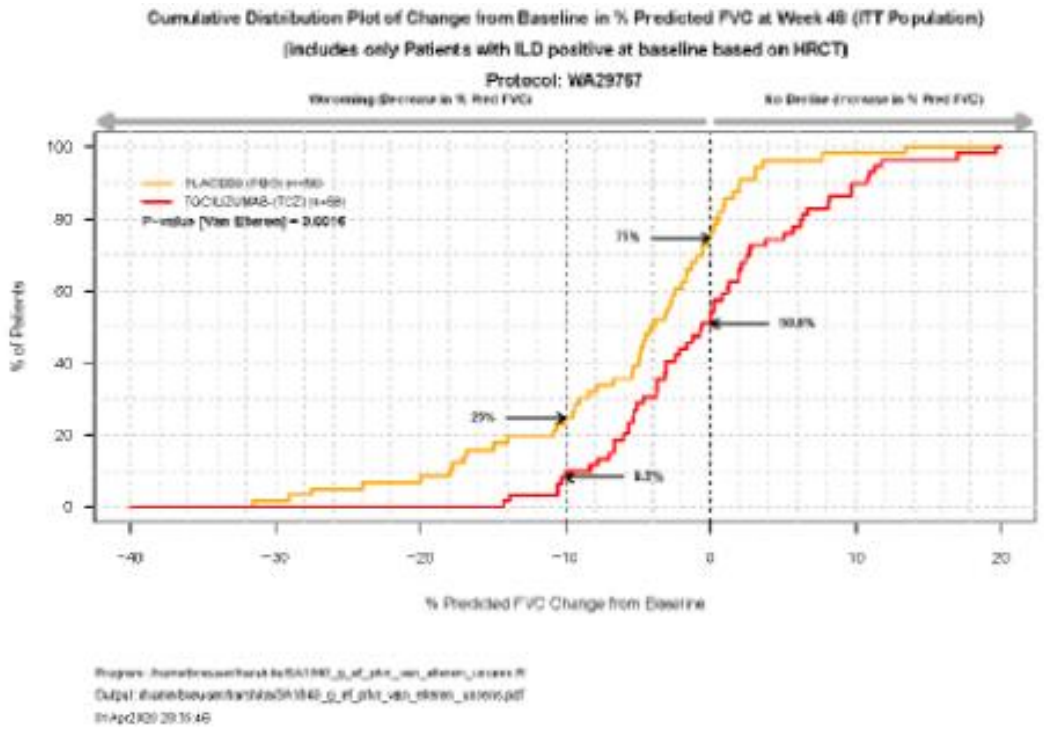
01APR2020 15:29 Page 1 of 1

FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ITT = intent-to-treat; PBO = placebo; ppFVC = percent predicted forced vital capacity; Q = quarter; QW = weekly; SC = subcutaneous; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ = tocilizumab.

A difference was seen in the median change from baseline I ppFVC at Week 48 in favour of the TCZ arm over placebo among patients with SSc-ILD (difference between treatment groups 3.40%; nominal p = 0.0016). The result was statistically significant.

Figure 25 Cumulative Distribution Plot of Change from Baseline in ppFVC at Week 48, Study WA29767, Patients with SSc-ILD



FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ITT = intent-to-treat;; ppFVC = percent predicted forced vital capacity; SSc-ILD = systemic sclerosis with interstitial lung disease;.

The Week 48 cumulative distribution plot for SSc-ILD patients shows that more patients in the placebo group experienced worsening of ppFVC compared with the TCZ group (placebo: 75% vs. TCZ: 50.8%). Furthermore, more patients in the placebo group experienced $\geq$ 10% worsening in ppFVC at Week 48 compared with the TCZ group (placebo: 25% vs. TCZ: 8.5%)

The proportion of patients with SSc-ILD with improvements, worsening, or no change in ppFVC at Week 48 was analysed. Among patients with SSc-ILD, a greaternproportion of patients had any improvement in ppFVC and fewer patients had any decline in ppFVC in the TCZ arm versus the placebo arm (

Table 35).

Table 35 Proportion of Patients with Improvement/Worsening/No Change in ppFVC at Week 48, Study 29767, Patients with SSc-ILD

Proportion of Patients Improving, Worsening or with No Change in Percent Predicted FVC at Week 48(includes only Patients with ILD positive at baseline based on HRCT), ITT Population
Protocol: WA29767
Up to Week 48

	PBO 162 mg qw SC (N=68)	TCZ 162 mg qw SC (N=68)
n	56	59
Increase from Baseline in %Predicted FVC >=10%	1 (1.8%)	6 (10.2%)
Increase from Baseline in %Predicted FVC >0% to <10%	12 (21.4%)	21 (35.6%)
No change from Baseline in %Predicted FVC	1 (1.8%)	2 (3.4%)
Decrease from Baseline in %Predicted FVC >-10% to <0%	28 (50.0%)	25 (42.4%)
Decrease from Baseline in %Predicted FVC <=-10%	14 (25.0%)	5 (8.5%)

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01APR2020 15:51 Page 1 of 1

FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ITT = intent-to-treat; PBO = placebo; ppFVC = percent predicted forced vital capacity; QW = weekly; SC = subcutaneous; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ = tocilizumab.

There was a clinically meaningful improvement with TCZ compared with placebo in the mean change from baseline in ppFVC at Week 48 among patients with SSc-ILD (difference between treatment groups 6.465%; nominal p = 0.0001)

Observed forced vital capacity in patients with SSc-ILD

At Week 48, there was a meaningful improvement with TCZ compared with placebo in the mean change from baseline in observed FVC among patients with SSc-ILD (difference between treatment groups 241 mL). The results were statistically significant.

Table 36 Change from Baseline in Observed FVC at Week 48, Study WA29767, Patients with SSc-ILD

Repeated-Measures Analysis of the Change from Baseline in Pulmonary Function (Absolute FVC in Litres) at Week 48 (Patients with ILD Positive at baseline based on HRCT), ITT Population
Protocol: WA29767
Up to Week 48

	PBO 162 mg qw SC (N=68)	TCZ 162 mg qw SC (N=68)
Change from baseline in Observed FVC at Week 48		
n	66	68
Least Square Means (LSM)	-0.255	-0.014
Difference in LSM		0.241
95% CI for Difference in LSM		(0.124,0.358)
P-value		<.0001

A mixed model for repeated-measures analysis was implemented.
The analysis included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level (<10; >=10 pg/mL) at screening, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Program: root/clinical_studies/RO4877533/CDPT3724/WA29767/data_analysis/CSRPrimary_wk48/prod/program/SA1840_t_ef_cb_repm.sas
Output: root/clinical_studies/RO4877533/CDPT3724/WA29767/data_analysis/CSRPrimary_wk48/prod/output/SA1840_t_ef_cb_repm_IT_OFVC_WK48_RAW.out
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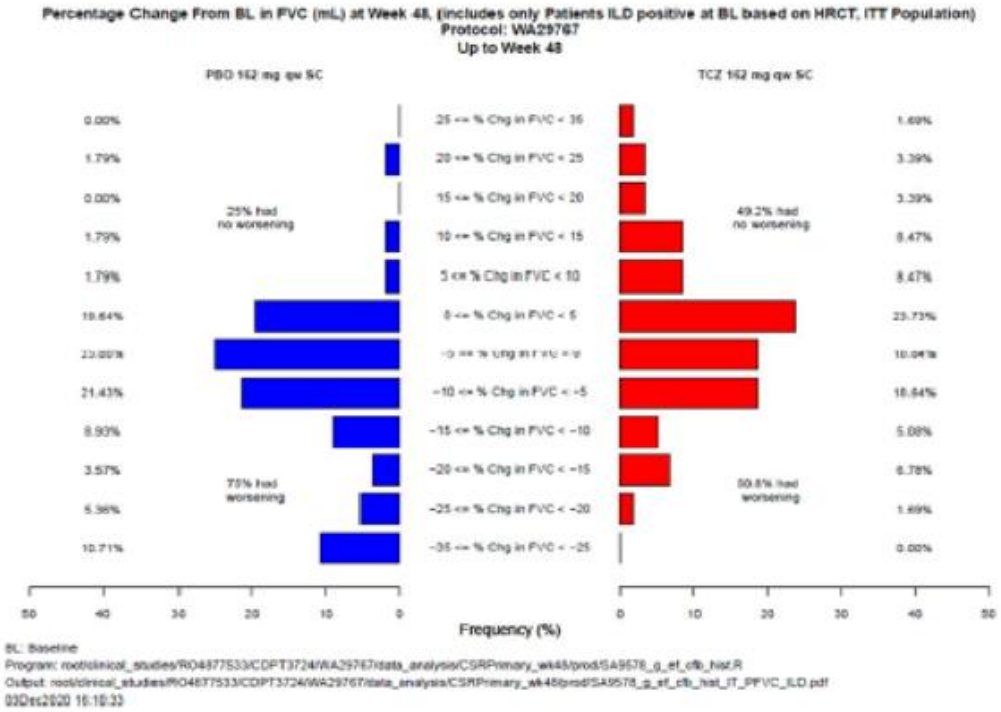
FVC = forced vital capacity; HRCT = high-resolution computed tomography; IL-6 = interleukin 6; ILD = interstitial lung disease; ITT = intent-to-treat; LSM = least square means; PBO = placebo; QW = weekly; SC = subcutaneous; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ = tocilizumab.

Percentage change from baseline in observed FVC (mL) at Week 48 for patients with SSc-ILD was evaluated. Patients who received TCZ experienced less worsening in FVC compared with patients who received placebo (

Figure 26).

Figure 26 Percentage Change from Baseline in Observed FVC at Week 48, Study WA29767, Patients with SSc-ILD



FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ITT = intent-to-treat; PBO = placebo; QW = weekly; SC = subcutaneous; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ = tocilizumab.

HRCT scan results in patients with SSc-ILD

The following HRCT lung scan results were analysed at Week 48: QLF-LM, QLF-WL, and QILD-WL. These analyses were also conducted post hoc on the subgroup of patients with SSc-ILD.

The median change from baseline in QLF-LM, QLF-WL, and QILD-WL at Week 48 showed a treatment effect in favour of TCZ over placebo in improving lung function (

Table 37). This treatment effect was more marked in the subgroup of patients with SSc-ILD.

Table 37 HRCT Scan Results at Week 48, Study WA29767, ITT Population and Patients with SSc-ILD

Exploratory Endpoint [b]	ITT Population			Patients with SSc-ILD [a]		
	Placebo (N=106)	TCZ (N=104)	p-value [c]	Placebo (N=68)	TCZ (N=68)	p-value [c]
QLF-LM						
n [d]	66	60		36	35	
Median CFB	0.25	0.00	0.0179	1.35	-0.20	0.0017
Q1–Q3	-0.70–1.90	-1.80–0.35		-0.15–3.05	-2.60–0.70	
Min–Max	-6.4–16.6	-28.9–4.2		-6.4–16.6	-28.9–4.2	
Mean CFB (95% CI)	0.89 (0.05, 1.74)	-1.36 (-2.75, 0.04)		1.89 (0.56, 3.23)	-2.17 (-4.55, 0.21)	
QLF-WL						
n [d]	81	84		48	54	
Median CFB	0.10	0.00	0.0049	0.40	-0.20	0.0008
Q1–Q3	-0.30–0.80	-0.90–0.25		-0.15–1.40	-1.20–0.30	
Min–Max	-3.3–5.7	-10.0–7.5		-2.2–5.7	-10.0–7.5	
Mean CFB (95% CI)	0.37 (0.04,0.69)	-0.38 (-0.90,0.14)		0.74 (0.27, 1.22)	-0.57 (-1.37, 0.24)	
QILD-WL						
n [d]	80	84		47	54	
Median CFB	0.40	-0.90	0.0356	1.60	-1.65	0.0082
Q1–Q3	-3.55–2.95	-3.85–1.10		-2.10–5.20	-4.40–0.30	
Min–Max	-21.5–18.7	-23.4–15.5		-14.0–18.7	-23.4–15.5	
Mean CFB (95% CI)	0.12 (-1.40,1.64)	-1.71 (-3.00,-0.41)		1.54 (-0.31,3.39)	-2.09 (-3.99,-0.19)	

CFB = change from baseline; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ITT = intent-to-treat; max = maximum; min = minimum; Q1=first quartile; Q3=third quartile; QILD-WL=quantitative interstitial lung disease-whole lung; QLF-LM=quantitative lung fibrosis-lobe of most involvement; QLF-WL=quantitative lung fibrosis-whole lung; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ=tocilizumab.

[a] Subset of patients who had ILD at baseline on visual read of HRCT by a thoracic radiologist.

[b] A negative change from baseline indicates improvement.

[c] All p-values (Van Elteren) are nominal because the result of the primary endpoint analysis was not significant, and the SSc-ILD subgroup analyses were post hoc.

[d] Only patients with both a Baseline and a Week 48 value are included in this analysis

Source: WA29767 Primary CSR 1081912, Table 29; WA29767 ad hoc analyses SA1840_t_ef_cb_IT_PQLF_HRCT, SA1840_g_ef_cb_cdf_IT_PQLF_ESI_WK48_RAW, SA1840_t_ef_cb_IT_PQLF, SA1840_g_ef_cb_cdf_IT_PQLF_WK48_RAW, SA1840_t_ef_cb_IT_PILD, SA1840_g_ef_cb_cdf_IT_PILD_WK48_RAW.

Modified rodnan skin score in patients with SSc-ILD

At Week 48, there was numerical improvement with TCZ compared with placebo in the mean change from baseline in mRSS among patients with SSc-ILD. The difference between treatment arms was not clinically meaningful.

CHMP comment

For Study WA29767 a post hoc subgroup analyses in patients with SSc-ILD at baseline were performed for ppFVC, observed FVC, and mRSS.

For Study WA29767 it is reported that he most common protocol deviations were baseline high-resolution computed tomography (HRCT) scans performed prior to randomization or other informed consent deviations, with slight imbalances noted between treatment arms.

High-resolution computed tomography (HRCT) scans were performed and as described in the Summary of clinical safety, ILD was identified visually post-hoc by a thoracic radiologist using a diagnostic algorithm for SSc as the presence of ground-glas opacification and/or fibrosis with a basal predominance. Potential causes other than SSc for the pattern of ground-glass opacification were excluded.

This approach is questionable, HRCT is used to define the relevant sub-population to support the i.e. indication claim, i.e. SSC-ILD patients while patient with history of previous/concomitant pulmonary

disease defined by certain ppFVC and ppDLCO level were excluded from the study (see inclusion / exclusion criteria). Please justify the approach.

Further there is no apparent correlation between the results of the scan and the lung function which does not support the validity of the chosen endpoints for the subgroup analysis i.e. ppFVC, observed FVC.

A difference was seen in the median change from baseline ppFVC at Week 48 in favour of the TCZ arm over placebo among patients with SSc-ILD (difference between treatment groups 3.40%; nominal p = 0.0016). The result was nominally statistically significant. At Week 48, there was an improvement with TCZ compared with placebo in the mean change from baseline in observed FVC among patients with SSc-ILD (difference between treatment groups 241 mL). The results were nominally statistically significant.

The results based on secondary endpoints evaluated in a post-hoc subgroup analysis in a poorly defied population and thus are not generated with the same scientific/statistical rigor, and are considered exploratory. An ad-hoc interpretation may be possible, but has substantial uncertainties.

Study WA27788

Table 38 Overview of Key Efficacy Endpoints at Weeks 24 and 48 in Study WA27788, ITT Population

Efficacy Variable [a]	Week 24		Week 48	
	Placebo (N=44)	TCZ (N=43)	Placebo (N=44)	TCZ (N=43)
mRSS [b]				
Change from BL	-1.22	-3.92	-2.77	-6.33
ΔLSM (95% CI), p-value	-2.70 (-5.85, 0.45), p=0.0915		-3.55 (-7.23, 0.12), p=0.0579	
HAQ-DI				
Change from BL	0.118	0.137	0.205	-0.002
ΔLSM (95% CI), p-value	0.020 (-0.186, 0.225), p=0.8503		-0.207 (-0.471, 0.056), p=0.1212	
Patient's Global Assessment				
Mean change from BL	1.53	-2.33	-2.70	-11.00
ΔLSM (95% CI), p-value	-3.85 (-13.04, 5.34), p=0.4063		-8.30 (-19.31, 2.71), p=0.1371	
Physician's Global Assessment				
Mean change from BL	-7.25	-8.24	-9.39	-18.41
ΔLSM (95% CI), p-value	-0.99 (-9.20, 7.23), p=0.8118		-9.02 (-19.04, 1.00), p=0.0768	

Efficacy Variable [a]	Week 24		Week 48	
	Placebo (N=44)	TCZ (N=43)	Placebo (N=44)	TCZ (N=43)
SHAQ-VAS Scores				
Overall Disease				
Change from BL	1.89	1.81	3.46	−4.36
ΔLSM (95% CI), p-value	-0.08 (-9.93, 9.78), p=0.9876		-7.82 (-19.11, 3.48), p=0.1717	
Breathing				
Change from BL	8.54	4.42	0.55	2.09
ΔLSM (95% CI), p-value	-4.12 (−15.21, 6.96), p=0.4609		1.54 (-9.18, 12.26), p=0.7742	
FACIT-Fatigue Scale				
Mean change from BL	1.26	2.68	0.36	3.11
ΔLSM (95% CI), p-value	1.43 (-2.97, 5.82), p=0.5197		2.75 (-1.38, 6.88), p=0.1886	
Pruritus 5-D Itch Scale				
Mean change from BL	-1.73	-0.94	-1.08	-2.19
ΔLSM (95% CI), p-value	0.79 (-0.94, 2.51), p=0.3651		-1.11 (-3.16, 0.94), p=0.2841	

ΔLSM = difference in least squares mean; BL = baseline; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire-Disability Index; ITT = intent-to-treat; mRSS = modified Rodnan skin score; SHAQ-VAS = Scleroderma Health Assessment Questionnaire visual analogue scale; TCZ = tocilizumab.

[a] A negative change from baseline shows improvement for all efficacy measures, except the FACIT-Fatigue Scale, where a positive change from baseline indicates improvement.

[b] At Week 48, 9 of 33 placebo patients and 4 of 32 TCZ-treated patients with mRSS data had received escape therapy. For these patients, their mRSS data from the first receipt of escape therapy and thereafter were excluded from the data analyses.

Source: WA27788 Primary CSR 1060804, Table 10; WA27788 Update CSR 1061598, Table 9.

Primary efficacy endpoint

Modified rodnan skin score

The primary efficacy endpoint was the change in mRSS from baseline at Week 24. A numerically greater but not statistically significant effect of TCZ over placebo on mRSS was noted at Week 24 (Table 38). The higher treatment effect of TCZ versus placebo was also observed in all sensitivity analyses.

At Week 48, a numerically greater but not statistically significant effect of TCZ over placebo on mRSS was observed (Table 38). Among patients with improvement in mRSS at Week 24, a greater proportion of TCZ-treated patients than placebo patients maintained or had further improvement in their mRSS at Week 48 (placebo: 44.4% and TCZ: 68.2%).

Secondary efficacy endpoints

Health assessment questionnaire-disability index

Neither treatment arm showed improvement in HAQ-DI scores at Week 24 (Table 38).

At Week 48, the placebo arm showed a worsening trend in HAQ-DI scores from baseline, whereas on average no change from baseline was apparent in the TCZ arm (Table 38).

Patient's global assessment

At Week 24, mean change from baseline in Patient's Global Assessment scores showed a numerically better, but not statistically significant, outcome for the TCZ arm compared with the placebo arm (Table 38).

By Week 48, both treatment arms had improved relative to baseline, with a greater improvement on average observed with TCZ than with placebo; however, the difference was not statistically significant (Table 38).

Physician's global assessment

At Week 24, mean change from baseline in Physician's Global Assessment scores showed improvement in both treatment arms, with a small and not statistically significant treatment difference (Table 38).

By Week 48, both treatment arms had improved relative to baseline, with a greater improvement on average observed with TCZ than with placebo; however, the difference was not statistically significant (Table 38).

Scleroderma health assessment questionnaire

At Week 24, neither treatment group showed a clinically meaningful or statistically significant improvement on SHAQ-VAS scales assessing breathing problems and overall disease. Mean change from baseline in SHAQ-VAS breathing score showed a numerically better, but not statistically significant, outcome with TCZ compared with placebo (Table 38).

At Week 48, there was a numerical difference in mean SHAQ-VAS overall disease score between treatment arms favouring TCZ; however, the difference was not statistically significant. There was no meaningful difference between treatment arms in mean change from baseline in SHAQ-VAS breathing score (Table 38).

FACIT-fatigue

At Week 24, both treatment groups showed slight improvement in fatigue, with treatment difference that was not statistically significant (Table 38).

At Week 48, both treatment arms showed an improvement in fatigue, with no statistically significant treatment difference (Table 38).

Pruritus 5-D itch scale

At Week 24 and Week 48, both treatment arms showed improvement in Pruritus 5-D Itch Scale scores with no statistically significant treatment difference.

CHMP comment

The study failed to demonstrated a statistically significant treatment effect of TCZ over PBO with regard to the primary and secondary efficacy endpoints, namely mRSS, health assessment questionnaire-disability index, patient's global assessment, physician's global assessment, scleroderma health assessment questionnaire, FACIT-fatigue and pruritus 5-D itch scale.

Exploratory efficacy analyses

Table 39 Overview of Exploratory Efficacy Endpoints at Weeks 24 and 48 in Study WA27788, ITT Population

Efficacy Variable [a]	Week 24		Week 48	
	Placebo (N=44)	TCZ (N=43)	Placebo (N=44)	TCZ (N=43)
ppFVC				
Median change from BL (95% CI)	-3.6 (-7.4, -0.4)	0.0 (-2.5, 1.6)	-5.7 (-8.6, -1.6)	-1.5 (-4.1, 1.2)
p-value	p=0.009		p=0.0373	
Proportion of patients with ≥ 10% decline in ppFVC [a]	—	—	7 (22.6%)	3 (10.0%)
Observed FVC (mL)				
Mean change from BL	—	—	-237	-117
ΔLSM (95% CI), p-value	—		120 (-23, 262), p=0.0990	
Proportion of patients with ≥ 10% decline in FVC	—	—	9 (28.1%)	3 (10.0%)
ppDL$_{CO}$				
Median change from BL	—	—	-3.9	-2.7
Min–Max	—	—	-22.9–18.6	-26.1–12.2
Mean change from BL	—	—	-3.7	-3.1

ΔLSM = difference in least squares mean; BL = baseline; FVC = forced vital capacity; ITT = intent-to-treat; max = maximum; min = minimum; ppDL$_{CO}$ = percent predicted diffusion capacity of the lung for carbon monoxide; ppFVC = percent predicted forced vital capacity; TCZ = tocilizumab.

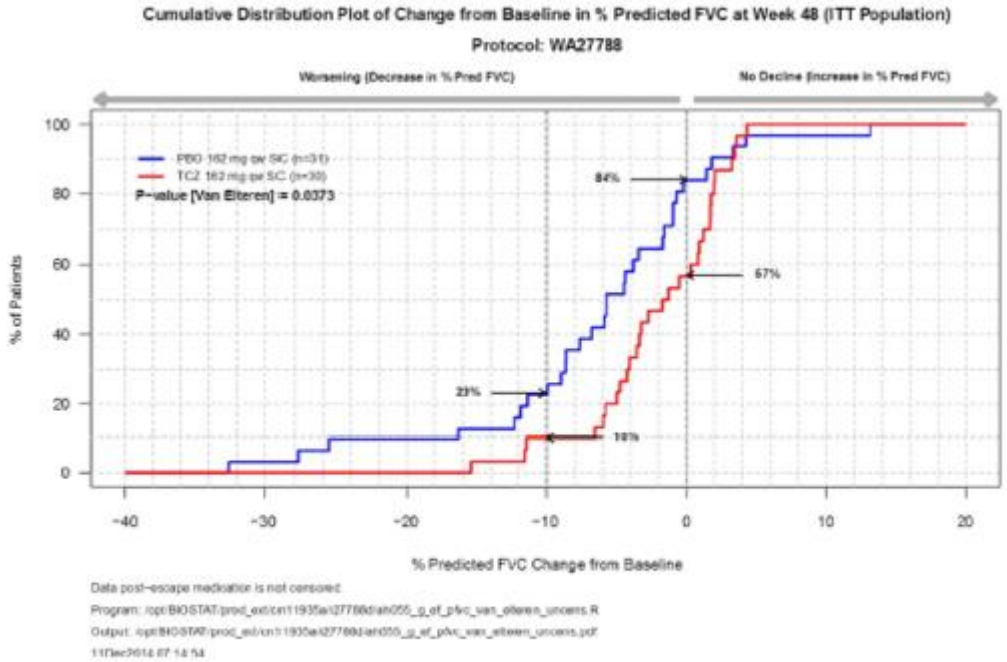
[a] The proportion of patients with a ≥ 10% decline in ppFVC was a post hoc analysis.

Source: WA27788 Update CSR 1061598, Table 13, Figure 10, ah060_g_ef_pfvc_van_elteren, ah025_t_ef_cb_repm_IT_OFVC_RAW, ah029_t_ef_cb_IT_PDLCO_RAW; WA27788 ad hoc analyses SA1183_t_ef_cb_IT_PFVC_RAW, I27788a_SA1183_t_ef_cb_IT_PFVC_RAW, SA1155_t_ef_cb_prop_IT_PFVC_RAW.

Percent predicted forced vital capacity

A treatment effect in favour of TCZ over placebo was seen in the median change from baseline in ppFVC at both Week 24 (difference between treatment groups 3.6%; nominal p = 0.009) and Week 48 (difference between treatment groups 4.2%; nominal p = 0.0373). The proportion of patients with ≥ 10 decline in ppFVC at Week 48 was lower with TCZ than with placebo (placebo: 22.6% vs. TCZ: 10.0%) (Table 39).

Figure 27 Cumulative Distribution Plot of Change from Baseline in ppFVC at Week 48, Study WA27788, ITT Population



FVC = forced vital capacity; ITT = intent-to-treat; PBO = placebo; ppFVC = percent predicted forced vital capacity; QW = weekly; SC = subcutaneous; TCZ = tocilizumab.

Source: WA27788 Update CSR 1061598, Figure 10

The Week 48 cumulative distribution plots show that more patients in the placebo group experienced worsening of ppFVC compared with the TCZ group in both studies (84% vs. 57%)

Observed forced vital capacity

At Week 48, the mean change from baseline in observed FVC was greater in placebo patients compared with TCZ-treated, representing a treatment difference of 120 mL in favour of TCZ. More placebo patients than TCZ-treated patients had a ≥10% decline from baseline in observed FVC (Table 39).

Diffusion Capacity of the Lung for Carbon Monoxide at Week 48, the placebo arm and TCZ arm showed similar mean and median change from baseline in ppDL$_{CO}$ (Table 39).

Post Hoc Efficacy Analyses

Combined response index for systemic sclerosis

The results of the composite CRISS index at Week 48 showed a shift towardchigher CRISS scores in favour of TCZ over placebo (nominal p = 0.0314 [Van Elteren]). More patients in the TCZ arm achieved an improvement in CRISS scores of ≥0.6 (the MCID) compared with the placebo arm; however, the difference between treatment arms was not clinically meaningful or statistically significant (difference in responses = 9.0% [95% CI: -8.9, 26.9]; nominal p = 0.323, Cochran- Mantel-Haenszel test).

CHMP comment

It has been shown that TCZ has a benefit over placebo on endpoints related to lung function i.e. ppFVC a statistically nominally significant treatment effect in favour of TCZ over placebo was seen. The effect on observed FVC showed a trend for a benefit of TCZ, no statistical significance was reached. Diffusion

Capacity of the Lung for Carbon Monoxide at Week 48, the placebo arm and TCZ arm showed similar mean and median change from baseline in ppDLCO.

Ancillary analyses

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 40 Summary of Efficacy for Trial WA29767 (FocuSSced)

Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients with Systemic (FocuSSced) **Sclerosis**			
Study identifier	WA29767		
Design	multicentre, double-blinded, placebo-controlled, parallel-group, randomized study Open-label extension		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks <not applicable> 48 weeks
Hypothesis	Superiority		
Treatments groups	TCZ		tocilizumab 162 mg SC QW, 48 weeks, n=105
	Placebo		Placebo SC QW, 48 weeks, n= 107
Endpoints and definitions	Primary endpoint	mRSS at week 48	Change in mRSS from baseline to week 48
	Secondary endpoint	mRSS at week 24	Change in mRSS from baseline to week 24
	Secondary endpoint	ppFVC at week 48	Change from baseline to week 48 in percent predicted forced volume capacity (ppFVC)
Database lock	15 January 2018		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Placebo	TCZ	
	Number of subject	n=106	n=104	
	mRSS at week 48 (n)	N=92	N=96	
	LSmean	-4.41	-6.14	
	95% CI	-5.96,-2.86	-7.71,-4.57	
	mRSS at week 24 (n)	N=99	N=98	
	LSmean	-3.06	-3.69	
	95% CI	-4.31,-1.81	-4.96,-2.42	

Effect estimate per comparison	Primary endpoint mRSS at week 48	Comparison groups	TCZ vs Placebo
		LSmean difference	-1.73
		95% CI	-3.78, 0.32
		P-value	0.0983
	mrSS at week 24	Comparison groups	TCZ vs Placebo
		LSmean difference	-0.63
		95% CI	-2.29, 1.03
		P-value	0.4549

Notes	primary endpoint is not met, all further results are descriptive LSmeans derived from MMRM missing values were not imputed Sources: CSR table 13, CSR table 12, CSR p. 442			
Analysis description	**Secondary analysis (ppFVC)**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Placebo	TCZ	
	Number of subject	n=106	n=104	
	ppFVC at week 48 (n)	N=91	N=93	
	LSmean	-4.58	-0.38	
	95% CI	-6.22,-2.94	-2.06,1.30	
	median	-3.91	-0.6	
	Q1, Q3	-7.16, 0.57	-5.25, 3.93	

Effect estimate per comparison	ppFVC at week 48	Comparison groups	TCZ vs Placebo
		LSmean difference	4.2
		95% CI	2.0,6.4
		P-value	0.0002
		p-value (non-parametric)	0.0015
Notes	results are descriptive (primary endpoint not met, ppFVC was added to hierarchy only in SAP V1 (dated 08-Aug-2017)) parametric results from MMRM, non-parametric p-value from van-Elteren test missing values were not imputed reference: CSR table 12, CSR table 25, CSR p.675,		

Analysis description	**Secondary analysis (ppFVC) in SSc-ILD**			
Analysis population and time point description	Post-hoc subgroup SSc-ILD			
Descriptive statistics and estimate variability	Treatment group	Placebo	TCZ	
	Number of subject	N=68	N=68	
	ppFVC at week 48 (n)	N=not reported	N=not reported	
	LSmean	-6.4	0.1	
	95% CI	Not provided	Not provided	
	median	-4.0	-0.6	
	Q1, Q3	-9.80,-0.09	-5.27,5.05	

Effect estimate per comparison	ppFVC at week 48	Comparison groups	TCZ vs Placebo
		LSmean difference	6.5
		95% CI	3.4,9.5
		P-value	<0.0001
		Difference in medians	3.40
		95% CI	0.4,5.57
		p-value (non-parametric)	0.0016
Notes	Exploratory subgroup results parametric results from MMRM, non-parametric p-value from van-Elteren test missing values were not imputed Clinical Overview Table 7, Summary of clinical efficacy Table 8		

Table 41 Summary of Efficacy for trial WA27788 (FaSScinate)

Title: A Phase II/III, Multicenter, **Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety** **of Tocilizumab Versus Placebo in Patients with Systemic Sclerosis. – Research Report (FaSScinate)**			
Study identifier	WA27788		
Design	multicentre, double-blinded, placebo-controlled, parallel-group, randomized study Open-label extension		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks <not applicable> 48 weeks
Hypothesis	Superiority		
Treatments groups	TCZ		tocilizumab 162 mg SC QW, 24 weeks, n=43
	Placebo		Placebo SC QW, 48 weeks, n= 44
Endpoints and definitions	Primary endpoint	mRSS at week 24	Change in mRSS from baseline to week 24
	Secondary endpoint	mRSS at week 48	Change in mRSS from baseline to week 48
	Secondary endpoint	ppFVC at week 48	Change from baseline to week 48 in percent predicted forced volume capacity (ppFVC)
Database lock	Week 24: 14 January 2014, Week 48: 11 July 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Placebo	TCZ	
	Number of subject	n=44	n=43	
	mRSS at week 24 (n)	N=43	N=41	
	LSmean	-1.22	-3.92	
	95% CI	Not reported	Not reported	
	mRSS at week 48 (n)	N=43	N=41	
	LSmean	-2.77	-6.33	
	95% CI	Not reported	Not reported	

Effect estimate per comparison	Primary endpoint mRSS at week 24	Comparison groups	TCZ vs Placebo
		LSmean difference	-2.70
		95% CI	-5.85,0.45
		P-value	0.0915
	mrSS at week 48	Comparison groups	TCZ vs Placebo
		LSmean difference	-3.55
		95% CI	-7.23,0.12
		P-value	0.0579
Notes	primary endpoint is not met, all further results are descriptive LSmeans derived from MMRM missing values were not imputed Sources: Clinical Overview Table 6, CSR (week 48) p. 232		
Analysis description	**Secondary analysis (ppFVC)**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Placebo	TCZ	
	Number of subject	N=44	n=43	
	ppFVC at week 48 (n)	N=31	N=30	
	mean	-6.6	-2.1	
	SD	9.4	4.8	
	median	-5.7	-1.5	

Effect estimate per comparison	ppFVC at week 48	Comparison groups	TCZ vs Placebo
		LSmean difference	3.7
		95% CI	0.1,7.3
		P-value	0.0445
		p-value (non-parametric)	0.0373
Notes	results are exploratory parametric results from MMRM, non-parametric p-value from van-Elteren test missing values were not imputed reference: CSR (week 48) Table 14, p. 267 , clinical overview Table 7		

2.5.4 Analysis performed across trials (pooled analyses and meta-analysis)

Patient demographics in Studies WA29767 and WA27788

Patient demographics in Studies WA29767 and WA27788 are described above in detail.

Patient demographics were generally balanced between TCZ and placebo treatment arms in each study, and across the two studies. Patients were predominately female (74.4%-84.9%) and white (□80% in both arms of both studies), with a mean baseline body weight ranging from 66.80-71.79 kg and mean age ranging from 47.0-51.2 years, comparing treatment arms across studies. A higher proportion of all patients in Study WA29767 had never smoked compared with all patients in Study WA27788 (65.7% vs. 55.2%, respectively); however, median smoking history was similar across treatment arms between the two studies (15.0-24.0 years).

Baseline disease characteristics

The baseline disease characteristics in studies WA29767 and WA27788 were well balanced between treatment arms (

Table 42). The mean disease duration was higher in Study WA29767 (23.3 months [SD: 17.1] in the placebo arm and 22.3 months [SD: 16.1] in the TCZ arm) than in Study WA27788 (19.7 months [SD: 17.1] in the placebo arm and 17.8 months [SD:13.8] in the TCZ arm). The mRSS showed moderate to severe skin involvement in both studies, with lower mean scores in Study WA29767 compared with Study WA27788 (mean mRSS 20 in WA29767 vs. 26 in WA27788). ppFVC continued to be indicative of normal function to mild impairment (mean ~82% in both studies), and ppDLco indicative of mild impairment (mean ~75% in both studies) (Medsger et al. 2003). In both studies, the placebo and TCZ arms had similar mean HAQ-DI scores of 1 to 2 indicative of moderate to severe functional impairment (Clements et al. 1999). Additionally, Patient's and Physician's Global Assessment scores were comparable in bothstudies. The proportion of patients with IL-6 <10 ng/mL was higher in Study WA29767 compared with Study WA27788 (73% in WA29767 vs. 60% in WA27788). Approximately 44% and 50% of patients enrolled in Study WA27788 and Study WA29767 were positive for anti-topoisomerase antibody, respectively. A lower proportion of patients positive for anti-RNA polymerase antibody were enrolled in Study WA29767 (18% WA29767 vs. 34% WA27788); however, Study WA29767 enrolled a higher proportion of patients positive for anti-centromere antibody (8.5% WA29767 vs. 0% WA27788).

Comparison of primary and secondary efficacy results

An overview of results for primary and key secondary endpoints in StudiesWA29767 and WA27788 is presented in

Table 42.

Table 42 Overview of Key Efficacy Endpoints in Studies WA29767 and WA27788, ITT Population

Efficacy Variable [b]	WA29767 Placebo (N=106)	WA29767 TCZ (N=104)	WA27788 [a] Placebo (N=44)	WA27788 [a] TCZ (N=43)
mRSS				
Change in mRSS at Week 48 [c]				
Mean change from BL	-4.41	-6.14	-2.77	-6.33
ΔLSM (95% CI), p-value	-1.73 (-3.78, 0.32), p=0.0983		-3.55 (-7.23, 0.12), p=0.0579	
Change in mRSS at Week 24 [c]				
Mean change from BL	-3.06	-3.69	-1.22	-3.92
ΔLSM (95% CI), p-value	-0.63 (-2.29, 1.03), p=0.4549		-2.70 (-5.85, 0.45), p=0.0915	
≥20% Improvement in mRSS at Week 48				
Responders, n (%)	53 (50.0%)	75 (72.1%)	13 (29.5%)	18 (41.9%)
Difference in response (95% CI), p-value	21.91 (9.2, 34.6), p=0.0007		11.5 (-8.6, 31.7), p=0.270	
≥40% Improvement in mRSS at Week 48				
Responders, n (%)	40 (37.7%)	44 (42.3%)	3 (6.8%)	10 (23.3%)
Difference in response (95% CI), p-value	4.32 (-8.7, 17.3), p=0.5139		16.2 (1.0, 31.3), p=0.038	
≥60% Improvement in mRSS at Week 48				
Responders, n (%)	24 (22.6%)	18 (17.3%)	0 (0.0%)	5 (11.6%)
Difference in response (95% CI), p-value	-5.41 (-16.2, 5.4), p=0.3276		11.6 (0.5, 22.6), p=0.023	
ppFVC				
Change in ppFVC at Week 48				
Median change from BL (95% CI)	-3.9 (-4.8, -1.6)	-0.6 (-2.4, 0.9)	-5.7 (-8.6, -1.6)	-1.5 (-4.1, 1.2)
p-value	p=0.0015		p=0.0373	
LSM change from BL	-4.6	-0.4	-6.3	-2.6
ΔLSM (95% CI), p-value	4.2 (2.0, 6.4), p=0.0002		3.7 (0.1, 7.3), p=0.0445	
Change in ppFVC at Week 24				
Median change from BL (95% CI)	-2.6 (-3.2, -0.8)	-0.3 (-1.2, 0.8)	-3.6 (-7.4, -0.4)	0.0 (-2.5, 1.6)
p-value	p=0.0366		p=0.009	

Efficacy Variable [b]	WA29767 Placebo (N=106)	WA29767 TCZ (N=104)	WA27788 [a] Placebo (N=44)	WA27788 [a] TCZ (N=43)
Proportion of patients with improvement/worsening/no change in ppFVC at Week 48				
n	91	93	31	30
Increase from BL ≥ 10%	1 (1.1%)	8 (8.6%)	1 (3.2%)	0
Increase from BL > 0% to < 10%	25 (27.5%)	35 (37.6%)	4 (12.9%)	13 (43.3%)
No change from BL	1 (1.1%)	3 (3.2%)	0	0
Decrease from BL ≥ -10% to < 0%	49 (53.8%)	42 (45.2%)	19 (61.3%)	14 (46.7%)
Decrease from BL ≤ -10%	15 (16.5%)	5 (5.4%)	7 (22.6%)	3 (10.0%)
Observed FVC				
Change in FVC at Week 48 (mL)				
Mean change from BL	-190	-24	-237	-117
ΔLSM (95% CI), p-value	167 (83, 250), p=0.0001		120 (-23, 262), p=0.0990	
Proportion of patients with ≥ 10% decline in FVC at Week 48	17/91 (18.7%)	10/93 (10.8%)	9/32 (28.1%)	3/30 (10.0%)
Other Endpoints				
HAQ-DI at Week 48				
Mean change from BL	-0.06	-0.11	0.205	-0.002
ΔLSM (95% CI), p-value	-0.05 (-0.19, 0.09), p=0.4489		-0.207 (-0.471, 0.056), p=0.1212	
Patient's Global Assessment at Week 48				
Mean change from BL	-7.66	-10.10	-2.70	-11.00
ΔLSM (95% CI), p-value	-2.44 (-8.57, 3.70), p=0.4339		-8.30 (-19.31, 2.71), p=0.1371	
Physician's Global Assessment at Week 48				
Mean change from BL	-19.99	-22.45	-9.39	-18.41
ΔLSM (95% CI), p-value	-2.46 (-8.72, 3.79), p=0.4378		-9.02 (-19.04, 1.00), p=0.0768	

ΔLSM = difference in least squares mean; BL = baseline; FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire-Disability Index; ITT = intent-to-treat; LSM = least square means; mRSS = modified Rodnan skin score; ppFVC = percent predicted forced vital capacity; TCZ = tocilizumab.

[a] For Study WA27788, data were censored for escape therapy for the following endpoints at Week 48: mRSS, HAQ-DI, and Patient's and Physician's Global Assessment.

[b] A negative change from baseline shows improvement for all efficacy measures, except for FVC and binary endpoints.

[c] Statistical significance ($p < 0.05$) of the primary endpoint (WA29767: mRSS at Week 48, WA27788: mRSS at Week 24) was not met; therefore, subsequent secondary endpoints were not formally tested for statistical significance. All observed p-values other than the primary endpoint are considered nominal.

Source: WA29767 Primary CSR 1081912, Table 12, Table 23, Table 28, t_ef_cb_repm_IT_PFVC_WK48_RAW, t_ef_cb_repm_IT_OFVC_WK48_RAW; WA27788 Primary CSR 1060804, Table 10; WA27788 Update CSR 1061598, Table 9, Table 13, Figure 10, ah060_g_ef_pfvc_van_elteren, ah025_t_ef_cb_repm_IT_OFVC_RAW; WA27788 ad hoc analyses t_ef_prop_cmh_SA942_IT_MRSS20_RAW, t_ef_prop_cmh_SA942_IT_MRSS40_RAW, t_ef_prop_cmh_SA942_IT_MRSS60_RAW, SA1183_t_ef_cb_repm_IT_PFVC_RAW, SA1183_t_ef_cb_IT_PFVC_RAW, i27788a_SA1183_t_ef_cb_IT_PFVC_RAW, SA1155_t_ef_cb_prop_IT_PFVC_RAW.

Both studies, Studies WA29767 and WA27788, did not meet the primary endpoints (no significant difference between TCZ and placebo arms in mean change from baseline in mRSS at Week 48 and Week 24 in Studies WA29767 and WA27788, respectively).

However, both studies showed a numeric improvement in mean change in mRSS for the TCZ arm relative to the placebo arm at Week 48 (

Table 42). While the mean change in mRSS from baseline to Week 48 in the TCZ arm was consistent in both studies, mRSS improvement in the placebo arm was greater in Study WA29767 compared with Study WA27788.

In Study WA29767 at Week 48, more patients in the TCZ arm had mRSS improvement of at least 20%, but this differential between groups was not apparent at the higher thresholds of 40% and 60% improvement. In Study WA27788, more patients in the TCZ arm had mRSS improvement of at least 20%, 40%, and 60% compared with patients in the placebo arm (

Table 42).

A treatment effect in favour of TCZ over placebo was seen in the median change from baseline in ppFVC at Week 48 in both Study WA29767 (difference between treatment groups 3.3%; nominal p = 0.0015) and Study WA27788 (difference between treatment groups 4.2%; nominal p = 0.0373). These results were consistent with the results observed at Week 24.

There was no meaningful difference in other endpoints HAQ-DI scores, Patient's Global Assessment, Physician's Global Assessment at Week 48 between studies or between treatment groups.

Ad hoc analysis of Study WA27788 Week 48 endpoints without censoring for escape therapy was completed in order to better align the estimand with that of Study WA29767. Results of this analysis are consistent with those of the main analysis presented in

Table 42.

Comparison of exploratory efficacy endpoints

Table 43 Overview of Exploratory Efficacy Endpoints in Studies WA29767 and WA27788, ITT Population

	WA29767		WA27788	
Efficacy Variable [a]	Placebo (N=106)	TCZ (N=104)	Placebo (N=44)	TCZ (N=43)
$ppDL_{CO}$ at Week 48				
Median change from BL	-2.1	-2.4	-3.9	-2.7
Min–Max	-48.2–29.6	-24.7–22.5	-22.9–18.6	-26.1–12.2
Mean change from BL	-2.6	-1.3	-3.7	-3.1
Proportion of patients with ≥ 15% decline in observed DL_{CO} n/N (%)	12/87 (13.8%)	8/84 (9.5%)	8/39 (20.5%)	6/34 (17.6%)
SHAQ-VAS Scores at Week 48 [b]				
Overall Disease				
Mean change from BL	-0.30	-0.30	3.46 [c]	-4.36 [c]
(95% CI)	(-0.48, -0.12)	(-0.45, -0.15)		
Breathing				
Mean change from BL	0.11	0.05	0.55 [c]	2.09 [c]
(95% CI)	(-0.06, 0.27)	(-0.07, 0.16)		
FACIT-Fatigue Score [d]				
Mean change from BL	2.64	5.05	0.36	3.11
ΔLSM (95% CI), p-value	2.40 (0.08, 4.73), p=0.0430		2.75 (−1.38, 6.88), p=0.1886	

ΔLSM = difference in least squares mean; BL = baseline; DL_{CO} = diffusion capacity of the lung for carbon monoxide; FACIT=Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; max = maximum; min = minimum; $ppDL_{CO}$ = percent predicted diffusion capacity of the lung for carbon monoxide; SHAQ-VAS = Scleroderma Health Assessment Questionnaire Visual Analogue Scale; TCZ = tocilizumab.

[a] Negative change from BL indicates improvement for SHAQ-VAS scores; positive change from BL indicates improvement for $ppDL_{CO}$ and FACIT-Fatigue.

[b] The SHAQ-VAS score was converted to a continuous scale from 0–3 for Study WA29767, scores can range from 0 to 100 for Study WA27788.

[c] Least square means from repeated-measures analysis.

[d] FACIT-Fatigue scores range from 0 to 52.

Source: WA29767 Primary CSR 1081912, Table 23, t_ef_cb_median_IT_PDLCO_RAW; WA27788 Update CSR 1061598, Table 9, ah029_t_ef_cb_IT_PDLCO_RAW, ah015_t_ef_cb_prop_IT_ODLCOP_RAW.

No effect of treatment on the mean and median change from baseline in $ppDL_{CO}$ at Week 48 was observed in either study; the results were similar between treatment arms in both Study WA29767 and Study WA27788. The proportion of patients that experienced a $\geq$ 15% decline in observed DLCO at Week 48 was also comparable between treatment arms in both studies.

In Study WA27788, there was a numerical improvement in mean change from baseline in SHAQ-VAS overall disease score at Week 48 with TCZ versus placebo; however, this difference between treatment arms was not statistically significant. In Study WA29767, mean change from baseline in SHAQ-VAS overall disease score at Week 48 was similar between treatment arms (Table 43).

There was no meaningful difference between treatment arms in mean change from baseline in SHAQ-VAS breathing score at Week 48 in Study WA29767 or Study WA27788 (Table 43).

Both treatment arms showed an improvement in mean change from baseline in

FACIT-Fatigue score at Week 48, and a higher numerical improvement was observed in the TCZ arm versus the placebo arm in both Studies WA29767 and WA27788. The nominal p-value was significant (<0.05) in Study WA29767, but not in Study WA27788 (Table 43).

CRISS was an exploratory analysis for Study WA29767 and a post hoc analysis for Study WA27788.

The first step in calculating the CRISS score is the evaluation of clinically significant decline in renal or cardiopulmonary involvement that requires treatment, resulting in the classification of a patient as not improved. The second step of CRISS computes the predicted probability of improving for each patient based on the change from baseline in mRSS, ppFVC, HAQ-DI, Patient's Global Assessment, and Physician's Global Assessment. In both Studies WA29767 and WA27788, more patients in the TCZ arm achieved an improvement in CRISS score of $\geq$ 0.6 (the MCID) compared with the placebo arm (Table 44).

Table 44 Proportion of Patients with CRISS score of > 0.6 at Week 48, Studies WA29767 and WA27788, ITT Population

	Study WA29767		Study WA27788	
CRISS Events	Placebo N=106	TCZ N=104	Placebo N=44	TCZ N=43
n	106	104	43	43
Patients with CRISS response [a]	39 (36.8%)	53 (51.0%)	8 (18.2%)	12 (27.9%)
95% CI for response rate [b]	(27.14, 46.44)	(40.87, 61.05)	(5.8%, 31.4%)	(13.3%, 42.5%)
Weighted difference TCZ vs. placebo	13.9%		9.0%	
95% CI of weighted difference	(1.0%, 26.8%)		(-8.9%, 26.9%)	
p-value [c]	0.0350		0.323	

CRISS = Combined Response Index for Systemic Sclerosis; ITT = intent-to-treat; TCZ = tocilizumab.

[a] CRISS response is defined as CRISS score of ≥ 0.6.

[b] Wald with continuity correction.

[c] Cochran-Mantel-Haenszel analysis was used to calculate p-values.

Source: WA29767 Primary CSR 1081912, t_ef_mcid_IT_CRIS6W48_RAW; WA27788 post hoc analysis t_ef_prop_cmh_SA942_IT_CRISS_RAW.

Comparison of results in subpopulations

Subgroup analyses of change from baseline in ppFVC, observed FVC, and mRSS at Week 48 were performed for patients with SSc-ILD in Study WA29767. For mean change from baseline to Week 48 in ppFVC and observed FVC, there was an improvement with TCZ compared with placebo among patients with SSc-ILD. There was no clinically meaningful difference in mean change from baseline in mRSS at Week 48 for patients with SSc-ILD.

Table 45 Overview of FVC Resulta (Percent Predicted and Observed [mL]) at Week 48 for Patients with SSc and SSc-ILD

Efficacy Variable	WA27788		WA29767		Patients with SSc-ILD in WA29767	
	Placebo (N=44)	TCZ (N=43)	Placebo (N=106)	TCZ (N=104)	Placebo (N=68)	TCZ (N=68)
ppFVC						
Median change from BL (95% CI)	-5.7 (8.6, 1.6)	-1.5 (-4.1, 1.2)	-3.9 (-4.8, -1.6)	-0.6 (-2.4, 0.9)	-4.0 (-5.3, -1.7)	-0.6 (-3.2, 2.0)
p-value	p=0.0373		p=0.0015		p=0.0016	
LSM	-6.3	-2.6	-4.6	-0.4	-6.4	0.1
ΔLSM (95% CI), p-value	3.7 (0.1, 7.3), p=0.0445		4.2 (2.0, 6.4), p=0.0002		6.5 (3.4, 9.5), p<0.0001	
n	31	30	91	93	56	59
Increase from BL ≥ 10%	1 (3.2%)	0	1 (1.1%)	8 (8.6%)	1 (1.8%)	6 (10.2%)
Increase from BL > 0% to < 10%	4 (12.9%)	13 (43.3%)	25 (27.5%)	35 (37.6%)	12 (21.4%)	21 (35.6%)
No change from BL	0	0	1 (1.1%)	3 (3.2%)	1 (1.8%)	2 (3.4%)
Decrease from BL > -10% to < 0%	19 (61.3%)	14 (46.7%)	49 (53.8%)	42 (45.2%)	28 (50.0%)	25 (42.8%)
Decrease from BL ≤ -10%	7 (22.6%)	3 (10.0%)	15 (16.5%)	5 (5.4%)	14 (25.0%)	5 (8.5%)
Observed FVC						
LSM (mL)	-237	-117	-190	-24	-255	-14
ΔLSM (95% CI), p-value	120 (-23, 262), p=0.0990		167 (83, 250), p=0.0001		241 (124, 358), p<0.0001	
Proportion of patients with ≥ 10% decline in FVC at Week 48	9/32 (28.1%)	3/30 (10.0%)	17/91 (18.7%)	10/93 (10.8%)	N/A	N/A

ΔLSM = difference in least squares mean; BL = baseline; CI = confidence interval; FVC = forced vital capacity; LSM = least square mean; ppFVC = percent predicted forced vital capacity; SSc-ILD = systemic sclerosis with interstitial lung disease; TCZ = tocilizumab.

Note: Statistical significance (p < 0.05) of the primary endpoint (WA29767: mRSS at Week 48, WA27788: mRSS at Week 24) was not met; therefore, subsequent secondary endpoints were not formally tested for statistical significance. All observed p-values other than the primary endpoint are considered nominal.

Source: 2.7.3 SCE, Table 4, Table 8, Table 9, Table 10, Table 11, Table 19.

CHMP comment

Both studies did not meet the primary endpoints (no significant difference between TCZ and placebo arms in mean change from baseline in mRSS at Week 48 and Week 24 in Studies WA29767 and WA27788, respectively). However, both studies showed a numeric improvement in mean change in mRSS for the TCZ arm relative to the placebo arm at Week 48 (Table 45).

In both studies a difference in FVC decline was observed between TCZ and placebo.

A statistically nominally significant treatment effect in favour of TCZ over placebo was seen in the median change from baseline in ppFVC at Week 48 in both Study WA29767 (difference of medians between

treatment groups 3.3%; nominal p = 0.0015) and Study WA27788 (difference of medians between treatment groups 4.2%; nominal p = 0.0373).

Replication is acknowledged in principle, but there remain substantial uncertainties on the possibility of a false positive, related to the probability of a Type-I-error, upward bias in ppFVC estimates conditional on post-hoc selection of a promising result (see discussion of replication in the statistical methods).

Change from baseline in observed FVC was lower in the TCZ arm than the placebo arm in both studies, and the difference in least squares means between treatment arms was similar: 167 mL in Study WA28767 and 120 mL WA27788

The applicant claims that the effects of TCZ were more pronounced in subjects with SSc-ILD, however, the median change from baseline to week 48 in ppFVC is rather similar in patients with SSc (-3.9 vs. -0.6) and SSc-ILD (-4.0 vs. -0.6). It is acknowledged that LSmean estimates differ somewhat between the overall population and the subgroup in study WA29767, but the applicant argued elsewhere that the MMRM model was possibly not suitable due to the underlying statistical assumptions (last minute change of model to a non-parametric model). Thus, there is uncertainty whether the post-hoc subgroup of SSc-ILD patients really is the driver of the results in ppFVC. Detailed results in mutually exclusive subgroups were not presented.

The applicant is asked to present detailed results on efficacy in mutually exclusive subgroups of SSc-ILD at baseline (i.e. please present results in those patients without SSc-ILD as well, and using the non-parametric as well as the parametric model for ppFVC) (OC).

No meaningful difference in mean change from baseline in mRSS at Week 48 for patients with SSc-ILD was observed.

In conclusion both studies failed to demonstrate a treatment benefit of TCZ over PBO in the overall SSc population with regard to measurement of skin thickness (mRSS). The primary endpoint was not met. An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Given the presumed influence of elevated IL-6 on the skin involvement this outcome is unexpected.

In both studies an effect of TCZ treatment on prevention of FVC decline was suggested. The results are further supported by analysis of a post-hoc subpopulation.

The outcome of the two studies could be seen as hypothesis generating and further evaluation in a pre-specified SSc-ILD population ideally stratified according different disease stages might support the hypothesis.

2.5.5. Supportive study(ies)

The supportive Study WA27788 is discussed above

Ancillary analyses

CHMP comment

The main evidence supporting the indication claim is derived from a post-hoc subgroup analysis of the secondary endpoint ppFVC in SSC-ILD patients identified in Study WA29767. This analysis is discussed above together with the main study.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The submission is supported by the pivotal study WA29767 and the supportive study WA27788. Both studies have a quite similar design.

The pivotal study consisted of two periods: a 48-week, double-blind (DB), placebo-controlled period, followed by a 48-week open-label (OL) treatment period (from Week 48 to 96). The indication claim is supported by the Week 48 data; the Week 96 data are included the integrated safety analysis.

The patient populations included in Study WA27788 and WA29767 are largely similar. Patients with the diagnosis of SSc were enrolled, organ involvement e.g. cardiac, renal or lung involvement was not an including criterion. Moreover, patients with history of previous/concomitant pulmonary disease defined by certain ppFVC and ppDLCO level were excluded from the study. However, the indication claim based on a post-hoc subgroup analysis in patients with SSc-ILD at a certain degree as relevant population. (OC)

In both studies patients received TCZ 162 mg SC QW versus placebo for 48 weeks during the double-blind treatment period, followed by the same dose in the open label treatment period.

In Study WA29767 the primary efficacy objective was assessed at Week 48, while originally in Study WA27788 the assessment of the primary efficacy objective was planned for week 24. In order to provide comparative results, the secondary efficacy objective, change from baseline in mRSS at Week 48, is used for comparison of the outcome of the two studies. For the purpose of the comparison this approach can be accepted.

Of note, in Study WA29767 measurement of ppFVC at Week 48 was a secondary objective, while in Study WA27788 it was an exploratory objective. However, outcome of this measurement is used as main evidence in supporting the claimed indication.

Sample size considerations are acceptable. For both studies, it is noted that a relevant drop-out was expected (15-20%). In both studies there is no clear justification for the assumptions in the sample size considerations in the study protocol. It is assumed that the assumptions for study WA29767 were based on results from study WA27788, and this would be reasonable.

A 1:1 randomization is endorsed.

The stratification variables differ, and this may reflect that study WA29767 was designed to confirm findings from study WA27788. Stratification in both studies seems feasible and reasonable. However, it is not clear why randomization was not stratified by study site or geographic region. The applicant is asked to clarify and to discuss whether lack of such stratification might have had any impact on study results, in particular in the subgroup of patients with SSc-ILD (OC).

Importantly, randomization was not stratified for SSc-ILD, suggesting that there was no prospective hypothesis for this subgroup.

There are some inconsistencies in the way stratification is described in the study protocol for study WA29767 (i.e. stratification is not mentioned in the section "method of treatment assignment" and the stratum is not included in the listings of treatment allocation). The applicant is asked to please confirm that IL-6 level (< 10; ≥ 10 pg/mL) at screening was used as a stratification factor for randomization and describe the method of randomized allocation (e.g. permuted block randomization with block length x) (OC).

Double blinding is endorsed, and the methods to ensure blinding are in principle appropriate.

It is noted that the applicant has defined a set of variables (laboratory) for which access of personnel was planned to be restricted. This is endorsed.

Study WA29767

Overall, the current application has a focus on the potential effect of tocilizumab on secondary endpoints (change in ppFVC and observed FVC from baseline to week 48) in a subgroup of patients (SSc-ILD). The planned statistical methodology had a different focus, namely to show that tocilizumab is efficacious in reducing mRSS in patients with SSc. The primary endpoint was not met.

Although the methods are in principle acceptable for the originally planned objective, the results supporting the application are not generated with the same scientific/statistical rigor, and are considered exploratory. An ad-hoc interpretation may be possible, but has substantial uncertainties.

Estimands for FVC or for SSc-ILD are not discussed. Given that the analysis of FVC was planned to use the same methodology as the primary analysis, it may be assumed that the estimand for FVC is similar to the primary estimand defined for mRSS, and this could be acceptable.

Only the intercurrent event of premature discontinuation of study drug is discussed, whereby it was defined that data would be used irrespective of this intercurrent event. This approach is endorsed. Further intercurrent event are not discussed and are therefore assumed to be ignored as well.

A two-sided significance level of 5% was defined and is acceptable. The primary endpoint was not met, results on secondary endpoints, in particular FVC, are descriptive only.

Multiplicity control for the secondary endpoint of ppFVC might provide some reassurance, however the support through pre-specification of hypotheses for change in ppFVC and observed FVC to Week 48 is rather weak. Procedures to account for multiplicity were not specified in the protocol, but only in the SAP. The first version of the SAP (Version 1), in which the multiplicity approach for secondary endpoints was defined, is dated 08 Aug 2017. This is approximately 6 months after the last patient was randomized (14 Feb 2017). Although it is acknowledged that mean change of FVC from baseline to week 48 was mentioned in early versions of the study protocol as one of several secondary endpoints, the importance of FVC hypotheses for statistical testing is not well supported by early, prospective documentation.

Results across the pivotal and supportive study might be considered a replication. However, there are substantial uncertainties. It seems that the applicant would have considered a benefit shown at least under the following outcomes: primary endpoint met or any secondary or exploratory finding from study WA27788 replicated with nominal statistical significance at the one-sided level of 0.025. This would result in a much higher Type-I-error probability than claimed by the applicant (OC).

There is concern about upward-bias in ppFVC estimates due to the multiplicity of analysing several secondary/exploratory endpoints: Conditional on selecting the outcome with the smallest p-value, even under the null hypothesis of no effect the distribution of the estimator may no longer be centered around zero, but may be biased depending on the number of endpoints analysed. The applicant is asked to discuss and provide bias-adjusted estimates for ppFVC (OC).

The primary analysis was planned to be conducted in all randomized patients who received study treatment. Of note, the current application focusses on SSc-ILD. SSc-ILD is a subgroup and was not prospectively specified as such. Prospective documentation of the subgroup expectation (e.g. through stratification of randomization) might have provided reassurance, but SSc-ILD discussions appear to be entirely post-hoc.

The primary analysis model is a longitudinal mixed model with several covariates and interaction terms. The covariates (treatment, visit, stratification factor IL-6 at baseline and baseline value of mRSS) and

respective covariate*visit interaction terms appear reasonable. Nonetheless, there may be a risk of overfitting, given the planned sample size of n=210, and no imputation of missing values.

It was planned that the analysis of FVC endpoints would use the same methodology as specified for the primary analysis. Eventually, the assumption of normally distributed FVC was not considered plausible and a non-parametric model was applied (Van Elteren test stratified by screening IL-6 level (<10; ≥10 pg/mL)). It is acknowledged that results from a MMRM (as planned) are provided as well.

It is assumed that the MMRM for ppFVC is adjusted for baseline ppFVC (instead of mRSS). The applicant is asked to confirm or provide results from a respective model adjusted for baseline ppFVC. Please provide further information on the model, including point estimates, confidence intervals and p-values for the coefficients of all fixed effects included in the model (OC).

Missing data in continuous variables were not imputed. Instead the longitudinal model assumes MAR. This assumption may be challenged, as it can be assumed that data would be missing for a reason. The extent of missing values is considered relevant. It is acknowledged that sensitivity analyses were provided (tipping point analyses).

The applicant is asked to provide individual longitudinal FVC data for those patients who had missing data in the FVC change from baseline to week 48 analysis (e.g. in a spaghetti plot) and reasons for missingness. Please discuss the plausibility of (i) the MAR assumption (ii) the tipping point derived from the tipping point analyses for these patients (ppFVC difference of 16 points between placebo and tcz patients, according to figure 7 of the CSR) (OC).

A futility analysis was conducted after the first 76 patients reached the Week 24 visit or withdrew. According to the applicant, this futility analysis was prespecified, but apart from the intention to do a futility analysis, there are no details on the timing or methodology in the study protocol. A blinded futility analysis does not raise any concerns in principle, but the lack of prospective documentation in the study protocol is not optimal.

The protocol for the pivotal study WA29767 was amended five times. The first and second protocol amendments (Version 2 and Version 3) were implemented before the first patient was randomized. None of the changes in the protocol are considered to have an impact on the data supporting the claimed indication.

For Study WA29767 it is reported that he most common protocol deviations were baseline high-resolution computed tomography (HRCT) scans performed prior to randomization or other informed consent deviations, with slight imbalances noted between treatment arms. This does not impact the integrity of the study.

Patients demographics as well as baseline disease characteristics are well balanced between the groups. Some imbalance was seen in the number of patients recruited by country.

Regarding lung involvement, both placebo and TCZ arms had a baseline ppFVC indicative of normal lung function to mild impairment (means: 83.9% and 80.3%, respectively; medians: 85.9% and 80.0%, respectively), and baseline ppDLCO indicative of mild impairment (means: 76.8% and 74.4%, respectively; medians: 75.6% and 71.5%, respectively). However, a total of 66 patients (28 in the placebo arm and 38 in the TCZ arm) were reported as having previous or concurrent ILD at screening. At study start, ILD was ongoing with treatment in 8 patients in the placebo arm and 10 patients in the TCZ arm (based on manual review of data). A post-hoc subgroup analysis in patients with SSc-ILD was performed to support the indication claim. A total of 136 patients (68 in the placebo group and 68 in the TCZ group) had SSc-ILD at baseline. Thus, the numbers reported in the different sections are contradictory, please clarify. (OC)

Study WA27788

The methods are overall agreeable for an exploratory study. However, FVC endpoints were exploratory and patients with SSc-ILD were not considered as a subgroup in the study protocol.

The study failed to demonstrated a statistically significant treatment effect of TCZ over PBO with regard to the primary and secondary efficacy endpoints, namely mRSS, health assessment questionnaire-disability index, patient's global assessment, physician's global assessment, scleroderma health assessment questionnaire, FACIT-fatigue and pruritus 5-D itch scale.

The exploratory analysis suggests that TCZ has a benefit over placebo on endpoints related to lung function i.e. ppFVC a statistically nominally significant treatment effect in favour of TCZ over placebo was seen. The effect on observed FVC showed a trend for a benefit of TCZ, no nominal statistical significance was reached. Diffusion Capacity of the Lung for Carbon Monoxide at Week 48, the placebo arm and TCZ arm showed similar mean and median change from baseline in ppDLCO.

Efficacy data and additional analyses

Study WA29767

The primary efficacy endpoint was planned to be the mean change in mRSS from baseline to Week 48. Measurement of skin thickness is used as a surrogate for disease activity, severity and mortality. An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Moreover,skin thickness score was found to significantly correlate with quantitative measurements of lung involvement in patients with SSc (Matsuda et al, 20219: https://doi.org/10.1186/s13075-019-1919-6). Thus, the endpoint is considered clinically meaningful.

In both treatment groups patients had moderate skin involvement that was comparable at baseline. The Week 48 results showed a numerical improvement in the TCZ arm, but the results were not statistically significant or considered clinically meaningful. The primary endpoint was not met.

A difference in the proportion of patients with an mRSS improvement of >40% and >60% in favour of TCZ over placebo was not observed, a difference in the proportion of patients with an mRSS improvement of >20% in favour of TCZ over placebo was seen.

A favourable effect on the overall disease activity could not be demonstrated.

Forced vital capacity at week 48 was the was a key secondary endpoint for the study. At baseline, the ppFVC values in both arms were indicative of normal to mildly impaired lung function. At Week 48 a median change from baseline in favor of TCT was observed suggesting that TCZ has an impact in conservation of the lung function.

Regarding further secondary endpoints, a numerical difference in TTF was seen in favour for TCZ compared to placebo. This numerical difference was seen for all TTF defining event i.e. death, decline in percent-predicted FVC > 10% relative to baseline or 20% increase in mRSS and an increase in mRSS of ≥ 5 points occurrence of a predefined SSc-related complication. The results are not statistically significant and not considered clinical meaningful.

Health assessment questionnaire-disability index and patient's and physician's global assessments did not show a notable difference between treatment arms.

Comparing the treatment effect defined as change from baseline in the mRSS at Week 48 for the subgroups based on IL-6 levels at screening and for subgroups of baseline CRP, ESR, platelet count, baseline disease duration, baseline mRSS score, sex, and age suggest that certain subgroups of patients experienced a greater mean improvement in mRSS on TCZ compared with placebo. However, because a

treatment effect was not shown in the overall population (primary endpoint not met), an interpretation of subgroup findings is difficult. 95% CIs were wide and generally overlapping with the mean treatment difference in the overall population, no firm conclusions on these subgroups

For Study WA29767 a post hoc subgroup analyses in patients with SSc-ILD at baseline were performed for ppFVC, observed FVC, and mRSS. Detailed information on patients without ILD was not presented.

The applicant is asked to present detailed results on efficacy in mutually exclusive subgroups of SSc-ILD at baseline (i.e. please present results in those patients without SSc-ILD as well, and using the non-parametric as well as the parametric model for ppFVC) (OC).

For Study WA29767 it is reported that he most common protocol deviations were baseline high-resolution computed tomography (HRCT) scans performed prior to randomization or other informed consent deviations, with slight imbalances noted between treatment arms.

High-resolution computed tomography (HRCT) scans were performed and as described in the Summary clinical safety, ILD was identified visually post-hoc by a thoracic radiologist using a diagnostic algorithm for SSc as the presence of ground-glas opacification and/or fibrosis with a basal predominance. Potential causes other than SSc for the pattern of ground-glass opacification were excluded.

This approach is questionable, HRCT is used to define the relevant sub-population to support the i.e. indication claim, i.e. SSC-ILD patients while patient with history of previous/concomitant pulmonary disease defined by certain ppFVC and ppDLCO level were excluded from the study (see inclusion / exclusion criteria). Please justify the approach. (OC)

Further there is no apparent correlation between the results of the scan and the lung function which does not support the validity of the chosen endpoints for the subgroup analysis i.e. ppFVC, observed FVC.

A difference was seen in the median change from baseline ppFVC at Week 48 in favour of the TCZ arm over placebo among patients with SSc-ILD (difference between treatment groups 3.40%; nominal p = 0.0016). The result was nominally statistically significant. At Week 48, there was a improvement with TCZ compared with placebo in the mean change from baseline in observed FVC among patients with SSc-ILD (difference between treatment groups 241 mL). The results were nominally statistically significant.

The results based on secondary endpoints evaluated in a post-hoc subgroup analysis in a poorly defied population and thus are not generated with the same scientific/statistical rigor, and are considered exploratory. An ad-hoc interpretation may be possible, but has substantial uncertainties.

2.5.7. Conclusions on the clinical efficacy

Both studies did not meet the primary endpoints (no significant difference between TCZ and placebo arms in mean change from baseline in mRSS at Week 48 and Week 24 in Studies WA29767 and WA27788, respectively). However, both studies showed a numeric improvement in mean change in mRSS for the TCZ arm relative to the placebo arm at Week 48 (Table 45).

In both studies a difference in FVC decline was observed between TCZ and placebo.

An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Moreover, in a Japanese study skin thickness score was found to significantly correlate with quantitative measurements of lung involvement in patients with SSc (Matsuda et al, 20219: https://doi.org/10.1186/s13075-019-1919-6). Under the light of these data the study outcome i.e. no effect on mRSS under TCZ therapy but a favourable effect on FVC decline under therapy is not understandable. The MAH is requested to comment the outcome under light of this study (MO).

A statistically nominally significant treatment effect in favour of TCZ over placebo was seen in the median change from baseline in ppFVC at Week 48 in both Study WA29767 (difference of medians between treatment groups 3.3%; nominal p = 0.0015) and Study WA27788 (difference of medians between treatment groups 4.2%; nominal p = 0.0373).

Despite replication, this finding has uncertainties, related to the possibility of a type-I-error and upward bias in estimates (two OCs).

A similar clinically difference occurred for observed FVC. Change from baseline in observed FVC was lower in the TCZ arm than the placebo arm in both studies, and the difference in least squares means between treatment arms was similar: 167 mL in Study WA28767 and 120 mL WA27788

The role of the post-hoc subgroup of SSc-ILD is not clear and further information is requested (OC).

No meaningful difference in mean change from baseline in mRSS at Week 48 for patients with SSc-ILD was observed.

In conclusion both studies failed to demonstrate a treatment benefit of TCZ over PBO in the overall SSc population with regard to measurement of skin thickness (mRSS). The primary endpoint was not met. An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Given the presumed influence of elevated IL-6 on the skin involvement this outcome is unexpected.

In both studies an effect of TCZ treatment on prevention of FVC decline was suggested. The results are further supported by analysis of a post-hoc subpopulation.

The outcome of the two studies could be seen as hypothesis generating and further evaluation in a pre-specified SSc-ILD population ideally stratified according different disease stages might support the hypothesis.

2.6. Clinical safety

Introduction

The clinical safety data supporting this application are derived from the pivotal Phase III Study WA29767 (otherwise known as "FocuSSced") and the supportive Phase II/III Study WA27788 (otherwise known as "FaSScinate"), both conducted in patients with SSc.

Both studies evaluated the efficacy and safety of TCZ compared with placebo in adult patients with SSc for a 48-week double-blind treatment period, followed by a 48-week open-label treatment period (total of 96 weeks).

The safety objectives of the two studies were similar. Both included:

- To evaluate the safety of TCZ SC compared with placebo
- To assess the long-term safety of TCZ SC
- To characterise the immunogenic potential of TCZ SC by measuring anti-drug antibodies (ADA)

The main difference between the two studies is that assessing the number of digital ulcers was changed from an efficacy objective in Study WA27788 to a safety objective in Study WA29767.

Data from the two studies were pooled for placebo-controlled and TCZ treated patients up to Week 48 and then again at Week 96 for TCZ treated patients for long-term safety. The safety results based on the pooled data of the two studies.

In addition, the following supportive data are presented in this SCS:

- Safety data from published literature on clinical reports of patients with SSc treated with TCZ outside of Roche-sponsored clinical studies

In both studies patients were allowed to receive the escape therapy (i.e., any immuno-modulating agent discussed with the Medical Monitor) in case of worsening SSc symptoms. However, in Study WA29767, treatment of SSc-ILD (as per local treatment guidelines but excluding cyclophosphamide) or escape therapy could be initiated as early as Week 16 in patients with a decrease of >10 relative percentage points in percent predicted forced vital capacity (ppFVC) compared with baseline. In addition, at Week 24 methotrexate and hydroxychloroquine could be used for patients.

with worsening SSc complications and/or mRSS of a >5 points and $\geq$20% increase, relative to baseline. Other immuno-modulating drugs (such as mycophenolate mofetil) could be used for patients who were intolerant or inadequate responders to methotrexate or hydroxychloroquine.

In Study WA27788, escape therapy options were limited to methotrexate, hydroxychloroquine, or mycophenolate mofetil, and could be initiated after Week 24 for worsening skin symptoms (defined as $\geq$20% worsening in mRSS from baseline) and/or worsening SSc-associated complications.

Other concomitant treatments for SSc complications and disease manifestations (e.g., prostacyclin at study entry for treatment of Raynaud phenomenon or digital ulcers, oralcorticosteroids or nonsteroidal anti-inflammatory drugs [NSAIDs], and analgesics), including treatments for new and existing organ complications were allowed during the double-blind treatment period in both Studies WA29767 and WA27788.

Safety definitions

Injection-site reactions (ISRs) were AEs that occurred at the site of injection. Hypersensitivity events were defined as AEs occurring immediately after or within 24 hours of the end of injection (excluding ISRs) that were not deemed unrelated to study drug. Clinically significant hypersensitivity events were AEs occurring immediately after or within 24 hours of the end of injection (excluding ISRs) that were not deemed unrelated to study drug, and that led to study treatment discontinuation. These events were reported as AESIs in Study WA29767 and Study WA27788.

Selected AEs were grouped and predefined as AESI for the purposes of expedited reporting, using Standardised MedDRA Queries (SMQs), System Organ Classes (SOCs), or AE Grouped Terms (AEGTs) defined by the Sponsor's Drug Safety department, based on the established safety profile of TCZ as well as safety concerns in the SSc population

Patient exposure

In both studies, the population for safety analyses was the Safety Population, defined as all randomised patients who received at least one dose of study drug and provided data from at least one post dose safety assessment (withdrawal, AE, death, laboratory assessment, or vital signs assessment). Patients were grouped according to the treatment actually received.

Two pooled Safety Populations are discussed

- Treatment up to Week 48 (n=297): This population includes all safety-evaluable patients enrolled in Studies WA29767 and WA27788 who had safety data up to the completion of the Week 48 visit.

Of note, some AEs reported in the Study WA27788 Update (Week 48) CSR are not reported in pooled safety analysis of Week 48 in this SCS. This occurred because of the data cut rules (the WA27788 Week

96 dataset was used for analysis), meaning that some AEs now fall outside of the Week 48 cut-off date of Study WA27788 Update CSR. A listing of these events is provided, including a total of 7 patients with 9 AEs. One patient experienced a Grade 3 SAE of osteomyelitis that was related to study medication and resolved as of the CCOD (Refer to Study WA27788 Update CSR Report Number 1061598, Patient Narrative 240122/5553).

- TCZ Treatment up to Week 96 (n=267): This population includes long-term safety data from all safety-evaluable patients enrolled in Studies WA29767 and WA27788 up to Week 96.

Treatment up to Week 48

The median treatment duration up to Week 48 was the same in both treatment arms of both studies (337.0 days: ranging from 30 to 344 days in the placebo arm and 15 to 378 days in the TCZ arm in WA27788; 8 to 400 days in the placebo arm and 15 to 365 days in the TCZ arm in WA29767) (Table 46), and the majority of the patients in both studies had a treatment duration between 333 and 339 days.

The median duration of exposure to the study drug was also the same in both treatment arms of both studies (0.920 years: ranging from 0.08 to 0.94 years in the placebo arm and 0.04 to 1.38 years in the TCZ arm in WA27788; 0.02 to 1.09 years in the placebo arm and 0.04 to 1.11 years in the TCZ arm in WA29767). Given that more than double the number of patients were treated in Study WA29767 compared with Study WA27788, the number of PY of exposure, used for the calculation of AE rates, was higher in Study WA29767 (90.64 PY in the placebo arm and 89.45 PY in the TCZ arm) compared with Study WA27788 (33.40 PY in the placebo arm and 32.55 PY in the TCZ arm), but was similar between treatment arms within each study.

Compliance to treatment was high (>85% mean dose intensity) in both studies.

The mean number of doses taken was higher in Study WA29767. The majority of patients (>60% of patients in either arm) in both studies missed at least one dose(133/210 [63.3%] patients in Study WA29767 and 59/87 [67.8%] patients in Study WA27788).

Table 46 Treatment Duration and Dose Intensity up to Week 48 (Safety Population)

Treatment Duration and Dose Intensity (Week 48), Safety Population
Project: CN119351

	WA27788 (N=87)		WA29767 (N=210)	
	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)
Treatment duration (D)				
n	44	43	106	104
Mean (SD)	277.6 (104.6)	274.0 (110.8)	303.8 (79.1)	308.9 (78.0)
Median	337.0	337.0	337.0	337.0
Min - Max	30 - 344	15 - 378	8 - 400	15 - 365
Dose intensity (%)				
n	44	43	106	104
Mean (SD)	86.8 (21.6)	86.1 (22.5)	91.0 (15.3)	91.1 (18.9)
Median	97.9	97.9	97.9	97.9
Min - Max	21 - 102	12 - 102	35 - 119	8 - 108
Number of doses				
n	44	43	106	104
Mean (SD)	38.2 (15.1)	37.3 (15.7)	41.7 (11.2)	42.4 (11.0)
Median	47.0	46.0	47.0	47.0
Min - Max	4 - 49	2 - 49	1 - 57	2 - 52
Total cumulative dose (mg)				
n	0	43	0	104
Mean (SD)	NE (NE)	6035.4 (2542.6)	NE (NE)	6866.3 (1782.0)
Median	NE	7452.0	NE	7614.0
Min - Max	NE - NE	324 - 7938	NE - NE	324 - 8424
Missed doses				
n	44	43	106	104
No missed dose	15 (34.1%)	13 (30.2%)	36 (34.0%)	41 (39.4%)
At least one missed dose	29 (65.9%)	30 (69.8%)	70 (66.0%)	63 (60.6%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose of TCZ plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses.
(D) is days.

Program: /opt/BIOSTAT/prod/cn119351/p11935h/t_ex.sas
Output: /opt/BIOSTAT/prod/cn119351/p11935h/reports/t_ex_SE_W48.out
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TCZ Treatment up to Week 96

In the TCZ treatment up to Week 96 data pooled population, the median TCZ treatment duration was 344.0 days (range: 15-696 days) (

Table 47). The pooled median duration of TCZ exposure was 1.112 years.

Table 47 Treatment Duration and Dose Intensity (TCZ Treatment up to Week 96, Safety Population)

Treatment Duration and Dose Intensity (All Exposure), Safety Population
Project: SSc Pooled Q22020

	WA27788 (N=74)	WA29767 (N=193)	Pooled (N=267)
	TCZ 162 mg qw SC (N=74)	TCZ 162 mg qw SC (N=193)	TCZ 162 mg qw SC (N=267)
Treatment duration (D)			
n	74	193	267
Mean (SD)	417.5 (227.1)	470.3 (194.3)	455.7 (204.9)
Median	344.0	345.0	344.0
Min - Max	15 - 685	15 - 696	15 - 696
Number of doses			
n	74	193	267
Mean (SD)	55.4 (31.2)	63.3 (27.6)	61.1 (28.8)
Median	49.0	48.0	48.0
Min - Max	2 - 97	2 - 97	2 - 97
Total cumulative dose (mg)			
n	74	193	267
Mean (SD)	8969.1 (5055.6)	10255.5 (4476.4)	9899.0 (4670.2)
Median	7938.0	7776.0	7776.0
Min - Max	324 - 15714	324 - 15714	324 - 15714
Missed doses			
n	74	193	267
No missed dose	23 (31.1%)	58 (30.1%)	81 (30.3%)
At least one missed dose	51 (68.9%)	135 (69.9%)	186 (69.7%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose of TCZ plus one day.
(D) is days.
Program: root/clinical_studies/RO4877533/share/pool_SSc_Q22020/prod/program/t_ex.sas
Output: root/clinical_studies/RO4877533/share/pool_SSc_Q22020/prod/output/t_eX_SE_ALL.out
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Previous and concurrent diseases

The SOCs with the highest proportion of patients (☐30% of patients in any arm) with at least one previous or concurrent disease or condition (other than SSc) at baseline were:

- Vascular Disorders (Study WA29767: 49.1% placebo vs. 47.1% TCZ; Study WA27788: 77.3% placebo vs. 79.1% TCZ)
- Gastrointestinal Disorders (Study WA29767: 50.0% placebo vs. 48.1% TCZ; Study WA27788: 65.9% placebo vs. 74.4% TCZ)
- Musculoskeletal and Connective Tissue Disorders (Study WA29767: 45.3% placebo vs. 37.5% TCZ; Study WA27788: 54.5% placebo vs. 65.1% TCZ)
- Metabolism and Nutrition Disorders (Study WA29767: 27.4% placebo vs. 31.7% TCZ; Study WA27788: 20.5% placebo vs. 32.6% TCZ)
- Respiratory, Thoracic and Mediastinal Disorders (Study WA29767: 21.7% placebo vs. 14.4% TCZ; Study WA27788: 52.3% placebo vs. 34.9% TCZ)
- Skin and Subcutaneous Tissue Disorders (Study WA29767: 18.9% placebo vs. 20.2% TCZ; Study WA27788: 43.2% placebo vs. 34.9% TCZ)
- Nervous System Disorders (Study WA29767: 22.6% placebo vs. 5.8% TCZ; Study WA27788: 31.8% placebo vs. 25.6% TCZ)

The two treatment arms were generally well balanced in both studies with respect to other previous or concurrent diseases. However, notable differences between treatment arms were seen in the following SOCs, wherein events were reported more commonly in the placebo arm (difference of >10% of patients between arms): in Study WA29767, Nervous System Disorders (22.6% placebo vs. 5.8% TCZ) and General Disorders and Administration Site Conditions (13.2% placebo vs. 2.9% TCZ); in Study WA27788, Respiratory, Thoracic and Mediastinal Disorders (52.3% placebo vs. 34.9% TCZ) and Immune System Disorders (18.2% placebo vs. 7.0% TCZ). Previous or concurrent diseases were more frequent in the TCZ arm (difference of >10% of patients between arms) in the following SOCs: in Study WA27788: Musculoskeletal and ConnectiveTissue Disorders (54.5% placebo vs. 65.1% TCZ) and Metabolism and Nutrition Disorders (20.5% placebo vs. 32.6% TCZ).

Previous and concomitant medications

The majority of patients in both studies had received previous medications that were stopped prior to the first dose of study drug. In both studies, more than 10% of patients in any treatment arm received medications from the following classes before starting the study for treatment of SSc:

- Anti-metabolites (Study WA29767: 23.6% placebo vs. 26.0% TCZ; Study WA27788: 29.5% placebo vs. 34.9% TCZ): mainly, methotrexate
- Immunosuppressants (Study WA29767: 11.3% placebo vs. 14.4% TCZ; Study WA27788: 11.4% placebo vs. 18.6% TCZ): mainly, mycophenolate mofetil
- Folic acid and derivatives (Study WA29767: 13.2% placebo vs. 14.4% TCZ; Study WA27788: 13.6% placebo vs. 14.0% TCZ): mainly, folic acid
- Steroids (Study WA29767: 17.0% placebo vs. 14.4% TCZ; Study WA27788: 6.8% placebo vs. 14.0% TCZ): mainly, prednisone
- Prostaglandins (Study WA29767: 5.7% placebo vs. 10.6% TCZ; Study WA27788: 9.1% placebo vs. 7.0% TCZ): mainly, alprostadil

The proportion of patients who received previous or concomitant medications, excluding medications that ended prior to first study treatment dose, was comparable between treatment arms in both studies. The most common medication classes (>30% of patients in any treatment arm) were:

- Proton pump inhibitors (Study WA29767: 58.5% placebo vs. 60.6% TCZ; Study WA27788: 90.9% placebo vs. 86.0% TCZ): mainly, omeprazole
- Steroids (Study WA29767: 51.9% placebo vs. 52.9% TCZ; Study WA27788: 40.9% placebo vs. 60.5% TCZ): mainly, prednisone and prednisolone
- Vitamins and minerals (Study WA29767: 45.3% placebo vs. 49.0% TCZ; Study WA27788: 43.2% placebo vs. 39.5% TCZ): mainly, cholecalciferol
- Calcium channel blocking agents (Study WA29767: 35.8% placebo vs. 39.4% TCZ; Study WA27788: 47.7% placebo vs. 46.5% TCZ): mainly, nifedipine and amlodipine
- Analgesics (Study WA29767: 36.8% placebo vs. 33.7% TCZ; Study WA27788: 45.5% placebo vs. 53.5% TCZ): mainly, paracetamol
- NSAIDs (Study WA29767: 38.7% placebo vs. 28.8% TCZ; Study WA27788: 61.4% placebo vs. 39.5% TCZ): mainly, ibuprofen

In both studies, in the following classes, more patients in the placebo arm had received previous-concomitant and concomitant medications, when compared with the TCZ arm:

- Immunosuppressants (Study WA29767: 14.2% placebo vs. 5.8% TCZ; Study WA27788: 11.4% placebo vs. 2.3% TCZ): mainly, mycophenolate mofetil as escape therapy
- NSAIDs (presented above): mainly, ibuprofen

In Study WA29767 alone, in addition to immunosuppressants and NSAIDs, more patients in the placebo arm also received anti-convulsants (mainly gabapentin), anti-infectives (anti-fungals [mainly, fluconazole and nystatin] and miscellaneous anti-microbials), and laxative and stool softeners (mainly, senna). More patients in the TCZ arm received SSRIs (mainly, fluoxetine). In Study WA27788 alone, more patients in the TCZ arm received steroids (mainly, prednisone), ACE inhibitors (mainly, ramipril), and cephalosporin antibiotics (mainly, cephalexin).

Adverse events

Treatment up to Week 48

An overview of key safety results in the pooled population for the double-blind period is presented in Table 48:

Table 48 Overview of Adverse Events by Incidence and Rate up to Week 48 (Safety Population)

	WA27788 (N=87)		WA29767 (N=210)		Pooled (N=297)	
	PBO 162 mg QW SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg QW SC (N=106)	TCZ 162 mg QW SC (N=104)	PBO 162 mg QW SC (N=150)	TCZ 162 mg QW SC (N=147)
Exposure (PY)	33.40	32.55	90.64	89.45	124.05	122.00
Patients with:						
Any AE, n (%)	40 (90.9%)	42 (97.7%)	82 (77.4%)	89 (85.6%)	122 (81.3%)	131 (89.1%)
Total no. of AEs	240	283	493	422	733	705
Rate per 100 PY	718.5	869.5	543.9	471.8	590.9	577.9
(95% CI)	(630.4, 815.3)	(771.1, 976.9)	(496.9, 594.1)	(427.8, 519.0)	(548.9, 635.3)	(536.0, 622.2)
Any SAE, n (%)	15 (34.1%)	14 (32.6%)	18 (17.0%)	13 (12.5%)	33 (22.0%)	27 (18.4%)
No. of AEs	24	23	30	14	54	37
Rate per 100 PY	71.8	70.7	33.1	15.7	43.5	30.3
(95% CI)	(46.0, 106.9)	(44.8, 106.0)	(22.3, 47.2)	(8.6, 26.3)	(32.7, 56.8)	(21.4, 41.8)
Grade 3 SAEs, n (%)	12 (27.3%)	10 (23.3%)	11 (10.4%)	11 (10.6%)	23 (15.3%)	21 (14.3%)
No. of AEs	18	16	16	12	34	28
Rate per 100 PY	53.9	49.2	17.7	13.4	27.4	23.0
(95% CI)	(31.9, 85.2)	(28.1, 79.8)	(10.1, 28.7)	(6.9, 23.4)	(19.0, 38.3)	(15.3, 33.2)
Grade 4 SAEs, n (%)	5 (11.4%)	3 (7.0%)	7 (6.6%)	0	12 (8.0%)	3 (2.0%)
No. of AEs	5	3	7	0	12	3
Rate per 100 PY	15.0	9.2	7.7	0	9.7	2.5
(95% CI)	(4.9, 34.9)	(1.9, 26.9)	(3.1, 15.9)	(0.0, 4.1)	(5.0, 16.9)	(0.5, 7.2)
Deaths, n (%)	1 (2.3%)	3 (7.0%)	3 (2.8%)	1 (1.0%)	4 (2.7%)	4 (2.7%)
No. of AEs	1	3	3	1	4	4
Rate per 100 PY	3.0	9.2	3.3	1.1	3.2	3.3
(95% CI)	(0.1, 16.7)	(1.9, 26.9)	(0.7, 9.7)	(0.0, 6.2)	(0.9, 8.3)	(0.9, 8.4)
AEs leading to withdrawal, n (%)	5 (11.4%)	6 (14.0%)	11 (10.4%)	6 (5.8%)	16 (10.7%)	12 (8.2%)
No. of AEs	5	6	11	6	16	12
Rate per 100 PY	15.0	18.4	12.1	6.7	12.9	9.8
(95% CI)	(4.9, 34.9)	(6.8, 40.1)	(6.1, 21.7)	(2.5, 14.6)	(7.4, 20.9)	(5.1, 17.2)
AEs leading to dose modification or interruption						
n (%)	10 (22.7%)	13 (30.2%)	27 (25.5%)	20 (19.2%)	37 (24.7%)	33 (22.4%)
No. of AEs	19	17	42	36	61	53
Rate per 100 PY	56.9	52.2	46.3	40.2	49.2	43.4
(95% CI)	(34.2, 88.8)	(30.4, 83.6)	(33.4, 62.6)	(28.2, 55.7)	(37.6, 63.2)	(32.5, 56.8)
AESI						
Infections and Infestations, n (%)	22 (50.0%)	26 (60.5%)	53 (50.0%)	54 (51.9%)	75 (50.0%)	80 (54.4%)
No. of AEs	45	43	108	88	153	131
Rate per 100 PY	134.7	132.1	119.1	98.4	123.3	107.4
(95% CI)	(98.3, 180.3)	(95.6, 178.0)	(97.7, 143.9)	(78.9, 121.2)	(104.6, 144.5)	(89.8, 127.4)
Serious Infections, n (%)	1 (2.3%)	9 (20.9%)	7 (6.6%)	2 (1.9%)	8 (5.3%)	11 (7.5%)
No. of AEs	2	12	8	3	10	15
Rate per 100 PY	6.0	36.9	8.8	3.4	8.1	12.3
(95% CI)	(0.7, 21.6)	(19.1, 64.4)	(3.8, 17.4)	(0.7, 9.8)	(3.9, 14.8)	(6.9, 20.3)
Opportunistic Infections, n (%)	0	1 (2.3%)	1 (0.9%)	0	1 (0.7%)	1 (0.7%)
No. of AEs	0	1	1	0	1	1
Rate per 100 PY	0	3.1	1.1	0	0.8	0.8
(95% CI)	(0.0, 11.0)	(0.1, 17.1)	(0.0, 6.1)	(0.0, 4.1)	(0.0, 4.5)	(0.0, 4.6)

	WA27788 (N=87)		WA29767 (N=210)		Pooled (N=297)	
	PBO 162 mg QW SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg QW SC (N=106)	TCZ 162 mg QW SC (N=104)	PBO 162 mg QW SC (N=150)	TCZ 162 mg QW SC (N=147)
Injection-site reaction, n (%)	2 (4.5%)	3 (7.0%)	3 (2.8%)	8 (7.7%)	5 (3.3%)	11 (7.5%)
No. of AEs	3	4	3	30	6	34
Rate per 100 PY (95% CI)	9.0 (1.9, 26.2)	12.3 (3.3, 31.5)	3.3 (0.7, 9.7)	33.5 (22.6, 47.9)	4.8 (1.8, 10.5)	27.9 (19.3, 38.9)
AEs leading to dose modification or interruption						
n (%)	10 (22.7%)	13 (30.2%)	27 (25.5%)	20 (19.2%)	37 (24.7%)	33 (22.4%)
No. of AEs	19	17	42	36	61	53
Rate per 100 PY (95% CI)	56.9 (34.2, 88.8)	52.2 (30.4, 83.6)	46.3 (33.4, 62.6)	40.2 (28.2, 55.7)	49.2 (37.6, 63.2)	43.4 (32.5, 56.8)
AESI						
Infections and Infestations, n (%)	22 (50.0%)	26 (60.5%)	53 (50.0%)	54 (51.9%)	75 (50.0%)	80 (54.4%)
No. of AEs	45	43	108	88	153	131
Rate per 100 PY (95% CI)	134.7 (98.3, 180.3)	132.1 (95.6, 178.0)	119.1 (97.7, 143.9)	96.4 (78.9, 121.2)	123.3 (104.8, 144.5)	107.4 (89.8, 127.4)
Serious Infections, n (%)	1 (2.3%)	9 (20.9%)	7 (6.6%)	2 (1.9%)	8 (5.3%)	11 (7.5%)
No. of AEs	2	12	8	3	10	15
Rate per 100 PY (95% CI)	6.0 (0.7, 21.6)	36.9 (19.1, 64.4)	8.8 (3.8, 17.4)	3.4 (0.7, 9.8)	8.1 (3.9, 14.8)	12.3 (6.9, 20.3)
Opportunistic Infections, n (%)	0	1 (2.3%)	1 (0.9%)	0	1 (0.7%)	1 (0.7%)
No. of AEs	0	1	1	0	1	1
Rate per 100 PY (95% CI)	0 (0.0, 11.0)	3.1 (0.1, 17.1)	1.1 (0.0, 6.1)	0 (0.0, 4.1)	0.8 (0.0, 4.5)	0.8 (0.0, 4.6)
Injection-site reaction, n (%)	2 (4.5%)	3 (7.0%)	3 (2.8%)	8 (7.7%)	5 (3.3%)	11 (7.5%)
No. of AEs	3	4	3	30	6	34
Rate per 100 PY (95% CI)	9.0 (1.9, 26.2)	12.3 (3.3, 31.5)	3.3 (0.7, 9.7)	33.5 (22.6, 47.9)	4.8 (1.8, 10.5)	27.9 (19.3, 38.9)
Hypersensitivity *, n (%)	3 (6.8%)	5 (11.6%)	5 (4.7%)	7 (6.7%)	8 (5.3%)	12 (8.2%)
No. of AEs	3	9	8	8	11	17
Rate per 100 PY (95% CI)	9.0 (1.9, 26.2)	27.7 (12.6, 52.5)	8.8 (3.8, 17.4)	8.9 (3.6, 17.6)	8.9 (4.4, 15.9)	13.9 (8.1, 22.3)
Malignancies (SMQ Narrow), n (%)	0	0	1 (0.9%)	2 (1.9%)	1 (0.7%)	2 (1.4%)
No. of AEs	0	0	1	2	1	2
Rate per 100 PY (95% CI)	0 (0.0, 11.0)	0 (0.0, 11.3)	1.1 (0.0, 6.1)	2.2 (0.3, 8.1)	0.8 (0.0, 4.5)	1.6 (0.2, 5.9)
Serious Stroke (Ischaemic or Haemorrhagic Cerebrovascular Conditions, SMQ Narrow), n (%)	1 (2.3%)	0	0	0	1 (0.7%)	0
No. of AEs	1	0	0	0	1	0
Rate per 100 PY (95% CI)	3.0 (0.1, 16.7)	0 (0.0, 11.3)	0 (0.0, 4.1)	0 (0.0, 4.1)	0.8 (0.0, 4.5)	0 (0.0, 3.0)
Myocardial Infarctions (SMQ Narrow), n (%)	1 (2.3%)	0	2 (1.9%)	0	3 (2.0%)	0
No. of AEs	1	0	2	0	3	0
Rate per 100 PY (95% CI)	3.0 (0.1, 16.7)	0 (0.0, 11.3)	2.2 (0.3, 8.0)	0 (0.0, 4.1)	2.4 (0.5, 7.1)	0 (0.0, 3.0)
AESI (continued)						
Serious or Medically Significant Bleeding Event (SMQ Wide), n (%)	1 (2.3%)	0	1 (0.9%)	0	2 (1.3%)	0
No. of AEs	1	0	1	0	2	0
Rate per 100 PY (95% CI)	3.0 (0.1, 16.7)	0 (0.0, 11.3)	1.1 (0.0, 6.1)	0 (0.0, 4.1)	1.6 (0.2, 5.8)	0 (0.0, 3.0)
Infected Skin Ulcers (PT) [a], n (%)	5 (11.4%)	3 (7.0%)	2 (1.9%)	4 (3.8%)	7 (4.7%)	7 (4.8%)
No. of AEs	7	4	3	4	10	8
Rate per 100 PY (95% CI)	21.0 (8.4, 43.2)	12.3 (3.3, 31.5)	3.3 (0.7, 9.7)	4.5 (1.2, 11.4)	8.1 (3.9, 14.8)	6.6 (2.8, 12.9)

AE = adverse event; AESI = adverse event of special interest; ISR = injection-site reactions; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; PBO = placebo; PT = Preferred Term; PY = patient-years; QW = weekly; SAE = serious adverse event; SC = subcutaneous; SMQ = Standardised MedDRA Query; TCZ = tocilizumab.

Notes: Investigator text for AEs encoded using MedDRA v20.1. Percentages of patients are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Event rate = number of events / (exposure in PY/100); multiple events with the same preferred term within a patient are counted; 95% confidence intervals are calculated based on Poisson distribution of the event rate.

There were no events for the following AESI: anaphylactic reactions, serious or medically significant hepatic events, serious gastrointestinal perforations, and serious demyelinating disorders.

* Hypersensitivity events were AEs occurring immediately after or within 24 hours of the end of injection (excluding ISRs) that were not deemed to be unrelated to study drug.

[a] "Infected Skin Ulcers" were identified as AESI after reviewing the Study WA27788 data. Patient narratives were written for this AESI in both studies.

Source: t_ae_ov_SE_W48, t_ae_rate_esi_SE_W48

- At Week 48, the proportion of patients who experienced at least 1 AE was comparable between the two arms, 81.3% in the pooled placebo arm compared with 89.1% in the pooled TCZ arm. The overall rate of AEs in the pooled population was also comparable: 590.0 (95% CI: 548.9, 635.3) AEs per 100 PY in the placebo arm and 577.9 (95% CI: 536.0, 622.2) AEs per 100 PY in the TCZ arm.
- The most commonly reported AEs by SOC (>25% of patients in either arm) was Infections and Infestations (50.0% in the placebo arm and 54.4% in the TCZ arm).
    - The most commonly reported AEs by PT (>10% patients in any arms of the individual and pooled studies) were: skin ulcers, arthralgia, nasopharyngitis, upper respiratory tract infection, diarrhoea, fatigue, gastroesophageal reflux disease, pruritus, headache, back pain, infected skin ulcer, pain in extremity, and Raynaud's phenomenon.
- The rates of any AEs, SAEs, Grade 3 and 4 SAEs were higher in Study WA27788.
- The SAE rate was numerically higher in the pooled placebo arm, 43.5 (95% CI: [32.7, 56.8]) AEs per 100 PY compared with 30.3 (95% CI: [21.4, 41.8]) AEs per 100 PY in the pooled TCZ arm.
    - Grade 3 SAE rate was comparable between the two arms, 27.4 (95% CI: [19.0, 38.3]) AEs per 100 PY in the pooled placebo arm compared with 23.0 (95% CI: [15.3, 33.2]) AEs per 100 PY in the pooled TCZ arm.
    - Grade 4 SAE rate was higher in the pooled placebo arm, 9.7 (95% CI: [5.0, 16.9]) AEs per 100 PY compared with 2.5 (95% CI: [0.5, 7.2]) AEs per 100 PY in the pooled TCZ arm.
- A total of 8 deaths were reported up to Week 48, equally split between the two pooled arms. Seven fatal events were assessed by the investigator as unrelated to study drug, and 1 event in the TCZ arm (pneumonia) was assessed as related to study drug by the investigator.
- The proportion of patients who experienced AE leading to withdrawal was comparable, 10.7% in the pooled placebo arm and 8.2% in the pooled TCZ arm. The proportion of patients who experienced AE leading to dose modification or interruption was also comparable, 24.7% in the pooled placebo arm and 22.4% in the pooled TCZ arm.
- The proportion of patients who experienced AESI was in general low, with the exceptions of Infection and Infestation and serious infections:
    - Infection and Infestation was the most commonly reported AESI. The incidence was comparable in the pooled placebo arm (50.0%) compared with the pooled TCZ arm (54.4%). In Study WA27788, the incidence was higher on the TCZ arm (50.0% in placebo vs. 60.5% in TCZ). In Study WA29767, the incidence was comparable in both arms (50.0% in placebo and 51.9% in TCZ).
    - The incidence of serious infection AESI was slightly higher in the pooled TCZ arm (7.5%), compared to the pooled placebo arm (5.3%). Of note, in Study WA27788 there was a higher incidence of serious infections in the TCZ arm compared to placebo (2.3% in placebo and 20.9% in TCZ), whereas in Study WA29767, the incidence of serious infections was higher on the placebo arm (6.6% in placebo and 1.9% in TCZ).
    - The incidence of ISRs and hypersensitivity was higher in the TCZ arms compared to the placebo arms in both studies and in the pooled data.

- There were no notable differences in the AESI of opportunistic infections, malignancies, serious stroke, myocardial infarctions, serious or medically significant bleeding events or infected skin ulcers between the pooled arms. In addition, there were no serious demyelinating AEs, serious or medically significant hepatic AEs, serious gastrointestinal perforations, nor anaphylactic reactions in any arms.

TCZ Treatment up to Week 96 Data

An overview of key safety results in the TCZ treated patients during the open-label period is presented in Table 49.

Table 49 Overview of Adverse Events by Incidence and Rate – TCZ Treatment up to Week 96 (Safety Population)

Overview of Rates of Adverse Events of Special Interest (All Exposure), Safety Population
Project: SSc Pooled Q22020

	WA27788	WA29767	Pooled
	TCZ 162 mg qw SC (N=74)	TCZ 162 mg qw SC (N=193)	TCZ 162 mg qw SC (N=267)
Exposure (Patient Years)	96.19	270.56	366.75
Any AE			
Patients (Number of Events)	68 (563)	161 (970)	229 (1533)
Rate per 100 PY	585.3	358.5	418.0
(95% CI for rate)	(538.0, 635.7)	(336.3, 381.8)	(397.3, 439.5)
Any SAE			
Patients (Number of Events)	24 (39)	28 (41)	52 (80)
Rate per 100 PY	40.5	15.2	21.8
(95% CI for rate)	(28.8, 55.4)	(10.9, 20.6)	(17.3, 27.1)
Grade 3 SAEs			
Patients (Number of Events)	18 (28)	20 (22)	38 (50)
Rate per 100 PY	29.1	8.1	13.6
(95% CI for rate)	(19.3, 42.1)	(5.1, 12.3)	(10.1, 18.0)
Grade 4 SAEs			
Patients (Number of Events)	6 (6)	6 (9)	12 (15)
Rate per 100 PY	6.2	3.3	4.1
(95% CI for rate)	(2.3, 13.6)	(1.5, 6.3)	(2.3, 6.7)
Death			
Patients (Number of Events)	3 (3)	3 (3)	6 (6)
Rate per 100 PY	3.1	1.1	1.6
(95% CI for rate)	(0.6, 9.1)	(0.2, 3.2)	(0.6, 3.6)
AE leading to withdrawal from treatment			
Patients (Number of Events)	10 (10)	9 (9)	19 (19)
Rate per 100 PY	10.4	3.3	5.2
(95% CI for rate)	(5.0, 19.1)	(1.5, 6.3)	(3.1, 8.1)
AE leading to dose modification or interruption			
Patients (Number of Events)	32 (42)	60 (105)	92 (147)
Rate per 100 PY	43.7	38.8	40.1
(95% CI for rate)	(31.5, 59.0)	(31.7, 47.0)	(33.9, 47.1)
Local injection-site reaction			
Patients (Number of Events)	8 (11)	7 (29)	15 (40)
Rate per 100 PY	11.4	10.7	10.9
(95% CI for rate)	(5.7, 20.5)	(7.2, 15.4)	(7.8, 14.9)
Hypersensitivity Excluding ISR			
Patients (Number of Events)	7 (12)	10 (16)	17 (28)
Rate per 100 PY	12.5	5.9	7.6
(95% CI for rate)	(6.4, 21.8)	(3.4, 9.6)	(5.1, 11.0)
AESI			
Infections and Infestations			
Patients (Number of Events)	52 (109)	106 (235)	158 (344)
Rate per 100 PY	113.3	86.9	93.8
(95% CI for rate)	(93.0, 136.7)	(76.1, 98.7)	(84.1, 104.3)

Table 50 Overview of Adverse Events by Incidence and Rate – TCZ Treatment up to Week 96 (Safety Population)

	WA27788	WA29767	Pooled
	TCZ 162 mg qw SC (N=74)	TCZ 162 mg qw SC (N=193)	TCZ 162 mg qw SC (N=267)
Serious Infections			
Patients (Number of Events)	13 (18)	6 (8)	19 (26)
Rate per 100 PY	18.7	3.0	7.1
(95% CI for rate)	(11.1, 29.6)	(1.3, 5.8)	(4.6, 10.4)
Opportunistic Infections			
Patients (Number of Events)	1 (1)	2 (2)	3 (3)
Rate per 100 PY	1.0	0.7	0.8
(95% CI for rate)	(0.0, 5.8)	(0.1, 2.7)	(0.2, 2.4)
Malignancies (SMQ Narrow)			
Patients (Number of Events)	1 (1)	3 (3)	4 (4)
Rate per 100 PY	1.0	1.1	1.1
(95% CI for rate)	(0.0, 5.8)	(0.2, 3.2)	(0.3, 2.8)
Malignancies (excluding NMSC)			
Patients (Number of Events)	1 (1)	3 (3)	4 (4)
Rate per 100 PY	1.0	1.1	1.1
(95% CI for rate)	(0.0, 5.8)	(0.2, 3.2)	(0.3, 2.8)
Serious or Medically Significant Bleeding Event (SMQ Wide)			
Patients (Number of Events)	1 (1)	0 (0)	1 (1)
Rate per 100 PY	1.0	0.0	0.3
(95% CI for rate)	(0.0, 5.8)	(0.0, 1.4)	(0.0, 1.5)
Infected Skin Ulcers			
Patients (Number of Events)	9 (13)	8 (12)	17 (25)
Rate per 100 PY	13.5	4.4	6.8
(95% CI for rate)	(7.2, 23.1)	(2.3, 7.7)	(4.4, 10.1)

AE = adverse event; AESI = adverse event of special interest; qw = every week; SAE = serious adverse event; SC = subcutaneous; PY = patient years.
Investigator text for AEs encoded using MedDRA version 22.1.
Hypersensitivity events were defined as AEs occurring immediately after or within 24 hours of the end of injection that were not deemed to be unrelated to study drug.
Only anaphylactic AEs occurred within 24 hours after the injection are included.
The category 'Infected Skin Ulcers' was identified as an AESI after reviewing the WA27788 study data; patient narratives were written for this AESI.
Event rate = number of events / (exposure in patient-years/100).
95% confidence intervals are calculated based on Poisson distribution of the event rate.
Multiple events with the same preferred term within a patient are counted.
TCZ exposure includes open label TCZ exposure as well as the initial exposure from the double blind period for patients initially treated with TCZ.

Program: root/clinical_studies/RO4877533/share/pool_SSc_Q22020/prod/program/t_ae_rate_esi.sas
Output: root/clinical_studies/RO4877533/share/pool_SSc_Q22020/prod/output/t_ae_rate_esi_SE_ALL.out
08APR2020 20:44

- The rate of overall AEs, SAEs, Grade 3 or Grade 4 SAEs, deaths, AEs leading to withdrawal, and AEs leading to dose modification/interruption were all comparable or lower on TCZ treatment at Week 96 (Table 50) compared to Week 48 (Table 48).
- A total of 6 deaths occurred on the TCZ treatment by Week 96 (3 patients from each study), of which 4 occurred during the double-blind period (Table 48). The 2 additional deaths occurred in Study WA29767 during the open-label period.
- For AESIs, the rate of ISRs, hypersensitivity events, Infections and Infestations, serious infections, opportunistic infections, malignancies and infected skin ulcers were all comparable or lower on TCZ treatment at Week 96 (Table 50) compared to Week 48 (Table 48).

- The rate of serious infections on TCZ treatment remained higher in Study WA27788 compared to Study WA29767 by Week 96.
- By Week 96, 1 patient on TCZ treatment had experienced a serious or medically significant bleeding event versus 0 patients by Week 48.
- There remained no serious demyelinating AEs, serious or medically significant hepatic AEs, gastrointestinal perforations, stroke, or anaphylactic reactions on TCZ treatment through Week 96.

Common adverse events

Treatment up to Week 48

In the pooled population, AEs were most commonly reported (>25% of patients in either treatment arm) in the following SOCs, expressed as percentages of patients with AEs) (Table 48):

- Infections and Infestations (50.0% placebo vs. 54.4% TCZ [123.3 vs. 107.4 AEs per 100 PY])
- Gastrointestinal Disorders (36.0% placebo vs. 36.7% TCZ [75.0 vs. 66.4 AEs per 100 PY])
- Musculoskeletal and Connective Tissue Disorders (38.0% placebo vs. 31.3% TCZ [80.6 vs. 64.8 AEs per 100 PY])
- Skin and Subcutaneous Tissue Disorders (32.0% placebo vs. 35.4% TCZ [75.8 vs. 94.3 AEs per 100 PY])
- General Disorders and Administration Site Conditions (22.0% placebo vs. 25.9% TCZ [33.9 vs. 62.3 AEs per 100 PY])

By SOC, the incidence of AEs was generally similar between the pooled treatment arms, except for the following notable differences (>5%):

- Higher in the placebo arm:
  - Musculoskeletal and Connective Tissue Disorders (presented above): driven by a higher incidence in Study WA29767 in the placebo arm
  - Cardiac Disorders (13.3% placebo vs. 6.8% TCZ [21.8 vs. 9.8 AEs per 100 PY]): driven by a higher incidence in Study WA29767 in the placebo arm – Respiratory, Thoracic and Mediastinal Disorders (20.7% placebo vs. 15.0% TCZ [33.1 vs. 21.3 AEs per 100 PY]): driven by a higher incidence in StudyWA29767 in the placebo arm

By PT the incidence of common AEs (Table 51) was generally similar between the two pooled treatment arms. However, compared with the TCZ arm, a higher number of patients with ILD was reported in the placebo arm (6.0% placebo vs. 1.4% TCZ) in pooled analysis; this was driven by a higher proportion of patients with ILD reported in the placebo arm in Study WA29767. The most commonly reported AEs by PT (>10% patients in either arms) were skin ulcers, arthralgia, nasopharyngitis, and upper respiratory tract infection.

Table 51 Summary of Adverse Events by Preferred Term (Week 48), Safety Population

Project: CNL1935I

MedDRA Preferred Term	WA27788 (N=87) PBO 162 mg qw SC (N=44)	WA27788 (N=87) TCZ 162 mg qw SC (N=43)	WA29767 (N=210) PBO 162 mg qw SC (N=106)	WA29767 (N=210) TCZ 162 mg qw SC (N=104)	Pooled (N=297) PBO 162 mg qw SC (N=150)	Pooled (N=297) TCZ 162 mg qw SC (N=147)
Total number of patients with at least one adverse event	40 (90.9%)	42 (97.7%)	82 (77.4%)	89 (85.6%)	122 (81.3%)	131 (89.1%)
Total number of events	240	282	492	422	732	705
SKIN ULCER	8 (18.2%)	8 (18.6%)	12 (11.3%)	15 (14.4%)	20 (13.3%)	22 (15.6%)
ARTHRALGIA	8 (18.2%)	6 (14.0%)	12 (11.3%)	11 (10.6%)	20 (13.3%)	17 (11.6%)
NASOPHARYNGITIS	4 (9.1%)	5 (11.6%)	8 (7.5%)	13 (12.5%)	12 (8.0%)	18 (12.2%)
UPPER RESPIRATORY TRACT INFECTION	6 (13.6%)	1 (2.3%)	11 (10.4%)	12 (11.5%)	17 (11.3%)	13 (8.8%)
DIARRHOEA	4 (9.1%)	7 (16.3%)	8 (7.5%)	6 (5.8%)	12 (8.0%)	13 (8.8%)
FATIGUE	2 (4.5%)	5 (11.6%)	7 (6.6%)	8 (7.7%)	9 (6.0%)	13 (8.8%)
URINARY TRACT INFECTION	3 (6.8%)	3 (7.0%)	10 (9.4%)	5 (4.8%)	13 (8.7%)	8 (5.4%)
GASTROOESOPHAGEAL REFLUX DISEASE	6 (13.6%)	5 (11.6%)	5 (4.7%)	4 (3.8%)	11 (7.3%)	9 (6.1%)
PRURITUS	4 (9.1%)	6 (14.0%)	4 (3.8%)	6 (5.8%)	8 (5.3%)	12 (8.2%)
HEADACHE	4 (9.1%)	5 (11.6%)	7 (6.6%)	3 (2.9%)	11 (7.3%)	8 (5.4%)
BACK PAIN	3 (6.8%)	6 (14.0%)	5 (4.7%)	2 (1.9%)	8 (5.3%)	8 (5.4%)
INFECTED SKIN ULCER	5 (11.4%)	3 (7.0%)	2 (1.9%)	4 (3.8%)	7 (4.7%)	7 (4.8%)
NAUSEA	3 (6.8%)	2 (4.7%)	6 (5.7%)	3 (2.9%)	9 (6.0%)	5 (3.4%)
DYSPNOEA	3 (6.8%)	4 (9.3%)	3 (2.8%)	3 (2.9%)	6 (4.0%)	7 (4.8%)
PAIN IN EXTREMITY	2 (4.5%)	5 (11.6%)	3 (2.8%)	3 (2.9%)	5 (3.3%)	8 (5.4%)
RAYNAUD'S PHENOMENON	3 (6.8%)	5 (11.6%)	2 (1.9%)	3 (2.9%)	5 (3.3%)	8 (5.4%)
DIZZINESS	2 (4.5%)	4 (9.3%)	3 (2.8%)	3 (2.9%)	5 (3.3%)	7 (4.8%)
HERPES ZOSTER	2 (4.5%)	3 (7.0%)	5 (4.7%)	2 (1.9%)	7 (4.7%)	5 (3.4%)
RASH	2 (4.5%)	1 (2.3%)	7 (6.6%)	2 (1.9%)	9 (6.0%)	3 (2.0%)
ABDOMINAL PAIN	3 (6.8%)	2 (4.7%)	5 (4.7%)	1 (1.0%)	8 (5.3%)	3 (2.0%)
DYSPEPSIA	3 (6.8%)	3 (7.0%)	2 (1.9%)	3 (2.9%)	5 (3.3%)	6 (4.1%)
INTERSTITIAL LUNG DISEASE	1 (2.3%)	2 (4.7%)	8 (7.5%)	0	9 (6.0%)	2 (1.4%)
CONSTIPATION	3 (6.8%)	1 (2.3%)	4 (3.8%)	2 (1.9%)	7 (4.7%)	3 (2.0%)
GASTROENTERITIS	1 (2.3%)	1 (2.3%)	2 (1.9%)	6 (5.8%)	3 (2.0%)	7 (4.8%)
ANAEMIA	1 (2.3%)	1 (2.3%)	6 (5.7%)	1 (1.0%)	7 (4.7%)	2 (1.4%)
OEDEMA PERIPHERAL	2 (4.5%)	3 (7.0%)	3 (2.8%)	1 (1.0%)	5 (3.3%)	4 (2.7%)
WEIGHT DECREASED	0	0	6 (5.7%)	3 (2.9%)	6 (4.0%)	3 (2.0%)
ERYTHEMA	2 (4.5%)	1 (2.3%)	1 (0.9%)	4 (3.8%)	3 (2.0%)	5 (3.4%)
HYPERTENSION	3 (6.8%)	3 (7.0%)	0	1 (1.0%)	3 (2.0%)	4 (2.7%)
SCLERODERMA	3 (6.8%)	2 (4.7%)	1 (0.9%)	1 (1.0%)	4 (2.7%)	3 (2.0%)
VOMITING	1 (2.3%)	3 (7.0%)	1 (0.9%)	2 (1.9%)	2 (1.3%)	5 (3.4%)
ASTHENIA	3 (6.8%)	0	3 (2.8%)	0	6 (4.0%)	0
SLEEP DISORDER	3 (6.8%)	1 (2.3%)	1 (0.9%)	0	4 (2.7%)	1 (0.7%)
CELLULITIS	3 (6.8%)	0	0	0	3 (2.0%)	0

Investigator text for AEs encoded using MedDRA version 26.1

Percentages are based on N in the column headings.

For incidence counts by preferred term, multiple occurences of the same AE in an individual are counted only once.
For incidence counts of 'Total number of events', multiple occurences of the same AE in an individual are counted seperately.
Program: /opt/BIOSTAT/prod/cnl1935i/pl1935h/t_ae.sas / Output: /opt/BIOSTAT/prod/cnl1935i/pl1935h/reports/t_ae_SE_PT.out
Some Adverse Events reported in the FaSSinate Week 48 CSR were not reported in this output. This is due to changes in the data cut rules meaning the adverse events now fall outside of the week 48 period. A full list of events not included can be found at Program: /opt/BIOSTAT/prod/cnl1935i/pl1935h/SA1102_l_ae_nw48.sas Output: /opt/BIOSTAT/prod/cnl1935i/pl1935h/reports/SA1102_l_ae_nw48_SE.out

CHMP comment

The MAH stated that "However, compared with the TCZ arm, a higher number of patients with ILD was reported in the placebo arm (6.0% placebo vs. 1.4% TCZ) in pooled analysis; this was driven by a higher proportion of patients with ILD reported in the placebo arm in Study WA29767. This cannot be verified by the data provided (OC).

TCZ Treatment up to Week 96

In the pooled Safety Population at Week 96 (n =267), the majority (85.8%) of patients in the TCZ arm experienced at least 1 AE corresponding to an overall AE rate of 418.0 (95% CI: 397.3, 439.5) (Table 50) AEs per 100 PY. This is lower than the overall AE rate of 577.9 (95% CI: 536.0, 622.2) observed in the Week 48 pooled TCZ arm. Common AEs observed in the long-term study by Week 96 showed similar patterns in SOC and PT compared to Week 48 and also comparable in rates. No new or unexpected safety concerns were observed.

CHMP comment

In the section common adverse events the MAA provided a "conclusion" of the safety data up to Week 96, however the statement is not substantiated by data. Please provide a summary of the safety date of the OL study part in the same manner as for the Week 48 data.

Serious adverse event/deaths/other significant events

Death

Treatment up to Week 48

In the pooled Safety Population, up to Week 48 there were 8 events, 4 [2.7%] patients in both arms reported

Study WA29767

- Placebo arm: 3 events (chronic cardiac failure, myocarditis, and myocardial infarction)
- TCZ arm: 1 event (unexplained cause)

Study WA27788

- Placebo arm: 1 event (cardiac failure)
- TCZ arm: 3 events (arrhythmia, pneumonia, and multiple organ dysfunction syndrome)

Of the 8 fatal AEs, 7 were considered by the investigator to be unrelated to study drug. One event in the TCZ arm (Study WA27788, pneumonia) was assessed as related to study drug by the investigator. The majority of fatal AEs were cardiac, with a higher incidence reported in the placebo arm (4 events) compared with the TCZ arm (1 event).

CHMP comment

Altogether, in both studies there were 8 death reported in both arms of each study. Four death in each arm. Details were provided in the respective CSRs. It can be agreed with the assessment of the investigators that one event (pneumonia) was assesses related to the study drug, the other 7 events deemed rather related to the underlying disease.

TCZ Treatment up to Week 96

In the TCZ treatment up to Week 96 pooled population, 2 additional deaths were reported, resulting in a total of 6 deaths on TCZ treatment and a death rate of 1.6 [95% CI: 0.6, 3.6] deaths per 100 PY This was lower than the rate of deaths observed in the Week 48 pooled TCZ arm.

These 2 additional deaths occurred during the open-label period in Study WA29767.

One patient who was randomised to placebo arm at study entry experienced arrhythmia, cardiorespiratory arrest, pneumonia aspiration, sepsis and died of brain injury. The other patient was in the TCZ treatment arm and experienced cardiac failure and died of pulmonary hypertension. Both events were assessed as related to study drug by the investigator.

Other serious adverse events

Treatment up to Week 48

In the pooled Safety Population, the proportion of patients who experienced SAEs were comparable between treatment arms (22.0% in the placebo arm vs. 18.4% in the TCZ arm, Table 48).

However, the SAE rates were higher in the placebo arm (43.5 [95% CI: 32.7, 56.8] AEs per 100 PY) compared with the TCZ arm (30.3 [95% CI: 21.4, 41.8] AEs per 100 PY), driven by the higher rates of SAEs seen in the placebo arm in Study WA29767.

Between studies, the SAE rates were higher in Study WA27788 (71.8 AEs per 100 PY in the placebo arm and 70.7 AEs per 100 PY in the TCZ arm) compared with Study WA29767 (33.1 AEs per 100 PY in the placebo arm and 15.7 AEs per 100 PY in the TCZ arm).

Table 52 Summary of Serious Adverse Events by System Organ Class (Week 48, Safety Population)

Summary of Serious Adverse Events by System Organ Class (Week 48), Safety Population
Project: CN119351

	WA27788 (N=87)		WA29767 (N=210)		Pooled (N=297)	
MedDRA System Organ Class	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)	PBO 162 mg qw SC (N=150)	TCZ 162 mg qw SC (N=147)
Total number of patients with at least one adverse event	15 (34.1%)	14 (32.6%)	18 (17.0%)	13 (12.5%)	33 (22.0%)	27 (18.4%)
Total number of events	24	23	30	14	54	37
INFECTIONS AND INFESTATIONS	1 (2.3%)	9 (20.9%)	7 (6.6%)	2 (1.9%)	8 (5.3%)	11 (7.5%)
CARDIAC DISORDERS	5 (11.4%)	1 (2.3%)	6 (5.7%)	2 (1.9%)	11 (7.3%)	3 (2.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.3%)	2 (4.7%)	3 (2.8%)	1 (1.0%)	4 (2.7%)	3 (2.0%)
GASTROINTESTINAL DISORDERS	4 (9.1%)	1 (2.3%)	1 (0.9%)	0	5 (3.3%)	1 (0.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (4.5%)	2 (4.7%)	1 (0.9%)	0	3 (2.0%)	2 (1.4%)
RENAL AND URINARY DISORDERS	2 (4.5%)	0	1 (0.9%)	2 (1.9%)	3 (2.0%)	2 (1.4%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (2.3%)	1 (2.3%)	2 (1.9%)	0	3 (2.0%)	1 (0.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	2 (4.7%)	1 (0.9%)	1 (1.0%)	1 (0.7%)	3 (2.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	2 (1.9%)	2 (1.9%)	2 (1.3%)	2 (1.4%)
VASCULAR DISORDERS	2 (4.5%)	1 (2.3%)	0	0	2 (1.3%)	1 (0.7%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.3%)	0	0	1 (1.0%)	1 (0.7%)	1 (0.7%)
NERVOUS SYSTEM DISORDERS	1 (2.3%)	0	0	1 (1.0%)	1 (0.7%)	1 (0.7%)
PSYCHIATRIC DISORDERS	0	1 (2.3%)	1 (0.9%)	0	1 (0.7%)	1 (0.7%)
INVESTIGATIONS	0	0	0	1 (1.0%)	0	1 (0.7%)
METABOLISM AND NUTRITION DISORDERS	0	0	1 (0.9%)	0	1 (0.7%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (0.9%)	0	1 (0.7%)	0

Investigator text for AEs encoded using MedDRA version 20.1.
Percentages are based on N in the column headings.
For incidence counts by system organ class adverse events are counted once per SOC, per patient.
For incidence counts of 'Total number of events', multiple occurences of the same AE in an individual are counted seperately.
Program: /opt/BIOSTAT/prod/cn119351/pl1935h/t_ae.sas / Output: /opt/BIOSTAT/prod/cn119351/pl1935h/reports/t_ae_SE_SER_SOC.out
23MAR2018 12:48
Some Adverse Events reported in the FaSSinate Week 48 CSR were not reported in this output. This is due to changes in the data cut rules meaning the adverse events now fall outside of the week 48 period. A full list of events not included can be found at Program: /opt/BIOSTAT/prod/cn119351/pl1935h/SA1102_1_ae_nw48.sas Output: /opt/BIOSTAT/prod/cn119351/pl1935h/reports/SA1102_1_ae_nw48_SE.out
21MAR2018 17:12

In the pooled population, SAEs were most commonly reported in the following SOCs (2% of patients in either treatment arm), expressed as percentages of patients with AEs [AE rates per 100 PY] (Table 51) were:

- Infections and Infestations (5.3% placebo vs. 7.5% TCZ [8.1 vs. 12.3 AEs per 100 PY]). Serious infection events are discussed in Section 2.2.7.1.
- Cardiac Disorders (7.3% placebo vs. 2.0% TCZ [9.7 vs. 2.5 AEs per 100 PY])
- Gastrointestinal Disorders (3.3% placebo vs. 0.7% TCZ [5.6 vs. 0.8 AEs pe 100 PY]): driven by a higher number of SAEs reported in Study WA27788 in the placebo arm

By PT the incidence of common SAEs (>1 patient in either pooled treatment arm) was generally similar between treatment arms (

Table 53), with the exceptions that more patients in the TCZ arms reported osteomyelitis (0 in the placebo arm vs. 3 [2.0%] in the TCZ arm).

Table 53 Summary of Serious Adverse Events by Preferred Term (Reported by >1 Patient in Any Arm) up to Week 48 (Safety Population)

Summary of Serious Adverse Events by Preferred Term (Week 48), Safety Population
Project: CN119351

	WA27788 (N=87)		WA29767 (N=210)		Pooled (N=297)	
MedDRA Preferred Term	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)	PBO 162 mg qw SC (N=150)	TCZ 162 mg qw SC (N=147)
Total number of patients with at least one adverse event	15 (34.1%)	14 (32.6%)	18 (17.0%)	13 (12.5%)	33 (22.0%)	27 (18.4%)
Total number of events	24	23	30	14	54	37
PNEUMONIA	0	1 (2.3%)	3 (2.8%)	0	3 (2.0%)	1 (0.7%)
SKIN ULCER	1 (2.3%)	2 (4.7%)	1 (0.9%)	0	2 (1.3%)	2 (1.4%)
INFECTED SKIN ULCER	0	2 (4.7%)	1 (0.9%)	0	1 (0.7%)	2 (1.4%)
OSTEOMYELITIS	0	2 (4.7%)	0	1 (1.0%)	0	3 (2.0%)
ACUTE KIDNEY INJURY	1 (2.3%)	0	1 (0.9%)	0	2 (1.3%)	0
ACUTE MYOCARDIAL INFARCTION	1 (2.3%)	0	1 (0.9%)	0	2 (1.3%)	0
SCLERODERMA	1 (2.3%)	0	1 (0.9%)	0	2 (1.3%)	0

Investigator text for AEs encoded using MedDRA version 20.1.
Percentages are based on N in the column headings.
For incidence counts by preferred term, multiple occurences of the same AE in an individual are counted only once.
For incidence counts of 'Total number of events', multiple occurences of the same AE in an individual are counted seperately.
Program: /opt/BIOSTAT/prod/cn119351/p11935h/t_ae.sas / Output: /opt/BIOSTAT/prod/cn119351/p11935h/reports/t_ae_SE_SER_P7.out
12MAR2018 12:48 Page 1 of 1
Some Adverse Events reported in the FaSScinate Week 48 CSR were not reported in this output. This is due to changes in the data cut rules meaning the adverse events now fall outside of the week 48 period. A full list of events not included can be found at Program: /opt/BIOSTAT/prod/cn119351/p11935h/SA1102_1_ae_nw48.sas Output: /opt/BIOSTAT/prod/cn119351/p11935h/reports/SA1102_1_ae_nw48_SE.out
21MAR2018 17:12

TCZ Treatment up to Week 96

In the TCZ treatment up to Week 96 pooled population, the SAE rate was 21.8 (95% CI: 17.3, 27.1) AEs per 100 PY (Table 50), which was lower than the SAE rate of 30.3 (95% CI: 21.4, 41.8) observed in the Week 48 pooled TCZ arm (Table 48).

Between studies, the TCZ treatment up to Week 96 SAE rates were higher in Study WA27788 (40.5 [95% CI: 28.8, 55.4] AEs per 100 PY) compared with Study WA29767 (15.2 [95% CI: 10.9, 20.6] AEs per 100 PY).

Overall, SAEs were most commonly reported in the following SOCs;

- Infections and Infestations: 7.1 AEs per 100 PY, driven primarily by the higher SAE rate in Study WA27788
- Cardiac Disorders: 2.2 AEs per 100 PY, rates comparable between the two studies

By 6-monthly intervals, the highest rates of SAEs was observed in the first 6 months of TCZ exposure (32.0 AEs per 100 PY). The rates were lower and similar during 7-12 months and 13-18 months of TCZ treatment (23.0 and 26.4 AEs per 100 PY, respectively). The rates were the lowest during 19-24 months of treatment (10.5 AEs per 100 PY). Following 24 months of TCZ treatment, 4 patients had 5 SAEs.

The majority of SAEs in the TCZ treatment up to Week 96 pooled population were Grade 3 in severity, with a rate of 13.6 (95%CI: 10.1, 18.0) AEs per 100 PY (Table 49). The rate of Grade 4 SAEs was 4.1 (95% CI: 2.3, 6.7) AEs per 100 PY.

Adverse events of special interest

Infections

All infections in treatment up to Week 48

In the pooled Safety Population up to Week 48, approximately half the patients (50.0% of patients in the placebo arm and 54.4% in the TCZ arm) had at least 1 infection. The rate of infections was higher in the placebo arm (123.3 [95% CI: 104.6, 144.5] AEs per 100 PY) compared with the TCZ arm (107.4 [95% CI: 89.8, 127.4] AEs per 100 PY), which was driven by the higher rate of infections reported in the placebo arm in Study WA29767 (119.1 [95% CI: 97.7, 143.9] AEs per 100 PY) (Table 48). The most

commonly reported infections (≥5% of patients) were nasopharyngitis (8.0% in the placebo arm vs. 12.2% in the TCZ arm), upper respiratory tract infection (11.3% in placebo vs. 8.8% in TCZ), and urinary tract infection (8.7% in placebo vs. 5.4% in TCZ).

In the 48-week double-blind treatment period, the highest rates of infection events were observed during the first 6 months of treatment, with a higher rate in the placebo arm: 138.2 [95% CI: 111.1, 169.9] AEs per 100 PY in the placebo arm and 110.8 [95% CI: 86.3, 139.9] AEs per 100 PY in the TCZ arm. Between 7 and 12 months, the rate of infection was lowered to 108.8 [95% CI: 83.6, 139.2] AEs per 100 PY in the placebo arm and 102.8 [95% CI: 78.3, 132.6] AEs per 100 PY in the TCZ arm.

All infections in TCZ treatment up to Week 96

In the TCZ treatment up to Week 96 pooled population, 158 (59.2%, n=267) patients had infection events resulting in a rate of 93.8 (95% CI: 84.1, 104.3) AEs per 100 PY, which was driven by a higher rate of infections in Study WA27788 (113.3 vs. 86.9 AEs per 100 PY in Study WA29767) (Table 49). The most commonly reported PTs (pooled rate of ≥3.0 AEs per 100 PY) were upper respiratory tract infection (11.2 AEs per 100 PY), nasopharyngitis (10.4 AEs per 100 PY), infected skin ulcer (6.8 AEs per 100 PY), urinary tract infection (6.8 AEs per 100 PY), bronchitis (4.9 AEs per 100 PY), and gastroenteritis (3.0 AEs per 100 PY).

In the TCZ treatment up to Week 96 pooled population, the highest rates of infection events were observed during the first 6 months of treatment (106.8 [95% CI: 83.3, 135.0] AEs per 100 PY) and between 13 and 18 months during the open label treatment period (104.6 [95% CI: 86.4, 125.6] AEs per 100 PY). Between 7 and 12 months and between 19 and 24 months, similarly lowered infection rates were observed (98.4 [95% CI: 75.1, 126.7] AEs per 100 PY and 86.8 [95% CI: 69.9, 106.6] AEs per 100 PY, respectively).

Serious infections and opportunistic infections in treatment up to Week 48

In the pooled Safety Population up to Week 48, the incidence of serious infections was higher in the TCZ arm compared with the placebo arm: 8 (5.3%) patients in the placebo arm had 10 serious infection events (8.1 [95% CI: 3.9, 14.8] AEs per 100 PY) versus 11 (7.5%) patients in the TCZ arm had 15 serious infections (12.3 [95% CI: 6.9, 20.3] AEs per 100 PY), including 2 opportunistic infections, 1 each reported in Studies WA29767 and WA27788 (Table 48). The opportunistic infection events were oesophageal candidiasis in both studies

In the pooled population, the most frequent serious infections were pneumonia (3 [2.0%] patients in the placebo arm and 1 [0.7%] patient in the TCZ arm), infected skin ulcer (1 [0.7%] patient in the placebo arm and 2 [1.4%] patients in the TCZ arm), and osteomyelitis (3 [2.0%] patients in the TCZ arm only). All other serious infection events were reported in no more than 1 patient per treatment arm.

The higher rate of serious infections in the pooled TCZ arm was driven by the higher rate of these events in the TCZ arm in Study WA27788, with 9 (20.9%) patients with 12 serious infections (36.9 [95% CI: 19.1, 64.4]) (Table 48). Six patients experienced serious infections in the first 24 weeks of TCZ treatment. Except for the one patient who experienced oesophageal candidiasis on Day 1, the events in the other 5 patients were all considered to be related to study drug by the investigator. One patient had a serious lung infection which resulted in death. Two patients reported with osteomyelitis, 1 patient with bronchitis, and 1 patient with infected skin ulcer.

The higher rate of serious infections in the pooled placebo arm was driven by the higher rate of these events in the placebo arm in Study WA29767, with 7 (6.6%) patients with 8 serious infections (8.8 AEs per 100 PY [95% CI: 3.8, 17.4]) (Table 48). The most commonly reported serious infection was pneumonia, which occurred in 3 patients in the placebo arm. Other events included soft tissue infection and sepsis.

The rate of serious infection events in the first 6 months of treatment in the pooled population were 10.7 [95% CI: 4.3, 22.1] AEs per 100 PY in the placebo arm and 12.7 [95% CI: 5.5, 24.9] in the TCZ arm. Between 7 and 12 months of treatment, the rate of serious infections was lowered to 5.2 [95% CI: 1.1, 15.1] in the placebo arm and 8.7 [95% CI: 2.8, 20.3] in the TCZ arm.

Serious infections and opportunistic infections in TCZ treatment up to Week 96

In the TCZ treatment up to Week 96 pooled population, 19 (7.1%) patients in the TCZ arm had 26 serious infection events (7.1 [95% CI: 4.6, 10.4] AEs per 100 PY) (Table 49), including 3 serious opportunistic infection events, 2 in Study WA29767 (both oesophageal candidiasis, 1 occurred before Week 48 and the other before Week 96) and 1 in Study WA27788 (oesophageal candidiasis that occurred before Week 24).

In the pooled population, the most frequent serious infections were infected skin ulcer (6 patients in Study WA27788 and no patient in Study WA29767), osteomyelitis (3 patients in Study WA27788 and 1 patient in Study WA29767), and pneumonia (2 patients in Study WA27788 and 2 patients in Study WA29767) (Table 48). All other serious infection events were reported in no more than 1 patient per treatment arm.

The highest rate of serious infections in the TCZ treatment up to Week 96 pooled population was reported during the first 6 months of treatment (12.2 [95% CI: 5.3, 24.1] AEs per 100 PY) (Table 49). Between 7 and 12 months and between 13 and 18 months of treatment, the rates were lowered: 8.2 [95% CI: 2.7, 19.1] and 8.2 [95% CI: 3.7, 15.5] AEs per 100 PY, respectively. The lowest rates of serious infection were observed between 19 and 24 months of treatment (3.8 AEs [95% CI: 1.0, 9.8] per 100 PY).

Hypersensitivity

Hypersensitivity reactions were defined as all AEs (excluding ISRs) which occurred within 24 hours of a SC injection of placebo or TCZ which were not deemed unrelated to study medication. This conservative approach was taken to identify potential hypersensitivity reactions and included all AEs, regardless of whether they were medically consistent with hypersensitivity.

In Study WA29767 Final CSR Report the majority of hypersensitivity events in the TCZ arm were in the SOC of Infections and Infestations, including pharyngitis bacterial, tonsillitis, nasopharyngitis, sinusitis and pharyngitis.

In Study WA27788 Final CSR the hypersensitivity events in the TCZ arm were fatigue, headache, tension headache, pruritus, hot flush, vertigo, and pollakiuria (benign frequent daytime urination syndrome).

CHMP comment

The conservative approach to define hypersensitivity as all AEs (excluding ISRs) which occurred within 24 hours of a study drug reaction regardless of whether the AEs were medically consistent with hypersensitivity ensures that no event was missed. However, the incidence of reactions consistent with the hypersensitivity is missed and the analysis is not meaningful as demonstrated by data included in the Study WA29767 Final CSR, the events included Infections and Infestations, including pharyngitis bacterial, tonsillitis, nasopharyngitis, sinusitis and pharyngitis.

Clinically significant hypersensitivity

Clinically significant hypersensitivity AEs were defined as any AE within 24 hours of injection (excluding ISRs), not deemed unrelated to trial treatment, which led to treatment discontinuation.

In Study WA29767 Primary CSR, 2 patients (1.9%) in the placebo arm and no patient in the TCZ arm experienced clinically significant hypersensitivity AEs up to Week 48. Both patients experienced Grade 3 events (pneumonia [SAE] and abdominal pain) that were assessed to be related to study

drug (placebo). There was no clinically significant hypersensitivity experienced by any patient in the open-label period up to Week 96 in Study WA29767.

In Study WA27788 Final CSR, no patients in the TCZ arm experienced clinically significant hypersensitivity AEs by Week 24. One patient (2.3%) in the placebo arm experienced an SAE of hypertensive emergency prior to Week 24 which was retrieved as a hypersensitivity reaction due to its occurrence within 24 hours after injection of study drug (placebo). However, the clinical signs and symptoms of the event were not consistent with a hypersensitivity reaction. After Week 24, no hypersensitivity events were reported in either arm up to Week 96.

CHMP comment

None of the reported events were consistent with a hypersensitivity reaction.

Injection-site reactions

At Week 48, in the pooled Safety Population, the incidence and rate of ISRs was higher in the TCZ arm (11 [7.5%] patients; 27.9 [95% CI: 19.3, 38.9] AEs per 100 PY) compared with the placebo arm (5 [3.3%] patients; 4.8 [95% CI: 1.8, 10.5] AEs per 100 PY) (Table 48). At Week 96, in the pooled TCZ Safety Population, the incidence of ISRs was comparable but the rate was lowered (15 [5.6%] patients; 10.9 [95% CI: 7.8, 14.9] AEs per 100 PY) (Table 49) compared with those of Week 48 in the TCZ arm.

The most common ISR was General Disorders and Administration Site Conditions by SOC and Injection site erythema by PT, consistently through Week 48. The majority of ISRs were mild or moderate in intensity by Week 48 and by Week 96.

Infected Skin Ulcers

In the pooled Safety Population up to Week 48, 7 (4.7%) patients in the placebo arm had 10 infected skin ulcer events (8.1 [95% CI: 3.9, 14.8] AEs per 100 PY) and 7 (4.8%) patients in the TCZ arm had 8 events (6.6 [95% CI: 2.8, 12.9] AEs per 100 PY) (Table 48). Study WA27788 contributed more than Study WA29767 to the rates in both treatment arms. The rate in the TCZ arm up to Week 96 was 6.8 (95% CI: 4.4, 10.1) AEs per 100 PY (Table 49), comparable to that of Week 48.

Malignancies

In the pooled Safety Population during the first 48 weeks of treatment, the incidence of malignancies was low and comparable between treatment arms: 0.8 (95% CI: 0.0, 4.5) AEs per 100 PY in the placebo arm and 1.6 (95% CI: 0.2, 5.9) AEs per 100 PY in the TCZ arm (Table 48). Three cases were reported, all in Study WA29767: 1 event in the placebo arm and 2 events in the TCZ arm. The events were lung adenocarcinoma, B-cell lymphoma, and breast cancer; all 3 events were reported as SAEs.

During the open-label treatment period, 2 new cases of malignancy were reported in the TCZ arm: 1 (metastatic breast cancer) in Study WA27788 and the other (lung adenocarcinoma) in Study WA29767. The rate of malignancies in the TCZ treatment up to Week 96 pooled population was 1.1 (95% CI: 0.3, 2.8) AEs per 100 PY (Table 49).

Serious stroke

Up to Week 48, 1 patient in the placebo arm of Study WA27788 had 1 event of serious subarachnoid haemorrhage resulting in a rate of 0.8 (95% CI: 0.0, 4.5) AEs per 100 PY in the pooled placebo arm (Table 48).

There were no events of stroke reported in Study WA29767. There were no cases of serious stroke following TCZ treatment in the open-label period in either study.

Myocardial infarction

In the pooled Safety Population up to Week 48, 3 patients in the placebo arm and no patients in the TCZ arm had events of myocardial infarction, resulting in rates per 100 PY of 2.4 (95% CI: 0.5, 7.1) in the placebo arm (Table 48). These events were reported in 1 patient from Study WA27788 (acute myocardial infarction) and in 2 patients from Study WA29767 (1 resolved and 1 fatal event of acute myocardial infarction.

There were no cases of myocardial infarction in the open-label period in either study.

Anaphylactic reactions

During the full 96-week study period, no patients experienced any anaphylactic reaction in either study.

Bleeding events

In the pooled Safety Population up to Week 48, 1 patient each from the placebo arms in Study WA29767 and Study WA27788 had a serious or medically significant bleeding event (Table 48). The events were serious ecchymosis in 1 patient from Study WA29767 and serious subarachnoid haemorrhage in 1 patient from Study.

Up to Week 96, 1 serious bleeding event of uterine haemorrhage was reported in the TCZ arm of Study WA27788.

Laboratory findings

In the pooled Safety Population at Week 48, the incidence of laboratory values outside the normal range was generally similar in the two treatment arms (or up to 5 patients higher in the placebo arm), with the exception of the following parameters, which were represented with at least 10 patients more in the TCZ arm.

- Neutropenia (neutrophils $<1.5x10^9$/L): 2 patients (2 events) with placebo versus 13 patients (33 events) with TCZ
- Cholesterol (fasting, $\geq$6.18 mmol/L): 23 patients (44 events) with placebo versus 48 patients (104 events) with TCZ

- LDL Cholesterol (fasting, ☐4.13 mmol/L): 13 patients (25 events) with placebo versus 36 patients (61 events) with TCZ

At baseline, patients in the pooled Safety Population had mean laboratory values generally within normal ranges for all laboratory parameters tested. At Week 48, shifts from baseline in the pooled Safety Population were most common with haematology and hepatic laboratory parameters. In the following parameters, the proportion of patients who experienced a shift from baseline that was more than 5% higher in the TCZ group compared to the placebo group (expressed in percentage of patients in the placebo vs. TCZ arm):

- NCI CTCAE Grade 1 high ALT: 10.1% versus 30.4%
- NCI CTCAE Grade 1 high AST: 14.3% versus 25.4%
- NCI CTCAE Grade 1 low neutrophils: 1.4% versus 17.6%
- NCI CTCAE Grade 1 low platelets: 0.7% versus 9.5%
- NCI CTCAE Grade1 high bilirubin: 0.7% versus 7.5%

In both arms, most parameters had shifts from baseline with highest NCI CTCAE Grade 1 or 2. In the pooled population, patients treated with placebo had a higher incidence of Grade 1 shifts from baseline for high cholesterol (34.4% placebo vs. 16.7% TCZ).

In the pooled Safety Population, for patients treated with TCZ SC for up to 48 weeks:

- Neutrophil count $<1x10^9$/L (CTC Grade 3) was experienced by 9 (5%) patients, and was not associated with the occurrence of serious infections
- Platelet count $<100 \times 10^9$/L (☐CTC Grade 1) was experienced by 0 (0%) patients, and no patients with low platelets experienced serious bleeding events.
- ALT or AST >3 x ULN was experienced by 2 (2%) and 4 (3%) patients, respectively, and ALT or AST >5 x ULN was experienced by 3 (2%) and 1 (1%) patients, respectively, and there were no Hy's law cases (i.e., > 3 × ULN transaminase elevation concurrently with >2 × ULN total bilirubin elevation); there were no hepatic events associated with Grade $\geq$3 ALT or AST elevation.

Vital signs

Table 52 Summary of Abnormal Vital Signs (Week 48)

Summary of Abnormal Vital Signs (Week 48), Safety Population
Project: CN11935I

	WA27788 (N=87)		WA29767 (N=210)	
	PBO 162 mg qw SC (N=44)	TCZ 162 mg qw SC (N=43)	PBO 162 mg qw SC (N=106)	TCZ 162 mg qw SC (N=104)
SBP - High				
n	44	43	104	104
No	40 (90.9%)	36 (83.7%)	99 (96.2%)	93 (89.4%)
Yes	4 (9.1%)	7 (16.3%)	5 (4.8%)	11 (10.6%)
SBP - Low				
n	44	43	104	104
No	43 (97.7%)	42 (97.7%)	101 (97.1%)	103 (99.0%)
Yes	1 (2.3%)	1 (2.3%)	3 (2.9%)	1 (1.0%)
DBP - High				
n	44	43	104	104
No	43 (97.7%)	42 (97.7%)	103 (99.0%)	102 (98.1%)
Yes	1 (2.3%)	1 (2.3%)	1 (1.0%)	2 (1.9%)
DBP - Low				
n	44	43	104	104
No	41 (93.2%)	40 (93.0%)	100 (96.2%)	99 (95.2%)
Yes	3 (6.8%)	3 (7.0%)	4 (3.8%)	5 (4.8%)

Percentages are based on n.
Systolic Blood Pressure normal range - 90 - 140 mmHg.
Diastolic Blood Pressure normal range - 60 - 90 mmHg.
H = Above reference range and >20 change from baseline in either direction.
L = Below reference range and >20 change from baseline in either direction.

Program: /opt/BIOSTAT/prod/cn11935i/p11935h/t_vs_abn.sas
Output: /opt/BIOSTAT/prod/cn11935i/p11935h/reports/t_vs_abn_SE_W48.out

Week 48 a lower proportion of patients in the placebo arm had high SBP values (9.1% placebo vs. 16.3% TCZ in Study WA27788 and 4.8% placebo vs. 10.6% TCZ in Study WA29767)

Safety in special populations

SSc-ILD Status

In Study WA29767 Safety Population up to Week 48, post hoc analyses were performed for the subgroup of patients who had ILD at baseline.

Table 53 Overview of Adverse Events for All Patients and Patients with SSc-ILD up to Week 48

	Patients with SSc in WA29767 and WA27788 Pooled		Patients with SSc-ILD in WA29767	
	PBO 162 mg QW SC (N=150)	TCZ 162 mg QW SC (N=147)	PBO 162 mg QW SC (N=68)	TCZ 162 mg QW SC (N=68)
Total number of patients with at least one adverse event	122 (81.3%)	131 (89.1%)	57 (83.8%)	63 (92.6%)
Total number of events	733	705	333	295
Total number of deaths	4 (2.7%)	4 (2.7%)	3 (4.4%)	1 (1.5%)
Total number of patients withdrawn from study due to an AE	16 (10.7%)	12 (8.2%)	2 (2.9%)	3 (4.4%)
Total number of patients with at least one				
Serious AE	33 (22.0%)	27 (18.4%)	15 (22.1%)	9 (13.2%)
AE leading to withdrawal from treatment	16 (10.7%)	12 (8.2%)	9 (13.2%)	6 (8.8%)
AE leading to dose modification/interruption	37 (24.7%)	33 (22.4%)	19 (27.9%)	15 (22.1%)
AESI - Total number of patients with at least one				
Infections and Infestations Adverse Events	75 (50.0%)	80 (54.4%)	38 (55.9%)	40 (58.8%)
Serious Infections and Infestations Adverse Events*	8 (5.3%)	11 (7.5%)	7 (10.3%)	2 (2.9%)
Opportunistic Infections Adverse Events	1 (0.7%)	1 (0.7%)	1 (1.5%)	0
Malignancy Adverse Events	1 (0.7%)	2 (1.4%)	1 (1.5%)	2 (2.9%)
Malignancy Adverse Events (excluding NMSC)	1 (0.7%)	2 (1.4%)	1 (1.5%)	2 (2.9%)
Serious Myocardial Infarction Adverse Events	3 (2.0%)	0	1 (1.5%)	0
Serious Bleeding Adverse Events	2 (1.3%)	0	1 (1.5%)	0

AE –adverse event; AESI –adverse event of special interest; MedDRA –Medical Dictionary for Regulatory Activities; NMSC –non-melanoma skin cancer; PBO –placebo; QW –weekly; SC –subcutaneous; SSc –systemic sclerosis; SSc-ILD –systemic sclerosis with interstitial lung disease; TCZ –tocilizumab.

*Listing (l_ae_SE_SAE_INF)of serious infections and infestations AEs is provided.

Notes: Investigator text for AEs is coded using MedDRA version 20.1. Only anaphylactic AEs occurred within 24 hours after the injection are included.

Percentages are based on N in the column headline. Multiple occurrences of the same AE in 1 individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Source: SA8811_t_saf_sum_SE_ILD, SA9701_t_ae_ov_SE_W48

The fey findings are:

- Overall, the safety profile of the patients with SSc-ILD was consistent with that observed in the pooled population of Studies WA29767 and WA27788.
- The most commonly reported AEs by PT (☐10% of patients in either arm) in patients with SSc-ILD were upper respiratory tract infection, nasopharyngitis, diarrhoea, arthralgia, skin ulcer, and interstitial lung disease.
- The most commonly reported AEs by SOC (>25% of patients in either arm) in the patients with SSc-ILD was Infections and Infestations, consistent with the pooled population. The incidence in the patients with SSc-ILD was 55.9% in the placebo arm and 58.8% in the TCZ arm, comparable to 50.0% in the placebo arm and 54.4% in the TCZ arm in the pooled population.
    - The most common reported Infections and Infestations by PT (≥10% patients in any arms) in the patients with SSc-ILD were upper respiratory tract infection and nasopharyngitis
- The incidence of SAE was comparable between the SSc-ILD subgroup and the pooled population, 22.1% in the placebo arm and 13.2% in the TCZ arm in the SSc-ILD subgroup versus 22.0% in the placebo arm and 18.4% in the TCZ arm in the pooled population.

- The incidence of AEs leading to withdrawal was lower in the SSc-ILD group than in the pooled SSc population, for both TCZ (4.4% vs. 8.2%) and placebo (2.9% vs. 10.7%)
- Similar with the pooled SSc population, the proportion of patients who experienced AESIs in the SSc-ILD subgroup was in general low, with the exceptions of all and serious infections:
    - Infections were the most commonly reported AESI. The incidence was comparable across the pooled SSc and SSc-ILD subgroups (Pooled placebo arm 50.0% and TCZ arm 54.4%; SSc-ILD: placebo arm 55.9% and the TCZ arm 58.8%). The incidence of serious infection AESI was higher in the placebo arm (10.3%) compared with the TCZ arm (2.9%) in the SSc-ILD subgroup. The most frequent PT was pneumonia. In the pooled population, the incidence was lower in the placebo arm (5.3%) while higher in the TCZ arm (7.5%).
- The incidence of serious SSc-related complications was low in the patients with SSc-ILD 6 [8.8%] in the placebo arm and 5 [7.4%] in the TCZ arm). The most frequent SOC was Cardiac Disorder.
- There were no serious demyelinating AEs, serious or medically significant hepatic AEs, gastrointestinal perforations, stroke, nor anaphylactic reactions in the patients with SSc-ILD.

Discontinuation due to adverse events

Treatment up to Week 48

In the pooled Safety Population, the proportion of patients who experienced AEs leading to treatment withdrawal was comparable between the placebo arm and the TCZ arm (10.7% [16 patients) in the placebo arm vs. 8.2% [12 patients] in the TCZ arm) (Table 49). This corresponded to comparable AE rates in the placebo arm versus TCZ arm (12.9 [95% CI: 7.4, 20.9] vs. 9.8 [95% CI: 5.1, 17.2] AEs per 100 PY). The pooled rates for AEs leading to treatment withdrawal were driven by the higher rates observed in Study WA27788 compared with Study WA29767.

In the pooled population, these AEs were most commonly reported ($\geq$3 patients in either treatment arm) in the following SOCs: Infections and Infestations; Respiratory, Thoracic and Mediastinal Disorders; and Cardiac Disorders.

TCZ Treatment up to Week 96

In the TCZ treatment up to Week 96 pooled Safety Population, AEs leading to withdrawal of study treatment were reported in 19 (7.1%, n=267) patients, resulting in a pooled rate of 5.2 (95% CI: 3.1, 8.1) AEs per 100 PY, comparable to the pooled rate of 9.8 (95% CI: 5.1, 17.2) by Week 48 (Table 49). The most common AE by SOC is Infections and Infestations.

Adverse Events That Led to Dose Modification or Interruption

At Week 48, in the pooled Safety Population, the incidence and rate of AEs leading to dose modification or interruption was comparable between the placebo arm (37 [24.7%] patients; 49.2 [95% CI: 37.6, 63.2] AEs per 100 PY) and the TCZ arm (33 [22.4%] patients; 43.4 [95% CI: 32.5, 56.8] AEs per 100 PY). Study WA27788 contributed more to the rates per 100 PY than Study WA29767 (Table 49).

At Week 96, in the pooled TCZ Safety Population, the rate of AEs leading to dose modification or interruption was comparable with that of Week 48 (92 [34.5%] patients; 40.1 [95% CI: 33.9, 47.1] AE per 100 PY) (Table 50).

Immunogenicity

At Week 48, 1 patient in the TCZ arm of Study WA29767 (0.7% of patients in the pooled TCZ arm) tested positive for treatment-induced ADA (the patient was ADA-negative at baseline and developed an ADA response following TCZ administration), and the ADA were of neutralising potential.

At Week 96, 2 patients in the TCZ arm of Study WA27788 tested positive for treatment-induced ADA which were of neutralising potential. Including the patient who tested positive before Week 48 in Study WA29767, this resulted in 3 (1.8%) of patients in the pooled Safety Population developing treatment-induced ADA on TCZ treatment by Week 96, which were all of neutralising potential.

The patients who developed ADA did not experience any AEs indicative of hypersensitivity. No patients had ADA of the IgE isotype.

Post marketing experience

Since the IBD (11 April 2005) to 31 March 2022 (inclusive), an estimated total of 3,454,753 patients (3,036,654 PY) have received TCZ in the post-authorization phase. The cumulative post-marketing exposure of patients to TCZ IV was estimated to be 2,496,823 patients (2,256,429 PY). The cumulative post-marketing exposure of patients to TCZ SC was 957,930 (780,226 PY).

Source of Post marketing Safety Data

Post marketing safety data presented in PBRER 1113952 (reporting interval: 11 April 2019-10 April 2021) included non-interventional studies (NIS; including post authorisation safety studies), reports from other solicited sources, and spontaneous Individual Case Safety Reports (ICSRs) (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature) in the approved indications.

Table 54 Total Numbers of Adverse Events and SOCs of the Most Frequently reported AEs from Post-Authorisation Sources

SOC	Spontaneous, including health authority (worldwide) and literature				Non-interventional post-marketing study and reports from other solicited sources [a]	
	Serious		Non-serious		Serious	
	interval	cum.	interval	cum.	interval	cum.
Total no. of AEs (all SOCs)	62101	95257	101122	153636	18374	68372
SOCs of the most frequently reported AEs in the reporting interval and cumulatively						
General disorders and administration site conditions	12883	17258	38835	53881	2082	6803
Injury, poisoning and procedural complications	5878	7132	47484	55185	1872	6071
Musculoskeletal and connective tissue disorders	9214	12184	2725	6813	1455	6518
Infections and infestations	7077	13300	1694	4976	3927	14689

AE = adverse event; cum. = cumulative; SOC = System Organ Class.

Source: PBRER 1113952 Appendix 2b (Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post marketing data sources).

Note: Post-authorization Sources include non-interventional studies (including post-authorization safety studies), reports from other solicited sources, and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature).

[a] This does not include interventional clinical trials.

Off-Label Use

Roche captures off-label use as 1) preferred terms Off-label use, and/or either 2) preferred terms of product used in unapproved indications, 3) Intentional product use issue. Detailed analysis of off-label use with TCZ is provided in the most current PBRER 1113952. Review of TCZ off-label use data during the reporting period of this PBRER has not identified any new safety concerns in reported off-label indications including SSc-ILD (off-label indication in countries other than the United States). SAEs were consistent with the underlying condition and the observed safety profile of TCZ in other approved indications.

2.6.1. Discussion on clinical safety

In both studies, the population for safety analyses was the Safety Population, defined as all randomised patients who received at least one dose of study drug and provided data from at least one post dose safety assessment (withdrawal, AE, death, laboratory assessment, or vital signs assessment). Patients were grouped according to the treatment actually received.

- Treatment up to Week 48 (n=297): This population includes all safety-evaluable patients enrolled in Studies WA29767 and WA27788 who had safety data up to the completion of the Week 48 visit.

- TCZ Treatment up to Week 96 (n=267): This population includes long-term safety data from all safety-evaluable patients enrolled in Studies WA29767 and WA27788 up to Week 96.

At Week 48, the proportion of patients who experienced at least 1 AE was comparable between the two arms, 81.3% in the pooled placebo arm compared with 89.1% in the pooled TCZ arm. The most commonly reported AEs by SOC (>25% of patients in either arm) was Infections and Infestations (50.0% in the placebo arm and 54.4% in the TCZ arm).

In the section common adverse events the MAA provided a "conclusion" of the safety data up to Week 96, however the statement is not substantiated by data. Please provide a summary of the safety date of the OL study part in the same manner as for the Week 48 data (OC).

In the pooled Safety Population, up to Week 48 there were 8 death reported in both arms of each study. Four death in each arm. Details were provided in the respective CSRs. It can be agreed with the assessment of the investigators that one event (pneumonia) was assesses related to the study drug, the other 7 events deemed rather related to the underlying disease.

In the TCZ treatment up to Week 96 pooled population, 2 additional deaths were reported. One patient who was randomised to placebo arm at study entry experienced arrhythmia, cardiorespiratory arrest, pneumonia aspiration, sepsis and died of brain injury. The other patient was in the TCZ treatment arm and experienced cardiac failure and died of pulmonary hypertension. Both events were assessed as related to study drug by the investigator.

The SAE rate was numerically higher in the pooled placebo arm, 43.5 (95% CI: [32.7, 56.8]) AEs per 100 PY compared with 30.3 (95% CI: [21.4, 41.8]) AEs per 100 PY in the pooled TCZ arm.

The proportion of patients who experienced AE leading to withdrawal was comparable, 10.7% in the pooled placebo arm and 8.2% in the pooled TCZ arm. The proportion of patients who experienced AE leading to dose modification or interruption was also comparable, 24.7% in the pooled placebo arm and 22.4% in the pooled TCZ arm.

The proportion of patients who experienced AESI was in general low, with the exceptions of Infection and Infestation and serious infections.

Infection and Infestation was the most commonly reported AESI. The incidence was comparable in the pooled placebo arm (50.0%) compared with the pooled TCZ arm (54.4%). In Study WA27788, the incidence was higher on the TCZ arm (50.0% in placebo vs. 60.5% in TCZ). In Study WA29767, the incidence was comparable in both arms (50.0% in placebo and 51.9% in TCZ).

The incidence of serious infection AESI was slightly higher in the pooled TCZ arm (7.5%), compared to the pooled placebo arm (5.3%). Of note, in Study WA27788 there was a higher incidence of serious infections in the TCZ arm compared to placebo (2.3% in placebo and 20.9% in TCZ), whereas in Study WA29767, the incidence of serious infections was higher on the placebo arm (6.6% in placebo and 1.9% in TCZ).

The incidence of ISRs and hypersensitivity was higher in the TCZ arms compared to the placebo arms in both studies and in the pooled data. Hypersensitivity reactions were defined as all AEs (excluding ISRs) which occurred within 24 hours of a SC injection of placebo or TCZ which were not deemed unrelated to study medication. This conservative approach was taken to identify potential hypersensitivity reactions and included all AEs, regardless of whether they were medically consistent with hypersensitivity. The conservative approach to define hypersensitivity as all AEs (excluding ISRs) which occurred within 24 hours of a study drug reaction regardless of whether the AEs were medically consistent with hypersensitivity ensures that no event was missed. However, the incidence of reactions consistent with

the hypersensitivity is missed and the analysis is not meaningful as demonstrated by data included in the Study WA29767 Final CSR, the events included Infections and Infestations, including pharyngitis bacterial, tonsillitis, nasopharyngitis, sinusitis and pharyngitis. None of the reported events were consistent with a hypersensitivity reaction.

There were no notable differences in the AESI of opportunistic infections, malignancies, serious stroke, myocardial infarctions, serious or medically significant bleeding events or infected skin ulcers between the pooled arms. In addition, there were no serious demyelinating AEs, serious or medically significant hepatic AEs, serious gastrointestinal perforations, nor anaphylactic reactions in any arms.

No signals were observed evaluating laboratory parameter and vital signs.

The safety profile of the patients with SSc-ILD was consistent with that observed in the pooled population of Studies WA29767 and WA27788.

2.6.2. Conclusions on clinical safety

Overall, safety data of TCZ in Studies WA29767 and WA27788 were consistent with the known safety profile of TCZ, and no new or unexpected safety concerns were identified. Treatment of patients with SSc with TCZ was generally well tolerated.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated risk management plan (RMP) version 28.0 with this application. The (main) proposed RMP changes were the following:

- Update regarding the use of the subcutaneous (SC) formulation of tocilizumab in systemic sclerosis associated interstitial lung disease (SSc-ILD)
- Updates to the relevant sections from the recently completed long-term extension study WA29231 with tocilizumab SC in pediatric patients with polyarticular-course or systemic juvenile idiopathic arthritis

- Part I: Product overview updated to reflect proposed indication and dosage in systemic sclerosis associated interstitial lung disease (SSc-ILD).
- Part II: Module SI: updated to reflect pertinent epidemiological literature on SSc-ILD and information pertinent to pregnancy rates and adverse pregnancy outcomes for the indications.
- Part II: Module SIII: clinical trial exposure updated to include exposure in SSc-ILD patients from the WA29767 (focuSSced) trial and updated exposure for polyarticular-course (pJIA) and systemic juvenile idiopathic arthritis (sJIA) indications from Study WA29231 (JIGSAW long-term extension study with tocilizumab SC).
- Part II: Module SIV.3: updated as per the EMA Pregnancy and Breastfeeding Guidance (GVP P.III).
- Part II: Module SV: updated with cumulative and interval post-authorisation exposure to tocilizumab as of latest PBRER 1113952 (data lock point: 10 April 2022).

- Part II: Module SVII.3: information specific for SSc-ILD is included wherever applicable for important identified and potential risks. Minor corrections were made to the risk tables of hepatotoxicity presenting laboratory data from phase III studies WA42380 (COVACTA), ML42528 (EMPACTA) and WA42511 (REMDACTA) with tocilizumab IV for the COVID-19 indication.
- Part III.1: Added other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding.
- Part IV, Part V, Part VI: Information updated to include the SSc-ILD indication, wherever appropriate.
- Annex 6 was updated to include the indication SSc-ILD and removal of cytokine release syndrome (CRS) as no additional risk minimisation measure is applicable for the treatment of CRS.
- Annex 7 was updated with the new references for the indication SSc-ILD and epidemiological data for the adverse pregnancy outcomes for the indications. It has been also updated with the pregnancy data having interval and cumulative outputs.

3.1. Safety Specification

Epidemiology of the indications and target population

In the new version of the RMP, where available from the literature, the MAH added information on pregnancy rates and outcomes for the diseases for which tocilizumab is approved. The percentage of subfertile individuals is higher in RA patients than in the general population, and RA has been associated with increased risks of adverse pregnancy outcomes. Studies suggested an increased risk of pregnancy complications and adverse outcomes in women with JIA. Besides, the MAH cites literature indicating an increased risk of adverse pregnancy and neonatal outcomes in pregnant women with COVID-19.

A section on systemic sclerosis-associated interstitial lung disease (SSc-ILD) has been added. According to the MAH, data on the epidemiology of SSc-ILD is scarce in literature. A systematic review of studies published between 2009 and 2015 reported an annual incidence of SSc-ILD in Europe between 0.1 and 0.4 per 100,000 population. The prevalence of SSc-ILD was estimated to range between 1.7 and 4.2 per 100,000 population. Another study generated a prevalence of 2.32 cases per 100,000 population in Canada. In the United States, a retrospective cohort study over the period 2011-2016 gave an overall crude and age-sex standardised incidence rate of SSc-ILD of 1.2 and 1.1 per 100,000 person-years, respectively. The crude and age-sex standardised prevalence was reported to be 6.9 and 7.3 per 100,000, respectively. SSc-ILD predominantly affects women. The MAH states that common comorbidities are Raynaud's phenomenon, gastroesophageal reflux disease, pulmonary arterial hypertension, dysrhythmia, rheumatoid arthritis, systemic lupus erythematosus, peripheral vascular disease, and depression.

PRAC comment:

The amendments in Part II, Module SI, "Epidemiology of the indication(s) and target population(s)", regarding pregnancy/adverse pregnancy outcomes and the new indication SSc-ILD are endorsed.

Comment on the literature on pregnancy cited by the MAH: Chen et al [1] write that "the differences in rates of severe neonatal morbidity and admission to a NICU disappeared after adjusting for these predictors [i.e. maternal age at birth, nulliparity, hypertension, diabetes, socio-economic status and smoking during pregnancy] and preterm birth". This is not clear from the MAH's summary. The articles cited by the MAH do not mention an increased risk of congenital malformations in JIA patients. This can be found in the study by Ehrmann Feldman et al [2].

[1] Chen JS, Ford JB, Roberts CL, Simpson JM, March LM. Pregnancy outcomes in women with juvenile idiopathic arthritis: a population-based study. Rheumatology (Oxford) 2013;52(6):1119–25.

[2] Ehrmann Feldman D, Vinet É, Bernatsky S, Duffy C, Hazel B, Meshefedjian G et al. Birth Outcomes in Women with a History of Juvenile Idiopathic Arthritis. J Rheumatol 2016;43(4):804–9.

In the section on SSc-ILD, the MAH should strive for a clear terminology. Here it is unclear what is meant by dysrhythmia.

Related to the entire chapter and not just the new contents: Some of the comorbidities mentioned – for example of GCA patients – are observed more frequently as a consequence of corticosteroid therapy. At the time of the data lock point of this RMP (April 2022), five vaccines against COVID-19 were authorised in the European Union: Comirnaty, Spikevax, Vaxzevria, Jcovden, and Nuvaxovid. In addition to vaccination, distance, masks and avoidance of contact by infected and to infected persons provide protection. On 06 December 2021, the human medicines committee of the European Medicines Agency (CHMP) recommended extending the indication of RoActemra (tocilizumab) to include the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation. The MAH is kindly requested to keep this section of the RMP up to date.

Clinical trial exposure

The MAH reports the number of individuals exposed to IV tocilizumab in clinical trials as 7,014, corresponding to 16,146.3 person-years, and the number of individuals exposed to SC tocilizumab in clinical trials as 1,752, corresponding to 2,017.8 person-years. For the targeted indication SSc-ILD, the exposure data (SC tocilizumab) are 122 persons – 24 males and 98 females – and 149.2 person-years, respectively.

Populations not studied in clinical trials

The exclusion criteria in clinical studies are either included in the contraindications (for example hypersensitivity, active severe infections) or special warnings and precautions (for example liver disease, tuberculosis), or reflect non-safety aspects that should ensure the feasibility of the studies (for example uncontrolled disease states, lack of peripheral venous access). Data on use in pregnancy is poor.

The MAH added some sentences on the use of tocilizumab in pregnancy and lactation. Tocilizumab was not teratogenic in a cynomolgus monkey study at a daily dose of 50 mg/kg/day (highest dose) associated with a high systemic cumulative exposure of > 100 above the expected human efficacious concentration. However, a higher rate of abortion was noted in this dose group compared with the placebo and other low dose groups, but still within historical background rates for cynomolgus monkeys in captivity. IL-6 deficient mice are fertile and their offspring does not show an abnormal phenotype. According to the MAH, no IL-6-inhibition-related effects were observed on murine fertility, pre-natal and postnatal development. All in all, IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface. Since preclinical data suggest an increased risk of spontaneous abortion, tocilizumab may represent a potential risk to pregnant women.

PRAC comment:

A relevant proportion of RA patients is female and of childbearing age. The note in the SmPC and the register (cf. PBRER 1113952) are therefore essential.

Identified and potential risks

Data on SSc-ILD patients were added where available.

PRAC comment:
There were no new important identified or potential risks identified in the SSc-ILD population.

3.2. Summary of the safety concerns

Table 55 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	– Serious infection* – Complications of diverticulitis* – Neutropenia – Hepatotoxicity
Important potential risks	– Thrombocytopenia and the potential risk of bleeding – Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events – Malignancies – Demyelinating disorders – Immunogenicity
Missing information	None

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

3.3. Pharmacovigilance plan

Routine Pharmacovigilance Activities

New information has been included in the RMP concerning the Roche standard pregnancy follow-up process.

As unchanged routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, the MAH mentions specific adverse reaction follow-up forms (guided questionnaires) for serious infections, complications of diverticulitis (including gastrointestinal perforation), thrombocytopenia and the potential risk of bleeding, hepatotoxicity, elevated lipid levels and the potential risk of cardiovascular/cerebrovascular events, malignancies, and demyelinating disorders. In addition, the MAH addresses its data collection on hematogenous bacterial arthritis in the sJIA population < 18 years of age, and its collection and analysis of anti-tocilizumab antibodies in all patients treated with tocilizumab

(routine sampling) and in patients who experience hypersensitivity that lead to study withdrawn (event driven sampling) in ongoing clinical trials.

Additional Pharmacovigilance Activities

Two category 3 register studies are still ongoing; there are no changes in the new version of the RMP.

Table 56 On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
ML28664 (formerly tracked as GA28719) (RABBIT) registry study (category 3)	To provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA	Serious infections, complications of diverticulitis (including gastrointestinal perforation), neutropenia, thrombocytopenia and the potential risk of bleeding, hepatotoxicity, elevated lipid levels and potential risk of cardiovascular/cerebrovascular events, malignancies, demyelinating disorders	ongoing	Q4 2022
WA29358 (paediatrics registry study, category 3)	Collecting long-term efficacy and safety data for tocilizumab in the treatment of pJIA	Impact of tocilizumab therapy on the increased risk of atherosclerosis (cardiovascular events), growth and development, influence on the occurrence/treatment of uveitis and to evaluate the risk of malignancies, serious infections, and gastrointestinal perforation, and the efficacy of the 10 mg/kg IV Q4W regimen, and the impact of RF status on efficacy	ongoing	Q1 2026

*Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)
Q, quarter; Q4W, once every 4 weeks; RF, rheumatoid factor

Additional risk minimisation measures are targeted for the indications of RA, GCA, pJIA, sJIA, and SSc-ILD. These measures are not applicable for the COVID-19 indication.

Safety concern	**Serious infections***
Additional risk minimisation measure	Patient alert card; patient brochure; healthcare provider brochure; dosing guide
Objectives	To ensure that patients seek medical attention early, and that healthcare providers are aware of the need for timely and appropriate measures to diagnose and treat infections
Rationale for the additional risk minimisation activity	Patient alert card: To inform both the patient and healthcare providers that tocilizumab increases the risk of getting infections which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of infections Patient brochure: To inform the patient of the risk of serious infections and provide additional guidance beyond that provided in the patient information leaflet (PIL) Healthcare provider brochure: To inform and provide more detailed guidance to healthcare providerson the risk of serious infections Dosing guide: To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704 the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Complications of diverticulitis***
Additional risk minimisation measure	Patient alert card; patient brochure; healthcare provider brochure; dosing guide
Objectives	To ensure that patients seek medical attention early, and that the healthcare providers are aware of the need for timely and appropriate measures to diagnose and treat complications of diverticulitis
Rationale for the additional risk minimisation activity	Patient alert card: To inform both the patient and healthcare providers that patients using tocilizumab may develop complications of diverticulitis which can become serious if not

	treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events Patient brochure: To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL Healthcare provider brochure: To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis Dosing guide: To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704, the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Neutropenia**
Additional risk minimisation measure	Patient brochure; healthcare provider brochure; dosing guide
Objectives	To ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat neutropenia
Rationale for the additional risk minimisation activity	Patient brochure: To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of neutropenia Dosing guide: To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704, the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Hepatotoxicity**
Additional risk minimisation measure	Patient brochure; healthcare provider brochure; patient alert card, direct healthcare professional communication (DHPC)

Objectives	To ensure that patients seek medical attention early, and that healthcare providers are aware of the risk of hepatotoxicity and the need for timely and appropriate measures to detect hepatotoxicity
Rationale for the additional risk minimisation activity	Patient brochure: To inform the patient of the risk of hepatotoxicity and provide additional guidance beyond that provided in the PIL Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of hepatotoxicity Patient alert card: To inform both the patient and health care providers that patients using tocilizumab may develop hepatotoxicity, and on rare occasions, patients have experienced serious life-threatening liver problems, some of which have required liver transplant. Patients will be monitored closely for changes in blood liver enzyme level. DHPC (one time only RMM activity): To inform healthcare professionals of serious drug-induced liver injury, including acute liver failure, hepatitis, and jaundice, in some cases requiring liver transplant, that have been observed with the administration of Actemra/RoActemra® (tocilizumab). The frequency of serious hepatotoxicity is considered rare. Healthcare professionals should follow the guidance including dose modification and tocilizumab discontinuation as per the approved label.
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	– Metrics of distribution channels of educational materials to patients and healthcare professionals. – Comparison of exposure-adjusted reporting rates for the relevant events by PSUR period as proxy for comprehension/readability evaluation of patients and healthcare professions on the content of the educational materials and compliance with recommendations. The intervention will be assessed as effective, if no indication of sustained or increasing trend in exposure-adjusted response rate for serious hepatic events over time per PSUR interval
Safety concern	**Thrombocytopenia and the potential risk of bleeding**
Additional risk minimisation measure	Healthcare provider brochure; patient brochure
Objectives	To ensure that patients seek medical attention early, and that the healthcare providers are aware of the need for timely and appropriate measures to diagnose and treat thrombocytopenia

Rationale for the additional risk minimisation activity	Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of thrombocytopenia Patient brochure: To inform the patient of the risk of thrombocytopenia beyond that provided in the PIL
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704 the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Elevated lipid levels and potential risk of cardiovascular/cerebrovascular events**
Additional risk minimisation measure	Patient brochure; healthcare provider brochure; dosing guide
Objectives	To ensure that patients seek medical attention early, and that the healthcare providers are aware of the need for timely and appropriate measures to detect elevated lipid levels and evaluate further.
Rationale for the additional risk minimisation activity	Patient brochure: To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of elevated lipid levels Dosing guide: To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704 the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Malignancies**
Additional risk minimisation measure	Patient brochure; healthcare provider brochure; dosing guide
Objectives	To ensure that patients seek medical attention early, and that the healthcare providers are aware of the need for timely and appropriate measures to diagnose and treat malignancies.
Rationale for the additional risk minimisation activity	Patient brochure: To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL

	Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of malignancies Dosing guide: To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704 the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.
Safety concern	**Demyelinating disorders**
Additional risk minimisation measure	Healthcare provider brochure
Objectives	To ensure that the healthcare providers are aware of the need for timely and appropriate measures to diagnose and treat demyelinating disorders.
Rationale for the additional risk minimisation activity	Healthcare provider brochure: To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Target audience and planned distribution path	Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. EMEA/H/C/PSUSA/00002980/201704 the commitment of the MAH to present evaluations of effectiveness of additional risk minimisation measure metrics is considered fulfilled as of PSUR 17.

1.1. ***Risk minimisation measures***

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Serious infections*	SmPC IV and SC formulation: Section 4.3 Contraindications active, severe infections (see Section 4.4) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet: IV and SC formulation: Section 2. What you need to know before you are given tocilizumab	Patient alert card Patient brochure Healthcare provider brochure Dosing guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4 Possible serious side effects: tell a doctor straightaway. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	
Complications of Diverticulitis*	SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet: Section 2 Warnings and precautions Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	Patient alert card Patient brochure Healthcare provider brochure Dosing guide
Neutropenia	SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations Patient information leaflet	Patient brochure Healthcare provider brochure Dosing guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 2 What you need to know before you used RoActemra Section 4 Possible Side Effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	
Hepatotoxicity	SmPC Section 4.2 Posology and method of administration (IV formulation) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet (IV/SC formulation) Section 2 Warning and precautions Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: In patients with RA, GCA, pJIA, sJIA, SSc-ILD, ALT and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	Patient brochure Healthcare provider brochure Patient alert card DHPC

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Thrombocytopenia and the potential risk of bleeding	SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.2 Posology and method of administration (IV formulation) Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	Patient brochure Healthcare provider brochure
Elevated lipid levels and potential risk of cardiovascular/cerebrovascular events	SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warning and precautions Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	Patient brochure Healthcare provider brochure Dosing guide
Malignancies	SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	Patient brochure Healthcare provider brochure Dosing guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	
Demyelinating disorders	SmPC Section 4.4 Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	Healthcare provider brochure
Immunogenicity	SmPC Section 4.8 Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the product information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine.	No additional risk minimisation measure.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

PRAC comment:

The risk-minimising measures described by MAH appear appropriate.

The summary of the RMP for RoActemra (tocilizumab) and the annexes have been updated accordingly.

The summary of the RMP for RoActemra (tocilizumab) has been updated accordingly

Annexes

The updated Annex 6 indicates that dose calculation for infusion is also required for the newly sought SSc-ILD indication, while it seems only the fixed dose formulation (i.e., 162 mg injection) is proposed in this application. SSc-ILD may therefore be removed from the key message regarding dose calculation.

Except for Annex 6 (see above) the annexes have been updated accordingly.

3.4. Overall conclusion on the RMP

The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

4. Changes to the Product Information

As a result of this variation procedure, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC of RoActemra 20 mg/mL concentrate for solution for infusion are being updated to reflect the treatment of new indication for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for RoActemra. The Package Leaflet (PL) is updated accordingly in section 1, 2, and 3.

Changes are also made to the PI to bring it in line with the current QRD template version, the Annex of the excipients guideline and other QRD recommendations.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

4.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The MAH submitted a Type II variation to include the treatment of new indication for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). The amendments of the content of the package leaflet related to 162 mg/ mL are minor and no significant changes to the key safety messages are inserted compared to the already user tested version. The update follows the same structure and uses similar descriptions. The patient target group does not fundamentally change so that readability is affected. In addition. the posology is the same as for the already approved indication.

Therefore, neither a consultation with target patient groups nor a focus test should be performed. The justification submitted by the company is acceptable.

4.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, RoActemra (tocilizumab) was removed from the additional monitoring list as new active substance , biological after five years after the Union reference date.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, was removed from the summary of product characteristics and the package leaflet.

4.3. Quick Response (QR) code

Not applicable

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Systemic sclerosis (SSc, also known as a form of scleroderma) is a rare, multisystem, connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs. It is characterized by microvascular damage and fibrosis of the skin and of various internal organs. Although the pathogenesis of SSc is not yet fully understood, it is believed to result from increased systemic fibrosis, vasculopathy, and immune dysfunction.

The clinical manifestations of SSc can range from limited skin involvement to severe internal organ dysfunction. Internal visceral organ pathology is a major factor contributing to the morbidity of this disease, with the kidneys, oesophagus, heart, and lungs being the most frequently involved.

Systemic sclerosis (SSc) is a rare disease. The prevalence is estimated at about 1/6,500 adults. Women are predominantly affected (F/M sex ratio around 4:1) (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=90291)

5.1.2. Available therapies and unmet medical need

The therapy option for treatment of SSc including SSc-ILD are limited. However immunosuppressive therapy is an important and established aspect of the treatment for SSC including SSc-ILD.

Exact criteria for initiation of immunosuppressive treatment for SSc-ILD have not been established. As the benefits of existing therapies are modest and the toxicities significant, patients with SSc-ILD are treated on an individualized basis when their disease is extensive and/or progressive. The goal of treatment is stabilization or prevention of progressive disease.

CYC is widely used in the treatment of SSc-ILD, especially in induction therapy as reflected by the EULAR recommendations for SSc-ILD treatment (Kowal-Bielecka et al. 2017). However, the toxicity of CYC makes it unsuitable for long-term use with significant adverse effects such as myeloproliferative or lymphoproliferative malignancies, haemorrhagic cystitis, sterility, and teratogenicity.

MMF has been suggested as an alternative for induction and maintenance based on the results from Scleroderma Lung study II (SLS II) which showed a comparable efficacy to CYC and a better adverse effect profile for MMF (Tashkin et al. 2016). The optimal duration of MMF therapy is unknown.

Nintedanib is the only approved therapy in SSc-ILD. The multi-tyrosine kinase inhibitor slowed the decline of lung function in patients with radiographically evident, established clinical SSc-ILD (Distler et al. 2019). Nintedanib would be used in patients with SScILD who demonstrate disease progression despite MMF or CYC or as alternative treatment for SSc-ILD in patients who are unable to take MMF or CYC. Nintedanib is an oral medication and is associated with gastrointestinal side effects such as diarrhea and vomiting which may preclude use in certain SSc patients with gastric involvement.

5.1.3. Main clinical studies

The submission is supported by the pivotal study WA29767 and the supportive study WA27788. Both studies have a similar design and are aimed to investigate the safety and efficacy in SSc patients

The patient populations included in Study WA27788 and WA29767 are largely similar. Patients with the diagnosis of SSc were enrolled, organ involvement e.g. cardiac, renal or lung involvement was not an including criterion. Moreover, patient with history of previous/concomitant pulmonary disease defined by certain ppFVC and ppDLCO level were excluded from the study. However, the indication claim based on a post-hoc subgroup analysis in patients with SSc-ILD at a certain degree as relevant population. (OC)

In Study WA29767 the primary efficacy objective change from baseline in mRSS was assessed at Week 48, while originally in Study WA27788 the assessment of the primary efficacy objective was planned for week 24. In order to provide comparative results, the secondary efficacy objective, change from baseline in mRSS at Week 48, is used for comparison of the outcome of the two studies.

In Study WA29767 measurement of ppFVC at Week 48 was a secondary objective, while in Study WA27788 it was an exploratory objective. However, outcome of this measurement is used as main evidence in supporting the claimed indication.

5.2. Favourable effects

In both studies a difference in FVC decline was observed between TCZ and placebo.

A statistically nominally significant treatment effect in favour of TCZ over placebo was seen in the median change from baseline in ppFVC at Week 48 in both Study WA29767 (difference of medians between treatment groups 3.3%; nominal p = 0.0015) and Study WA27788 (difference of medians between treatment groups 4.2%; nominal p = 0.0373).

A similar difference occurred for observed FVC. Change from baseline in observed FVC was lower in the TCZ arm than the placebo arm in both studies, and the difference in least squares means between treatment arms was similar: 167 mL in Study WA28767 and 120 mL WA27788.

5.3. Uncertainties and limitations about favourable effects

Both trials did not meet the primary endpoint and therefore failed to demonstrate a treatment benefit of TCZ over PBO in the overall SSc population.. An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Given the presumed influence of elevated IL-6 on the skin involvement this outcome is unexpected.

Suggested effects of TCZ on ppFVC are not type-I-error controlled and the suggested effects on ppFVC may overestimate the true effect (potential upward bias due to multiplicity across a high number of endpoints).

There is only little support for an effect of TCZ through other secondary endpoints.

The SSc-ILD subgroup is an exploratory (post-hoc) subgroup.

The applicant claims that the effects of TCZ were more pronounced in subjects with SSc-ILD, however, the median change from baseline to week 48 in ppFVC is rather similar in patients with SSc (-3.9 vs. -0.6) and SSc-ILD (-4.0 vs. -0.6). It is acknowledged that LSmean estimates differ somewhat between the overall population and the subgroup in study WA29767, but the applicant argued elsewhere that the MMRM model was possibly not suitable due to the underlying statistical assumptions (last minute change

of model to a non-parametric model). Thus, there is uncertainty whether the post-hoc subgroup of SSc-ILD patients really is the driver of the results in ppFVC. Detailed results in mutually exclusive subgroups were not presented.

Furthermore the exclusion criteria in both trials indicate that patients with limited cutaneous SSc that generally have a better prognosis were not part of the overall trial populations. However, based on the currently proposed indication statement these patients would be included. The applicant therefore needs to discuss the possibility of extrapolation from the trial population to the population with limited cutaneous SSc and external validity of the obtained results.

5.4. Unfavourable effects

In the pooled analysis, up to Week 48 the rates in the majority of the parameters were higher or similar in the pooled placebo arm compared with the pooled TCZ arm, with the exceptions of ISRs, hypersensitivity, and serious infections, which were higher in the pooled TCZ arm. The higher incidences of hypersensitivity and serious infections in the TCZ arm were mainly driven by the higher numbers of events from Study WA27788.

The safety analysis for patients with SSc-ILD in Study WA29767 up to Week 48 showed similar patterns with the pooled population of Study WA29767 and Study WA27788

5.5. Uncertainties and limitations about unfavourable effects

TCZ is well characterise and no new safety signals were detected in the clinical studies. The disease is rare; thus the safety data base is limited since the studies include a small patient number.

5.6. Effects Table

Table 57 Effects Table for [Tocilizumab and SSc (SSc-ILD)] (data cut-off: 15 January 2018 (pivotal study), 11 July 2014 (supportive study))

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ppFVC week 48	Change from baseline to week 48 in ppFVC (median) in SSc-ILD subgroup in pivotal study	%	TCZ -4.0	Placebo -0.6	Descriptive result (not significant in confirmatory sense, primary endpoint failed) Not well supported by other endpoints Missing values were not imputed Post-hoc subgroup Subgroup not defined on clinical grounds (but on radiologic	Overview of clinical efficacy, CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					imaging), no correlation between radiological and clinical findings established	
	Change from baseline to week 48 in ppFVC (median) in supportive study	%	TCZ -5.7	Placebo -1.5	Post-hoc exploratory result Not well supported by other endpoints Missing values were not imputed	Overview of clinical efficacy, CSR
Unfavourable Effects						
	Any AE	%	TCZ 89.1	Placebo 81.3		Summary clinical safety, CSR
	Any SAE	%	TCZ 18.4	Placebo 22		Summary clinical safety, CSR

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Both studies failed to demonstrate a treatment benefit of TCZ over PBO in the overall SSc population with regard to measurement of skin thickness (mRSS) (primary endpoint). However, in both studies a difference in FVC decline was observed between TCZ and placebo. These data were confirmed in a post-hoc subgroup analysis. There is only little support for an effect of TCZ through other secondary endpoints.

An increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Moreover, in a Japanese study skin thickness score was found to significantly correlate with quantitative measurements of lung involvement in patients with SSc (Matsuda et al, 20219: https://doi.org/10.1186/s13075-019-1919-6).

The results based on secondary endpoints evaluated in a post-hoc subgroup analysis in a poorly defined population and thus are not generated with the expected scientific/statistical rigor, and are considered exploratory. An ad-hoc interpretation may be possible, but has substantial uncertainties.

The target population i.e. SSc-ILD patients is not clearly defined. HRCT was used to define this relevant sub-population i.e. SSC-ILD patients, however patient with history of previous/concomitant pulmonary disease defined by certain ppFVC and ppDLCO level were excluded from the study.

The safety data are in line with the know favourable safety profile of TCZ

5.7.2. Balance of benefits and risks

A clinically meaningful benefit in a defined patient population has not been demonstrated.

The risk profile is acceptable.

5.7.3. Additional considerations on the benefit-risk balance

N/A

5.8. Conclusions

The overall B/R of RoActemra is negative.