CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125276Orig1s131

Trade Name:	ACTEMRA
Generic or Proper Name:	tocilizumab
Sponsor:	Genentech, Inc
Approval Date:	March 4, 2021
Indications:	**Rheumatoid Arthritis (RA)** • Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). **Giant Cell Arteritis (GCA)** • Adult patients with giant cell arteritis. **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)** • Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. **Systemic Juvenile Idiopathic Arthritis (SJIA)**

- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS)

- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125276/S-131

SUPPLEMENT APPROVAL

Genentech, Inc.
1 DNA Way, Bldg 45-1
South San Francisco, CA 94080-4990

Attention: Dhushy Thambipillai
Regulatory Program Management

Dear Ms. Thambipillai:

Please refer to your supplemental biologics license application (sBLA), dated July 24, 2020, received July 24, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Actemra (Tocilizumab) for Intravenous Injection.

We also refer to our approval letter dated March 4, 2021, which contained the following error: revision dates that were not updated in the Medication Guide and Instructions for Use.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain March 4, 2021, the date of the original approval letter.

This supplemental biologics application provides for alignment of the common prescribing information for two routes of administration of Actemra by adding the labeling changes proposed for BLA 125472/S-044 Actemra SC for the new indication of slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Elaine Sit, Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
03/04/2021 12:00:00 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s131

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTEMRA safely and effectively. See full prescribing information for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	03/2021
Dosage and Administration (2.4, 2.9)	05/2020
Dosage and Administration (2.3, 2.10)	03/2021
Warnings and Precautions (5.3, 5.4)	03/2021

---------- INDICATIONS AND USAGE----------
ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)
- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Giant Cell Arteritis (GCA) (1.2)
- Adult patients with giant cell arteritis.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) (1.3)
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.4)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.5)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS) (1.6)
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

----------DOSAGE AND ADMINISTRATION----------
For RA, pJIA and sJIA, ACTEMRA may be used alone or in combination with methotrexate: and in RA, other DMARDs may be used. (2)

Rheumatoid Arthritis (2.1)
Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

Giant Cell Arteritis (2.2)
Recommended Adult Subcutaneous Dosage:
The recommended dose of ACTEMRA for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

ACTEMRA subcutaneous formulation is not intended for intravenous administration.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) (2.3)
Recommended Adult Subcutaneous Dosage:
The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

Polyarticular Juvenile Idiopathic Arthritis (2.4)

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis (2.5)

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Cytokine Release Syndrome (2.6)

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

General Dosing Information (2.7)
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN). (2.1, 5.4)
- ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA or CRS patients. (2.1, 2.6, 12.3)

Administration of Intravenous formulation (2.8)
- For adults with RA, CRS, PJIA and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For PJIA, SJIA and CRS patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

Administration of Subcutaneous formulation (2.9)
- Follow the Instructions for Use for prefilled syringe and prefilled ACTPen® autoinjector

Dose Modifications (2.10)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

---------- DOSAGE FORMS AND STRENGTHS ----------
Intravenous Infusion
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)
Subcutaneous Injection
Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled ACTPen® autoinjector (3)

---------- CONTRAINDICATIONS ----------

- ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity- Monitor patients for signs and symptoms of hepatic injury. Modify or discontinue ACTEMRA if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (2.10, 5.3)
- Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.10 5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.6)
- Live vaccines—Avoid use with ACTEMRA. (5.9, 7.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Lactation:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

1.2 Giant Cell Arteritis (GCA)

ACTEMRA® (tocilizumab) is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

1.3 Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

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

1.4 Polyarticular Juvenile Idiopathic Arthritis (PJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

1.5 Systemic Juvenile Idiopathic Arthritis (SJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

1.6 Cytokine Release Syndrome (CRS)

ACTEMRA® (tocilizumab) is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs as an intravenous infusion or as a subcutaneous injection.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

- Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10), Warnings and Precautions (5.3, 5.4), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended in RA patients *[see Clinical Pharmacology (12.3)]*.

Recommended Subcutaneous Dosage Regimen:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose or reduction in frequency of administration of subcutaneous dose from every week to every other week dosing is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10), Warnings and Precautions (5.3, 5.4), and Adverse Reactions (6.2)]*.

2.2 Giant Cell Arteritis

The recommended dose of ACTEMRA for adult patients with GCA is 162 mg given once every week as a subcutaneous injection in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection in combination with a tapering course of glucocorticoids may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10)]*.
- Intravenous administration is not approved for GCA.

2.3 Systemic Sclerosis-Associated Interstitial Lung Disease

The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10)]*.
- Subcutaneous administration with the prefilled ACTPen® autoinjector has not been studied in SSc-ILD.
- Intravenous administration is not approved for SSc-ILD.

2.4 Polyarticular Juvenile Idiopathic Arthritis

ACTEMRA may be used as an intravenous infusion or as a subcutaneous injection alone or in combination with methotrexate. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for PJIA patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every 3 weeks
Patients at or above 30 kg weight	162 mg once every 2 weeks

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10)]*.

2.5 Systemic Juvenile Idiopathic Arthritis

ACTEMRA may be used as an intravenous infusion or as a subcutaneous injection alone or in combination with methotrexate. Do not change a dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dose of ACTEMRA for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg once every two weeks
Patients at or above 30 kg weight	162 mg once every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose when the next scheduled intravenous dose is due.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.10)]*.

2.6 Cytokine Release Syndrome (CRS)

Use only the intravenous route for treatment of CRS. The recommended dose of ACTEMRA for treatment of CRS given as a 60-minute intravenous infusion is:

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids	

- If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours.
- Doses exceeding 800 mg per infusion are not recommended in CRS patients.
- Subcutaneous administration is not approved for CRS

2.7 General Considerations for Administration

- ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection. Avoid using ACTEMRA with biological DMARDs.

- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).
  - Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the lymphodepleting chemotherapy or the CRS. The decision to administer ACTEMRA should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with ACTEMRA.

2.8 Preparation and Administration Instructions for Intravenous Infusion

ACTEMRA for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle, and then follow steps 1 and 2 below.

- Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle *[see Dosage and Administration (2.1, 2.4, 2.5, 2.6)]*.

For Intravenous Use: Volume of ACTEMRA Injection per kg of Body Weight		
Dosage	Indication	Volume of ACTEMRA injection per kg of body weight
4 mg/kg	Adult RA	0.2 mL/kg
8 mg/kg	Adult RA SJIA, PJIA and CRS (greater than or equal to 30 kg of body weight)	0.4 mL/kg
10 mg/kg	PJIA (less than 30 kg of body weight)	0.5 mL/kg
12 mg/kg	SJIA and CRS (less than 30 kg of body weight)	0.6 mL/kg

- Step 2. Withdraw the amount of ACTEMRA for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

- The fully diluted ACTEMRA solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 36° to 46°F (2° to 8°C) or room temperature for up to 24 hours and should be protected from light.
- The fully diluted ACTEMRA solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 36° to 46°F (2° to 8°C) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
- ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
- Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
- ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
- Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

2.9 Preparation and Administration Instructions for Subcutaneous Injection

- ACTEMRA for subcutaneous injection is not intended for intravenous drip infusion.
- Assess suitability of patient for subcutaneous home use and instruct patients to inform a healthcare professional before administering the next dose if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions. ACTEMRA subcutaneous injection is intended for use under the guidance of a healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject ACTEMRA or the patient's caregiver may administer ACTEMRA if a healthcare practitioner determines that it is appropriate. PJIA and SJIA patients may self-inject with the ACTEMRA prefilled syringe or ACTPen® autoinjector, or the patient's caregiver may administer ACTEMRA if both the healthcare practitioner and the parent/legal guardian determines it is appropriate *[see Use in Specific Populations (8.4)]*. Patients, or patient caregivers, should be instructed to follow the directions provided in the Instructions for Use (IFU) for additional details on medication administration.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use ACTEMRA prefilled syringes (PFS) or prefilled ACTPen® autoinjectors exhibiting particulate matter, cloudiness, or discoloration. ACTEMRA for subcutaneous administration should be clear and colorless to pale yellow. Do not use if any part of the PFS or ACTPen® autoinjector appears to be damaged.
- Patients using ACTEMRA for subcutaneous administration should be instructed to inject the full amount in the syringe (0.9 mL) or full amount in the ACTPen® autoinjector (0.9 mL), which provides 162 mg of ACTEMRA, according to the directions provided in the IFU.
- Injection sites should be rotated with each injection and should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

2.10 Dosage Modifications due to Serious Infections or Laboratory Abnormalities

Hold ACTEMRA treatment if a patient develops a serious infection until the infection is controlled.

Rheumatoid Arthritis, Giant Cell Arteritis and Systemic Sclerosis-Associated Interstitial Lung Disease

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3,5.4)]:*	
Lab Value	**Recommendation**
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs (RA, SSc-ILD) or immunomodulatory agents (GCA) if appropriate For persistent increases in this range: • For patients receiving intravenous ACTEMRA, reduce dose to 4 mg per kg or hold ACTEMRA until ALT or AST have normalized • For patients receiving subcutaneous ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.
Greater than 3 to 5x ULN (confirmed by repeat testing)	Hold ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue ACTEMRA
Greater than 5x ULN	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) *[see Warnings and Precautions (5.4)]:*	
Lab Value (cells per mm^3)	**Recommendation**
ANC greater than 1000	Maintain dose
ANC 500 to 1000	Hold ACTEMRA dosing When ANC greater than 1000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
ANC less than 500	Discontinue ACTEMRA

Low Platelet Count *[see Warnings and Precautions (5.4)]:*	
Lab Value (cells per mm^3)	**Recommendation**
50,000 to 100,000	Hold ACTEMRA dosing When platelet count is greater than 100,000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
Less than 50,000	Discontinue ACTEMRA

Polyarticular and Systemic Juvenile Idiopathic Arthritis:

Dose reduction of ACTEMRA has not been studied in the PJIA and SJIA populations. Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined above for patients with RA and GCA. If appropriate, dose modify or stop concomitant methotrexate and/or other medications and hold ACTEMRA dosing until the clinical situation has been evaluated. In PJIA and SJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Intravenous Infusion

Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Subcutaneous Injection
Injection: 162 mg/0.9 mL clear, colorless to slightly yellowish solution in a single-dose prefilled syringe or single-dose prefilled ACTPen® autoinjector.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

Do not administer ACTEMRA in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.7), Adverse Reactions (6.1), and Patient Counseling Information (17)]*.

Hold ACTEMRA if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating ACTEMRA.

Consider anti-tuberculosis therapy prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in patients treated with ACTEMRA. Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking intravenous or subcutaneous ACTEMRA. Some of these cases have resulted in liver transplant or death. Time to onset for cases ranged from months to years after treatment initiation with tocilizumab. While most cases presented with marked elevations of transaminases (> 5 times ULN), some cases presented with signs or symptoms of liver dysfunction and only mildly elevated transaminases.

During randomized controlled studies, treatment with ACTEMRA was associated with a higher incidence of transaminase elevations *[see Adverse Reactions (6.1, 6.2, 6.5, 6.7)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

For RA, GCA and SSc-ILD patients, obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating ACTEMRA, every 4 to 8 weeks after start of therapy for the first 6 months of treatment and every 3 months thereafter. It is not recommended to initiate ACTEMRA treatment in RA, GCA or SSc-ILD patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN, discontinue ACTEMRA. For recommended modifications based upon increase in transaminases *see Dosage and Administration (2.10)*.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, such as fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (e.g., ALT greater than three times the upper limit of the reference range, serum total bilirubin greater than two times the upper limit of the reference range), ACTEMRA treatment should be interrupted and investigation done to establish the probable cause. ACTEMRA should only be restarted in patients with another explanation for the liver test abnormalities after normalization of the liver tests.

A similar pattern of liver enzyme elevation is noted with ACTEMRA treatment in the PJIA and SJIA populations. Monitor liver test panel at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA.

5.4 Laboratory Parameters

Rheumatoid Arthritis, Giant Cell Arteritis and Systemic Sclerosis-Associated Interstitial Lung Disease

Neutropenia

Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

– It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an absolute neutrophil count less than 500 per mm^3 treatment is not recommended.

– Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results *see Dosage and Administration (2.10).*

Thrombocytopenia

Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1, 6.2)]*.

– It is not recommended to initiate ACTEMRA treatment in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3 treatment is not recommended.

– Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on platelet counts *see Dosage and Administration (2.10).*

Elevated Liver Enzymes

Refer to 5.3 Hepatotoxicity. For recommended modifications *[see Dosage and Administration (2.10)]*

Lipid Abnormalities

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1, 6.2)]*.

– Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy.

– Subsequently, manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Polyarticular and Systemic Juvenile Idiopathic Arthritis

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with ACTEMRA treatment in the PJIA and SJIA populations. Monitor neutrophils, platelets, ALT and AST at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Monitor lipids as above for approved adult indications *[see Dosage and Administration (2.10)]*.

5.5 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.6 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA *[see Adverse Reactions (6)]* and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Injection site reactions were categorized separately [s*ee Adverse Reactions (6)*].

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA *[see Adverse Reactions (6.7)]*. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA *[see Contraindications (4) and Adverse Reactions (6)]*.

5.7 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.8 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.9 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.2)]*
- Laboratory Parameters *[see Warnings and Precautions (5.4)]*
- Immunosuppression *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions, Including Anaphylaxis *[see Warnings and Precautions (5.6)]*
- Demyelinating Disorders *[see Warnings and Precautions (5.7)]*
- Active Hepatic Disease and Hepatic Impairment *[see Warnings and Precautions (5.8)]*

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA-IV. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*. The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with ACTEMRA-IV monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA-IV and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA-IV were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 24 week, controlled clinical studies, the rate of infections in the ACTEMRA-IV monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA-IV in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections

In the 24 week, controlled clinical studies, the rate of serious infections in the ACTEMRA-IV monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

In the cardiovascular outcomes Study WA25204, the rate of serious infections in the ACTEMRA 8 mg/kg IV every 4 weeks group, with or without DMARD, was 4.5 per 100 patient-years, and the rate in the etanercept 50 mg weekly SC group, with or without DMARD, was 3.2 per 100 patient-years. *[see Clinical Studies (14.1)]*

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with ACTEMRA-IV therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as

complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus ACTEMRA-IV to the development of GI perforations is not known.

Infusion Reactions

In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis

Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with ACTEMRA-IV were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA-IV. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions 5.6)]*.

Laboratory Abnormalities

Neutropenia

In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.4)]*.

Thrombocytopenia

In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm^3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions 5.4)]*.

Elevated Liver Enzymes

Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA-IV, or reduction in ACTEMRA-IV dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.7]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3, 5.4)]*.

Table 1 Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg per kg + DMARDs N = 774 (%)	ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal
*For a description of these studies, see Section 14, Clinical Studies.

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials.

In Study WA25204, of the 1538 patients with moderate to severe RA (*see Section 14, Clinical Studies)* and treated with tocilizumab, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with tocilizumab.

Lipids

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

– Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.

– Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.

– Mean LDL/HDL ratio increased by an average of 0.14 in the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.

– ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

Malignancies

During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24 week, controlled period *[see Warnings and Precautions (5.5)]*.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg ACTEMRA-IV plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

24 Week Phase 3 Controlled Study Population					
Preferred Term	**ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)**	**Methotrexate N = 284 (%)**	**ACTEMRA 4 mg per kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)**	**Placebo + DMARDs N = 1170 (%)**
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA-IV in controlled trials were:

Infections and Infestations: oral herpes simplex
Gastrointestinal disorders: stomatitis, gastric ulcer
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: edema peripheral
Respiratory, thoracic, and mediastinal disorders: dyspnea, cough
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

6.2 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The ACTEMRA-SC data in rheumatoid arthritis (RA) includes 2 double-blind, controlled, multicenter studies. Study SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab 162 mg administered every week subcutaneously and 8 mg/kg intravenously every four weeks in 1262 adult subjects with rheumatoid arthritis. Study SC-II was a placebo controlled superiority study that evaluated the safety and efficacy of tocilizumab 162 mg administered every other week subcutaneously or placebo in 656 patients. All patients in both studies received background non-biologic DMARDs.

The safety observed for ACTEMRA-SC administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), which were more common with ACTEMRA-SC compared with placebo SC injections (IV arm).

Injection Site Reactions

In the 6-month control period, in SC-I, the frequency of ISRs was 10.1% (64/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo SC (IV-arm) groups, respectively. In SC-II, the frequency of ISRs was 7.1% (31/437) and 4.1% (9/218) for the every other week ACTEMRA-SC and placebo groups, respectively. These ISRs (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity

In the 6-month control period in SC-I, 0.8% (5/625) in the ACTEMRA-SC arm and 0.8% (5/627) in the IV arm developed anti-tocilizumab antibodies; of these, all developed neutralizing antibodies. In SC-II, 1.6% (7/434) in the ACTEMRA-SC arm compared with 1.4 % (3/217) in the placebo arm developed anti- tocilizumab antibodies; of these, 1.4% (6/434) in the ACTEMRA-SC arm and 0.5% (1/217) in the placebo arm also developed neutralizing antibodies.

A total of 1454 (>99%) patients who received ACTEMRA-SC in the all exposure group have been tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed anti-tocilizumab antibodies, and, of these, 12 patients (0.8%) developed neutralizing antibodies.

The rate is consistent with previous intravenous experience. No correlation of antibody development to adverse events or loss of clinical response was observed.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the 6-month controlled clinical trials, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% and 3.7% of patients receiving ACTEMRA-SC weekly and every other week, respectively.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-SC 6-month controlled clinical trials, none of the patients had a decrease in platelet count to ≤50,000/mm^3.

Elevated Liver Enzymes

During routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively, receiving ACTEMRA-SC weekly and 3.4% and 0.7% receiving ACTEMRA-SC every other week.

Lipid Parameters Elevations

During routine laboratory monitoring in the ACTEMRA-SC 6-month clinical trials, 19% of patients dosed weekly and 19.6% of patients dosed every other week and 10.2% of patients on placebo experienced sustained elevations in total cholesterol > 6.2 mmol/l (240 mg/dL), with 9%, 10.4% and 5.1% experiencing a sustained increase in LDL to 4.1 mmol/l (160 mg/dL) receiving ACTEMRA-SC weekly, every other week and placebo, respectively.

6.3 Clinical Trials Experience in Giant Cell Arteritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the ACTEMRA GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the ACTEMRA treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the ACTEMRA weekly group and 160.2/4.4 events per 100 patient years in the ACTEMRA every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.

6.4 Clinical Trials Experience in Systemic Sclerosis-Associated Interstitial Lung Disease Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA was evaluated in two double-blind, placebo-controlled, multicenter studies (WA29767 and WA27788). In the Phase 3 Study WA29767, 212 patients with SSc were randomized to tocilizumab 162 mg administered every week subcutaneously or placebo for 48 weeks, followed by open-label tocilizumab 162 mg administered subcutaneously every week for another 48 weeks. In the Phase 2/3 Study WA27788, 87 patients were randomized to tocilizumab 162 mg administered every week subcutaneously or placebo for 48 weeks, followed by open-label tocilizumab 162 mg administered subcutaneously every week for another 48 weeks.

The safety profile for ACTEMRA through week 48 in WA29767 was comparable for SSc-ILD and SSc patients overall, and in both studies was consistent with the known safety profile of ACTEMRA.

Immunogenicity

In the two clinical studies, WA29767 and WA27788, the incidence of treatment-induced anti-TCZ antibodies at week 96 was low (3 out of 169 patients, 1.8%). These anti-drug antibodies were of neutralizing potential, and none of the patients experienced hypersensitivity reactions.

6.5 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Intravenous ACTEMRA (ACTEMRA-IV)

The safety of ACTEMRA-IV was studied in 188 pediatric patients 2 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the ACTEMRA-IV all exposure population (defined as patients who received at least one dose of ACTEMRA-IV) was 184.4 patient years. At baseline, approximately half of the patients were taking oral corticosteroids and almost 80% were taking methotrexate. In general, the types of adverse drug reactions in patients with PJIA were consistent with those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.7)]*.

Infections

The rate of infections in the ACTEMRA-IV all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (21%) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (8%).

Infusion Reactions

In PJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the ACTEMRA-IV all exposure population, 11 patients (6%) experienced an event during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension, and occurring within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.7)]*.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

One patient, in the 10 mg/kg less than 30 kg group, developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 3.7% of patients.

There was no clear relationship between decreases in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, 1% of patients had a decrease in platelet count at or less than 50,000 per mm^3 without associated bleeding events.

Elevated Liver Enzymes

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, elevation in ALT or AST at or greater than 3 x ULN occurred in 4% and less than 1% of patients, respectively.

Lipids

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol greater than 1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL greater than 1.5-2 x ULN occurred in one patient (0.5%).

6.6 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of ACTEMRA-SC was studied in 52 pediatric patients 1 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the PJIA ACTEMRA-SC population (defined as patients who received at least one dose of ACTEMRA-SC and accounting for treatment discontinuation) was 49.5 patient years. In general, the safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), and neutropenia.

Injection Site Reactions

During the 1-year study, a frequency of 28.8% (15/52) ISRs was observed in ACTEMRA-SC treated PJIA patients. These ISRs occurred in a greater proportion of patients at or above 30 kg (44.0%) compared with patients below 30 kg (14.8%). All ISRs were mild in severity and none of the ISRs required patient withdrawal from treatment or dose interruption. A higher frequency of ISRs was observed in ACTEMRA-SC treated PJIA patients compared to what was seen in adult RA or GCA patients [*see Adverse Reactions (6.2 and 6.3)*].

Immunogenicity

Three patients, 1 patient below 30 kg and 2 patients at or above 30 kg, developed positive anti-tocilizumab antibodies with neutralizing potential without developing a serious or clinically significant hypersensitivity reaction. One patient subsequently withdrew from the study.

Neutropenia

During routine laboratory monitoring in the ACTEMRA-SC all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 15.4% of patients, and was more frequently observed in the patients less than 30 kg (25.9%) compared to patients at or above 30 kg (4.0%). There was no clear relationship between decreases in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

6.7 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The data described below reflect exposure to ACTEMRA-IV in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension. In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with ACTEMRA-IV (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA-IV in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA-IV treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections

In the 12 week controlled phase, the rate of all infections in the ACTEMRA-IV group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the ACTEMRA-IV group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with ACTEMRA-IV. One patient in the placebo group escaped to ACTEMRA-IV 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA-IV dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the ACTEMRA-IV SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions

Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of ACTEMRA-IV and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the ACTEMRA-IV treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA-IV group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis

Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with ACTEMRA-IV during the controlled and open label extension study *[see Warnings and Precautions (5.6)]*.

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Abnormalities

Neutropenia

During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the ACTEMRA-IV group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of the ACTEMRA-IV group. There was no clear relationship between decrease in neutrophils below 1×10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA-IV group and 3% in the placebo group had a decrease in platelet count to no more than 100,000 per mm^3.

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the ACTEMRA-IV group, with no associated bleeding.

Elevated Liver Enzymes

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA-IV group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of ACTEMRA-IV treated patients, respectively.

Lipids

During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA-IV group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA-IV group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

6.8 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety profile of ACTEMRA-SC was studied in 51 pediatric patients 1 to 17 years of age with SJIA who had an inadequate clinical response to NSAIDs and corticosteroids. In general, the safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of ISRs where a higher frequency was observed in ACTEMRA-SC treated SJIA patients compared to PJIA patients and adult RA or GCA patients [*see Adverse Reactions (6.2, 6.3 and 6.6)*].

Injection Site Reactions (ISRs)

A total of 41.2% (21/51) SJIA patients experienced ISRs to ACTEMRA-SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

Immunogenicity

Forty-six of the 51 (90.2%) patients who were tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline.

6.9 Clinical Trials Experience in Patients with Cytokine Release Syndrome Treated with Intravenous ACTEMRA (ACTEMRA-IV)

In a retrospective analysis of pooled outcome data from multiple clinical trials 45 patients were treated with tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered. No adverse reactions related to tocilizumab were reported *[see Clinical Studies (14.8)]*.

6.10 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ACTEMRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis *[see Warnings and Precautions (5.6)]*
- Stevens-Johnson Syndrome
- Pancreatitis
- Drug-induced liver injury, Hepatitis, Hepatic failure, Jaundice *[see Warnings and Precautions (5.3)]*

7 DRUG INTERACTIONS

7.1 Concomitant Drugs for Treatment of Adult Indications

In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.1)]*.

In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed.

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect

of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Avoid use of live vaccines concurrently with ACTEMRA *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant *[see Clinical Considerations]*. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition *[see Data]*. Based on the animal data, there may be a potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ACTEMRA *in utero [see Warnings and Precautions 5.9)]*

Data

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/ kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/ kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation (GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 ($ll6^{-/-}$ null mice), parturition was

delayed relative to wild-type ($Il6^{+/+}$) mice. Administration of recombinant IL-6 to $Il6^{-/-}$ null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

8.4 Pediatric Use

ACTEMRA by intravenous use is indicated for the treatment of pediatric patients with:

- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older
- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Severe or life-threatening CAR T cell-induced cytokine release syndrome (CRS) in patients 2 years of age and older.

ACTEMRA by subcutaneous use is indicated for the treatment of pediatric patients with:

- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older

The safety and effectiveness of ACTEMRA in pediatric patients with conditions other than PJIA, SJIA or CRS have not been established. The safety and effectiveness in pediatric patients below the age of 2 have not been established in PJIA, SJIA, or CRS.

Systemic Juvenile Idiopathic Arthritis – Intravenous Use

A multi-center, open-label, single arm study to evaluate the PK, safety and exploratory PD and efficacy of ACTEMRA over 12-weeks in SJIA patients (N=11) under 2 years of age was conducted. Patients received intravenous ACTEMRA 12 mg/kg every two weeks. Concurrent use of stable background treatment with corticosteroids, MTX, and/or non-steroidal anti-inflammatory drugs was permitted. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (C_{max}, C_{trough} and AUC_{2weeks}) of ACTEMRA at steady-state in this study were within the ranges of these parameters observed in patients with SJIA aged 2 to 17 years.

The safety and immunogenicity of ACTEMRA for patients with SJIA under 2 years of age was assessed descriptively. SAEs, AEs leading to discontinuation, and infectious AEs were reported by 27.3%, 36.4%, and 81.8% of patients. Six patients (54.5%) experienced hypersensitivity reactions, defined as all adverse events occurring during or within 24 hours after an infusion considered related to ACTEMRA. Three of these patients experienced serious hypersensitivity reactions and were withdrawn from the study. Three patients with hypersensitivity reactions (two with serious hypersensitivity reactions) developed treatment induced anti-tocilizumab antibodies after the event. There were no cases of MAS based on the protocol-specified criteria, but 2 cases of suspected MAS based on Ravelli criteria[1].

[1] Ravelli A, Minoia F, Davì S on behalf of the Paediatric Rheumatology International Trials Organisation, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society, *et al.* 2016 Classification Criteria for Macrophage Activation

Cytokine Release Syndrome – Intravenous Use

In the retrospective analysis of pooled outcome data for patients treated with ACTEMRA for CAR T cell-induced CRS, 25 patients were children (2 years up to 12 years of age), and 17 patients were adolescents (12 years up to 18 years of age). There were no differences between the pediatric patients and the adults for safety or efficacy.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. Of the 1069 patients who received ACTEMRA-SC in studies SC-I and SC-II there were 295 patients 65 years of age and older, including 41 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Clinical studies that included ACTEMRA for CRS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions 5.8)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. ACTEMRA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for ACTEMRA to cause dependence have been performed. However, there is no evidence from the available data that ACTEMRA treatment results in dependence.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported with intravenous ACTEMRA in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

11 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

Intravenous Infusion

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to pale yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.5. Each single-dose vial, formulated with a

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Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. Annals of the Rheumatic Diseases 2016;75:481-489.

disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

Subcutaneous Injection

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to slightly yellowish, preservative-free, histidine buffered solution for subcutaneous use with a pH of approximately 6.0.

It is supplied in a ready-to-use, single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or a ready-to-use, single-dose 0.9 mL autoinjector that delivers 162 mg tocilizumab, L-arginine hydrochloride (19 mg), L-histidine (1.52 mg), L-histidine hydrochloride monohydrate (1.74 mg), L-methionine (4.03 mg), polysorbate 80 (0.18 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

In clinical studies in RA patients with the 4 mg per kg and 8 mg per kg intravenous doses or the 162 mg weekly and every other weekly subcutaneous doses of ACTEMRA, decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A, fibrinogen and increases in hemoglobin) with doses, however the greatest improvements were observed with 8 mg per kg ACTEMRA. Pharmacodynamic changes were also observed to occur after ACTEMRA administration in GCA, SSc-ILD, PJIA, and SJIA patients (decreases in CRP, ESR, and increases in hemoglobin). The relationship between these pharmacodynamic findings and clinical efficacy is not known.

In healthy subjects administered ACTEMRA in doses from 2 to 28 mg per kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to the nadir 3 to 5 days following ACTEMRA administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis and GCA patients demonstrated a similar pattern of absolute neutrophil counts following ACTEMRA administration *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

PK of tocilizumab is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of tocilizumab elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

Rheumatoid Arthritis - Intravenous and Subcutaneous Administration

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.

The population PK model was developed from an analysis dataset composed of an IV dataset of 1793 patients from Study I, Study III, Study IV, and Study V, and from an IV and SC dataset of 1759 patients from Studies SC-

I and SC-II. C_{mean} is included in place of AUC_{tau}, since for dosing regimens with different inter-dose intervals, the mean concentration over the dosing period characterizes the comparative exposure better than AUC_{tau}.

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

For doses of 4 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab at steady state were 86.1 (44.8–202) mcg/mL, 0.1 (0.0–14.6) mcg/mL, and 18.0 (8.9–50.7) mcg/mL, respectively. For doses of 8 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 176 (75.4–557) mcg/mL, 13.4 (0.1–154) mcg/mL, and 54.0 (17–260) mcg/mL, respectively. C_{max} increased dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, while a greater than dose-proportional increase was observed in C_{mean} and C_{trough}. At steady-state, C_{mean} and C_{trough} were 3.0 and 134 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg IV Q4W are low, while the accumulation ratios for C_{trough} are higher (2.62 and 2.47, respectively). For C_{max}, greater than 90% of the steady-state value was reached after the 1st IV infusion. For AUC_{tau} and C_{mean}, 90% of the steady-state value was reached after the 1st and 3rd infusion for 4 mg/kg and 8 mg/kg IV, while for C_{trough}, approximately 90% of the steady-state value was reached after the 4th IV infusion after both doses.

For doses of 162 mg given every other week subcutaneously, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 12.1 (0.4–49.3) mcg/mL, 4.1 (0.0–34.2) mcg/mL, and 9.2 (0.2–43.6) mcg/mL, respectively.

For doses of 162 mg given every week subcutaneously, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 49.8 (3–150) mcg/mL, 42.9 (1.3–144) mcg/mL, and 47.3 (2.4–147) mcg/mL, respectively. Exposures after the 162 mg SC QW regimen were greater by 5.1 (C_{mean}) to 10.5 fold (C_{trough}) compared to the 162 mg SC Q2W regimen.

Accumulation ratios after multiple doses of either SC regimen were higher than after IV regimen with the highest ratios for C_{trough} (6.02 and 6.30, for 162 mg SC Q2W and 162 mg SC QW, respectively). The higher accumulation for C_{trough} was expected based on the nonlinear clearance contribution at lower concentrations. For C_{max}, greater than 90% of the steady-state value was reached after the 5th SC and the 12th SC injection with the Q2W and QW regimens, respectively. For AUC_{tau} and C_{mean}, 90% of the steady-state value was reached after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens, respectively. For C_{trough}, approximately 90% of the steady-state value was reached after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens, respectively.

Population PK analysis identified body weight as a significant covariate impacting the pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients with RA (*see section 2.1 Dosage and Administration*). Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

Giant Cell Arteritis – Subcutaneous Administration

The pharmacokinetics of tocilizumab in GCA patients was determined using a population pharmacokinetic analysis on a dataset composed of 149 GCA patients treated with 162 mg subcutaneously every week or with 162 mg subcutaneously every other week.

For the 162 mg every week dose, the estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab were 72.1 (12.2–151) mcg/mL, 67.2 (10.7–145) mcg/mL, and 70.6 (11.7–149) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 10.9, 9.6, and 8.9, respectively. Steady state was reached after 17 weeks. For the 162 mg every other week dose, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 17.2 (1.1–56.2) mcg/mL, 7.7 (0.1–37.3) mcg/mL, and 13.7 (0.5–

49) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 2.8, 5.6, and 2.3 respectively. Steady-state was reached after 14 weeks.

Systemic Sclerosis-Associated Interstitial Lung Disease – Subcutaneous Administration

The pharmacokinetics of tocilizumab in SSc-ILD patients was determined using a population pharmacokinetic analysis on a dataset composed of 66 SSc-ILD patients treated with 162 mg tocilizumab SC every week.

The estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab were 52.5 (14.8-121) mcg/mL, 47.2 (10.8-114) mcg/mL, and 50.4 (13.4-119) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 7.11, 6.56, and 5.89, respectively. Steady-state was reached after 13 weeks.

Polyarticular Juvenile Idiopathic Arthritis—Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in PJIA patients was characterized by a population pharmacokinetic analysis which included 188 patients who were treated with TCZ IV or 52 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab at steady state were 181 (114–331) mcg/mL, 3.28 (0.02–35.4) mcg/mL, and 38.6 (22.2–83.8) mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 167 (125–220) mcg/mL, 0.35 (0–11.8) mcg/mL, and 30.8 (16.0–48.0) mcg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{trough} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. No accumulation for C_{max} was observed. Following 10 mg/kg and 8 mg/kg TCZ IV every 4 weeks doses in PJIA patients (aged 2 to 17 years), steady state concentrations (trough and average) were within the range of exposures in adult RA patients following 4 mg/kg and 8 mg/kg every 4 weeks, and steady state peak concentrations in PJIA patients were comparable to those following 8 mg/kg every 4 weeks in adult RA patients.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 29.7 (7.56–50.3) mcg/mL, 12.7 (0.19–23.8) mcg/mL, and 23.0 (3.86–36.9) mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 3 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 62.4 (39.4–121) mcg/mL, 13.4 (0.21–52.3) mcg/mL, and 35.7 (17.4–91.8) mcg/mL, respectively.

The accumulation ratios were 1.46 and 2.04 for AUC_{4weeks}, 2.08 and 3.58 for C_{trough}, and 1.32 and 1.72 for C_{max}, for 162 mg given every 3 weeks (BW less than 30 kg) and 162 mg given every 2 weeks (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state C_{trough} was comparable for patients in the two body weight groups, while steady-state C_{max} and C_{mean} were higher for patients in the less than 30 kg group compared to the group at or above 30 kg. All patients treated with TCZ SC had steady-state C_{trough} at or higher than that achieved with TCZ IV across the spectrum of body weights. The average and trough concentrations in patients after subcutaneous dosing were within the range of those achieved in adult patients with RA following the subcutaneous administration of the recommended regimens.

Systemic Juvenile Idiopathic Arthritis—Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in SJIA patients was characterized by a population pharmacokinetic analysis which included 89 patients who were treated with TCZ IV or 51 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 253 (120–404) mcg/mL, 70.7 (5.26–127) mcg/mL, and 117 (37.6–199) mcg/mL, respectively. For doses of 12 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks intravenously, the estimated

median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 274 (149–444) mcg/mL, 65.9 (19.0–135) mcg/mL, and 124 (60–194) mcg/mL, respectively.

The accumulation ratios were 1.95 and 2.01 for AUC_{4weeks}, and 3.41 and 3.20 for C_{trough} for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Accumulation data for C_{max} were 1.37 and 1.42 for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Following every other week dosing with tocilizumab IV, steady state was reached by 8 weeks for both body weight groups. Mean estimated tocilizumab exposure parameters were similar between the two dose groups defined by body weight.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every week subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 89.8 (26.4–190) mcg/mL, 72.4 (19.5–158) mcg/mL, and 82.4 (23.9–169) mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 127 (51.7–266) mcg/mL, 64.2 (16.6–136) mcg/mL, and 92.7 (38.5–199) mcg/mL, respectively.

The accumulation ratios were 2.27 and 4.28 for AUC_{4weeks}, 3.21 and 4.39 for C_{trough}, and 1.88 and 3.66 for C_{max}, for 162 mg given every 2 weeks (BW less than 30 kg) and 162 mg given every week (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state was reached by 12 weeks for both body weight groups. All patients treated with tocilizumab SC had steady-state C_{max} lower than that achieved with tocilizumab IV across the spectrum of body weights. Trough and mean concentrations in patients after SC dosing were similar to those achieved with tocilizumab IV across body weights.

Absorption

Following subcutaneous dosing, the absorption half-life was around 4 days in RA and GCA patients and 3 days in SSc-ILD patients. The bioavailability for the subcutaneous formulation was 80%.

Following subcutaneous dosing in PJIA patients, the absorption half-life was around 2 days, and the bioavailability for the subcutaneous formulation in PJIA patients was 96%.

Following subcutaneous dosing in SJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in SJIA patients was 95%.

In RA patients the median values of T_{max} were 2.8 days after the tocilizumab every week dose and 4.7 days after the tocilizumab every other week dose.

In GCA patients, the median values of T_{max} were 3 days after the tocilizumab every week dose and 4.5 days after the tocilizumab every other week dose.

In SSc-ILD patients, the median value of T_{max} was 2.8 days after the tocilizumab every week dose.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L resulting in a volume of distribution at steady state of 7.46 L.

In SSc-ILD patients, 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.

In pediatric patients with PJIA, the central volume of distribution was 1.98 L, the peripheral volume of

distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In pediatric patients with SJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L.

Elimination

ACTEMRA is eliminated by a combination of linear clearance and nonlinear elimination. The concentration-dependent nonlinear elimination plays a major role at low tocilizumab concentrations. Once the nonlinear pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The saturation of the nonlinear elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of ACTEMRA do not change with time.

Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

The linear clearance in the population pharmacokinetic analysis was estimated to be 12.5 mL per h in RA patients, 6.7 mL per h in GCA patients, 8.8 mL per h in SSc-ILD patients, 5.8 mL per h in pediatric patients with PJIA, and 5.7 mL per h in pediatric patients with SJIA.

Due to the dependence of total clearance on ACTEMRA serum concentrations, the half-life of ACTEMRA is also concentration-dependent and varies depending on the serum concentration level.

For intravenous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

In GCA patients at steady state, the effective $t_{1/2}$ of tocilizumab varied between 18.3 and 18.9 days for 162 mg subcutaneously every week dosing regimen and between 4.2 and 7.9 days for 162 mg subcutaneously every other week dosing regimen.

In SSc-ILD patients at steady state, the effective $t_{1/2}$ of tocilizumab varied between 12.1 and 13.0 days for the 162 mg subcutaneous every week dosing regimen.

The $t_{1/2}$ of tocilizumab in children with PJIA is up to 17 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg or 10 mg/kg for body weight below 30 kg) during a dosing interval at steady state. For subcutaneous administration, the $t_{1/2}$ of tocilizumab in PJIA patients is up to 10 days for the two body weight categories (every other week regimen for body weight at or above 30 kg or every 3 week regimen for body weight less than 30 kg) during a dosing interval at steady state.

The $t_{1/2}$ of tocilizumab intravenous in pediatric patients with SJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg and 12 mg/kg for body weight below 30 kg every other week) during a dosing interval at steady-state. Following subcutaneous administration, the effective $t_{1/2}$ of tocilizumab subcutaneous in SJIA patients is up to 14 days for both the body weight categories (162 mg every week for body weight at or above 30 kg and 162 mg every two weeks for body weight below 30 kg) during a dosing interval at steady state.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients and GCA patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. In RA patients, the body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg. There was an inverse relationship between tocilizumab exposure and body weight for flat dose subcutaneous regimens.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state C_{mean} was 51% higher in patients with body weight less than 60 kg compared to

patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state C_{mean} was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the RA, GCA, and SSc-ILD patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab.

Approximately one-third of the patients in the GCA clinical trial had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on tocilizumab exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Drug Interactions

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when ACTEMRA is coadministered with drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives (CYP3A4 substrates) *[see Drug Interactions (7.2)]*.

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients not treated with ACTEMRA, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (10 mg per kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of ACTEMRA in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of ACTEMRA (due to normalization of CYP3A4) or higher exposures after discontinuation of ACTEMRA.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after ACTEMRA infusion (8 mg per kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following

administration of a single infusion of ACTEMRA (8 mg per kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab. Literature indicates that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. However, available published evidence also supports that IL-6 signaling through the IL-6 receptor may be involved in pathways that lead to tumorigenesis. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as tocilizumab, is presently unknown.

Fertility and reproductive performance were unaffected in male and female mice that received a murine analogue of tocilizumab administered by the intravenous route at a dose of 50 mg/kg every three days.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis—Intravenous Administration

The efficacy and safety of intravenously administered ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. ACTEMRA was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I (NCT00109408) evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis less than 2 years. Patients received ACTEMRA 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of ACTEMRA patients who achieved an ACR 20 response at Week 24.

Study II (NCT00106535) was a 104-week study with an optional 156-week extension phase that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with ACTEMRA 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in HAQ-DI score.

Study III (NCT00106548) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study IV (NCT00106574) evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study V (NCT00106522) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy

was discontinued prior to randomization. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Clinical Response

The percentages of intravenous ACTEMRA-treated patients achieving ACR 20, 50 and 70 responses are shown in **Table 3.** In all intravenous studies, patients treated with 8 mg per kg ACTEMRA had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24 week controlled portions of Studies I to V, patients treated with ACTEMRA at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg per kg.

Table 3 Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous ACTEMRA (Percent of Patients)

Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
Response Rate	MTX N=284	ACTEMRA 8 mg per kg N=286 (95% CI)[a]	Placebo + MTX N=393	ACTEMRA 4 mg per kg + MTX N=399 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=398 (95% CI)[a]	Placebo + MTX N=204	ACTEMRA 4 mg per kg + MTX N=213 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=205 (95% CI)[a]	Placebo + DMARDs N=413	ACTEMRA 8 mg per kg + DMARDs N=803 (95% CI)[a]	Placebo + MTX N=158	ACTEMRA 4 mg per kg + MTX N=161 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=170 (95% CI)[a]
ACR 20													
Week 24	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52	N/A	N/A	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 50													
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 70													
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses[b]													
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)

[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

In study II, a greater proportion of patients treated with 4 mg per kg and 8 mg per kg ACTEMRA + MTX achieved a low level of disease activity as measured by a DAS 28-ESR less than 2.6 compared with placebo +MTX treated patients at week 52. The proportion of ACTEMRA-treated patients achieving DAS 28-ESR less than 2.6, and the number of residual active joints in these responders in Study II are shown in **Table 4**.

Table 4 Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints in Trials of Intravenous ACTEMRA

Study II			
	Placebo + MTX N = 393	**ACTEMRA 4 mg per kg + MTX N = 399**	**ACTEMRA 8 mg per kg + MTX N = 398**
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n)	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n)	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joints (n)	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joints (n)	33% (4)	41% (29)	47% (59)

*n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at Week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in **Table 5**. Similar results to Study III were observed in Studies I, II and IV.

Table 5 Components of ACR Response at Week 24 in Trials of Intravenous ACTEMRA

	Study III						**Study V**					
	ACTEMRA 4 mg per kg + MTX N=213		**ACTEMRA 8 mg per kg + MTX N=205**		**Placebo + MTX N=204**		**ACTEMRA 4 mg per kg + MTX N=161**		**ACTEMRA 8 mg per kg + MTX N=170**		**Placebo + MTX N=158**	
Component (mean)	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**
Number of tender joints (0-68)	33	19 -7 0 (-10 0, -4 1)	32	14 5 -9 6 (-12 6, -6 7)	33	25	31	21 -10 8 (-14 6, -7 1)	32	17 -15 1 (-18 8, -11 4)	30	30
Number of swollen joints (0-66)	20	10 -4 2 (-6 1, -2 3)	19 5	8 -6 2 (-8 1, -4 2)	21	15	19 5	13 -6 2 (-9 0, -3 5)	19	11 -7 2 (-9 9, -4 5)	19	18
Pain[b]	61	33 -11 0 (-17 0, -5 0)	60	30 -15 8 (-21 7, -9 9)	57	43	63 5	43 -12 4 (-22 1, -2 1)	65	33 -23 9 (-33 7, -14 1)	64	48
Patient global assessment[b]	66	34 -10 9 (-17 1, -4 8)	65	31 -14 9 (-20 9, -8 9)	64	45	70	46 -10 0 (-20 3, 0 3)	70	36 -17 4 (-27 8, -7 0)	71	51
Physician global assessment[b]	64	26 -5 6 (-10 5, -0 8)	64	23 -9 0 (-13 8, -4 2)	64	32	66 5	39 -10 5 (-18 6, -2 5)	66	28 -18 2 (-26 3, -10 0)	67 5	43
Disability index (HAQ)[c]	1 64	1 01 -0 18 (-0 34, -0 02)	1 55	0 96 -0 21 (-0 37, -0 05)	1 55	1 21	1 67	1 39 -0 25 (-0 42, -0 09)	1 75	1 34 -0 34 (-0 51, -0 17)	1 70	1 58
CRP (mg per dL)	2 79	1 17 -1 30 (-2 0, -0 59)	2 61	0 25 -2 156 (-2 86, -1 46)	2 36	1 89	3 11	1 77 -1 34 (-2 5, -0 15)	2 80	0 28 -2 52 (-3 72, -1 32)	3 705	3 06

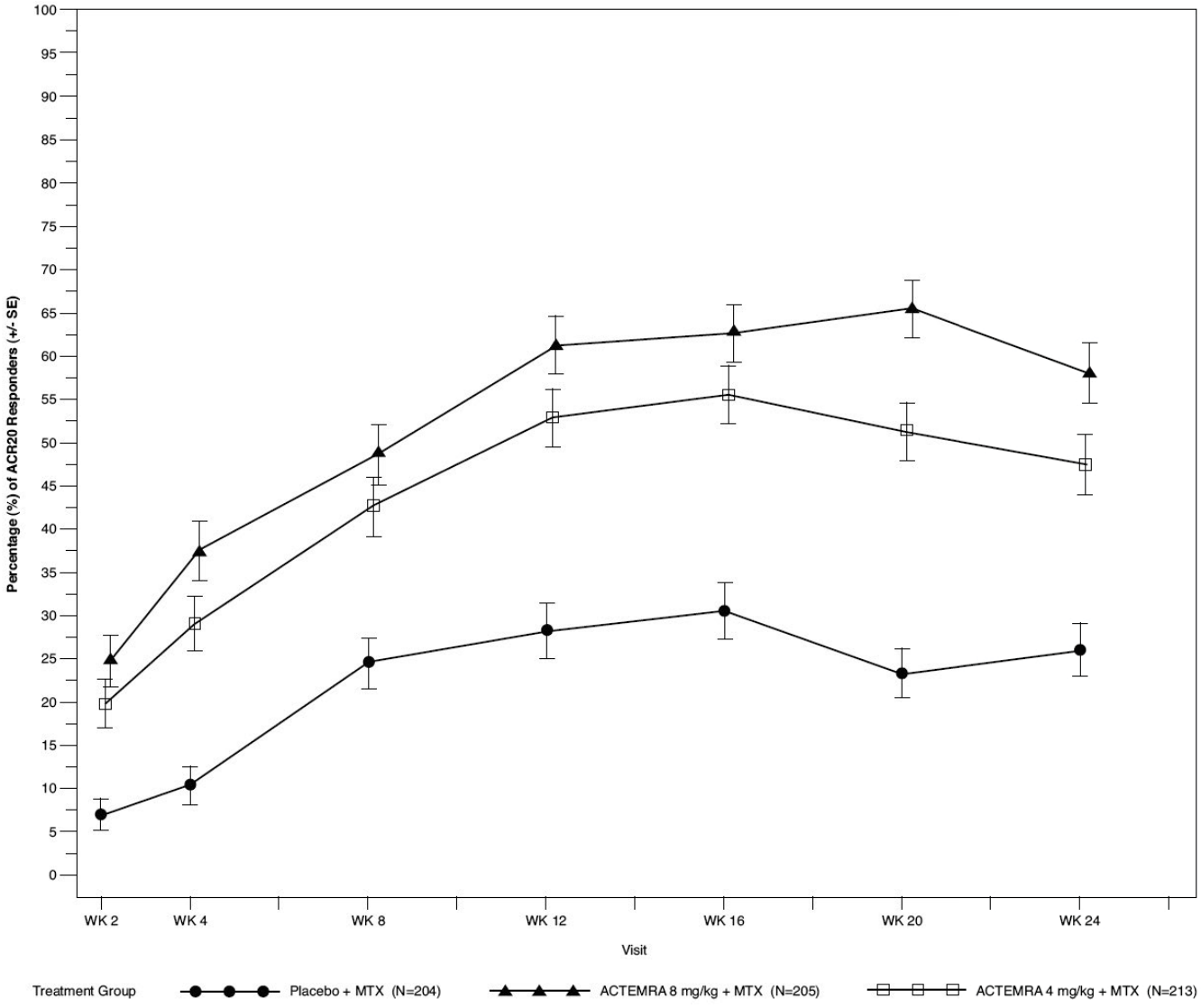
[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

[b] Visual analog scale: 0 = best, 100 = worst

[c] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR 20 responders by visit for Study III is shown in **Figure 1**. Similar response curves were observed in studies I, II, IV, and V.

Figure 1 Percent of ACR 20 Responders by Visit for Study III (Inadequate Response to MTX)*



*The same patients may not have responded at each timepoint.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in **Table 6**. ACTEMRA 4 mg per kg slowed (less than 75% inhibition compared to the control group) and ACTEMRA 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 6 Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX N=294	ACTEMRA 4 mg per kg + MTX N=343	ACTEMRA 8 mg per kg + MTX N=353
Week 52*			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean difference (95%CI)**		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean difference (95%CI)**		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean difference (95%CI)**		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.
** Difference between the adjusted means (ACTEMRA + MTX - Placebo + MTX)
SD = standard deviation

The mean change from baseline to week 104 in Total Sharp-Genant Score for the ACTEMRA 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the ACTEMRA 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to ACTEMRA 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of ACTEMRA demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the ACTEMRA 8 mg per kg and ACTEMRA 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Other Health-Related Outcomes

General health status was assessed by the Short Form Health Survey (SF-36) in Studies I – V. Patients receiving ACTEMRA demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), Mental Component Summary (MCS), and in all 8 domains of the SF-36.

Cardiovascular Outcomes

Study WA25204 (NCT01331837) was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multi-center, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with ACTEMRA compared with a TNF inhibitor standard of care (etanercept).

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ≥50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV ACTEMRA 8 mg/kg Q4W or SC etanercept 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events (83/1538 [5.4%] for ACTEMRA; 78/1542 [5.1%] for etanercept) reviewed by an independent and blinded adjudication committee.

Non-inferiority of ACTEMRA to etanercept for cardiovascular risk was determined by excluding >80% relative increase in the risk of MACE. The estimated hazard ratio (HR) for the risk of MACE comparing ACTEMRA to etanercept was 1.05; 95% CI (0.77, 1.43).

14.2 Rheumatoid Arthritis—Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in two double-blind, controlled, multicenter studies in patients with active RA. One study, SC-I (NCT01194414), was a non-inferiority study that compared the efficacy and safety of ACTEMRA 162 mg administered every week subcutaneously to 8 mg per kg intravenously every four weeks. The second study, SC-II (NCT01232569), was a placebo controlled superiority study that evaluated the safety and efficacy of ACTEMRA 162 mg administered every other week subcutaneously to placebo. Both SC-I and SC-II required patients to be >18 years of age with moderate to severe active rheumatoid arthritis diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline (SC-I) or at least 8 tender and 6 swollen joints at baseline (SC-II), and an inadequate response to their existing DMARD therapy, where approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biologic DMARD(s).

In SC-I, 1262 patients were randomized 1:1 to receive ACTEMRA-SC 162 mg every week or intravenous ACTEMRA 8 mg/kg every four weeks in combination with DMARD(s). In SC-II, 656 patients were randomized 2:1 to ACTEMRA-SC 162 mg every other week or placebo, in combination with DMARD(s). The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24.

The clinical response to 24 weeks of ACTEMRA-SC therapy is shown in **Table 7**. In SC-I, the primary outcome measure was ACR20 at Week 24. The pre-specified non-inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of ACTEMRA with respect to ACR20 at Week 24; ACR50, ACR70, and DAS28 responses are also shown in **Table 7**. In SC-II, a greater portion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved ACR20, ACR50, and ACR70 responses compared to placebo-treated patients (Table 7). Further, a greater proportion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved a low level of disease activity as measured by a DAS28-ESR less than 2.6 at Week 24 compared to those treated with placebo (Table 7).

Table 7 Clinical Response at Week 24 in Trials of Subcutaneous ACTEMRA (Percent of Patients)

	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8mg/kg + DMARD N=537	TCZ SC 162 mg every other week + DMARD N=437	Placebo + DMARD N=219
ACR20				
Week 24	69%	73.4%	61%	32%

Weighted difference (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
Week 24	47%	49%	40%	12%
Weighted difference (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
Week 24	24%	28%	20%	5%
Weighted difference (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
Change in DAS28 [Adjusted mean]				
Week 24	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
Week 24	38.4%	36.9%	32.0%	4.0%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)		28.6 (22.0, 35.2)	

TCZ = tocilizumab

[a] Per Protocol Population

[b] Intent To Treat Population

The results of the components of the ACR response criteria and the percent of ACR20 responders by visit for ACTEMRA-SC in Studies SC-I and SC-II were consistent with those observed for ACTEMRA-IV.

Radiographic Response

In study SC-II, the progression of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified total Sharp score (mTSS). At week 24, significantly less radiographic progression was observed in patients receiving ACTEMRA-SC every other week plus DMARD(s) compared to placebo plus DMARD(s); mean change from baseline in mTSS of 0.62 vs. 1.23, respectively, with an adjusted mean difference of -0.60 (-1.1, -0.1). These results are consistent with those observed in patients treated with intravenous ACTEMRA.

Health Related Outcomes

In studies SC-I and SC-II, the mean decrease from baseline to week 24 in HAQ-DI was 0.6, 0.6, 0.4 and 0.3, and the proportion of patients who achieved a clinically relevant improvement in HAQ-DI (change from baseline of $\geq$ 0.3 units) was 65%, 67%, 58% and 47%, for the subcutaneous every week, intravenous 8 mg/kg, subcutaneous every other week, and placebo treatment groups, respectively.

Other Health-Related Outcomes

General health status was assessed by the SF-36 in Studies SC-I and SC-II. In Study SC-II, patients receiving ACTEMRA every other week demonstrated greater improvement from baseline compared to placebo in the PCS, MCS, and in all 8 domains of the SF-36. In Study SC-I, improvements in these scores were similar between ACTEMRA-SC every week and ACTEMRA-IV 8 mg/kg.

14.3 Giant Cell Arteritis—Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in a single, randomized, double-blind, multicenter study in patients with active GCA. In Study WA28119 (NCT01791153), 251 screened patients with new-onset or relapsing GCA were randomized to one of four treatment arms. Two subcutaneous doses of ACTEMRA (162 mg every week and 162 mg every other week) were compared to two different placebo control groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1. The study consisted of a 52-week blinded period, followed by a 104-week open-label extension.

All patients received background glucocorticoid (prednisone) therapy. Each of the ACTEMRA-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 52 weeks designed to be more in keeping with standard practice.

The primary efficacy endpoint was the proportion of patients achieving sustained remission from Week 12 through Week 52. Sustained remission was defined by a patient attaining a sustained (1) absence of GCA signs and symptoms from Week 12 through Week 52, (2) normalization of erythrocyte sedimentation rate (ESR) (to < 30 mm/hr without an elevation to ≥ 30 mm/hr attributable to GCA) from Week 12 through Week 52, (3) normalization of C-reactive protein (CRP) (to < 1 mg/dL, with an absence of successive elevations to ≥ 1mg/dL) from Week 12 through Week 52, and (4) successful adherence to the prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52. ACTEMRA 162 mg weekly and 162 mg every other week + 26 weeks prednisone taper both showed superiority in achieving sustained remission from Week 12 through Week 52 compared with placebo + 26 weeks prednisone taper (Table 8). Both ACTEMRA treatment arms also showed superiority compared to the placebo + 52 weeks prednisone taper (Table 8).

Table 8 Efficacy Results from Study WA28119

	PBO + 26 weeks prednisone taper N=50	**PBO + 52 weeks prednisone taper N=51**	**TCZ 162mg SC QW + 26 weeks prednisone taper N=100**	**TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49**
Sustained remission [a]				
Responders, n (%)	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Unadjusted difference in proportions vs PBO + 26 weeks taper (99.5% CI)	N/A	N/A	42.0% (18.0, 66.0)	39.1% (12.5 , 65.7)
Unadjusted difference in proportions vs PBO + 52 weeks taper (99.5% CI)	N/A	N/A	38.4% (14.4, 62.3)	35.4% (8.6, 62.2)
Components of Sustained Remission				
Sustained absence of GCA signs and symptoms[b], n (%)	20 (40.0%)	23 (45.1%)	69 (69.0%)	28 (57.1%)
Sustained ESR<30 mm/hr[c], n (%)	20 (40.0%)	22 (43.1%)	83 (83.0%)	37 (75.5%)
Sustained CRP normalization[d], n (%)	17 (34.0%)	13 (25.5%)	72 (72.0%)	34 (69.4%)
Successful prednisone tapering[e], n (%)	10 (20.0%)	20 (39.2%)	60 (60.0%)	28 (57.1%)

[a] Sustained remission was achieved by a patient meeting all of the following components: absence of GCA signs and symptoms[b], normalization of ESR[c], normalization of CRP[d] and adherence to the prednisone taper regimen[e].
[b] Patients who did not have any signs or symptoms of GCA recorded from Week 12 up to Week 52.
[c] Patients who did not have an elevated ESR ≥30 mm/hr which was classified as attributed to GCA from Week 12 up to Week 52.
[d] Patients who did not have two or more consecutive CRP records of ≥ 1mg/dL from Week 12 up to Week 52.
[e] Patients who did not enter escape therapy and received ≤ 100mg of additional concomitant prednisone from Week 12 up to Week 52.
Patients not completing the study to week 52 were classified as non-responders in the primary and key secondary analysis: PBO+26: 6 (12.0%), PBO+52: 5 (9.8%), TCZ QW: 15 (15.0%), TCZ Q2W: 9 (18.4%).
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
PBO = placebo
Q2W = every other week dose
QW = every week dose
TCZ = tocilizumab

The estimated annual cumulative prednisone dose was lower in the two ACTEMRA dose groups (medians of 1887 mg and 2207 mg on ACTEMRA QW and Q2W, respectively) relative to the placebo arms (medians of 3804 mg and 3902 mg on placebo + 26 weeks prednisone and placebo + 52 weeks prednisone taper, respectively).

14.4 Systemic Sclerosis-Associated Interstitial Lung Disease– Subcutaneous Administration

The clinical efficacy of ACTEMRA was assessed in a phase 3 multicenter, randomized, double-blind, placebo controlled study in patients with SSc (Study WA29767). A phase 2/3 multicenter, randomized, double-blind, placebo controlled study in patients with SSc (Study WA27788) provided supportive information. Study WA29767 (NCT02453256) enrolled adult patients with SSc defined by the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc, with onset of disease (first non-Raynaud symptom) of ≤ 5 years, modified Rodnan Skin Score (mRSS) of ≥ 10 and ≤ 35 at screening, elevated inflammatory markers (or platelets), and active disease based on at least one of the following: disease duration ≤ 18 months, increase in mRSS ≥ 3 units over 6 months, involvement of one new body area and an increase in mRSS of ≥ 2 over 6 months, or involvement of two new body areas within the previous 6 months, or presence of at least one tendon friction rub. Study WA27788 (NCT01532869) enrolled adult patients with SSc with onset of disease ≤ 5 years, mRSS of ≥ 15 and ≤ 40 at screening, active disease, and elevated inflammatory markers or platelets. Patients in both studies were not permitted to use biologic agents (such as TNF antagonists), alkylating agents, or cyclophosphamide.

In Study WA29767, 212 patients were randomized in a 1:1 ratio to receive weekly SC injections of 162 mg of ACTEMRA or placebo during the 48-week, double-blinded, placebo controlled period. Rescue treatment was allowed during the treatment period after 16 weeks for >10% percent predicted FVC (ppFVC) decline or after 24 weeks for worsening skin fibrosis. The primary efficacy endpoint was change from baseline at Week 48 in mRSS. Change from baseline in FVC at Week 48 was a key secondary endpoint.

In the overall population of Study WA29767, there was not a statistically significant difference in the mean change from baseline to Week 48 in mRSS (primary endpoint) in patients receiving ACTEMRA compared to placebo (difference: -1.73; 95% CI: -3.78, 0.32). There also was not a statistically significant effect on the primary endpoint of mRSS in Study WA27788.

In the overall population of Study WA29767, patients treated with ACTEMRA, as compared to placebo treated patients, were observed to have less decline from baseline in ppFVC and observed FVC at 48 weeks. FVC results from Study WA27788 were similar.

Of the 212 patients who were randomized in Study WA29767, 68 patients (65%) in the ACTEMRA arm and 68 patients (64%) in the placebo arm had SSc-ILD at baseline, as confirmed by a visual read of high resolution computed tomograph (HRCT) by blinded thoracic radiologists. The mean ppFVC at baseline for patients with SSc-ILD identified by HRCT was 79.6% (median 80.5%). Post-hoc analyses were performed to evaluate results within the subgroups of patients with and without SSc-ILD.

Table 9 shows results from Study WA29767 for the changes from baseline to Week 48 in ppFVC, observed FVC, and mRSS both in the overall population and within subgroups based on SSc-ILD status at baseline. The ppFVC and observed FVC results in the overall population were primarily driven by results in the SSc-ILD subgroup. In the SSc-ILD subgroup, the differences in mean changes from baseline to Week 48 for ACTEMRA, as compared to placebo, were 6.47% and 241 mL for ppFVC and observed FVC, respectively. Figure 2 illustrates the mean change from baseline through Week 48 in observed FVC in patients with SSc-ILD.

The results of the key FVC secondary endpoints from Study WA29767 support a conclusion of effectiveness of ACTEMRA in reducing the rate of progressive loss of lung function in the study population. However, in settings where a trial does not provide evidence of an effect on the primary endpoint, the estimated magnitude of effect on other endpoints should be interpreted with caution, and comparisons to results of other products and studies may be misleading.

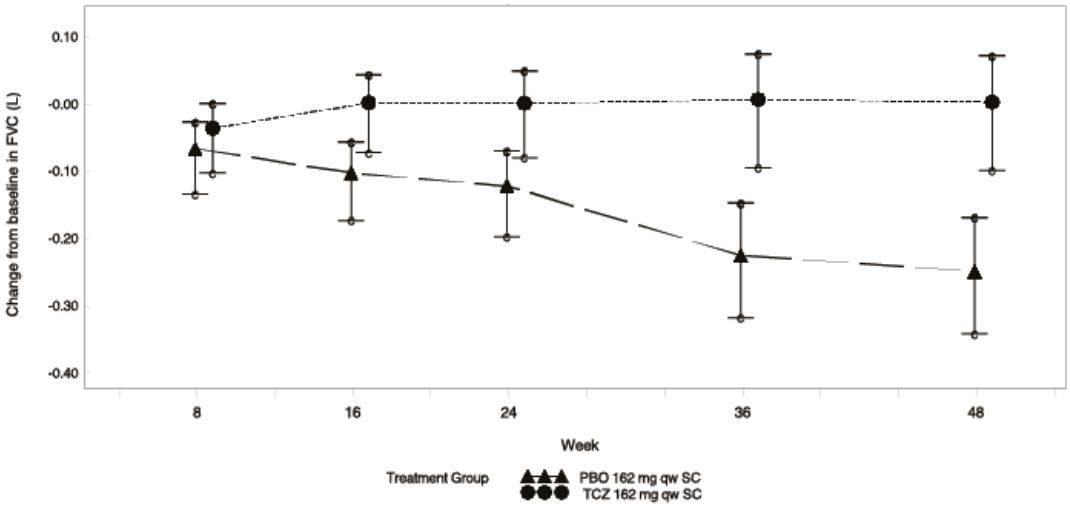
Table 9 Efficacy Results from Study WA29767

	Overall Population		Subgroup Without SSc-ILD*		SSc-ILD Subgroup*	
	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW
Number of patients	**106**	**104**	**36**	**34**	**68**	**68**
Change from Baseline in mRSS at Week 48						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM, TCZ-placebo (95% CI)	-1.73 (-3.78, 0.32)		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from Baseline in ppFVC at Week 48						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM, TCZ-placebo (95% CI)	4.20 (2.00, 6.40)		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from Baseline in Observed FVC (mL) at Week 48						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM, TCZ-placebo (95% CI)	167 (83, 250)		43 (-60, 145)		241 (124, 358)	

PBO=placebo; TCZ tocilizumab; ppFVC percent predicted forced vital capacity; LSM=least squares mean; mRSS modified Rodnan skin score; CI=confidence interval

*Post-hoc results are shown for these subgroups. Four patients had ILD status missing at baseline.

Figure 2 Mean Change from Baseline to Week 48 in Observed Forced Vital Capacity in SSc-ILD Patients from Study WA29767



PBO = placebo; TCZ = tocilizumab; QW = every week dose

14.5 Polyarticular Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of ACTEMRA was assessed in a three-part study, WA19977 (NCT00988221), including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but was not required during the study. Concurrent use of disease

modifying antirheumatic drugs (DMARDs), other than methotrexate, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted in the study.

Part I consisted of a 16-week active ACTEMRA treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Eligible patients weighing at or above 30 kg received ACTEMRA at 8 mg/kg intravenously once every four weeks. Patients weighing less than 30 kg were randomized 1:1 to receive either ACTEMRA 8 mg/kg or 10 mg/kg intravenously every four weeks. At the conclusion of the open-label Part I, 91% of patients taking background MTX in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study. The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background MTX in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy.

In Part II, patients (ITT, n=163) were randomized to ACTEMRA (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16.

ACTEMRA treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

During the withdrawal phase (Part II), more patients treated with ACTEMRA showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo.

14.6 Polyarticular Juvenile Idiopathic Arthritis—Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA) was assessed in WA28117 (NCT01904279), a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen. PJIA patients aged 1 to 17 years with an inadequate response or inability to tolerate MTX, including patients with well-controlled disease on treatment with ACTEMRA-IV and ACTEMRA-naïve patients with active disease, were treated with subcutaneous ACTEMRA based on body weight.

Patients weighing at or above 30 kg (n 25) were treated with 162 mg of ACTEMRA-SC every 2 weeks and patients weighing less than 30 kg (n 27) received 162 mg of ACTEMRA-SC every 3 weeks for 52 weeks. Of these 52 patients, 37 (71%) were naive to ACTEMRA and 15 (29%) had been receiving ACTEMRA-IV and switched to ACTEMRA-SC at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in polyarticular JIA patients and subcutaneous ACTEMRA in patients with RA [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2 and 14.5*)].

14.7 Systemic Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of ACTEMRA for the treatment of active SJIA was assessed in WA18221 (NCT00642460), a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (ACTEMRA:placebo = 2:1) to one of two treatment groups: 75 patients received ACTEMRA infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and 37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the

time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days). JIA ACR (American College of Rheumatology) responses are defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ).

Primary endpoint result and JIA ACR response rates at Week 12 are shown in **Table 11**.

Table 11 Efficacy Findings at Week 12

	ACTEMRA N=75	**Placebo N=37**
Primary Endpoint: JIA ACR 30 response + absence of fever		
Responders	**85%**	**24%**
Weighted difference (95% CI)	**62 (45, 78)**	**-**
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders Weighted difference[a] (95% CI)[b]	91% 67 (51, 83)	24% -
JIA ACR 50		
Responders Weighted difference[a] (95% CI)[b]	85% 74 (58, 90)	11% -
JIA ACR 70		
Responders Weighted difference[a] (95% CI)[b]	71% 63 (46, 80)	8% -

[a]The weighted difference is the difference between the ACTEMRA and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).
[b] CI: confidence interval of the weighted difference.

The treatment effect of ACTEMRA was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features

Of patients with fever or rash at baseline, those treated with ACTEMRA had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of 22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering

Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), ACTEMRA patients achieved a JIA ACR 70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) ACTEMRA patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to

week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) ACTEMRA patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes

Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the ACTEMRA treatment group achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of ≥ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

14.8 Systemic Juvenile Idiopathic Arthritis—Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with systemic juvenile idiopathic arthritis (SJIA) was assessed in WA28118 (NCT01904292), a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen.

Eligible patients received ACTEMRA subcutaneously dosed according to body weight, with patients weighing at or above 30 kg (n 26) dosed with 162 mg of ACTEMRA every week and patients weighing below 30 kg (n 25) dosed with 162 mg of ACTEMRA every 10 days (n=8) or every 2 weeks (n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to subcutaneous ACTEMRA and 25 (49%) had been receiving ACTEMRA intravenously and switched to subcutaneous ACTEMRA at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in systemic JIA patients [*see Clinical Pharmacology (12.3) and Clinical Studies (14.7)*]

14.9 Cytokine Release Syndrome—Intravenous Administration

The efficacy of ACTEMRA for the treatment of CRS was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The study population included 24 males and 21 females (total 45 patients) of median age 12 years (range, 3–23 years); 82% were Caucasian. The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0-18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment. Thirty-one patients (69%; 95% CI: 53%–82%) achieved a response. Achievement of resolution of CRS within 14 days was confirmed in a second study using an independent cohort that included 15 patients (range: 9–75 years old) with CAR T cell-induced CRS.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ACTEMRA (tocilizumab) injection is a preservative-free, sterile clear, colorless to pale yellow solution. ACTEMRA is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

For Subcutaneous Injection

ACTEMRA (tocilizumab) injection is supplied as a preservative-free, sterile, clear, colorless to slightly yellowish solution for subcutaneous administration. The following packaging configurations are available:

- Each single-dose prefilled syringe delivers 162 mg/0.9 mL (NDC 50242-138-01).
- Each single-dose ACTPen® autoinjector delivers 162 mg/0.9 mL (NDC 50242-143-01).

Storage and Stability: Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Patient Counseling

Advise patients and parents or guardians of minors with PJIA, SJIA, or CRS of the potential benefits and risks of ACTEMRA.

- **Infections**
  Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.
- **Gastrointestinal Perforation**
  Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.
- **Hypersensitivity and Serious Allergic Reactions**
  Assess patient suitability for home use for subcutaneous injection. Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Instruction on Injection Technique

Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ACTEMRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ACTEMRA and the suitability for home use *[See Patient Instructions for Use]*.

Prior to use, remove the prefilled syringe (PFS) or autoinjector from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes (PFS) or 45 minutes (autoinjector), out of the reach of children. Do not warm ACTEMRA in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper needle, syringe and autoinjector disposal, and caution against reuse of these items.

Pregnancy Exposure Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ACTEMRA *[see Use in Specific Populations (8.1)]*.

Pregnancy

Inform female patients of reproductive potential that ACTEMRA may cause fetal harm and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

ACTEMRA® (tocilizumab)
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

Medication Guide

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for intravenous use

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for subcutaneous use

What is the most important information I should know about ACTEMRA?

ACTEMRA can cause serious side effects including:

1. **Serious Infections**. ACTEMRA is a medicine that affects your immune system. ACTEMRA can lower the ability of your immune system to fight infections. Some people have serious infections while taking ACTEMRA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Your healthcare provider should test you for TB before starting ACTEMRA.

Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with ACTEMRA.

- You should not start taking ACTEMRA if you have any kind of infection unless your healthcare provider says it is okay.

Before starting ACTEMRA, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection, with or without a fever, such as:
  - sweating or chills
  - shortness of breath
  - warm, red, or painful skin or sores on your body
  - feel very tired
  - muscle aches
  - blood in phlegm
  - diarrhea or stomach pain
  - cough
  - weight loss
  - burning when you urinate or urinating more often than normal
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use ACTEMRA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.

After starting ACTEMRA, call your healthcare provider right away if you have any symptoms of an infection. ACTEMRA can make you more likely to get infections or make worse any infection that you have.

2. **Tears (perforation) of the stomach or intestines.**
   - Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
   - Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

3. **Liver problems (Hepatotoxicity):** Some people have experienced serious life-threatening liver problems, which required a liver transplant or led to death. Your healthcare provider may tell you to stop taking ACTEMRA if you develop new or worse liver problems during treatment with ACTEMRA. Tell your healthcare provider right away if you have any of the following symptoms:
   - feeling tired (fatigue)
   - lack of appetite for several days or longer (anorexia)
   - yellowing of your skin or the whites of your eyes (jaundice)
   - abdominal swelling and pain on the right side of your stomach-area
   - light colored stools
   - weakness
   - nausea and vomiting
   - confusion
   - dark “tea-colored” urine

4. **Changes in certain laboratory test results**. Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA), giant cell arteritis (GCA), or systemic sclerosis-interstitial lung disease (SSc-ILD) your healthcare provider should do blood tests every 4 to 8 weeks after you start receiving ACTEMRA for the first 6 months and then every 3 months after that. If you have polyarticular juvenile idiopathic arthritis (PJIA) you will have blood tests done every 4 to 8 weeks during treatment. If you have systemic juvenile idiopathic arthritis (SJIA) you will have blood tests done every 2 to 4 weeks during treatment. These blood tests are to check for the following side effects of ACTEMRA:
   - low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
   - low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
   - increase in certain liver function tests.
   - increase in blood cholesterol levels. You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving ACTEMRA.

   Your healthcare provider will determine how often you will have follow-up blood tests. Make sure you get all your follow-up blood tests done as ordered by your healthcare provider.
   You should not receive ACTEMRA if your neutrophil or platelet counts are too low or your liver function tests are too high.

   Your healthcare provider may stop your ACTEMRA treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.
5. **Cancer.** ACTEMRA may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See **"What are the possible side effects with ACTEMRA?"** for more information about side effects.

What is ACTEMRA?

ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor antagonist. ACTEMRA is used:

- To treat adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well.
- To treat adults with giant cell arteritis (GCA).
- For slowing the rate of decline in lung function in adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD) (also known as scleroderma associated ILD).
- To treat people with active PJIA ages 2 and above.
- To treat people with active SJIA ages 2 and above.
- To treat people age 2 years and above who experience severe or life-threatening Cytokine Release Syndrome (CRS) following chimeric antigen receptor (CAR) T cell treatment.
- ACTEMRA is not approved for subcutaneous use in people with CRS.

It is not known if ACTEMRA is safe and effective in children with PJIA, SJIA, or CRS under 2 years of age or in children with conditions other than PJIA, SJIA or CRS.

Do not take ACTEMRA: if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA. See the end of this Medication Guide for a complete list of ingredients in ACTEMRA.

Before you receive ACTEMRA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. **See "What is the most important information I should know about ACTEMRA?"**
- have liver problems.
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have had a reaction to tocilizumab or any of the ingredients in ACTEMRA before.
- have or had a condition that affects your nervous system, such as multiple sclerosis.
- have recently received or are scheduled to receive a vaccine:
  - All vaccines should be brought up-to-date before starting ACTEMRA.
  - People who take ACTEMRA should not receive live vaccines.
  - People taking ACTEMRA can receive non-live vaccines.
- plan to have surgery or a medical procedure.
- are pregnant or plan to become pregnant or are pregnant. ACTEMRA may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with ACTEMRA.
  - **Pregnancy Registry:** Genentech has a registry for pregnant women who take ACTEMRA. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant

while taking ACTEMRA, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- are breastfeeding or plan to breastfeed. It is not known if ACTEMRA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ACTEMRA.

Tell your healthcare provider about all of the medicines you take, including prescription, over-the-counter medicines, vitamins and herbal supplements. ACTEMRA and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. You should not take etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), or golimumab (Simponi®), while you are taking ACTEMRA. Taking ACTEMRA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ACTEMRA?

Into a vein (IV or intravenous infusion) for Rheumatoid Arthritis, PJIA, SJIA, or CRS:

- If your healthcare provider prescribes ACTEMRA as an IV infusion, you will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm. The infusion will take about 1 hour to give you the full dose of medicine.
- For rheumatoid arthritis or PJIA you will receive a dose of ACTEMRA about every 4 weeks.
- For SJIA you will receive a dose of ACTEMRA about every 2 weeks.
- For CRS you will receive a single dose of ACTEMRA, and if needed, additional doses.
- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis, PJIA, or SJIA such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

Under the skin (SC or subcutaneous injection) for Rheumatoid Arthritis, Giant Cell Arteritis, SSc-ILD, PJIA or SJIA:

- **See the Instructions for Use at the end of this Medication Guide for instructions about the right way to prepare and give your ACTEMRA injections at home.**
- ACTEMRA is available as a single-dose Prefilled Syringe or single-dose prefilled ACTPen® autoinjector.
- You may also receive ACTEMRA as an injection under your skin (subcutaneous). If your healthcare provider decides that you or a caregiver can give your injections of ACTEMRA at home, you or your caregiver should receive training on the right way to prepare and inject ACTEMRA. Do not try to inject ACTEMRA until you have been shown the right way to give the injections by your healthcare provider.
- For PJIA or SJIA, you may self-inject with the Prefilled Syringe or prefilled ACTPen® autoinjector, or your caregiver can give you ACTEMRA, if both your healthcare provider and parent/legal guardian find it appropriate.
- Your healthcare provider will tell you how much ACTEMRA to use and when to use it.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

- See **"What is the most important information I should know about ACTEMRA?"**
- **Hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. Your healthcare provider may do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:
  - o feel very tired
  - o vomiting
  - o chills
  - o dark urine
  - o skin or eyes look yellow
  - o clay-colored bowel movements
  - o stomach discomfort
  - o skin rash
  - o little or no appetite
  - o fevers
  - o muscle aches
- **Serious Allergic Reactions.** Serious allergic reactions, including death, can happen with ACTEMRA. These reactions can happen with any infusion or injection of ACTEMRA, even if they did not occur with an earlier infusion or injection. Tell your healthcare provider before your next dose if you had hives, rash or flushing after your injection. Seek medical attention right away if you have any of the following signs of a serious allergic reaction:
  - o shortness of breath or trouble breathing
  - o swelling of the lips, tongue, or face

- chest pain
- feeling dizzy or faint
- moderate or severe abdominal pain or vomiting

- **Nervous system problems**. While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

The most common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)
- injection site reactions

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

General information about the safe and effective use of ACTEMRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not give ACTEMRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab.
Inactive ingredients of Intravenous ACTEMRA: disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, polysorbate 80, sucrose, and water for Injection.
Inactive ingredients of Subcutaneous ACTEMRA: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, and water for Injection.

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For more information, go to www.ACTEMRA.com or call 1-800-ACTEMRA.

Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 03/2021

Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Injection, For Subcutaneous Use
Single-dose Prefilled Syringe

Read and follow the Instructions for Use that come with your ACTEMRA prefilled syringe before you start using it and each time you get a prescription refill. Before you use ACTEMRA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

- **Do not remove the needle cap until you are ready to inject ACTEMRA.**
- **Do not try to take apart the syringe at any time.**
- **Do not reuse the same syringe.**

Parts of your ACTEMRA Prefilled Syringe **(See Figure A).**

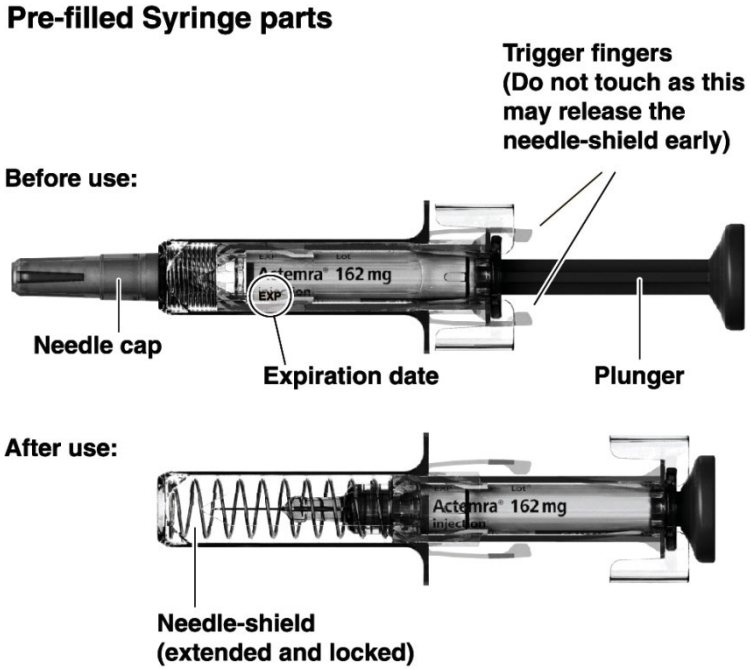


Figure A

Supplies needed for your ACTEMRA Prefilled Syringe Injection (See Figure B):

- ACTEMRA prefilled syringe
- alcohol pad
- sterile cotton ball or gauze
- puncture-resistant container or sharps container for safe disposal of needle cap and used syringe **(See Step 4 "Dispose of the syringe")**

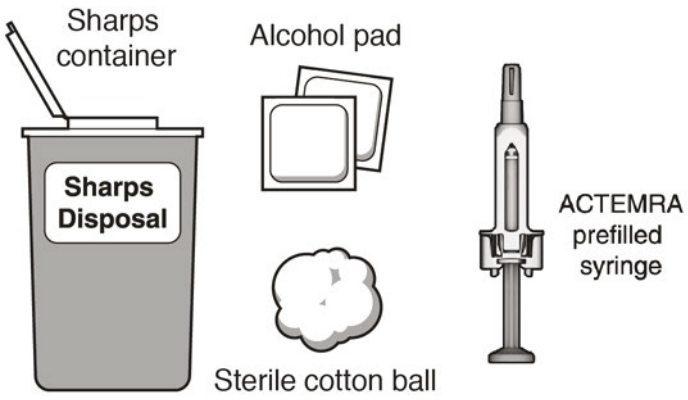


Figure B

Step 1. Preparing for an ACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the syringe out of the refrigerator and open the box. **Do not** touch the trigger fingers on the syringe as this may damage the syringe.
- Remove 1 single-use ACTEMRA prefilled syringe from the box and let it warm up for 30 minutes to allow it to reach room temperature. If the syringe does not reach room temperature, this could cause your injection to feel uncomfortable and make it difficult to push the plunger in.
- **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- Check the expiration date on the ACTEMRA prefilled syringe **(See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed safely dispose of the syringe in a sharps container and get a new one.

Do not remove the needle cap while allowing your ACTEMRA prefilled syringe to reach room temperature.

- Keep your unused syringes in the original carton and keep in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** freeze.
- Hold your ACTEMRA prefilled syringe with the covered needle pointing down **(See Figure C).**

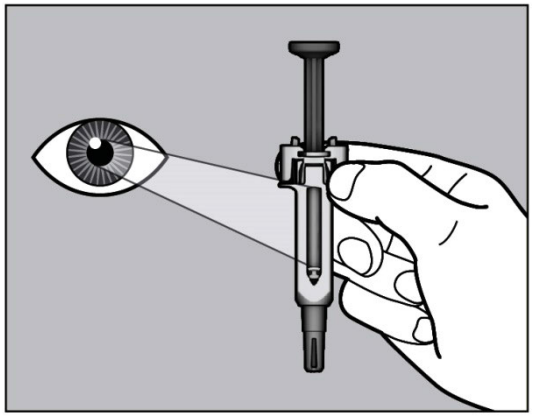


Figure C

- Check the liquid in the ACTEMRA prefilled syringe. It should be clear and colorless to pale yellow. Do not inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the syringe in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh and your abdomen except for the 2-inch area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1-inch from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

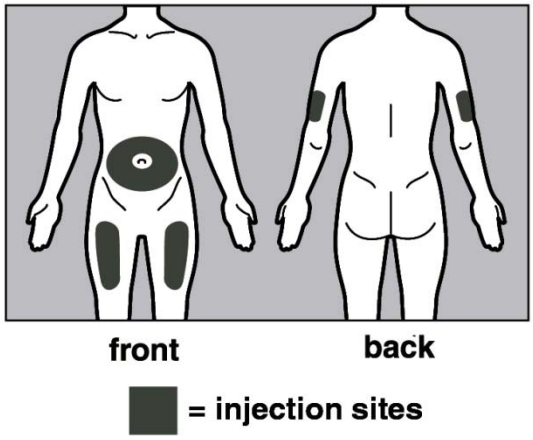


Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject ACTEMRA

- Hold the ACTEMRA prefilled syringe with 1 hand and pull the needle cap straight off with your other hand **(See Figure E). Do not** hold the plunger while you remove the needle cap. If you cannot remove the needle cap you should ask a caregiver for help or contact your healthcare provider.

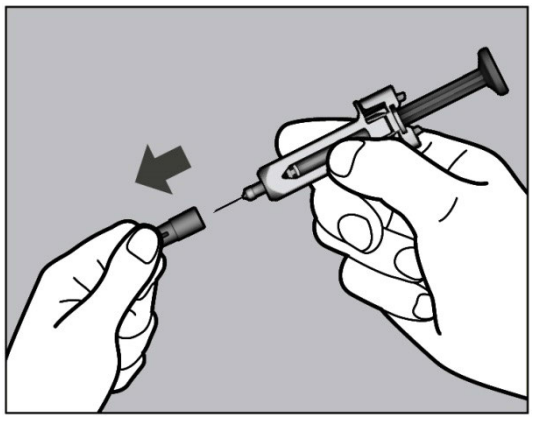


Figure E

- Throw away the needle cap in a sharps container.
- There may be a small air bubble in the ACTEMRA prefilled syringe. You do not need to remove it.
- You may see a drop of liquid at the end of the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.

- **Do not** use the prefilled syringe if it is dropped.
- If it is not used within 5 minutes of needle cap removal, the syringe should be disposed of in the puncture resistant container or sharps container and a new syringe should be used.
- Never reattach the needle cap after removal.
- Hold the ACTEMRA prefilled syringe in 1 hand between the thumb and index finger **(See Figure F).**

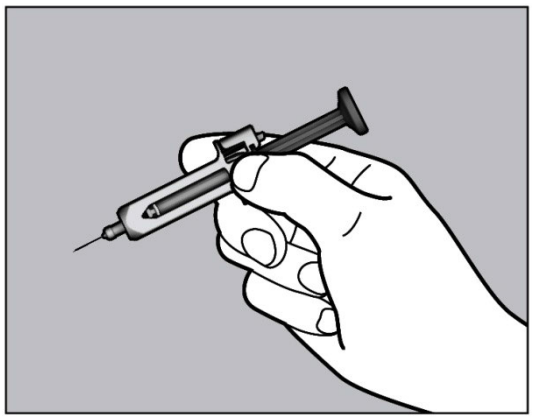


Figure F

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold the pinched skin firmly. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.
- **Do not** hold or push on the plunger while inserting the needle into the skin.
- Use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90° **(See Figure G).** It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

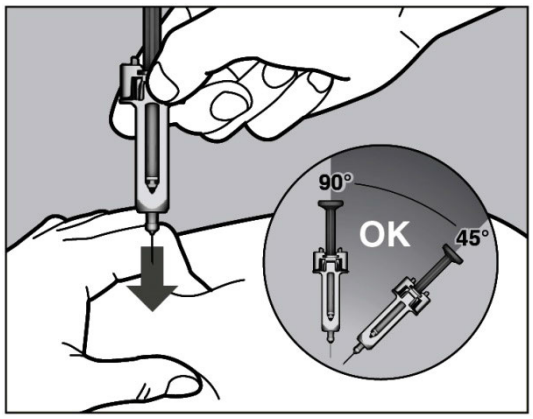


Figure G

- Keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down **(See Figure H).** You must press the plunger all the way down to get the full dose of medicine and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered, carefully place the syringe into the puncture resistant container to avoid injury with the needle.

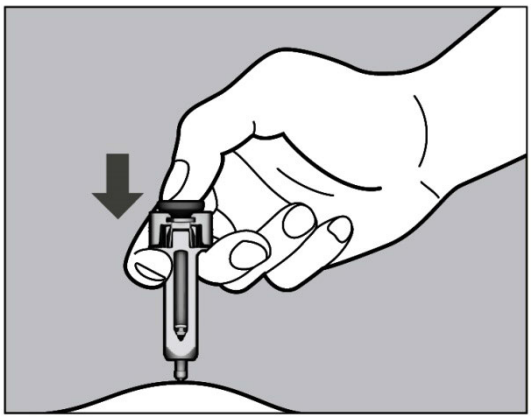


Figure H

- After the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted **(See Figure I).**

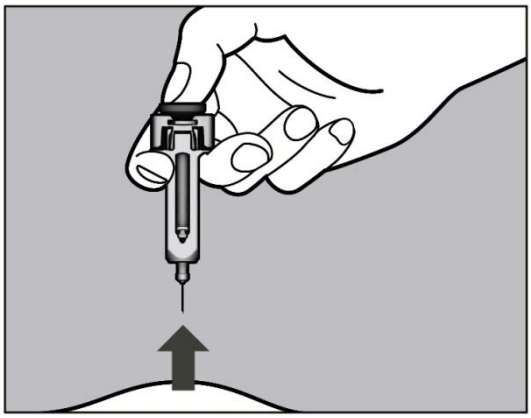


Figure I

- After the needle is removed completely from the skin, release the plunger, allowing the needle-shield to protect the needle **(See Figure J).**

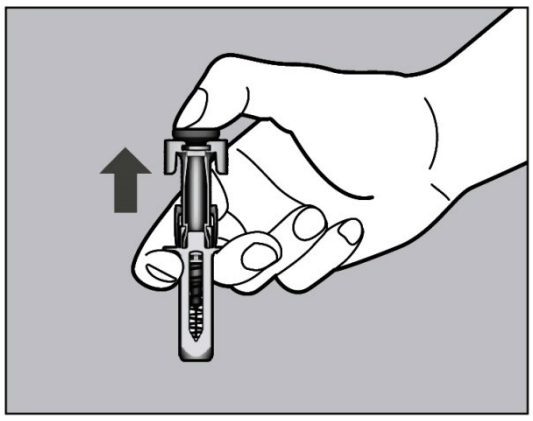


Figure J

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the syringe

- The ACTEMRA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container **(See "How do I throw away used syringes?")**
- **Do not** put the needle cap back on the needle.
- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

- Put your used needles and syringes including ACTEMRA in a FDA-cleared sharps disposal container right away after use **(See Figure K). Do not throw away (dispose of) loose needles and syringes in your household trash.**

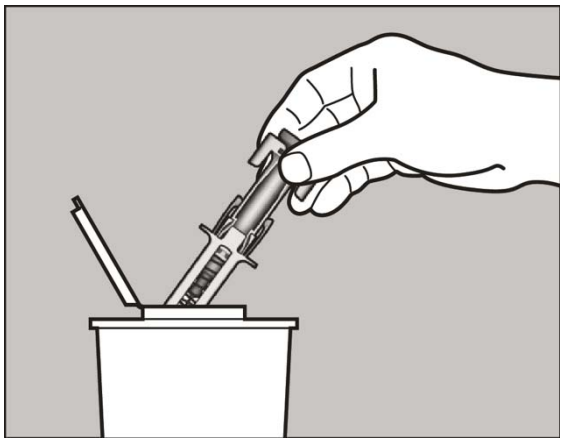


Figure K

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
    - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
    - Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- **Keep ACTEMRA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ACTEMRA prefilled syringe, please contact your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Medication Guide Revised: 03/2021

Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Injection, For Subcutaneous Use
Single-dose Prefilled ACTPen® (AKT-PEN) Autoinjector

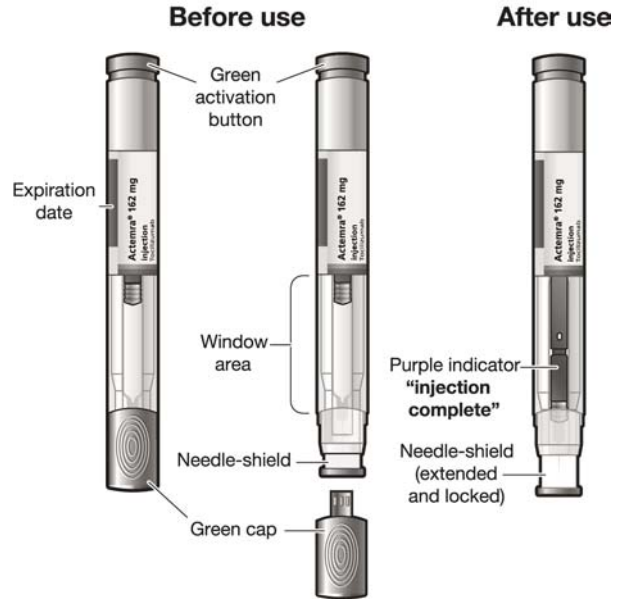
Read and follow the Instructions for Use that come with your ACTEMRA ACTPen autoinjector before you start using it and each time you get a prescription refill. Before you use the ACTEMRA ACTPen autoinjector for the first time, make sure your healthcare provider shows you the right way to use it.

Important: Keep your unused Autoinjectors in the original carton and keep in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** freeze.

- **Do not** remove the Autoinjector cap until you are ready to inject ACTEMRA.
- **Do not** try to take apart the Autoinjector at any time.
- **Do not** reuse the same Autoinjector.
- **Do not** use the Autoinjector through clothing.
- **Do not** leave the Autoinjector unattended.
- **Do not** use the Autoinjector if it appears to be damaged or if you have accidentally dropped the Autoinjector.
- Keep out of the reach of children.

Parts of your ACTEMRA ACTPen autoinjector **(See Figure A).**

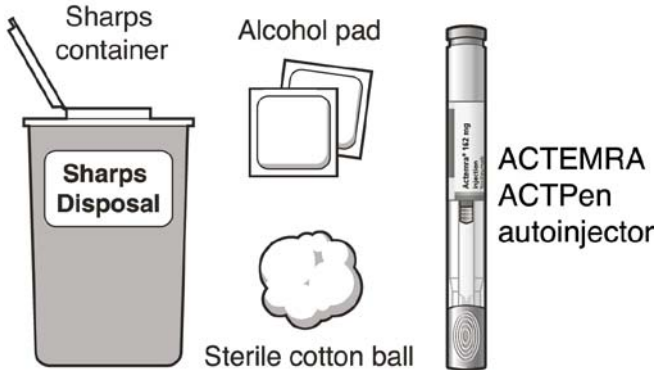
Figure A



Supplies needed for an injection using your ACTEMRA ACTPen autoinjector (See Figure B):

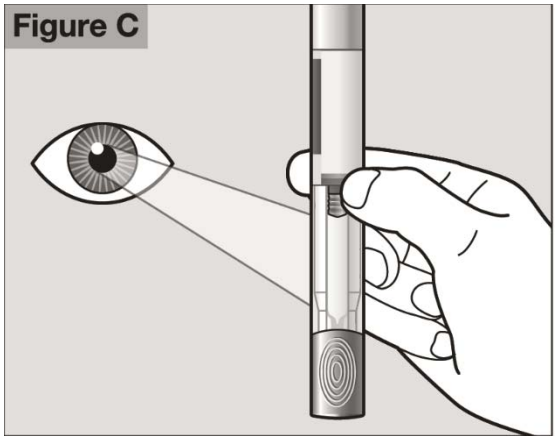
- 1 ACTEMRA ACTPen autoinjector
- 1 Alcohol pad
- 1 Sterile cotton ball or gauze
- 1 Puncture-resistant container or sharps container for safe disposal of Autoinjector cap and used Autoinjector **(See Step 4 "Dispose of the Autoinjector")**

Figure B



Step 1. Preparing for an ACTEMRA Injection
Find a comfortable space with a clean, flat, working surface.

- Take the box containing the Autoinjector out of the refrigerator.
- If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the Autoinjector if the box looks like it has already been opened.
- Check that the Autoinjector box is not damaged. **Do not** use ACTEMRA ACTPen autoinjector if the box looks damaged.
- **Check the expiration date on the Autoinjector box**. **Do not** use the Autoinjector if the expiration date has passed because it may not be safe to use.
- Open the box, and remove 1 single-use ACTEMRA ACTPen autoinjector from the box.
- Return any remaining autoinjectors in the box to the refrigerator.
- **Check the expiration date on the ACTEMRA ACTPen autoinjector (See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the Autoinjector in a sharps container and get a new one.
- **Check the Autoinjector to make sure it is not damaged. Do not** use the Autoinjector if it appears to be damaged or if you have accidentally dropped the Autoinjector.
- Place the Autoinjector on a clean, flat surface and let the Autoinjector warm up for 45 minutes to allow it to reach room temperature. If the Autoinjector does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the Autoinjector in warm water.
    - **Do not** leave the Autoinjector to warm up in direct sunlight.
    - **Do not** remove the green cap while allowing your ACTEMRA ACTPen autoinjector to reach room temperature.
- Hold your ACTEMRA ACTPen autoinjector with the green cap pointing down **(See Figure C).**
- Look in the clear Window area. Check the liquid in the ACTEMRA ACTPen autoinjector **(See Figure C)**. It should be clear and colorless to pale yellow. **Do not** inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the Autoinjector in a sharps container and get a new one.



- Wash your hands well with soap and water.

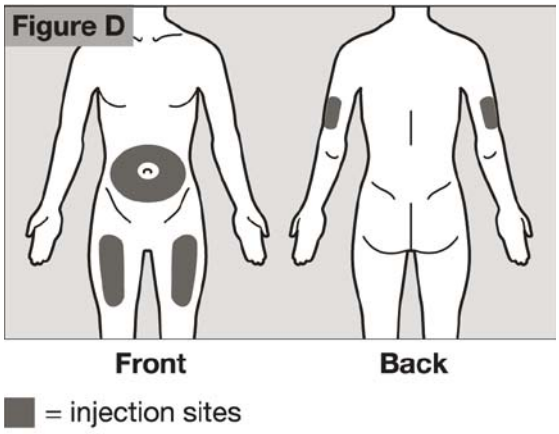
Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh or your abdomen except for the 2-inch (5cm) area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. **Do not** attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch (2.5cm) from the last area you injected.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

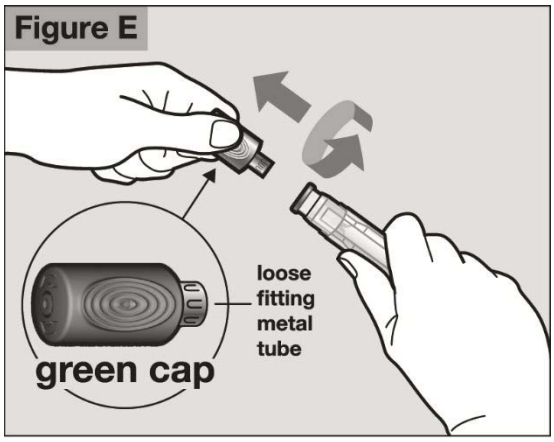


Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

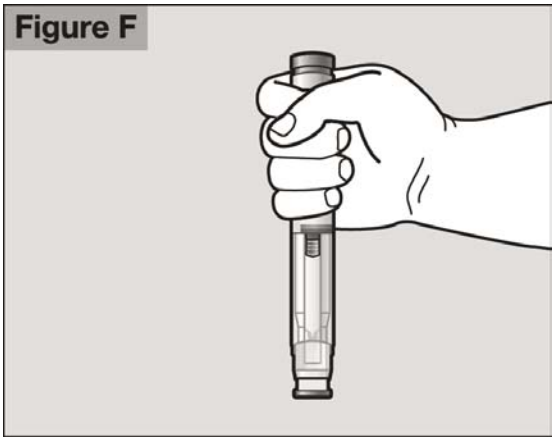
Step 3. Inject ACTEMRA

- Hold the ACTEMRA ACTPen autoinjector firmly with one hand. Twist and pull off the green cap with the other hand **(See Figure E).** The green cap contains a loose fitting metal tube.
- If you cannot remove the green cap you should ask a caregiver for help or contact your healthcare provider.

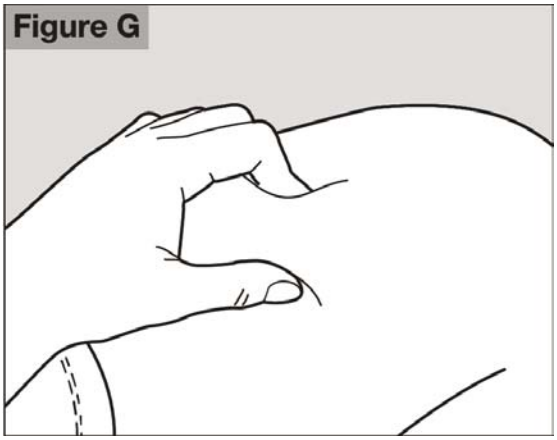


Important: Do not touch the needle shield which is located at the tip of the Autoinjector below the Window area (See Figure A), to avoid accidental needle stick injury.

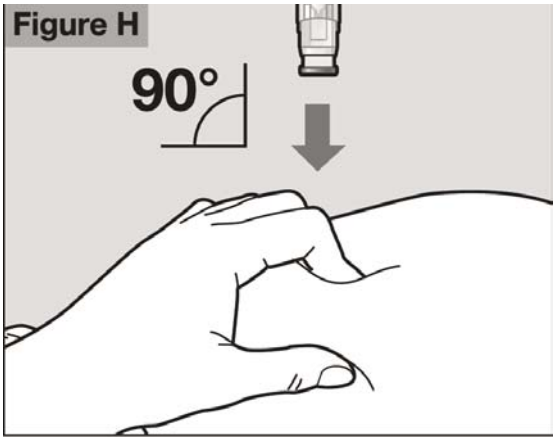
- Throw away the green cap in a sharps container.
- After you remove the green cap, the Autoinjector is ready for use. **If the Autoinjector is not used within 3 minutes of the cap removal, the Autoinjector should be disposed of in the sharps container and a new Autoinjector should be used.**
- Never reattach the green cap after removal.
- Hold the Autoinjector comfortably in 1 hand by the upper part, so that you can see the Window area of the Autoinjector **(See Figure F)**.



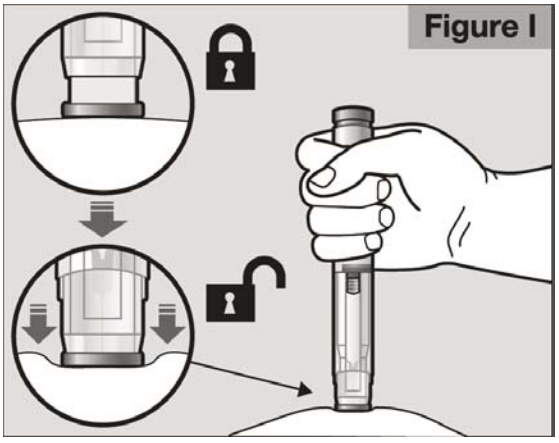
- Use your other hand to gently pinch the area of skin you cleaned, to prepare a firm injection site **(See Figure G)**. The Autoinjector requires a firm injection site to properly activate. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.



- **Do not** press the green Activation button yet.
  Place the needle-shield of the Autoinjector against your pinched skin at a 90° angle **(See Figure H)**.
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.
- **Continue to gently pinch throughout the injection procedure**.

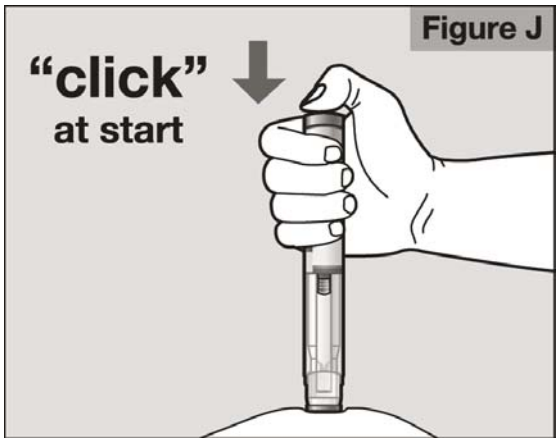


- To use the Autoinjector, you first have to unlock the green Activation button. To unlock it, press the Autoinjector firmly against your pinched skin until the needle-shield is completely pushed in **(See Figure I)**.

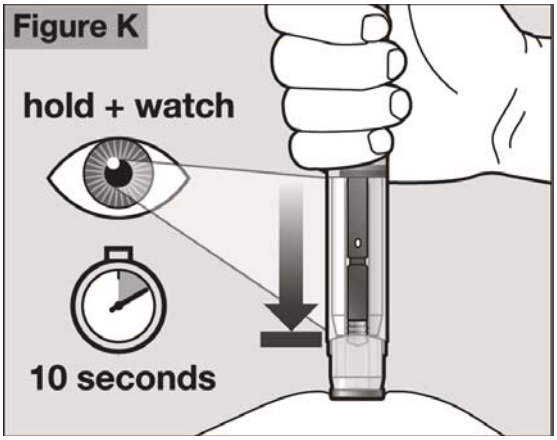


- Continue to keep the needle-shield pushed in. If you do not keep the needle-shield completely pushed against the skin, the green Activation button will not work. Continue to pinch the skin while you keep the Autoinjector in place.

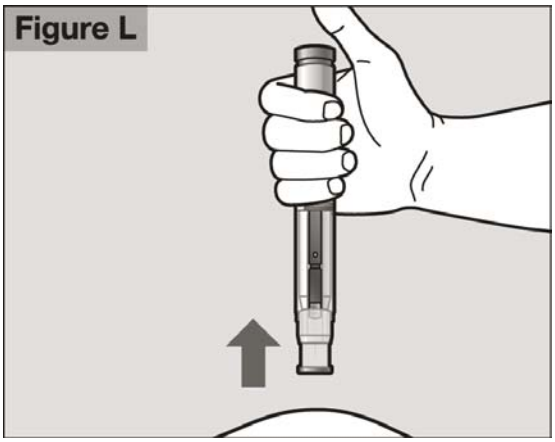
- Press the green Activation button to start the injection. A “click” sound indicates the **start** of the injection. Keep the green button pressed in and continue holding the Autoinjector pressed firmly against your skin **(See Figure J)**. If you cannot start the injection you should ask for help from a caregiver or contact your healthcare provider.



- The purple indicator will move along the Window area during the injection **(See Figure K)**.
- **Watch the purple indicator until it stops moving** to be sure the full dose of medicine is injected. This may take up to **10 seconds**.



- You may hear a second “click” during the injection but you should continue to hold the Autoinjector firmly against your skin until the purple indicator stops moving.
- When the purple indicator has stopped moving, release the green button. Lift the Autoinjector straight off of the injection site at a 90° angle to remove the needle from the skin. The needle-shield will then move out and lock into place covering the needle **(See Figure L)**.



- Check the Window area to see that it is filled with the purple indicator **(See Figure L).**
- If the Window area is not filled by the purple indicator then:
  - The needle-shield may not have locked. **Do not** touch the needle-shield of the Autoinjector, because you may stick yourself with the needle. If the needle is not covered, carefully place the Autoinjector into the sharps container to avoid any injury with the needle.
  - You may not have received your full dose of ACTEMRA. **Do not** try to re-use the Autoinjector. **Do not** repeat the injection with another Autoinjector. Call your healthcare provider for help.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

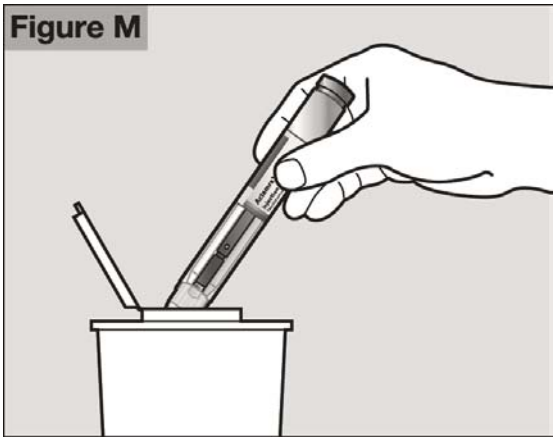
Step 4. Dispose of the Autoinjector

- The ACTEMRA ACTPen autoinjector should not be reused.
- Put the used Autoinjector into your sharps container **(See "How do I dispose of used Autoinjectors?").**
- **Do not** put the cap back on the Autoinjector.
- **If your injection is given by another person, this person must also be careful when removing the Autoinjector and disposing of it to prevent accidental needle stick injury and passing infection.**

How do I dispose of used Autoinjectors?

- Put your used ACTEMRA ACTPen autoinjector and green cap in a FDA-cleared sharps disposal container right away after use **(See Figure M)**.
- **Do not** throw away (dispose of) the Autoinjector and the green cap in your household trash.

Figure M



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
    - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should dispose of used Autoinjectors. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
    - **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Keep the ACTEMRA ACTPen autoinjector and disposal container out of the reach of children.

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have any questions or concerns about your ACTEMRA ACTPen autoinjector, talk to your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Medication Guide Revised: 03/2021

Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s131

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplement
Application Number(s)	BLA 125472/S-044, BLA 125276/S-131
Priority or Standard	Priority
Submit Date(s)	July 24, 2020
Received Date(s)	July 24, 2020
PDUFA Goal Date	January 24, 2021
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII)
Review Completion Date	See electronic stamp date
Established/Proper Name	tocilizumab
(Proposed) Trade Name	Actemra
Pharmacologic Class	humanized monoclonal antibody against the interleukin-6 receptor
Applicant	Genentech, Inc.
Dosage form	Single-dose prefilled syringe or single-dose prefilled autoinjector for subcutaneous administration
Applicant proposed Dosing Regimen	162 mg once every week as a subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Recommended Dosing Regimen	162 mg once every week as a subcutaneous injection

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Elaine Sit
Nonclinical Reviewer	Brett Jones
Nonclinical Acting Team Leader	Eleni Salicru
Office of Clinical Pharmacology Reviewer(s)	Dipak Pisal, Yuan Xu (Pharmacometrics)
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, Jiang Liu (Pharmacometrics)
Clinical Reviewer	Khalid Puthawala
Clinical Team Leader	Rachel Glaser
Statistical Reviewer	Sara Jimenez
Statistical Team Leader	David Petullo
Cross-Disciplinary Team Leader	Rachel Glaser
Division Deputy Director (OB)	Gregory Levin
Division Director (designated signatory authority)	Nikolay Nikolov

Additional Reviewers of Application

OPQ	Zach Kraus, Gerry Feldman (TL), Teshara Bouie (RBPM)
OPMA	Zhong Li, Thuy Thanh Nguyen (TL)
OPDP	Adewale Adeleye
OSE/DMEPA	Sarah Vee, Idalia Rychlik (TL)
Patient Labeling	Maria Nguyen, Marcia Williams (TL)

OB = Office of Biostatistics
OPQ = Office of Pharmaceutical Quality
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dipak Pisal, MS, PhD	OCP/DIIP	Section:6	Select one: _X__ Authored _X__ Approved
	Signature: Dipak Pisal -S Digitally signed by Dipak Pisal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dipak Pisal -S, 0.9.2342.19200300.100.1.1=2001808716 Date: 2021.03.03 16:17:29 -05'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen, MD, PhD	OCP/DIIP	Section:6	Select one: ___ Authored _X__ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2021.03.04 08:42:33 -05'00'			
Pharmacometrics Reviewer	Yuan Xu, PhD	OCP/DPM	Section:15.4	Select one: _X__ Authored ___ Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan Xu -S, 0.9.2342.19200300.100.1.1=2001686060 Date: 2021.03.04 10:03:59 -05'00'			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Section:15.4	Select one: _X__ Authored ___ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.03.03 17:27:08 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Khalid Puthawala	OII/DPACC	Sections: 2, 3, 7, 8, 11	**Select one:** _X__ Authored _X__ Approved
	Signature: Khalid Puthawala -S Digitally signed by Khalid Puthawala -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002317280, cn=Khalid Puthawala -S Date: 2021.03.03 16:21:02 -05'00'			
Clinical Team Leader	Rachel Glaser	OII/DRTM	Sections: All	**Select one:** _X__ Authored 1.3, 8.4 __X_ Approved All
	Signature: Rachel Glaser -S Digitally signed by Rachel Glaser -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rachel Glaser -S, 0.9.2342.19200300.100.1.1=0013432915 Date: 2021.03.03 16:11:14 -05'00'			
Division Director (Clinical)	Nikolay Nikolov	OII/DRTM	Sections:	**Select one:** _X_ Authored, 1.2, 14 _X__ Approved All
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2021.03.03 16:04:44 -05'00'			
Statistical Reviewer	Sara Jimenez, PhD	OB/DBIII	Sections: 8.1, 8.3, 15.5	**Select one:** _X__ Authored ___ Approved
	Signature: Sara Jimenez -S Digitally signed by Sara Jimenez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sara Jimenez -S, 0.9.2342.19200300.100.1.1=2002241423 Date: 2021.03.03 18:52:06 -05'00'			
Statistical Team Leader	David Petullo	OB/DBIII	Sections:1, 7, 8	**Select one:** ___ Authored _X_ Approved
	Signature: David M. Petullo -S Digitally signed by David M. Petullo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300376368, cn=David M. Petullo -S Date: 2021.03.03 17:12:06 -05'00'			
Division Deputy Director (OB)	Gregory Levin	OB/DBIII	Sections: 1, 7, 8	**Select one:** ___ Authored _X__ Approved
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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
ATS	American Thoracic Society
BHPR	British Health Professionals in Rheumatology
BIMO	bioresearch monitoring
BLA	biologics license application
BSR	British Society for Rheumatology
CDF	cumulative distribution function
CFR	Code of Federal Regulations
CI	confidence interval
CRP	c-reactive protein
CRS	Cytokine Release Syndrome
CSR	clinical study report
DB	double blind
DLCO	diffusing capacity of the lungs for carbon monoxide
FDA	Food and Drug Administration
FPFV	First patient first visit
FVC	forced vital capacity
GCA	giant cell arteritis
GCP	good clinical practice
GERD	gastroesophageal reflux disease
HAQ-DI	health assessment questionnaire-disability index
HRCT	high resolution computed tomography
HCQ	hydroxychloroquine
ICH	International Council for Harmonisation
IL	interleukin
ILD	interstitial lung disease
IND	investigational new drug
ITT	intent-to-treat
IV	intravenous
LVEF	left ventricular ejection fraction
MAR	missing at random
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MPD	major protocol deviation
MTX	methotrexate

NDA	new drug application
OL	open-label
OLE	open-label extension
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	pre-filled syringe
PI	prescribing information
PJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PRO	patient reported outcome
QLF	quantitative lung fibrosis
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SJIA	systemic juvenile idiopathic arthritis
SOC	system organ class
TCZ	tocilizumab
TEAE	treatment-emergent adverse event
TTF	time to treatment Failure
VAS	visual analog scale

1 Executive Summary

1.1. Product Introduction

Tocilizumab (TCZ) is a recombinant humanized interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1 subtype with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively, and the four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. TCZ binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and competitively inhibits IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T and B lymphocytes, monocytes, and fibroblasts.

TCZ is available in intravenous (IV) and subcutaneous (SC) presentations. IV TCZ is supplied in single use vials containing 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL. SC TCZ is supplied in a 1.0 mL single-dose prefilled syringe with a needle safety device, as well as an autoinjector, that each deliver 0.9 mL (162 mg) of TCZ.

SC TCZ is approved for moderate to severely active rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), and systemic juvenile idiopathic arthritis (SJIA). IV TCZ is approved for treatment of moderate to severely active RA, SJIA, PJIA, and Cytokine Release Syndrome (CRS).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The results from Study WA29767, an adequate and well-controlled phase 3, multicenter, randomized, double-blind, placebo controlled study in 212 patients with active SSc, and Study WA27788, a phase 2/3, multicenter, randomized, double-blind, placebo controlled study in 87 patients with active SSc, provide the primary evidence for the effectiveness in SSc-ILD in this supplement. In both studies, the primary endpoint, change in modified Rodnan Skin Score (mRSS) at Week 48, was not met. However, in both studies, consistent clinically meaningful improvement was observed on forced vital capacity (FVC), a pre-specified secondary endpoint in Study WA29767 and an exploratory endpoint in Study WA27788, in the TCZ treatment groups as compared to the placebo groups.

Clinical and Statistical Considerations About Whether There is Substantial Evidence of Effectiveness

Clinical trial design in SSc has historically been challenged by the clinical diversity of the disease manifestations and the complex underlying pathophysiology and natural history of each manifestation, as well as limitations in the currently used endpoints to assess them. Although mRSS is one of the most common endpoints used in trials of SSc and there is clear evidence of a

correlation between mRSS and clinical outcomes such as mortality and risk of major internal organ involvement in observational studies, use of the mRSS endpoint in interventional trials is confounded by the diversity of mRSS trajectory over time, in which at least half of all diffuse cutaneous SSc cases will demonstrate spontaneous significant improvement over the first 3-5 years from disease onset. This has led to difficulty in differentiating between active treatment and placebo at a group level and may suggest a need for better identification of case subsets at baseline or a different approach to the endpoint, such as responder analyses (Denton 2019). With respect to this point, the performance of mRSS in Studies WA27788 and WA29767 is not surprising, and is consistent with results for the mRSS in other interventional trials, including the SENSCIS trial, the SSc-ILD registrational trial for nintedanib (Labeling 2014a).

In contrast, the timing and frequency of the development of significant lung fibrosis is less heterogeneous, and therefore easier to characterize, and the impact of change in pulmonary function tests and outcome has been well documented. Change in forced vital capacity is not only known to be associated with pulmonary fibrosis pathophysiologically (Berend 2014),but also has the reliability and responsiveness to have been successfully used to distinguish active treatment from placebo in multiple randomized, controlled trials, including the Scleroderma Lung Study trials, the SENSCIS trial, and the two tocilizumab trials, while also providing negative results in multiple trials.

With respect to results of Studies WA27788 and WA29767, the Division has considered the overall context of the literature, what is known about the endpoints, and supportive trends in the data to make its conclusions. The Division believes that FVC has been adequately characterized in interventional trials of SSc-ILD and has served as a robust endpoint for documenting a clinically meaningful improvement in lung status. In contrast, results for mRSS in historical trials have been less consistent, and the mRSS results from Studies WA27788 and WA29767 do not preclude a conclusion of benefit of tocilizumab in SSc-ILD. While the possibility of a type 1 error is a concern due to the lack of statistical superiority on the primary mRSS endpoint, with FVC being one of multiple secondary or exploratory endpoints in the studies, we believe there is sufficient evidence to conclude that the benefit in FVC is real and clinically meaningful. Our rationale for this conclusion is as follows:

Statistical persuasiveness of the ppFVC results

- *Strength of the treatment effect:* The p-values for the pre-specified ppFVC analyses in Studies WA27788 and WA29767 were 0.03 and 0.0015, respectively. Thus, putting aside the multiple comparisons, the strength of evidence against the null hypothesis of no effect on ppFVC was borderline in Study WA27788 but fairly strong in Study WA29767. It is notable that FVC was one of many exploratory endpoints evaluated in Study WA27788 and one of many secondary endpoints (albeit selected as a “key” secondary endpoint after the hypothesis was generated in the phase 2/3 Study WA27788) evaluated in Study WA29767. Although multiplicity is a potential concern, the chance that the observed FVC effect represents a spurious finding due to multiplicity is reduced by the positive FVC results in

both WA27788 and WA29767. This is important and adds to the persuasiveness of the evidence. For example, if 20 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 on at least one of the endpoints in both studies is 0.0125,[1] or 1 in 80. This is fairly low. These kinds of approximations, especially given the very low nominal p-value in Study WA29767 and the unique regulatory context and additional considerations described below, suggest that it is unlikely that the positive findings in both studies are spurious.

- Consistency of effect on ppFVC: Cumulative distribution plots (Figure 7 and Figure 8) suggested separations between tocilizumab and placebo across the entire FVC distribution, not just on the mean/median, including with respect to the probability of experiencing different magnitudes of decline in ppFVC (such as a 10-percentage-point decline).
- Consistency of effect across studies: Estimated effects were similar across the two studies (e.g., the mean differences between arms in ppFVC change at Week 48 were 4.3 and 4.2 percentage points in the overall population for Studies WA27788 and WA29767, respectively).
- Robustness to assumption violations: Sensitivity analyses for missing data suggest that the nominal significance in Study WA29767 appears to be robust to alternative missing data assumptions.

Biological and scientific plausibility, supporting trends in other related endpoints, and unique regulatory context

- Reliability of the methodology to assess FVC: Pulmonary function tests in Studies WA27788 and WA29767 were administered per the American Thoracic Society (ATS) and the European Respiratory Society standards while patients were blind to treatment assignment, and therefore, unlikely to be biased. Further, FVC has been recognized as a feasible-to-obtain reflection of total lung capacity and has long been used to diagnose restrictive lung disease and evaluate the effect of treatment. In addition, forced expiratory volume-based measures such as FVC have correlated with consolidation on high resolution computed tomography (HRCT) (Lang et al. 2020). While HRCT was not assessed in phase 2/3 Study WA27788, in Study WA29767, blinded readings of HRCT were supportive of and FVC results in the subset of patients with SSc ILD, with reduced FVC decline correlating with stabilization or improvement on HRCT, providing additional support of the treatment effect of tocilizumab on the pulmonary involvement of SSc.
- Results for other endpoints would not be expected to reliably correlate with FVC results: The results for the other secondary and exploratory endpoints in the two studies do not provide conclusive evidence of effects. For example, there was no significant evidence of effects for patient-reported outcome measures such as health assessment questionnaire-

[1] Probability (at least 1 of 20 endpoints has a 1-sided p-value<0.025 in two independent studies) ≤20*Probability (Endpoint#1 has a 1-sided p-value<0.025 in two independent studies) = 20*0.025^2=0.0125.

disability index (HAQ-DI) and patient global assessment that were secondary endpoints in both studies. It is a relevant question whether the lack of evidence on the other endpoints in any way calls into question the likelihood that the observed difference in FVC represents a real treatment effect (e.g., based on the clinical plausibility of a true and detectable effect on FVC but not on other outcomes assessed in the studies). However, there haven't been patient or clinician reported outcomes established to reliably assess direct benefit in programs in fibrotic lung diseases. For example, HAQ-DI is a physical functioning instrument designed for a different context of use (dressing, arising, eating, walking, hygiene, reach, grip, and activities) and it is not established whether or to what extent it could change with changes in FVC. Further, it is unclear what degree of improvement in FVC would be expected to result in meaningful HAQ-DI change. Of note, the nintedanib program demonstrated an effect on FVC without effect on secondary endpoints, including mRSS and patient-reported outcomes (PROs) (Labeling 2014a). Thus, a lack of a detected difference between treatment groups in HAQ-DI may not be surprising and doesn't contradict the results and the meaningfulness of the FVC analyses.

- Biological plausibility of the mechanism of action: Another important factor is the strength of the a priori belief going in to the studies that tocilizumab was likely to have an effect on FVC (e.g., based on biologic plausibility or external data on drugs with similar mechanisms of action), as well as any currently available independent information on the plausibility of effectiveness. There is biological plausibility for IL-6 inhibition as a therapeutic intervention for interstitial lung disease (ILD), supported by pre-clinical and observational clinical data, as discussed in the background section. Indeed, a clinically relevant effect in FVC was observed in the SSc-ILD subgroup in Study WA29767 (nominal p-value=0.0016 with larger estimated effect than in overall population). This effect was also corroborated by the effect on quantitative lung fibrosis scores, as assessed by HRCT imaging. Further, immunosuppressive therapy has been the cornerstone in the management of SSc-ILD (Denton et al. 2018), supporting the use of tocilizumab, an immunosuppressant with established efficacy in multiple immune-mediated conditions.
- Consideration for a rare disease with unmet need: While adherence to a pre-specified statistical testing hierarchy is important in most clinical trial settings, all evidence must be considered when establishing clinical meaningfulness and the existence of substantial evidence of efficacy in a rare disease setting with an unmet need and diseases with significant morbidity and mortality, such as SSc and SSc-ILD (October 2018; December 2019).
- Unique regulatory context: At the time of the trial design of both studies, FVC had not been agreed upon as a meaningful endpoint. Therefore, based on the data from the phase 2/3 study, the Applicant retained mRSS as the primary endpoint for the phase 3 trial and elevated FVC from an exploratory to a key secondary endpoint. However, since that time, the regulatory landscape around FVC has evolved and FVC has been used as the primary basis for traditional approval of products for restrictive pulmonary diseases, including SSc-ILD. The regulatory history makes this situation unique and not generally applicable to other settings where there is a lack of evidence of an effect on the primary endpoint. The focus on

the FVC results is in large part related to the uncertainty around mRSS and the evolving regulatory landscape around appropriate endpoints during the drug development program.

- This unique regulatory history and context of use mitigate the concerns about the impact of multiplicity in studies without evidence of statistical effects on the primary endpoint, and combined with the other considerations described above, leads to confidence in the evidence of effectiveness.

Based on this contextual information, the review team concluded, that the data from the tocilizumab clinical program is persuasive to inform the treatment effect of tocilizumab in SSc-ILD on FVC, an endpoint expected to result in mortality benefit, and support a conclusion that the data constitute substantial evidence of effectiveness of tocilizumab in SSc-ILD, a rare and serious disease associated with significant morbidity and mortality. Specifically, the tocilizumab clinical program included:

- One adequate and well-controlled clinical study, the phase 3 Study WA29767, which was designed and conducted as a multicenter, randomized, double-blind, placebo-controlled study in patients with diffuse cutaneous systemic sclerosis. The study failed to provide statistical evidence of a treatment effect on its pre-specified primary endpoint, change in mRSS from baseline, although favorable trends in tocilizumab treated patients were observed. However, the evidence on FVC, a key secondary endpoint that predicts long-term mortality, a clearly meaningful clinical benefit, was persuasive and supported by several lines of data, as detailed in the section on Statistical persuasiveness of the ppFVC results above.
- A body of confirmatory evidence, as detailed in the section on Clinical and Statistical Considerations About Whether There is Substantial Evidence of Effectiveness.

Given that the tocilizumab effect on pulmonary function was primarily driven by the effect in patients with pulmonary involvement, as evidenced by high-resolution CT imaging, and not in those without SSc-ILD, limiting the indication to patients with SSc-ILD is warranted. Based on the regulatory precedent of labeling of an indication primarily based on the FVC results (Labeling 2014a), an indication of "Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)" would be appropriate.

Overall, in the context of SSc-ILD being a rare and serious disease with significant morbidity and mortality, we (the review team and the Division Signatory) have determined that the benefit-risk for TCZ is favorable in SSc-ILD to support an Approval action with appropriate labeling. This determination also considers the discussion and input from the Food and Drug Administration (FDA) Medical Policy and Program Review Council.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Systemic sclerosis (SSc) is a rare, multisystem, connective tissue disease, characterized by microvascular damage and fibrosis of the skin and of various internal organs, including the lung, heart, kidneys and the gastrointestinal tract. SSc is a serious disease associated with increased morbidity and mortality with a 10-year survival rate less than 70% from the time of diagnosis (Steen and Medsger 2007). The primary causes of SSc-related deaths are pulmonary fibrosis/interstitial lung disease, pulmonary arterial hypertension, heart failure, and cardiac arrhythmia. Interstitial lung disease (ILD), as detected by high resolution computed tomography (HRCT), is present in 55-65% of patients with SSc (Launay et al. 2006). Median survival is 5-8 years in systemic sclerosis interstitial lung disease (SSc-ILD) (Herzog et al. 2014). Interleukin-6 (IL-6) level elevations have been noted in nonclinical models, as well as in clinical studies in SSc. In patients with systemic sclerosis, elevated IL-6 levels correlate with poorer survival, worse skin involvement, and increased pulmonary decline (Khan et al. 2012). Nintedanib, approved for slowing the rate of decline in pulmonary function in patients with SSc-ILD, is the only approved therapy in the US for management of SSc or SSc-ILD. There remains significant unmet need for additional therapeutic options in this population.

Tocilizumab (TCZ, Actemra) is a recombinant humanized interleukin 6 (IL-6) receptor monoclonal antibody, available in both intravenous (IV) and subcutaneous (SC) formulations. SC TCZ is approved for moderate to severely active rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), and systemic juvenile idiopathic arthritis (SJIA). IV TCZ is approved for treatment of moderate to severely active RA, SJIA, PJIA, and Cytokine Release Syndrome (CRS).

Genentech submitted this supplemental biologics license application (BLA) for SC TCZ for (b) (4) The proposed dosing regimen is SC TCZ 162 mg weekly, which is within the range of dosing regimens approved for RA and GCA. To support the application, the Applicant submitted the results of Study WA29767, an adequate and well-controlled phase 3, multicenter, randomized, double-blind, placebo controlled study in 212 patients with active SSc and mRSS of ≥ 10 and ≤ 35 at screening randomized to weekly SC TCZ 162 mg or placebo for 48 weeks. Additional supportive evidence was provided by Study WA27788, a phase 2/3, multicenter, randomized, double-blind, placebo controlled study in 87 patients with active SSc and mRSS of ≥ 10 and ≤ 40 at screening, randomized to weekly SC TCZ 162 mg or placebo for 48 weeks. In both studies, the primary endpoint, change in modified Rodnan Skin Score (mRSS) at Week 48, was not met. However, in both studies, consistent clinically meaningful improvement was observed on forced vital capacity (FVC), a pre-

specified key secondary endpoint in Study WA29767 and an exploratory endpoint in Study WA27788, in the TCZ treatment groups as compared to the placebo groups. In a post-hoc analysis of patients with SSc-ILD at baseline in Study WA29767, greater improvement was observed on FVC. The persuasiveness of the FVC data were informed by the quality of the FVC data, including the magnitude, time course, and consistency of the treatment effect on FVC seen in two similarly designed multicenter, randomized, double-blind, placebo controlled studies, as well as the reasonable clinical plausibility of the immunosuppression using tocilizumab, a product with established efficacy in multiple immune-mediated conditions. This effect on FVC was also corroborated by the effect on quantitative lung fibrosis scores, as assessed by exploratory quantitative HRCT assessments of lung fibrosis in Study WA29767. Therefore, although both studies failed to meet the primary endpoint, the data submitted, are adequate to provide substantial evidence of effectiveness of TCZ in SSc-ILD. The regulatory history and the evolving understanding of the FVC as a clinical endpoint makes this situation unique and not generally applicable to other settings where there is a lack of evidence of an effect on the primary endpoint.

The safety of TCZ in Studies WA29767 and WA27788 was generally consistent with the known safety of TCZ in adults in other indications. In the pooled safety analysis, deaths were balanced by treatment group. There were fewer serious adverse events (SAEs), AEs leading to discontinuation, and AEs leading to dose modification in the TCZ group compared to the placebo group. Similar findings were observed in the SSc-ILD subgroup of Study WA29767. No new safety signals were identified.

In summary, given the current understanding of FVC as a clinical endpoint in fibrotic lung diseases, including SSc-ILD, and given the magnitude and consistency of the treatment effect seen in Studies WA29767 and WA27788, further supported by the FVC results and exploratory HRCT assessments in the SSc-ILD subgroup in Study WA29767, the data submitted provide substantial evidence for effectiveness of TCZ in SSc-ILD. While efficacy was observed in the overall population of patients with SSc, the benefit in Study WA29767 was largely driven by the effect in the SSc-ILD subgroup. No new safety concerns were identified in the studies in patients with SSc, or in the SSc-ILD subgroup. The benefit risk profile is favorable for the proposed SC TCZ 162 mg weekly dosing regimen for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease. The review team recommends approval of BLA 125472/S-044, and the associated labeling supplement BLA 125276/S-131. TCZ provides an additional treatment option in the US for patients with SSc-ILD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SSc is a rare connective tissue disease characterized by microvascular damage and fibrosis of skin and internal organs. • ILD is present in over half of patients diagnosed with SSc. • ILD is one of the primary causes of SSc-related death. • Median survival is 5-8 years in SSc-ILD.	• SSc-ILD is a serious condition with high morbidity and mortality and a high unmet need for treatment options.
Current Treatment Options	• Nintedanib, a tyrosine kinase inhibitor, was approved in 2019 for slowing the rate of decline in pulmonary function in patients with SSc-ILD based on a single study in SSc-ILD patients who demonstrated a treatment effect on observed FVC of 41 mL. • There are no other approved therapies for either SSc-ILD or SSc. • Expert consensus treatment guidelines recommend the off label use of cyclophosphamide or mycophenolate for treatment of progressive SSc-ILD. Available therapies are associated with toxicities including cytopenias, infections, malignancies, and others.	• Nintedanib is the only approved treatment for slowing the rate of decline in pulmonary functions in patients with SSc-ILD. There are no other approved treatments for SSc or SSc-ILD.
Benefit	• TCZ is proposed for (b) (4) . • The efficacy of TCZ was supported by Study WA29767. Additional supportive evidence was provided by Study WA27788. Study WA29767 was a phase 3, multicenter, randomized, double-blind, placebo controlled study in 212 patients with active SSc and mRSS of ≥ 10 and ≤ 35 at screening randomized to weekly SC TCZ 162 mg or placebo for 48 weeks. Study WA27788 was a phase 2/3, multicenter, randomized, double-blind, placebo	• FVC is an endpoint that reliably predicts clinical benefit in fibrotic lung diseases. • Both Studies WA29767 and WA27788 failed to achieve the primary endpoint of change in mRSS at Week 48. • In both Studies WA29767 and WA27788, there was less decline in ppFVC and observed FVC at 48 weeks in TCZ-treated patients as compared to placebo-treated patients. • In a post-hoc analysis of patients with SSc-ILD

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	controlled study in 87 patients with active SSc and mRSS of ≥ 10 and ≤ 40 at screening. • The primary endpoint in Studies WA29767 and WA27788 was change from baseline in mRSS at Week 48. • Change from baseline in ppFVC at Week 48 was a key secondary endpoint in Study WA29767, and it was an exploratory endpoint in Study WA27788. • In both Studies WA27788 and WA29767, TCZ use was not associated with a statistically significant improvement in mRSS, and the primary endpoint was not met. • In Study WA29767, there was less decline in ppFVC (4.2%) and observed FVC (167 mL) at 48 weeks in TCZ-treated patients as compared to placebo-treated patients. • A post-hoc analysis of Study WA29767 in patients with SSc-ILD based on baseline HRCT demonstrated a mean change from baseline (decline) to Week 48 in placebo-treated patients as compared to TCZ-treated patients of 6.5% and 241 mL for ppFVC and observed FVC, respectively. • In Study WA29767, quantitative assessment of fibrosis based on HRCT was a pre-specified exploratory analysis. While there is no defined minimum clinically important difference (MCID) and no regulatory precedent for use of this endpoint, there was greater improvement in the TCZ-treated patients as compared to the placebo-treated patients in the overall SSc population, as well as the SSc-ILD subgroup.	in Study WA29767, a greater magnitude of change was observed in change from baseline in ppFVC and observed FVC, with less decline from baseline in TCZ-treated patients as compared to placebo-treated patients. • Acknowledging the limitations of cross-study comparisons, the treatment effect of TCZ on observed FVC in the post-hoc subgroup of SSc-ILD (241 mL) was larger than the effect of nintedanib in SSc-ILD (41 mL). • The evidence from Studies WA29767 and WA27788 demonstrate a clinically meaningful effect of TCZ on FVC, an accepted endpoint in patients with pulmonary fibrosis, including SSc-ILD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Study WA29767 and Study WA27788 provided the data for the safety assessment. • In the pooled safety analysis, deaths were balanced by treatment group. There were fewer SAEs, AEs leading to discontinuation, and AEs leading to dose modification in the TCZ group (18.4%; 8.2%; 22.4%) compared to the placebo group (22.0%; 10.7%; 24.7%). Similar findings were observed in the SSc-ILD subgroup of Study WA29767. • Overall infections were similar between treatment groups in the pooled SSc population and SSc-ILD subgroup of Study WA29767. Serious infections were greater in the TCZ group than placebo group in the pooled analysis (7.5% versus 5.3%, respectively); however, serious infections were greater in the placebo treated patients than the TCZ-treated patients in the SSc-ILD group (10.3% versus 2.9%, respectively). Overall, the differences in observed infections between groups were based on small numbers of patients. • The safety profile was generally consistent with the known safety profile of TCZ in adults in the approved indications. • There were no new safety signals.	• The safety profile in SSc and SSc-ILD was generally consistent with the known safety profile of TCZ. No new safety signals were identified to require further risk management.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.2
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Systemic sclerosis (SSc) 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, including the lung, heart, kidneys and the gastrointestinal tract. The first disease manifestation in SSc is most frequently the onset of Raynaud's phenomenon. As a result of these changes, patients with SSc may develop tightening and thickening of the skin over their faces, necks, trunks, fingers, hands, arms and legs and fibrotic changes in internal organs. Patients with widespread skin involvement are classified as having diffuse cutaneous systemic sclerosis, while those with predominantly distal skin changes below the elbows and knees are classified as limited cutaneous scleroderma. Patients without skin thickening but with internal organ involvement and serological abnormalities are classified as SSc sine scleroderma. Other cutaneous manifestations include calcinosis and digital ulcers. GI manifestations of SSc include gastroesophageal reflux disease (GERD), dysphagia, poor gastric emptying and hypomotility of the small intestine resulting in bloating, bacterial overgrowth, diarrhea, malabsorption and weight loss. Renal involvement includes scleroderma renal crisis, as well as interstitial nephritis, glomerulonephritis, and renal vasculitis. In addition, patients with SSc are also at risk for developing interstitial lung disease, pulmonary arterial hypertension, heart failure, and arrhythmia.

SSc is a serious disease associated with increased morbidity and mortality with a 10-year survival rate less than 70% from the time of diagnosis (Steen and Medsger 2007). The primary causes of SSc-related deaths are pulmonary fibrosis, pulmonary arterial hypertension, heart failure, or cardiac arrhythmia.

Interstitial lung disease (ILD), as detected by high resolution computed tomography (HRCT), is present in 55-65% of patients with SSc (Launay et al. 2006). Severe ILD usually presents relatively early in the disease course within the first 3 years from time of diagnosis (Steen and Medsger 2000). Median survival is 5-8 years in SSc-ILD (Herzog et al. 2014). Patients with diffuse cutaneous SSc are approximately twice as likely to be affected by moderate to severe lung fibrosis than patients with limited cutaneous disease (Wells et al. 2009; Nihtyanova et al. 2014). The presence of antitoposisomerase I antibody (or Scl-70) is higher in patients with diffuse cutaneous SSc and are associated with a higher risk of severe ILD. While the severity of skin fibrosis has been shown to be predictive of disease outcomes, spontaneous improvement early in the disease course can occur suggesting an additional relationship with disease duration, thus complicating the interpretation of change in skin fibrosis during therapeutic trials (Shand et al. 2007; Hanitsch et al. 2009). As such, in the context of intervention trials, changes in skin fibrosis may not accurately reflect visceral organ involvement (e.g. SSc-ILD) or improvement (or worsening) of extra-cutaneous aspects of the disease.

The etiology of SSc is currently unknown, but is thought to involve both inflammatory and fibrotic processes. IL-6 is increased in the peripheral blood and lesional skin from patients with SSc, and induces fibroblast collagen directly and indirectly by inducing profibrotic M2 macrophages. In SSc-ILD, IL-6 production is believed to occur locally through the interaction between pulmonary B cells and fibroblasts (Kondo et al. 2001). Elevated IL-6 levels have been observed in murine models of systemic sclerosis with improvement in skin fibrosis after treatment with a murine surrogate IL-6 receptor antibody (Saito et al. 2008; Pedroza et al. 2011). In patients with systemic sclerosis, elevated IL-6 levels correlate with poorer survival, worse skin involvement, and increased pulmonary decline (Khan et al. 2012; De Lauretis et al. 2013). Case reports and case series of favorable outcomes using IL-6 receptor inhibitors are also reported in the literature (Manfredi et al. 2020; Vacchi et al. 2020). Thus, there is biological plausibility for evaluation of IL-6 inhibition as a therapeutic intervention for systemic sclerosis interstitial lung disease (SSc-ILD), supported by pre-clinical and observational clinical data.

2.2. Analysis of Current Treatment Options

There are no currently approved therapies for systemic sclerosis. There is one FDA-approved therapy for patients with SSc-ILD. Nintedanib (approved September 2019), a tyrosine kinase inhibitor, is approved to slow the rate of decline in pulmonary function in patients with SSc-ILD. Given its recent approval, its role in clinical practice (e.g. timing of initiation, use as add-on or monotherapy) for patients with systemic sclerosis has not been well-defined. Patients are treated based on expert-derived recommendations for the management of organ-specific manifestations and empirically with off-label products used for other rheumatic diseases. Of note, updated treatment guidelines have not been published since the approval of nintedanib. The Update of European League Against Rheumatism recommendations for the treatment of systemic sclerosis (April 2017) recommends consideration of cyclophosphamide for treatment of SSc-ILD, particularly in patients with progressive ILD (Kowal-Bielecka et al. 2017). Hematopoietic stem cell transplantation may be considered in selected patients with rapidly progressive SSc at risk of organ failure. The British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) guidelines for the treatment of systemic sclerosis (June 2016) recommends treatment of extensive or progressive ILD with immunosuppression, including intravenous cyclophosphamide. Mycophenolate mofetil (MMF) may also be used as an alternative or after cyclophosphamide (Denton et al. 2016). There remains a high unmet medical need for therapies in SSc and SSc-ILD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TCZ is an approved therapeutic biologic product that is available and marketed in the United States as an IV formulation (original BLA 125276, approved January 2010) and as a SC formulation (original BLA 125472, approved October 2013). The BLAs share one product label. IV TCZ is approved for treatment of moderate to severely active rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (SJIA), polyarticular juvenile idiopathic arthritis (PJIA), and cytokine release syndrome (CRS). SC TCZ is approved for moderate to severely active RA, PJIA, SJIA, and giant cell arteritis (GCA).

3.2. Summary of Presubmission/Submission Regulatory Activity

The summary of presubmission regulatory history is presented in chronological order.

On September 28, 2011, investigational new drug (IND) 112406 was opened for tocilizumab (TCZ) for the treatment of systemic sclerosis (SSc) with study WA27788, a phase 2/3 multicenter, randomized, double-blind, placebo-controlled, parallel group trial in patients with diffuse cutaneous SSc.

On April 17, 2013, orphan drug designation was granted for TCZ in SSc.

On November 12, 2014, the end-of-phase 2 meeting included discussion of endpoints. The Agency stated that the proposed primary endpoint for WA29767, modified Rodnan Skin Score (mRSS), was a surrogate measure requiring additional clinically important information that would demonstrate improvement in other organ systems or improvement on how patients function, feel, or survive. Also, forced vital capacity (FVC) results were discussed with regard to clinically meaningful improvement and percentage change thresholds. FDA stated that it may not be possible that TCZ could alter the natural decline in FVC in a one year study, and that, at the discretion of the Sponsor, an adequately-controlled study of longer duration to evaluate the effects of TCZ on slowing FVC decline and disease progression would provide important information. The Agency also provided guidance about steps to reduce missing data in the proposed phase 3 study. In addition, FDA encouraged the Sponsor to consider inclusion of more than one dosing regimen in Study WA29767.

On February 6, 2015, Breakthrough Therapy Designation was granted to TCZ for SSc, based on results from study WA27788 demonstrating numerically favorable mRSS scores, favorable FVC treatment effects, and improvements on Health Assessment Questionnaire-Disability Index (HAQ-DI).

On August 4, 2016, a type B Breakthrough Therapy-Initial Comprehensive face-to-face meeting was held to primarily discuss the accelerated approval pathway. While the Division agreed that systemic sclerosis was a serious life-threatening disease with unmet medical need, there were several comments discussed as to why the accelerated pathway may not be appropriate for Genentech to pursue:

- Improvement in skin thickening alone (mRSS primary endpoint) would be insufficient to reliably predict an effect on irreversible morbidity or mortality to support accelerated approval, and that additional endpoint support would be needed.
- The standards for breakthrough therapy designation were different from accelerated approval, requiring convincing statistical evidence to establish with high confidence that the effect on surrogate endpoints was real and meaningful. It was unclear whether Genentech had met this standard given the failed primary endpoint in Study WA27788, and additional information (separate from Study WA27788) may need to be provided.
- Approval of TCZ under an accelerated pathway may impact the conduct of Study WA29767 (ongoing at the time of the meeting) by affecting recruitment and retention. FDA suggested the Sponsor consider whether there is sufficient data on the natural history of lung function in historical controls to serve as a comparator in the event too many patients discontinue randomized treatment.

The Division noted that depending on the strength of the results from Study WA29767, it may be sufficient for full approval, rather than accelerated approval.

On July 31, 2018, a pre-sBLA meeting was held to discuss Genentech's plan to submit a supplemental BLA for the indication for the treatment of active SSc. Overall, the Division noted that the available data at that time were unlikely to support the proposed indication. The following points were discussed:

- Genentech proposed an accelerated approval pathway (b) (4)
- Genentech discussed the possibility that (b) (4)
- While the numerical improvements in change in percent predicted FVC (ppFVC) at Week 48 were encouraging, evaluation of pulmonary function was not the primary objective and the results of ppFVC were not considered statistically significant according to the planned multiple testing procedures. The Division noted that both studies failed on their primary endpoints (mRSS), not meeting the criteria for substantial evidence on the primary endpoint.
- FVC improvements were nominally significant in Study WA29767, and only numerically favorable in Study WA27788. Respectively, an additional study using pulmonary function as the primary objective could support an indication for a pulmonary specific indication (e.g. SSc-ILD), rather than a general indication for systemic sclerosis. Thus, selecting a study

population based on these studies would be reasonable. Importantly, additional information supporting the clinical relevance of improvement in FVC would be critical and should be considered. Of note, at the time of the July 2018 meeting, FVC had not been established as an endpoint for regulatory decisions in SSc.

- Genentech inquired regarding submitting the sBLA with the current level of information, and the likelihood for an Advisory Committee (AC) meeting. The Division responded that submission of an sBLA was at their discretion and that an AC was likely. In response to questioning about the content of a sBLA, the Division stated that a sBLA should include a clear description of the intended patient population, justification of the benefit-risk in that population, data such as mortality from the open label portion of the study, and information on the natural history of SSc-ILD.

At a follow-up teleconference on November 27, 2018, the Division noted the high unmet medical need and encouraged Genentech to submit the results of Studies WA27788 and WA29767 for review. The Division noted the serious nature of SSc, and FVC, while not the primary focus of the development program, is a measure of major organ involvement, and stated the importance of discussion of the clinical relevance of the findings of the program at an AC meeting. The following points were discussed:

- Determination of the appropriate population that would benefit from TCZ would be a review issue. It is unlikely that the available studies (WA27788 and WA29767) would support TCZ use in (b) (4)
- (b) (4)

While not directly related to the regulatory history of this application, it is important to note that an Arthritis Advisory Committee meeting to discuss the benefit risk of nintedanib for the treatment of SSc-ILD (New Drug Application (NDA) 205832 supplement 12) occurred on July 25, 2019. During this AC meeting, the use (and clinical meaningfulness) of FVC in the context of SSc-ILD was discussed. In the nintedanib development program, a single study in approximately 600 patients with SSc-ILD patients had a modest improvement in FVC (~40 mL), in the absence of support of efficacy from secondary endpoints. The panel members voted 10-7 (in favor of nintedanib) that the data provided substantial evidence of efficacy of nintedanib for treatment of SSc-ILD.

In light of this important scientific community discussion on the clinical relevance of FVC in SSc-ILD, the Division initiated a teleconference with the Sponsor to continue discussion of a potential submission of the results of Studies WA27788 and WA29767 for review (November 6, 2019). Points discussed at that teleconference were as follows:

- The Division again encouraged Genentech to submit the data from the two completed studies for review given the breakthrough designation and the recent developments with approval of nintedanib for SSc-ILD.

- The Division noted the clinical meaningfulness of FVC had been discussed and there would be no expectation for additional data to demonstrate the clinical meaningfulness of FVC in the population.
- The Division also noted that a public discussion on the meaningfulness of FVC had already occurred, and that the need for another public discussion would not be the same.

Genentech stated their position was unchanged, but that they would have additional internal discussions.

BLA 125472/S-044 was submitted the current sBLA on July 24, 2020 and was granted a priority review.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No OSI inspections were necessary for this supplement.

4.2. Product Quality

No new chemistry, manufacturing, and controls information was submitted and was not required for the regulatory decision for this supplement. The relevant information was reviewed in the original BLA and previous supplements.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

The Applicant submitted a use-related risk analysis and human factors validation study report for SSc and the Actemra PFS. The human factors validation study was reviewed by DMEPA. While use errors with critical tasks were observed, the product user interface for the proposed indication is identical to the approved PFS user interface. There were no reported use issues/subjective feedback related to the product user interface due to the physical manifestations of the disease state of the representative participants. The DMEPA team found the study methodology reasonable, the residual risk minimized to the extent possible, and the human factors validation study results demonstrate that the user interface supports safe and effective use for the proposed indication. See Human Factors review by DMEPA reviewer, Matthew Barlow, for additional details. The review team concurs with the assessment by DMEPA.

No other device or companion diagnostic issues are submitted for review in support of this supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

All nonclinical pharmacology and toxicology studies were reviewed with the original BLA submission and no new nonclinical studies were provided with this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of Actemra® [Tocilizumab,(TCZ)] subcutaneous (SC) formulation for treatment of systemic sclerosis with interstitial lung disease (SSc-ILD). The clinical pharmacology information in this sBLA consists of pharmacokinetic (PK), pharmacodynamic (PD), and exposure response (ER) data from a completed global phase 3 study (WA29767) and phase 2/3 study (WA27788).

The PK of TCZ following 162 mg TCZ SC once weekly (QW) administration is comparable between Study WA29767 and Study WA27788. The PK of TCZ following 162 mg TCZ SC QW administration is comparable between patients with SSc and SSc-ILD; and both are similar to the PK properties in rheumatoid arthritis (RA) patients.

There was no clear exposure response relationship for efficacy, as measured by median changes in modified Rodnan skin score (mRSS) and median change in percent predicted forced vital capacity (ppFVC) from baseline over 48 weeks. In the time to treatment failure analysis, the plots indicate a trend of prolonged time to treatment failure with increased TCZ exposure (Cmean, 6wk). However, the data are too limited to confirm this exposure-response relationship statistically. Only one dosing regimen of 162 mg SC QW was evaluated in patients with SSc in Study WA29767. Therefore, no dose response analysis was feasible, and the exposure response findings were limited to the observed exposure range in Study WA29767. See Section 8.1.2 for detailed assessment of efficacy.

Treatment-induced ADAs (all neutralizing) were detected and confirmed in only three patients across both studies. For one patient, individual PK parameters and TCZ concentration-time course were not affected by ADAs, while for two patients the observed TCZ concentrations were much lower than expected. Overall, the small number of subjects who were positive for antibodies to tocilizumab (total n=3) limits a definitive conclusion of the effect of immunogenicity on tocilizumab PK.

Recommendations

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under BLA 125472 /S-044 and finds the sBLA approvable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings of the current review:

Dose/Exposure Response

- In patients with SSc the median mRSS change from baseline improved over time in all treatment groups, including the PBO group (Figure 20, Figure 21). The improvement was numerically higher in the TCZ treatment group compared to PBO. No exposure-response relationship was observed in the TCZ treatment arm.
- In patients with SSc-ILD the median change from baseline of mRSS improved over time in all treatment groups, including the PBO group (Figure 22). As was seen for the SSc patients, the improvement was numerically higher in the TCZ treatment group compared to PBO and no exposure-response relationship was observed in the TCZ treatment arm in SSc-ILD patients.
- In the time to treatment failure analysis, the plots indicated a trend of prolonged time to treatment failure with increased exposure (C_{mean},6wk). However, the data are too limited to confirm this exposure-response relationship statistically. For more information, refer to pharmacometrics review in Appendix 15.4.

Pharmacokinetics

- The PK of TCZ following 162 mg TCZ SC QW administration is comparable between Study WA29767 and Study WA27788. The PK of TCZ following 162 mg TCZ SC QW administration is comparable between patients with SSc and SSc-ILD; and both are similar to the PK properties in rheumatoid arthritis (RA) patients.
- 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, which was originally developed for patients with RA.
- A population PK 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 dataset for PopPK analysis was comprised of a total of 170 patients with SSc treated with TCZ from the double blind (DB) period of Study WA29767 and from the DB and open label (OL) period of Study WA27788. The SSc-ILD dataset for the sub-analysis consisted of 66 patients from the DB period of Study WA29767. For more information, refer to pharmacometrics review in Appendix 15.4.
- The estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab were 52.5 (14.8-121) mcg/mL, 47.2 (10.8-114) mcg/mL, and 50.4 (13.4-119) mcg/mL,

respectively. The accumulation ratios for Cmean or AUC_{tau}, C_{trough}, and C_{max} were 7.11, 6.56, and 5.89, respectively. Steady-state was reached after 13 weeks.

- Among all identified covariate relationships, the only strong covariate dependence was the influence of body weight on TCZ clearance and volume parameters. TCZ clearance and volumes increased with increasing body weight. No other covariate influence had a clinically relevant effect on TCZ PK. As a flat dose was used in the phase 3 study, and there is no clear exposure response for efficacy or safety, no dose adjustment is necessary based on body weight.

Immunogenicity

- Treatment-induced ADAs (all neutralizing) were detected and confirmed in only three patients across both studies. For one patient, individual PK parameters and TCZ concentration-time course were not affected by ADAs, while for two patients the observed TCZ concentrations were much lower than expected. Overall, the small number of subjects who were positive for antibodies to tocilizumab (total n=3) limits a definitive conclusion of the effect of immunogenicity on tocilizumab PK.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of TCZ for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

The clinical efficacy of the proposed dosing regimen was demonstrated in WA27788 and WA29767 (see Sections 8.1 and 8.2). Overall there are no clear exposure-efficacy or exposure-safety relationship, and the proposed dose is based on the pivotal studies. Refer to the pharmacometrics review in Appendix 15.4 for details on the population PK and ER analysis.

Therapeutic Individualization

Intrinsic factors were not found to have a clinically meaningful effect on TCZ PK in adult patients with SSC-ILD. Therefore, no dose adjustment is necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Characteristics of TCZ in Adult Subjects with SSc-ILD following SC Administration

The PK of tocilizumab has been assessed and reviewed during prior approvals for the RA, GCA, pJIA, SJIA and CRS indications. In the submitted studies WA27788 and WA29767 for this submission, the Applicant used dose of 162 mg qw in SSc and SSc-ILD subjects, which is within the range of approved doses for the adult indications of SC TCZ.

The PK of TCZ following 162 mg TCZ SC QW administration is comparable between Study WA29767 and Study WA27788. The PK of TCZ following 162 mg TCZ SC QW administration is comparable between patients with SSc and SSc-ILD; and both are similar to the PK properties in rheumatoid arthritis (RA) patients.

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, which was originally developed for patients with RA.

In SSc-ILD patients, the estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab were 52.5 (14.8-121) mcg/mL, 47.2 (10.8-114) mcg/mL, and 50.4 (13.4-119) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 7.11, 6.56, and 5.89, respectively. Steady-state was reached after 13 weeks.

Among all identified covariate relationships, the only strong covariate dependence was the influence of body weight on TCZ clearance and volume parameters. TCZ clearance and volumes increased with increasing body weight. No other covariate influence had a clinically relevant effect on TCZ PK. For more information, refer to pharmacometrics review in Appendix 15.4.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

This sBLA for SSc-ILD is supported by safety and efficacy data from studies WA29767 and WA27788. Refer to Section 8.1 for assessment of the primary and secondary endpoints in the pivotal study.

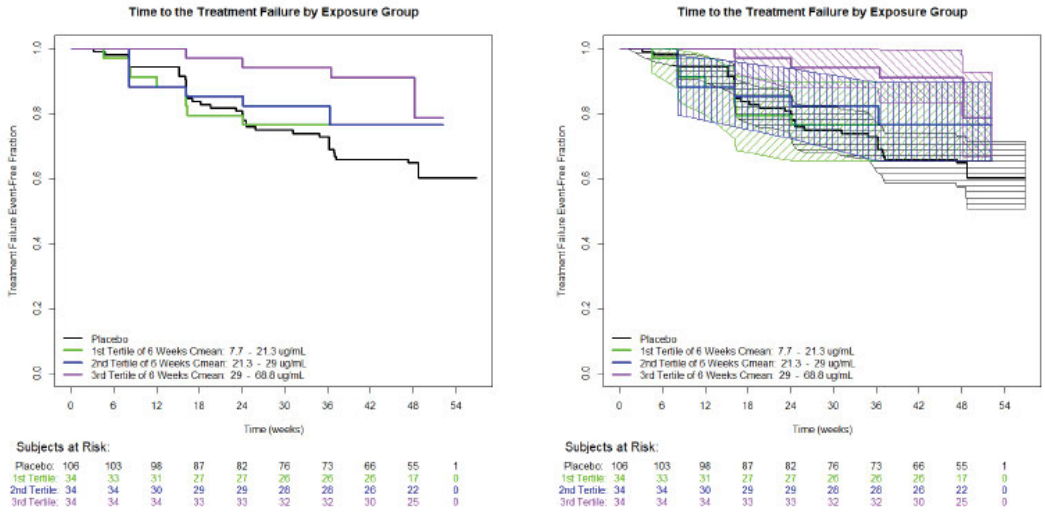
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the sponsor's proposed dosing regimen is acceptable based on the efficacy and safety data from pivotal studies (See section 8). Only one dosing regimen of 162 mg SC QW was evaluated in patients with SSc in Study WA29767. Therefore, no dose response analysis was feasible, and the exposure response findings were limited to the observed exposure range in Study WA29767.

There was no clear exposure response relationship for efficacy, as measured by median changes in modified Rodnan skin score (mRSS) (Figure 20, Figure 21, Figure 22) and median change in percent predicted forced vital capacity (ppFVC) (Figure 23, Figure 24, Figure 25) from baseline over 48 weeks, in both SSc and in SSc-ILD patients.

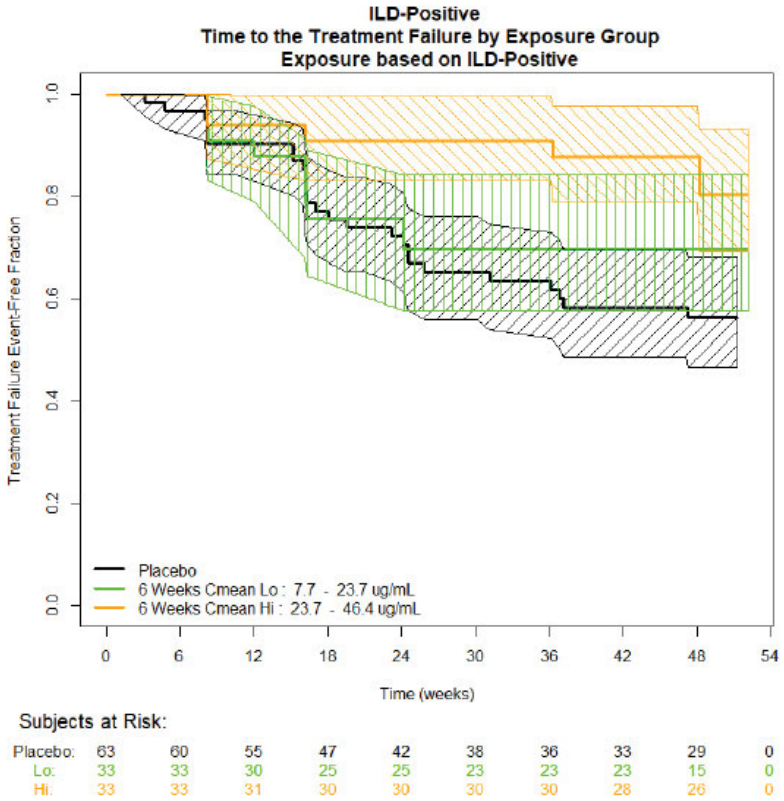
Time to treatment failure is illustrated in Figure 1 for patients with SSc and in Figure 2 for patients with SSc-ILD using Kaplan-Meier plots with different groupings of patients by exposure. The plots indicate a trend of prolonged time to treatment failure with increased TCZ exposure (C_{mean},6wk) in both SSc and SSc-ILD patients; however, the data are too limited to confirm this exposure-response relationship statistically.

Figure 1: SSc Patients: KM Plot for Time to Treatment Failure Versus TCZ Exposure (Cmean,6wk); Placebo and Exposure Tertiles (WA29767) With 90% CI (Left) or Without CI (Right)



Source: Figure 24 of Summary of Clinical Pharmacology Studies
Abbreviations: KM, Kaplan-Meier; TCZ, tocilizumab

Figure 2: SSc-ILD Patients: KM Plot for Time to Treatment Failure Versus TCZ Exposure (Cmean,6wk); Placebo and Exposure Tertiles (WA29767)



Source: Figure 25 of Summary of Clinical Pharmacology Studies
Abbreviations: KM, Kaplan-Meier; ILD, interstitial lung disease; TCZ, tocilizumab

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Consistent with RA patients, body weight was a significant covariate for typical values of PK. TCZ clearance and volumes increased with increasing body weight. As a flat dose was used in the phase 3 study, and there is no clear exposure response for efficacy or safety, no dose adjustment would be recommended based on body weight.

Body weight was the primary covariate contributing to the observed PK variability of TCZ. Heavier subjects tended to have higher CL/F and V/F, and therefore, lower exposure to TCZ.

Steady-state AUCτ (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 AUCτ (and Cmean), respectively, compared to patients in the middle weight category. The number of patients with SSc above 100 kg was small (N=6). In addition, there was limited data for patients with SSc-ILD above 100 kg (n=1), hence, no percent change was calculated by the Applicant for SSc-ILD patients with a body weight > 100 kg. Nevertheless,

there were no significant exposure-safety and exposure-efficacy relationships across the body weight and TCZ exposure range observed. Therefore, no dose adjustment is recommended with respect to the PK covariates. For more information, refer to pharmacometrics review in Appendix 15.4.

What Was the Impact of Immunogenicity on tocilizumab Exposure?

The overall incidence of ADA was very low. As in the SSc-ILD subpopulation from Study WA29767 no treatment-induced ADAs were reported, immunogenicity was described for SSc patients only. 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 2 studies). For one patient, individual PK parameters and TCZ concentration-time course were not affected by ADAs, while for two patients the observed TCZ concentrations were much lower than expected.

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 2 studies). For one patient, individual PK parameters and TCZ concentration-time course were not affected by ADAs, while for two patients the observed TCZ concentrations were much lower than expected.

Overall, the small number of subjects who were positive for antibodies to tocilizumab (total n=3) limits a definitive conclusion of the effect of immunogenicity on tocilizumab PK.

Are the Bioanalytical Methods Properly Validated to Measure PK in Plasma Samples?

A validated sandwich enzyme-linked immunoassay was used to determine the concentration of TCZ in human serum samples. The assay has a lower limit of quantification of 100 ng/mL for TCZ in human serum. This is the same method that was used in the tocilizumab SC clinical development program. A description of the method was included and reviewed as a part of the original BLA submission for RA. Please refer to the archived clinical pharmacology review (Reference ID: 3374458).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 1: Key Design Elements of Studies WA27788 and WA29767

Study	Description	Subjects	Design	Treatment	Duration	Endpoints
WA27788 NCT01532869	Phase 2/3 safety and efficacy	87 patients with SSc	R, DB, PC, PG	TCZ 162 mg SC weekly PBO	48 week DB 48 week OLE*	Primary: Change from BL in mRSS Secondary: Change from BL in HAQ-DI Exploratory: Change from BL in FVC
WA29767 NCT02453256	Phase 3 safety and efficacy	212 patients with SSc	R, DB, PC, PG	TCZ 162 mg SC weekly PBO	48 week DB 48 week OLE*	Primary: Change from BL in mRSS Key secondary: Change from BL in FVC Change from BL in HAQ-DI

* Placebo patients from the 48 week DB period were changed to TCZ 162 mg SC weekly in the OLE
** WA29767 – first patient first visit 11-20-2015 and last patient last visit (clinical cutoff date for last patient week 48 visit) 1-15-2018
** WA27788 – first patient first visit 3-13-2012 and last patient last visit 1-14-2014
Abbreviations: BL, baseline; DB, double blind; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire-Disability Index; mRSS, modified Rodnan skin score; OLE, open-label extension; PBO, placebo; PC, placebo controlled; PG, parallel group; R, randomized; SC, subcutaneous; SSc, systemic sclerosis; TCZ, tocilizumab

7.2. Review Strategy

The clinical data reviewed in this document are obtained from two studies conducted in SSc patients (Table 1). Efficacy and safety data were obtained from the double-blind treatment period in each study. Open-label extension (OLE) data are provided when appropriate as supplemental information. The analysis populations and analysis methods are discussed in the Statistical Analysis Plan sections below.

As Study WA29767 was similar to Study WA27788 in design and conduct (Table 1), the study protocols for both of these studies are discussed together below. However, efficacy analyses are discussed separately, and safety analyses are presented for individual studies as well as pooled analyses. Study WA29767 as compared to Study WA27788 had a larger sample size (n=212 versus n=87, respectively), was conducted more recently (first patient first visit [FPFV] 2015 versus 2012, respectively), and had less missing efficacy data. Important for this application, the SSc-ILD subgroup of patients, the focus for this review as the target population, could only be identified in Study WA29767 as only Study WA29767 collected the HRCT assessments used to identify patients with SSc-ILD. As a result, this study forms the primary basis for all efficacy and safety analyses of the SSc-ILD subgroup. Study WA27788 provides supportive safety and efficacy information on the overall SSc population.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Protocol for WA29767 and WA27788

Administrative Details

Study WA29767

- FPFV: 11-20-2015
- Last patient last visit: January 15, 2018
- Planned enrollment: 210 patients (105 each arm)
- Actual enrollment: 212 patients (107 placebo, 105 TCZ)
- Study sites: 75 global sites in 20 countries (Asia, Europe, North and South America)

Study WA27788

- FPFV: 3-13-2012
- Last patient last visit: January 14, 2014
- Planned enrollment 86 patients (43 each arm)
- Actual enrollment: 87 patients (43 placebo, 44 TCZ)
- Study sites: 35 global sites in 5 countries (Canada, Germany, France, England, US)

Study Objectives

Primary efficacy objective: to evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by modified Rodnan Skin Score (mRSS) over 48 weeks (over 24 weeks in Study WA27788).

Secondary efficacy objectives: to evaluate the efficacy of TCZ on pulmonary function (Study WA29767), physical function (Study WA27788), clinician-reported outcomes, time to treatment failure (Study WA29767, defined below in Study Endpoints section), and patient-reported outcomes (PROs).

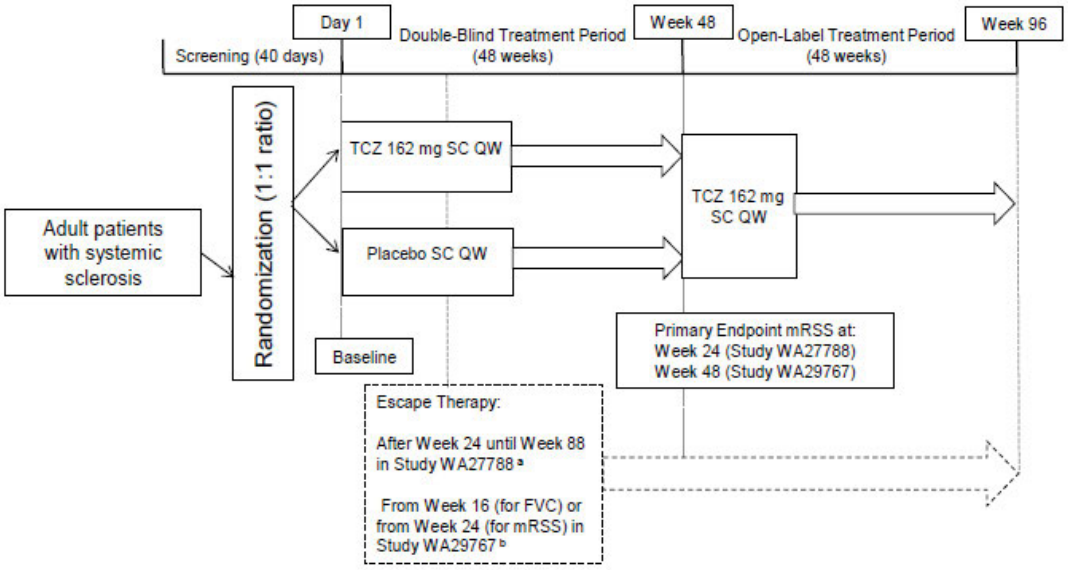
Safety objectives: to evaluate the safety of TCZ compared with placebo on the frequency and severity of serious and non-serious AEs, SSc-related complications, vital signs, physical exam findings, clinical laboratory results, the number of digital ulcers, and long-term safety.

Other PK/PD and exploratory objectives are not discussed in this review.

Study Design

The study design for trials WA29767 and WA27788 were similar. Both had a screening period (40 days), after which patients were randomized (1:1) to either TCZ 162 mg SC weekly or placebo SC weekly. Randomization was performed on day 1 through a centralized interactive voice/web response system (IxRS). In Study WA29767, randomization was stratified by IL-6 levels at baseline (< 10 and ≥ 10 pg/mL). In Study WA27788, randomization was stratified by joint involvement at baseline (< 4 and ≥ 4 tender joints of 28 tender joint count [TJC]). The double-blind controlled treatment period continued for 48 weeks, after which patients could transition to an OLE phase of 48 weeks. In the OLE, all patients received TCZ 162 mg SC weekly. This is shown schematically in Figure 3.

Figure 3: Study Design for Studies WA29767 and WA27788



Source: SCE Figure 1, p. 12
Abbreviations: FVC, forced vital capacity; mRSS, modified Rodnan skin score; QW, weekly; SC, subcutaneous; TCZ, tocilizumab

Blinding for certain efficacy assessments used a dual-assessor approach such that personnel assessing the mRSS did not have access to laboratory tests (inflammatory markers) that could potentially break the blind. The principal investigator was allowed to serve as the safety assessor, but not as an efficacy assessor. In addition to maintaining the blind, this was also used to ensure consistency of assessments and limit inter-observer variability (particularly for the mRSS evaluations).

For Study WA29767, a pre-planned blinded interim futility analysis was performed when 76 patients completed Week 24.

With regard to key assessments during the 48 week double-blind controlled treatment period, safety assessments [clinical labs (hematology, chemistry, liver profiles, urinalysis), biomarkers, anti-drug antibodies, adverse event assessments, vital signs, concomitant medication assessments, pregnancy testing], and efficacy assessments [PROs, spirometry, mRSS] were generally performed every 4 weeks (FVC and PROs were performed every 4 weeks after the 1st 8 week assessment). Other assessments, such as HRCT and optional skin biopsies, were performed at baseline and at the end of the controlled treatment period (48 weeks). A full schedule of assessments can be found in Section 15.2 Schedule of Assessments.

Differences in design between the two studies included the use of escape therapy and timing of assessment for the primary endpoint. In Study WA29767, escape therapy was allowed from Week 16 for worsening lung function (>10% reduction in ppFVC from baseline [confirmed on two separate tests 4 weeks apart]) or at Week 24 for worsening SSc (mRSS decrease of 5 points and at least 20% increase from baseline, or worsening SSc complications). For worsening skin fibrosis, escape therapies were methotrexate, hydroxychloroquine, or other disease-modifying anti-rheumatic drugs (after discussion with the Medical Monitor); for worsening lung function, local treatment guidelines were followed (excluding cyclophosphamide) and discussed with the Medical Monitor. Only one escape therapy was permitted, and study drug was continued in addition to escape therapy. In Study WA27788, escape therapy was allowed after Week 24 until Week 88, and consisted of methotrexate (MTX), hydroxychloroquine (HCQ), or mycophenolate mofetil (MMF). This was permitted for patients with worsening skin symptoms (≥ 20% worsening in mRSS from baseline) and/or worsening SSc-associated complications, based on investigator assessment. Of note, MMF escape therapy was permitted only after review by the Medical Monitor. Another difference between the studies was the timepoint of assessment for the primary endpoint. The primary endpoint (mRSS) was assessed at Week 48 in Study WA29767 and at Week 24 in Study WA27788.

Study Population

Both studies were conducted in adult SSc patients with active disease. When there were differences in eligibility criteria between studies, the criteria for Study WA27788 are indicated in parentheses and italicized.

Key inclusion criteria

- Age ≥ 18 years at baseline
- Diagnosis of SSc as defined by the American College of Rheumatology/ European League Against Rheumatism criteria from 2013 (*Study WA27788 used criteria from 1980*)
- mRSS ≥10 and ≤ 35 units at screening (*Study WA27788 used cutoffs of 15 and 40 for lower and upper bounds, respectively*)
- SSc duration ≤ 60 months (time from first non-Raynaud phenomenon manifestation)
- Active disease defined by one of the following:
  - Duration ≤ 18 months from non-Raynaud phenomenon (*Study WA27788 used ≤ 12*

months)
  - Increase in mRSS of ≥3 units in previous 6 months
  - Involvement of one new body area with an increase in ≥ 2 units in mRSS, or involvement of two new body areas, either in previous 6 months
  - Presence of at least one tendon friction rub
- Presence of one of the following:
  - CRP ≥ 0.6 mg/dL (*Study WA27788 used a cutoff of 1.0 mg/dL*)
  - Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr
  - Platelet count ≥ 330,000/µL

Key exclusion criteria
- Pregnancy or lactation
- Previous treatment with other immunosuppressives (within 1-4 weeks of screening)
  - Anti-IL-6 therapy, chlorambucil, anakinra, etanercept, systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, hydroxychloroquine, cyclosporine, azathioprine, rapamycin, colchicine, D-penicillamine, prostacyclin, infliximab, certolizumab, golimumab, abatacept, adalimumab, cyclophosphamide, or any investigational agent
  - Previous treatment with mycophenolate mofetil
- Previous treatment with an anti-fibrotic (nintedanib or pirfenidone) [*not excluded in Study WA27788*], JAK inhibitor, tyrosine-kinase inhibiters (e.g. imatinib), or endothelin-receptor antagonists
- Significant cardiopulmonary, infectious, or immune system concerns:
  - Significant pulmonary disease: restrictive pulmonary disease (FVC ≤ 55%) [*FVC ≤ 50% in Study WA27788],* significant diffusion impairment (diffusing capacity of the lungs for carbon monoxide (DLCO) ≤ 45%) [*DLCO ≤ 40% in Study WA27788*], or significant PAH (WHO class 2 or higher)
  - Significant cardiac disease: significant arrhythmia, congestive heart failure (New York Heart Association class 2-4), unstable angina, uncontrolled hypertension, cor pulmonale, symptomatic pericardial effusion, history of recent MI
  - Infectious concerns: active current or history of recurrent bacterial, viral, fungal, mycobacterial infections; recurrent tuberculosis
  - Immunodeficiencies
  - Autoimmune disease other than SSc
- History of drug abuse (alcohol, illicit drugs, or chemical abuse)

Overall, the eligibility criteria for Studies WA29767 and WA27788 selected for patients with SSc with active skin disease and elevated inflammatory markers, and excluded patients with severe pulmonary disease. The minor differences in eligibility criteria noted between Studies WA29767 and WA27788 (italicized) were not felt to have an impact on the comparability between the patient populations.

Study Treatments

During the 48-week double-blind controlled treatment periods in Studies WA29767 and WA27788, patients received one of the following:

- Tocilizumab 162 mg SC weekly
- Matching placebo SC weekly

The selected dose of SC TCZ is within the approved dose range for the RA and GCA indications.

One pre-filled syringe (PFS) was used for each dosing per week. The first SC injection was given at the site under close supervision. Patients (and caregivers if applicable) were trained on self-administration. Once competency was demonstrated, patients and/or caregivers were permitted to self-administer TCZ at home. Recommended sites of injection were uninvolved (or minimally thickened) areas of skin in the thigh, abdomen or outer arm (caregivers only).

Study treatments could be modified, interrupted, or discontinued for management of toxicity or safety concerns (occurrence of AEs of special interest or specific laboratory abnormalities). The only modification allowed was changing dosing frequency from weekly to every 2 weeks.

Specific treatment modifications for various safety concerns or toxicity were as follows:

- Opportunistic or serious infections: treatment interruption until infection resolved
- Gastrointestinal perforation: treatment was to be discontinued
- Demyelinating disorders: treatment interruption with resuming treatment only if benefit-risk balance favored continuing study drug
- Neutropenia: for ANC < 500 cells/µL, treatment was discontinued; for ANC between 500 to 1000 cells/ µL, treatment dosing was interrupted or modified
- Thrombocytopenia: for platelet counts < 50,000/ µL, treatment was discontinued; for platelet counts between 50,000 to 100,000/ µL, treatment dosing was interrupted or modified
- Hepatotoxicity (confirmed on repeat blood testing): for AST or ALT >5X ULN, treatment was discontinued; for AST or ALT between 3 to 5X ULN, TCZ was interrupted but if persistent then discontinued. Additionally, treatment was discontinued for AST or ALT elevation > 3X ULN accompanied by total bilirubin elevation (>2X ULN), INR elevation (>1.5), alkaline phosphatase elevation (>2X ULN), or presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia
- Malignancy: treatment was discontinued
- Hypersensitivity: for anaphylaxis or serious hypersensitivity, treatment was discontinued.

Concomitant Medications

The following treatments were not permitted during the study: investigational agents, cell-depleting therapies, biologic agents (e.g., tumor necrosis factor antagonists), tyrosine-kinase inhibitors, endothelin receptor antagonists, terguride, alkylating agents such as chlorambucil,

cyclophosphamide, bone marrow transplantation with total lymphoid irradiation, thalidomide, IV gamma globulin, antithymocyte globulin, plasmapheresis, or extracorporeal photopheresis.

Escape therapy for worsening skin fibrosis or pulmonary function was allowed, as described above. In Study WA29767, for worsening skin fibrosis, escape therapies included MTX, HCQ, or other disease-modifying anti-rheumatic drugs (after discussion with the Medical Monitor); for worsening lung function, local treatment guidelines were followed (excluding cyclophosphamide) and discussed with the Medical Monitor. In Study WA27788, escape therapy included MTX, HCQ, or MMF for management of worsening skin symptoms and/or worsening SSc-associated complications. Escape therapies were given as add-on to study drug. Intolerance to or inadequate response to these medications could result in mycophenolate use after discussion with the Medical Monitor. Patients could initiate or continue escape therapy through the open-label period.

Study Endpoints

Study WA29767

The primary efficacy endpoint was change from baseline in mRSS at Week 48.

The following key secondary endpoints were included in the statistical testing hierarchy:

- Change from baseline in ppFVC at Week 48
- Time to treatment failure (TTF)
- Change from baseline in HAQ-DI at Week 48
- Proportion of patients with ≥ 40% improvement in mRSS at Week 48 compared with baseline
- Proportion of patients with ≥ 60% improvement in mRSS at Week 48 compared with baseline
- Change from baseline in Patient's Global Assessment at Week 48
- Change from baseline in Physician's Global Assessment at Week 48
- Change from baseline in ppFVC at Week 24
- Change from baseline in mRSS at Week 24
- Proportion of patients with ≥ 20% improvement in mRSS at Week 48 compared with baseline.

Exploratory efficacy endpoints included percent predicted DLCO, St. George Respiratory questionnaire, HRCT lung fibrosis scores, and Composite Response Index in Systemic Sclerosis (CRISS) scores.

Study WA27788

The primary efficacy endpoint was change from baseline in mRSS at Week 24.

Secondary efficacy endpoints were as follows, without an adjustment for multiplicity:

- Change from baseline in HAQ-DI score at Weeks 24 and 48
- Change from baseline in Patient's Global Assessment at Weeks 24 and 48
- Change from baseline in Physician's Global Assessment at Weeks 24 and 48
- Change from baseline in FACIT-Fatigue score at Weeks 24 and 48
- Change from baseline in Pruritus 5-D Itch Scale at Weeks 24 and 48
- Change from baseline in mRSS at Week 48
- Proportion of patients with change from baseline in mRSS at Week 48 greater than or equal to the change from baseline in mRSS at Week 24
- Change baseline in visual analog scale (VAS) scores from (intestinal, breathing, Raynaud's, finger ulcers, overall disease VAS scores from SHAQ-DI) at Weeks 24 and 48.

Exploratory endpoints included the following:

- Change from baseline at Weeks 24 and 48 in the following parameters:
- EQ-5D™ and pulmonary function (ppFVC, DLCO)
- 28 TJC in patients with joint involvement at baseline
- Digital ulcer count at Weeks 24 and 48
- Tendon friction rub count at Weeks 24 and 48.

These endpoints are described below:

- mRSS is a measure of skin thickness, which is assessed by palpation. Ratings in the scale range from 0 (normal) to 3 (severe skin thickening) across 17 different body sites (e.g., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet). The total score is the sum of the individual skin scores from all of these sites and ranges from 0 to 51 in whole units. A negative change from baseline shows improvement.
- FVC assessments were based on ATS/ERES guidelines. FVC maneuver acceptability/reproducibility was reviewed centrally by over-readers blinded to treatment assignment. Reference values used were NHANES III (ppFVC calculations).
- TTF was defined as time from the first dose of study drug to the first of the following occurrences: time to death, decline in ppFVC > 10% (from baseline), increase in mRSS ≥ 20% and increase of ≥ 5 points, or occurrence of a predefined SSc-related serious complication (adjudicated by clinical adjudication committee [CAC])
- HAQ-DI is a measure of physical function that consists of 20 questions and 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The total score ranges from 0 to 3 (3=worst functioning) and indicates the patient's self-assessed level of disability; a decrease in score indicates improvement.
- Patient's Global Assessment is a PRO assessed on a 100-mm horizontal VAS, with higher scores indicating worse disease. The MCID for improvement has been reported to be -6.7 (Sekhon et al. 2010).
- Physician's Global Assessment is assessed by the physician on a VAS ranging 0 to 100, with

higher scores indicating worse disease. The MCID for improvement has been reported to be 8 to 13 (Gazi et al. 2007).

Statistical Analysis Plan for Study WA29767

The primary analysis population of Study WA29767 was the intent to treat (ITT) population, which consisted of all randomized patients who received any study drug. The randomized population consisted of all randomized patients. All but two randomized patients received at least one dose of study drug.

Analysis for Primary Endpoint

The primary efficacy endpoint, the change from baseline in mRSS at Week 48, was analyzed with a mixed model for repeated measurements (MMRM), which included the 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, and the continuous covariates of baseline mRSS score and baseline mRSS score by visit interaction. An unstructured covariance structure was used to model the within-patient errors, and the Kenward–Roger approximation was used to estimate the denominator degrees of freedom.

The treatment comparison for the primary endpoint was the contrast between treatment groups at Week 48. Least squares means (LSMs) for each treatment group, the difference in LSMs, a 95% confidence interval (CI) for the difference in LSMs, and the corresponding p-value were reported.

Analysis for Key Secondary Endpoints

The primary analysis method for the change from baseline in the FVC key secondary endpoints (observed and percent predicted) was a non-parametric Van Elteren test stratified by screening IL-6 level. The median change from baseline for each treatment group and the corresponding 95% CI for the median were also derived.

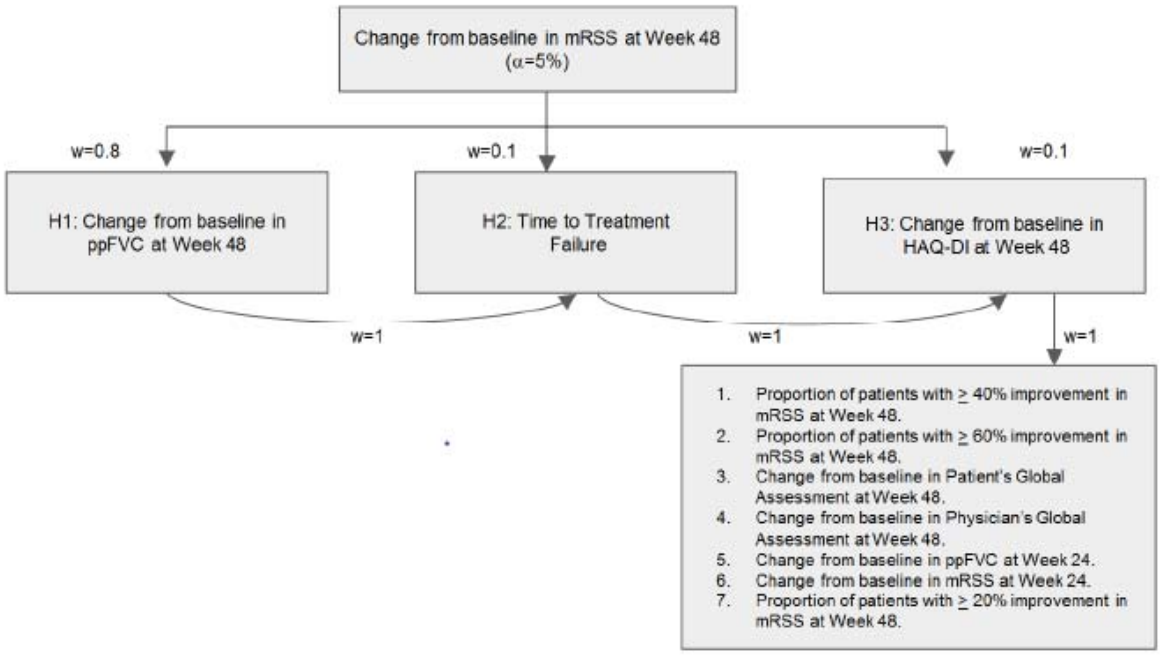
An additional analysis for the FVC endpoints used the same MMRM model as the primary efficacy endpoint (with baseline FVC variables used as the continuous covariates). LSMs for each treatment group, the difference in LSMs, a 95% CI for the difference in LSMs, and the corresponding p-value were reported.

Other continuous secondary endpoints were analyzed with an MMRM with similar factors and covariates used for the primary endpoint. For those endpoints, the relevant baseline covariate and baseline covariate by visit interaction were utilized in the model.

Multiple Testing Approach

Figure 4 displays the multiple testing procedure applied to the testing of the primary, secondary, and selected exploratory endpoints.

Figure 4: Multiple Testing Procedure for Study WA29767



Source: Study WA29767 SAP, p. 3095
Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; mRSS, modified Rodnan skin score; ppFVC, percent predicted forced vital capacity

If the primary efficacy endpoint was significant at alpha = 0.05, then ppFVC was to be weighted at 0.8 and tested at alpha = 0.04. The time to treatment failure and HAQ-DI endpoints were to be weighted at 0.1 so that if ppFVC failed to meet significance at alpha = 0.04, each could still be tested at a minimum alpha level of 0.005. If ppFVC was statistically significant, then its alpha was to be transferred to the time to treatment failure endpoint, which was to be tested at alpha = 0.045. If ppFVC and time to treatment failure were significant at the 0.04 and 0.045 alpha levels, respectively, then their alpha was to be passed to the HAQ-DI endpoint, and HAQ-DI was to be tested at alpha = 0.05. If ppFVC was not significant, but time to treatment failure was, the 0.005 alpha was to be transferred to HAQ-DI, which could then be tested at alpha = 0.01. If the time to treatment failure endpoint was not significant, then HAQ-DI was to be tested at alpha = 0.005.

If HAQ-DI was significant at the acquired significance level, then the other secondary endpoints listed below HAQ-DI in the testing hierarchy were to be tested in order at the alpha level passed down by HAQ-DI. If the endpoint being tested was not significant at the acquired significance

level, then that endpoint and those below in the testing hierarchy were to be considered not significant.

If the primary endpoint was not significant at alpha = 0.05, testing of subsequent endpoints was to cease.

Handling of Missing Data

Analyses of continuous endpoints used available data; missing efficacy and safety data were not imputed. Efficacy data were collected on patients who discontinued study drug or received rescue therapies during the double-blind treatment period. In the analyses of binary endpoints, patients with missing assessments were assigned as non-responders.

Sensitivity Analyses

For continuous endpoints in the multiple testing procedure except for the TTF endpoint, tipping point analyses and pattern mixture models were to be implemented. Tipping-point analyses were to be conducted by adding or subtracting a constant delta to the missing at random (MAR) imputed values at the Week 48 analysis time point in the direction of lack of efficacy for TCZ and in the direction of improvement for placebo. Pattern-mixture models were also to be implemented, where missing data in the placebo arm were to be imputed using a MAR assumption, and missing data in the TCZ arm were to be imputed using data from placebo-treated patients as the basis for the imputation. After data were imputed for each relevant endpoint, the analysis method for the imputed datasets was to be the same method specified for the primary analysis.

Protocol Amendments

There were five protocol amendments to the original protocol (version 1 finalized 2-28-2015). The first two protocol amendments occurred prior to the first patient being randomized and are not discussed further as there would not be any substantial impact anticipated from these on the results of the study.

Protocol amendment 3 dated 12-17-2015 made the following key changes:

- Baseline HRCT time period reduced from 12 months prior to screening to 3 months
- To increase study enrollment and retention, an option was introduced to allow patients discontinuing study drug to participate in the OLE.

Other changes included addition of HAQ-DI assessments for patients discontinuing study drug, CRP result reporting change to prevent unblinding of the Applicant, MTX dose change in escape therapy to conform to country-specific requirements, and clarification of the interim futility analysis.

Protocol amendment 4 dated 9-6-2015 made the following key changes:

- Clarification of exclusion criteria for limited cutaneous SSc and corticosteroids
- Addition of details on the timing of the interim analysis
- Addition of a week 36 HAQ-DI assessment.

Protocol amendment 5 dated 5-5-2017 made the following key changes:

- Clarification of the follow-up assessments after study drug discontinuation
- Escape therapy allowed to be initiated in the OLE period as well as continued from the DB period
- Washout period elimination for those patients deciding to participate in the OLE who had discontinued study drug in the DB period
- Revisions made to emphasize need for the same assessor to conduct mRSS evaluations for a given patient at all visits, to ensure consistency
- pulmonary function tests rejected by over-readers were required to be repeated within 4 weeks.

Overall, there are no concerns raised from the protocol amendments as the aforementioned protocol amendments are not expected to impact safety and efficacy results in an unbalanced fashion.

Statistical Analysis Plan for Study WA27788

The primary analysis population of Study WA27788 was the ITT population, which consisted of all randomized patients who received any study drug. The safety population consisted of all patients who received any study drug and provided at least one post-dose safety assessment (i.e., withdrawal, AE, death, laboratory assessment, vital sign).

Analysis for Primary Endpoint

The primary efficacy endpoint, the change from baseline in mRSS at Week 24, was analyzed with an MMRM, which included the categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment by visit interaction, and the continuous covariates of baseline mRSS score and baseline mRSS score by visit interaction. An unstructured covariance structure was used to model the within-patient errors, and the Kenward–Roger approximation was used to estimate the denominator degrees of freedom.

The treatment comparison for the primary endpoint was the contrast between treatment groups at Week 24. LSMs for each treatment group, the difference in LSMs, a 95% CI for the difference in LSMs, and the corresponding p-value were reported.

Although the primary endpoint was evaluated at Week 24, patients and investigators in the study remained blinded through Week 48. Additional ad-hoc analyses for exploratory endpoints were performed after the study was unblinded at Week 24. These analyses were conducted

because the endpoints were considered clinically relevant in terms of the overall disease and functional status of patients, and because results from pre-planned analyses warranted further exploratory analyses for phase 3 program development.

This review therefore presents results at Week 48 rather than Week 24 for the following reasons: (1) SSc is a chronic illness; (2) there is prior experience with evaluating FVC outcomes at approximately one-year study duration (e.g. in IPF, SSc-ILD, and PF-ILD); and, (3) both studies had 48 week double blinded treatment periods.

Analysis for FVC Exploratory Endpoints

There were no pre-specified formal statistical analyses of exploratory endpoints, including FVC (observed and percent predicted). As stated above, additional ad-hoc analyses for exploratory endpoints were performed after the study was unblinded at Week 24. These analysis results were included in the Study 27788 clinical study report (CSR) and in the Summary of Clinical Efficacy (SCE).

The analysis method for the change from baseline in the ppFVC exploratory endpoint was a non-parametric Van Elteren test stratified by the baseline stratification variable of tender joint count category. The median change from baseline for each treatment group and the corresponding 95% CI for the median were also calculated. The statistical reviewer conducted a similar analysis for the observed FVC exploratory endpoint.

An additional analysis for the two exploratory FVC endpoints used the same MMRM model as the primary efficacy endpoint (with baseline FVC variables used as the continuous covariates). LSMs for each treatment group, the difference in LSMs, a 95% CI for the difference in LSMs, and the corresponding p-value were reported.

Multiple Testing Approach

The study did not have a pre-specified method to adjust for multiplicity. There was a single primary endpoint at Week 24, which was compared between two treatment groups. The significance test for the primary endpoint was based on a two-sided alpha of 0.05.

Handling of Missing Data

Analyses of continuous endpoints used available data; missing efficacy and safety data were not imputed. In the analyses of binary endpoints, patients with missing assessments were assigned as non-responders.

Sensitivity Analyses

Sensitivity analyses were pre-specified only for the mRSS primary endpoint at Week 24. These sensitivity analyses included the use of pattern mixture models; use of a last observation

carried forward method, where the last mRSS observation available for each patient up to and including Week 24 was used to impute missing values; and a completers analysis, in which only patients with mRSS observations at Week 24 were included.

Protocol Amendments

The study protocol was finalized on 8-23-2011 and amended three times. The first amendment was implemented before the first patient was randomized on 3-13-2012. The first protocol amendment occurred prior to the first patient being randomized and is not discussed further as there would not be any substantial impact anticipated from these on the results of the study.

In addition to the protocol amendments described below, a change in study conduct was the unblinding of some of the Applicant's team to individual patient data after the Week 24 data analysis. 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 at Week 24, the Applicant decided that further review and analysis of the data were required. Consequently, some members of the Applicant's team were completely unblinded and granted access to the data. Those individuals were then removed from the study management team, did not participate in discussions about ongoing study conduct activities, and ceased direct interaction with study sites. Procedures to maintain the treatment blind were in place until after the Week 48 database lock and after the study was fully unblinded.

Protocol amendment 2 dated 11-2-2012 made the following key changes:

- Removal of patient recruitment barriers to allow for completion and closeout of recruitment for the study.
- Clarification on the use of SSc medications, including those initiated after baseline, specifically allowing modification of the dose regimen after Week 24 if clinically warranted.
- Clarification that after the baseline visit, and per the investigator's clinical judgment, if ACE inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or vasodilators needed to be initiated for chronic use, then the dose regimen was to remain stable up to and including Week 24, unless dose adjustments were required for safety reasons or cytochrome P450 (CYP450) interactions.
- Clarification that escape therapy was only for treating worsening of skin symptoms defined as ≥ 20% worsening in mRSS from baseline.

Protocol amendment 3 was dated 11-20-2012. The purpose of the third protocol amendment was to add the sampling schedule for the PK substudy, which was inadvertently removed from the previous version of the protocol. In addition, to take into account the recent use of approved tyrosine kinase inhibitors for the treatment of SSc, a new exclusion criterion was added to exclude tyrosine kinase inhibitors, such as imatinib, nilotinib, and dasatinib, within ≤ 4 weeks prior to baseline.

Overall, there are no concerns raised from the protocol amendments as the aforementioned protocol amendments are not expected to impact safety and efficacy results in an unbalanced fashion.

8.1.2. Study WA29767 Results

Compliance with Good Clinical Practices

The IECs and/or IRBs met the requirements of the International Council for Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and local legislation. The constitution of the IRBs/IECs met the requirements and definitions of ICH GCP (ICH E6), 21 CFR 312.3, and of the participating countries.

Studies were conducted in accordance with the principles of the Declaration of Helsinki, code of federal regulations (CFR), and GCP. Investigators agreed to carry out all terms in accordance with the applicable regulations and law under ICH GCP guidelines. Approval from the appropriate IECs/IRBs was obtained before study start.

Data Quality and Integrity

No issues were discovered with respect to data quality or data integrity. In general, the quality of the data submitted for review was adequate.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with the investigators. All but one investigator in Study WA29767 had no disclosable interests, discussed next.

(b) (6) received a grant from Intermune (acquired by Roche) totaling $254,000 for a 3-year prospective cohort study in ILD. Given the double-blind nature of the study, the role of (b) (6) (b) (6), and the presence of a global data monitoring committee, it is unlikely that outcomes were influenced appreciably.

One investigator in Study WA29767 provided an incomplete disclosure form (not all questions were answered). In addition, a signed disclosure form was not obtained for 16 subinvestigators from 10 sites. The Applicant conducted due diligence in all these cases (two attempts made to obtain appropriate information) to obtain full disclosure information. One site enrolled 5 patients, and the remainder of the sites for which financial disclosures were not available all enrolled ≤ 3 patients; therefore, these are unlikely to influence the outcome of the study.

Patient Disposition

A total of 343 patients were screened across 75 sites in 20 countries. Of these 343 patients, 212 patients were randomized into the study. Screen failures were primarily due to inability to meet eligibility criteria (100 of 131 screen failures; 67 exclusion criteria failures and 33 inclusion criteria failures). The first patient was randomized on November 20, 2015, and the last patient was randomized on February 14, 2017.

Geographical regions with recruitment are as follows: Central Europe (63 patients), Western Europe (57 patients), North America (43 patients), Latin America (29 patients), and Japan (20 patients). Allocation across treatment arms were balanced for each country and site with the exception of North America (27 patients in placebo versus 15 patients in TCZ).

All but two randomized patients received at least one dose of study drug. One patient randomized to placebo withdrew consent prior to receiving the first dose of study drug, and one patient randomized to TCZ was randomized in error and withdrawn prior to first dose. Of the treated patients, the majority (188 [90%]) of patients completed Week 48. Slightly more patients in the TCZ arm completed study and remained on study drug. Patient disposition for the randomized population is summarized in Table 2.

Table 2: Study WA29767 Patient Disposition (Randomized Population)

	Placebo n (%)	TCZ n (%)
Randomized	107	105
Treated*	106	104
Discontinued from study before 48 weeks		
Yes	13 (12)	9 (9)
Reasons for discontinuing study		
Subject withdrawal	9 (8)	5 (5)
AE	3 (3)	2 (2)
Death	1 (1)	1 (1)
Other**	0	1 (1)
Discontinued study drug before 48 weeks		
Yes	17 (16)	12 (11)
Reasons for discontinuing study drug		
Subject withdrawal	7 (7)	6 (6)
AE	7 (7)	4 (4)
Death	1 (1)	1 (1)
Lack of efficacy	2 (2)	0
Other	0	1 (1)

Source: Study WA29767 CSR Table 7, p.84
* One patient in each treatment arm was not treated after randomization.
** Incomplete disposition record at CCOD (clinical cut-off date)
Abbreviations: AE, adverse event; TCZ, tocilizumab

Protocol Violations/Deviations

In Study WA29767, as there were no per-protocol analyses, no protocol deviations led to exclusion of patients from any analyses.

As of the Week 48 database lock, about a third of patients had major protocol violations (30% placebo versus 27% TCZ). The most common single major protocol deviation (MPD) was related to baseline HRCT performance (9%), whereas the largest general category for MPDs was eligibility criteria violations/deviations (12%). The next most common single MPDs were as follows in order of frequency: informed consent deviation (5%) and other procedural deviation (3%). There were no significant imbalances between treatment arms.

Overall, given the relatively balanced MPDs between treatment arms, the lack of exclusion of MPD patients from any analysis, and the type and frequencies of the MPDs, it is unlikely that MPDs significantly impacted final outcomes.

Demographics and Baseline Characteristics

Overall, the enrolled patients were mostly white, middle-aged women, consistent with other SSc trials and the known SSc population. There were no major imbalances in demographics between treatment arms. While the majority of patients were from central and western Europe (57%), the US had the largest enrollment contribution as a single country (39 of 212 patients, 18%). Demographic characteristics of the ITT population are summarized by treatment group in Table 3.

Similar demographic characteristics were observed in the SSc-ILD subgroup of Study WA29767. Approximately 64% of the study population had SSc-ILD at baseline as defined by HRCT and was balanced by treatment group (68/arm). The mean (SD) age values were 49 (13) years and 47 (13) years in the placebo and TCZ groups, respectively. Most patients were white (57 [84%] and 51 [75%] in the placebo and TCZ groups, respectively) and female (55 [81%] and 53 [78%] in the placebo and TCZ groups, respectively).

Table 3: Study WA29767 Demographic Characteristics (ITT Population)

	Placebo N=106	TCZ N=104
Age (years)		
N	106	104
Mean (SD)	49 (13)	47 (12)
Median	50	48
Min, max	20, 73	18, 72
Sex, n (%)		
Female	90 (85)	81 (78)
Male	16 (15)	23 (22)
Race, n (%)		
White	90 (85)	85 (82)
Asian	9 (9)	16 (15)
American Indian or Alaska Native	3 (3)	1 (1)
Black or African American	3 (3)	2 (2)
Ethnicity, n (%)		
Not Hispanic or Latino	79 (75)	89 (86)
Hispanic or Latino	26 (25)	13 (13)
Not reported	1 (1)	2 (2)
Smoking status, n (%)		
Never smoker	66 (62)	72 (69)
Previous smoker	28 (26)	24 (23)
Current smoker	12 (11)	8 (8)
Country, n (%)		
US	25 (24)	14 (14)
Ex-US*	81 (76)	90 (87)
Bulgaria	14 (13)	12 (12)
Mexico	13 (12)	8 (8)
Japan	8 (8)	12 (12)
Poland	6 (6)	13 (13)
Great Britain	3 (3)	8 (8)
Germany	3 (3)	7 (7)

Source: Study WA29767 CSR Table 10, p. 90
* Countries with <10 total patients are not shown.
Abbreviations: ITT, intent-to-treat; TCZ, tocilizumab

Geographic regions with highest to lowest recruitment are as follows: Central Europe (63 patients), Western Europe (57 patients), North America (43 patients), Latin America (29 patients), Japan (20 patients). Allocation across treatment arms were balanced for each country and site with the exception of North America (27 placebo versus 15 TCZ).

Baseline disease characteristics were generally balanced between the treatment groups. The median duration of SSc was slightly longer in the placebo group than the TCZ group; however, baseline serologic status, inflammatory markers, and mRSS scores were similar between treatment groups. Previous or concurrent ILD was more frequent in the TCZ group (36% vs. 26%); however, mean ppFVC and ppDLCO were similar between treatment groups. Otherwise, treatment arms were generally balanced for most disorders (such as GERD, constipation, Raynaud's phenomenon, hypertension, arthralgia, osteoarthritis, vitamin D deficiency, hyperlipidemia, and hypercholesterolemia).

Table 4: Study WA29767 Baseline Characteristics (ITT Population)

	Placebo N=106	TCZ N=104
Duration of SSc (days)		
Mean	704	674
Median	545	524
Total mRSS		
Mean	20	20
Median	19	19
Physician's Global Assessment VAS		
Mean	60	59
Median	61	62
Patient's Global Assessment VAS		
Mean	59	54
Median	58	53
Serum markers		
C-reactive protein (mean)	7.0	8.9
ESR (mean, mm/hr)	35	35
Platelet count (10^9/L, mean)	299	311
Antibodies		
ANA positive	90 (92)	91 (93)
Anti-centromere positive	9 (9)	8 (8)
Anti-topoisomerase positive	49 (49)	52 (52)
Spirometry		
ppFVC (mean)	84%	80%
ppDLCO (mean)	77%	74%
Prior or concurrent comorbidities		
Ongoing latent TB treatment	12 (11)	6 (6)
Previous or concurrent ILD	28 (26)	38 (36)

Source: Study WA29767 CSR Table 11, p. 92, Table from p. 312
Abbreviations: ANA, antinuclear antibodies; DLCO, diffusing capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; ITT, intent-to-treat; mRSS, modified Rodnan skin score; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TB, tuberculosis; TCZ, tocilizumab; VAS, visual analog scale

With regard to the SSc-ILD subgroup, baseline characteristics were generally similar to those described in Table 4 (data for SSc-ILD subgroup not shown), and fairly balanced across treatment arms. Specifically, there were no notable differences between treatment arms for disease duration (mean: 705 days placebo vs. 709 days TCZ), baseline serologic status (antinuclear antibodies and ATA positive status slightly lower in placebo – 86% vs. 96% and 63% vs. 69%, respectively), inflammatory markers (ESR 35 vs. 38), baseline mRSS scores (21 each), digital ulcer count (mean: 0.3 placebo vs. 0.1 TCZ), and baseline lung function (ppFVC 82% vs. 78% TCZ, ppDLCO 73% vs. 69% placebo).

Previous and Concomitant Medications

The majority of patients in Study WA29767 had received prior medications, many of which were stopped prior to the first dose of study drug. Previous use of treatments for SSc were similar by treatment group. While corticosteroids, balanced between treatment arms, were commonly used and continued, new immunomodulating agents were more commonly started

in placebo patients compared to TCZ patients (21% placebo versus 9% TCZ). The majority of these newly initiated immunomodulatory therapies were started after Week 36 and taken concurrently with study drug. The majority of placebo patients who received escape therapy did so after meeting escape criteria (64%; 14 of 22 patients), whereas fewer TCZ patients met escape criteria for initiating new immunomodulatory therapy (22% placebo; 2 of 9 patients). A greater proportion of patients in the placebo group initiated treatment with MMF (12%) and cyclophosphamide (2%), as compared to the TCZ group (5% and 0%, respectively). Previous and concomitant medications are summarized in Table 5.

Table 5: Study WA29767 Previous and Concomitant Medications (ITT Population)

	Placebo N=106 n (%)	TCZ N=104 n (%)
Previous medications, >5% usage in any arm		
Total number of patients with at least one previous medication	63 (59)	66 (64)
Methotrexate*	25 (24)	27 (26)
Corticosteroids**	18 (17)	15 (14)
Folic acid	14 (13)	15 (14)
Mycophenolate mofetil	10 (9)	9 (9)
Cyclophosphamide	12 (11)	8 (8)
Hydroxychloroquine	8 (8)	8 (8)
Prostaglandins***	6 (6)	11 (11)
Penicillamine	9 (9)	2 (2)
Medications continued during treatment period (categories), >20% usage in any arm		
Proton pump inhibitors	62 (59)	63 (61)
Corticosteroids^^	55 (52)	55 (53)
Vitamins and minerals	48 (45)	51 (49)
Calcium channel blocking agents	38 (36)	41 (39)
Analgesics	39 (37)	35 (34)
Non-steroidal anti-inflammatories	41 (39)	30 (29)
Salicylates	30 (28)	21 (20)
Herbal, homeopathic, and dietary supplements	25 (24)	22 (21)
Medications initiated during treatment period (categories), >10% usage in any arm		
Analgesics	21 (20)	21 (20)
Non-steroidal anti-inflammatories	17 (16)	15 (14)
Quinolone antibiotics	16 (15)	15 (14)
Corticosteroids	17 (16)	13 (13)
Penicillins	14 (13)	12 (12)
Cephalasporin antibiotics	12 (11)	6 (6)
Supplements	12 (11)	5 (5)
Immunomodulating treatments initiated	22 (21)	9 (9)
Mycophenolate mofetil	13 (12)	5 (5)
Methotrexate	4 (4)	3 (3)
Cyclophosphamide	2 (2)	0

Source: Study WA29767 CSR pp.328-329, 341-347, 385-389, 413
^medications listed with >5% usage in any one treatment arm
^^majority of corticosteroids accounted for by prednisone, prednisolone, methylprednisolone, and betamethasone
*includes methotrexate sodium
**includes prednisone, methylprednisolone, prednisolone, betamethasone, clobetasol
***includes alprostadil, beraprost, iloprost, limaprost

Abbreviations: ITT, intent-to-treat; TCZ, tocilizumab

Treatment Compliance

Compliance was high in both treatment arms, with a mean dose density of 91.0% in the placebo arm and 91.2% in the TCZ arm. Dose intensity was defined as the number of doses received divided by the expected number of doses. Patients in the placebo and TCZ arms received a similar number of doses (mean of 41.7 in the placebo arm and 42.4 in the TCZ arm), with 66.0% of patients in the placebo arm and 60.6% of patients in the TCZ arm missing at least one dose of the study drug.

Efficacy Results – Primary Endpoint

The primary endpoint for Study WA29767 was change from baseline to Week 48 in the mRSS. The mRSS is based on physician assessment of 17 anatomic locations, determining skin thickness on a scale of 1 to 3. Lower scores indicate less skin thickening and fibrosis. The minimum clinically important difference (MCID) of the mRSS has been estimated in the range of 3.2 to 5.3 mRSS (Khanna et al. 2006).

Treatment with TCZ did not result in a statistically significant difference between treatment groups in the primary endpoint (adjusted difference in LSM = -1.73, 95% CI: [-3.78, 0.32], p=0.098). While the observed treatment difference resulted in the failure to reject the null hypothesis of no difference in treatment effect between both groups, it was numerically favorable for TCZ (-4.41 placebo versus -6.14 TCZ).

Supportive results regarding the mRSS were observed in additional analyses. Responder analyses using threshold improvements of $\geq$ 20%, 40%, and 60% at Week 48 compared to baseline were performed (pre-specified hierarchical endpoints #5, #6, and #11 below). In these analyses, there was a nominally significantly higher proportion of patients with a $\geq$ 20% improvement in mRSS with TCZ use compared to placebo (50.0% placebo versus 72.1% TCZ, p=0.001), but no statistically significant differences in responder proportions were observed in the other improvement thresholds ($\geq$ 40%, $\geq$ 60%). Additionally, changes in mRSS over time suggested favorable trends for TCZ over placebo. Specifically, treatment arm differences in mean mRSS by visit at week 8, 16, 24, 36, and 48 indicate increasing improvement in mRSS over time favoring TCZ (0.35, -0.38, -0.63, -1.59, and -1.73, respectively).

In the proposed target population (SSc-ILD), the treatment effect for mRSS, as assessed by change from baseline to Week 48, was also favorable for TCZ users compared to placebo (-3.77 placebo versus -5.88 TCZ, per the statistical reviewer's analysis), with a slightly larger magnitude of effect than that seen in the ITT population (treatment difference: -1.73 overall versus -2.11 in the SSc-ILD subgroup, 95% CI: [-4.89, 0.67]).

For context, the treatment effect for TCZ on mRSS can be compared to the treatment effect for nintedanib (approved 2019 for SSc-ILD) on mRSS in the pivotal SSc-ILD trial. Cross-study comparison limitations notwithstanding, use of nintedanib in Study 1199.214 resulted in an adjusted difference of -0.21 between treatment groups in mean change from baseline (-1.96 placebo versus -2.17 nintedanib). This difference of -0.21 is numerically less than (and less favorable than) the difference of -1.73 between treatment groups in mean change from baseline observed in the ITT population and the treatment group difference of -2.11 in the SSc-ILD subgroup in Study WA29767, again recognizing the limitations of cross-study comparisons. Notably, mRSS was not the primary endpoint in Study 1199.214, but was assessed as a key secondary endpoint.

As a result of the failed primary analysis in Study WA29767, the results from the analysis of the sequentially tested secondary endpoints (order shown below), when applicable, will be referred to as nominally significant. The endpoints were assessed at Week 48 unless otherwise specified.

- mRSS
- ppFVC
- TTF
- HAQ-DI
- ≥ 40% improvement in mRSS
- ≥ 60% improvement in mRSS
- Patient's Global Assessment
- Physician's Global Assessment
- ppFVC at Week 24
- mRSS at Week 24
- ≥ 20% improvement in mRSS

FVC is a spirometric measure used as the basis for approval in several interstitial lung diseases (ILDs) such as IPF, PF-ILD, and, most importantly, SSc-ILD (nintedanib). As discussed previously, the proposed indication for this application is for treatment of a population of SSc-ILD, which is different from the study population in WA29767 (SSc). Given that lung disease is one of the major causes of SSc deaths, it is reasonable to evaluate this SSc-ILD subgroup within Study WA29767, defined by HRCT findings at baseline. To that end, the key secondary endpoint of FVC in the ITT population is discussed next, followed by a discussion of the key secondary endpoint of FVC in the SSc-ILD subgroup.

Efficacy Results - FVC in ITT Population

Despite the failure of Study WA29767 to meet the primary endpoint, FVC remains an important assessment in this application. FVC is an endpoint that reliably predicts clinical benefit in fibrotic lung diseases, including SSc-ILD, and in which FVC is monitored clinically. An FVC decline of ≥ 10% has been associated with an increased risk of mortality in idiopathic pulmonary fibrosis, however, the available data from SSc-ILD studies are insufficient to determine the

threshold at which a change in FVC becomes relevant in a clinical setting. FVC was used as the basis for approval in several ILD development programs (e.g. IPF, PF-ILD), and most notably, nintedanib's SSc-ILD program. Importantly, FVC has been discussed by the larger rheumatologic academic community (Arthritis Advisory Committee meeting in July 2019) with support for the clinical meaningfulness of this measure in SSc-ILD.

The change from baseline in ppFVC at Week 48 was a key secondary endpoint. TCZ use was associated with a favorable nominally significant treatment difference in ppFVC and observed FVC (mL) in the overall population of Study WA29767. The mean decline in FVC from baseline in the placebo group was -190 mL, while the mean decline from baseline in the TCZ group was -24 mL. Assessment of FVC over time supports the relative stability of FVC in the TCZ group compared to decline in observed FVC over time in the placebo group. These results are summarized for the ITT population in Table 6, Table 7, and Figure 5.

Table 6: Study WA29767 ppFVC Results at Week 48 (ITT Population)

	Placebo N=106	TCZ N=104
Median change from baseline in ppFVC		
N	91	93
Change from baseline, 95% CI	-3.91 (-4.82, -1.62)	-0.60 (-2.38, 0.88)
P-value for comparison of medians	0.0015*	
Difference in medians (TCZ-placebo)	3.31	
Mean change from baseline in ppFVC		
N	104	104
Change from baseline, 95% CI	-4.58 (-6.22, -2.94)	-0.38 (-2.06, 1.30)
Difference in LSM (TCZ-placebo), 95% CI	4.20 (2.00, 6.40)	
P-value for difference in LSM	0.0002**	

Source: Study WA29767 CSR Table 12, p.99, p. 109, statistical reviewer's analysis
*Nominal p-value from pre-specified comparison of medians in the multiple testing procedure using Van Elteren test stratified by screening IL-6 level
**Nominal p-value from pre-specified additional analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab; ITT, intent-to-treat

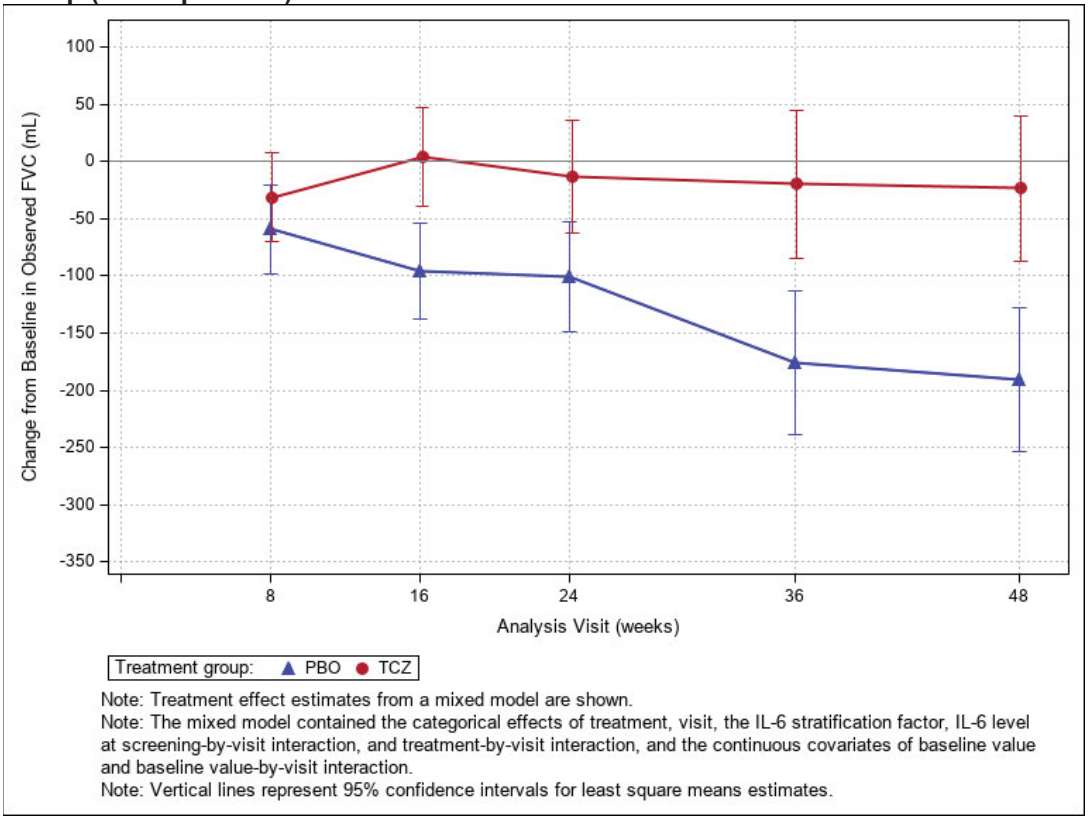
Table 7: Study WA29767 Observed FVC Results at Week 48 (ITT Population)

	Placebo N=106	TCZ N=104
Median change from baseline in FVC (mL)		
N	91	93
Change from baseline, 95% CI	-130 (-170, -40)	-20 (-90, 40)
P-value for comparison of medians	0.0031*	
Difference in medians (TCZ-placebo)	110	
Mean change from baseline in FVC (mL)		
N	104	104
Change from baseline, 95% CI	-190 (-253, -128)	-24 (-88, 40)
Difference in LSM (TCZ-placebo), 95% CI	167 (83, 250)	
P-value for difference in LSM	0.0001**	

Source: Study WA29767 CSR, p. 109, 672, 677, statistical reviewer's analysis
*Nominal p-value from pre-specified comparison of medians in the multiple testing procedure using Van Elteren test stratified by

screening IL-6 level
**Nominal p-value from pre-specified additional analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; FVC, forced vital capacity; ITT, intent-to-treat; LSM, least squares mean; mL, milliliter; TCZ, tocilizumab

Figure 5: Study WA29767 Observed FVC (mL) Mean Change From Baseline by Visit and Treatment Group (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; mL, milliliter; PBO, placebo; TCZ, tocilizumab

Given the importance of the FVC endpoint as a measure of pulmonary function in fibrosing lung diseases, sensitivity analyses were performed to confirm the (nominal) significance of the results discussed in Table 6 and Table 7, despite the position of FVC in the statistical testing hierarchy and the failed primary analysis.

Applicant-reported sensitivity analyses conducted on the change from baseline in ppFVC at Week 48 revealed the robustness of the analysis results to alternative missing data assumptions. Sensitivity analyses using a pattern-mixture model on ppFVC at Week 48 assuming missing TCZ data were MNAR and missing placebo data were MAR resulted in statistical significance (nominal p=0.0011). Additionally, tipping point analyses for the change from baseline in ppFVC at Week 48 (with an adjustment to MAR imputed values for TCZ and no

adjustment to the MAR imputed values for placebo) resulted in an adjustment of -32% to the imputed ppFVC values in the TCZ arm. Thus, the implausibility of a decrease of 32% in ppFVC in TCZ dropouts to "tip" significance of the primary analysis method results (placebo arm decreased 5% over trial duration) suggests that ppFVC results were robust to missing data assumptions. The statistical reviewer conducted additional sensitivity analyses on the ppFVC and observed FVC endpoints which are presented later in this review.

While results from the OLE portion of Study WA29767 (Week 48 to 96) were unblinded and uncontrolled, they were consistent with the aforementioned TCZ treatment effect on FVC. Specifically, median change in ppFVC from Week 48 to Week 96 in patients switching from placebo to TCZ was 0.27%, which is similar to the negligible (-0.60%) change seen in the TCZ arm in the first 48 weeks. In contrast (but supportive of a treatment effect), these results differ from the 3.9% decline from baseline in ppFVC noted in the placebo arm in the first 48 weeks. Thus, the OLE results are consistent with results observed during the 48 week controlled treatment period and are supportive of a treatment response.

The aforementioned FVC results support the efficacy of TCZ treatment in the overall study population. FVC results in the SSc-ILD subgroup are discussed in the next section.

Efficacy Results – FVC in SSc-ILD Subgroup

Post-hoc FVC results (ppFVC and observed FVC) in the SSc-ILD subgroup at Week 48 were consistent with results seen in the overall study population, with larger magnitudes of treatment response. In the SSc-ILD subgroup, the mean decline from baseline in FVC in the placebo group was -255 mL, while the mean decline from baseline in the TCZ group was -14 mL (difference 241 mL). Assessment of FVC over time supports the relative stability of FVC in the TCZ group compared to decline in observed FVC over time in the placebo group. These results are summarized in Table 8, Table 9, and Figure 6.

Table 8: Study WA29767 Post-hoc ppFVC Results at Week 48 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
Median change from baseline in ppFVC		
N	56	59
Change from baseline, 95% CI	-4.01 (-5.34, -1.65)	-0.60 (-3.20, 1.95)
P-value for comparison of medians	0.0016*	
Difference in medians (TCZ-placebo)	3.41	
Mean change from baseline in ppFVC		
N	66	68
Change from baseline, 95% CI	-6.40 (-8.62, -4.17)	0.07 (-2.13, 2.27)
Difference in LSM (TCZ-placebo), 95% CI	6.47 (3.43, 9.50)	
P-value for difference in LSM	<0.0001**	

Source: SCE Table 8, p. 39, Table 10, p. 41, statistical reviewer's analysis
*Nominal p-value from comparison of medians using Van Elteren test stratified by screening IL-6 level
**Nominal p-value from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of

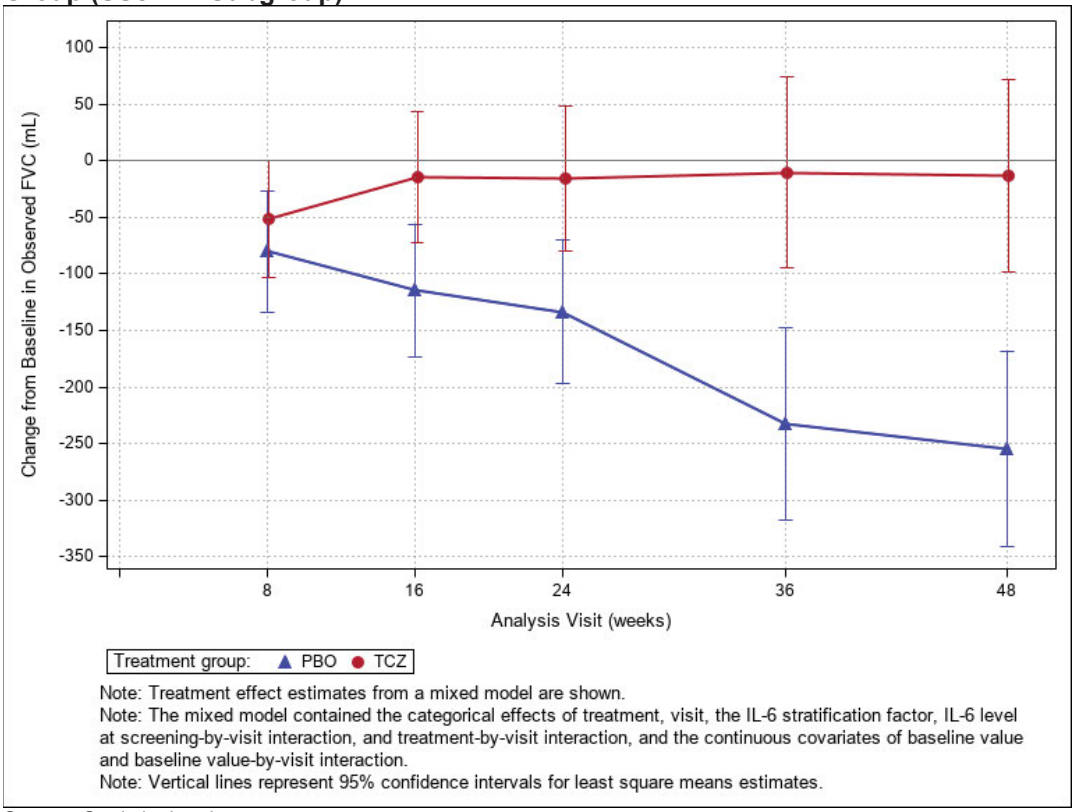
baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; ILD, interstitial lung disease; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Table 9: Study WA29767 Post-hoc Observed FVC Results at Week 48 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
Median change from baseline in FVC (mL)		
N	56	59
Change from baseline, 95% CI	-130 (-190, -50)	-20 (-120, 60)
P-value for comparison of medians	0.0027*	
Difference in medians (TCZ-placebo)	110	
Mean change from baseline in FVC (mL)		
N	66	68
Change from baseline, 95% CI	-255 (-341, -169)	-14 (-99, 71)
Difference in LSM (TCZ-placebo), 95% CI	241 (124, 358)	
P-value for difference in LSM	<0.0001**	

Source: SCE Table 11, p. 43, statistical reviewer's analysis
*Nominal p-value from comparison of medians using Van Elteren test stratified by screening IL-6 level
**Nominal p-value from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; FVC, forced vital capacity; LSM, least squares mean; mL, milliliter; TCZ, tocilizumab

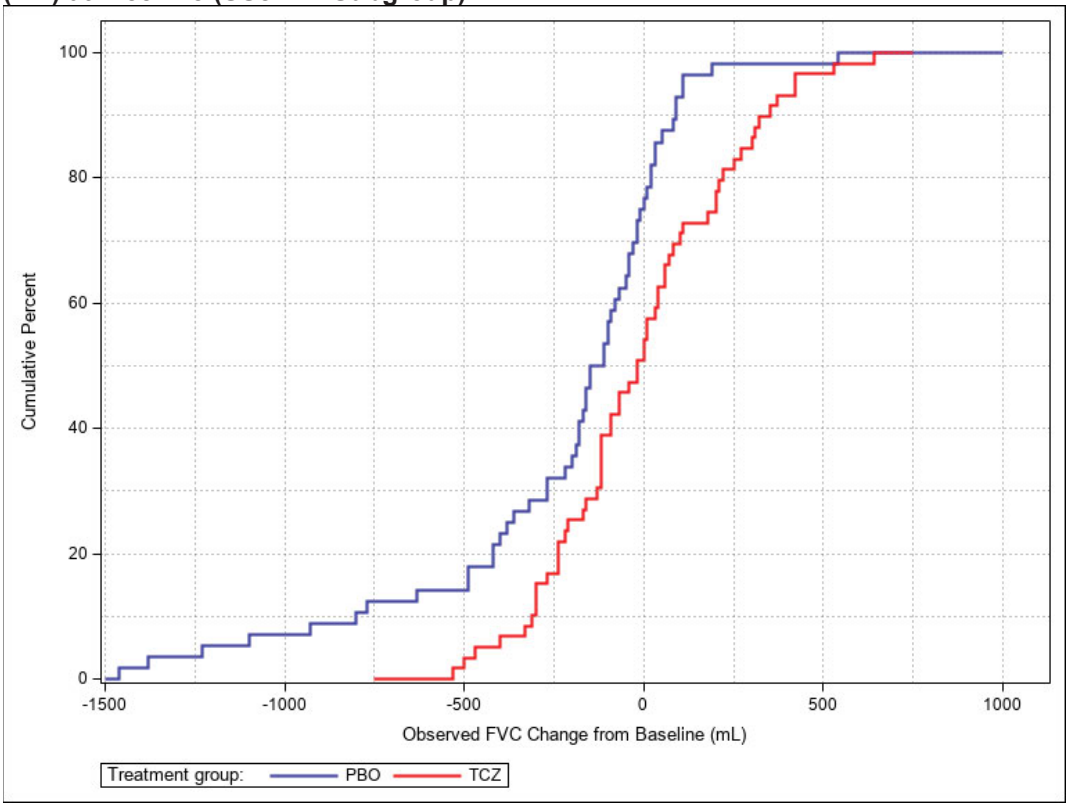
Figure 6: Study WA29767 Observed FVC (mL) Mean Change From Baseline by Visit and Treatment Group (SSc-ILD Subgroup)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; mL, ILD, interstitial lung disease; milliliter; PBO, placebo; SSc, systemic sclerosis; TCZ, tocilizumab

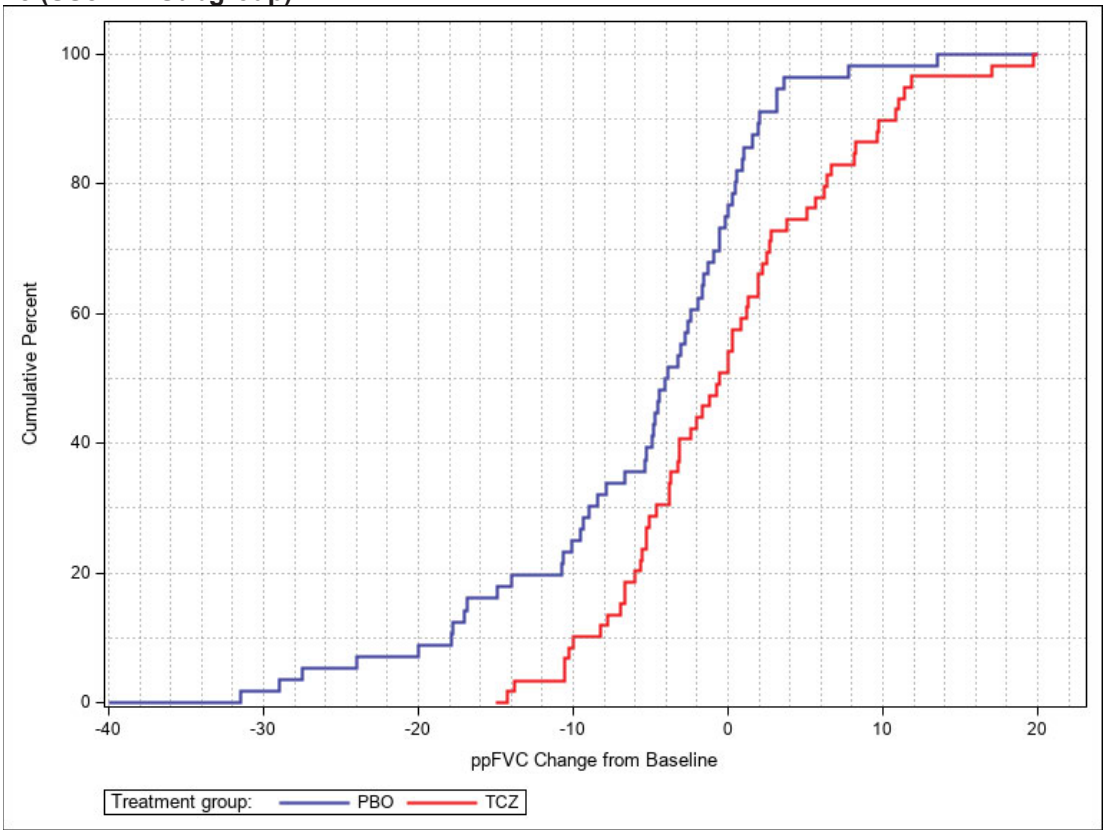
To further examine the consistency of effect on FVC, cumulative distribution function (CDF) plots were examined to look at all levels of response at Week 48. These plots showed a consistent separation across different magnitudes of change in FVC and suggested separations between TCZ and placebo across the entire FVC distribution. Figure 7 and Figure 8 contain CDF plots for observed FVC and ppFVC, respectively, for the SSc-ILD subgroup. CDF plots for observed FVC and ppFVC for the ITT population (Figure 31 and Figure 32, respectively, in Appendix Section 15.5.1) were consistent with those for the SSc-ILD subgroup.

Figure 7: Study WA29767 Cumulative Distribution Plot of Change From Baseline in Observed FVC (mL) at Week 48 (SSc-ILD Subgroup)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ILD, interstitial lung disease; mL, milliliter; SSc, PBO, placebo; systemic sclerosis; TCZ, tocilizumab

Figure 8: Study WA29767 Cumulative Distribution Plot of Change From Baseline in ppFVC at Week 48 (SSc-ILD Subgroup)



Source: Statistical reviewer
Abbreviations: ILD, interstitial lung disease; PBO, placebo; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Additional exploratory analyses for ppFVC and observed FVC were conducted for the subgroup of patients in the ITT population that did not have SSc-ILD. For both tests of the comparison of medians and LSMs, the results were not significant. At Week 48, TCZ appeared to have more favorable median and LSM values for both endpoints compared to placebo. Results are displayed in Table 10.

Table 10: Study WA29767 Post-hoc ppFVC and Observed FVC Results at Week 48 (Subgroup Without SSc-ILD)

	Placebo N=36	TCZ N=34
ppFVC		
Median change from baseline		
Change from baseline, 95% CI	-3.12 (-5.08, 1.12)	0 (-3.16, 3.74)
P-value for comparison of medians	0.3516*	
Difference in medians (TCZ-placebo)	3.12	
Mean change from baseline		
Change from baseline, 95% CI	-0.82 (-3.03, 1.39)	-0.32 (-2.92, 2.29)
Difference in LSM (TCZ-placebo), 95% CI	0.50 (-2.27, 3.27)	
p-value for difference in LSM	0.7182**	
Observed FVC (mL)		
Median change from baseline		
Change from baseline, 95% CI	-80 (-170, 40)	0 (-130, 110)
P-value for comparison of medians	0.3675*	
Difference in medians (TCZ-placebo)	80	
Mean change from baseline		
Change from baseline, 95% CI	-53 (-136, 29)	-11 (-106, 85)
Difference in LSM (TCZ-placebo), 95% CI	43 (-60, 145)	
P-value for difference in LSM	0.4093**	

Source: Statistical reviewer's analysis
*Nominal p-value from comparison of medians using Van Elteren test stratified by screening IL-6 level
**Nominal p-value from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Two patients in each group had a baseline ILD status of 'missing' or 'not evaluable'.
Abbreviations: CI, confidence interval; FVC, forced vital capacity; ILD, interstitial lung disease; LSM, least squares mean; mL, milliliter; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Sensitivity Analyses - FVC in ITT Population

The statistical reviewer conducted sensitivity analyses for the FVC endpoints in the ITT population in Study WA29767 in order to examine the departures from the assumptions regarding missing data in the Applicant's pre-specified efficacy analyses. The non-parametric Van Elteren test was the pre-specified primary analysis method for the FVC endpoints; it was conducted on observed data and did not have an assumption regarding the underlying distribution of the data. The parametric mixed model for repeated measurements (MMRM) for the comparison of means was a pre-specified additional analysis method and was based on the assumption that data were missing at random (MAR).

The statistical reviewer's sensitivity analyses were conducted for both FVC endpoints in the ITT population and for both pre-specified tests. These sensitivity analyses include pattern mixture models and tipping point analyses. In the pattern mixture models, missing data from the TCZ arm were imputed under an MNAR assumption and utilized data from the placebo arm as a reference. Missing data from the placebo arm were also imputed under this assumption. In the tipping point analyses, data from the placebo and TCZ arms were imputed under an MNAR assumption. In this method, missing values in each treatment group were imputed separately using observed values in each group, and an adjustment for each group was applied to the

imputed values. Adjustments for each treatment group were varied to find conditions that would result in a treatment effect that was not significant. The plausibility of the adjustments that resulted in non-significance was then evaluated.

Before sensitivity analyses for the ITT population were conducted, non-monotone missing data were first imputed using a MAR assumption, and monotone missing data were then imputed using a MNAR assumption. Since the MAR assumption cannot be tested, sensitivity analyses based on the MNAR assumption provide a comprehensive examination of the effect of missing efficacy data. For each sensitivity analysis, 50 datasets with imputed data were created, and analysis results were combined using Rubin's rule.

There were 26 patients with missing FVC data at Week 48 (15 in the placebo arm, 11 in the TCZ arm). Most of the reasons for discontinuation of the double-blind phase of the study were due to withdrawal by patient, which occurred for 12 patients (8 in the placebo arm, 4 in the TCZ arm). Five patients discontinued due to an adverse event (3 in the placebo arm, 2 in the TCZ arm).

Sensitivity analysis results from the ITT population are shown in Appendix Section 15.5.2. Pattern mixture model results are shown in Table 35 and Table 36. The results are consistent with those from the primary analyses for both FVC endpoints and the additional MMRM analysis method.

Figure 33 and Figure 34 contain the ppFVC tipping point analysis results, and Figure 35 and Figure 36 contain the observed FVC endpoint tipping point analysis results. The assumption that patients with missing data in the two arms would have had changes as large as the magnitude of adjustment values for ppFVC and observed FVC as described in Appendix Section 15.5.2 does not seem plausible, given the fact that such large changes were observed in very few individual patients in the study.

Thus, sensitivity analyses conducted for the two FVC endpoints in the ITT population demonstrated that the results from the post-hoc analyses were robust to alternate scenarios for missing data assumptions.

Sensitivity Analyses - FVC in SSc-ILD Subgroup

For the SSc-ILD subgroup, the statistical reviewer conducted the same sensitivity analyses described above for the ITT population.

There were 21 patients with missing FVC data at Week 48 (12 in the placebo arm, 9 in the TCZ arm). Most of the reasons for discontinuation of the double-blind phase of the study were due to withdrawal by patient, which occurred for 11 patients (8 in the placebo arm, 3 in the TCZ arm). Four patients discontinued due to an adverse event (2 patients in each arm).

Sensitivity analysis results from the SSc-ILD subgroup are shown in Appendix Section 15.5.3. Pattern mixture model results are shown in Table 37 and Table 38. The results are consistent with those from the primary analyses for both FVC endpoints and the additional MMRM analysis method.

Figure 37 and Figure 38 contain the ppFVC tipping point analysis results, and Figure 39 and Figure 40 contain the observed FVC endpoint tipping point analysis results. The assumption that patients with missing data in the two arms would have had changes as large as the magnitude of such adjustment values for ppFVC and observed FVC as described in Appendix Section 15.5.3 does not seem plausible, given the fact that such large changes were observed in very few individual patients in the study.

Thus, sensitivity analyses conducted for the two FVC endpoints in the SSc-ILD subgroup demonstrated that the results from the post-hoc analyses were robust to alternate scenarios for missing data assumptions. These sensitivity analysis results for the SSc-ILD subgroup therefore add to the body of evidence in support of TCZ for the treatment of SSc-ILD.

In summary, TCZ use resulted in nominally significant and robust FVC treatment effects, with a greater magnitude of effect, in the SSc-ILD subgroup.

Efficacy Results – Other Endpoints

Time to treatment failure (TTF) was assessed as a key secondary endpoint in Study WA29767. The components of the composite endpoint include death, decline in ppFVC > 10% relative to baseline, relative increase in mRSS ≥ 20% and increase in mRSS of ≥ 5 points, and occurrence of a pre-defined SSc-related serious complication as adjudicated by the CAC. At Week 48, more placebo-treated patients experienced treatment failure than TCZ-treated patients (37 versus 23, 35% versus 22% [Table 11]). Per the Applicant, the median time to treatment failure was not estimable due to the low number of patients with events. These observations resulted in a hazard ratio of 0.63, 95% CI: [0.37, 1.06], nominal p=0.0821. The greatest differences between placebo and TCZ groups were observed in the ppFVC > 10% decline (24% versus 13%, respectively) and mRSS increase > 20% and ≥ 5 points (15% versus 10%, respectively). Differences between other components were due to 2 patients between treatment groups.

Table 11: Study WA29767 Proportion of Patients With Components of Time to Treatment Failure at Week 48 (ITT Population)

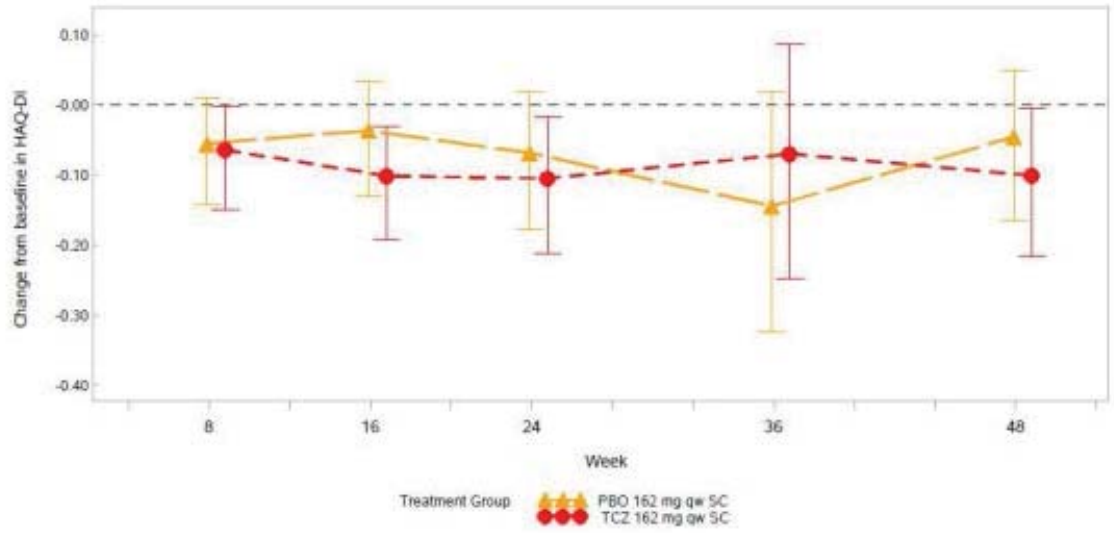
	Number of Patients with Event, n (%)				
	Placebo (N=106)	TCZ (N=104)	HR	95% CI	p-value [a]
Treatment Failure	37 (34.9%)	23 (22.1%)	0.63	0.4, 1.1	0.0821
ppFVC >10% decline	25 (23.6%)	13 (12.5%)	0.55	0.3, 1.1	0.0802
mRSS increase >20% and ≥5%	16 (15.1%)	10 (9.6%)	0.64	0.3, 1.4	0.2609
SSc-related complication	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: Study WA29767 CSR Table 18, p.112

The effect of TCZ on treatment failure was largely driven by the FVC effects. In a post-hoc analysis, when treatment failure did not include the > 10% decline in ppFVC criterion, more placebo-treated patients experienced treatment failure than TCZ-treated patients (19% versus 13%, respectively). Thus, discussion of the TTF endpoint does not provide independent additional support to the efficacy of TCZ on FVC.

Health Assessment Questionnaire-Disability Index (HAQ-DI): Change from baseline at Week 48 in HAQ-DI was also a key secondary endpoint. No significant difference in treatment arms was noted (-0.06 placebo versus -0.11 TCZ, adjusted difference in LSM = -0.05, 95% CI: [-0.19, 0.09]). While the observed results for HAQ-DI are numerically favorable for TCZ at Week 48, the favorable trend was not sustained across the study period (Figure 9). HAQ-DI is a general measure of physical function and may not be expected to accurately reflect the impact of SSc-ILD as the measure was not designed for the context of ILD use (see Section 8.1.1 *Study Endpoints* for additional details regarding HAQ-DI).

Figure 9: Study WA29767 HAQ-DI Mean Change From Baseline by Visit and Treatment Group (ITT Population)



Mean and 95% Confidence Interval are shown on the plot.
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.

Source: Study WA29767 CSR Figure 10, p. 118
Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; PBO, placebo; QW, weekly; SC, subcutaneous; TCZ, tocilizumab

Analyses of endpoints of Patient's Global Assessments and Physician's Global Assessments were also reviewed. Baseline values for both measures were similar across arms (Patient's Global Assessment baseline scores: 59 placebo vs. 54 TCZ; Physician's Global Assessment baseline scores: 60 placebo vs. 59 TCZ). At Week 48, there was no significant change in either of these endpoints (Patient's Global Assessment: -8 placebo vs. -10 TCZ, difference LSM -2 [95% CI: -8.57, 3.70], nominal p=0.43; Physician's Global Assessment: -20 placebo vs. -22 TCZ, difference LSM -2 [95% CI: -8.72, 3.79], nominal p=0.44), where decrease indicates improvement in both measures.

Quantitative Lung Fibrosis (QLF) Scores

Similar to the complementary information thoracic radiography provides to pulmonary function measures in clinical practice, radiographic endpoints in Study WA29767 provide additional support to the FVC results previously discussed. HRCT scans, obtained at baseline and at Week 48, were centrally reviewed and scored based on texture-based analysis (change in fibrosis using pre-specified qualitative and quantitative algorithms). QLF scores were generated for the 5 lobes and the highest score (worst fibrosis) was used for the QLF-LM score (QLF-most affected lobe). QLF scores for the whole lung in patients without ILD at baseline (QLF-WL) as well as those with ILD (QILD-WL) were also calculated.

Change from baseline in QLF for the most affected lobe (QLF-LM) was a pre-specified exploratory analysis. Other analyses conducted by the Applicant were post-hoc (i.e., Van Elteren test for the comparison of median change from baseline). QLF scoring based on HRCT findings were favorable for TCZ over placebo and generally consistent with FVC findings previously discussed. A positive change from baseline value indicated worsening or increased fibrosis. While the results were supportive in terms of the directionality (i.e. positive versus negative), the threshold for meaningful clinical change is unknown. These results for the ITT population and the SSc-ILD subgroup at Week 48 are summarized in Table 12.

Table 12: Study WA29767 Quantitative Lung Fibrosis HRCT Results at Week 48 (ITT Population and SSc-ILD Subgroup)

		Overall		SSc-ILD Subgroup	
		Placebo N=106	TCZ N=104	Placebo N=68	TCZ N=68
QLF-LM		N=66	N=60	N=36	N=35
Change from baseline at week 48	Median	0.25	0	1.35	-0.20
	Mean	0.89	-1.36	1.89	-2.17
Nominal p-value		0.0179*		0.0017*	
QLF-WL		N=81	N=84	N=48	N=54
Change from baseline at week 48	Median	0.10	0	0.40	-0.20
	Mean	0.37	-0.38	0.74	-0.57
Nominal p-value		0.0049*		0.0008*	
QILD-WL		N=80	N=84	N=47	N=54
Change from baseline at week 48	Median	0.40	-0.90	1.60	-1.65
	Mean	0.12	-1.71	1.54	-2.09
Nominal p-value		0.0356*		0.0082*	

Source: Study WA29767 CSR Table 29, p. 132, SCE Table 12, p. 46, statistical reviewer's analysis
*Nominal p-value from Van Elteren test for comparison of medians
Abbreviations: ILD, interstitial lung disease; ITT, intent-to-treat; LM, lobe of most involvement; QLF, quantitative lung fibrosis; SSc, systemic sclerosis; TCZ, tocilizumab; WL, whole lung

Overall, there was improvement in lung fibrosis at Week 48, as assessed by each of the assessments of QLF, for the TCZ treatment group compared to the placebo group (Table 12). All mean and median QLF change from baseline values in placebo patients were positive, whereas all mean and median QLF change from baseline values in TCZ patients were either negative or zero (i.e., without change). These contrasting directionalities (positive versus zero/negative) support the FVC findings that suggested very little to no change in TCZ patients versus worsened restriction in placebo patients. Also, categorical qualitative visual assessments (worse, same, or better) by blinded thoracic radiologists were consistent with the QLF results in that larger proportions of placebo patients had “worse” (11-12% placebo versus 3-4% TCZ) recordings and smaller proportions had “better” (2% placebo versus 9-11% TCZ).

In summary, radiographic results from HRCT assessments captured at the beginning and end of the 48 week treatment period in Study WA29767, while exploratory, are supportive of and consistent with the FVC findings previously discussed.

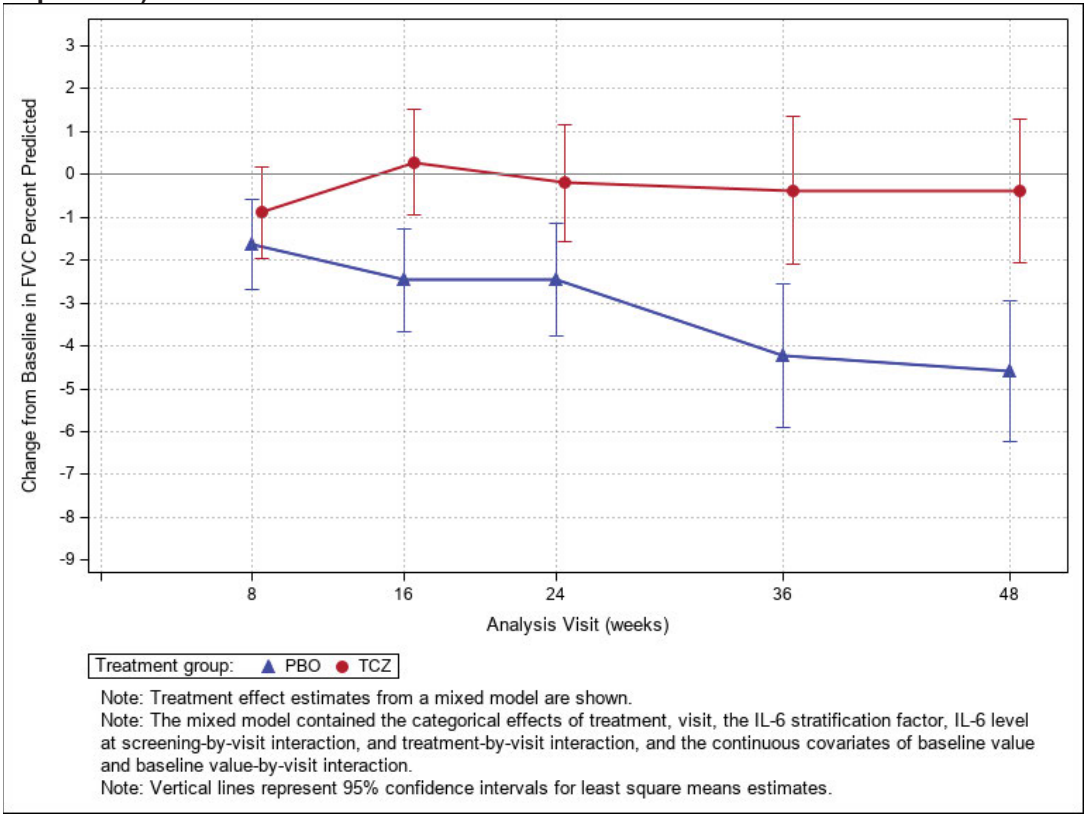
Dose/Dose Response

Dose response was not explored in Study WA29767. A single fixed treatment dose, 162 mg weekly, was used throughout the study. The studied dose and dosing regimen is within the ranges of approved dosing for SC TCZ in RA and GCA.

Durability of Response

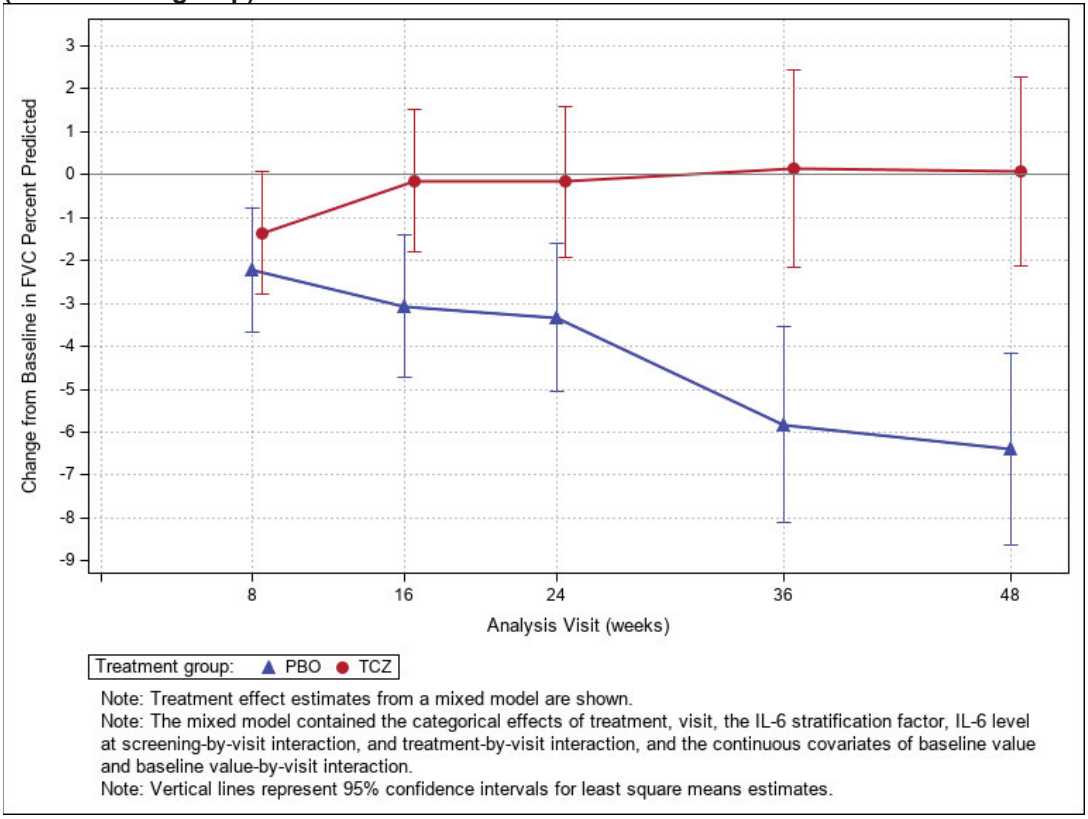
The favorable treatment effect for TCZ over placebo was durable over the 48 week blinded controlled treatment period, as shown in Figure 5 for observed FVC in the ITT population. By Week 48, there was a greater improvement in LSMs observed with TCZ compared to placebo. Similar results were seen in the SSc-ILD subgroup (Figure 6). Figure 10 and Figure 11 show a similar trend for ppFVC for the ITT population and SSc-ILD subgroup, respectively.

Figure 10: Study WA29767 ppFVC Mean Change From Baseline by Visit and Treatment Group (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Figure 11: Study WA29767 ppFVC Mean Change From Baseline by Visit and Treatment Group (SSc-ILD Subgroup)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ILD, interstitial lung disease; PBO, placebo; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Results from the 48 week OLE, while supportive, were not blinded or controlled. As such, the support for the durability of response is primarily based on the 48 week double-blind treatment period.

Persistence of Effect

Study WA29767 was not designed to evaluate persistence of effect. The follow-up period was not of sufficient duration and did not include additional assessments of spirometry to assess persistence of effect. Further, given the biological activity of the drug and its mechanism of action, a persistent drug effect in the absence of use of TCZ would not be expected.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (COA) Endpoints

For discussion of results of endpoints of TTF, HAQ-DI, and QLF, refer to Section 8.1.2 *Efficacy Results – Other Endpoints.* Refer to Other Endpoints section above for discussion of results of Patient's Global Assessment and Physician's Global Assessments.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.1.3. Study WA27788 Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the principles of the Declaration of Helsinki, ICH E6 guidelines, and Good Clinical Practice (GCP). Study documentation and audit certificates were provided by the Applicant.

Data Quality and Integrity

In general, the quality of the data submitted for review was adequate. However, some of the statistical reviewer's results for the analyses of FVC and mRSS differ from results reported in Applicant's CSR and the SCE. On 12-17-2020, the Agency issued an information request to the Applicant, which requested clarification regarding variables used in the MMRM analyses for the FVC endpoints. Although the Applicant provided such clarification, the Applicant's sample statistical software code resulted in discrepancies with their submitted FVC results. The statistical reviewer's independent results matched the results obtained when the Applicant's sample statistical software code was utilized. The FVC and mRSS results in this review are based on the analysis datasets that the Applicant originally submitted on 7-24-2020, which, according to the Applicant, is the most up-to-date version of the study data.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with the investigators.

No investigators or subinvestigators in Study WA27788 had disclosable financial interests.

There were 15 subinvestigators (6.85%) who provided an incomplete form (not all questions were answered) and was determined as an invalid response. The Applicant conducted due diligence in all these cases (two attempts made to obtain appropriate information via two different methods e.g. email and phone) to obtain full disclosure information.

Of the 15 subinvestigators across 8 sites with invalid/incomplete disclosure forms (sites 239621, 239891, 240040, 240234, 240257, 240279, 241140, 252830), the principal investigators from 7 of those sites had no disclosable interests. Enrollment from the 7 sites totaled 31 patients, with two sites (sites 239621 and 241140) accounting for nearly half of these patients (9 and 6 patients, respectively). There were no patients enrolled at the study sites for 7 of the subinvestigators.

The aforementioned 8 sites where principal investigators or subinvestigators did not provide complete financial disclosure were cross-checked with the risk ranking analysis conducted by the Office of Scientific Investigations (OSI) using bioresearch monitoring (BIMO) data obtained to assess site risk for bias. Additionally, the statistical reviewer conducted an analysis on the FVC endpoints assessing the impact from exclusion of the two highest enrolling sites (239621 and 241140). No appreciable change in efficacy results was noted.

Given the double-blind nature of the study, the oversight present for subinvestigators under the principal investigator, the lack of appreciable impact on a key efficacy endpoint for sites with incomplete financial disclosure, and the presence of a global data monitoring committee, it is unlikely that outcomes were influenced by the above financial disclosure information.

Patient Disposition

A total of 141 patients were screened across 35 sites in 5 countries. Of these 141 patients, 87 patients were randomized into the study. All 87 patients received at least one dose of study drug. Screen failures were primarily due to inability to meet eligibility criteria (32 of 55 screen failures). The first patient was randomized on March 13, 2012. The last patient's last visit occurred on June 16, 2015.

Countries with highest to lowest recruitment were as follows: US (41%), Great Britain and Germany (22% each), France (9%), and Canada (6%). Allocation across treatment arms were balanced for each country.

Of the randomized patients, the majority (72%) of patients completed Week 48. Disposition results are summarized in Table 13.

Table 13: Study WA27788 Patient Disposition (All Patients Population)

	Placebo n (%)	TCZ n (%)
Randomized	44	43
Discontinued from study before 48 weeks		
No	33 (75)	30 (70)
Yes	11 (25)	13 (30)
Reasons for discontinuing study		
Subject withdrawal	5 (11)	3 (7)
AE	4 (9)	5 (12)
Death*	0	3 (7)
Other**	2 (5)	2 (5)

Source: Study WA27788 CSR Table 6, p. 42
*One death recorded in placebo arm occurred 133 days after patient withdrew from study
**Other includes: Non-compliance (1 placebo), Physician decision (1 placebo), Loss to follow-up (1 TCZ), lack of efficacy (1 TCZ)
Abbreviations: AE, adverse event; TCZ, tocilizumab

As specified in the clinical study protocol, study treatment discontinuation would lead to study withdrawal. This likely explains the higher discontinuation rate observed in Study WA27788 as compared to Study WA29767.

Protocol Violations/Deviations

In Study WA27788, as there were no per-protocol analyses, no protocol deviations led to exclusion of patients from any analyses.

Through 48 weeks, 33 patients had had major protocol deviations [MPDs] (16 placebo, 17 TCZ), for the following reasons: informed consent issues, eligibility criteria issues, efficacy assessor issues, use of excluded medication issue, safety issues, or other. The most common of these categories for MPDs were related to eligibility criteria baseline HRCT performance (9%), whereas the largest general category for MPDs was eligibility criteria violations/deviations (12%). The next most common MPDs were as follows in order of frequency: informed consent deviation (5%) and other procedural deviation (3%). There were no significant imbalances between treatment arms.

Overall, given the relatively balanced MPDs between treatment arms, the lack of exclusion of MPD patients from any analysis, and the type and frequencies of the MPDs, it is unlikely that MPDs significantly impacted final outcomes.

Demographics and Baseline Characteristics

Overall, given the demographics of the disease studied (SSc), it is not surprising that the enrolled patients were primarily white, middle-aged women, consistent with other SSc trials and the general SSc population. There were no major imbalances in demographics between treatment arms. While the majority of patients were ex-US (59%), the US had the largest enrollment contribution as a single country (36 of 87 patients, 41%). Demographics are summarized by treatment group in Table 14.

Table 14: Study WA27788 Demographic Characteristics (Safety Population)

	Placebo N=44	TCZ N=43
Age (years)		
Age (mean)	48	51
Age (median)	50	50
Gender, n (%)		
Female	35 (80)	32 (74)
Race, n (%)		
White	40 (91)	38 (88)
Asian	1 (2)	1 (2)
Black or African American	2 (5)	4 (9)
Smoking status, n (%)		
Never smoker	27 (61)	21 (49)
Country, n (%)		
US	18 (41)	18 (42)
Ex-US	26 (59)	25 (58)
Canada	4 (9)	1 (2)
Germany	7 (16)	12 (28)
France	4 (9)	4 (9)
Great Britain	11 (25)	8 (19)

Source: Study WA27788 CSR Table 7, p. 47
Abbreviations: TCZ, tocilizumab

Allocation across treatment arms was generally balanced for each country, with the exception of Germany (16% placebo versus 28% TCZ). Baseline disease characteristics, as well as other comorbidities, were also relatively balanced, considering the small sample sizes (Table 15).

Table 15: Study WA7788 Baseline Characteristics (Safety Population)

	Placebo N=44	TCZ N=43
Duration of SSc (days)		
Mean	594	535
Median	336	357
Total mRSS		
Mean	26	26
Median	25	28
Clinician's (Physician's) Global Assessment (VAS)		
Mean	61	64
Median	62	64
Patient's Global Assessment		
Mean	62	60
Median	64	62
Overall HAQ-DI Score		
Mean	1.4	1.3
Median	1.5	1.3
Serum markers		
C-reactive protein (mean) [mg/L]	10.3	10.0
Antibodies		
ANA positive	41 (93)	38 (88)
Anti-centromere positive	0	0
Anti-topoisomerase positive	20 (46)	18 (42)
Pulmonary function		
ppFVC (mean)	82%	80%
ppDLCO (mean)	74%	73%
Prior or concurrent comorbidities, >15% in any arm, n (%)		
Raynaud's phenomenon	28 (64)	27 (63)
GERD	15 (34)	19 (44)
Arthralgia	13 (30)	13 (30)
Hypertension	5 (11)	12 (28)
Skin ulcer	8 (18)	5 (12)
Dysphagia	8 (18)	3 (7)
Anemia	7 (16)	4 (9)
Depression	7 (16)	2 (5)

Source: Study WA27788 CSR Table 8, p. 49, Table from p. 200
Abbreviations: ANA, antinuclear antibodies; DLCO, diffusion in lung of carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; GERD, gastro esophageal reflux disease; HAQ-DI, Health Assessment Questionnaire Disability Index ; mRSS, modified Rodnan skin score; SSc, systemic sclerosis; TCZ, tocilizumab; VAS, visual analog scale

The baseline disease characteristics, including disease duration, mRSS, and c-reactive protein (CRP), were generally similar by treatment group. Presence of anti-topoisomerase antibody was similar by treatment group (placebo 46%, TCZ 42%), and all patients were negative for anti-centromere antibodies. Baseline measures of pulmonary function were also similar by treatment group. A history of ILD, pulmonary fibrosis or SSc lung involvement was reported by 8 (18.2%) placebo treated patients as compared to 5 (11.6%) TCZ-treated patients. Prior or concurrent comorbidities were generally balanced, with minor imbalances in certain conditions (e.g. hypertension) due to small numbers of patients and not likely to have impacted the overall analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medications were generally balanced. All patients had at least one concomitant medication being used, with proton pump inhibitors the most common (91% placebo and 86% TCZ). There were more TCZ patients using (or having used) corticosteroids (58% versus 41%). High dose, IV, and IM corticosteroids were prohibited during the treatment period; there was one patient with a systemic corticosteroid use protocol violation. Therefore, it is unlikely that systemic corticosteroid use impacted the overall analysis despite the slight imbalance in use prior to the 48-week treatment period.

Escape therapy was allowed after Week 24 for worsening of SSc disease. Therapeutic options were methotrexate, hydroxychloroquine, or mycophenolate mofetil (MMF). By Week 48, the completion of the blinded controlled treatment period, of the patients not discontinuing from the study, more placebo patients than TCZ patients had received escape therapy (22% versus 16%, respectively). MMF was the most commonly used escape treatment, used in the majority of placebo patients (6 of 10 patients), but in less than half of TCZ patients (2 of 7). Hydroxychloroquine and methotrexate were used in similar numbers of patients in each treatment group.

Efficacy Results – Primary Endpoint

The primary endpoint for Study WA27788 was change from baseline to Week 24 in the mRSS. However, as mentioned above, the focus of this review is on results at Week 48 rather than at Week 24.

Treatment with TCZ did not result in a statistically significant difference between treatment groups for the change from baseline to Week 24 in the mRSS (adjusted difference in LSM = -2.67, 95% CI: [-5.81, 0.46], p=0.0937). While the observed treatment difference resulted in the failure to reject the null hypothesis of no difference in treatment effect between both groups, it was numerically favorable for TCZ (-1.25 placebo versus -3.93 TCZ).

At Week 48, treatment with TCZ did not result in a nominally statistically significant difference between treatment groups for the change from baseline in the mRSS (adjusted difference in LSM = -3.36, 95% CI: [-7.03, 0.32], nominal p=0.0726). The observed treatment difference was numerically favorable for TCZ (-2.10 placebo versus -5.46 TCZ).

Efficacy Results - FVC in ITT Population

FVC was an exploratory endpoint in Study WA27788. However, as mentioned above, additional ad-hoc analyses for exploratory endpoints, such as FVC, were performed after the study was unblinded at Week 24. These analyses are of interest since FVC results from Study WA27788 are considered supportive for Study WA29767.

TCZ use was associated with a favorable nominally significant treatment difference in ppFVC, as shown in Table 16. The mean decline from baseline in ppFVC at Week 48 was greater in the placebo group (-6.31%) as compared to the TCZ group (-2.04%). Similarly, TCZ use was also associated with a favorable treatment difference in observed FVC; however, p-values were slightly larger than 0.05 and were not nominally significant (Table 17). The mean decline from baseline in FVC in the placebo group was -230 mL, while the mean decline from baseline in the TCZ group was -91 mL.

Table 16: Study WA27788 ppFVC Results at Week 48 (ITT Population)

	Placebo N=44	TCZ N=43
Median change from baseline in ppFVC		
N	26	28
Change from baseline, 95% CI	-4.40 (-8.61, -0.97)	-0.93 (-3.55, 1.71)
P-value for comparison of medians	0.03*	
Difference in medians (TCZ-placebo)	3.47	
Mean change from baseline in ppFVC		
N	26	28
Change from baseline, 95% CI	-6.31 (-8.89, -3.74)	-2.04 (-4.54, 0.47)
Difference in LSM (TCZ-placebo), 95% CI	4.27 (0.68, 7.87)	
P-value for difference in LSM	0.02**	

Source: Statistical reviewer's analysis
*Nominal p-value from comparison of medians using Van Elteren test stratified by joint involvement at the baseline visit
**Nominal p-value from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

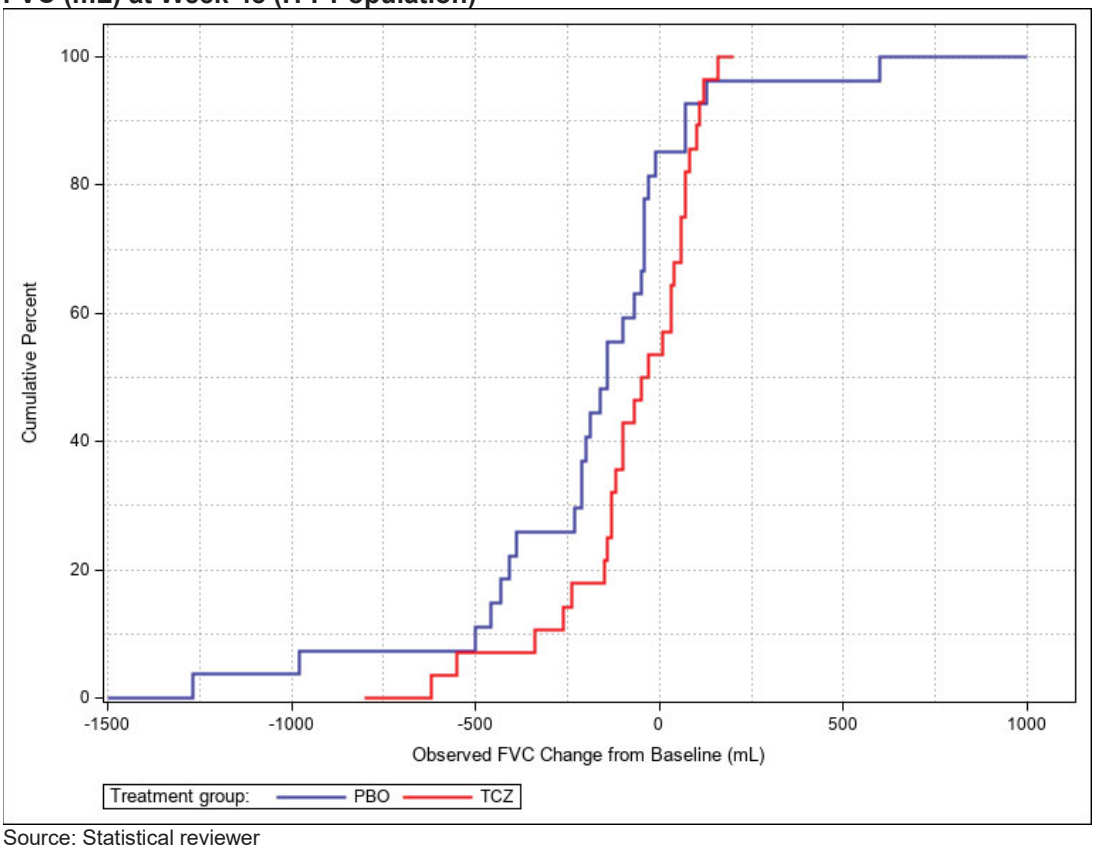
Table 17: Study WA27788 Observed FVC Results at Week 48 (ITT Population)

	Placebo N=44	TCZ N=43
Median change from baseline in FVC (mL)		
N	27	28
Change from baseline, 95% CI	-140 (-210, -40)	-40 (-130, 60)
P-value for comparison of medians	0.05*	
Difference in medians (TCZ-placebo)	100	
Mean change from baseline in FVC (mL)		
N	27	28
Change from baseline, 95% CI	-230 (-330, -130)	-91 (-190, 8)
Difference in LSM (TCZ-placebo), 95% CI	138 (-2, 279)	
P-value for difference in LSM	0.05**	

Source: Statistical reviewer's analysis
*Nominal p-value from comparison of medians using Van Elteren test stratified by joint involvement at the baseline visit
**Nominal p-value from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI: confidence interval; FVC, forced vital capacity; ITT, intent-to-treat; LSM: least squares mean; mL: milliliter; TCZ, tocilizumab

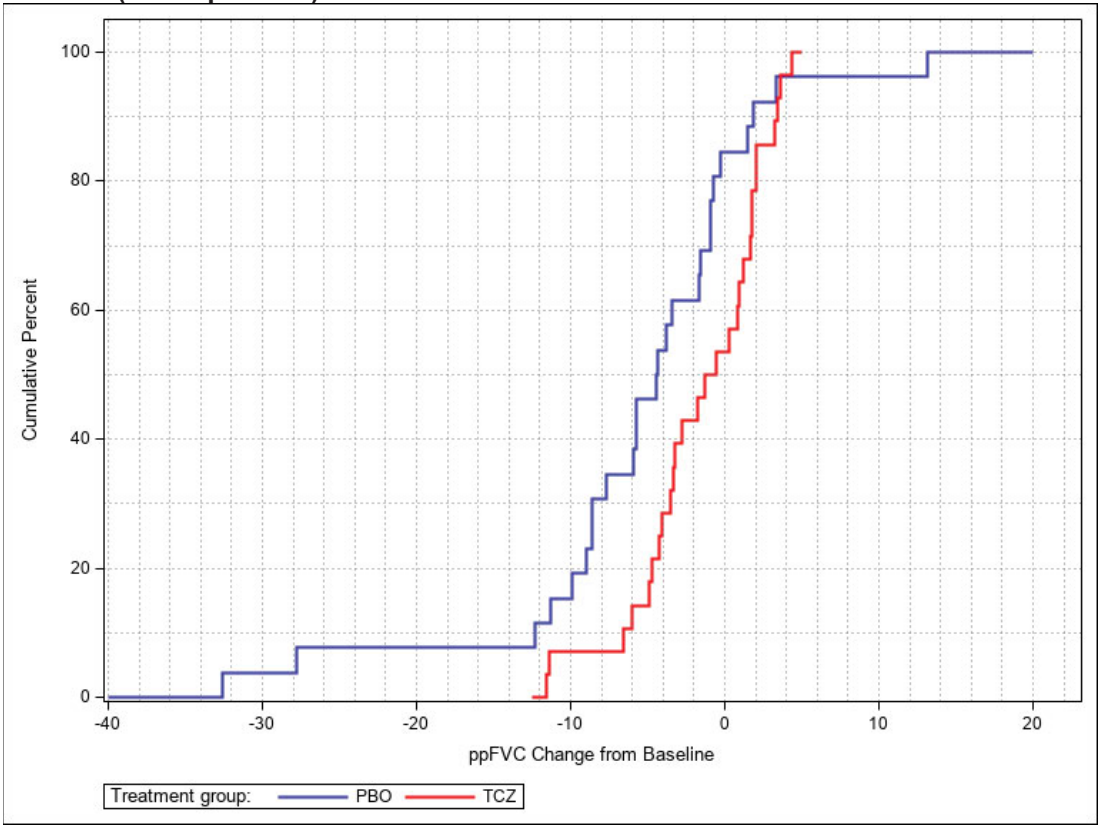
To further examine the consistency of effect on FVC, CDF plots were examined to look at all levels of response at Week 48. Figure 12 and Figure 13 contain CDF plots for observed FVC and ppFVC, respectively, for the ITT population. There was an overall consistent separation across different magnitudes of change in ppFVC but not for observed FVC, which contains an overlap of the CDF curves for both treatment groups at the change from baseline value of ~-500 mL. Two patients and 3 patients in the TCZ and placebo groups, respectively, had an observed FVC change from baseline value ≤ -500 mL. In general, both CDF plots show larger magnitudes of decrease from baseline at Week 48 in the placebo group compared to the TCZ group.

Figure 12: Study WA27788 Cumulative Distribution Plot of Change From Baseline in Observed FVC (mL) at Week 48 (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; mL, milliliter; PBO, placebo; TCZ, tocilizumab

Figure 13: Study WA27788 Cumulative Distribution Plot of Change From Baseline in ppFVC at Week 48 (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Sensitivity Analyses - FVC in ITT Population

The statistical reviewer conducted sensitivity analyses for the ppFVC endpoint in the ITT population in Study WA27788 in order to examine the departures from the assumptions regarding missing data in the Applicant's efficacy analyses. The non-parametric Van Elteren test for the comparison of medians was conducted on observed data and did not have an assumption regarding the underlying distribution of the data. The parametric MMRM for the comparison of means was an additional analysis method and was based on the assumption that data were MAR.

The statistical reviewer's sensitivity analyses included tipping point analyses that were conducted for the ppFVC endpoint in the ITT population, since results from the ppFVC endpoint were nominally significant. In the tipping point analyses, monotone missing data from the placebo and TCZ arms were imputed under an MNAR assumption using the same methods described in Section 8.1.2. Since the MAR assumption cannot be tested, sensitivity analyses based on the MNAR assumption provide a comprehensive examination of the effect of missing efficacy data. Non-monotone missing data were imputed using a MAR assumption as described in Section 8.1.2.

There were 33 patients with missing ppFVC data at Week 48 (18 in the placebo arm, 15 in the TCZ arm). Most of the reasons for discontinuation were due to withdrawal by patient, which occurred for 8 patients (5 in the placebo arm, 3 in the TCZ arm). Seven patients discontinued due to an adverse event (3 in the placebo arm, 4 in the TCZ arm).

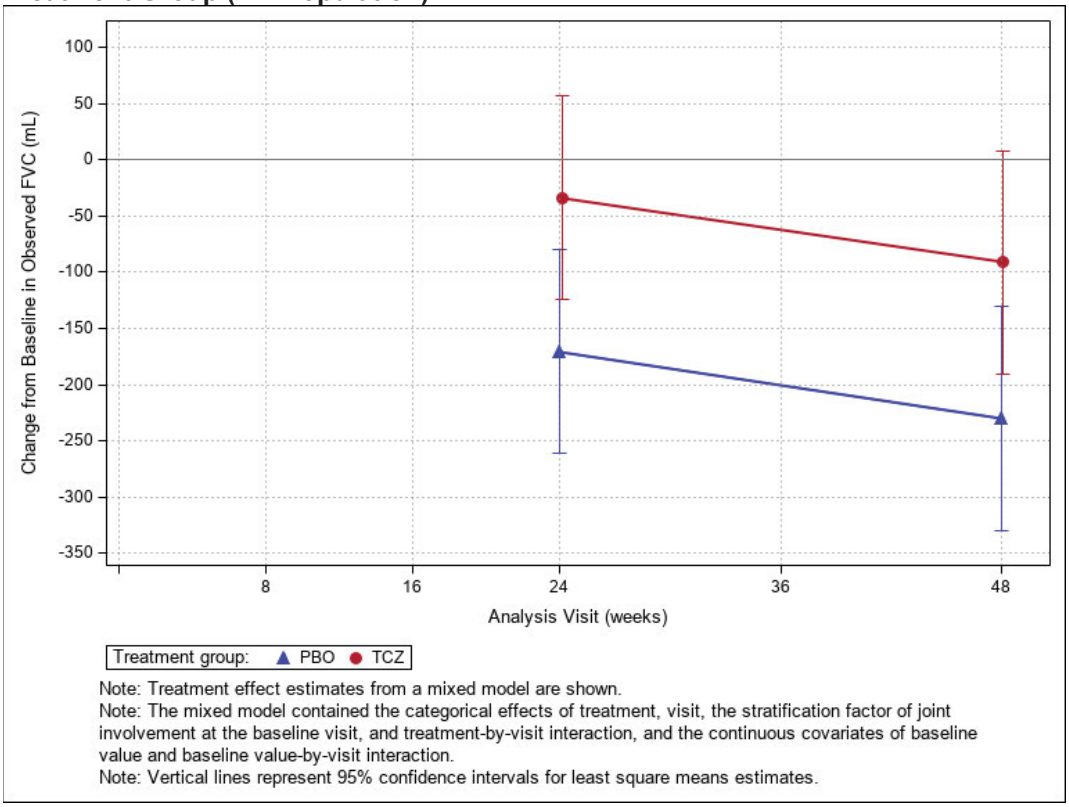
Results from the tipping point sensitivity analyses for the ppFVC endpoint in the ITT population are shown in Figure 41 and Figure 42 in Appendix Section 15.5.4. Some of the adjustment values that tipped the results (i.e., resulted in a loss of nominal statistical significance) may be plausible. For example, the adjustments of -1 to the imputed TCZ values and +1 to the imputed placebo values for the comparisons of means could be plausible assumptions about the missing outcomes.

Thus, the sensitivity analyses conducted for the ppFVC endpoint in the ITT population did not demonstrate convincing robustness of the nominally significant ppFVC analysis results to missing data assumptions.

Durability of Response

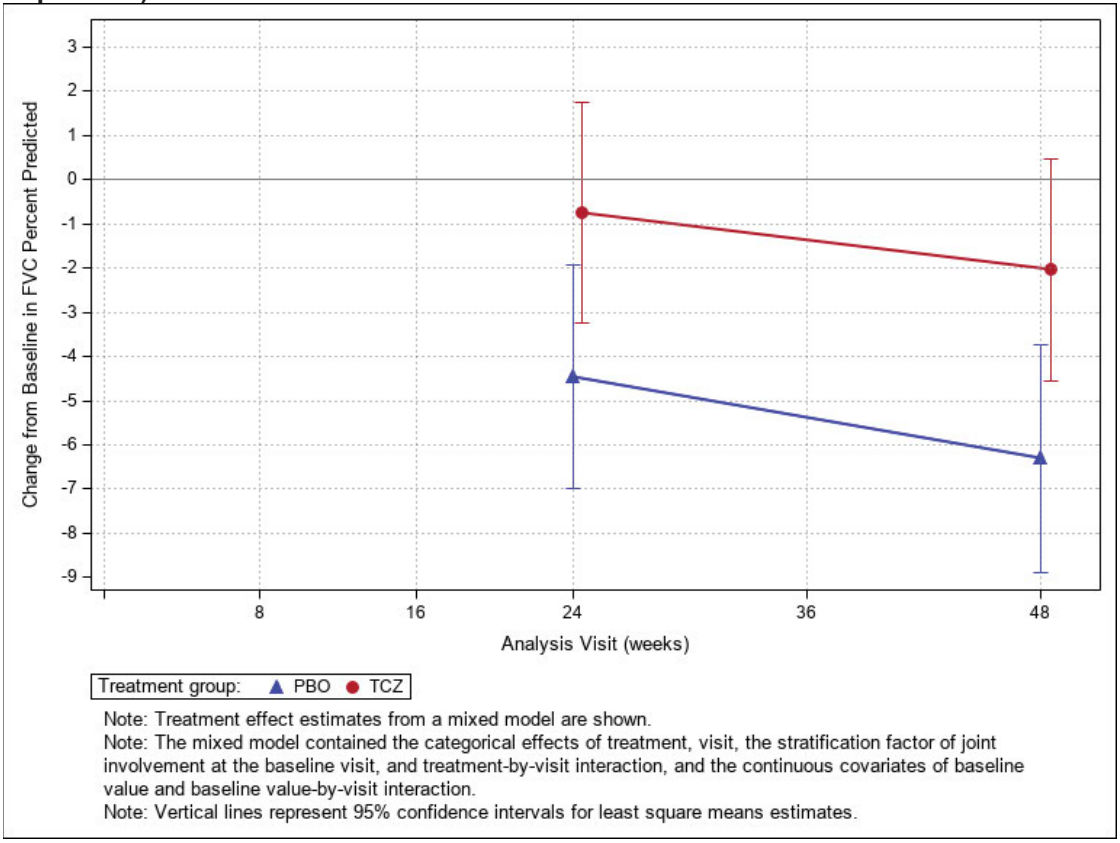
The favorable treatment effect for TCZ over placebo was durable over the 48 week blinded controlled treatment period, as shown in Figure 14 for observed FVC and Figure 15 for ppFVC. FVC was measured in the study at baseline, Week 24, and Week 48. By Week 48, there was a greater improvement in LSMs observed with TCZ compared to placebo; however, the difference in LSMs was nominally statistically significant for ppFVC and not nominally significant for observed FVC.

Figure 14: Study WA27788 Observed FVC (mL) Mean Change From Baseline by Visit and Treatment Group (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; mL, milliliter; PBO, placebo; TCZ, tocilizumab

Figure 15: Study WA27788 ppFVC Mean Change From Baseline by Visit and Treatment Group (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

8.1.4. Assessment of Efficacy Across Trials

The primary evidence for the effectiveness in SSc-ILD in this supplement is derived from two similarly designed multicenter, randomized, double-blind, placebo-controlled studies:

- Study WA29767, a phase 3 study in 212 patients with active SSc, and
- Study WA27788, a phase 2/3 study in 87 patients with active SSc.

Primary Endpoints

In both studies, for the primary endpoint, change in mRSS at Week 48, patients treated with TCZ failed to demonstrate a statistically significant difference from patients treated with placebo.

Secondary and Other Endpoints

In both studies, a consistent clinically relevant improvement was observed on FVC, a pre-

specified secondary endpoint in Study WA29767 and an exploratory endpoint in Study WA27788, in the TCZ treatment groups as compared to the placebo groups.

The results for the other secondary and exploratory endpoints in the two studies do not provide conclusive evidence of effects. For example, there was no significant evidence of effects for PRO measures, such as HAQ-DI and patient global assessment, which were secondary endpoints in both studies. It is a relevant question whether the lack of evidence on the primary endpoint calls into question the likelihood that the observed difference in FVC represents a real treatment effect (e.g., based on the clinical plausibility of a true and detectable effect on FVC but not on other outcomes assessed in the studies). However, there haven't been patient or clinician reported outcomes established to reliably assess direct benefit in programs in fibrotic lung diseases. HAQ-DI is a physical functioning instrument designed for a different context of use (dressing, arising, eating, walking, hygiene, reach, grip, and activities), and it is not established whether or to what extent it could change with changes in FVC. Currently, there are no established PROs to capture such an effect in SSc, SSc-ILD, or in any ILD. Of note, the nintedanib program demonstrated an effect on FVC without effect on secondary endpoints, including mRSS and PROs. Thus, a lack of a detected difference between treatment groups in HAQ-DI may not be surprising and doesn't contradict the results and the meaningfulness of the FVC analyses.

Subpopulations

While the key secondary FVC endpoints in Study WA29767 are considered nominally significant according to the study's statistical testing procedure, the endpoint results are clinically meaningful, particularly in the study's SSc-ILD subgroup. Sensitivity analysis results suggest that the nominal significance of the FVC endpoints in the SSc-ILD subgroup appears to be robust to alternative missing data assumptions. The SSc-ILD subgroup results are further supported by FVC endpoint results in Study 27788, the Study WA29767 overall population and open-label extension, and by the biological plausibility of TCZ's effect on FVC. Thus, when evaluated as part of the existing evidence, and along with the low likelihood of chance FVC findings discussed (Section 8.3), FVC results in the SSc-ILD subgroup appear substantial and convincing. Given that the TCZ effect on pulmonary function was primarily driven by the effect in patients with pulmonary involvement, determined by baseline HRCT imaging, and not in those without SSc-ILD, limiting the indication to patients with SSc-ILD is warranted.

Table 39, Table 40, and Table 41 in Appendix Section 15.5.5 contain exploratory analyses of ppFVC by sex, age, and race subgroups in the Study WA29767 SSc-ILD subgroup. The subgroup analyses are limited by small patient counts, and results should be interpreted with caution. In general, the subgroup analysis results were consistent with the SSc-ILD subgroup results.

Additional Efficacy Considerations

None.

8.1.5. Integrated Assessment of Effectiveness

The primary evidence for the effectiveness in SSc-ILD in this supplement is derived from two similarly designed multicenter, randomized, double-blind, placebo-controlled studies:

- Study WA29767, a phase 3 study in 212 patients with active SSc, and
- Study WA27788, a phase 2/3 study in 87 patients with active SSc.

The baseline demographics and disease characteristics were similar between groups in both studies, and both included a 48-week double-blind treatment period followed by a 48-week open-label extension. Both studies were conducted as planned. In both studies, the primary endpoint, change in mRSS at Week 48, was not met, although favorable trends in tocilizumab patients were observed.

Pulmonary function tests were prospectively collected in both studies. At the time of the trial design of both studies, FVC had not been agreed upon as a meaningful endpoint. Therefore, based on the data from the phase 2/3 study, the Applicant retained mRSS as the primary endpoint for the phase 3 trial and elevated FVC from an exploratory to a key secondary endpoint. However, since that time, the regulatory landscape around FVC has evolved and FVC has been used as the primary basis for traditional approval of products for restrictive pulmonary diseases, including SSc-ILD, as detailed in the section on pertinent regulatory history. Results for ppFVC for the overall population, patients without SSc-ILD and patients with SSc-ILD are shown for the phase 3 study in Table 18. See Section 8.1.3 for the results from the phase 2/3 study, WA27788.

Table 18: Efficacy Results From Study WA29767

	Overall Population		Subgroup Without SSc-ILD*		SSc-ILD Subgroup*	
	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW
Number of patients	**106**	**104**	**36**	**34**	**68**	**68**
Change from baseline in mRSS score at Week 48**						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM (TCZ-placebo), 95% CI	-1.73 (-3.78, 0.32)		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from baseline in ppFVC at Week 48						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM (TCZ-placebo), 95% CI	4.20 (2.00, 6.40)		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from baseline in observed FVC (mL) at Week 48						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM (TCZ-placebo), 95% CI	167 (83, 250)		43 (-60, 145)		241 (124, 358)	

Source: FDA statistician
*Post-hoc results are shown for these subgroups.
**primary efficacy endpoint
Two patients in each group had a baseline ILD status of 'missing' or 'not evaluable'.
Abbreviations: CI, confidence interval; LSM, least squares mean; mRSS, modified Rodnan skin score; PBO, placebo; ppFVC, percent predicted forced vital capacity; QW, weekly; SSc-ILD, interstitial lung disease; TCZ, tocilizumab

The mean ppFVC change from baseline by visit for each treatment group for Study WA29767 was presented in Figure 10.

In both studies, a consistent clinically relevant improvement was observed on FVC in the TCZ treatment groups as compared to the placebo groups. Even though these results would be considered exploratory as the primary endpoint failed to reach statistical significance in both studies, the Division felt these data were clinically relevant and adequate to inform an overall favorable benefit-risk profile based on (1) current understanding of FVC as an endpoint in interstitial lung disease that reliably predicts long-term mortality benefit, (2) quality and persuasiveness of the FVC data, including the magnitude, time course, and consistency of the treatment effect on FVC seen in two similarly designed multicenter, randomized, double-blind, placebo-controlled studies, (3) biological plausibility of immunosuppression with an IL-6 inhibitor, (4) context of unmet medical need for this rare disease, and (5) a clinically relevant effect in FVC was observed in the SSc-ILD subgroup in Study WA29767. Further, the information supported a conclusion that the data constitute substantial evidence of effectiveness based on one adequate and well-controlled clinical study, the phase 3 Study WA29767 with persuasive evidence of efficacy on FVC, and confirmatory evidence provided by the results from the phase 2/3 Study WA27788, supportive HRCT findings, and a reasonable clinical plausibility of immunosuppression with tocilizumab, a product with established efficacy in multiple immune-mediated conditions.

The results for the other secondary and exploratory endpoints in the two studies do not provide supportive evidence of the FVC results. For example, there was no significant evidence of effects for PRO measures such as HAQ-DI and patient global assessment that were secondary endpoints in both studies. However, there haven't been patient or clinician reported outcomes established to reliably assess direct benefit in programs in fibrotic lung diseases. Thus, a lack of a detected difference between treatment groups in HAQ-DI may not be surprising and doesn't contradict the results and the meaningfulness of the FVC analyses.

See Sections 8.3 and 8.4 for further discussion.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety assessment of TCZ in SSc-ILD is based on the safety database from Studies WA29767 and WA27788. The safety population includes all patients who received at least one dose of study drug. Given the similarities of the study designs and populations, pooled analyses of safety are presented below. Due to some differences in the two studies (e.g. Study WA29767 conducted over a wider geographical area, timing of the two studies), individual safety analyses are also shown in addition to the pooled analyses.

The focus in the safety portion of this review is on the pooled population of patients from Studies WA27788 and WA29767. Given the proposed target population of SSc-ILD patients, safety analyses for this subgroup from Study WA29767 are also presented. It is worth noting that although SSc-ILD could not be clearly identified in patients in Study WA27788 (due to lack of HRCTs at baseline), the population in Study WA27788 included patients with decreased lung function, and the eligibility criteria between the two studies (WA27788 and WA29767) were similar. Therefore, the results from WA27788 provide relevant information on the safety of TCZ in SSc and SSc-ILD.

AE analyses are based on number of patients with AEs rather than number of events.

Although some patients were followed beyond 48 weeks (continued in the open-label extension [OLE]), the primary focus of this safety evaluation is the 48 week double-blind treatment period. Pertinent findings from the OLE are discussed when relevant.

8.2.2. Review of the Safety Database

Overall Exposure

Overall, across Studies WA27788 and WA29767, 147 patients were exposed to SC TCZ 162 mg weekly and 150 patients received SC placebo weekly. Over the 48 week blinded and controlled treatment period, mean exposure in Study WA27788 was slightly lower than WA29767. The median exposure between the two treatment arms in both Studies WA27788 and WA29767 was similar (337 days). These exposure results are summarized in Table 19.

Table 19: Studies WA27788 and WA29767, Exposure

	WA27788		WA29767	
	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104
Duration of exposure				
Mean duration (days)	278	274	304	309
Median duration (days)	337	337	337	337
Range (min-max, days)	30-344	15-378	8-400	15-365
Duration of exposure, categories, (n, %)				
≤3 months	5 (11)	5 (12)	3 (3)	7 (7)
>3-6 months	5 (11)	6 (14)	10 (9)	2 (2)
>6-9 months	1 (2)	1 (2)	6 (6)	4 (4)
>9-12 months	33 (75)	31 (72)	85 (80)	91 (88)
>12 months	0	0	2 (2)	0
Number of doses				
Mean	38	37	42	42
Median	47	46	47	47
Patients with at least one missed dose, (n,%)	29 (66)	30 (70)	70 (66)	63 (61)

Source: Study WA29767 CSR, Table 34, p. 149; SCS Table 4, p.19; Study WA27788 CSR week 48, Table 16, p. 80, Reviewer verified
Abbreviations: TCZ, tocilizumab

While there were slightly more patients in Study WA27788 with an exposure ≤ 6 months, the majority of patients in both studies had a duration of exposure >9 months (>72%), generally balanced by treatment arms by study. The median number of doses was similar in both treatment arms in both studies. There were generally similar percentages of patients with at least one missed dose in both studies, across both treatment arms.

Pertinent to this review, the exposure for the SSc-ILD subgroup of patients from Study WA29767 was also analyzed and found to be similar to the exposure in the overall SSc-ILD population enrolled in WA29767 described above, with the majority of patients having >9 months exposure and with no notable treatment arm imbalances (reviewer analysis, not shown).

Overall, patients in each treatment group in both studies, including the SSc-ILD subgroup of Study WA29767, received similar numbers of doses and durations of treatment. The exposure

analysis results do not raise concerns for pooling safety results from both studies, nor do they raise concerns for significant intolerability of TCZ in the SSc population, or the SSc-ILD subgroup.

Adequacy of the Safety Database

The sample size was appropriate for the population and objectives of the study, in the context of SSc being an orphan disease. The types of safety assessments conducted were also reasonable given the known AEs of tocilizumab and for the patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no specific concerns regarding data integrity and submission quality as they relate to the safety assessment.

Categorization of Adverse Events

The definitions used for adverse events (AEs) and serious AEs (SAEs) were per 21 CFR 312.32. Within the 48 week treatment period, all AEs that occurred after the first dose of study drug were considered 'treatment-emergent.' AEs that worsened during the treatment period (even if starting prior to first dose of study drug) were also considered 'treatment-emergent' (provided data supporting this observation, such as start date and worsening date, was present). All AEs that occurred during the studies until 8 weeks after the last dose of study drug or completion of the final study visit were reported.

Adverse events of special interest (AESI) were defined by Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries or Adverse Event Grouped Terms as defined by Applicant Drug Safety department, based on the known safety profile of TCZ and safety concerns in the SSc population, and include:

- Infections (Serious and All infections)
- Opportunistic infections
- All and Serious Hepatic Events
- Laboratory Abnormalities: Neutropenia, Thrombocytopenia, and Lipid changes
- Hypersensitivity Reactions, including Anaphylaxis
- Injection Site reactions
- Malignancies
- Stroke
- Myocardial Infarction
- Gastrointestinal Perforations
- All and Serious Bleeding events
- Demyelinating disorders

Injection site reactions 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 that were not deemed unrelated to study drug.

All AEs were assessed for seriousness, severity, and causality. AEs were graded by the NCI CTCAE scale (version 4.0 for Study WA29767 and version 4.02 for Study WA27788), graded 1 to 5 (1: mild; 2: moderate; 3: severe; 4: life-threatening; 5: death). In this categorization methodology, mild indicates asymptomatic or awareness of symptoms but tolerated and without intervention; moderate indicates minimal or noninvasive intervention needed with some age-appropriate ADL limitation; severe indicates disabling, requiring hospitalization or prolonging hospitalization; life-threatening indicates urgent intervention needed.

MedDRA version 16.1 was initially used in Study WA27788 with subsequent updated versions used as updated CSRs were released (version 17.0, 18.0). Similarly, for Study WA29767, version 20.1 was initially used with later updated CSRs using updated MedDRA versions (21.1). The Summary of Clinical Safety, the most recent document provided in the current submission, used version 22.1. Datasets provided by the sponsor (and used for reviewer analyses) used version 22.1.

Routine Clinical Tests

Clinical laboratory evaluations in both studies included tests in the following categories: hematology, biochemistry, coagulation, lipids, serology, acute-phase reactants, urinalysis tests.

Specific tests within the above noted categories are further delineated below:

- Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, WBC count, RBC count, platelet count, absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Biochemistry: BUN or urea, uric acid, creatinine, random glucose, potassium, sodium, chloride, calcium, phosphorus, total protein, albumin, creatine phosphokinase, C3, C4, creatine clearance, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total bilirubin
- Serum lipids: fasting total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Serology: anti-nuclear antibodies, SSc-specific auto-antibodies (e.g., anti-PM/Scl, anti-topoisomerase, anti-RNA polymerase, anti-histone, anti-U1 snRP, and anti-centromere), hepatitis B surface antigen, and hepatitis C antibody
- Acute phase reactants: CRP, ESR,
- Coagulation: international normalized ratio, partial thromboplastin time, prothrombin time
- Urinalysis: semi-quantitative measurements of pH, glucose, red blood cells, white blood cells, protein, nitrite, pregnancy testing (dipstick, serum testing for confirmation); microscopic analysis if indicated (erythrocytes, leukocytes, casts, crystals, bacteria)

8.2.4. Safety Results

Overall Summary of Adverse Events

In the 48 week blinded, controlled treatment period, the majority of patients in both treatment arms experienced at least one AE. In the pooled safety data, deaths were similar by treatment arm. A greater proportion of patients in the pooled placebo group experienced SAEs, treatment discontinuations, and treatment interruptions as compared to TCZ-treated patients, while a greater proportion of TCZ-treated patients experienced at least one AE. Similarly, the SSc-ILD subgroup was generally consistent with the overall safety in Study WA29767. This is summarized in Table 20.

Table 20: Overall Safety Summary, Both Studies and SSc-ILD Subgroup, 48 week Treatment Period, Safety Population

	WA27788		WA29767		Pooled WA27788 and WA29767		SSc-ILD Subgroup From WA29767	
	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147	Placebo N=68	TCZ N=68
Patients with any AE	40 (91)	42 (98)	82 (77)	89 (86)	122 (81)	131 (89)	57 (84)	63 (93)
Patients with AEs leading to treatment withdrawal	5 (11)	6 (14)	11 (10)	6 (6)	16 (11)	12 (8)	9 (13)	6 (9)
Patients with AEs leading to dose modification or interruption	10 (23)	13 (30)	27 (26)	20 (19)	37 (25)	33 (22)	19 (28)	15 (22)
Patients with SAEs	15 (34)	14 (33)	18 (17)	13 (13)	33 (22)	27 (18)	15 (22)	9 (13)
Deaths	1 (2)	3 (7)	3 (3)	1 (1)	4 (3)	4 (3)	3 (4)	1 (2)

Source: SCS Table 24, p.74; SCS Table 6, p.26; reviewer verified
Abbreviations: AE, adverse event; SAE, serious adverse event; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Deaths

In this section, deaths occurring in the 48 week double blind controlled treatment period from Studies WA29767 and WA27788 are reviewed as well as deaths from the OLE. As previously noted, treatment emergent (on-treatment) AEs were defined as AEs occurring any time after initiation of study drug (no time window cutoff for determining TE status). As a result, all deaths are considered on-treatment deaths (no comparison of on-treatment to on-study deaths).

There were 8 deaths in the 48 week DB treatment period, 4 in each study, and balanced between treatment arms. There were two deaths in the OLE, also balanced by treatment arm. Death narratives for TCZ treated patients are discussed below Table 21.

Table 21: Deaths From Studies WA27788 and WA29767, Double Blind and Open-Label Treatment Periods

	Patient ID#	Study Arm	Age	Sex	Site	Study Day of Death	Treatment Duration	AE Leading to Death
Double Blind Period								
WA29767	(b) (6)	TCZ	31	F	POL	(b) (6)	78	Unknown (death)
		PBO	41	M	POL		99	Cardiac failure, chronic
		PBO	68	F	GBR		99	Myocarditis
		PBO	59	F	MEX		10	MI
WA27788		TCZ	50	M	CAN		169	Arrhythmia
		PBO	68	F	FRA		51	Cardiac failure
		TCZ	69	F	FRA		107	Lung infection**
		TCZ	32	F	USA		232	Multi-organ failure
Open-Label Period*								
WA29767		PBO	34	M	USA		357	Brain injury
		TCZ	52	F	POL		365	Pulmonary hypertension

Source: Narrative reviews, WA29767 Final week 96 CSR p.726, reviewer verified
* there were no deaths in the open-label period for study WA27788
** determined by investigator to be related
Abbreviations: AE, adverse event; CAN – Canada; DB – double blind, F- female, GBR – Great Britain, M – male, MEX – Mexico, MI – myocardial infarction, OLE – open-label extension, PBO – placebo, POL – Poland, R – investigator determined to be related to study drug; TCZ – tocilizumab

In the double blind treatment period for Study WA29767, there was one TCZ arm death (patient (b) (6)). This was a 31 year old Polish female with SSc of nearly 6 months duration who was randomized to TCZ on 9-22-16. She had a history of GERD, vitamin D deficiency, and hepatic steatosis. At screening, she was tachycardic but an echo revealed normal left ventricular ejection fraction (LVEF) and no PAH. On 12-6-16 (study day 76) she developed depression (grade 1). She received her last dose on 12-8-16 (study day 78), and died on (b) (6) (study day (b) (6)). The death was reported by the family and no information was provided as to the cause of death or autopsy. The sponsor noted that numerous requests for information were sent with no further information obtained. Of note, this patient was in the SSc-ILD subgroup from Study WA29767.

In the double blind treatment period for Study WA27788, there were three deaths in the TCZ arm (patients (b) (6), (b) (6), and (b) (6)):

- Patient ID# (b) (6) was a 50 year old Canadian male with SSc of 8 months duration randomized to TCZ on 7-25-12. His medical history included duodenal ulcer, arthralgia, GERD, Raynaud's, dysphagia, and hypertension. His treatment with prednisone ongoing for 9 months prior to study entry was continued at 10 mg daily for his SSc. Of note, the patient had a normal electrocardiogram on study day 13. The last dose of medication (25th dose) was given on 1-9-13 (study day 169) at which time he had no new medical issues and unremarkable laboratory tests. He was reported to have died on (b) (6) (study day (b) (6)), however, the exact date of death was unknown. He had been found in an armchair deceased with the television turned on. While the cause of death was reported as "malignant arrhythmia", details were not available and no autopsy was performed.
- Patient ID# (b) (6) was a 69 year old French female with SSc of 8 months duration randomized to TCZ on 6-6-13. Her medical history included dyslipidemia, lichen sclerosis, cataracts, and glaucoma. She had tried hydroxychloroquine, phototherapy, and methotrexate for her SSc prior to enrolling. She had a normal CXR at screening (4-22-13) and normal WBC, lymphocytes and neutrophils at time of randomization. On 9-12-13 (study day 99) she had dyspnea, with her last dose (17th) of study medication given on 9-20-13 (study day 107). She was hospitalized (b) (6) (study day (b) (6)) for altered mentation and dyspnea and diagnosed with a lung infection. At that time she was hypothermic, had intercostal retractions and paradoxical respirations and found to have profound respiratory acidosis (pH 6.98, pCO2 86). She became asystolic and died, with no autopsy performed.
- Patient ID# (b) (6) was a 32 year old US female with SSc of 4 years duration randomized to TCZ on 1-29-13. Her medical history included Raynaud's, dyspepsia, anemia, sclerodactylia, and joint pains. She was receiving methotrexate for her SSc. At screening, the patient had anemia despite iron supplementation, but no other significant cardiopulmonary issue identified. The patient received 31 doses of study drug up to 9-17-13 (study day 232). On (b) (6) (b) (6) (study day (b) (6)) she developed dyspnea and hematemesis and was hospitalized for an upper gastrointestinal bleed. An EGD showed gastritis and an echo showed low EF. On (b) (6) (b) (6) (study day (b) (6)), a pericardiocentesis was performed for a pericardial effusion, leading to endotracheal intubation and mechanical ventilation ((b) (6), study day (b) (6)). Within 24

hours the patient had multiorgan failure and died (b) (6) (study day (b) (6)).

In the open label extension period (Study WA29767), the single death in the TCZ arm was in a 52 year old Polish female with GERD, depression, osteoporosis, hyperlipidemia, and SSc of approximately 4 months duration. Baseline therapy included methylprednisolone and codeine, and the patient had received MTX in the past. Vital signs at screening were stable. She was randomized to and received her first dose of TCZ on 4-25-2016. Of note, an echocardiogram one month after screening (3-17-16) revealed a normal LVEF and an estimated PASP of 30 without mention of other signs suggestive of RV overload or pulmonary hypertension (RVH, systolic flattening of the interventricular septum, RAE, tricuspid regurgitation, pulmonic valve insufficiency, PA dilation). After receiving 11 treatments of TCZ, the patient was hospitalized for heart failure on (b) (6) (study day (b) (6)). An echocardiogram revealed an LVEF of 21%, RV dysfunction, pulmonary hypertension, and tricuspid regurgitation. She was treated with heart failure therapy and discharged on (b) (6) (study day (b) (6)). During the hospitalization, her treatment arm had been unblinded, treatment with TCZ interrupted, and MMF initiated for SSc. An echo on study day 94 (7-27-2016) normalized and her study treatment (TCZ already unblinded) was discontinued. She completed the DB period (having discontinued TCZ on study day 94) but received her first dose of open-label TCZ on 4-3-17 (study day 344). After receiving 4 open-label treatments in the OLE, the patient had a nearly identical presentation and hospital course to her prior heart failure hospitalization. She was hospitalized on (b) (6) (study day (b) (6)), had an echo with decreased EF and elevated pulmonary pressures, and was treated with a good response. Hospital medications were stopped in preparation for discharge on study day (b) (6) and (b) (6) (2 days after admission). The patient died on study day (b) (6) (b) (6)). An autopsy showed findings consistent with SSc as well as focal ischemic changes in the myocardium.

Given the focus in this review on the SSc-ILD subgroup, a reviewer analysis of deaths in this subgroup was conducted. The deaths noted above from Study WA29767 were all in patients with SSc-ILD. Thus, there were 3 placebo treated SSc-ILD patient deaths and 1 TCZ treated patient who died (patient (b) (6) discussed above). No difference in deaths is noted in the SSc-ILD subgroup.

In summary, the majority of the death narratives described above for the TCZ-treated patients describe a cardiac etiology to death. However, there were also 4 cardiac-related deaths in the placebo treated patients. Cardiac disease, including heart failure and cardiac arrhythmia, are two of the primary causes of SSc-related deaths. The aforementioned case (patient ID# (b) (6)) with lung infection leading to death was thought to be related to TCZ by the investigator; the risk of serious infections is included as a boxed warning in TCZ labeling.

Overall, the types and frequencies of AEs leading to death were balanced by treatment group, and consistent with the known safety profile for TCZ.

Serious Adverse Events

Overall, in the pooled safety population, 20% of patients had serious adverse events (SAEs), largely driven by higher frequencies of SAEs in Study WA27788 as compared to Study WA29767 (33% versus 15%). In each study, as well as in the pooled population, SAEs were reported by similar or fewer proportions of patients in the TCZ treatment arms as compared to the placebo arms. SAEs from both studies, the pooled analysis, and the SSc-ILD subgroup are summarized in Table 22.

Table 22: Studies WA27788 and WA29767, Serious Adverse Events, Week 48, >1 Patient in Any Pooled Arm (PT), Safety Population

	WA27788		WA29767		Pooled WA27788 and WA29767		SSc-ILD Subgroup From WA29767*	
SOC/PT	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147	Placebo N=68	TCZ N=68
Patients with at least one SAE	15 (34)	14 (33)	18 (17)	13 (13)	33 (22)	27 (18)	15 (22)	9 (13)
Infections and Infestations	1 (2)	9 (21)	7 (7)	2 (2)	8 (5)	11 (8)	8 (12)	3 (4)
Pneumonia	0	2 (5)	3 (3)	0	3 (2)	2 (1)	3 (4)	0
Infected skin ulcer	0	2 (5)	1 (1)	0	1 (1)	2 (1)	1 (1)	0
Osteomyelitis	0	2 (5)	0	1 (1)	0	3 (2)	0	1 (1)
Cardiac disorders	5 (11)	1 (2)	6 (6)	2 (2)	11 (7)	3 (2)	4 (6)	1 (1)
Acute myocardial infraction	1 (2)	0	1 (1)	0	2 (1)	0	1 (1)	0
Skin and subcutaneous tissue disorders	1 (2)	2 (5)	3 (3)	1 (1)	4 (3)	3 (2)	1 (1)	0
Skin ulcer	1 (2)	2 (5)	1 (1)	0	2 (1)	2 (1)	0	0
Gastrointestinal disorders	4 (9)	1 (2)	1 (1)	0	5 (3)	1 (1)	1 (1)	0
Musculoskeletal and connective tissue disorders	2 (5)	2 (5)	1 (1)	1 (1)	3 (2)	3 (2)	1 (1)	0
Scleroderma	1 (2)	0	1 (1)	0	2(1)	0	1 (2)	0
Renal and urinary disorders	2 (5)	0	1 (1)	2 (2)	3 (2)	2 (1)	1 (1)	0
Acute kidney injury	1 (2)	0	1 (1)	0	2 (1)	0	1 (1)	0
Blood and lymphatic system disorders	1 (2)	1 (2)	2 (2)	0	3 (2)	1(1)	2 (3)	0
General disorders and administration site conditions	0	2 (5)	1 (1)	1 (1)	1 (1)	3 (2)	1 (1)	1 (1)
Neoplasms benign, malignant and unspecified	0	0	2 (2)	2 (2)	2 (1)	2 (1)	2 (3)	2 (3)
Vascular disorders	2 (5)	1 (2)	0	0	2 (1)	1 (1)	0	0
Nervous system disorders	2 (5)	0	0	0	2 (1)	0	0	1 (1)

Source: Reviewer Analysis
*In the SSc-ILD subgroup, one event each for the following PTs are not shown: pelvic inflammatory disease, wound infection, cardiac failure, B-cell lymphoma, breast cancer, death, weight decreased, hypokinesia (TCZ patients); pyelonephritis chronic, respiratory tract infection, sepsis, soft tissue infection, atrial f brillation, cardiac failure chronic, myocarditis, benign bone neoplasm, lung adenocarcinoma, anemia megaloblastic, lymphadenopathy mediastinal, pain, ileus paralytic, scleroderma, pleural effusion, ecchymosis (placebo patients). Raynaud's
Abbreviations: PT, preferred term; SAE, serious adverse event; SOC, system organ class; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

There were generally fewer SAEs in TCZ-treated patients as compared to placebo (pooled studies: 18% TCZ versus 22% placebo). This was true across studies and in the SSc-ILD subgroup. However, when focusing on particular system organ classes (SOC), the Infections and Infestations SOC revealed an imbalance disfavorable for TCZ (pooled: 8% TCZ versus 5% placebo), largely driven by Study WA27788 results.

In Study WA27788, there were more patients with pneumonias, infected skin ulcers, and osteomyelitis in TCZ-treated patients as compared to placebo (2 TCZ patients each versus 0 placebo). The higher incidence of serious infections for TCZ treated patients in Study WA27788 was not seen in Study WA29767 (7% placebo versus 2% TCZ), nor in the SSc-ILD subgroup (4% TCZ versus 12% placebo). Serious infections are further discussed under section 8.2.5 *Infections* below.

SAEs in other SOCs were generally balanced or lower in the TCZ-treatment group as compared to the placebo group. Given the focus in this review on the SSc-ILD population, all SAEs in this subgroup were further explored as shown in Table 23.

Table 23: SAEs, SSc-ILD Subgroup From Study WA29767, SOCs With >1 Patient Any Arm

	Placebo N=68	TCZ N=68
Patients with at least one SAE	15 (22)	9 (13)
Infections and Infestations	7 (10)	2 (3)
Pneumonia	3 (4)	0
Infected skin ulcer	1 (2)	0
Osteomyelitis	0	1 (2)
Pelvic Inflammatory disease	0	1 (2)
Pyelonephritis chronic	1 (2)	0
Respiratory tract infection	1 (2)	0
Sepsis	1 (2)	0
Soft tissue infection	1 (2)	0
Wound infection	0	1 (2)
Cardiac Disorders	5 (7)	1 (2)
Atrial Fibrillation	1 (2)	0
Cardiac failure	0	1 (2)
Cardiac failure chronic	1 (2)	0
Microvascular coronary artery disease	1 (2)	0
Myocarditis	1 (2)	0
Myocardial infarction	1 (2)	0
Blood and Lymphatic system disorders	2 (3)	0
Anemia megaloblastic	1 (2)	0
Lymphadenopathy mediastinal	1 (2)	0
Neoplasms Benign, malignant and unspecified	2 (3)	2 (3)
B-cell Lymphoma	0	1 (2)
Benign bone neoplasm	1 (2)	0
Breast cancer	0	1 (2)
Lung adenocarcinoma	1 (2)	0

Source: SCS Supporting data presentations, pp.821-822
Abbreviations: SAE, serious adverse event; SOC, system organ class; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

In the SSc-ILD subpopulation, there were no concerning SAE imbalances in AEs based on SOC or preferred terms. Serious infections were reported by fewer TCZ-treated patients (4%), compared to placebo treated patients (12%).

As the SSc population may be at risk for different serious infections than the RA or GCA populations (particularly skin, soft tissue, and osteomyelitis infections) and because preferred terms for skin and soft tissue infections may overlap (e.g. infected skin ulcer and skin ulcer), a reviewer analysis was performed broadly grouping various possibly overlapping terms (infected skin ulcer, osteomyelitis, skin necrosis, skin ulcer, soft tissue infection). This analysis was limited to serious infections; however, a similar analysis was performed for all treatment-emergent adverse events (TEAEs), not just SAEs, and is discussed in *Treatment Emergent Adverse Events and Adverse Reactions.* These reviewer analyses did not reveal any new safety signals.

In summary, there were no new concerning safety findings from the SAE analyses discussed above. Serious infections were slightly more common in TCZ-treated patients than placebo, consistent with the known safety profile of TCZ.

Treatment Discontinuations, Modifications, or Interruptions Due to Adverse Effects

In the pooled safety population from Studies WA27788 and WA29767, AEs leading to drug withdrawal occurred in 9% of patients, whereas dose interruption (or modification) was more common (24%). TCZ was generally well tolerated with drug withdrawals occurring at similar or lower frequencies than placebo. Similarly, drug interruptions were slightly less frequent in TCZ treated patients. These results are summarized in Table 24.

Table 24: Studies WA27788 and WA29767, Treatment Withdrawals and Interruptions, Week 48, > 1 Patient in Any Pooled Arm (SOC)

	Study WA27788		Study WA29767		Pooled Studies		SSc-ILD Subgroup	
SOC/PT	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147	Placebo N=68	TCZ N=68
Patients with ≥1 AE leading to drug withdrawal, n (%)	5 (11)	6 (14)	11 (10)	6 (6)	16 (11)	12 (8)	9 (13)	6 (9)
Cardiac disorders	1 (2)	0	2 (2)	1 (1)	3 (2)	1 (1)	2 (3)	1 (1)
Cardiac failure	1 (2)	0	0	1 (1)	1 (1)	1 (1)	0	1 (1)
Cardiac failure chronic	0	0	1 (1)	0	1 (1)	0	1 (1)	0
Myocarditis	0	0	1 (1)	0	1 (1)	0	1 (1)	0
Infections and infestations	0	2 (5)	2 (2)	1 (1)	2 (1)	3 (2)	2 (3)	1 (1)
Pneumonia	0	0	1 (1)	0	1 (1)	0	1 (1)	0
Pulmonary tuberculosis	0	0	0	1 (1)	0	1 (1)	0	1 (1)
Sepsis	0	0	1 (1)	0	1 (1)	0	1 (1)	0
Infected skin ulcer	0	1 (2)	0	0	0	1 (1)	0	0
Osteomyelitis	0	1 (2)	0	0	0	1 (1)	0	0
Neoplasms benign, malignant and unspecified	0	0	0	2 (2)	0	2 (1)	0	2 (3)
B-cell lymphoma	0	0	0	1 (1)	0	1 (1)	0	1 (1)
Breast cancer	0	0	0	1 (1)	0	1 (1)	0	1 (1)
Respiratory, thoracic and mediastinal disorders	1 (2)	1 (2)	2 (2)	0	3 (2)	1 (1)	2 (3)	0
Pneumonitis	0	0	1 (1)	0	1 (1)	0	1 (1)	0
Interstitial lung disease	0	1 (2)	1 (1)	0	1 (1)	1 (1)	1 (1)	0
Pulmonary fibrosis	1 (2)	0	0	0	1 (1)	0	0	0
Patients with ≥1 AE leading to dose interruption[1], n (%)	10 (23)	13 (30)	27 (26)	20 (19)	37 (25)	33 (22)	19 (28)	15 (22)
Infections and infestations	5 (11)	9 (21)	20 (19)	16 (15)	25 (17)	25 (17)	14 (21)	12 (18)
Herpes zoster	1 (2)	1 (2)	4 (4)	2 (2)	5 (3)	3 (2)	3 (4)	1 (1)
UTI	0	0	3 (3)	2 (2)	3 (2)	2 (1)	1 (1)	1 (1)
URTI	0	0	1 (1)	2 (2)	1 (1)	2 (1)	0	2 (3)
Infected skin ulcer	2 (5)	2 (5)	0	2 (2)	2 (1)	4 (3)	0	2 (3)
Latent TB	0	0	0	2 (2)	0	2 (1)	0	0
Pneumonia[2]	2 (5)	0	2 (2)	0	4 (3)	0	2 (3)	0
Nasopharyngitis	0	2 (5)	0	1(1)	0	3 (2)	0	1 (1)
Investigations	2 (5)	0	6 (6)	5 (5)	8 (5)	5 (3)	4 (6)	4 (6)
Liver function test abnormality[3]	2 (5)	0	6 (6)	5 (5)	8 (5)	5 (3)	4 (6)	4 (6)
Skin and subcutaneous tissue disorders[4]	1 (2)	1 (2)	0	3 (3)	1 (1)	4 (3)	0	3 (4)
Cardiac disorders	2 (5)	0	0	0	2 (1)	0	0	0

Source: SCS Table 24, p.74, CSR WA29767 p.156; CSR WA27788 p. 290, 292; reviewer analysis
[1] Dose reduction discussed separately in text; PTs for dose interruptions shown for > 1 patient in any pooled arm
[2] Refers to "lower respiratory tract infection" for 2 patients in Study WA27788

[3] Includes “ALT increased”, “AST increased”, “hepatic enzyme increased”, “transaminases increased”, “liver function test abnormal”
[4] One patient each in Study WA29767 for “blister”, “excessive granulation tissue”, “skin ulcer”
Abbreviations: AE, adverse event; PT, preferred term; SOC, system organ class; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TB, tuberculosis; TCZ, tocilizumab; URTI, upper respiratory tract infection; UTI, urinary tract infection

With regard to individual study safety results, there were slightly more drug withdrawals and dose interruptions in TCZ treated patients in Study WA27788 as compared to Study WA29767, largely driven by infections. This was similar to the results from previously discussed SAE analyses where more serious infections occurred in TCZ treated patients in study WA27788 but not in study WA29767 (Table 22).

In the pooled safety results, treatment withdrawal and interruption occurred less frequently in TCZ treated patients, with small differences between treatment groups. For treatment withdrawals, there were slightly more infectious AEs in TCZ patients (infected skin ulcer, osteomyelitis, pulmonary tuberculosis) than placebo (sepsis, pneumonia). With regard to non-infectious AEs leading to treatment withdrawal, there were also small differences between treatment arms (TCZ: 1 cardiac AE of cardiac failure; 2 neoplasm related AEs of B-cell lymphoma and breast cancer; and 2 respiratory related AEs of interstitial lung disease; Placebo: 3 cardiac AEs of cardiac failure (2) and myocarditis (1); 3 respiratory AEs of interstitial lung disease, pneumonitis, and pulmonary fibrosis). The two AEs of malignancy in TCZ treated patients occurred in SSc-ILD patients and is discussed further in this section. Overall, there were no significant imbalances in AEs leading to treatment withdrawals in the pooled safety population.

For AEs leading to treatment interruptions in the pooled safety population, there were fewer TCZ treated patients than placebo overall, and equal numbers for infectious AEs leading to treatment interruption. For specific infectious PTs (infected skin ulcer, latent TB, nasopharyngitis, and upper respiratory tract infection), small imbalances were noted with more TCZ treated patients reporting AEs. Non-infectious AEs leading to treatment interruption in TCZ patients were related to either abnormal liver enzyme tests or skin or subcutaneous AEs (skin ulcer, blister, excessive granulation tissue, pruritus, rash). Differences in AEs leading to treatment interruptions were generally due to small differences in numbers of patients between treatment groups.

In the SSc-ILD subpopulation, AEs leading to drug withdrawal and AEs leading to dose interruption occurred more frequently in the placebo treated patients (12% and 28%, respectively) than the TCZ-treated patients (7% and 22%, respectively). There were 2 malignancies leading to discontinuation, one event each of B-cell lymphoma and breast cancer, in the TCZ-treated patients. While no placebo treated patients in the SSc-ILD subgroup reported malignancy leading to drug withdrawal, there were few overall events and malignancies were not related by type. Malignancies are discussed further in Section 8.2.5.

AEs leading to treatment interruptions in the SSc-ILD subpopulation were reported by fewer TCZ-treated patients (22%), as compared to placebo treated patients (28%). There were small numerical differences by SOC and PT. In the Skin and subcutaneous tissue disorders SOC, dose interruption occurred in 4% of TCZ patients versus 0 placebo, but without a clustering of PTs (PT listing provided in footnotes of Table 24). There were fewer patients with infectious AEs leading to dose interruption in the TCZ group. In the TCZ group, there were 2 patients each with upper

respiratory tract infections and infected skin ulcers as compared to no placebo treated patients. In the placebo group, there were 2 patients with pneumonia and 3 patients with herpes zoster, as compared to 0 and 1 in the TCZ group respectively. Other infections were singular by PT.

In the pooled safety population, dose reductions were infrequent occurring in only 6 patients (2%), the majority being in placebo treated patients (5 placebo patients versus 1 TCZ patient). None of the AEs leading to dose reduction were serious, and all were related to blood test abnormalities (increased AST, ALT, triglycerides, transaminases). Of these 6 patients from the pooled safety population with dose reductions, only one patient ([redacted] (b) (6)) had SSc-ILD and was assigned to placebo.

In summary, the proportion of patients reporting AEs leading to drug withdrawal were generally fewer in the TCZ-treated groups of the SSc pooled population as well as the SSc-ILD subgroup. While there were numerically more infectious AEs in the pooled population, the differences between treatment arms were small. AEs leading to dose interruption were also reported by fewer TCZ-treated patients compared to placebo treated patients. The types of AEs leading to drug withdrawal and dose interruption were generally consistent with the known safety profile of TCZ. No new safety issues were identified.

Treatment-Emergent Adverse Events and Adverse Reactions

Most patients had treatment emergent AEs (TEAEs), with more TCZ-treated patients having TEAEs than placebo patients (89% versus 81%). A listing of common TEAEs is shown in Table 25.

Table 25: Studies WA27788 and WA29767, Treatment Emergent Adverse Events, Week 48, PTs with ≥ 5% and TCZ > Placebo in Any Pooled Arm

	Study WA27788		Study WA29767		Pooled Studies		SSc-ILD Subgroup	
SOC/PT	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147	Placebo N=68	TCZ N=68
Patients with ≥1 TEAE, n (%)	40 (91)	42 (98)	82 (77)	89 (86)	122 (81)	131 (89)	57 (84)	63 (93)
Infections and infestations	22 (50)	26 (61)	53 (50)	54 (52)	75 (50)	80 (54)	38 (56)	40 (59)
Nasopharyngitis	4 (9)	5 (12)	8 (8)	13 (13)	12 (8)	18 (12)	5 (7)	11 (16)
Gastroenteritis	1 (2)	1 (2)	2 (2)	6 (6)	3 (2)	7 (5)	1 (2)	6 (9)
Gastrointestinal disorders	23 (52)	25 (58)	31 (29)	29 (28)	54 (36)	54 (37)	22 (32)	25 (37)
Diarrhea	4 (9)	7 (16)	8 (8)	6 (6)	12 (8)	13 (9)	7 (10)	6 (9)
Musculoskeletal and connective tissue disorders	19 (43)	20 (47)	38 (36)	26 (25)	57 (38)	46 (31)	27 (40)	19 (28)
Pain in extremity	2 (5)	5 (12)	3 (3)	3 (3)	5 (3)	8 (5)	2 (3)	3 (4)
Skin and subcutaneous tissue disorders	18 (41)	20 (47)	30 (28)	32 (31)	48 (32)	52 (35)	18 (27)	25 (37)
Skin ulcer	8 (18)	8 (19)	12 (11)	15 (14)	20 (13)	23 (16)	9 (13)	13 (19)
Pruritis	4 (9)	6 (14)	4 (4)	6 (6)	8 (5)	12 (8)	1 (2)	5 (7)
General disorders and administration site conditions	14 (32)	18 (42)	19 (18)	20 (19)	33 (22)	38 (26)	12 (18)	15 (22)
Fatigue	2 (5)	5 (12)	7 (7)	8 (8)	9 (6)	13 (9)	5 (7)	6 (9)
Nervous system disorders	10 (23)	17 (40)	20 (19)	11 (11)	30 (20)	28 (19)	12 (18)	6 (9)
Dizziness	2 (5)	4 (9)	3 (3)	3 (3)	5 (3)	7 (5)	2 (3)	1 (2)
Respiratory, thoracic and mediastinal disorders	8 (18)	12 (28)	23 (22)	10 (10)	31 (21)	22 (15)	16 (24)	9 (13)
Dyspnea	3 (7)	4 (9)	3 (3)	3 (3)	6 (4)	7(5)	2 (3)	3 (4)
Vascular disorders	7 (16)	10 (23)	4 (4)	7 (7)	11 (7)	17 (12)	3 (4)	4 (6)
Raynaud's phenomenon	3 (7)	5 (12)	2 (2)	3 (3)	5 (3)	8 (5)	2 (3)	2 (3)

Source: SCS Table 8, 9, pp 35-37; SCS support data p.809, reviewer verified
* For the Injury, poisoning and procedural complications SOC and the Eye disorders SOC, frequencies for AEs were higher in TCZ treated patients (16% vs. 13% and 8% vs. 4%, respectively). PTs in these were not clustered and < 5% frequency for any given PT.
Abbreviations: PT, preferred term; SOC, system organ class; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TB, tuberculosis; TCZ, tocilizumab; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI urinary tract infection

Similar to the prior safety results discussed (*SAEs* and *Treatment Discontinuations/ Modifications*), TCZ-treated patients in Study WA27788 generally had more TEAEs (across multiple SOCs) than placebo treated patients in Study WA27788 and more than TCZ-treated patients in Study WA29767. AEs were most frequently reported in the following SOCs (PBO versus TCZ) in the SSc pooled population: Infections and Infestations (50% versus 54%), Gastrointestinal Disorders (36% versus 37%), Musculoskeletal and Connective Tissue Disorders (28% versus 31%), and Skin and Subcutaneous Tissue Disorders (32% versus 35%). Nasopharyngitis and gastroenteritis were the infections by PT occurring more frequently in TCZ patients than placebo (12% versus 8%, 5% versus 2%, respectively); both of these are labeled safety risks. Infections are further discussed as an AESI in section 8.2.5 .

With regard to the most common AEs, skin ulcers and nasopharyngitis were the two most common AEs that occurred in more TCZ treated patients than placebo (16% versus 12%, 12% versus 8%, respectively). As the possibility of overlap existed for several PTs for skin changes and related infections of those areas, a reviewer analysis using overlapping terms (skin ulcer, infected skin ulcer, osteomyelitis, skin fissures, soft tissue infection, chilblains, skin bacterial infection, skin erosion, skin lesion, skin necrosis) was performed. No significant differences were noted between treatment arms (19% placebo versus 20% TCZ). The Applicant also assessed digital ulcer counts as a safety assessment in Study WA29767 and an efficacy assessment in WA27788. In Study WA29767, at Week 48, the majority of patients in both treatment arms had no change in digital ulcer counts (placebo 85%, TCZ 87%); an increase in digital ulcer count was observed in fewer patients in the TCZ arm (6%) compared to the placebo arm (9%). In Study WA27788, at Week 48, a greater number of patients in the TCZ group than the placebo group had no change in number of digital ulcers (78% versus 63%), and fewer TCZ-treated patients had an increase in digital ulcer count (7% versus 11.4%). Thus, the numerical increase in TEAEs in skin ulcers in the TCZ group were not associated with an increase in digital ulcers, and were due to small differences in patients between treatment groups.

Other AEs reported more frequently in > 2 TCZ-treated patients compared to placebo treated patients in the SSc pooled population include Raynaud's phenomenon (5% versus 3%), fatigue (9% versus 6%), pruritis (8% versus 5%) diarrhea (9% versus 8%), vomiting (3% versus 1%), and pain in extremity (5% versus 3%).

With regard to severe TEAEs (≥ grade 3), a reviewer analysis was used on the pooled safety population to assess differences among treatment arms. Overall there were more placebo patients with severe TEAEs than TCZ (31% versus 24%). The most common SOC was Infections and infestations, balanced across treatment arms at 11%. Besides "scleroderma" (3% placebo versus 0 TCZ), no differences between arms of >2% were noted.

For TEAEs in the SSc-ILD subgroup, observations were generally consistent with what was described for the pooled SSc population. There were more TEAEs in TCZ-treated patients (93% versus 83%). The most common TEAEs were skin ulcers and nasopharyngitis, both occurring

more frequently in TCZ patients (18% versus 14% and 16% versus 6%, respectively). The most common infections in TCZ patients included nasopharyngitis, upper respiratory tract infections, and gastroenteritis.

Given the focus in this review on the SSc-ILD patients, a predominantly respiratory condition, and the role ILD exacerbations can play in morbidity and mortality, it is worth noting that in the SSc-ILD subgroup there were overall fewer TCZ patients with respiratory AEs, particularly ILD exacerbations (7 placebo versus 0 TCZ [10% versus 0%], not shown in Table 25).

Review of the common TEAEs from both studies, WA27788 and WA29767, the pooled analysis, and the SSc-ILD subgroup are generally consistent with the known safety profile of TCZ.

Laboratory Findings

As discussed previously, labeled risks with TCZ use with regard to laboratory changes, include neutropenia, thrombocytopenia, lipid abnormalities, and hepatic enzyme elevation. These are discussed in Section 8.2.5.

Vital Signs

Overall, there were no new clinically relevant changes in vital signs between the treatment arms. Consistent with a labeled adverse reaction for hypertension, a greater proportion of TCZ-treated patients than placebo had elevated systolic blood pressures (SBP >140) in Study WA29767 (11% versus 5%) and Study WA27788 (16% versus 9%). The same was not observed for diastolic blood pressures (normal range defined as 60-90 mm Hg). Importantly, the increased rate of systolic hypertension did not lead to concerning cardiovascular events (strokes or MI). A reviewer analysis, conducted on the 48 week double-blind treatment period, demonstrated more placebo patients than TCZ-treated patients in both studies having serious cardiac disorders and CNS disorders (WA27788: Serious Cardiac disorders 5 placebo patients versus 1 TCZ patient, serious CNS disorders 2 placebo versus 0 TCZ; WA29767: serious cardiac disorders 6 placebo versus 2 TCZ, serious CNS disorders 0 cases both arms). This reviewer analysis included all serious AEs with multiple PTs (acute MI, cardiac failure, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, cardiac failure chronic, cyanosis, microvascular CAD, MI, myocarditis as well as headache and subarachnoid hemorrhage). Of note, there was no adjudication for cardiovascular events.

There were no clinically relevant changes noted for pulse (mean change at week 48 in beats per minute: -1 placebo versus -2 TCZ) or respiratory rate (mean change at week 48 in breaths per minute: 0.2 placebo versus -0.4 TCZ) in Study WA29767. Similar findings were noted for Study WA27788 (mean change at week 48 in pulse: 0.5 placebo versus 1.9 TCZ; respiratory rate not assessed).

Immunogenicity

In the pooled analysis, the frequency of anti-drug antibodies (ADA) to TCZ was low during the 48-week period (1 patient in Study WA29767, 0.7% of pooled patients). This single patient was negative at baseline and became positive during the treatment period (treatment-induced). During the OLE, two additional patients (3 total (1.8%) at end of 96 weeks) from Study WA2788 also had treatment-induced ADA. All ADA observed were neutralizing. The patients with ADA did not experience AEs of hypersensitivity. Due to the small numbers of patients with ADA, conclusions on the impact of ADA on efficacy and safety are limited. For further details, see section 6.2.1.

8.2.5. Analysis of Submission-Specific Safety Issues - Adverse Events of Special Interest (AESI)

Based on TCZ's labeled safety profile, the following are discussed as adverse events of special interest (AESIs):

- Infections (all infections, serious infections, and opportunistic infections)
- GI perforations
- Hepatotoxicity
- Laboratory changes (neutropenia, thrombocytopenia, liver enzyme elevation, and lipid abnormalities)
- Hypersensitivity reactions, including anaphylaxis
- Demyelinating disorders
- Myocardial infarction (MI), acute coronary syndrome (ACS), and stroke
- Injection site reactions
- Malignancies
- Bleeding events (serious)

Of these, there were no GI perforations or demyelinating AEs. Therefore, these categories are not discussed further. Additionally, AESIs of stroke, myocardial infarction, and serious bleeding occurred only in placebo patients. As such, these AESIs are included in Table 26, but are not discussed in the sections below.

For malignancies, the rate of events was low with 3 cases reported in the pooled safety population during the 48 week double blind treatment period. The 3 reported malignancies were reported in Study WA29767 (2 TCZ cases versus 1 placebo), and included lung adenocarcinoma, B-cell lymphoma, and breast cancer. Higher rates of malignancy have been reported in patients with SSc. However, there were few cases of malignancy reported in the pooled safety population, relatively balanced by treatment group, and without clustering related to type or frequency of malignancy.

An overview of selected AESIs is summarized in Table 26. Results for hepatotoxicity and specific

laboratory based abnormalities (neutropenia, thrombocytopenia, lipid abnormalities) are discussed separately in their respective sections below.

Table 26: Adverse Events of Special Interest

	WA27788		WA29767		Pooled WA27788 and WA29767		SSc-ILD Subgroup**	
	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147	Placebo N=68	TCZ N=68
Infections and infestations	22 (50)	26 (61)	53 (50)	54 (52)	75 (50)	80 (54)	38 (56)	40 (59)
Serious infections	1 (2)	9 (21)	7 (7)	2 (2)	8 (5)	11 (8)	7 (10)	2 (3)
Opportunistic infections	0	1 (2)	1 (1)	0	1 (1)	1 (1)	1 (2)	0
Hypersensitivity reactions	3 (7)	5 (12)	5 (5)	7 (7)	8 (5)	12 (8)	3 (4)	7 (10)
Injection site reaction	2 (5)	3 (7)	3 (3)	8 (8)	5 (3)	11 (8)	1 (2)	5 (7)
Serious stroke*	1 (2)	0	0	0	1 (1)	0	0	0
Myocardial infarctions	1 (2)	0	2 (2)	0	3 (2)	0	1 (2)	0
Malignancies	0	0	1 (1)	2 (2)	1 (1)	2 (1)	1 (2)	2 (3)
Serious bleeding	1 (2)	0	1 (1)	0	2 (1)	0	1 (2)	0

Source: SCS Table 6, p.27-29; reviewer analyses
*Includes ischemic or hemorrhagic cerebrovascular conditions; does not include non-serious transient ischemic attack in 1 TCZ patient in Study WA27788; Patient WA27788 (b) (6) (placebo arm) had a subarachnoid hemorrhage and is included in the serious stroke and serious bleeding AESI categories.
**From Study WA29767
Abbreviations: SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Infections

The proportions of patients with infectious AEs in Study WA29767, Study WA27788, and the pooled studies are presented in Table 27. Overall, rates of infections were higher for TCZ-treated patients in both studies (WA27788: 61% TCZ versus 50% placebo; WA29767: 52% TCZ versus 50% placebo). The most common infections were nasopharyngitis, upper respiratory tract infections (URTI), urinary tract infection (UTI), and infected skin ulcer. Nasopharyngitis was more frequently reported by patients in the TCZ arm, while URTI and UTI were more frequently reported in the placebo arm. AEs of infected skin ulcers were balanced in the pooled safety analysis.

Table 27: Studies WA27788 and WA29767, Infections, Week 48

	Study WA27788		Study WA29767		Pooled Studies	
	Placebo N=44	TCZ N=43	Placebo N=106	TCZ N=104	Placebo N=150	TCZ N=147
Patients with infectious TEAE leading to death*	0	1	0	0	0	0
Patients with ≥1 serious infectious TEAE	1 (2)	9 (21)	7 (7)	2 (2)	8 (5)	11 (8)
Pneumonia	0	2 (5)	3 (3)	0	3 (2)	1 (1)
Infected skin ulcer	0	2 (5)	1 (1)	0	1 (1)	2 (1)
Osteomyelitis	0	2 (5)	0	1 (1)	0	3 (2)
Patients with ≥1 infectious TEAE leading to drug withdrawal	0	2 (5)**	2 (2)	1 (1)***	2 (1)	3 (2)
Patients with ≥1 infectious TEAE (infections and Infestations)	22 (50)	26 (61)	53 (50)	54 (52)	75 (50)	80 (54)
Nasopharyngitis	4 (9)	5 (12)	8 (8)	13 (13)	12 (8)	18 (12)
Upper respiratory tract infection	6 (14)	1 (2)	11 (10)	12 (12)	17 (11)	13 (9)
UTI	3 (7)	3 (7)	10 (9)	5 (5)	13 (9)	8 (5)
Infected skin ulcer	5 (11)	3 (7)	2 (2)	4 (4)	7 (5)	7 (5)
Herpes zoster	2 (5)	3 (7)	5 (5)	2 (2)	7 (5)	5 (3)
Gastroenteritis	1 (2)	1 (2)	2 (2)	6 (6)	3 (2)	7 (5)
Cellulitis	3 (7)	0	0	0	3 (2)	0

Source: reviewer analysis
*patient (b) (6) in Study WA27788 had lung infection leading to death, investigator reported related to study drug
**one patient each for "infected skin ulcer", "osteomyelitis"
***one patient had "pulmonary tuberculosis"
Abbreviations: TCZ, tocilizumab; TEAE, treatment-emergent adverse event; UTI, urinary tract infection

Serious infections occurred in 8% in all TCZ-treated patients as compared to 5% of the placebo treated patients in the pooled analysis. Differences in serious infections were driven by Study WA27788 in which serious infections occurred in 21% of the TCZ-treated patients as compared to 2% of the placebo-treated patients. Serious infections were less common in TCZ-treated patients in Study WA29767, and less common in TCZ-treated patients in the SSc-ILD subgroup (TCZ: 3%, placebo: 10%). The most common serious infections reported more frequently in TCZ-treated patients compared to placebo were infected skin ulcers (2% versus 1%, respectively) and osteomyelitis (3% versus 0, respectively), while pneumonia was reported more frequently in the placebo-treated patients (3% versus 1%). Other reported serious infections were singular by PT. Infections leading to drug withdrawal were infrequent and similar between treatment groups in the pooled analysis.

Opportunistic infections were infrequent as well, with one patient in each study (1 placebo patient in Study WA29767, 1 TCZ-treated patient in Study WA27788), reporting esophageal candidiasis. The TCZ-treated patient (WA27788-(b) (6)) developed the serious event on day (b) (6) of the study, whereas the placebo patient developed this infection on day 188. In addition, 1 TCZ-treated patient in Study WA29767 reported oropharyngeal candidiasis. Up to Week 96, there was one additional patient (TCZ to TCZ treatment) in Study WA29767 with a non-serious AE of esophageal candidiasis.

In summary, while overall infections and serious infections were more commonly seen in TCZ-treated patients in both studies, the differences were due to differences in small numbers of patients in the pooled analysis. The types of infections were generally consistent with the known safety profile of TCZ. Patients with SSc may be at increased risk for infected skin ulcers and osteomyelitis due to disease manifestations including digital ulcers, however the number of overall events and differences between treatment groups is small. The currently approved labeling for TCZ includes a boxed warning for serious infections and adequately communicates the risks of serious infections.

Hepatotoxicity

While mean and median values for AST, ALT, alkaline phosphatase, or bilirubin on laboratory testing shifted during the treatment period (generally increased), only abnormal values for these parameters are discussed in this review. Shifts occurring in these parameters that remained within normal limits are not discussed.

In Study WA29767, for patients starting with a normal baseline, liver enzyme elevations for AST and ALT (to abnormal levels) during the 48-week treatment period occurred in more TCZ-treated patients than placebo (AST: 24% versus 14%, ALT: 33% versus 15%, respectively). Similar results were observed in Study WA27788 (AST: 34% versus 19%, ALT: 29% versus 12%, respectively). AST and ALT elevations were generally mild (CTCAE grade 1). In Study WA29767, 2 TCZ patients had CTCAE grade 3 elevations in ALT (one with accompanying AST elevations) as compared to 1 placebo patient. In all patients the elevations were non-serious and resolved with drug interruption. In Study WA27788, one patient in each arm had CTCAE grade 3 elevations in ALT and one placebo patient had a grade 3 AST elevation.

The AST/ALT elevations were generally not accompanied by elevations in bilirubin or alkaline phosphatase, nor associated with clinically significant events such as jaundice. No Hy's law cases were reported in either study.

Investigator reported AEs of hepatic enzyme elevation AEs across the pooled population were more frequent in placebo patients than TCZ treated patients (11% versus 8%) [based on a reviewer analysis combining PTs of liver function test increased, liver function test abnormal, hepatic enzyme increased, aspartate aminotransferase increased, and alanine aminotransferase increased]. None of these AEs were serious or led to treatment discontinuation. Separately, other investigator reported hepatic AEs were also explored in the pooled population. The only other AE noted was for hepatic steatosis, balanced across treatment arms. One TCZ-treated patient in Study WA29767 ((b) (6)) had hepatic steatosis during the 48 week blinded treatment period; the patient recovered and the AE was deemed non-serious.

In summary, while more TCZ-treated patients had hepatic enzyme elevations during the 48 week treatment period, the majority of the enzyme elevations were mild and not associated

with AEs. Overall, the observed liver enzyme elevations are consistent with the known safety profile of TCZ.

Laboratory Abnormalities: Neutropenia, Lipid Changes, and Thrombocytopenia

Pooled safety data from Study WA27788 and Study WA29767 was reviewed.

- Neutropenia

Mean and median neutrophil counts decreased more in the TCZ arms over the 48 week treatment period in both studies. The majority of the decreased values were grade 1 in severity; neutropenia (with neutrophil counts < 1.5 x 10^9/L) was present in more TCZ-treated patients at Week 48 (13% versus 2%). Using a shift in value of 5% or higher as a threshold, more TCZ-treated patients had CTCAE grade 1 neutropenia (18% versus 1%). At Week 48, CTCAE grade 3 neutropenia was noted in more TCZ patients (3% versus 0). However, no serious infections were noted. These results are generally consistent with the labeled information on neutropenia, and the lack of correlation between neutropenia and occurrence of serious infections in the approved adult indications of TCZ.

- Cholesterol

At Week 48, more TCZ-treated patients had abnormal fasting total cholesterol values (≥ 6.18mmol/L) (48% versus 23%) as well as abnormal fasting LDL cholesterol elevations (≥ 4.13 mmol/L) (36% versus 13%), mostly grade 1. CTCAE grade 3 total fasting cholesterol elevation occurred in 2 TCZ patients (versus 0 placebo). These changes were not associated with any serious or non-serious cardiovascular events based on the reviewer analysis discussed under *Vital Signs* above. These results are consistent with the product label.

- Thrombocytopenia

Thrombocytopenia was more common in TCZ-treated patients. CTCAE grade 1 thrombocytopenia (no lower than 100 x 10^9/L) occurred in more TCZ treated patients (10% versus 1%). There were no grade 2 or higher occurrences, nor were there any associated serious bleeding events. This is consistent with the labeled thrombocytopenia descriptions in Section 6 of the approved product label.

Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions were defined as all AEs occurring within 24 hours of injection, excluding injection site reactions, not deemed “unrelated” to study treatment. Hypersensitivity reactions were more frequent in TCZ-treated patients in both Studies WA29767 and WA27788.

In Study WA29767, hypersensitivity events occurred in 5 placebo patients [5%] versus 7 TCZ patients [7%], without a predominant AE accounting for the events (PTs included pneumonia, nausea, myalgia, abdominal pain, dizziness, joint swelling, and dyspnea in placebo patients; and, included anemia, sinusitis, nasopharyngitis, erythema, respiratory tract infection, nausea, and dizziness in TCZ patients). One hypersensitivity event of pneumonia in a placebo-treated patient was considered serious; all of the hypersensitivity events in the TCZ arm were non-serious. Similarly, in Study WA27788, hypersensitivity events occurred in 3 placebo patients (7%) versus 6 TCZ patients (14%), with no clustering by PT (reported PTs included headache, fatigue, hypertensive emergency in the placebo-treated patients, and headache, somnolence, tension headache, fatigue, hot flush, vertigo, pruritis, and pollakiuria in the TCZ-treated patients).

Clinically significant hypersensitivity was defined as a hypersensitivity event that led to treatment discontinuation. There were no TCZ-treated patients who experienced clinically significant hypersensitivity AEs. A single clinically significant hypersensitivity event of hypertensive emergency occurred in the placebo group in Study WA28877. The SAE was a hypersensitivity reaction based on occurrence within 24 hours of injection, however, review of the clinical narrative was consistent with hypertensive emergency with elevated systolic blood pressure to 205, diastolic blood pressure to 116, and abnormal urinalysis. The patient was managed with anti-hypertensives and discharged from the hospital; she subsequently withdrew consent for study participation.

Results from a separate analysis of the SSc-ILD subgroup for hypersensitivity events did not reveal significantly different findings. The 7 TCZ-treated patients discussed above from Study WA29767 were all SSc-ILD patients, with only 3 of the 5 placebo treated patients having SSc-ILD. While this suggests a slightly higher incidence, none of the TCZ-treated patients had clinically significant hypersensitivity events and there were no treatment discontinuations resulting from these AEs. Overall, there is no increased concern for hypersensitivity in the SSc-ILD subgroup.

There were no anaphylactic reactions reported in either study (including the 48 week open-label extension period for both studies).

Injection Site Reactions (ISRs)

There were more ISRs in TCZ-treated patients than placebo in both studies (WA29767: 8% versus 3%; WA27788: 7% versus 5%). However, no ISR led to dosage modifications, interruptions, or discontinuations, nor were there any serious ISRs. As expected, the most common ISRs were “injection site erythema”, “injection site reaction”, and other PTs of bruising, pruritis, rash, or induration. Results for ISRs in the SSc-ILD subgroup of patients were similar.

These results are similar to the frequency of ISRs in the clinical trial experience with use of SC TCZ in RA patients as described in the approved prescribing information. The frequency of ISRs in TCZ treated patients in studies SC-I and SC-II was 10% and 7%, respectively; no ISRs in SC-I or SC-II led to treatment discontinuation and the majority resolved without treatment.

8.2.6. Safety Analyses by Demographic Subgroups

Safety subgroup analyses by gender, age, weight, region, and race were performed on the pooled safety population as reviewer analyses. This section discusses these demographic subgroup analyses by safety category. As discussed above, the study population in both studies was predominantly female, white, ≤ 100 kg body weight, and middle age.

Given the limited number of deaths, separate demographic analyses for deaths were not performed. Review of deaths in Table 21 (section 8.2.4) did not disclose any clear demographic predisposing factors. While there were more deaths in females (6 of 8 deaths across both studies) this is reflective of the female predominance in the study population (~80%). Similarly, most deaths were in white patients, also reflective of the racial distribution of the study population. There was no clear treatment arm imbalance for deaths within females or by race. In addition, there was no geographically predominant region for deaths.

For SAEs, the majority occurred in females, whites, those under 100 kg body weight, and those under 65 years of age, consistent with the demographics of the enrolled population. By region, SAE incidence tracked reasonably with enrollment (e.g., US was highest enroller and had most SAEs). There were no clear treatment arm imbalances for SAEs within the baseline characteristics of age, race, weight, or gender. Given the small sample sizes inherent to subgroup analyses and the relatively small number of SAEs, conclusions from further safety analyses on SAEs by preferred terms (PTs) or SAEs by system organ class (SOC) are limited .

Similar demographic subgroup analyses for AEs leading to drug withdrawal were also performed and were generally consistent with the demographics of the study population. The majority of AEs leading to drug withdrawals occurred in whites, females, and those < 65 years of age; regions with higher enrollment (e.g. US and Germany) had higher incidences. No treatment arm imbalances were noted within these subgroup analyses; however, conclusions are limited by the small numbers in these subgroups.

For common TEAEs, demographic analyses were again consistent with the study population with greater incidences of AEs in whites, females, those ≤ 100 kg body weight, and patients < 65 years. Given the larger subgroups, safety analyses by PTs and SOCs were performed. The most common TEAEs noted in the overall population (skin ulcers, nasopharyngitis, pruritus, and fatigue) [see section 8.2.4] were also relatively commonly seen when subgroup analyses were

conducted by gender, age, and race. No significant treatment arm imbalances were noted in these PT based analyses by demographic subgroup.

Overall, analysis of deaths, SAEs, AEs leading to discontinuation, and common TEAEs by demographic subgroup was generally similar to the safety profile of the pooled study populations. This analysis is limited by the small number of non-Caucasian and non-female patients enrolled in the studies.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information regarding human carcinogenicity is included nor required for this supplement.

Human Reproduction and Pregnancy

A single pregnancy was reported in Study WA27788 in a placebo-treated patient during the first 24 weeks of treatment, who subsequently underwent a therapeutic abortion. No pregnancies were reported in Study WA29767. The limited available data with TCZ in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. There is an ongoing pregnancy exposure registry.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new data on overdose with TCZ in patients with SSc are available in the ninth DSUR 11April2019 through 10April2020. In the 2019 DSUR, one case of accidental overdose was reported in a patient with multiple myeloma who received a single IV dose of 40 mg/kg. No adverse drug reactions (ADRs) were observed. No serious ADRs were observed in healthy volunteers who received single doses of IV TCZ up to 28 mg/kg. These are described in the product labeling.

No new information on drug abuse potential, withdrawal, and rebound are included nor required for this supplement.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A 90-day safety update was provided by the Applicant. No new information was submitted as both Studies WA27788 and WA29767 had been completed at the time of submission of this supplement.

The current safety profile of TCZ is largely based on approximately (b) (4) RA patients from the IV TCZ program and nearly (b) (4) RA patients from the SC TCZ program. Additional safety information is also present from the other approved indications (sJIA, pJIA, GCA, CRS). Moreover, the cumulative worldwide post-marketing exposure to TCZ, approved in 2005 in Japan and 2010 in the US (RA), has been in over (b) (4) patients ((b) (4) patient-years) of which approximately (b) (4) is with the SC formulation ((b) (4) patients), and the majority of which is in Europe and the US (Periodic Benefit-Risk Evaluation Report 11006 April 4, 2019 to April 2020).

Expectations on Safety in the Postmarket Setting

Based on the safety analyses in the SSc-ILD population, there are no new safety issues that cause concern when considering how the drug may be used in the postmarket setting. As discussed in Section 12, no new safety issues have been identified to warrant a need for additional risk management activities.

8.2.9. Integrated Assessment of Safety

The Applicant submitted results from Studies WA29767 and WA27788 to provide information on the safety of TCZ and support the sBLA for the use of TCZ in SSc-ILD. As discussed previously, the focus of this review is the proposed SSc-ILD population, identified in Study WA29767 based on baseline HRCT assessments. Baseline HRCT results were not available from Study WA27788, however, patients with mild-moderate decrease in lung function could meet the eligibility criteria. In addition, the eligibility criteria between Studies WA27788 and WA29767 were similar and approximately 64% of the study population of WA29767 had SSc-ILD at baseline as defined by HRCT. Therefore the results from WA27788 provide relevant information on the safety of TCZ in SSc and SSc-ILD. Safety analyses from each study were analyzed as well as pooled analyses from both studies. In addition, safety analyses on the SSc-ILD subgroup from Study WA29767 were also performed and reviewed. These analyses in the pooled SSc population, as well as the SSc-ILD subgroup from Study WA29767, are discussed in detail above.

The safety profile of TCZ in SSc and SSc-ILD was assessed in the context of the known adverse event profile of TCZ in rheumatoid arthritis and GCA. TCZ labeling includes a boxed warning for the risk of serious infections leading to hospitalization or death. There are warnings and precautions related to risks of serious infections, GI perforation, hepatotoxicity,

immunosuppression, hypersensitivity reactions, including anaphylaxis, demyelinating disorders, specified laboratory abnormalities (neutropenia, thrombocytopenia, elevated liver enzymes, and lipid abnormalities), and administration of live vaccinations.

With regard to the major safety categories, across safety analyses for the pooled studies, Study WA29767, and the SSc-ILD subgroup analyses, the following were consistently observed: there were more TCZ-treated patients with AEs overall, however, deaths, SAEs, and AEs leading to treatment discontinuation were similarly or less frequently reported in the TCZ-treated patients. Deaths were similar between treatment groups in the pooled analysis, lower in the TCZ arm in the overall and SSc-ILD analyses of Study WA29767, and generally balanced as to cause of death across the treatment arms. There were fewer patients with SAEs in the TCZ group in the pooled population, as well as in the SSc-ILD subgroup.

Consistent with the established safety profile of TCZ, a higher incidence of serious infections was observed in the pooled safety population; however, this was not observed in the overall or SSc-ILD subgroup analysis of Study WA29767. There were few opportunistic infections reported. No new tolerability issues were found in analyses of AEs leading to treatment withdrawal or treatment interruption. Common AEs in TCZ patients included skin ulcers, nasopharyngitis, fatigue, and pruritus, however differences between treatment groups were due to small numbers of patients. Notably, there was no increase in digital ulcers in TCZ-treated patients. Overall, the safety profile in the submitted two studies were generally consistent with the known safety profile of TCZ in the approved adult indications.

In summary, the safety of TCZ in the two submitted studies in SSc patients, and analysis of the SSc-ILD subgroup from Study WA29767, do not raise new safety concerns. The safety profile of TCZ in SSc and SSc-ILD is generally consistent with the safety as described in the currently approved labeling.

8.3. Statistical Issues

Since FVC was one of many secondary endpoints in Study WA29767 and one of many exploratory endpoints in Study WA27788, there is a statistical concern that we could be making a type 1 error, i.e. the effect of FVC that was observed could simply be due to chance. In Study WA27788, there were roughly 20 secondary endpoints (roughly 10 outcome measures, most evaluated at Week 24 and Week 48), as well as roughly 20 exploratory endpoints. FVC was pre-specified as one of the exploratory endpoints. In Study WA29767, there were roughly 10 secondary endpoints and roughly 20 exploratory endpoints. FVC was pre-specified as one of the key secondary endpoints and was to be given the most weight of all the secondary endpoints in the multiple testing strategy if the analysis of the primary endpoint was statistically significant.

If Applicants are able to search through results for many different endpoints (even if there is a fairly limited set of pre-specified and potentially meaningful endpoints) and use the most

favorable results among those endpoints to support an application, there can be a very high chance of false positive findings when the drug is truly ineffective. For example, if an Applicant evaluates 20 different endpoints in a trial and the drug truly has no effect on any of them, there is roughly a 20-40% probability that one of them will spuriously show statistical significance by chance alone, depending on the degree of correlation between the endpoints. The derivation of this range in probability covers scenarios ranging from where the endpoints are independent (~40% probability) to where the endpoints are moderately correlated (correlation=0.5; ~20% probability).

However, in considering the results of Studies WA27788 and WA29767, the Division has considered the overall context of the literature, what is known about the endpoints, and supportive trends in the data to make its conclusions. The Division believes that FVC has been adequately characterized in interventional trials of SSc-ILD and has served as a reliable endpoint for documenting a clinically meaningful improvement in lung status. In contrast, the results for mRSS have been less consistent, and the mRSS results from Studies WA27788 and WA29767 do not preclude a conclusion of benefit for SSc-ILD. While the possibility of a type 1 error is a statistical concern due to the lack of evidence on the primary mRSS endpoint, with FVC being one of multiple secondary or exploratory endpoints in the studies, we believe there is sufficient evidence to conclude that the benefit in FVC is real and clinically meaningful. Our rationale for this conclusion is as follows:

Statistical persuasiveness of the ppFVC results in the two studies

- Strength of p-values: The p-values for the pre-specified ppFVC analyses in Studies WA27788 and WA29767 were 0.03 and 0.0015, respectively. Thus, putting aside the multiple comparisons, the strength of evidence against the null hypothesis of no effect on ppFVC was borderline in Study WA27788 but fairly strong in Study WA29767. It is notable that FVC was one of many secondary and exploratory endpoints evaluated in both studies. Although multiplicity is a potential concern, the chance that the observed FVC effect represents a spurious finding due to multiplicity is reduced by the positive FVC results in both WA27788 and WA29767. This is important and adds to the persuasiveness of the evidence. For example, if 20 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 on at least one of the endpoints in both studies is 0.0125,[2] or 1 in 80. This is fairly low. These kinds of approximations, especially given the very low nominal p-value in Study WA29767 and the unique regulatory context and additional considerations described below, suggest that it is unlikely that the positive findings in both studies are spurious.
- Consistency of effect on ppFVC: Cumulative distribution plots suggested separations between tocilizumab and placebo across the entire FVC distribution, not just on the

[2] Probability (at least 1 of 20 endpoints has a 1-sided p-value<0.025 in two independent studies) ≤20*Probability (Endpoint#1 has a 1-sided p-value<0.025 in two independent studies) = 20*0.025^2=0.0125.

mean/median, including with respect to the probability of experiencing different magnitudes of decline in ppFVC (such as a 10-percentage-point decline).

- Consistency of effect across studies: Estimated effects were similar across the two studies (e.g., the mean differences between arms in ppFVC change at Week 48 were 4.3 and 4.2 percentage points in the overall population for Studies WA27788 and WA29767, respectively).
- Robustness to assumption violations: Sensitivity analyses for missing data suggest that the nominal significance in Study WA29767 appears to be robust to alternative missing data assumptions.
- Strength of ILD subgroup analyses: The ILD subgroup analysis of Study WA29767 was not pre-specified in any manner (i.e., was not even documented a priori as an exploratory analysis). However, it provides supportive evidence of a clinically relevant effect (p-value=0.0016; larger estimated effect than in overall population).

Biological and scientific plausibility, supporting trends in other related endpoints, and regulatory context

- Pulmonary function tests were administered while patients were blind to treatment assignment, and therefore unlikely to be biased.
- FVC has been recognized as a feasible-to-obtain reflection of total lung capacity and has long been used to diagnose restrictive lung disease and evaluate the effect of treatment. In addition, forced expiratory volume-based measures such as FVC have correlated with consolidation on HRCT (Lang et al. 2020). FVC findings were supported by the HRCT results in Study WA29767 in the subset of patients with SSc ILD, with reduced FVC decline correlating with stabilization or improvement on HRCT. Notably, HRCT readers were blind to treatment assignment at the time of imaging evaluation.
- Results for other endpoints would not be expected to reliably correlate with FVC results: The results for the other secondary and exploratory endpoints in the two studies do not provide conclusive evidence of effects. For example, there was no significant evidence of effects for PRO measures such as HAQ-DI and patient global assessment that were secondary endpoints in both studies. It is a relevant question whether the lack of evidence on the other endpoints in any way calls into question the likelihood that the observed difference in FVC represents a real treatment effect (e.g., based on the clinical plausibility of a true and detectable effect on FVC but not on other outcomes assessed in the studies). However, there haven't been patient or clinician reported outcomes established to reliably assess direct benefit in programs in fibrotic lung diseases. For example, HAQ-DI is a physical functioning instrument designed for a different context of use (dressing, arising, eating, walking, hygiene, reach, grip, and activities) and it is not established whether or to what extent it could change with changes in FVC. Further, it is unclear what degree of improvement in FVC would be expected to result in meaningful HAQ-DI change. Of note, the nintedanib program demonstrated an effect on FVC without effect on secondary endpoints, including mRSS and PROs (Labeling 2014a). Thus, a lack of a detected difference between treatment groups in HAQ-DI may not be surprising and doesn't contradict the

results and the meaningfulness of the FVC analyses.

- Biological plausibility of the mechanism of action: Another critical factor is the strength of the a priori belief going in to the studies that tocilizumab was likely to have an effect on FVC (e.g., based on biologic plausibility or external data on drugs with similar mechanisms of action), as well as any currently available independent information on the plausibility of effectiveness. There is biological plausibility for IL-6 inhibition as a therapeutic intervention for interstitial lung disease (ILD), supported by pre-clinical and observational clinical data, as discussed in the background section. Further, immunosuppressive therapy has been the cornerstone in the management of SSc-ILD (Denton et al. 2018).
- Consideration for a rare disease with unmet need: While adherence to a pre-specified statistical testing hierarchy is important in many clinical trial settings, all evidence must be considered when establishing clinical meaningfulness and the existence of substantial evidence of efficacy in a rare disease setting with an unmet need. As stated in FDA's Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings Guidance for Industry (October 2018), "While the approval standard for drugs treating rare diseases is the same as that for drugs treating nonrare diseases, it is appropriate for FDA to exercise the broadest possible scientific judgment in applying the evidentiary standard in the rare disease setting." This issue is also discussed in the 2019 draft guidance document Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Guidance 2019).
- Unique regulatory context: At the time of the trial design of both studies, FVC had not been agreed upon as a meaningful endpoint. Therefore, based on the data from the phase 2/3 study, the Applicant retained mRSS as the primary endpoint for the phase 3 trial and elevated FVC from an exploratory to a key secondary endpoint. However, since that time, the regulatory landscape around FVC has evolved and FVC has been used as the primary basis for traditional approval of products for restrictive pulmonary diseases, including SSc-ILD. The regulatory history makes this situation unique and not generally applicable to other settings where there is a lack of evidence of an effect on the primary endpoint. The focus on the FVC results is in large part related to the uncertainty around mRSS and the evolving regulatory landscape around appropriate endpoints during the drug development program. This unique regulatory history somewhat mitigates concerns about the impact of multiplicity in studies without evidence of effects on the primary endpoint, and combined with the other considerations described above, leads to confidence in the evidence of effectiveness.

Based on this contextual information, we conclude, that the data from the tocilizumab clinical program is persuasive to inform the treatment effect of tocilizumab in SSc-ILD on FVC, an endpoint expected to result in mortality benefit, and support the conclusion that the data constitute substantial evidence of effectiveness, despite that the primary endpoint of change in mRSS was not met in either of the two studies.

8.4. Conclusions and Recommendations

The results from Study WA29767, an adequate and well-controlled phase 3, multicenter, randomized, double-blind, placebo controlled study in 212 patients with active SSc, and Study WA27788, a phase 2/3, multicenter, randomized, double-blind, placebo controlled study in 87 patients with active SSc, provide the primary evidence for the effectiveness in SSc-ILD in this supplement. In both studies, the primary endpoint, change in mRSS at Week 48, was not met. However, in both studies, consistent clinically meaningful improvement was observed on FVC, a pre-specified secondary endpoint in Study WA29767 and an exploratory endpoint in Study WA27788, in the TCZ treatment groups as compared to the placebo groups.

In Study WA29767, there was less decline in ppFVC and observed FVC at 48 weeks in TCZ-treated patients as compared to placebo-treated patients. The differences between treatment groups (TCZ-placebo) in mean ppFVC change from baseline and mean observed FVC change from baseline were 4.2% and 167 mL, respectively. A consistent effect was seen in Study WA27788, in which the TCZ-treated patients had less decline in ppFVC and observed FVC compared to the placebo-treated patients. The differences between treatment groups (TCZ-placebo) in mean ppFVC change from baseline and mean observed FVC change from baseline were 4.3% and 138 mL, respectively. While a treatment effect was observed in the overall study populations, a post-hoc subgroup analysis in patients with SSc-ILD based on baseline HRCT in Study WA29767 demonstrated a greater magnitude of effect, with less decline from baseline in ppFVC and observed FVC in TCZ-treated patients as compared to placebo-treated patients. The differences between treatment groups (TCZ-placebo) in mean ppFVC change from baseline and mean observed FVC change from baseline were 6.5% and 241 mL, respectively. The treatment effect of TCZ in SSc-ILD is also supported by improvement in exploratory quantitative HRCT assessments of lung fibrosis in the SSc-ILD subgroup. The secondary endpoints provide limited support to the efficacy assessment of TCZ in SSc-ILD. Improvement in time to treatment failure was largely driven by the pulmonary component of this composite endpoint.

Both mRSS and FVC are endpoints that do not directly measure how a patient feels, functions, or survives. The role of mRSS in assessment of SSc-ILD has not been clearly defined; however, FVC is a clinically meaningful and accepted endpoint that reliably predicts clinical benefit in fibrotic lung diseases. FVC is routinely monitored clinically and is used to guide management decisions in this patient population. Additional considerations on the statistical persuasiveness of the ppFVC results in the two studies, as well as considerations on the biological and scientific plausibility of the mechanism of action of IL-6 inhibition in SSc-ILD, and the regulatory context for the FVC endpoint are discussed in Section 8.3.

The review team also recognizes that in situations where a trial does not show a statistically significant effect of treatment on the primary endpoint, interpretation of other results from the trial is complex and should be done with caution, i.e. the results for the FVC endpoint could be subject to random high bias. However, given the unique circumstances, including the evolving

regulatory landscape and understanding of the FVC endpoint during development, the team believes that the FVC data are sufficiently persuasive to provide substantial evidence of effectiveness. In addition, the data can be presented clearly in the label, and will be accompanied with appropriate cautionary language about interpreting results from studies that do not provide evidence on the primary endpoint.

The safety of TCZ in Studies WA29767 and WA27788 was generally consistent with the known safety of TCZ in adults in other indications. In the pooled safety analysis, deaths were balanced by treatment group. There were fewer SAEs, AEs leading to discontinuation, and AEs leading to dose modification in the TCZ group compared to the placebo group. Similar findings were observed in the SSc-ILD subgroup of Study WA29767. No new safety signals were identified.

In summary, the information submitted is adequate support an overall favorable benefit-risk profile to support approval of TCZ for the treatment of patients with SSc-ILD, based on the (1) current understanding of FVC as an endpoint in interstitial lung disease that reliably predicts long-term mortality benefit, (2) quality and persuasiveness of the FVC data, including the magnitude, time course, and consistency of the treatment effect on FVC seen in two similarly designed multicenter, randomized, double-blind, placebo-controlled studies, (3) biological plausibility of immunosuppression with an IL-6 inhibitor, (4) context of unmet medical need for this rare disease, and (5) well-characterized safety profile of TCZ with the approved dosing regimen and with no new safety concerns in this patient population.

Further, the information supported a conclusion that the data constitute substantial evidence of effectiveness based on one adequate and well-controlled clinical study, the phase 3 Study WA29767 with persuasive evidence of efficacy on FVC, and confirmatory evidence provided by the results from the phase 2/3 Study WA27788, supportive HRCT findings, and a reasonable clinical plausibility of immunosuppression with tocilizumab, a product with established efficacy in multiple immune-mediated conditions.

Therefore, the review team recommends approval of BLA 125472/S-044, and the associated labeling supplement BLA 125276/S-131. TCZ provides an additional treatment option in the US for patients with SSc-ILD.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this application. No issues were identified warranting advisory committee input.

10 Pediatrics

As tocilizumab was granted orphan drug designation for the treatment of SSc, a pediatric assessment was not required.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Key additions to the current product label are as follows:

- Section 1.3: Addition of a new indication: Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). The Applicant's proposed indication for (b) (4)
  (b) (4)
- Section 2.3: Addition of dosage and administration instructions for the newly added indicated population, including a statement that the ACTPen autoinjector has not been studied in SSc-ILD.
- Section 6.4: Addition of safety information in SSc and SSc-ILD from the clinical trial experience detailed in this review. The safety profile observed was comparable in the SSc-ILD and SSc patients overall, and consistent with the known safety profile.
- Section 6.4: Addition of immunogenicity information in SSc.
- Section 12.3: PK information for SSc-ILD patients was added.
- Section 14.4:
  - Summary of study designs for both studies (WA27788 and WA29767) including study population, treatment, endpoints, prohibited medications, and rescue therapy
  - Results on mRSS from the overall SSc population in each study are described.
  - Statement regarding need for caution in interpretation of other results from a trial which does not show a statistically significant effect of treatment on the primary endpoint, and that comparisons to results of other products and studies may be misleading.
  - The results of the ppFVC and observed FVC are described in the SSc population and the SSc-ILD subgroup.
  - Explanatory statement that results in the overall population driven by SSc-ILD group.
  - Key efficacy results from Study WA29767 were added in tabular format with results for overall population, subgroup without SSc-ILD, and SSc-ILD subgroup.
  - (b) (4)
  -

(b) (4)

Other Prescription Drug Labeling Changes

- Medication Guide

Indication for slowing the rate of decline in lung function in adults with systemic sclerosis-associated interstitial lung disease added. A statement indicating that (b) (4)

- Instructions for Use

Updates to presentation of storage temperatures to present Fahrenheit before Celsius to improve patient understanding of temperature readings commonly used in the United States.

Labeling consultants, including the DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency, improving readability and clarity of the labeling, the patient package insert, and instructions for use, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted as part of this supplement. As no new safety signals have been identified, no new risk evaluation and mitigation strategies are necessary.

13 Postmarketing Requirements and Commitment

There are no new safety or efficacy issues identified in this review that warrant a postmarketing requirement or postmarketing commitment.

14 Division Director (Clinical) Comments

Background

The Applicant, Genentech, submitted this supplemental biologics license application (sBLA), to support approval of tocilizumab for the (b) (4) Tocilizumab is a monoclonal antibody targeting the IL-6 receptor. It is approved for the treatment of rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular and systemic juvenile idiopathic arthritis, and cytokine release syndrome. The proposed dosing regimen in this sBLA is 162 mg SC once weekly, within the range of dosing currently approved for the treatment of RA and GCA.

Analysis of the Condition and Current Treatment Options

Systemic sclerosis (SSc) is a rare, multisystem, connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs that affects approximately 100,000 people in the United States (www.scleroderma.org 2021). It is characterized by microvascular damage and fibrosis of the skin and of various internal organs, including the lung, heart, kidneys and the gastrointestinal tract. SSc is a serious disease associated with increased morbidity and mortality with a 10-year survival rate less than 70% from the time of diagnosis (Steen and Medsger 2007). The primary causes of SSc-related death are pulmonary fibrosis, pulmonary arterial hypertension, heart failure, or cardiac arrhythmia.

Interstitial lung disease (ILD), as detected by high resolution computed tomography (HRCT), is present in 55 to 65% of patients with SSc (Launay et al. 2006). Severe ILD usually presents relatively early in the disease course within the first 3 years from time of diagnosis (Steen and Medsger 2000). Median survival is 5 to 8 years in SSc-ILD (Herzog et al. 2014). Of note, skin fibrosis may not reflect visceral organ involvement (e.g. SSc-ILD) (Shand et al. 2007; Hanitsch et al. 2009).

Systemic sclerosis and SSc-ILD are rare conditions with high unmet medical need. The first and only FDA-approved therapy is nintedanib (Ofev), an anti-fibrotic kinase inhibitor, for "slowing the rate of decline in pulmonary function in patients with SSc-ILD", approved September 2019 (Information 2014). In clinical practice, patients with SSc are treated based on expert-derived recommendations for the management of organ-specific manifestations and empirically with off-label products used for other rheumatic diseases, such as cyclophosphamide. The 2017 update of European League Against Rheumatism (EULAR) recommendations for the treatment of SSc, and 2016 British Society for Rheumatology (BSR) guidelines for the treatment of SSc, recommend consideration of immunosuppressives such as cyclophosphamide and mycophenolate mofetil (MMF) for treatment of SSc-ILD (Denton et al. 2016; Kowal-Bielecka et al. 2017). Such therapies have inherent toxicities including cytopenias, infections, and

malignancies, among others. Hematopoietic stem cell transplantation with intensive immunosuppression has been used for selected patients with lung fibrosis and poor prognosis (Del Papa et al. 2017).

Rationale for Targeting IL-6 in SSc-ILD

SSc-ILD is a leading cause of mortality in patients with SSc (Steen and Medsger 2007). Serum IL-6 elevations are associated with poorer survival in SSc (Khan et al. 2012). Therefore, it is reasonable to explore IL-6 inhibition as a therapeutic target in SSc-ILD. There is biological plausibility for IL-6 inhibition as a therapeutic intervention for interstitial lung disease (ILD), supported by pre-clinical and observational clinical data. Specifically, pre-clinical data suggest IL-6 neutralization decreases lung inflammation and fibrosis (Saito et al. 2008; Pedroza et al. 2011), and observational clinical data show that IL-6 levels have been predictive of morbidity and mortality in both IPF (Ioannis Tomos et al. 2016) and SSc-ILD (De Lauretis et al. 2013). Case reports and series of favorable outcomes using IL-6 receptor inhibitors are also reported in the literature (Saviola et al. 2016; Manfredi et al. 2020; Vacchi et al. 2020). To our knowledge, no prospective, controlled, interventional studies in any ILD patients (e.g. RA-ILD, SSc-ILD, IPF) with IL-6 receptor inhibitors (i.e. sarilumab or tocilizumab) have been conducted, and the studies discussed in this document represent the first such investigations for SSc-ILD using tocilizumab.

Pertinent Regulatory History

IND 112406 was opened in September 2011 for tocilizumab (TCZ) for the treatment of systemic sclerosis (SSc) with study WA27788. In April 2013, orphan drug designation was granted for TCZ in SSc.

In February 2015, a Breakthrough Therapy Designation was granted to TCZ based on the data from phase 2/3 study WA27788, suggesting a meaningful effect on endpoints that included FVC (see MPPRC meeting minutes). In August 2016, the Applicant requested a meeting to discuss an accelerated approval based on study WA27788 demonstrating effects of TCZ on mRSS, a measure of skin involvement in SSc based on skin thickness as measured by clinical palpation and in 17 different body areas. The proposal for accelerated approval was found problematic for a variety of reasons, including that mRSS had not been established as a surrogate endpoint reasonably likely to predict a clinical benefit.

In July 2018, the Applicant submitted a pre-sBLA meeting package with summary data from both studies (WA27788 and WA29767) proposing an indication of treatment of SSc although both studies failed to provide statistical evidence of a treatment effect on their pre-specified primary endpoint, change in mRSS from baseline, although favorable trends in tocilizumab treated patients were observed (Table 28). However, there appeared to be a benefit on FVC. The Division expressed concerns that the failed primary endpoints, lack of regulatory precedent

for the use of FVC as a surrogate in SSc (the relevance of this point is further detailed in the section on *Unique regulatory context* in the review), and limited benefit on other manifestations related to pulmonary components of assessments, would be problematic to support the proposed (b) (4) indication and that this would likely need to be discussed at an Advisory Committee. The Division indicated that additional confirmatory data targeting pulmonary benefit in patients with SSc-ILD may be needed. Based on this feedback, the Applicant decided not to pursue further development of TCZ in SSc.

Meanwhile, the understanding of FVC as an endpoint has evolved, and the Division has determined that FVC is an endpoint that reliably predicts clinical benefit in the context of fibrotic lung diseases (Karimi-Shah and Chowdhury 2015; Paterniti et al. 2017). Based on this new information, the Division approached the Applicant in 2018 and in 2019 to encourage the submission of the data from the TCZ SSc program for review. In the interim, in September 2019, nintedanib was also approved based on efficacy demonstrated in a single trial of 576 patients with SSc-ILD on a primary FVC endpoint (along with supportive evidence about effects of nintedanib on FVC in IPF). Based on this approval and the related discussions at the Arthritis Advisory Committee meeting (FDA July 25, 2019), the Division indicated to Genentech that additional public discussion on the clinical meaningfulness of FVC in SSc is likely not needed for the TCZ program.

On July 24, 2020, the Applicant submitted BLA 125472, S-044 for TCZ for the (b) (4) (b) (4). The application was granted a Priority review.

Clinical Program

The TCZ clinical development program consists of two double-blind, randomized, placebo-controlled studies, WA27788 and WA29767. The baseline demographics and disease characteristics were similar between groups in both studies, and both included a 48-week double-blind treatment period followed by a 48-week open-label extension. Both studies were conducted as planned. Notable differences were sample size (87 patients in WA27788 vs. 212 patients in WA29767) and timing of assessment for the primary endpoint (24 weeks in WA27788 vs. 48 weeks in WA29767). Even though the primary endpoint was evaluated at Week 24 in study WA27788, patients and investigators in the study remained blinded through Week 48. Some members of the Applicant were unblinded to Week 24 results while the study was ongoing, although procedures were in place to try to maintain appropriate study conduct and trial integrity through Week 48. Pulmonary function tests were prospectively collected in both studies. The endpoints evaluated are discussed separately for each study. The focus of the review was on the results through Week 48 rather than Week 24 for the following reasons: (1) SSc is a chronic illness; (2) there is prior experience with evaluating FVC outcomes at approximately one-year study duration (e.g. in idiopathic pulmonary fibrosis, SSc-ILD, and progressive fibrosing-ILD); and, (3) both studies had 48-week double blinded treatment periods.

Efficacy Endpoints and Analysis Plan

The phase 3 study, WA29767, had one primary endpoint, change in mRSS from baseline at Week 48; FVC was included as a key secondary endpoint.

The analysis method for the change from baseline in FVC endpoints (observed and percent predicted) was a non-parametric Van Elteren test stratified by screening IL-6 level. The median change from baseline for each treatment group and the corresponding 95% confidence interval (CI) for the median were also calculated. An additional analysis for the FVC endpoints used the same MMRM model as the primary efficacy endpoint to compare treatment groups with respect to the mean change at Week 48 (with baseline FVC variables used as the continuous covariates).

The Applicant submitted post-hoc analyses for the SSc-ILD subgroup in Study WA29767 as requested by the Agency in November 2019. Post-hoc analyses were performed for the subset of patients who had ILD at baseline on visual read of high-resolution CT. Pre-specified SSc-ILD subgroup analyses were not included in the study's statistical analysis plan. ILD was identified visually post-hoc by a thoracic radiologist (who was blinded to treatment assignment) using a diagnostic algorithm for SSc.

The phase 2/3 study, WA27788, had one primary endpoint, change in mRSS from baseline at Week 24, and roughly 20 secondary endpoints. There were roughly 20 exploratory endpoints that included FVC.

The study protocol and statistical analysis plan did not specify formal analysis methods for exploratory endpoints such as FVC in WA27788. The Applicant conducted additional analyses for such exploratory endpoints after the study was unblinded. The post-hoc FVC analyses included a Van Elteren test and an MMRM.

Efficacy Results

The results from the primary efficacy endpoint and the FVC endpoints are shown in Table 28. While neither of the studies met its primary endpoint, change from baseline in mRSS, numerically favorable trends of TCZ over placebo were seen over 48 weeks. The results for the SSc-ILD subgroup are also shown.

Table 28: mRSS and FVC Endpoint Results

	WA27788		WA29767		WA29767 SSc-ILD Subgroup	
Efficacy Endpoint at Week 48	**Placebo N=44**	**TCZ N=43**	**Placebo N=106**	**TCZ N=104**	**Placebo N=68**	**TCZ N=68**
mRSS						
Mean change from BL	-2.77	-6.33	-4.41	-6.14	-3.98	-6.07
Δ LSM [95% CI],	-3.55 [-7.23, 0.12],		-1.73 [-3.78, 0.32],		-2.09 [-4.68, 0.51],	
p-value	p=0.0579**		p=0.0983		p=0.1140	
FVC percent predicted						
Median change from BL,	-5.7	-1.5	-3.9	-0.6	-4.0	-0.6
[95% CI]	[-8.6, -1.6]	[-4.1, 1.2]	[-4.8, -1.6]	[-2.4, 0.9]	[-5.3, -1.7]	[-3.2, 2.0]
p-value for difference in medians*	p=0.0373*		p=0.0015*		p=0.0016*	
Mean change from BL	-6.3	-2.6	-4.6	-0.4	-6.4	0.1
Δ LSM [95% CI],	3.7 [0.1, 7.3],		4.2 [2.0, 6.4],		6.5 [3.4, 9.5],	
p-value*	p=0.0445*		p=0.0002*		p<0.0001*	
Observed FVC (mL)						
Mean change from BL	-237	-117	-190	-24	-255	-14
Δ LSM [95% CI],	120 [-23, 262],		167 [83, 250],		241 [124, 358],	
p-value*	p=0.0990*		p=0.0001*		p<0.0001*	

Source: Applicant submission SCE, Tables 4, 8, 9, 10, 11, 13, 19
*nominal p-value presented for informational purposes in setting of failed primary analysis
**These are the Week 48 results. The results for the primary endpoint, mRSS change at Week 24, were the following: Δ LSM [95% CI], p-value = -2.70 [-5.85, 0.45]; p=0.0915
Abbreviations:BL, baseline; CI, confidence interval; FVC, forced vital capacity; LSM, least squares mean; mRSS, modified Rodnan skin score; TCZ, tocilizumab;

While the analyses of the FVC endpoints do not reach statistical significance based on the pre-specified statistical testing hierarchies, the results from both studies were consistent with a clinically persuasive estimated magnitude of treatment difference between TCZ and placebo-treated patients (approximately 120 to 160 mL difference in mean FVC change at Week 48 in the overall analysis population in both studies, and 241 mL in the SSc-ILD patients from Study WA29767). The time course of the treatment effect also indicated that TCZ halted the decline in FVC over 48 weeks. Figure 16 and Figure 17 display the mean change from baseline in observed FVC for the overall analysis population in study WA29767 and in the study WA29767 SSc-ILD subgroup, respectively.

The ppFVC and observed FVC results in the overall population were primarily driven by results in the SSc-ILD subgroup, based on additional exploratory analyses conducted for the subgroup of patients in the ITT population that did not have SSc-ILD, as summarized in Table 29. In the SSc-ILD subgroup, the differences in mean changes from baseline to Week 48 for ACTEMRA, as compared to placebo, were 6.47% and 241 mL for ppFVC and observed FVC, respectively.

Table 29: Efficacy Results From Study WA29767

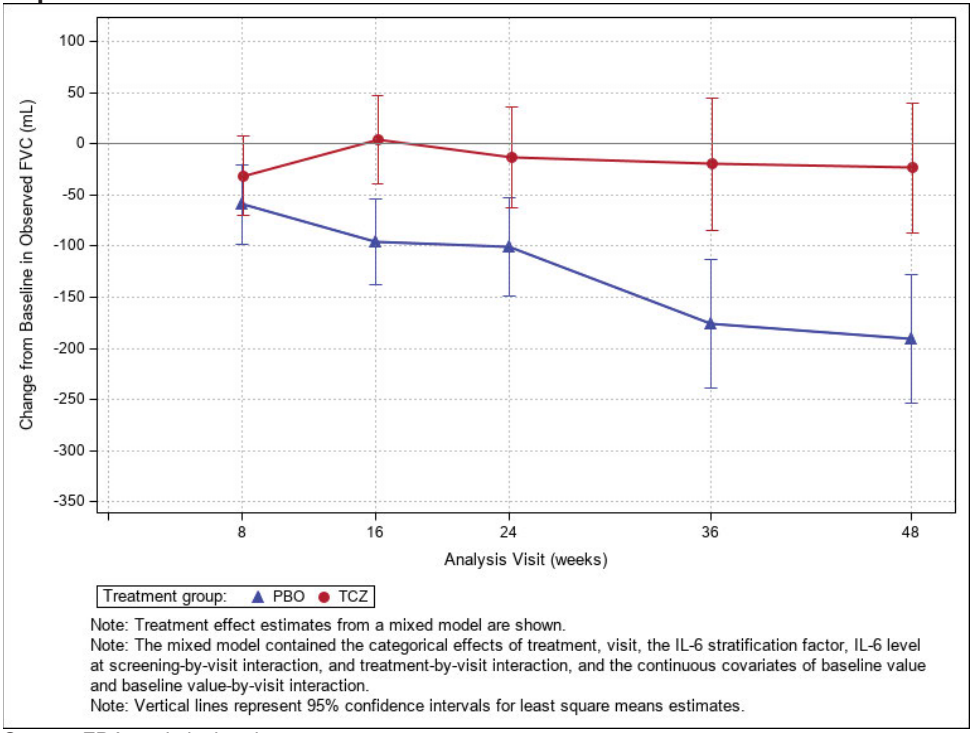
	Overall Population		Subgroup Without SSc-ILD*		SSc-ILD Subgroup*	
	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW	PBO QW	TCZ 162 mg QW
Number of patients	106	104	36	34	68	68
Change from baseline in ppFVC at week 48						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM (TCZ-placebo), 95% CI	4.20 (2.00, 6.40)		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from baseline in observed FVC (mL) at week 48						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM (TCZ-placebo), 95% CI	167 (83, 250)		43 (-60, 145)		241 (124, 358)	
Change from baseline in mRSS score at week 48**						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM (TCZ-placebo), 95% CI	-1.73 (-3.78, 0.32)		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	

*Post-hoc results are shown for these subgroups.
**primary efficacy endpoint
Two patients in each group had a baseline ILD status of 'missing' or 'not evaluable'.
Abbreviations: CI, confidence interval; FVC, forced vital capacity; PBO, placebo; QW, weekly; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab; ppFVC, percent predicted forced vital capacity; LSM, least squares mean;

For context, the magnitude of treatment effect estimated for tocilizumab is comparable to that of approved nintedanib and pirfenidone for the treatment of IPF (94 to 131 mL over 52 weeks, 157 to 193 mL over 52 weeks, respectively), and substantially larger than the effect of nintedanib in SSc-ILD (41 mL over 52 weeks). We recognize the significant limitations in cross-

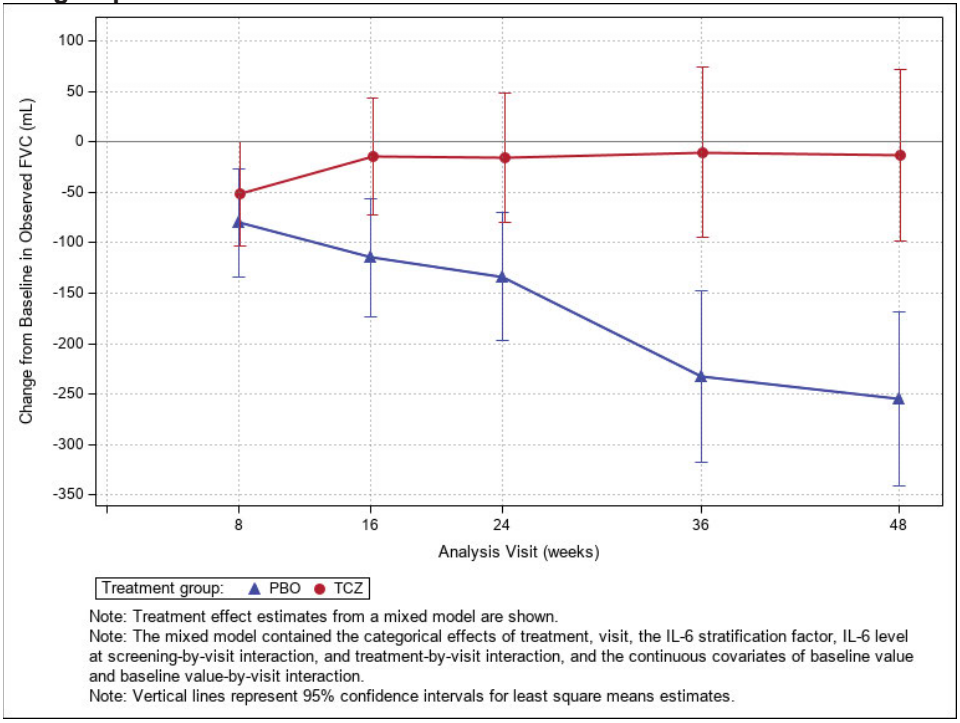
study comparisons, as differences between estimated effects across studies could be due to differences in design/analysis/conduct rather than actual differences in efficacy of the drugs. For example, roughly half of the 576 patients in the nintedanib SSc-ILD study were on stable therapy with mycophenolate, whereas there was minimal use of mycophenolate in the tocilizumab studies. This and/or other design differences might help explain the lesser average decline on placebo observed in the nintedanib study (-93 mL over 52 weeks) than the tocilizumab studies (~200 mL over 48 weeks). Furthermore, the nintedanib study included prospective criteria to define the SSc-ILD population, and a primary analysis of FVC in this population, so would not be subject to the potential random high biases that could be induced due to the secondary/exploratory nature of the FVC overall and subgroup analyses in the tocilizumab studies.

Figure 16: Study WA29767 Mean Change from Baseline in Observed FVC (mL) Over Time, ITT Population



Source: FDA statistical reviewer

Figure 17: Study WA29767 Mean Change from Baseline in Observed FVC (mL) Over Time, SSc-ILD Subgroup



Source: FDA statistical reviewer

Results for ppFVC were consistent, as detailed in the review. To further examine the consistency of effect on FVC, cumulative distribution plots were examined to look at all levels of response. These plots showed a consistent separation across different magnitudes of change in FVC, as detailed in the review.

In addition, missing data sensitivity analyses for the ITT population for ppFVC were consistent with the ppFVC endpoint results from the non-parametric and parametric pre-specified analyses. The statistical reviewer's sensitivity analyses conducted for the two FVC endpoints in the study WA29767 SSc-ILD subgroup demonstrated robustness of the nominally significant analysis results to alternative missing data assumptions.

Since the trial did not demonstrate statistical significance on the primary endpoint, the team recognizes that caution must be exercised to minimize the likelihood of drawing a false positive conclusion because of concerns of multiplicity. In addition to the importance of FVC being elevated to a key secondary endpoint in Study WA29767 (as opposed to one of many secondary or exploratory endpoints), it was important to consider the complementary evidence that would support confidence in the observed effect on FVC. In this case, additional contextual supportive efficacy information is provided by the HRCT data, a pre-specified exploratory endpoint in study WA29767 (quantitative lung fibrosis whole lung scores, mean change from baseline [95% CI]: 0.37 [0.04, 0.69] placebo vs. -0.38 [-0.90, 0.14] TCZ, nominal p = 0.0049;

negative values interpreted as decreased fibrosis), strengthening the confidence in the observed effect on FVC.

There was limited evidence to support potential effects on other secondary and exploratory endpoints that measure direct effect on how patients feel and function. Outcomes such as the patient-reported HAQ-DI score and patient global assessment and the clinician-reported physician global assessment at Week 24 and Week 48 were included as secondary endpoints in both studies, with no conclusive evidence of a treatment effect seen. Of note, results for such endpoints would not be expected to reliably correlate with FVC results, as detailed in section 1.2 (*Clinical and Statistical Considerations About Whether There is Substantial Evidence of Effectiveness).*

Safety

The safety of TCZ in SSc clinical program was consistent with the known safety profile of TCZ. No new safety signals have been identified.

Benefit-risk Assessment and Regulatory Action

The primary evidence for the effectiveness in SSc-ILD in this supplement is derived from two similarly designed multicenter, randomized, double-blind, placebo-controlled studies:

- Study WA29767, a phase 3 study in 212 patients with active SSc, and
- Study WA27788, a phase 2/3 study in 87 patients with active SSc.

In both studies, the primary endpoint, change in modified Rodnan Skin Score (mRSS) at Week 48, was not met, although favorable trends in tocilizumab patients were observed. In both studies, consistent clinically relevant improvement was observed on FVC, a pre-specified secondary endpoint in Study WA29767 and an exploratory endpoint in Study WA27788, in the TCZ treatment groups as compared to the placebo groups.

In assessing the data and information to support the conclusion of substantial evidence of effectiveness based on slowing FVC decline, the review team considered the following:

- The quality and the amount of the data on slowing the FVC decline demonstrated in two similarly designed multicenter, randomized, double-blind, placebo-controlled and well-conducted studies, WA27788 and WA29767, provide consistent evidence for a clinically relevant effect on a major organ manifestation of SSc associated with worse outcomes, including mortality. Specifically:
    - FVC is a reliable quantitative measure of lung function in restrictive pulmonary diseases, including SSc-ILD. It is an endpoint with clinical relevance that the Agency has determined reliably predicts clinical benefit on mortality, a clearly meaningful outcome, in fibrotic lung diseases. Further, FVC is routinely monitored clinically and is used to guide management decisions in this patient population. At the time of the trial design of both studies, FVC had not been

agreed upon as a meaningful endpoint. Therefore, based on the data from the phase 2/3 study, the Applicant retained mRSS as the primary endpoint for the phase 3 trial and elevated FVC from an exploratory to a key secondary endpoint. However, since that time, the regulatory landscape around FVC has evolved and FVC has been used as the primary basis for traditional approval of products for restrictive pulmonary diseases, including SSc-ILD (Labeling 2014a; Labeling 2014b).

  - Notwithstanding the multiple comparisons, the strength of evidence against the null hypothesis of no effect on ppFVC was strong in the phase 3 Study WA29767 and supported by the data from Study WA27788.
  - The FVC data reached nominal statistical significance in two different studies, WA27788 and WA29767, with a very low nominal p-value in Study WA29767, making the uncertainty about the findings (e.g., the likelihood that they result from chance alone) small. It is plausible that FVC would have been prioritized in the statistical hierarchy had the Agency accepted FVC as a meaningful endpoint to support approval for SSc [or SSc-ILD] at the time Study WA29767 was designed and conducted.
  - Additional analyses supporting a true effect of tocilizumab on lung function include the following:
    - The time course of the treatment effect also indicated that tocilizumab halted the decline in FVC over 48 weeks.
    - The cumulative distribution plots of FVC in both studies showed a consistent separation across different magnitudes of change in FVC.
    - The magnitude of the treatment effect was notable. The results from both studies were consistent with a clinically persuasive estimated magnitude of treatment difference between tocilizumab and placebo-treated patients (approximately 120 to 160 mL difference in mean FVC change at Week 48 in the overall analysis population in both studies, and 241 mL in the SSc-ILD patients from Study WA29767).
  - The phase 3 Study WA29767 provided additional supportive evidence of efficacy of tocilizumab based on high-resolution CT findings, as detailed in the review.
  - Both studies WA29767 and WA27788 provided supportive evidence of efficacy with favorable trends in tocilizumab-treated patients in change in mRSS.
- There is a reasonable biological plausibility of using immunosuppression and targeting IL-6 pathway in SSc-ILD, as detailed in the review.

The review team noted, and I agree, that the regulatory history and the evolving understanding of the FVC as a clinical endpoint makes this situation unique and not generally applicable to other settings where there is a lack of evidence of an effect on the primary endpoint.

There were no new safety concerns with TCZ in this sBLA.

Additional Discussions with CDER Medical Policy and Program Review Council (MPPRC)

The sBLA was discussed at the CDER MPPRC meeting on December 09, 2020. The Council acknowledged the complexity of the topic and was not unanimous in their recommendation. A number of Council members found the available data persuasive and, considering the unmet medical need for this rare disease, supported the Division's recommendations to approve an indication for SSc-ILD. The primary concern expressed by the Council was over the regulatory precedent that approval may set in this case for future programs that have unsuccessful phase 3 studies. The team and I are sensitive to this concern. However, we believe that the decision to approve is based on the quality and quantity of the data provided in this development program, the particulars of the disease (systemic sclerosis ILD) and endpoints, the context of evolving regulatory landscape around the endpoint (FVC) and its ability to predict long-term mortality benefit, and the high unmet need, as outlined in the section on *Statistical and Clinical Considerations About Whether There is Substantial Evidence of Effectiveness*.

Some Council members suggested that an Advisory Committee be held to discuss the issue publicly. While we acknowledge this suggestion, the team believes that the data are adequate to support a determination of substantial evidence of effectiveness and to inform the benefit-risk sufficiently to support approval; the outstanding questions about any potential impact of this regulatory action on other future actions are not likely to be meaningfully informed by such a public discussion. Of note, the scientific and regulatory considerations on the use of FVC as an endpoint for SSc-ILD were discussed at an Arthritis Advisory Committee meeting, as detailed in the pertinent regulatory history section. However, depending on the available resources, the team will consider other means of conveying the rationale of the regulatory action to the public and the community.

Conclusions and Regulatory Action

In summary, the information submitted in this application is adequate to inform an overall favorable benefit-risk profile to support approval of tocilizumab for the treatment of patients with SSc-ILD, based on the (1) current understanding of FVC as an endpoint in interstitial lung disease that reliably predicts long-term mortality benefit, (2) quality and persuasiveness of the FVC data, including the magnitude, time course, and consistency of the treatment effect on FVC seen in two similarly designed multicenter, randomized, double-blind, placebo-controlled studies, (3) biological plausibility of immunosuppression with an IL-6 inhibitor, (4) context of unmet medical need for this rare and serious disease associated with significant morbidity and mortality, and (5) well-characterized safety profile of tocilizumab with the approved dosing regimen and with no new safety concerns in this patient population.

Further, the review team fairly and responsibly concluded, and I agree, that the information submitted in this application supports a conclusion that the data constitute substantial evidence of effectiveness based on:

- One adequate and well-controlled clinical study, the phase 3 Study WA29767, which was

designed and conducted as a multicenter, randomized, double-blind, placebo-controlled study in patients with diffuse cutaneous systemic sclerosis. Although the study failed to provide statistical evidence of a treatment effect on its pre-specified primary endpoint, change in mRSS from baseline, favorable trends in tocilizumab treated patients were observed. However, the evidence on FVC, a key secondary endpoint that predicts long-term mortality, a clearly meaningful clinical benefit, was persuasive and supported by several lines of data, as detailed in *Statistical persuasiveness of the ppFVC results* in Section 1.2.

- A body of robust confirmatory evidence, as discussed in *Clinical and Statistical Considerations About Whether There is Substantial Evidence of Effectiveness* in Section 1.2.

The unique regulatory history and context of use mitigate the concerns about the impact of multiplicity in studies without evidence of statistical effects on the primary endpoint, and combined with the other considerations described in the *Clinical and Statistical Considerations About Whether There is Substantial Evidence of Effectiveness* in Section 1.2, leads to confidence in the evidence of effectiveness. In this context, the team also concluded, and I agree, that a requirement for additional confirmatory evidence, is not needed.

The review team believes that the data can be presented clearly and accurately in the label. Despite the lack of statistical significance for the primary endpoint of mRSS, the results for FVC support a conclusion that tocilizumab is effective for treatment of SSc-ILD patients. The team recognizes that in settings where a trial does not provide evidence of an effect on the primary endpoint, the estimated magnitude of effect on other endpoints may be biased. This may make comparisons of the magnitude of the treatment effect of tocilizumab on FVC to that of other products and studies particularly misleading. Therefore, cautionary language about such comparisons will be added to the labeling. Further, based on the regulatory precedent of labeling of an indication primarily based on the FVC results (Labeling 2014a), an indication of "Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)" would be appropriate.

Based on the above considerations, the regulatory action for BLA 125472, S-044 for TCZ for slowing the rate of decline in pulmonary function in patients with SSc-ILD is Approval upon agreement with Applicant on product labeling.

No REMS, PMRs, or PMCs are warranted based on this submission.

This approval will provide a new and much needed treatment option for this high unmet need population who face increased morbidity and mortality, if untreated.

15 Appendices

15.1. References

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15.2. Schedule of Assessments

Assessment or Procedure	Screen. (up to 40 d)	Double-Blind Treatment Period (± 7 d, except Day 1)							Unsch. Visit	Treat. Discon. [c]	Follow-Up [a]	
		Day 1, BL	Wk 4 [b]	Wk 8 [b]	Wk 16 [b]	Wk 24 [b]	Wk 36 [b]	Wk 48 [b]			Wk 4	Wk 8 [a]
Informed consent	x [d]											
Demographics	x											
Medical history [e]	x											
Review of inclusion and exclusion criteria	x	x										
Electronic device training (PROs and study drug compliance)		x										
PRO assessments [f]		x		x	x	x	x	x				
Review study drug compliance			x	x	x	x	x	x	x	x		
Urinalysis [g, h]	x		x	x	x	x	x	x	x	x		
Pregnancy test [g, i]	x	x	x	x	x	x	x	x		x		
HBsAg and HCV serology	x											
Tuberculosis screening [j]	x						x			x		
Serum sample for IL-6 for stratification purposes	x											
Hematology [g, k]	x	x	x	x	x	x	x	x	x	x		
Chemistry panel (serum or plasma) and creatinine clearance [g, l]	x	x	x	x	x	x	x	x	x	x		
Liver profile [g, m]	x	x	x	x	x	x	x	x	x	x		
Lipid panel [g,n]		x		x		x		x	x	x		
ANA sample		x										
SSc-specific auto-antibody panel [g, o]		x						x	x	x		
Serum anti-TCZ antibody sample [g, p]		x		x	x	x	x	x	x	x		x
Serum sample for PK analysis [g, p, q]		x	x	x	x	x	x	x	x	x		x
IL-6 sample [g, q]		x	x	x	x	x	x	x		x		
sIL-6R sample [g,p,q]		x	x	x	x	x	x	x	x	x		x
High-sensitivity CRP [g]	x	x	x			x		x	x	x		
ESR [g]	x	x	x			x		x	x	x		
Serum sample for candidate biomarkers [g]		x				x		x				
Plasma (EDTA) sample for candidate biomarkers [g]		x				x		x				
Whole blood sample for RNA extraction [g]		x				x		x				
Skin biopsies (RCR sample, optional) [r]		x						x				
Whole blood RCR sample for DNA exaction (optional)		x										
mRSS	x	x		x	x	x	x	x	x	x		
Forced vital capacity	x	x		x	x	x	x	x	x	x		
DL_{CO}	x	x				x		x	x	x		
Physician's Global Assessment [s]		x		x	x	x	x	x	x	x		
High-resolution CT scan [t]		x						x				

Assessment or Procedure	Screen. (up to 40 d)	Double-Blind Treatment Period (± 7 d, except Day 1)							Unsch. Visit	Treat. Discon. [c]	Follow-Up [a]	
		Day 1, BL	Wk 4 [b]	Wk 8 [b]	Wk 16 [b]	Wk 24 [b]	Wk 36 [b]	Wk 48 [b]			Wk 4	Wk 8 [a]
Physical examination [u]	x	x							x	x		
Height	x [v]											
Body weight [g]	x	x						x	x	x		
Vital signs [g, w]	x	x	x	x	x	x	x	x	x	x		
Digital ulcer count [g]		x		x	x	x	x	x	x	x		
ECG	x								x			
Echocardiogram	x								x	x		
Adverse events [g, x, y]	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [g, z]	x	x	x	x	x	x	x	x	x	x	x	x
Study drug distribution and administration [g, aa]		x [bb, cc]	x	x	x	x	x	x [bb]				

ANA = anti-nuclear antibody; BL = baseline; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; d = day; Discon. = discontinuation; DL_{CO} = diffusing capacity of the lung for carbon monoxide; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; EQ-5D-3L = EuroQol 5-Dimension Questionnaire (three levels of severity); FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire Disability Index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HRCT = high-resolution computed tomography; IL = interleukin; mRSS = modified Rodnan Skin Score; PK = pharmacokinetic; PRO = patient-reported outcome; RCR = Roche Clinical Repository; Screen. = screening; SGRQ = Saint George's Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; SkinPRO = Scleroderma Skin Patient-Reported Outcome; SSc = systemic sclerosis; TCZ = tocilizumab; Treat. = treatment; Unsch. = unscheduled; Wk = week; WPAI-GH = Work Productivity and Activity Impairment—General Health.

Note: Assessments and procedures should be performed in the sequence that is most practical for the site, as long as PROs are performed first and study drug administration is performed last.

[a] All patients will undergo follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation. For patients who discontinue study drug prematurely, a follow-up visit can be combined with the next scheduled visit (as outlined in Appendix 3), provided that the timing of the scheduled visit coincides with the specified timing for the follow-up visit. The follow-up visit at 4 weeks may be conducted by telephone.

[b] For patients at participating sites who have provided written informed consent to participate in home nursing services, specified assessments at Weeks 4, 8, 16, 24, 36, and 48, as well as Week 8 of the Follow-up Period may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[c] Patients who discontinue study drug prematurely should undergo assessments as outlined in Appendix 3, with the timing of those visits being relative to baseline. Assessments at the early treatment discontinuation visit should be performed *as soon as possible after discontinuing* study drug.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Medical history includes clinically significant diseases (including SSc complications) reproductive status, smoking history, and use of alcohol and drugs of abuse.

[f] PRO questionnaires are to be completed prior to all other assessments during the study visit, with the exception of ECGs. Patients will use an electronic PRO device to capture PRO data. The appropriate PRO assessments will be programmed to appear at specific visits. The HAQ-DI, will be completed at baseline and at Weeks 8, 16, 24, 36, and 48. The Patient's Global Assessment, SHAQ, SGRQ, FACIT-Fatigue, and SkinPRO questionnaire will be completed at baseline and at Weeks 8, 16, 24, and 48. The SkinPRO questionnaire will only be administered in North America. The WPAI-GH and EQ-5D-3L will be completed at baseline and at Weeks 24 and 48.

[g] For patients at participating sites who have provided written informed consent to participate in home nursing services, this assessment or procedure may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[h] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[i] All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] Tuberculosis screening *must* be performed *at screening and at Week 36. The screening method (e.g. PPD or QuantiFERON® test) is at the discretion of the investigator.*

[k] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
[l] Chemistry panel includes total protein, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN or urea, serum creatinine, C3, and C4. Creatinine clearance will be calculated by a central laboratory.
[m] Liver profile consists of AST, ALT, alkaline phosphatase, and total bilirubin (direct and indirect bilirubin will be performed if total bilirubin greater than the upper limit of normal).
[n] Overnight fasting (> 8 hours) is required. An additional fasting lipid panel should be obtained 8 weeks after initiation of lipid-lowering therapy.
[o] SSc-specific autoantibody panel includes anti-topoisomerase, anti-RNA polymerase, anti-PM/Scl, anti-histone, anti-U1 snRP, and anti-centromere antibodies.
[p] Additional samples for PK analysis and analysis of anti-TCZ antibodies and sIL-6R will be collected prior to resuming study drug for patients who have missed at least three consecutive doses and at the time of anaphylaxis or a serious hypersensitivity reaction.
[q] Samples for PK analysis and analysis of IL-6, sIL-6R, and candidate biomarkers will be obtained at a single blood draw and aliquoted according to the procedures in the Sample Handling and Logistics Manual.
[r] Two 3-mm punch biopsies are to be obtained from clinically involved skin, preferably at the forearm (optional).
[s] Physician's Global Assessment is to be completed by the investigator on the basis of examination and overall assessment of the patient.
[t] As accepted by the local regulations. Good-quality (as determined by the site radiologist and/or investigator), standard-of-care HRCT scans obtained within 3 months prior to screening and in accordance with study image acquisition guidelines can be used for baseline.
[u] A physical examination will be performed but will not be recorded on the eCRF, if normal; any abnormality will be reported either on the Medical History eCRF (for screening examination) or Adverse Event eCRF (for examinations after the screening).
[v] Height is required at screening only and will be recorded on the Vital Signs eCRF.
[w] Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Additional measurements may be performed in the event of an adverse event, at the discretion of the investigator. Temperature readings (as part of vital signs) will be measured but will not be recorded on the eCRF, if normal; any abnormal body temperature will be reported on the Adverse Event eCRF.
[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. However, for patients who discontinue study drug prematurely but continue scheduled visits, all adverse events will be reported until completion of the last scheduled visit or 8 weeks after the last dose of study drug, whichever occurs later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
[y] For all serious infectious adverse events, CBC, differentials, and platelets should be determined during the disease episode. Every effort should be made to collect appropriate specimens for serology, polymerase chain reaction, or culture to identify the infectious organism. The results of all laboratory assessments performed locally, except for CRP, should be reported on the eCRF.
[z] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. In addition, all medications taken for SSc since diagnosis will be recorded at screening.
[aa] If for any reason the weekly schedule cannot be kept (e.g., SC injections have to be administered to patients during a site visit), injections may be given a minimum of 5 days and a maximum of 11 days apart.
[bb] The first SC injection in both study periods (double-blind and open-label) will be administered to patients at the site under close supervision. The Week 48 injection is the first dose for the open-label treatment period.
[cc] Patients (and patient caregivers, if applicable) will be trained on how to perform SC injections at the Day 1 visit. For patients and caregivers at applicable sites who require additional training, study drug may be administered (or guidance provided) at Weeks 1 and 2 by a home nursing professional or by appropriately qualified site personnel.

Source: CSR week 48 study WA29767, p.2255

15.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): WA27788

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 219		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 15		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): WA29767

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 616		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: $254,000 for separate study (see section 8.1.3		

for details) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 17		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1. Key Review Questions

The purpose of this review is to address the following key questions:

Do E-R relationships for efficacy and safety support a 162 mg every week dose regimen of tocilizumab in adult patients with systemic sclerosis (b) (4) (SSc-ILD)?

Yes. Overall, the TCZ serum concentration-time course following SC administration in patients with SSc/SSc-ILD 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. Overall there are no positive exposure-efficacy or exposure-safety relationship, thus, current dose seems reasonable.

Is dose adjustment needed for specific population?

No. Consistent with RA patients, body weight was a significant covariate for typical values of PK. TCZ clearance and volumes increased with increasing body weight. As a flat dose was used in the phase 3 study, and there is no clear exposure response for efficacy or safety, no dose adjustment would be recommended to high body weight patients.

15.4.2. Recommendations

The sponsor's proposed dosing regimen is acceptable.

15.4.3. Applicant analysis

15.4.4. *Overview of Tocilizumab Pharmacokinetic Analysis*

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.

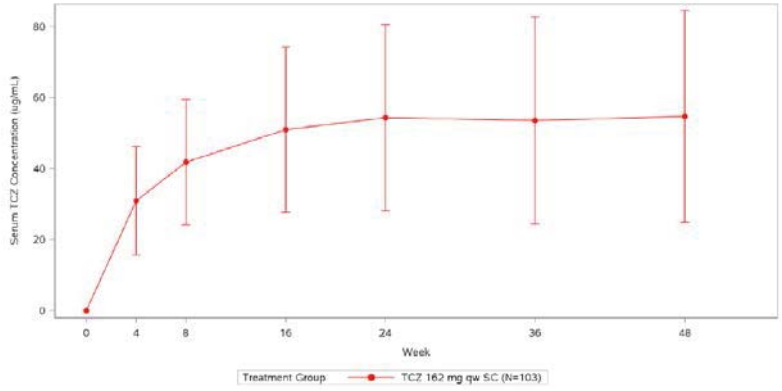
Study WA29767 was a Phase III, multicenter, randomized, DB, PBO-controlled two-arm, parallel-group study to assess the efficacy and safety of TCZ in patients with SSc. The primary efficacy objective of the study was to evaluate the efficacy of TCZ compared to PBO in patients

on skin sclerosis, as measured by mRSS at Week 48. In the DB period of the study, out of the 212 patients randomized, a total of 104 patients received TCZ 162 mg SC QW and 106 patients received PBO (2 out of 212 patients withdrew from the study prior to first dose). Data from 103 patients treated with TCZ were included in the PK population (one TCZ-treated patient had no available PK data). In the OL period of the study, data from 86 patients treated with TCZ were included in the PK population.

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 18). 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 18: Study SA29767: Mean (±SD) TCZ Concentrations by Visit Up to Week 48 (PK Population)



Source: Figure 1 of SCP.
Abbreviations: PK, pharmacokinetic; QW, weekly; SC, subcutaneous; TCZ, tocilizumab

Population Pharmacokinetic Analysis

The previously developed popPK model in patients with RA, a two-compartment PK model with first-order absorption and parallel linear and Michaelis-Menten elimination, was re-run with fixed parameters as Model 001. The diagnostic plots of the model did not indicate any significant model deficiencies that would warrant further model development.

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. However, this trend is strongly influenced by a few patients with low (≤ 40 kg) and high (≥ 130 kg) weight and could be an artifact of the small sample size.

Overall, the 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 and are listed in Table 30.

Table 30: 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 4 of SCP.

Individual Predictions of Steady-State Exposure

The summary of predicted individual steady-state exposure parameters is presented for patients with SSc in Table 31. 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 32. The median predicted steady-state values of Cmean, Cmax, and Ctrough were 50.4, 52.5, and 47.2 µg/mL respectively.

Table 31: Summary of Predicted Individual Steady-State Exposure Parameters in Patients With SSc

	N	AUCτ (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]

Source: Table 5 of SCP
Abbreviations: SSc, systemic sclerosis

Table 32: Summary of Predicted Individual Steady-State Exposure Parameters in Patients With SSc-ILD

	N	AUCτ (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]

Source: Table 6 of SCP.
Abbreviations: SSc-ILD, interstitial lung disease associated with systemic sclerosis

Impact of Body Weight on PK

With regard to intrinsic and extrinsic factors impacting the PK of TCZ, the identified covariates and their effect on the typical values of PK are for SSc/SSc-ILD the same as described for the RA population following SC administration. Of those, only body weight had an appreciable impact on clearance and volume terms of TCZ. TCZ clearance and volumes increased with increasing body weight. Table 33 and Table 34 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 AUCτ (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 AUCτ (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.

In summary, for SSc, SSc-ILD, and RA following administration of TCZ SC, consistently and comparable across the diseases, steady-state Cmean was low for patients over 100 kg and high for patients less than 60 kg compared to the majority of patients with 60 to 100 kg body weight.

Table 33: 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]

Source: Table 8 of SCP.
Abbreviations: SSc, systemic sclerosis

Table 34: 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]

Source: Table 9 of SCP.
Abbreviations: SSc-ILD, interstitial lung disease associated with systemic sclerosis

FDA's comments:

Applicant's analysis seems reasonable. Overall, the 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.

Consistent with RA patients, body weight was a significant covariate for typical values of PK. TCZ clearance and volumes increased with increasing body weight. However due to flat exposure response and lack of clinical practice of higher dose, no dose adjustment would be recommend to high body weight patients.

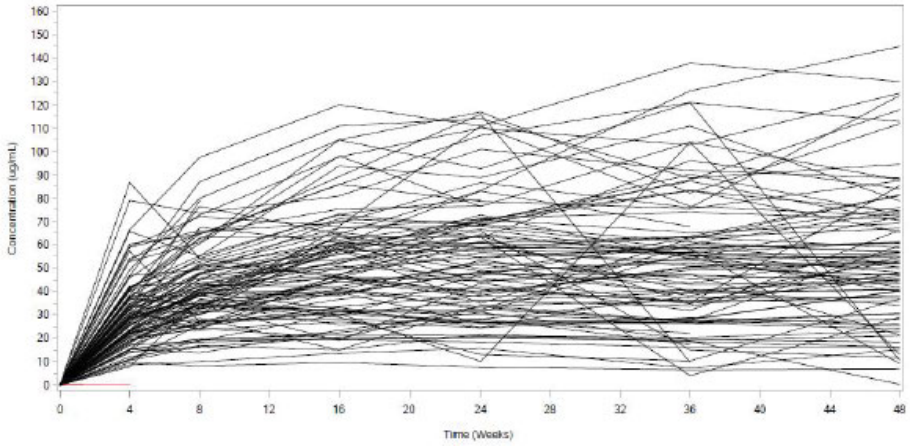
15.4.5. *Immunogenicity*

During the DB period of the study six patients in the PBO arm and 3 patients in the TCZ arm had a positive ADA (here refers to anti-TCZ antibody) as measured by the screening and/or confirmation assay result at baseline. Up to Week 48 only one of these patients in the TCZ arm tested positive for post-baseline ADAs at Week 8 in the screening assay (the confirmation assay was negative).

Three other patients in the TCZ arm were negative at baseline and tested positive for post-baseline ADAs (screening assay), of which only one patient, Patient # (b) (6), had a confirmed positive result by the screening, confirmatory, and neutralizing assays, and was considered to have a treatment-induced ADA response with neutralizing potential.

Patient # (b) (6) did not have a positive IgE assay result. This patient withdrew from the study on Day 205 (withdrawal by subject) 9 days after their last dose of TCZ SC. The ADAs in Patient # (b) (6) were observed at Weeks 8, 16, and 24. Patient # (b) (6) had low TCZ concentrations up to Week 4 and thereafter TCZ concentrations were below the limit of quantification. Figure 19 shows the TCZ concentration-time profile of Patient # (b) (6) (in red) in comparison to concentration-time profiles from patients who did not experience a treatment-induced ADA response (in black). Patient # (b) (6) did not experience any anaphylaxis, serious, and/or clinically significant hypersensitivity reactions, injection site reactions, and did not withdraw due to lack of efficacy. During the OL period of the study, none of the patients tested positive for ADA post baseline.

Figure 19: Study WA29767: Individual Observed TCZ Concentration Profiles for Patients With Treatment-Induced ADAs vs Patients With no Treatment-Induced ADAs up to Week 48



Source; Figure 8 of SCP.
Abbreviations: ADA, anti-drug antibodies; TCZ, tocilizumab

FDA's comments:

Sponsor's Analysis seems reasonable. Six patients in the PBO arm and 3 patients in the TCZ arm had a positive ADA. One patient had a treatment-induced neutralized ADA.

15.4.6. *Overall of Exposure-Efficacy Relationship*

The relationship of observed TCZ exposure to efficacy endpoints (mRSS, ppFVC, Health Assessment Questionnaire-Disability Index [HAQ-DI], Patients Global Assessment and Physicians Global Assessment) at Week 48 was investigated based on tertiles of Week 48 Ctrough using tabular comparisons and graphical analysis on the data collected in patients with SSc from Study WA29767.

A population-based approach was also applied on investigating the relationship between the model predicted PK data and efficacy outcomes of Study WA29767. The objectives of the graphical analysis were:

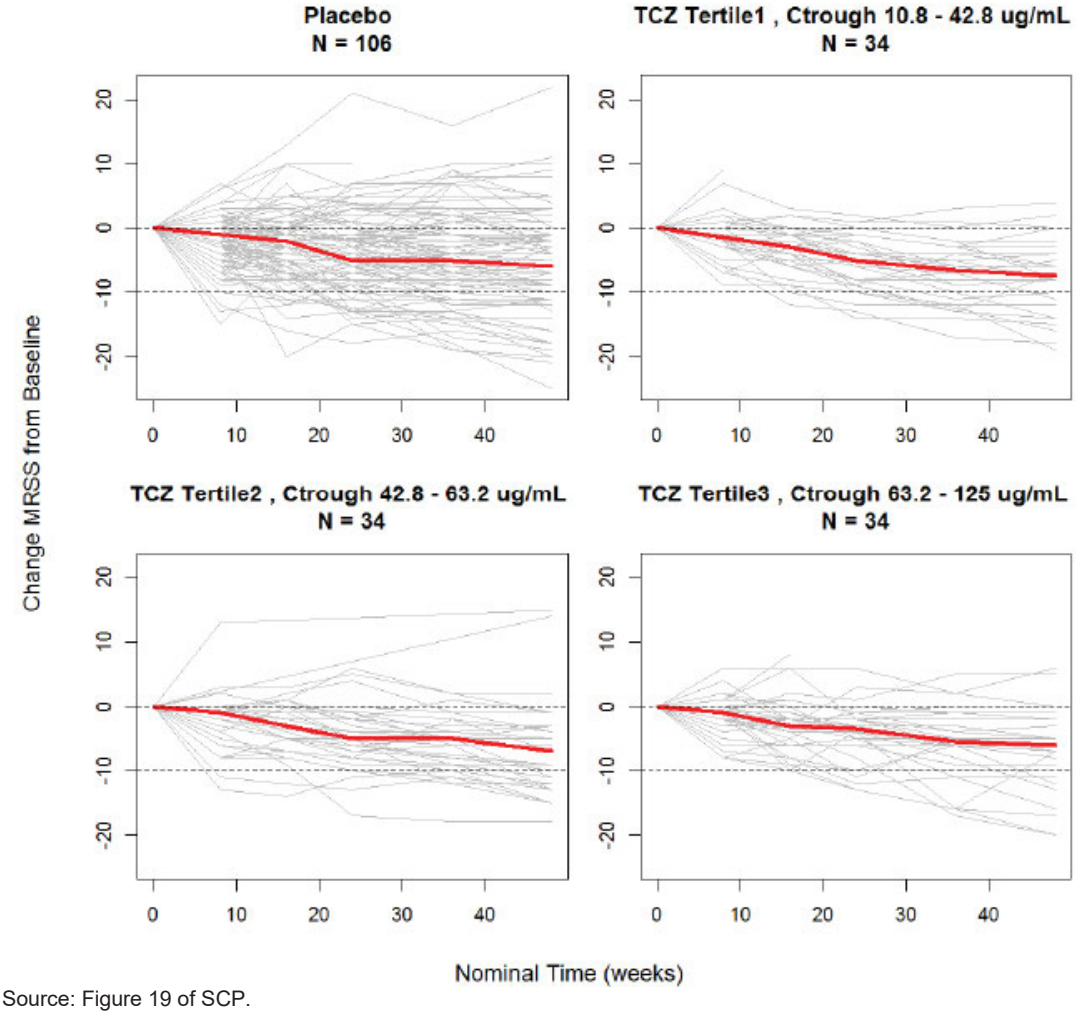
- To assess the relationships between TCZ exposure and time-course of the mRSS and ppFVC;
- To assess the relationships between TCZ exposure and change from baseline at Week 24 and Week 48 of mRSS and ppFVC;
- To assess the relationships of observed TCZ concentrations and predicted exposures with probability of treatment failure and time to treatment failure.

Relationship between TCZ Exposure and mRSS in Patients with SSc

In patients with SSc the median mRSS change from baseline improved over time in all treatment groups, including the PBO group (Figure 20, Figure 21). The improvement was

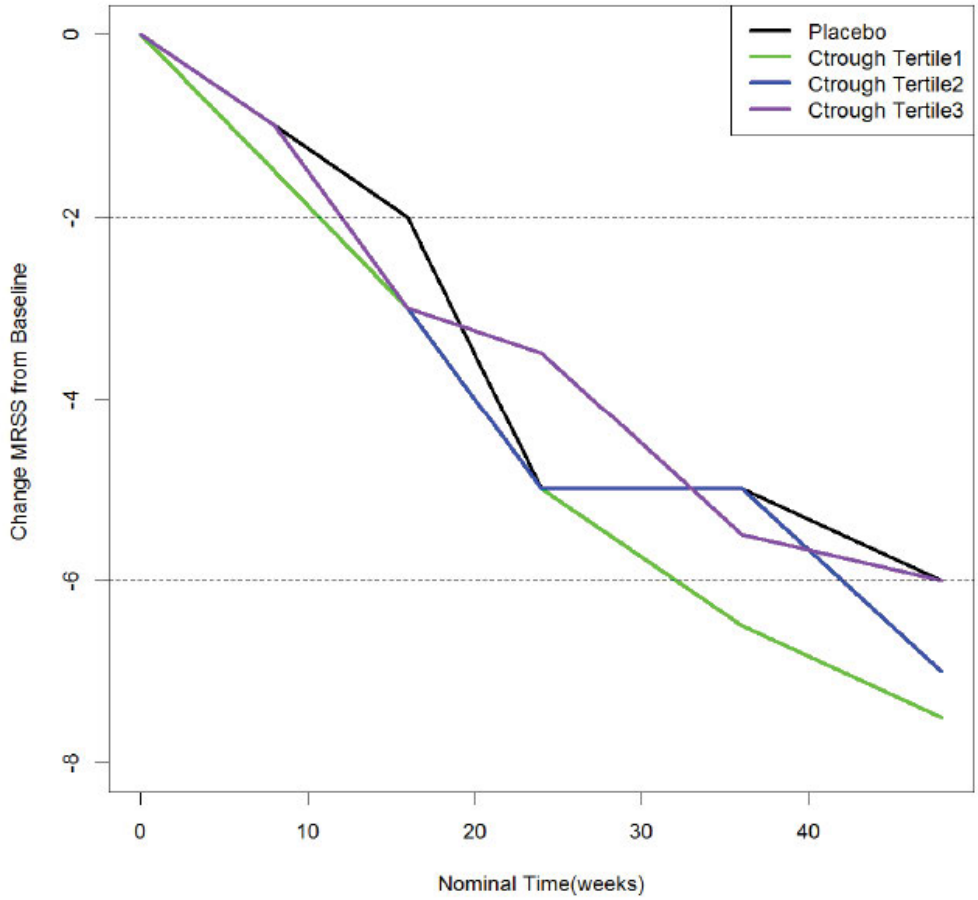
marginally higher in the TCZ treatment group compared to PBO. No exposure-response relationship was observed in the TCZ treatment arm.

Figure 20: SSc Patients: mRSS Change From Baseline over Time by Treatment Group and TCZ C_{trough} Tertiles (WA29767)



Source: Figure 19 of SCP.
Abbreviations: mRSS, modified Rodnan skin score; TCZ, tocilizumab

Figure 21: Median MRSS Change From Baseline Versus Time by Treatment Group and TCZ Exposure

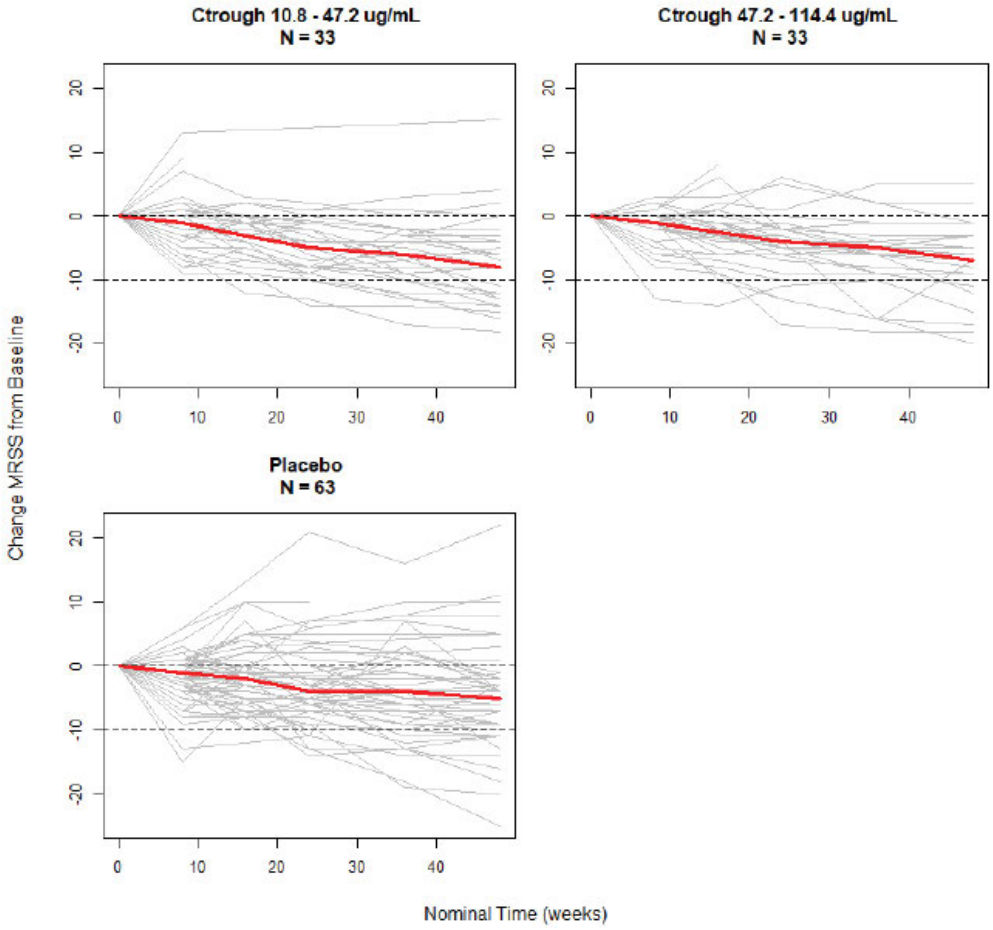


Source: Figure 55 of PKPD report. Medians of observed change from baseline value over time by treatment group (placebo) and tertiles of Ctrough, 48wk for TCZ treatment. Dashed lines indicate change from baseline of -2 and -6.
Abbreviations: mRSS, modified Rodnan skin score; TCZ, tocilizumab

Relationship between TCZ Exposure and mRSS in Patients with SSc-ILD

In patients with SSc-ILD the median change from baseline of mRSS improved over time in all treatment groups, including the PBO group (Figure 22). As was seen for the SSc patients, the improvement was marginally higher in the TCZ treatment group compared to PBO and no exposure-response relationship was observed in the TCZ treatment arm in SSc-ILD patients.

Figure 22: SSc-ILD Patients: Individual and Median mRSS Change From Baseline over Time for PBO, TCZ Low and TCZ High (WA29767)

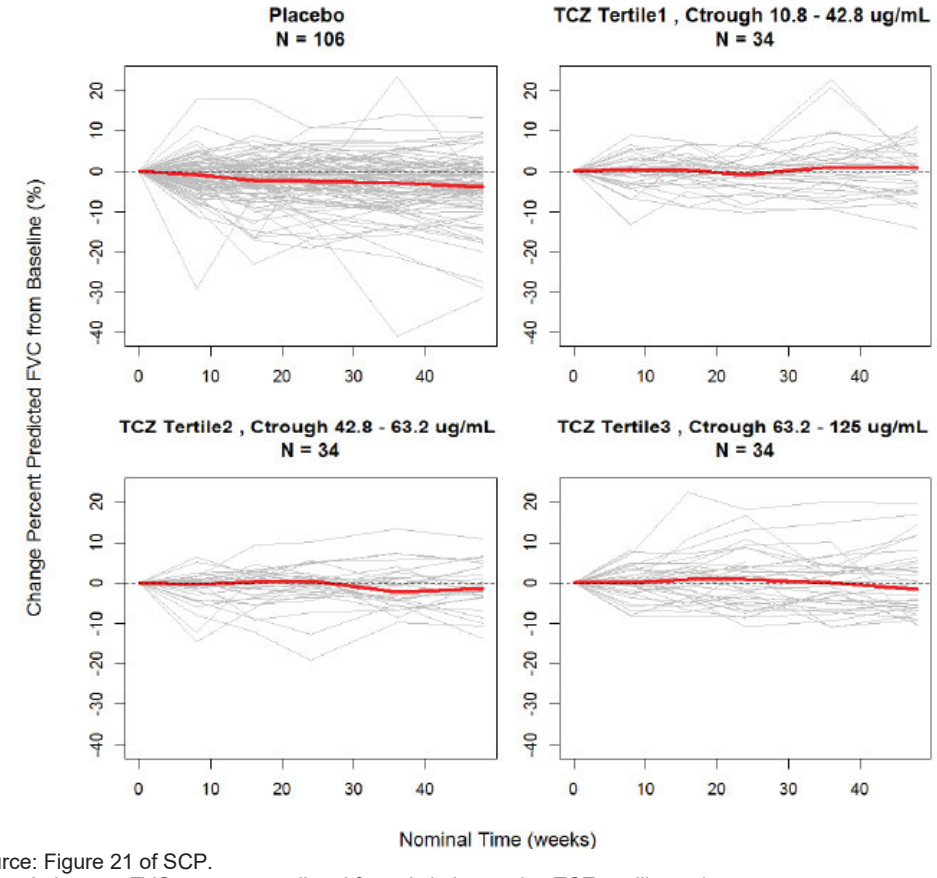


Source: Figure 20 of SCP.
Abbreviations: mRSS, modified Rodnan skin score; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Relationship between TCZ Exposure and ppFVC in Patients with SSc

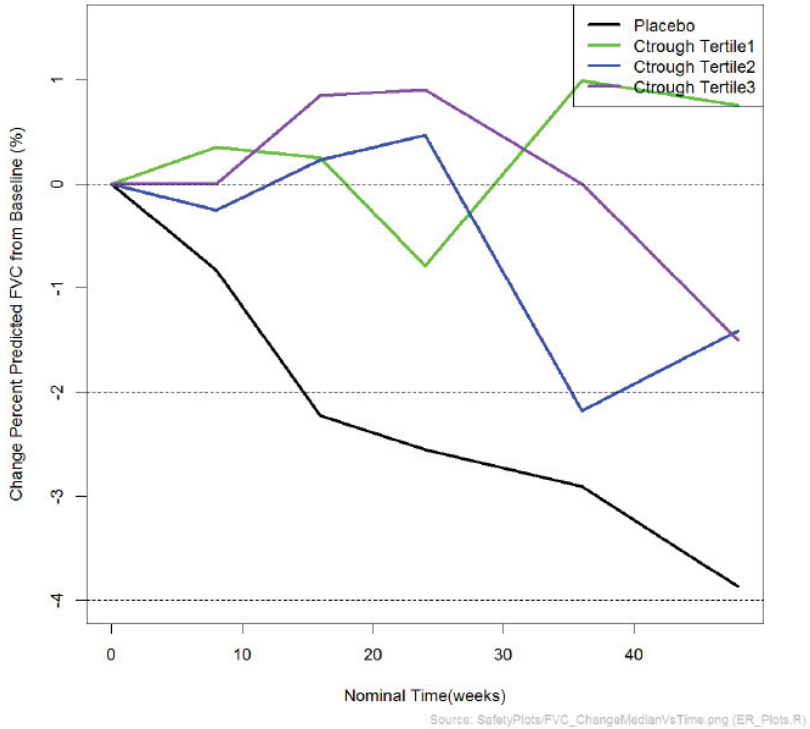
Median change from baseline in ppFVC was constant over time in all TCZ exposure groups, while it slightly declined in the PBO group (Figure 23, Figure 24). No exposure-response relationship was observed in the TCZ treatment arm.

Figure 23: SSc Patients: Change From Baseline of ppFVC Versus Time by Treatment Group and TCZ Ctrough Tertiles (WA29767)



Source: Figure 21 of SCP.
Abbreviations: ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Figure 24: Median Change From Baseline of ppFVC Versus Time by Treatment Group and TCZ Exposure Tertile

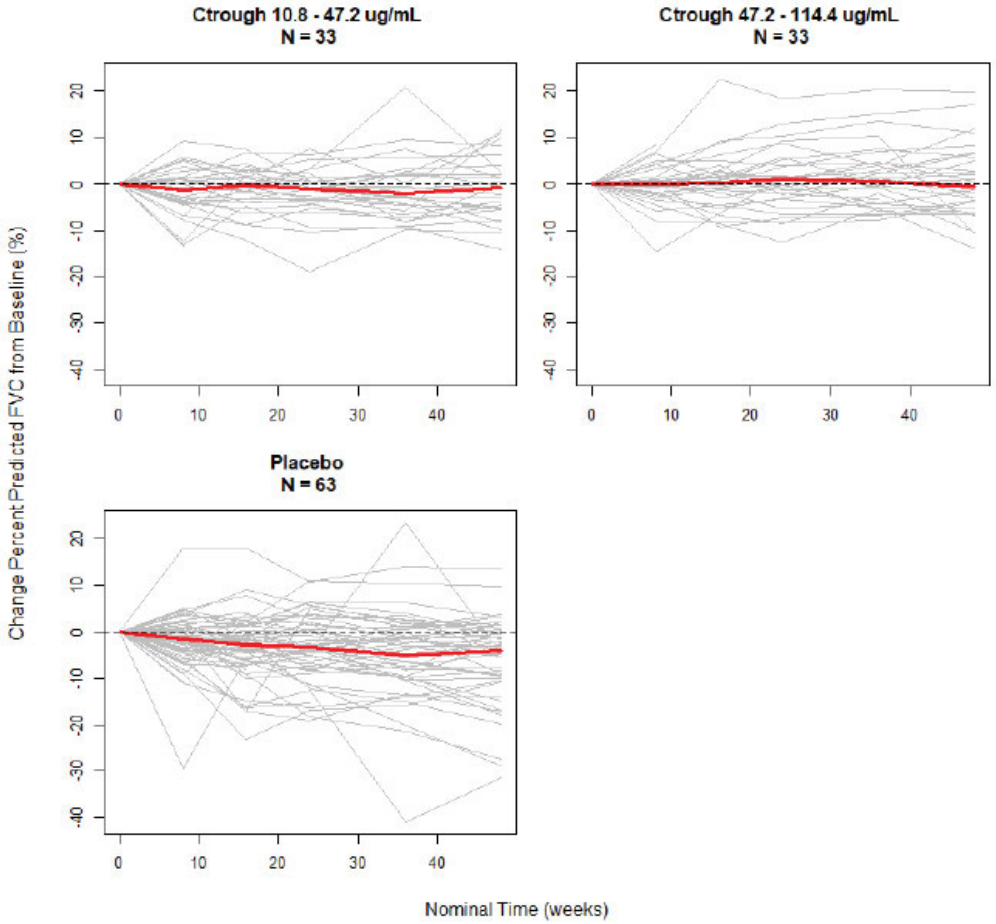


Source: Figure 65 of PKPD report. Medians of change from baseline values over time by treatment group (placebo) and tertiles of Ctrough, 49wk for TCZ treatment. Dashed reference lines indicate change from baseline of 0 and -2.
Abbreviations: ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Relationship between TCZ Exposure and ppFVC in Patients with SSc-ILD

In patients with SSc-ILD, median change from baseline in ppFVC was constant over time in the two TCZ exposure groups, while it declined in the PBO group (Figure 25). The difference in ppFVC change from baseline appeared to be more pronounced in the high TCZ exposure group compared to the PBO group, however, the data are too limited to confirm statistically this exposure-response relationship.

Figure 25: SSc-ILD Patients: Change From Baseline of ppFVC Versus Time by Treatment Group and TCZ Ctrough Tertiles (WA29767)

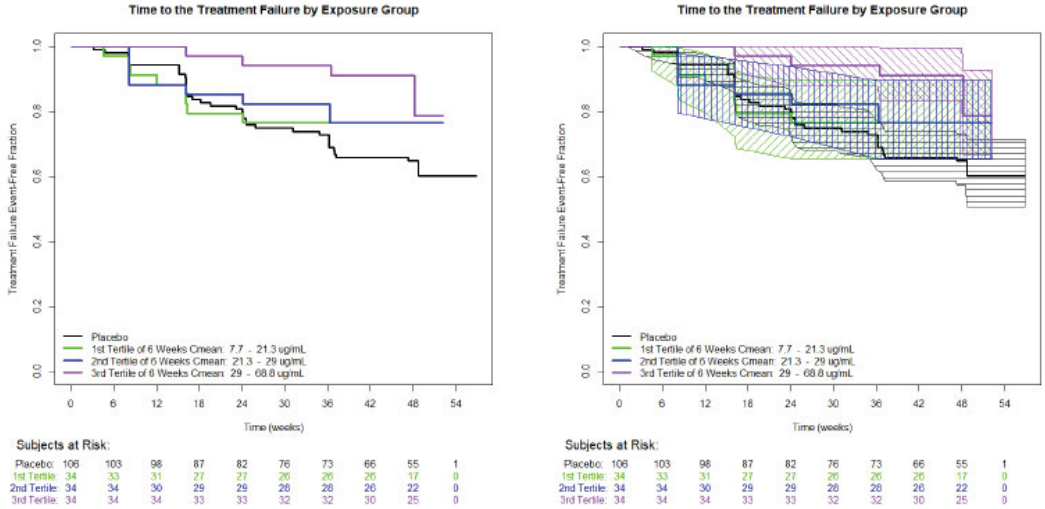


Source: Figure 22 of SCP.
Abbreviations: ppFVC, percent predicted forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Relationship between Tocilizumab Exposure and Treatment Failure in SSc Patients and SSc-ILD Patients

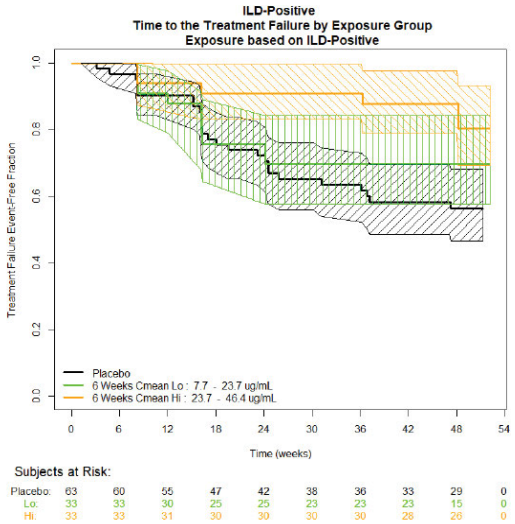
Time to treatment failure is illustrated in Figure 26 for patients with SSc and in Figure 27 for patients with SSc-ILD using Kaplan-Meier plots with different groupings of patients by exposure. The plots indicate some increase of time to treatment failure with increased exposure (Cmean,6wk) in both SSc and SSc-ILD patients; however, the data are too limited to confirm statistically this exposure-response relationship.

Figure 26: SSc Patients: KM Plot for Time to Treatment Failure Versus TCZ Exposure (Cmean,6wk); Placebo and Exposure Tertiles (WA29767) With 90% CI (Left) or Without CI (Right)



Source: Figure 24 of SCP.
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; SSc, systemic sclerosis; TCZ, tocilizumab

Figure 27: SSc-ILD Patients: KM Plot for Time to Treatment Failure Versus TCZ Exposure (Cmean,6wk); Placebo and Exposure Tertiles (WA29767)



Source: Figure 25 of SCP.
Abbreviations: KM, Kaplan-Meier; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

FDA's comments:

Sponsor's Analysis seems reasonable. Overall, exposure-efficacy relationship seems to be flat.

15.4.7. *Overall of Exposure-Safety Relationship*

The relationship of observed TCZ exposure to selected safety endpoints (serious adverse events [SAEs], AEs by system organ class [SOC]) was investigated by tertiles and graphical analysis on the data collected in patients with SSc from Study WA29767.

The relationship between model predicted exposure of TCZ and safety was investigated by graphical analysis on the data collected in patients with SSc from Study WA29767. The objectives of the graphical analysis were to assess the relationships between observed TCZ concentrations and occurrence of:

- SAEs;
- SAEs with Grade ≥ 3 (Grade 3 +);
- Any adverse events (AEs) Grade 3 +;
- AEs of Infections and Infestations (AE II);
- AE II Grade 3 +.

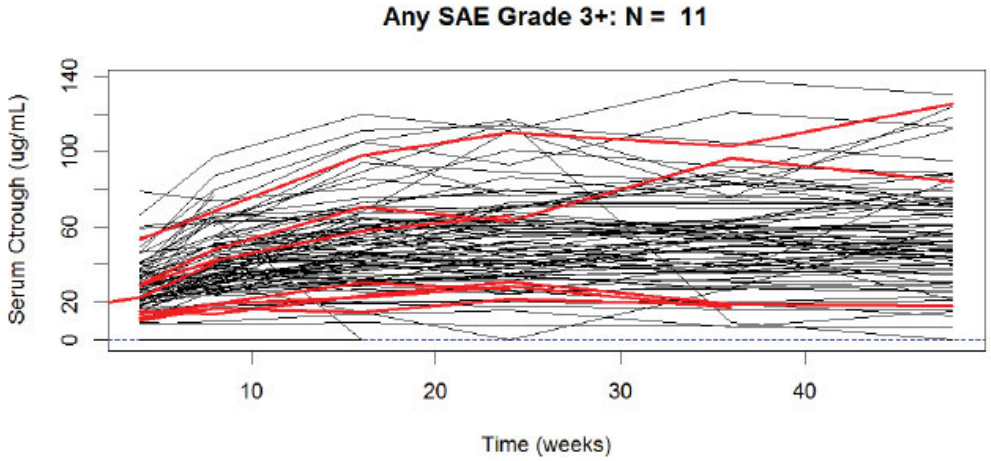
Relationship of TCZ Exposure with Occurrence of Adverse Events

In patients with SSc from the TCZ arm, occurrence of SAEs, SAEs Grade 3 +, AEs Grade 3 +, AEs of Infections and Infestations, AEs of Infections and Infestations Grade 3 + did not correlate with TCZ exposure: observed concentration-time profiles of patients with events were neither higher nor lower than the observed concentration-time profiles of patients without the events (Figure 28, Figure 29, Figure 30).

For all AE types except for AEs of Infections and Infestations of any grade, frequencies of AEs were lower in the TCZ treatment group and decreased with increased exposure. The logistic regression models for patients in TCZ treatment arm also suggested that probability of AEs of these types decreased with increased exposure, but these relationships were not statistically significant.

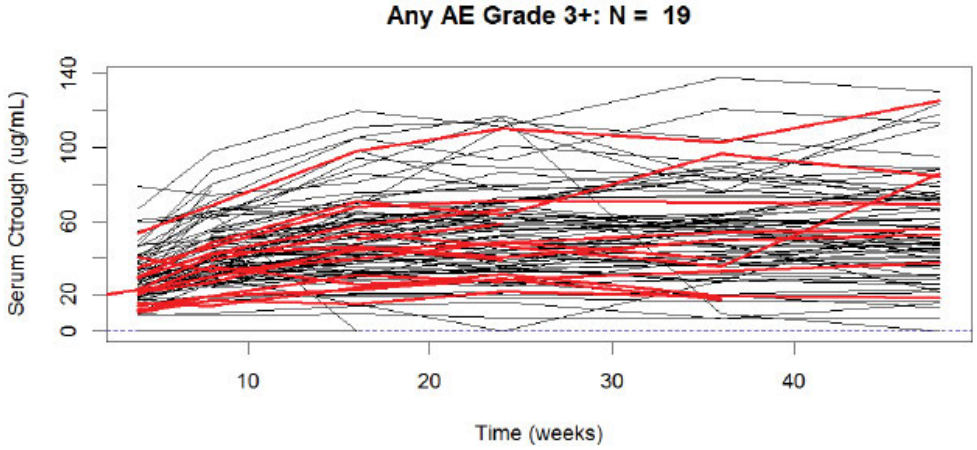
The incidence of AEs of Infections and Infestations of any grade was around 50% overall in all treatment and exposure groups. The logistic regression model for this type of AEs indicated no relationships between probability of adverse events and exposure.

Figure 28: Relationship Between Observed TCZ Concentrations and Occurrence of Any SAE Grade 3+ (WA29767)



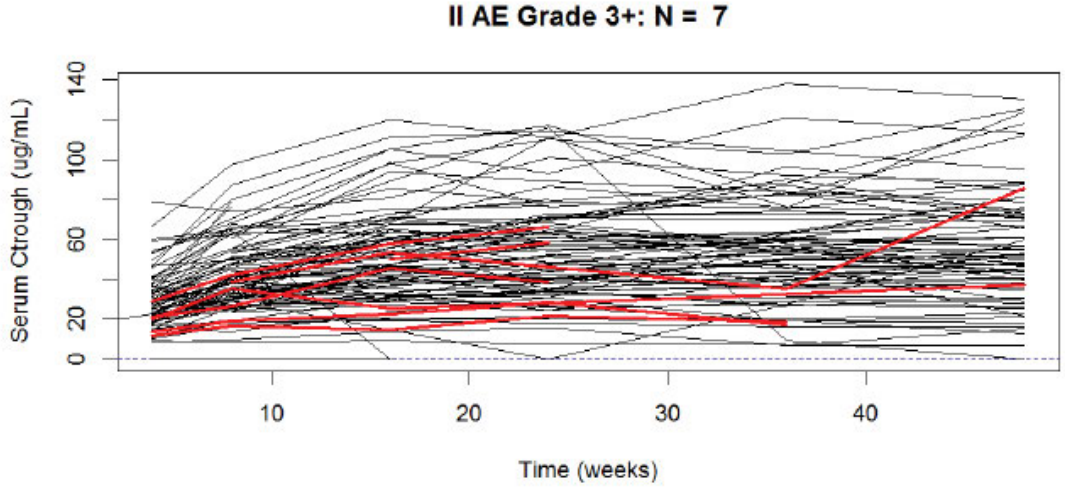
Source: Figure 26 of SCP.
Abbreviations: SAE, serious adverse event; TCZ, tocilizumab

Figure 29: Relationship Between Observed TCZ Concentrations and Occurrence of any AE Grade 3+ (WA29767)



Source: Figure 27 of SCP.
Abbreviations: AE, Adverse event; TCZ, tocilizumab

Figure 30: Relationships Between Observed TCZ Concentrations and Occurrence of AE of Infections and Infestations of Grade 3+ (WA29767)



Source: Figure 28 of SCP.
Abbreviations: AE, adverse event; TCZ, tocilizumab

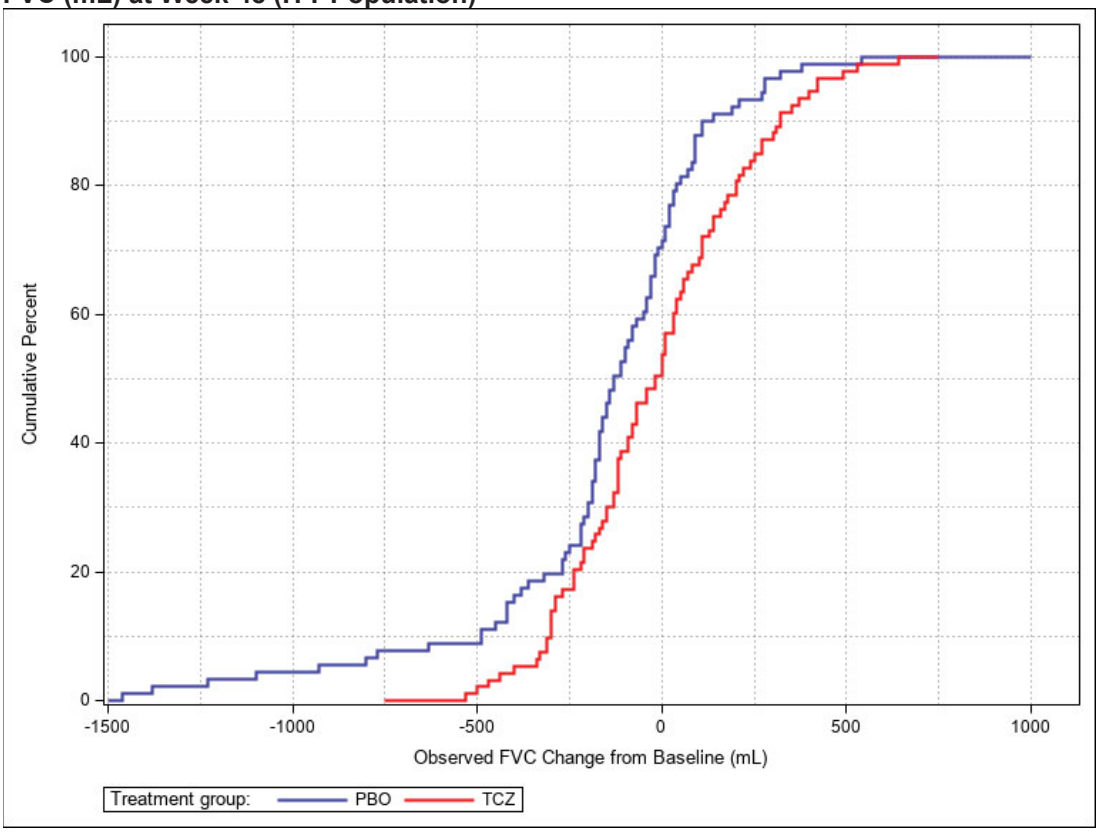
FDA's comments:

Sponsor's Analysis seems reasonable. Overall, the exposure-safety relationship seems to be flat.

15.5. Supplemental Efficacy Tables and Figures

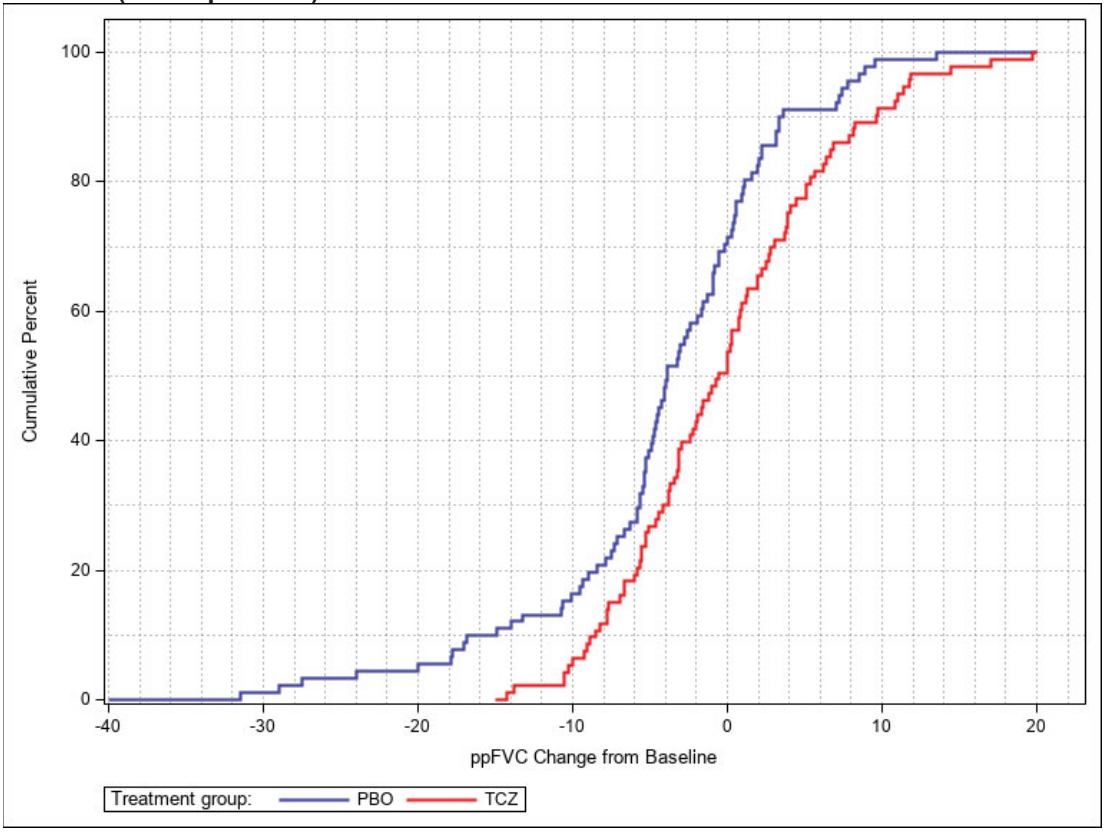
15.5.1. Study WA29767 CDF Plots – Observed FVC and ppFVC in ITT Population

Figure 31: Study WA29767 Cumulative Distribution Plot of Change From Baseline in Observed FVC (mL) at Week 48 (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; TCZ, tocilizumab

Figure 32: Study WA29767 Cumulative Distribution Plot of Change From Baseline in ppFVC at Week 48 (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

15.5.2. Study WA29767 Sensitivity Analyses - FVC in ITT Population

Table 35: Sensitivity Analysis: Pattern Mixture Model for Median Change in ppFVC and Observed FVC at Week 48 in Study WA29767 (ITT Population)

	Placebo N=106	TCZ N=104
ppFVC		
N in model (imputed N*)	106 (15)	104 (11)
P-value**		<0.0001
Observed FVC		
N in model (imputed N*)	106 (15)	104 (11)
P-value**		<0.0001

Source: Statistical reviewer's analysis
* Imputed N is the number of patients who had week 48 data imputed
**P-value from comparison of medians using Van Elteren test stratified by screening IL-6 level
Abbreviations: ITT, intent-to-treat; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Table 36: Sensitivity Analysis: Pattern Mixture Model for Mean Change in ppFVC and Observed FVC at Week 48 in Study WA29767 (ITT Population)

	Placebo N=106	TCZ N=104
ppFVC		
N in model (imputed N*)	106 (15)	104 (11)
Change from baseline, 95% CI	-4.71 (-6.42, -3.00)	-0.68 (-2.44, 1.08)
Difference in LSM (TCZ-placebo), 95% CI	4.03 (1.71, 6.34)	
P-value for difference in LSM**	0.0007	
Observed FVC (mL)		
N in model (imputed N*)	106 (15)	104 (11)
Change from baseline, 95% CI	-194 (-260, -128)	-33 (-101, 35)
Difference in LSM (TCZ-placebo), 95% CI	161 (72, 250)	
P-value for difference in LSM**	0.0004	

Source: Statistical reviewer's analysis
* imputed n is the number of patients who had week 48 data imputed
**p-value obtained from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

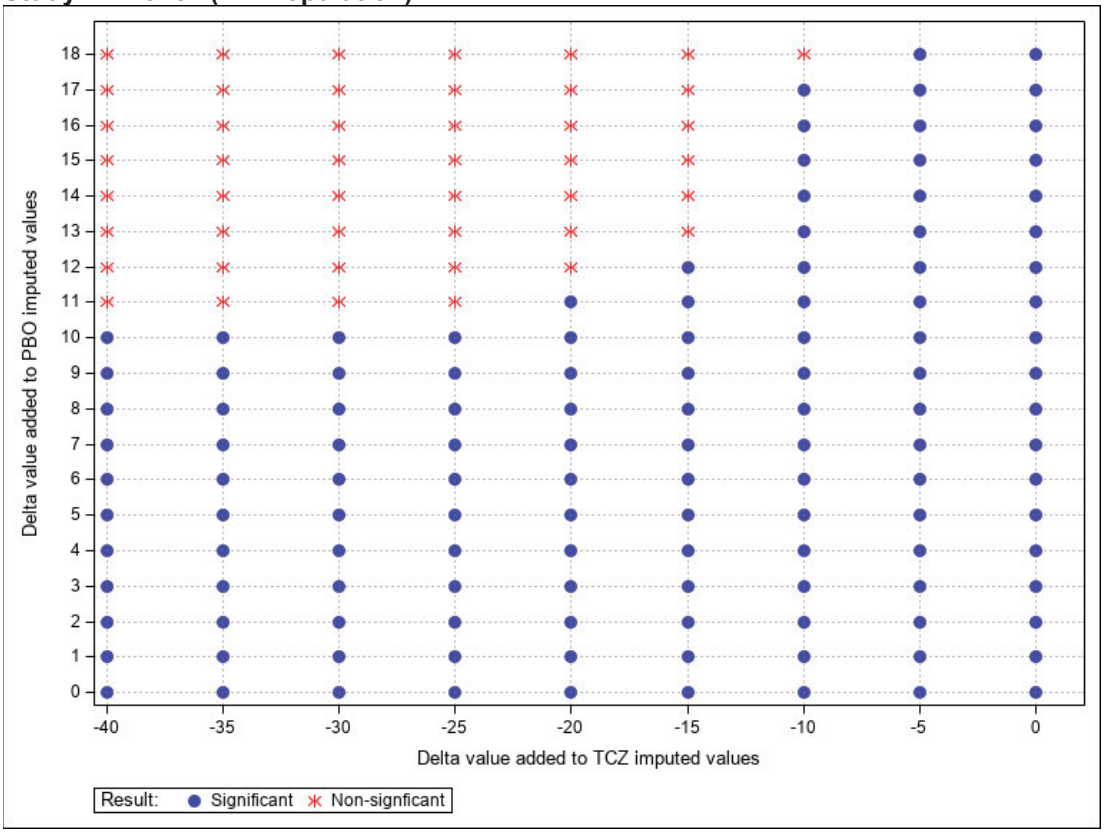
According to Figure 33, an adjustment of -40, -35, -30, and -25 to the imputed TCZ values and +11 to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. An adjustment of -20, -15, and -10 to the imputed TCZ values and +12, +13, and +18, respectively, to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. Other values that tipped the Van Elteren test p-value are shown in the figure.

According to Figure 34, an adjustment of -7, -6, and -5 to the imputed TCZ values and +2, +3, and +4, respectively, to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. Other values that tipped the comparison of LSMs p-value are shown in the figure.

According to Figure 35, an adjustment of -500, -400, and -300 mL to the imputed TCZ values and +400, +450, and +600 mL, respectively, to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. Other values that tipped the Van Elteren test p-value are shown in the figure.

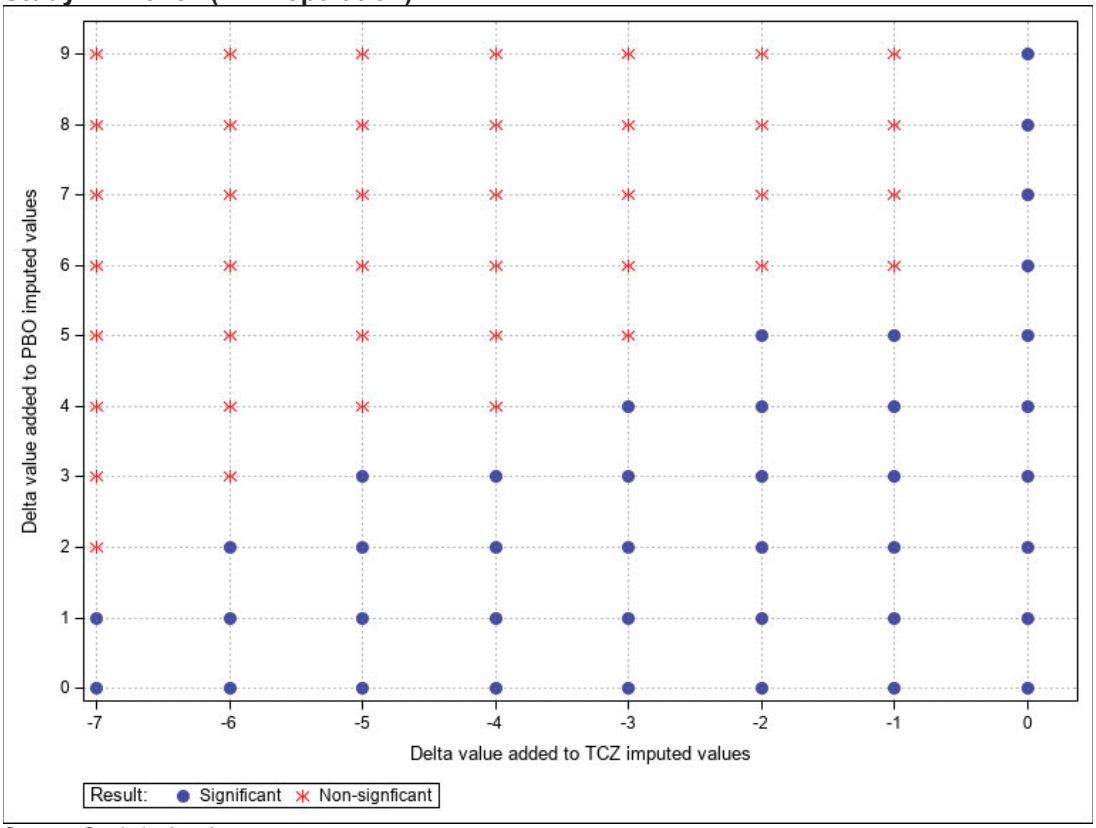
According to Figure 36, an adjustment of -250, -200, and -150 mL to the imputed TCZ values and +100, +150, and +200 mL, respectively, to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. Other values that tipped the comparison of LSMs p-value are shown in the figure.

Figure 33: Sensitivity Analysis: Tipping Point Analysis for Median Change in ppFVC at Week 48 in Study WA29767 (ITT Population)



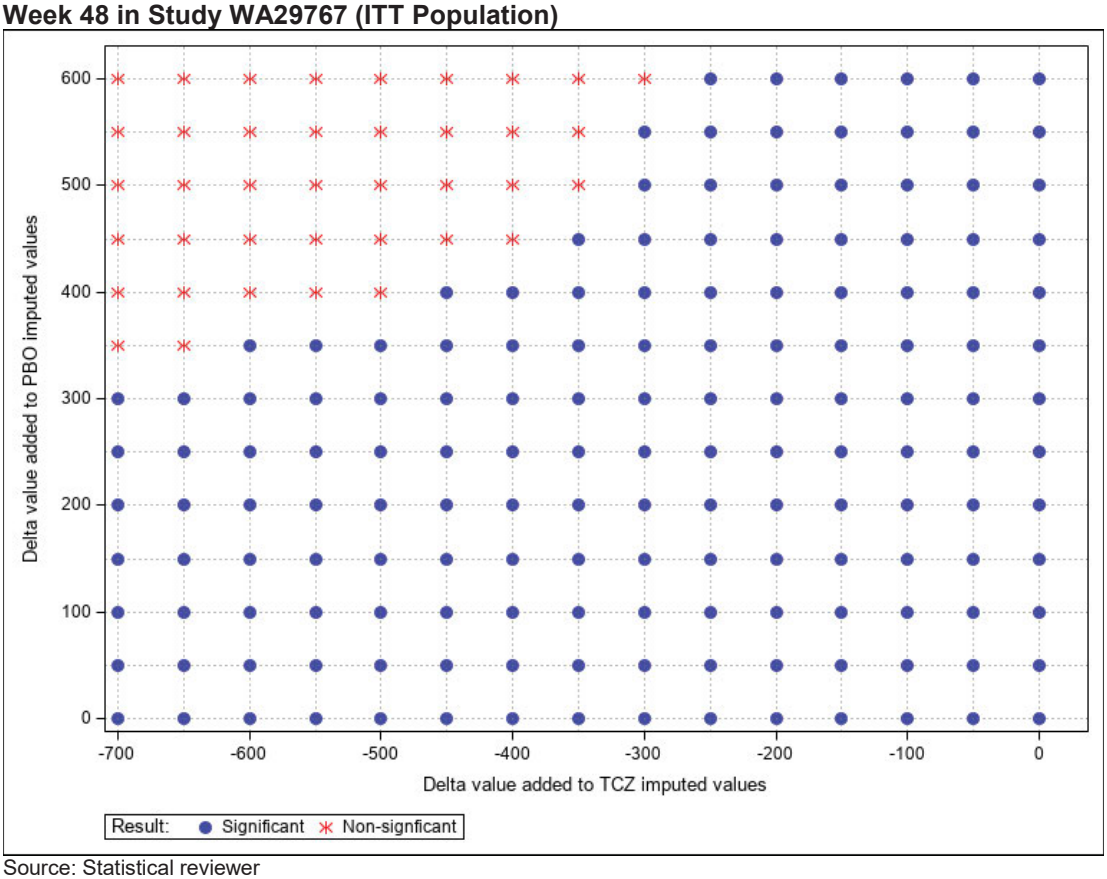
Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; ppFVC, percent predicted forced vital capacity

Figure 34: Sensitivity Analysis: Tipping Point Analysis for Mean Change in ppFVC at Week 48 in Study WA29767 (ITT Population)



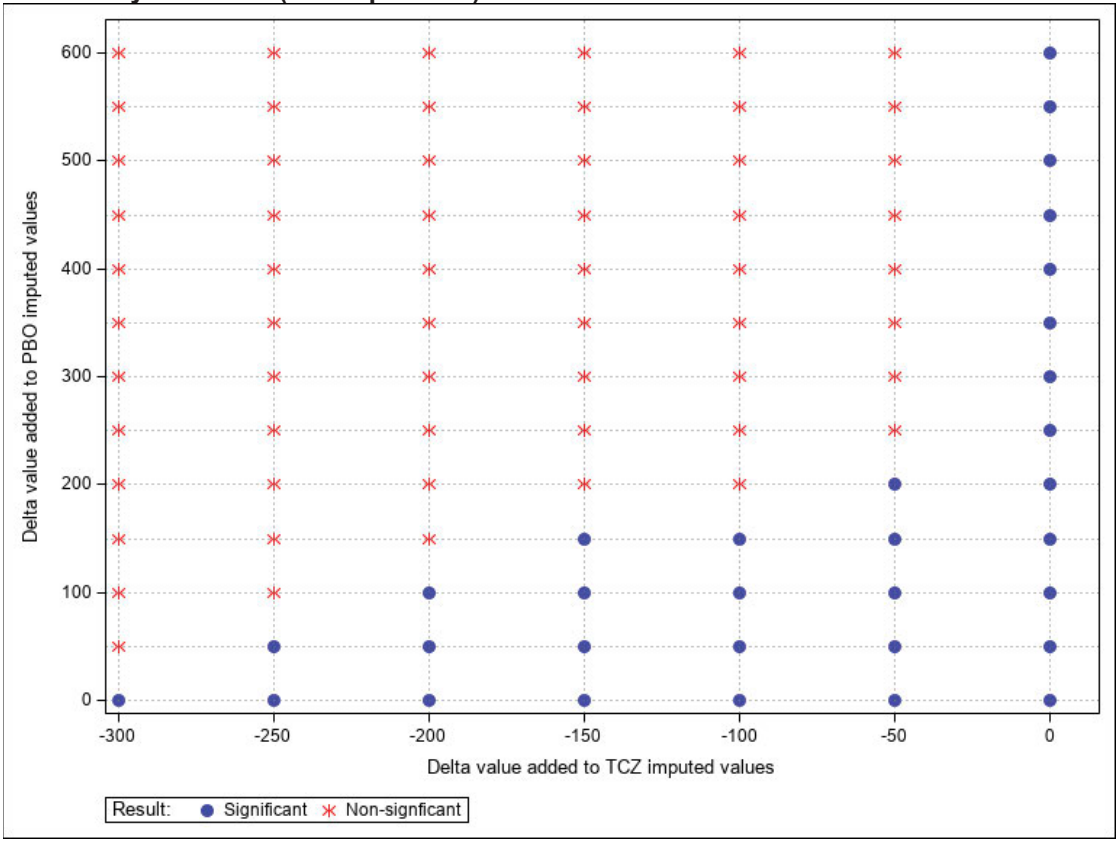
Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; ppFVC, percent predicted forced vital capacity

Figure 35: Sensitivity Analysis: Tipping Point Analysis for Median Change in Observed FVC at Week 48 in Study WA29767 (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; PBO, placebo; TCZ, tocilizumab

Figure 36: Sensitivity Analysis: Tipping Point Analysis for Mean Change in Observed FVC at Week 48 in Study WA29767 (ITT Population)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; ITT, intent-to-treat; PBO, placebo; TCZ, tocilizumab

15.5.3. Study WA29767 Sensitivity Analyses - FVC in SSc-ILD Subgroup

Table 37: Sensitivity Analysis: Pattern Mixture Model for Median Change in ppFVC and Observed FVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
ppFVC		
N in model (imputed N*)	68 (12)	68 (9)
P-value**		<0.0001
Observed FVC		
N in model (imputed N*)	68 (12)	68 (9)
P-value**		<0.0001

Source: Statistical reviewer's analysis
* Imputed N is the number of patients who had week 48 data imputed
**P-value from comparison of medians using Van Elteren test stratified by screening IL-6 level
Abbreviations: FVC, forced vital capacity; ppFVC, percent predicted forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Table 38: Sensitivity Analysis: Pattern Mixture Model for Mean Change in ppFVC and Observed FVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
ppFVC		
N in model (imputed N*)	68 (12)	68 (9)
Change from baseline, 95% CI	-6.61 (-8.92, -4.29)	-0.61 (-2.88, 1.66)
Difference in LSM (TCZ-placebo), 95% CI	6.00 (2.89, 9.10)	
P-value for difference in LSM**	0.0002	
Observed FVC (mL)		
N in model (imputed N*)	68 (12)	68 (9)
Change from baseline, 95% CI	-258 (-349, -168)	-35 (-125, 55)
Difference in LSM (TCZ-placebo), 95% CI	223 (102, 345)	
P-value for difference in LSM**	0.0003	

Source: Statistical reviewer's analysis
* Imputed N is the number of patients who had week 48 data imputed
**P-value obtained from analysis using an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction
Abbreviations: CI, confidence interval; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

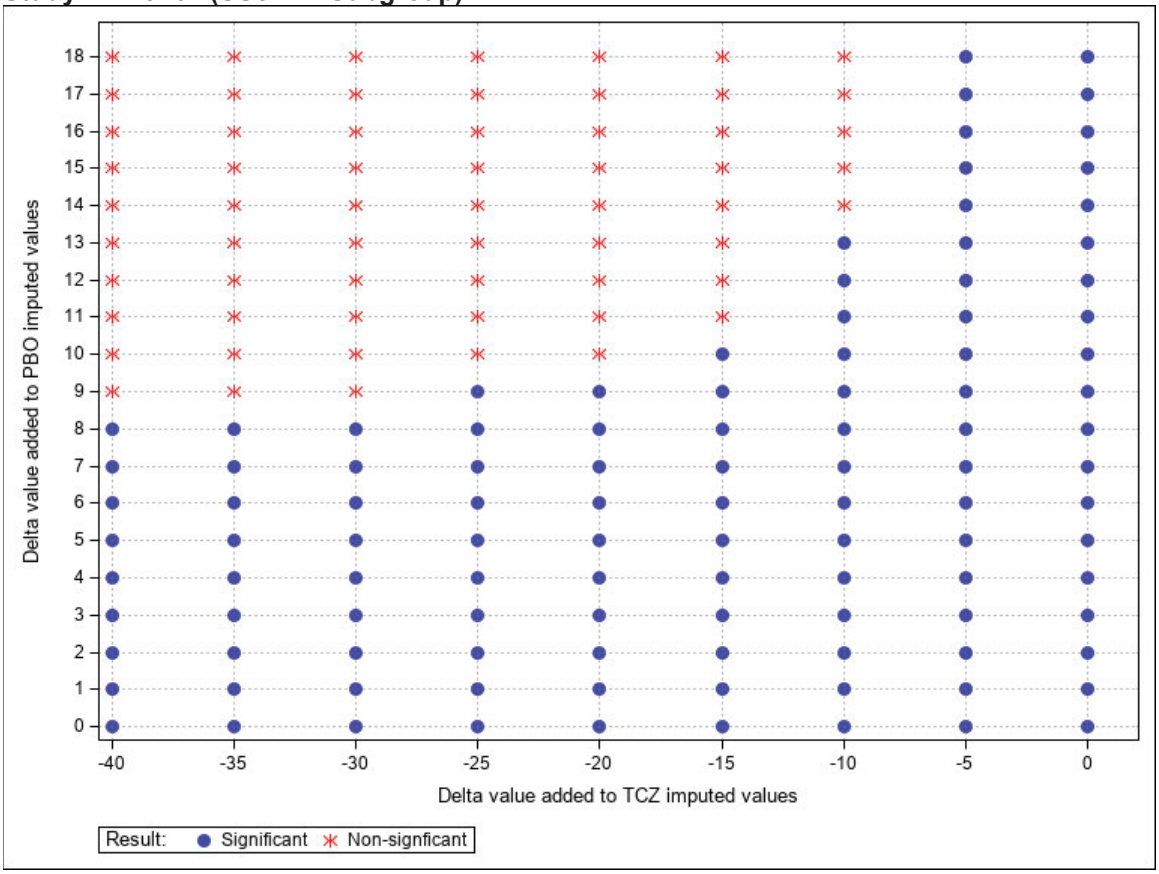
According to Figure 37, an adjustment of -40, -35, and -30 to the imputed TCZ values and +9 to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. An adjustment of -25 and -20 to the imputed TCZ values and +10 to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. Other values that tipped the Van Elteren test p-value are shown in the figure.

According to Figure 38, an adjustment of -7, -6, and -5 to the imputed TCZ values and +3, +4, and +5, respectively, to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. Other values that tipped the comparison of LSMs p-value are shown in the figure.

Results from the tipping point sensitivity analyses for the observed FVC endpoint in the SSc-ILD subgroup are shown in Figure 39 and Figure 40. According to Figure 39, an adjustment of -500, -400, and -300 mL to the imputed TCZ values and +400, +450, and +500 mL, respectively, to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. Other values that tipped the Van Elteren test p-value are shown in the figure.

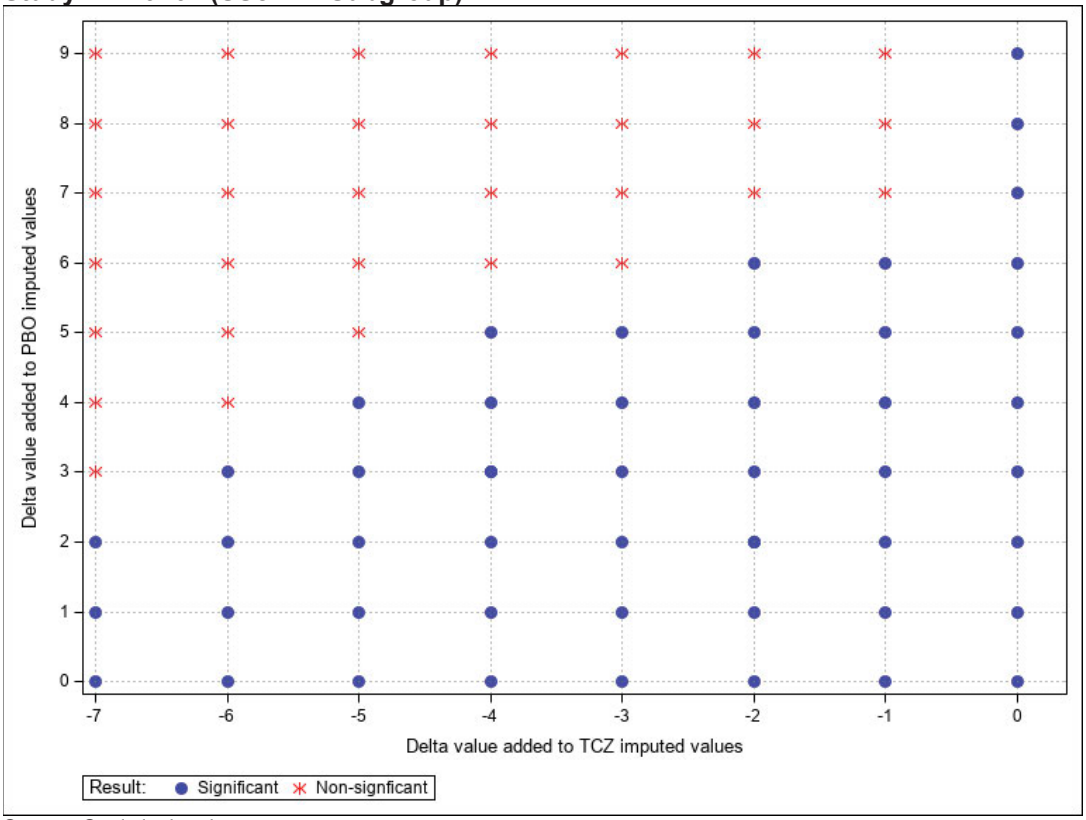
According to Figure 40, an adjustment of -250, -200, and -150 mL to the imputed TCZ values and +100, +150, and +200 mL, respectively, to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. Other values that tipped the comparison of LSMs p-value are shown in the figure.

Figure 37: Sensitivity Analysis: Tipping Point Analysis for Median Change in ppFVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)



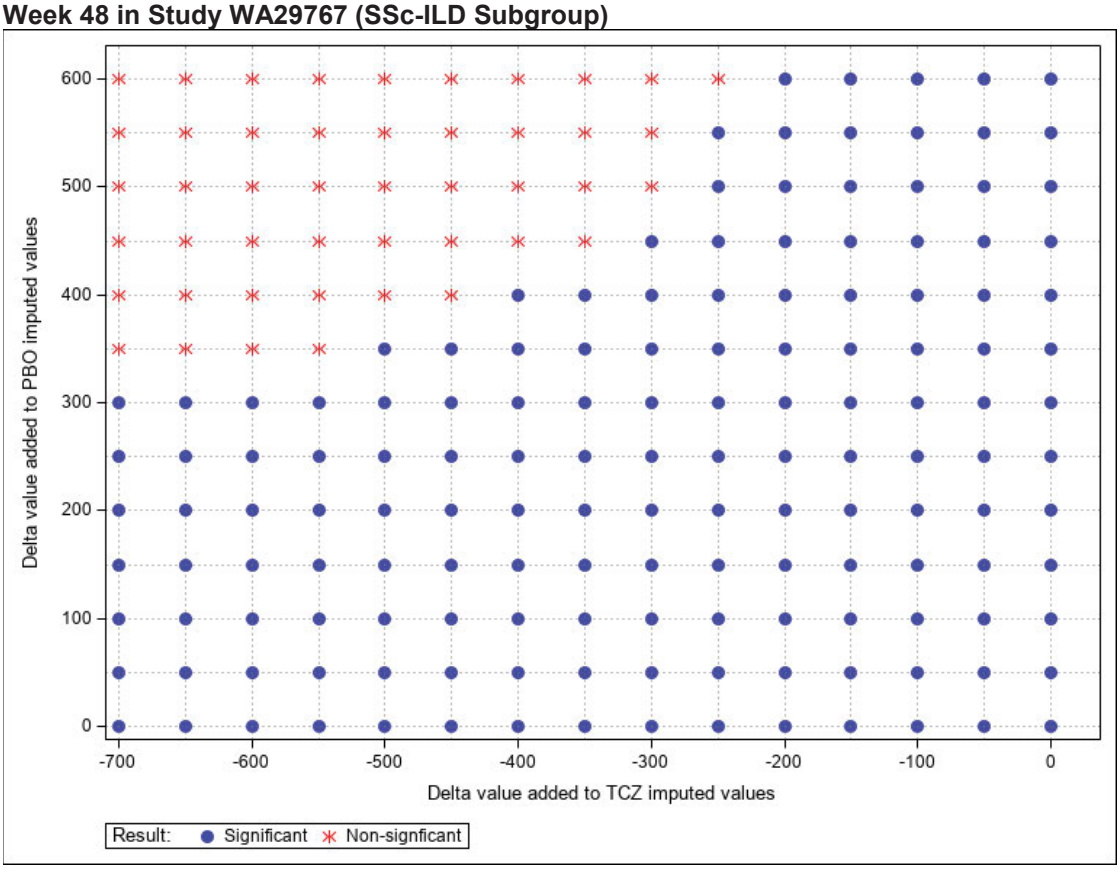
Source: Statistical reviewer
Abbreviations: PBO, placebo; ppFVC, percent predicted forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Figure 38: Sensitivity Analysis: Tipping Point Analysis for Mean Change in ppFVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)



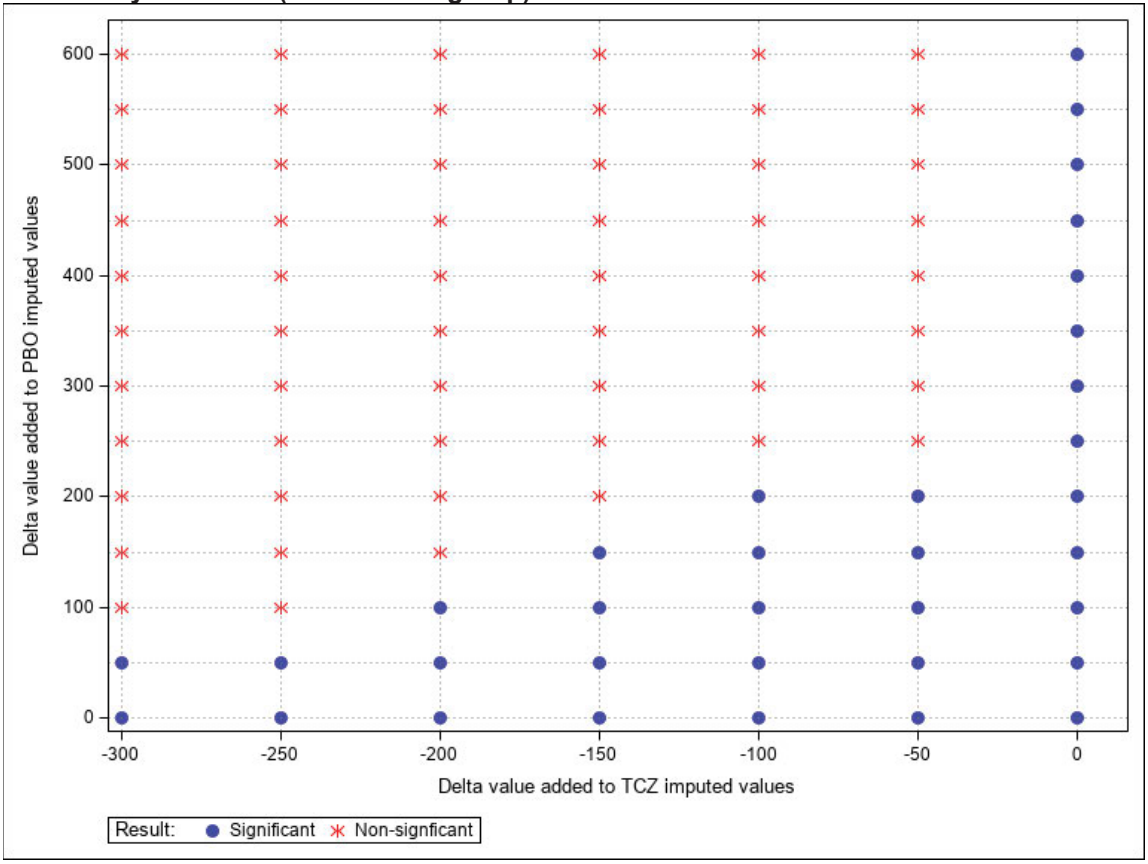
Source: Statistical reviewer
Abbreviations: PBO, placebo; ppFVC, percent predicted forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

Figure 39: Sensitivity Analysis: Tipping Point Analysis for Median Change in Observed FVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)



Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; SSc-ILD, interstitial lung disease associated with systemic sclerosis; PBO, placebo; TCZ, tocilizumab

Figure 40: Sensitivity Analysis: Tipping Point Analysis for Mean Change in Observed FVC at Week 48 in Study WA29767 (SSc-ILD Subgroup)



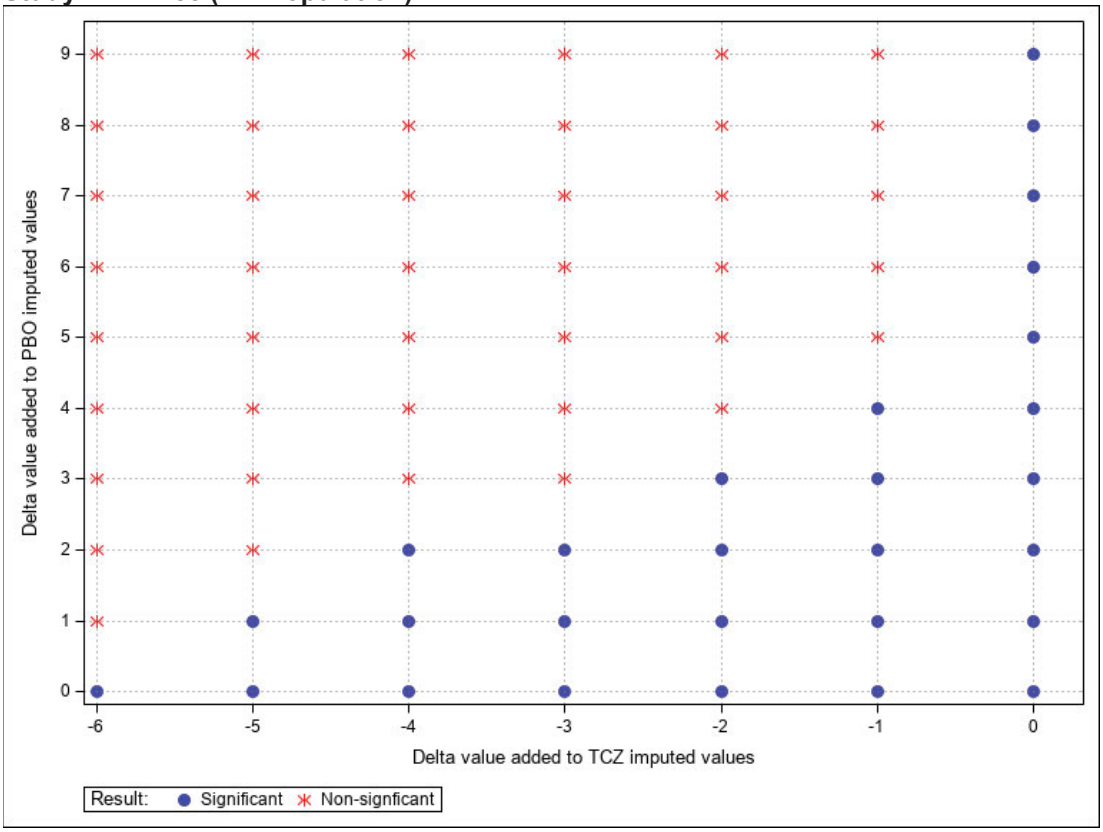
Source: Statistical reviewer
Abbreviations: FVC, forced vital capacity; PBO, placebo; SSc-ILD, interstitial lung disease associated with systemic sclerosis; TCZ, tocilizumab

15.5.4. Study WA27788 Sensitivity Analyses - FVC in ITT Population

According to Figure 41, an adjustment of -6, -5, and -4 to the imputed TCZ values and +1, +2, and +3, respectively, to the imputed placebo values tipped the resulting Van Elteren test p-value to a value > 0.5. Other values that tipped the Van Elteren test p-value are shown in the figure.

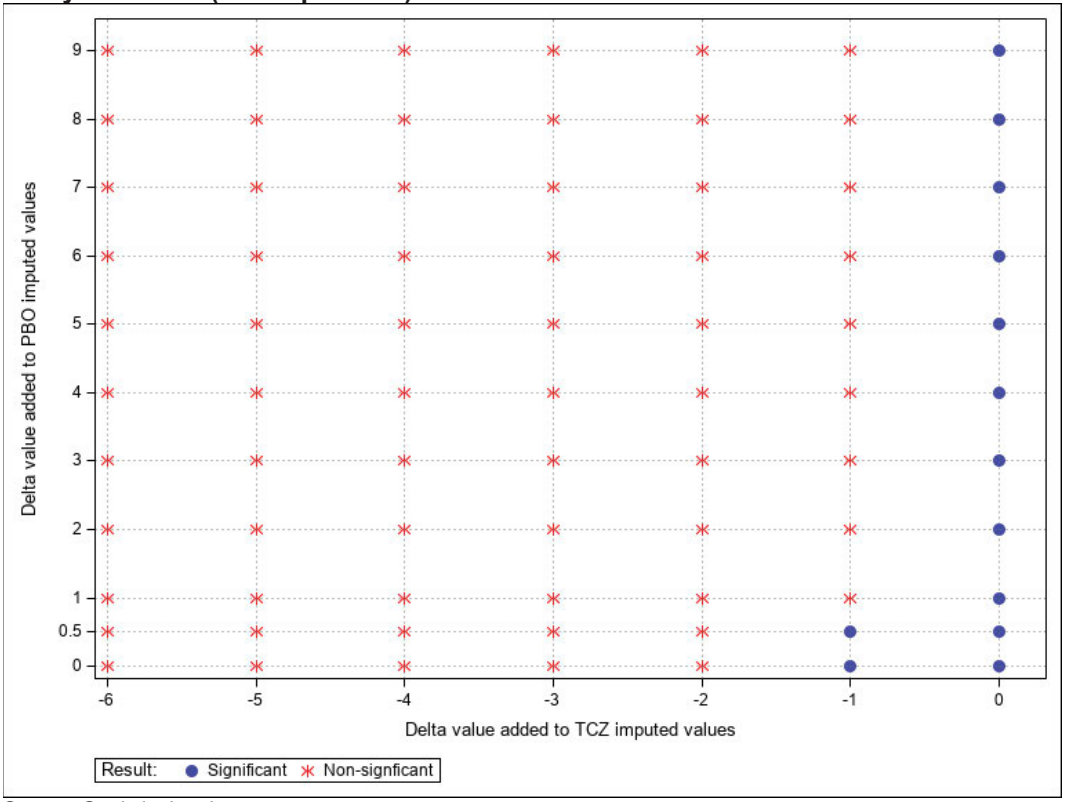
According to Figure 42, an adjustment of -1 to the imputed TCZ values and +1 to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. An adjustment of -2, -3, and -4 to the imputed TCZ values and 0 to the imputed placebo values tipped the resulting p-value for the comparison of LSMs to > 0.05. Other values that tipped the comparison of LSMs p-value are shown in the figure.

Figure 41: Sensitivity Analysis: Tipping Point Analysis for Median Change in ppFVC at Week 48 in Study WA27788 (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

Figure 42: Sensitivity Analysis: Tipping Point Analysis for Mean Change in ppFVC at Week 48 in Study WA27788 (ITT Population)



Source: Statistical reviewer
Abbreviations: ITT, intent-to-treat; PBO, placebo; ppFVC, percent predicted forced vital capacity; TCZ, tocilizumab

15.5.5. Study WA29767 Subgroup Analyses - FVC in SSc-ILD Subgroup

Table 39: Study WA29767 Post-hoc ppFVC Results by Sex at Week 48 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
Sex: Female		
Mean change from baseline in ppFVC		
N	53	53
Change from baseline	-4.51	0.14
Difference in LSM (TCZ-placebo), 95% CI	4.65 (1.42, 7.88)	
Sex: Male		
Mean change from baseline in ppFVC		
N	13	15
Change from baseline	-14.41	0.29
Difference in LSM (TCZ-placebo), 95% CI	14.70 (8.31, 21.08)	

Source: Table submitted by the Applicant as a response to the Agency's filing communication dated October 1, 2020
The analysis used an MMRM, which included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level at screening, sex, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, sex-by-visit interaction, treatment-by-sex interaction, and treatment-by-sex-by-visit interaction, as well as the continuous covariates of baseline ppFVC and baseline ppFVC-by-visit interaction.
Abbreviations: CI, confidence interval; ILD, interstitial lung disease; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Table 40: Study WA29767 Post-hoc ppFVC Results by Age at Week 48 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
Age: < 65 years		
Mean change from baseline in ppFVC		
N	58	64
Change from baseline	-6.64	-0.25
Difference in LSM (TCZ-placebo), 95% CI	6.39 (3.20, 9.59)	
Age: ≥ 65 years		
Mean change from baseline in ppFVC		
N	8	4
Change from baseline	-4.81	4.15
Difference in LSM (TCZ-placebo), 95% CI	8.96 (-2.09, 20.01)	

Source: Table submitted by the Applicant as a response to the Agency's filing communication dated October 1, 2020
The analysis used an MMRM, which included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level at screening, baseline age category, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, baseline age-by-visit interaction, treatment-by-baseline age interaction, and treatment-by-baseline age-by-visit interaction, as well as the continuous covariates of baseline ppFVC and baseline ppFVC-by-visit interaction.
Abbreviations: CI, confidence interval; ILD, interstitial lung disease; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

Table 41: Study WA29767 Post-hoc ppFVC Results by Race at Week 48 (SSc-ILD Subgroup)

	Placebo N=68	TCZ N=68
Race: Asian		
Mean change from baseline in ppFVC		
N	7	15
Change from baseline	-1.28	3.34
Difference in LSM (TCZ-placebo), 95% CI	4.62 (-1.66, 10.90)	
Race: White		
Mean change from baseline in ppFVC		
N	56	51
Change from baseline	-6.76	-1.11
Difference in LSM (TCZ-placebo), 95% CI	5.65 (2.23, 9.06)	

Source: Statistical reviewer's analysis
The analysis used an MMRM which included the categorical effects of treatment, visit, the stratification factor IL-6 level at screening, IL-6 level at screening by visit interaction, and treatment by visit interaction, and the continuous covariates of baseline value and baseline value by visit interaction.
The race categories shown reached mixed model convergence. Race categories not shown: American Indian or Alaska Native, Black or African-American, and Other.
Abbreviations: CI, confidence interval; ILD, interstitial lung disease; LSM, least squares mean; ppFVC, percent predicted forced vital capacity; SSc, systemic sclerosis; TCZ, tocilizumab

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/s/

RACHEL GLASER
03/04/2021 01:31:43 PM

NIKOLAY P NIKOLOV
03/04/2021 01:47:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s131

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Medical Policy and Program Review Council Meeting:
Tocilizumab (Actemra) for Treatment of Systemic Sclerosis-Associated Interstitial Lung Disease (OII/DRTM)

December 9, 2020

Input of the MPPRC sought on the approval of tocilizumab for the treatment of systemic sclerosis-associated interstitial lung disease based on a secondary study endpoint

Background

Systemic sclerosis (SSc) is a rare, multisystem, connective tissue disease that affects approximately 100,000 people in the United States[1]. It is characterized by microvascular damage and fibrosis of the skin and organs, including the lung. The 10-year survival rate for patients with SSc is less than 70% from time of diagnosis[2], and one of the leading causes of SSc mortality is interstitial lung disease (ILD), which is present in about 55 to 65% of patients with SSc[3]. Both SSc and SSc-associated ILD (SSc-ILD) are rare conditions with high unmet medical need; however, as of now, only a single FDA-approved therapy, nintedanib, is available for the treatment of these diseases[4].

Tocilizumab (TCZ) is a monoclonal antibody that inhibits the IL-6 cytokine receptor, thus inducing an anti-inflammatory response. TCZ is approved for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular and systemic juvenile idiopathic arthritis, and cytokine release syndrome. Because patients with SSc often exhibit elevated serum levels of IL-6, a marker predictive of poor survival, it is plausible that inhibition of the IL-6 receptor could be beneficial for patients with SSc; this hypothesis is supported by preclinical and observational clinical data. At the suggestion of the Division, Genentech (Sponsor) seeks approval for sBLA 125472-S044 for TCZ in the treatment of SSc-ILD.

In support of the sBLA, the Sponsor submitted results from two double-blind, randomized, placebo-controlled studies; one phase 2 and one phase 3 study. Results from the phase 2 study were originally used to support an application for Breakthrough Therapy Designation, which was granted in 2015. In July 2018, the Sponsor submitted a pre-sBLA meeting package containing the results from both trials, proposing an indication of treatment of SSc. Neither study met the primary efficacy endpoint of improvement in the modified Rodnan skin score (mRSS), a measure of skin involvement in SSc based on skin thickness. However, a meaningful clinical effect of TCZ treatment was demonstrated on the basis of forced vital capacity (FVC) supported by the results of high-resolution computed tomography (HRCT) at Week 48. FVC was a secondary endpoint in the phase 3 study, and was nominally statistically significant. At the time of the pre-sBLA meeting, however, the Division expressed concern over the failure to meet

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[1] https://www.scleroderma.org/

[2] Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis 2007;66:940–4

[3] Launay D, Remy-Jardin M, Michon-Pasturel U, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol 2006;33(9):1789-801

[4] https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Ofev/ofev.pdf

the primary endpoint and the lack of regulatory precedent for use of FVC as a surrogate endpoint in SSc. Consequently, the Division indicated to the Sponsor that confirmatory evidence demonstrating benefit to pulmonary function in SSc would likely be needed; the Sponsor subsequently decided not to pursue further development of TCZ for SSc.

Following the pre-sBLA meeting, scientific understanding of FVC as a viable endpoint evolved considerably[5,6], and the Division determined FVC to be an acceptable surrogate endpoint for trials in fibrotic lung diseases. In line with this shift, in September 2019, nintedanib was approved for the treatment of SSc-ILD based on the primary FVC endpoint.

Based on the outcome of the nintedanib program, as well as discussions with the Arthritis Advisory Committee regarding FVC, the Division encouraged the Sponsor to submit their findings from the TCZ SSc program. The Sponsor submitted sBLA 125471 S-044 on July 24, 2020. The Division plans to approve TCZ for the treatment of SSc-ILD based on the consistent and clinically persuasive benefit to FVC, despite the failure to meet the primary endpoint in each study.

Discussion at the MPPRC Meeting

- Both the phase 2 and 3 studies in TCZ failed to meet the specified primary endpoint of mRSS. However, analyses of the FVC endpoint revealed estimated effects that were clinically persuasive (i.e., 120 and 167 mL mean difference in FVC change at Week 48 in the phase 2 and 3 trials, respectively, and a 241 mL mean difference in FVC change in the SSc-ILD subgroup from the phase 3 trial), with nominal statistical significance, and consistent between studies. Notably, for the small phase 2 study, the p value for percent predicted FVC was < 0.05, and for the larger Phase 3 study, the p values for FVC and percent predicted FVC were very low.
- A nominally significant and meaningful estimated effect of TCZ on FVC was found within the SSc-ILD subgroup when compared to SSc-ILD patients who received placebo. In the case of idiopathic pulmonary fibrosis, drugs have previously been approved based on approximately 100 mL mean differences in FVC, and an FVC decline of ≥ 10% has been associated with an increased risk of mortality. The available data from SSc-ILD studies are insufficient to determine the threshold at which a change in FVC becomes relevant in a clinical setting, but the observed difference in FVC appears to be large and likely clinically important.
- The Sponsor seeks an indication for TCZ in patients with SSc-ILD; however, the patients participating in the phase 2 and 3 trials were from the general SSc population. Post-hoc analyses of the Phase 3 trial revealed a more pronounced effect of TCZ on FVC in patients in the SSc-ILD subgroup. Within the non-ILD subgroup, there was no evidence

[5] Karimi-Shah BA, Chowdhury BA, Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib, N Engl J Med. 2015 Mar 26;372(13):1189-91

[6] Paterniti MO, et al., Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis, Ann Am Thorac Soc. 2017 Sep;14(9):1395-1402

of an effect, although estimates were in the direction of benefit, with a slightly better estimate for the difference in medians relative to the difference in means. It was noted, however, that distinguishing patients with ILD from those without it within the SSc population is fairly subjective in clinical practice, and so a few patients with early ILD may have been classified as non-ILD, potentially affecting the results. Results from the non-ILD subgroup should be interpreted with caution due to its small sample size and considerable uncertainty around estimates. Despite these limitations, no overall effect on FVC was observed in the non-ILD subgroup.

- No data from other drugs in the IL-6 inhibitor class are available for comparison with TCZ for the treatment of SSc or SSc-ILD.
- In clinical practice, both radiography and pulmonary function are used to assess a patient's respiratory involvement. Therefore, the fact that high-resolution CT findings trended similarly to FVC in terms of improvement in the TCZ arm is supportive of efficacy. However, it is important to note that the magnitude of change considered clinically significant is not clear. Furthermore, in clinical practice, HRCT data are qualitative, not quantitative. It was noted that the diffusing capacity for carbon monoxide (DLCO) also did not substantively differ between treatment arms. However, there may be more variability in DLCO measurements, and a similar lack of effect was also observed in the nintedanib program.
- Although there were no differences in patient-reported outcomes (PROs), the Division noted that the PROs in this program were not specific for the assessment of respiratory symptoms, that the sensitivity may be limited, and that the PROs did not reflect improvement for nintedanib.
- No major differences in exploratory endpoints, such as fatigue, were observed between the TCZ and placebo groups. It should be noted, however, that these endpoints have not been properly evaluated in the context of SSc, and therefore the relevance of a lack of change in these events is unclear.
- The effects observed in both studies may be subject to "random high" bias (i.e., bias toward larger effects), under the assumption that the analysis has selected for the most favorable results among many endpoints. Thus, the size of the effect seen may be larger than the true effect. However, it was pointed out that the likelihood of falsely detecting a statistically significant effect on FVC in both studies, if there was truly no effect, considering 20 different endpoints in each study, is low, based both on findings of efficacy in two studies and the small p values in the phase 3 study.
- The sensitivity of the PROs was discussed, given that despite a significant effect of TCZ on FVC, PROs did not significantly differ between the TCZ and placebo arms. This lack of effect on PROs, despite an apparent treatment benefit, was also observed in the nintedanib program (i.e., no difference in PROs between treatment and placebo groups). One possible explanation for this phenomenon is that there is currently a lack of necessary SSc drug development experience to adequately identify meaningful outcomes using PRO measures.
- It was questioned as to why the Sponsor chose not to specify FVC as a co-primary endpoint for the phase 3 trial. At the time of the initial breakthrough therapy request

for TCZ, FVC had not yet been agreed upon as a meaningful endpoint. Therefore, despite the early phase 2 trial results showing a positive change in FVC, the Sponsor retained mRSS as the primary endpoint for the phase 3 trial and elevated FVC from an exploratory to a key secondary endpoint.

- Some discussion centered around the adequacy of trial design and whether a small confirmatory study should be conducted. Typically, clinical trials are designed to thoroughly evaluate primary efficacy endpoints, and secondary endpoints are used to inform labeling and support the primary efficacy findings. Given that the Sponsor now pursues an indication for SSc-ILD, trials would ideally have included only patients with SSc-ILD and an FVC-based primary endpoint. This was not the case, however, because the phase 2 and 3 trials enrolled a general SSc population. Consequently, some Council members held the opinion that the observed effect on FVC in the SSc-ILD subgroup should be viewed as a hypothesis-generating, rather than a hypothesis-confirming, finding. Thus, it was expressed that an additional small, confirmatory trial in the SSc-ILD population would bolster confidence in the efficacy claim. Unfortunately, an additional confirmatory trial is unlikely to be conducted at this stage as the Sponsor does not currently plan to pursue the TCZ program further and declined to conduct an additional study in SSc-ILD during pre-submission discussions.
- In contrast to the nintedanib study, in which a significant portion of enrolled patients were maintained on background medications (i.e., approximately half of patients were concomitantly treated with the immunosuppressant mycophenolate), patients on additional medications, other than glucocoritcoids, were largely absent from the TCZ trials. This is noteworthy given that in the nintedanib program, patients on mycophenolate experienced a 50% smaller effect on FVC; thus, the Council raised the possibility that TCZ's effect may be diminished when given in combination with immunosuppressants.
- Secondary endpoints alone are not typically accepted as proof of efficacy in the event that a study fails to meet one or more primary endpoints. Several members of the Council expressed concern over inconsistency with past regulatory decisions in the event that this application is approved. In particular, approval may incentivize other development programs to salvage failed trials by looking for secondary or exploratory endpoints that demonstrate a statistically significant effect. A decision of traditional approval would not be entirely without precedent, however; carvedilol, a beta-blocker used to treat high blood pressure and heart failure, was approved based on a secondary endpoint of death, despite failure to meet the primary endpoint. One caveat to this point is that carvedilol was accepted based in part on supporting evidence from other drugs of the same class. In addition to the case of carvedilol, two Advisory Committees are currently scheduled to reconsider drug trials that failed to reach primary endpoints but demonstrated persuasive effects on other endpoints. It is important to note that in the case of TCZ, the primary endpoint of mRSS was selected over FVC at least in part because at the time the trials were conducted, FVC was not yet considered a reliable endpoint. The regulatory outlook on FVC as an endpoint has since changed, and its assessment has led to traditional approval in in fibrotic lung diseases in several instances.

Recommendations: The Council acknowledged the complexity of the topic and was not unanimous in their recommendation. A number of Council members found the available data persuasive and, considering the unmet medical need for this rare disease, supported the Division's stance to approve an indication for SSc-ILD. Other Council members expressed concern over the regulatory precedent that approval may set in this case. It was agreed that if the Division proceeded to an approval decision, the rationale for supporting the approval with the current submitted data should be clearly articulated in a manner that avoided, as far as possible, setting a precedent for future programs that have unsuccessful phase 3 studies. It was suggested that the Division work closely with OND Policy to determine the appropriate framework for approval. It was also suggested that an Advisory Committee be held to discuss the issue publicly.

Council Members:

Peter Stein, OND
Jacqueline Corrigan-Curay, OMP
Robert Temple, CDER
Gerald Dal Pan, OSE
Issam Zineh, OCP
John Farley, OND/OID
James Smith, OND/ONDP/DCP
Mary Thanh Hai, OND
Judy Zander, OSE
Mark Levenson, OB
Christine Nguyen, OND/ORDPURM/DUOG
Aliza Thompson, OND/OCHEN/DCN
Kayla Holman, Project Manager

Attendees:

Aishah Ali, OND/OII/DPACC
Amit Golding, OND/OII/DRTM
Andrew Clerman, OND/OII/DPACC
Andrew Leboeuf, OND/ONDP/DRP
Anil Rajpal, OND/OII/DRTM
Ann Biehl, OSE
Audrey Gassman, OND/ORDPURM/DUOG
Austin Anderson, OND/OII/DRTM
Banu Karimi-Shah, OND/OII/DPACC
Billy Dunn, OND/ON
Bryon Pearsall, OMP
David Petullo, OB
Elaine Sit, OND/ORO/DROII
Elisabeth Boulos, OND/OII/DPACC
Elizabeth Ford, OTS
Emanuela Lacana, OND/OTBB
Ergun Velidedeoglu, OND/OII/DRTM
Erica Radden, OMP
Erica Boehm, OND/OPO/EOS
Francis Becker, OND/ONPD/DNPD2
Frank Anania, OND/OII/DHN
Stefanie Freeman, OND/OII/DRTM
Charles J Ganley, OSM
Rachel Glaser, OND/OII/DRTM
Gregory Levin, OB
Hylton Joffe, OND/ORDPURM
Hyon Kwon, OND/OCHEN/DDLO
Idalia Rychlik, OSE
Iilun Murphy, OGD
James Myers, OND/ONDP/DRP
Jane Filie, OND/ORDPURM/DRDMG
Javier Muniz, OND/ON/DP
Jeffrey Murray, OND/OID/DAV
Jessica Boehmer, OND/OOD
Joette Meyer, OND/OII/DG
John Alexander, OND/ORDPURM/DPMH
John Concato, OMP
Joseph Toerner, OND/OII/DHN

Juli Tomaino, OND/OII/DG
Julie Beitz, OND/OII
Juwaria Waheed, OND/OII/DRTM
Karen Mahoney, OND/ONPD
Kathleen Klemm, OPDP
Kelly Stone, OND/OII/DPACC
Kerry Jo Lee, OND/ORDPURM/DRDMG
Kevin Fain, OND/ONDP
Khalid Puthawala, OND/OII/DRTM
Kristiana Brugger, ORP
Kyle Snyder, OPDP
Laura Kangas, OSE
Laura Johnson, OB
Lauren Choi, OND
Lei Nie, OB
Leonard Sacks, OMP
Libero Marzella, OND/OSM/DIRM
Lisa Yanoff, OND/OCHEN/DDLO
Lisa Harinstein, OSE
Lois Freed, OND/ON/DPTN
Lynne Yao, OND/ORDPURM/DPMH
Maarika Kimbrell, OND/ONDP
Mahtab Niyyati, OND/OCHEN/DDLO
Diane Maloney, CBER
Mary Ross Southworth, OND/OCHEN/DCN
Davis Mathew, OSE
Matthew Barlow, OSE
Matthew Kowalik, OND/OII/DG
May Tun Saung, OND/OOD/DO3
Meghana Chalasani, OND
Meredith Chuk, OND/OOD
Mitra Ahadpour, OTS
Miya Paterniti, OND/OII/DPACC
Mona Shing, OMP
Monica Munoz, OSE
Nadia Habal, OND/OII/DRTM
Nadia Chaudhri, OND/OII/DRTM
Abhilasha Nair, OND/OOD
Nikolay Nikolov, OND/OII/DRTM
Ozlem Belen, OND/OII/DRTM
Patrick Archdeacon, OND/OCHEN/DDLO
Paul Gouge, OMP
Peter Kim, OND/OID/DAI
Philip Budashewitz, OMP
Raj Nair, OND/OII/DRTM
Rajanikanth Madabushi, OCP
Rebecca Rothwell, OB
Renee Kleris, OND/OII/DPACC
Robert Berlin, OND/ONDP/DCP
Robert Busch, OND/OII/DPACC
Robert Lim, OND/OII/DPACC
Sabiha Khan, OND/OII/DRTM
Sally Seymour, OND/OII/DPACC
Sally Loewke, OND/ONDP/DCO
Sara Jimenez, OB
Sarah Connelly, OND/OID/DAV
Sarah Yim, OND/OTBB
Sarah Zaidi, OND/OII/DPACC
Shaz Siddiqi, OND/OII/DPACC
Sheila Farrell, OND/ORDPURM/DRDMG
Stacy Chin, OND/OII/DPACC
Stefanie Kraus, ORP
Stephanie Omokaro, OMP
Stephen Page, OND
Suzette Peng, OND/OII/DRTM
Sylva Collins, OB
Theresa Michele
Nushin Todd, OND/ONPD/DNPD1
Wiley Chambers, OND/OSM/DO
Yodit Belew, OND/OID/DAV
Yuliya Yasinskaya, OND/OID/DAI